CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

BLA 125160/0

MEDICAL REVIEW(S)

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE
Food and Drug Administration

Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Silver Spring, MD 20993

Division of Gastroenterology Products
HFD-180

Date: **April 18, 2008**

From: **John Hyde, Ph.D., M.D., Clinical Team Leader, DGP** John E. Hyde 4-18-08

Subject: **Clinical Team Leader Summary Review of Resubmission to BLA/STN 125160**
CIMZIA for Crohn's Disease

To: **BLA 125160 File**
Joyce Korvick, M.D., Deputy Division Director, DGP
Julie Beitz, M.D., Office Director, ODE 3

Identifying information

BLA/STN#:	125160
Applicant:	UCB, Inc.
Biologic name:	Certolizumab Pegol
Proposed trade name:	CIMZIA
Submission date:	Original: February 28, 2006; Resubmission April 30, 2007
Stamp date:	Original: March 1, 2006; Resubmission May 1, 2007
PDUFA goal date:	January 30, 2008
Formulation:	200 mg certolizumab pegol, lyophilized powder in → glass vial, for solution with 1 mL sterile water, for subcutaneous administration.
Proposed indication:	Reducing signs and symptoms of Crohn's disease and maintaining clinical response in adult patients with moderately to severely active disease who have had an inadequate response to conventional therapy.
Proposed regimen:	400 mg subcutaneous injection at Weeks 0, 2, and 4, followed by 400 mg subcutaneous injection every four weeks.

Recommended regulatory action: Approval under 21 CFR 601.

Introduction and Regulatory Background

General Background

This resubmission, received May 1, 2007, is a complete response to the Complete Response (CR) Letter sent by the Division on December 21, 2006, and represents the second review cycle

for this product. Please refer the Team Leader memo dated December 19, 2006, and other primary review memos from the initial review cycle for more complete information about the regulatory history and the FDA's conclusions from that review cycle.

This BLA is for the new molecular entity Cimzia (certolizumab pegol), a humanized antibody Fab' fragment targeting human tumor necrosis factor alpha (TNFα). The antibody fragment is manufactured using recombinant technology in *E. coli*. The fragment is conjugated to polyethylene glycol to extend its plasma half-life. The product is a lyophilized powder and provided in glass vials for reconstitution into a solution with sterile water. Cimzia is to be administered at a dose of 400 mg as a subcutaneous (SC) injection every two weeks for the first three injections, then every four weeks indefinitely thereafter.

In the original BLA submission the Applicant proposed the indication of '

During the initial review cycle (on 11/10/06) the Applicant revised the proposed indication to '

In the labeling revised to the PLR format, which was submitted on 9/14/07, the proposed indication was changed to "

" Following labeling negotiations, the Applicant agreed to the indication "reducing signs and symptoms of Crohn's disease and maintaining clinical response in adult patients with moderately to severely active disease who have had an inadequate response to conventional therapy." The Applicant has proposed labeling that includes a boxed warning for TB risk, warnings and precautions for risk of infection, heart failure, use with anakinra, neurological events, hematologic events, malignancies, hypersensitivity reactions, autoimmunity, immunosuppression, and immunizations. These warnings and precautions are similar to those found in the labeling of other approved TNF blockers.

Cimzia was approved for treating Crohn's disease in Switzerland in September 2007, but reportedly has not yet been distributed. The EMEA published a negative opinion on Cimzia on 11/15/07, voicing concerns about efficacy, short duration of the maintenance study, questions about quality, and about bleeding events. In the EMEA's subsequent Refusal of Marketing Authorization on 3/20/08, the quality and bleeding concerns were not cited, but the basis for refusing authorization was that there was insufficient evidence to show a benefit, due to only marginal effectiveness that was too low to be relevant. In addition, the EMEA considered the study of maintenance to be too short.

Presubmission Communications between FDA and the IND Sponsors

See the Team Leader review from the initial review cycle for more information about the regulatory history leading up to the original BLA submission. One of the issues that emerged in the initial review cycle was the status of the agreements between the FDA and the IND holder regarding the adequacy of the development program. There had been significant modifications of the program following the End-of-Phase-2 Meeting on April 15, 2003, between GD Searle (the IND holder at that time) and CBER. The CDER GI Division currently asks sponsors of Crohn's disease and ulcerative colitis products to provide replicated evidence of efficacy for induction and to provided maintenance studies lasting one year. The Reviewers in the initial

cycle questioned, in particular, the adequacy of the evidence of efficacy for induction coming from a single controlled induction study.

After receiving the CR Letter, the Applicant requested a meeting with the Division and OND management, which was held on May 30, 2007. It was established by FDA participants that the meetings and subsequent discussions and agreements with CBER about the Phase 3 studies designs were viewed by the CBER review Division at the time as having standing as End-of-Phase-2 agreements, and therefore CDER would view them the same way. Thus, the Phase 3 development program presented in the BLA should be viewed as complying with the designs that were agreed upon with the FDA.

Submission and Review

The original BLA submission was dated February 28, 2006, and it was received on March 1, 2006. It was given Standard (ten month) review priority, and a CR Letter was issued on December 21, 2006. The resubmission was dated April 30, 2007, and it was received on May 1, 2007, classified as a six-month resubmission with a PDUFA deadline of October 31, 2007. A major amendment of safety data was received in October 2007, which extended the review clock to January 30, 2008.

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No Advisory Committee meeting was convened to discuss this application.

The relevant review disciplines for this review cycle have all written review documents. The primary review documents relied upon for the current review cycle are the following:

Clinical Review, by I. Chen, dated 4/15/08.
Statistical Review and Evaluation, by M. Fan, dated 4/15/08.
Pharmacologist's Review of BLA 125160, by S. Chakder, dated 4/2/08.
Tertiary Pharmacology Review, by P. Brown, dated 4/18/08.
Clinical Pharmacology Review, by T. Ghosh, dated 11/8/07.
Product Review, by G. Gill-Sangha, dated 9/26/07.
DMETS Proprietary Name Review, by L. Holmes, dated 8/24/07.
DMETS Final Proprietary Name, Label and Labeling Review, by L. Pincock, dated 4/3/08.
SEALD labeling review, by I. Masucci, dated 1/9/08.
DDMAC labeling comments for CIMZIA, by S. Skariah, dated 4/8/08.
DRISK Medication Guide Review, by J. Best, dated 4/1/08.
Carton and container labels review, by S. Rawls, dated 1/31/08.
OSE/DSRCS review of pharmacovigilance activities, by S. Kaplan, dated 1/18/08.
OSE Comments re: sample size calculation, by S. Kaplan, dated 4/15/08.

The reviews should be consulted for more specific details of the application. The reader is also referred to the Team Leader Review Memo dated December 19, 2006, for the initial review cycle, as well as to the primary review documents from that cycle. This memorandum

summarizes selected information from the review documents, with primary emphasis on the issues to be resolved in the current review cycle.

Clinical Background

Crohn's disease, also known as regional enteritis, terminal ileitis, or granulomatous colitis, is an inflammatory bowel disease of unknown etiology. The disease is manifest as discontinuous transmural inflammatory changes that can occur anywhere in the GI tract but it primarily involves small bowel or colon. Involved areas classically show noncaseating granulomas and fissuring. Complications include strictures, obstruction, malabsorption, malnutrition, and fistula formation. Growth retardation is a complication of concern in pediatric patients. There is an increased risk of malignancy with longstanding disease. Crohn's disease is more common in whites vs. non-whites and in Jews vs. non-Jews. The peak ages of initial diagnosis are the teens to twenties, but it can occur at any age. Presentation much before the age of five or six years is uncommon.

Approved therapies for Crohn's disease include formulations of oral and IV steroids. Commonly used therapies also include 5-aminosalicylates (5-ASA's) and immunomodulators (azathioprine, 6-mercaptopurine, and methotrexate), but these are not approved in the U.S. for treating Crohn's disease. Use of any of the preceding has come to be considered part of "conventional therapy" for the disease.

For the indication of reducing signs and symptoms and inducing and maintaining clinical remission in patients with moderately to severely active Crohn's disease who have had an inadequate response to conventional therapy, the currently approved treatments in adult patients are the TNF blockers Remicade (infliximab) and Humira (adalimumab), and the integrin receptor antagonist Tysabri (natalizumab).

Remicade is administered by intravenous infusion. It is also approved for treating Crohn's disease in pediatric patients and for reducing the number of draining fistulas and maintaining fistula closure in adult patients with fistulizing Crohn's disease (as well as other non-GI indications). Remicade was initially given accelerated approval for Crohn's disease in August 1998; validation studies led to full approval in 2002. Humira, the other TNF blocker approved for Crohn's disease, received approval for that indication in February 2007, but it does not carry indications for treating fistulizing Crohn's disease or for treating pediatric patients. It also is approved for other non-GI indications. Humira is administered subcutaneously, as is Cimzia. The dosing schedule for Humira is every two weeks for both induction and maintenance, but the two initial doses are higher than the maintenance dose. In a study published in 2001, the third currently marketed TNF blocker, Enbrel (etanercept), did not show evidence of efficacy in Crohn's disease.

The integrin receptor antagonist Tysabri, initially approved for certain forms of MS, was approved for treating Crohn's disease in January 2008. Due to the risk of progressive multifocal leukoencephalopathy (PML), it is only available under a restricted distribution program, and the indication is restricted to patients who have failed therapies including TNF blockers, and who are not using concomitant immunosuppressive therapy.

Chemistry, Manufacturing, and Controls Issues

The reader is referred to the Product Review by G. Gill-Sangha dated 9/26/07 and to the product reviews from the first review cycle.

Conclusions from the Initial Review Cycle
During the first review cycle the Product Reviewers concluded that the product from the commercial process had shown adequate stability for — months, and the clinical product had shown adequate stability for — months. The Reviewers recommended that the Applicant's request for 18 months expiry at the recommended storage temperature of 2 to 8 °C was reasonable.

Inspection of the drug substance and drug product manufacturing facilities uncovered issues as identified in the 483's, but those were resolved before the initial action was taken (see initial review cycle Drug Product Reviews for details). There are no remaining facilities issues that would preclude approval.

The Immunogenicity Reviewer concluded that the anti-certolizumab pegol assay has been qualified and was adequate. However, the Reviewer noted that the assay procedure did not

Issues for the Current Cycle
Minor CMC issues were raised late in the initial review cycle (FDA communication of 11/29/06 and submissions of 12/4/06 and 12/6/06) regarding an — in-process control level and a question about the need for a process change comparability protocol. These issues were not fully resolved, and the FDA's Complete Response Letter of 12/21/06 included two CMC items (see 12/21/06 CR Letter for specific wording of the deficiencies):

1) A request for data on — levels for batches supporting proposed in-process controls and an updated table for in-process controls to include — monitoring at —

2) A request for clarification on the reason for providing a comparability protocol for batches from manufacturing campaign — and a request to provide a revised comparability protocol if the commercial manufacturing process differs from the process used in the validating campaign.

Current Cycle Review
In response to a request from the Product Reviewer, UCB agreed in their reply of 8/2/07 to reduce the — limit to — The Pharm/Tox Reviewer in an E-mail memo dated 8/20/07 (reproduced in the Product Review) noted that this was lower than limits that had been approved in parenteral formulations, and therefore appeared to be safe, and was acceptable. The Product Reviewer determined that UCB had responded to item 1) adequately.

UCB clarified that there was no change in manufacturing between the validating campaign and the commercial process, so there was no need for the comparability protocol. UCB withdrew the comparability protocol. The Product Reviewer considered the response to item 2) acceptable.

Final Conclusions and Recommendations
The Product Reviewer concluded that UCB had responded adequately to the product items in the CR Letter of 12/21/06. The Product Reviewer concluded that the manufacture of Cimzia led to a pure and potent product; that the product was free of infectious agents in a way that met FDA's parameters, and that the manufacturing process produced a consistent product. The Reviewer felt an 18 month expiry was supported and that the product stability protocol was appropriate. The Product Team Leader and Product Acting Division Director concurred with the conclusions and recommendations.

From the initial review cycle, the Reviewer recommended that any eventual approval letter should include sentences [redacted]. Although these precise statements do not appear in the final action letter, the supervisory Product Reviewer (P. Swann) considered the product-related statements in the action letter to be adequate.

No Phase 4 requirements were recommended.

Pre-clinical Pharmacology and Toxicology Issues

No pre-clinical pharmacology and toxicology issues were included in the FDA's CR Letter of 12/21/06. A brief pre-clinical review memo was generated for the current review cycle to provide labeling recommendations; see Pharmacologist's Review of BLA 125160 by S. Chakder.

Conclusions from the Initial Review Cycle
The reader is referred to the initial Pharmacology/Toxicology Review and Evaluation by S. Chakder dated 10/31/06.

Due to the lack of affinity of certolizumab for rodent TNFα, toxicology studies were performed in cynomolgus monkeys, but high doses were still required to overcome the low cross-reactivity. Slight hematologic changes (decreased RBC and increased WBC) were observed, which were reversible. Vacuolation in hemolymphoreticular tissues was observed after a month at high doses (400 mg/kg), and foamy macrophages were observed in several tissues after various durations of treatment at 100 mg/kg. Elevated aPTT was seen with dosing of 50 and 100 mg/kg, and the effect on aPTT was also produced *in vitro*. (But see also under Clinical/Statistical Issues, below. It is now known that certolizumab pegol can interfere with certain aPTT assays. It is not clear if this was a factor in these pre-clinical findings.) Anti-certolizumab pegol antibodies developed in about 5% of animals.

Reproduction studies were conducted in rats using a [redacted] anti-TNF antibody. That product had no effect on fertility or early embryonic development, was not teratogenic, and had no effect on pre- or post-natal development. The [redacted] anti-TNF antibody was found to

be excreted in rat milk. The Reviewer concurred with the Applicant's proposed pregnancy category of B.

Certolizumab was not found to be genotoxic in the Ames test, the human lymphocyte chromosomal aberration test, or the mouse micronuclear test. No carcinogenicity studies were conducted.

Current Cycle Review
No new pre-clinical data were provided for the current review cycle and there are no new pre-clinical conclusions or recommendations apart from the labeling recommendations.

Final Conclusions and Recommendations
The Pre-clinical Reviewer concluded that the product was approvable. He recommended that the pregnancy category should be B, as the Applicant proposed, and that the labeling should mention

The Reviewer did not recommend any additional preclinical studies to be conducted in Phase 4.

Clinical Pharmacology Issues

The reader is referred to the Clinical Pharmacology Review by T. Ghosh, dated 11/8/07, and to reviews of the first review cycle.

Conclusions from the Initial Review Cycle
The Clinical Pharmacology Reviewers concluded that Cimzia and the IV formulations of certolizumab pegol used in Phase 2 studies were comparable. The bioavailability for subcutaneous Cimzia is about 80% compared to IV formulations. A drug-drug interaction study with methotrexate in RA patients found no significant interaction. No other interaction studies were performed, but the Reviewers felt any interactions would be unlikely, because therapeutic biologics are not CYP450 substrates.

PK parameters were found to be comparable between Caucasians and subjects of Japanese descent at the proposed therapeutic dose. Based on a population PK analyses, the data did not show any significant effect of age, gender, or creatinine clearance on PK. No conclusions could be drawn about the affect of liver dysfunction because of the limited number of patients. Repeated administration, weight, monocyte count, immunosuppressant intake, and ethnicity showed statistically significant effects, but they were not considered to be of a magnitude that would warrant dose adjustment. Only the presence of antibodies had more than a 30% effect on PK parameters. In the Reviewer's population PK modeling, only weight and presence of antibodies appeared to have any clinically significant impact on clearance. The Reviewer recommended dose adjustment for antibody-positive patients.

The probability of developing antibodies appeared to be inversely related to Cimzia dose. The percentage of subjects with antibodies increased with continued dosing. The presence of antibodies effects the pharmacokinetics; from population PK analysis the clearance was

estimated to increase by about four fold when antibodies were present, producing an estimated 86% reduction in trough levels and 72% reduction in AUC_{τ}.

The Reviewers noted a wide range in certolizumab pegol blood levels in the clinical efficacy studies. They felt there was evidence, most clearly seen in the Phase 2 SC study (Study 005), of an exposure-response relationship, and the Reviewers felt that higher doses should be investigated for induction. The Reviewers also noted that the exposure-response relationship was not seen when the analysis was restricted to U.S. study sites, but no reason for the difference was identified.

No pediatric PK data were provided.

Issues for the Current Cycle

From the initial review cycle, the Clinical Pharmacology Reviewers did not believe that the Applicant had fully explored the appropriate dose range and had not yet determined the proper dose for either induction or maintenance of remission. The Reviewers recommend that the Applicant redefine the dose-response relationship and use simulations based on current data for future clinical trial design to support product approval. The FDA's CR Letter of 12/21/06 included one Clinical Pharmacology issue (see 12/21/06 CR Letter for specific wording of the deficiency):

3) The appropriate dose range and regimen had not been fully explored for either induction or maintenance of clinical response, and additional clinical data would be needed to define further the expose-response relationship. Simulations based on current data were suggested for future clinical trial design to support product approval.

Current Cycle Review

The Applicant provided an analysis consistent with the Reviewer's previous finding that change in CDAI score correlated with certolizumab pegol concentrations, but the Applicant argued that use of higher doses leads to higher dropout, thus not increasing overall response rates for Crohn's disease.

The Reviewer noted [redacted] The Reviewers still recommended that an increased dose or increased dosing frequency be investigated in future Crohn's disease trials.

Final Conclusions and Recommendations

For the current cycle, the Reviewer found that the Applicant had provided an acceptable response to the FDA's CR Letter of 12/21/06. Recommendations regarding labeling were provided in the initial cycle Clinical Pharmacology Review, and no additional labeling recommendations were provided in this cycle.

Although the Reviewer recommended that any future trials in Crohn's disease include exploration of increased dose or dose frequency, no Phase 4 Clinical Pharmacology requirements were recommended.

Clinical/Statistical Issues

The reader is referred to the Statistical Review and Evaluation by M. Fan dated 4/15/08, and the Clinical Review by I. Chen dated 4/15/08, as well as to the reviews of the initial review cycle. (In particular, the Team Leader Review from the initial review cycle contained a section on clinical study results, which will not be repeated here.)

Conclusions from the Initial Review Cycle

The Statistical Reviewer concluded that the superiority of Cimzia over placebo in Study 031 (the study that included randomized induction), in the primary analysis stratum defined by elevated CRP, was not robust. Further, he concluded that the evidence of an effect on the major secondary endpoints was not statistically persuasive. He concluded that Study 032 (the maintenance study) had a statistically significant difference favoring Cimzia for the response rate at Week 26 in the stratum defined by CRP $\geq$ 10. The efficacy results in Study 032 were supported by the results for the secondary efficacy endpoints. However, the Statistical Reviewer was concerned that the results in Study 032 were driven by countries other than the U.S., and that the claim for maintenance was supported mainly by that single study; he considered the strength of evidence in support of a maintenance claim not statistically persuasive.

The Clinical Reviewer concluded that the application did not provide substantial evidence that Cimzia had efficacy for reducing signs and symptoms of active Crohn's disease (i.e., inducing a response). The Reviewer felt that Study 032 (maintenance) had a strong outcome. However, without sufficient evidence that Cimzia could be used to induce the response to be maintained, and without clinical experience maintaining the response achieved by any other approved therapy, he did not feel there was sufficient information to write adequate instructions for use. The Clinical Reviewer concluded that there was insufficient clinical efficacy data to approve the product, and that the Applicant should be sent a CR Letter describing the deficiencies in the clinical data.

The Clinical Reviewer concluded that the safety profile of Cimzia was reasonably consistent with that of other TNF blockers, and there were no new safety signals beyond what has been seen for that class. The predominant safety finding was an increased risk of infections, including serious infections, with an increased risk of TB in particular. There was a higher observed rate of SAE's in the subgroup with prior infliximab exposure.

Issues for the Current Cycle

From the initial review cycle, the Reviewers were concerned that there was insufficient evidence of efficacy, particularly for inducing a response in active disease. The Reviewers recommend that Cimzia not be approved and that the deficiencies regarding evidence of efficacy be cited in a CR Letter to the Applicant. The FDA's CR Letter of 12/21/06 included four Clinical/Statistical issues (see 12/21/06 CR Letter for specific wording of the deficiencies):

4) The results of Study 031 (induction) were not robust, and the results of Study 032 (maintenance) were not sufficient to provide support for the induction effect.

5) The appropriateness of including one patient (#525 from Site 22025) was questioned (which had the potential to affect the statistical significance of the study result).

6) The maintenance study could not stand alone in supporting approval for an indication.

7) Additional analyses were requested to explain the finding that Study 032 showed no treatment effect in the U.S. sites.

Current Cycle Review

In the Complete Response resubmission, the Applicant provided justifications for the inclusion and endpoint imputations for patient #525 as well as another patient (#401) that had been questioned. The Applicant also provided examples to further explain the imputation rules as pre-specified in the SAP and supplied additional tabulations regarding the extent of use of imputation. The Applicant was unable to identify any explanation for the finding of no effect in U.S. sites for Study 032. The Applicant proposed an indication for ' as response the issue of insufficient support for evidence of an induction effect. In response to the FDA's request for updated safety data, the Applicant also provided a major safety amendment late in the review cycle.

The Statistical Reviewer agreed to accept the Applicant's values for the p-values for the primary analysis from Study 031, but noted that the issue of lack of robustness remained because the results could be changed by reclassification of only one or two patients, and the results could be influenced by imputation technique.

The Statistical Reviewer also observed that post-hoc analyses suggested there might be better evidence of efficacy for patients with baseline CDAI scores above 300, but that that conclusion would require confirmation by a second study. Finally he performed additional analyses of the secondary endpoint of 70-point clinical response at Week 4, which are discussed further below.

The updated safety data included a fatal case of TB (previously there had been no fatalities). Also, additional cases of TB, serious infections and malignancies were reported. In response to the EMEA's citing of concerns about bleeding events in the negative opinion on 11/15/07, bleeding events were carefully reviewed by the Clinical Reviewer. A small number of serious bleeding events were identified; however, the severity of the events and the evidence of relationship to treatment did not appear to warrant a warning, but the Reviewer recommended they should be reported as adverse events in the labeling. The Clinical Reviewer did additional regroupings and analyses to provide event rates for common AE's for use in labeling, as presented in her review. The Clinical Reviewer also commented on finding several discrepancies and omissions in the safety database that required resolution in the course of the review.

Following the finding of abnormal coagulation testing in an RA Study in Europe, the Applicant identified that certolizumab pegol can produce artifactual elevations of aPTT for certain aPTT assay systems. The Clinical Reviewer noted that coagulation tests were not done in Crohn's trials, and recommended that they be included in any future studies.

Final Conclusions and Recommendations
The Statistical Reviewer concluded that the results for the primary endpoints in Study 032, clinical response at Week 6 and at Week 6 and 26 in patients with elevated baseline CRP, were statistically significant with p-values of 0.037 and 0.045, respectively. However, he noted the results lacked robustness in that reclassification of just one or two placebo patients could cause the p-values to rise above 0.05, and the results relied on imputed values.

The Clinical Reviewer for this cycle concurred with the Clinical Reviewer for the initial cycle in recommending against approval, citing that more statistically robust data in support of induction were warranted and that Cimzia should meet the standards of the other currently approved TNF blockers for Crohn's disease.

The Clinical Reviewer concluded that the safety update confirmed the previous conclusions of the original BLA review, that the safety profile was similar overall to that seem with other TNF blockers. The Reviewer recommended modifications to the Adverse Reactions section labeling, including revised rates of common adverse events and including bleeding events and alopecia totalis in the listing of less common adverse events. See the Clinical Review for details of the recommendations.

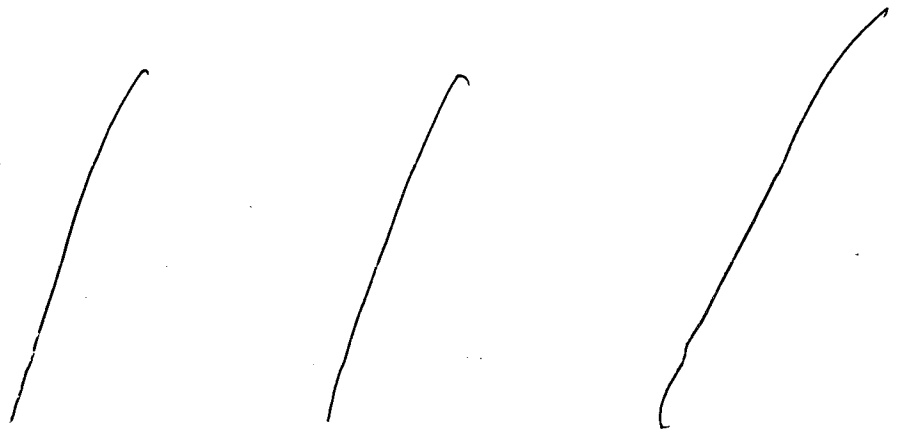
Office of Surveillance and Epidemiology Consults

Conclusions from the Initial Review Cycle
Review of the trade name "Cimzia" by DMETS identified some similarity to the approved products Amicar, Omacor, and Zenvia when scripted, and similarity in sound to Zenvia. However, DMETS concluded that the potential for confusion was minimal and that the name Cimzia was acceptable. DMETS also reported that DDMAC found the name acceptable from the promotional standpoint. The name was still acceptable as of the DMETS review of 4/3/08.

The Applicant's proposed postmarketing risk management activities include [redacted] in addition to the usual routine pharmacovigilance. No RiskMAP was proposed. The OSE RMP Team felt that insufficient detail was provided concerning the proposed additional pharmacovigilance activities, and they provided recommendations regarding those plans to be conveyed to the Applicant (see OSE/RMP Team memo).

Issues for the Current Cycle
The OSE RMP Team identified specific deficiencies regarding the detail in the postmarketing plans. The 12/21/06 CR Letter included the following items pertaining to the postmarketing proposal (see 12/21/06 CR Letter for specific wording of the deficiencies):

[redacted]



Subsequent to the Complete Response resubmission, Cimzia marketing authority was denied by the EMEA, . The Applicant provided a revised postmarketing proposal in which the would not be used. Instead, the Applicant proposal included a study of 2000 patients with 2000 matched controls to extend for ten years,

The Reviewer concluded that the alternative proposal was acceptable.

Final Conclusions

The Reviewer agreed with dispensing with the in favor of the other postmarketing studies in the Applicant's revised proposal.

Pediatrics

No pediatric data were provided in this application. The Applicant requested a deferral of pediatric studies for patients aged 6 to 17 years and a waiver for patients under 6 years, stating that Crohn's disease is uncommon in children less than 6 years of age. The Applicant also presented an outline of a program aimed at evaluating effectiveness, safety, and PK of Cimzia in the pediatric population. The proposal was presented to the Pediatric Review Committee (PeRC), which agreed with the partial waiver, but requested that the effectiveness evaluation The Applicant agreed to

Advisory Committee

If approved, Cimzia would be the fourth marketed TNF blocker, and the third TNF blocker approved for treatment of Crohn's disease. This application was not presented to an FDA advisory committee because the safety and efficacy data did not pose unique concerns beyond those applicable for other biologics, in the tumor necrosis factor (TNF)-blocker class and the integrin receptor antagonist, that are approved for the treatment of moderately to severely active Crohn's disease.

Team Leader Review and Discussion

Approval

Both of the Clinical Reviewers (initial and current review cycles) recommended against approval of Cimzia for Crohn's disease. The principal concerns were the weakness of evidence for efficacy and the small effect size for inducing clinical response in active disease. While the maintenance data were viewed by the Clinical Reviewers as relatively strong, they did not feel that adequate instructions for use could be written if use in active disease could not be recommended. The reviewers felt the safety profile of Cimzia was comparable to that of marketed TNF blockers, but there was an implied concern about the acceptability of the risks if induction efficacy was not adequate.

This reviewer acknowledges the observations and concerns of the primary reviewers, but does not agree that the concerns compel the conclusion that Cimzia should not be approved. This reviewer's analysis is provided in more detail in the bullet points below, but is briefly this: After review of the Applicant's Complete Response resubmission, the reviewers have concluded that the primary analysis of Study 031 can be accepted, and therefore it must be considered a positive study, albeit marginally so, and can be accepted as contributing toward substantial evidence of efficacy. Although the apparent inferiority of effectiveness compared to marketed products might be a consideration in an approval decision, it is not, in and of itself, adequate grounds to deny approval; the issue is whether the benefits and safety findings are within acceptable bounds, not whether they meet or exceed those of certain competitors. On further review of the clinical data, this reviewer finds there is adequate reason to expect the product to perform at least acceptably when used to treat active Crohn's disease, so that credible instructions for use can be written. Because the risk of this product is incurred primarily through its chronic use, and because there is strong evidence of its benefit in chronic use, the risk/benefit profile for Cimzia in Crohn's disease is similar to that of the marketed TNF blockers and is acceptable. These points are elaborated below:

- FDA accepts that the agreements in 2003 between the FDA and the IND holder about the Phase 3 studies for Cimzia are to be considered as End-of-Phase-2 agreements. Therefore, the evidence provided by these studies should not be faulted merely by the number and design of these studies, absent new public health concerns unrecognized at the time of the agreement. (However, this reviewer does not hold that all that is necessary for approval is that the studies produce statistically significant p-values; the actual results, consistency and interpretability of the findings, and safety must be considerations as well.)

- While the Division currently asks that maintenance studies have a duration of one year and that induction studies be replicated rather that supported by a maintenance study, it would not be reasonable to claim there are new public health concerns unrecognized at the time that would invalidate the agreements reached in 2003.

- The randomized withdrawal maintenance study (Study 032) had a clinically significant and highly statistically significant result. Although it was one study of only of six month's

duration, it is in accord with the 2003 agreements, and it is not unreasonable from a clinical standpoint to accept that study as contributing substantial evidence of efficacy in maintaining a clinical response. The anomalous finding of no difference between treatment arms in the subset of U.S. sites is not inconsistent with sampling variation, given the relatively small number of U.S. patients. Because the Applicant's analysis did not uncover reasons why the U.S. sites might be expected to have different outcomes, the study results can be viewed as supporting the application.

- The primary reviewers have expressed concern about the adequacy of the evidence of efficacy for induction that was provided by the only study that included a randomized, controlled evaluation of efficacy for induction of clinical response (Study 031). There are for several reasons for the concern: 1) the tenuousness of the strength of the statistical evidence, 2) the lack of replication of the findings, and 3) the relatively small magnitude of the estimated clinical effect.

- As to point 1), after review of the Complete Response resubmission, the Statistical Reviewer concluded that, albeit hinging on the classification of only one or two patients and not "robust," the Applicant's primary statistical analysis of Study 031 could be accepted.

- As to point 2), given the acceptance of the standing of the 2003 agreements as End-of-Phase-2 agreements, the FDA should not fault the evidence of efficacy merely on the basis of there being only a single induction study, because the Agency effectively implicitly agreed in 2003 that the maintenance finding could provide an acceptable means of supporting an induction efficacy finding. (But this does not preclude other factors, such as effect size and consistency with other data, being taken into account in assessing the value of the evidence.)

- Point 3), then, the magnitude of the clinical effect for induction, is crucial. The Clinical Reviewers have recommended not approving Cimzia based on their concern about the suitability of Cimzia for induction, i.e., initial treatment of active disease, and that absent support for Cimzia's use for induction, there is insufficient information to guide its proper use, even with the clear results of the maintenance study, because the results of the maintenance study are only established for Cimzia responders.

- The primary endpoint results from the Cimzia induction analysis suggest a much weaker effect than what is reported in the labeling for Remicade and Humira (the TNF blockers approved for moderately to severely active Crohn's disease), or for Tysabri (an integrin receptor antagonist approved for a similar indication). However, the endpoint in the Cimzia study had some important differences. For Cimzia, the endpoint assessment was made at Week 6 and the criterion for clinical response was a decrease in CDAI of at least 100 points. For the other TNF blockers, the primary assessment was at Week 4, and the definition of clinical response required a decrease of only 70 points. The first table below shows the principal study outcomes for the endpoint of clinical response (70-point drop in CDAI) at Week 4 for the other products approved for moderate to severely active Crohn's disease together with the outcomes calculated for Cimzia. The second table shows outcomes for the endpoint of clinical remission (CDAI score $\leq$ 150 points). (Data in these tables for marketed

products come from product labeling and clinical reviews. Data for Cimzia are from the current cycle Statistical Review and study reports in the application):

Week 4 Clinical Response Rates (≥ 70-Point Decrease in CDAI)

	Rate for Active Drug	Rate for Placebo	Difference	Odds Ratio	p
Remicade, 5 mg dose group	81%	17%	65%	22	<.001
Remicade all doses (5, 10, 20 mg)	65%	17%	48%	9.3	<.001
Humira, Study 1, labeled induction dose	58%	36%	22%	2.4	.007
Humira, Study 2	52%	34%	18%	2.1	<.001
Tysabri Confirmation Study (↑CRP)	51%	37%	15%	1.8	.001
Cimzia, ↑CRP Subgroup (1° Analysis)	50%	31%	19%	2.3	<.001
Cimzia, All Patients	44%	34%	10%	1.5	.011
Cimzia, Open Label, ↑CRP Subgroup (95%, C.I.)	83% (78%, 88%)				
Cimzia, Open Label, All Patients (95%, C.I.)	80% (76%, 84%)				

Week 4 Clinical Remission Rates (CDAI ≤ 150)

	Rate for Active Drug	Rate for Placebo	Difference	Odds Ratio	p
Remicade, 5 mg dose group	48%	4%	44%	21	<.001
Remicade, All doses (5, 10, 20 mg)	33%	4%	28%	11	.006
Humira Study 1, labeled induction dose	36%	12%	24%	4.0	.001
Humira Study 2	21%	7%	14%	3.5	<.001
Tysabri Confirmation Study (↑CRP)	24%	16%	8%	1.8	.009
Cimzia, ↑CRP Subgroup (1° Analysis)	20%	10%	10%	2.3	.018
Cimzia, All Patients	19%	11%	8%	1.9	.006
Cimzia, Open-Label, ↑CRP Subgroup (95% C.I.)	44% (37%, 51%)				
Cimzia, Open-Label, All Patients (95% C.I.)	43% (38%, 48%)				

- By these analyses, at least for the pre-specified primary analysis group (elevated CRP), the effect size for clinical response in controlled studies of Cimzia is reasonably comparable to the effect sizes of Humira and Tysabri. For remission, the effect of Cimzia appears weaker than that of the other TNF blockers but is like that of Tysabri.

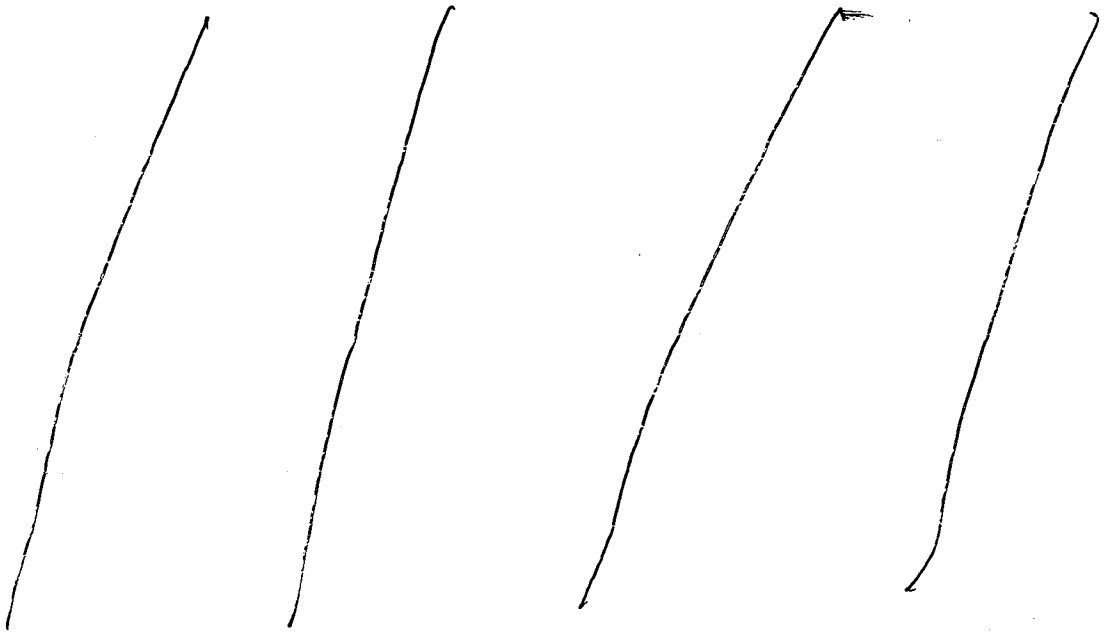
- Cimzia was used open label and without a control group in the induction phase leading into the maintenance phase of Study 032. The study was relatively large, and the confidence intervals around the rate estimates are fairly narrow. The rates, while uncontrolled, do appear to be appreciably greater than the historical placebo rates, even for the more recent Humira and Tysabri studies (the Remicade studies are much older). Although not adequately

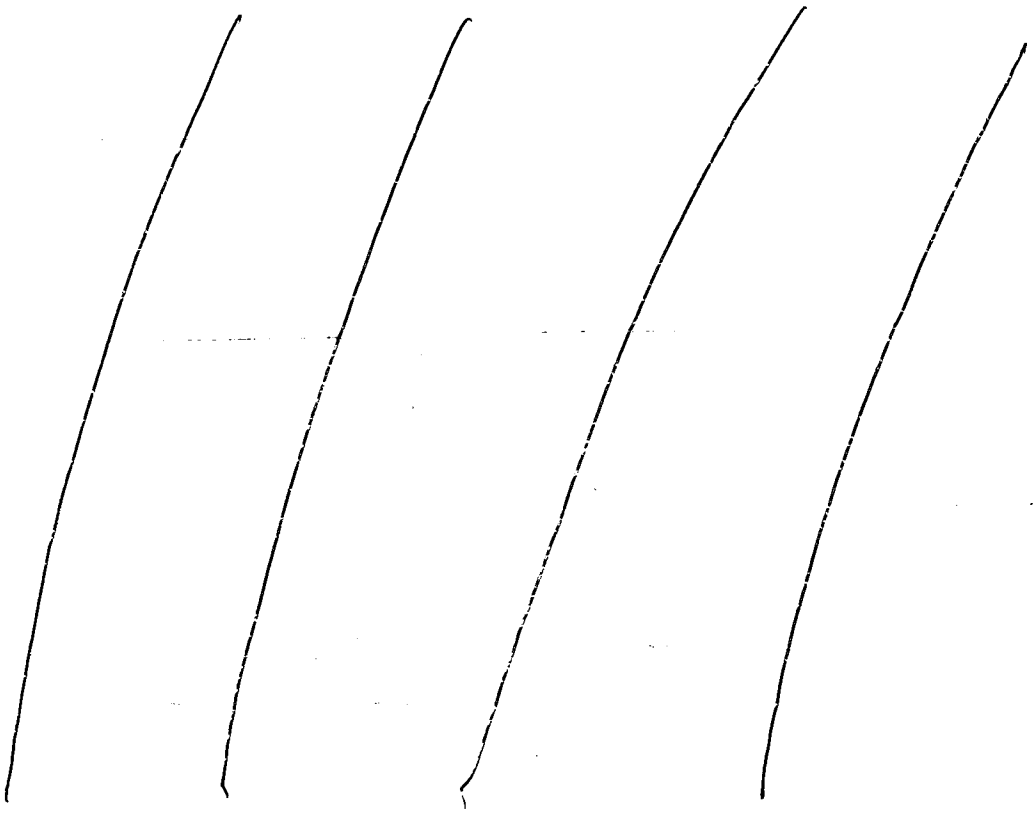
controlled to provide substantial evidence of efficacy, these results at least offer another estimate of effectiveness and provide some reassurance that a substantial proportion of patients would be expected to respond when Cimzia is used to treat active disease.

- Therefore this Reviewer concludes the following:
  - That there is definite evidence that Cimzia has activity in treating Crohn's disease, most clearly evidenced by its efficacy in maintaining clinical remission (Study 032).
  - That there is evidence of efficacy in inducing clinical response in the form of one positive trial (Study 031).
  - That the minimum necessary regulatory standard of evidence that was set for Cimzia in the 2003 agreements was met.
  - Based on the totality of clinical data, there is adequate reason to expect that Cimzia will perform in at least a minimally acceptable fashion when used according to labeling to treat active disease.
  - That the risk/benefit ratio is reasonably comparable to marketed TNF blockers, because the risk is largely determined by the risk of chronic use, and for that purpose the benefit is sufficiently well established and is of a clinically significant magnitude.
  - That approving Cimzia in accordance with the standard for evidence that was agreed upon would not produce an unacceptable or unreasonable outcome, and therefore those standards are appropriate to recognize in this case, provided that the labeling accurately reflects the modest expectations for Cimzia's effectiveness in inducing a clinical response.

Indication Statement

In the original BLA submission, the Applicant proposed an indication statement that included _____ (cf. Introduction and Regulatory Background – General Background, above). In response to the reviewers' questions and concerns about Study 031, the Applicant revised the proposed indication statement to _____





Safety

From review of the safety data in the original application and the updated safety information provided during review of the resubmission, it appears that the overall safety profile of Cimzia is similar to that of the currently marketed TNF blockers. Accordingly, the labeling should contain substantially similar information in the warnings and precautions section of labeling.

On a theoretical basis there is reason to be concerned about the risk of malignancy with TNF blockers, and an excess in malignancies (treatment vs. placebo) has been seen in controlled studies of some TNF blockers. In the controlled studies in the Cimzia development program, no excess over placebo was seen; however, the concern is reasonably applicable to the class of TNF blockers as a whole, and it would be appropriate to include a warning regarding malignancies in the Cimzia labeling, while also reporting the Cimzia-specific findings. Remicade, which is approved for pediatric as well as adult Crohn's disease, has a warning for the rare hepatosplenic T cell lymphoma that has been reported in several adolescents and young adults taking Remicade for Crohn's disease. At present, a similar warning does not appear to be indicated for Humira. Until a clearer picture emerges as to the generalizability of this rare adverse reaction to the whole class of TNF blockers, Cimzia should not carry the warning either.

Recently, reports have emerged of serious skin reactions (Stevens-Johnson syndrome, toxic epidermal necrolysis, erythema multiforme) in postmarketing experience with TNF blockers. Information about these reactions had been added to the Remicade labeling, and DAARP (the

"home" Division for the other approved TNF blockers is viewing the reactions as a class effect [redacted] The same information also should be included in the adverse reactions section of the Cimzia labeling.

The reference to a concern about bleeding reactions in the EMEA's negative opinion for Cimzia on 11/15/07, led the Clinical Reviewer to make a careful reassessment of the safety data regarding such events, and additional data and analyses were requested of the Applicant. Several bleeding events, some serious, were identified. Bleeding reactions should be included under the adverse reactions section, but the severity and frequency do not appear to indicate a risk that requires a special warning or precaution section in labeling (see the current cycle Clinical Review for details). In its 3/20/08 announcement regarding Cimzia, the EMEA had removed the statement of concern about bleeding events. It is recommended, however, that the Applicant be asked to continue providing expedited reporting of bleeding events.

Following the finding of apparent coagulation abnormalities in one of the studies being done for the RA [redacted], it was discovered that certolizumab pegol can interfere with certain assays for aPTT (see current cycle Clinical Review for details). This finding should be described in the interactions section of labeling.

Vaccinations

As for the other TNF blockers, it is appropriate to recommend against use of live vaccines in patients receiving Cimzia on the basis of Cimzia's expected immunosuppressive effect. The development program for Cimzia did not include an evaluation of whether the immunosuppression would affect the response to other vaccines. This information has been requested for other TNF blockers, and it would be reasonable to request the same for Cimzia.

[redacted]

At the end of the initial review cycle, there was an emerging issue regarding the reliability of laboratory testing done by [redacted] At the time of the action on 12/21/06 the extent of the problem was not clear. Subsequently, it was determined that the problem involved testing done at the [redacted]. For the Cimzia development program, the impact is limited to the results of a PK drug interaction study with methotrexate. Until and unless those data can be validated, the [redacted] should be omitted from the labeling.

Regulatory Conclusions

Approval Action

Cimzia should be approved under 21 CFR 601 for treating Crohn's disease.

The indication statement should refer to [redacted] and maintenance of response, but should avoid [redacted] The indication should be limited to those who do not response to conventional therapy, but does not need [redacted]

Labeling Recommendations

The labeling should include warnings and precautions substantially similar to those in recently approved products in the TNF blocker class, namely warnings for serious infections, TB, hepatitis B reactivation, malignancies, hypersensitivity reactions, neurologic reactions, hematologic reactions, use with anakinra, heart failure, autoimmunity, immunizations, and immunosuppression. The malignancy section should include general TNF class information but should also present rates from Cimzia experience. Information about the interference with some aPTT assays should appear in the drug interaction section. The warnings regarding serious infections and TB should also appear in a boxed warning.

The information about adverse reactions in clinical trials experience should be revised according to recommendations of the Clinical Reviewer. A section describing the skin reactions seen in postmarketing experience with other TNF blockers should be included as adverse event information from other sources.

Other revisions regarding formatting, style, and required wordings should be made along the lines recommended by SEALD and to comply with the guidelines of the PLR labeling review tool.

Cimzia should have a Medication Guide because there are significant risks that patients should be aware of and because patients need to be informed of the actions to take to control those risks.

Phase 4 Requirements

The Applicant should be required to conduct the following postmarketing activities:

1) A pediatric study to evaluate PK, safety, and clinical response in pediatric patients ages 6 to 17 years with moderately to severely active Crohn's disease.

2) An observational study in the U.S. to assess known, or identify unexpected, serious risks in approximately 2000 Cimzia-treated patients and 2000 matched controls monitored for ten years.

3) Continue assessment of the long-term safety of Cimzia in study CDP870-033, an open-label study of patients who completed Study 031 or 032, with follow-up extended to seven years from the start of treatment. Objectives should also include measurement of PK and antibody response.

4) Continue assessment of the long-term safety of re-exposure to Cimzia in study CDP870-034, an open-label study of patients who were withdrawn from Study 31 or 32 due to exacerbation of Crohn's disease, with follow-up extended to seven years from the start of treatment. Objectives should also include measurement of PK and antibody response.

5) Conduct study CDP870-088, an open-label study to assess the long-term safety of Cimzia in patients who complete study CDP870-085 or who were withdrawn due to an exacerbation of Crohn's disease, with follow-up to extend to five years from start of

treatment. Objectives should also include measurement of PK and antibody response.

6) Assess the effect of Cimzia on antibody response to a B cell-mediated immunization and a T cell-mediated immunization in a placebo-controlled study with approximately 100 patients in each arm, measuring both antibody titer and clinical response.

Other Issues

The dating period should be 18 months from date of manufacture with storage at 2 to 8 °C.

A requirement for pediatric studies for patients 5 years and younger can be waived due to the low incidence of Crohn's disease in that age range.

The Applicant should be asked to continue 15-day reporting of malignancies, serious infections, serious bleeding events, and serious skin reactions.

SAFETY REVIEW AND EVALUATION
CLINICAL STUDIES

DIVISION: FDA/CDER/OND/ODE III/Gastroenterology Products
BLA #: STN 125160/0
APPLICANT: UCB Inc.
DRUG NAME: CIMZIA (Certolizumab pegol lyophilized, 200mg/mL)
INDICATION:

DOCUMENTS REVIEWED:
1) Complete Response Resubmission Dated April 30, 2007
2) Additional Safety Data through July 15, 2007 Submitted October 22, 2007

DATE COMPLETED: April 15, 2008
MEDICAL REVIEWER: Ii-Lun Chen, MD MD April 15, 2008
John E Hyde 4-15-08

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Background

This BLA is for Cimzia (certolizumab pegol lyophilized), which is a new molecular entity. Cimzia is a humanized antibody Fab' fragment which targets human tumor necrosis factor alpha (TNF-α). Cimzia is designed to be administered as a 400 mg subcutaneous injection for the treatment of moderately to severely active Crohn's Disease.

The original BLA was submitted on February 28, 2006. On December 21, 2006 the division completed review of BLA #125160 for certolizumab pegol (CZP), Cimzia. The division's review found the Applicant's submitted information and data analysis were inadequate for final approval action. A complete response letter was sent to the Applicant. A teleconference between the division and the Applicant was held on March 8, 2007 to discuss deficiencies raised in the complete response letter. Subsequently, the Applicant submitted a complete response resubmission dated April 30, 2007. Additional safety data from ongoing clinical trials were submitted to the division on October 22, 2007. For details of the initial clinical review of the application, please refer to the review documents submitted by Dr. Shewit Bezabeh (primary reviewer of initial BLA) and Dr. John Hyde (medical team leader).

Of note, Cimzia was denied for marketing approval by EMEA on November 15, 2007 due to concerns of safety and manufacturing deficiencies. The following announcement was released:

The CHMP was concerned that there was insufficient evidence to show a benefit of CIMZIA. In the study of induction treatment, CIMZIA showed only marginal effectiveness, which was too low to be relevant for patients. In addition, the study of maintenance treatment did not last long enough to give meaningful information on the medicine's long-term effects.

The Committee was also concerned over CIMZIA's safety: although generally comparable with the safety of other medicines in the same class, there was also some concern over a possible increased risk of bleeding in patients receiving CIMZIA. In addition, the Committee was concerned that the company had not demonstrated that it would have been able to monitor the quality of the medicine to an acceptable level. Therefore, at that point in time, the CHMP was of the opinion that the benefits of CIMZIA in the treatment of severe, active Crohn's disease did not outweigh its risks. Hence, the CHMP recommended that CIMZIA be refused marketing authorization.

The Applicant requested re-examination of the original negative opinion from the EMEA. Results of the EMEA review was publicly announced on March 20, 2008:

In March 2008, following the re-examination, the CHMP removed its concern regarding the ability to monitor the medicine's quality. It also removed its concern over the possible increased risk of bleeding, but maintained a general concern over CIMZIA's safety. The other concerns remained. Therefore, at that point in time, the CHMP was of the opinion that the benefits of CIMZIA in the treatment of severe, active Crohn's disease did not outweigh its risks. Hence, the CHMP recommended that CIMZIA be refused marketing authorisation.

Content

This review evaluates:
1) Clinical portions of the complete response resubmission.

2) Newly submitted safety data, which include:

- Previously submitted treatment emergent adverse events (TEAEs) and serious adverse events (SAEs) from two Phase 2 studies (-005,-008), two pivotal Phase 3 studies (-031, -032), as well as additional summaries and analyses from open-label Phase 3 extensions (-033 and -034) March 28, 2006, through October 27, 2006 = pooled CD population.
- Listings of SAEs available through July 15, 2007, from pooled CD population and all other on-going CD population trials (Europe, Asia and Africa) =non-pooled CD population.
- Adverse events analysis from Rheumatoid arthritis and Psoriasis trials.

A. Complete Response Resubmission Comments Numbers 3 through 7

The following are the original clinical comments made to the Applicant in the CR letter:

3]. Although the results of your phase 2 studies implied otherwise, analysis of your phase 3 studies (CDP870-031 and CDP870-032) suggests that there is not a significant exposure-response relationship for Cimzia 400 mg at Week 6 or Week 26 for the patient stratum defined by a baseline CRP $\geq$ 10 mg/L. In addition, at Week 26, there does not appear to be an exposure-response relationship for Cimzia in patients enrolled at US sites in Study CDP870-032, whereas there is a fairly defined trend at non-US sites. The reasons for this are unclear. We believe that you have not fully explored the appropriate dose range and regimen for your product for either induction or maintenance of clinical response in patients with moderately to severely active Crohn's disease. You will need to generate additional clinical data to further define the exposure-response relationship for Cimzia. It may be useful to use simulations based on current data for future clinical trial design and analysis to support product approval.

4]. Study CDP870-031 showed a small treatment effect that is not statistically robust when clinical response is assessed for the true intent-to-treat population (i.e., all patients randomized with a baseline CRP $\geq$ 10 mg/L) and patients with missing information are counted as non-responders. We do not view the ability to maintain a response once it has been achieved, as shown in Study CDP870-032, as substantial evidence of an ability to accomplish the task of inducing a response by reducing symptoms in patients who have active disease.

5]. We are also not able to concur with the conclusion that Study CDP870-031 was a positive study for its primary objective, because we believe there was inadequate

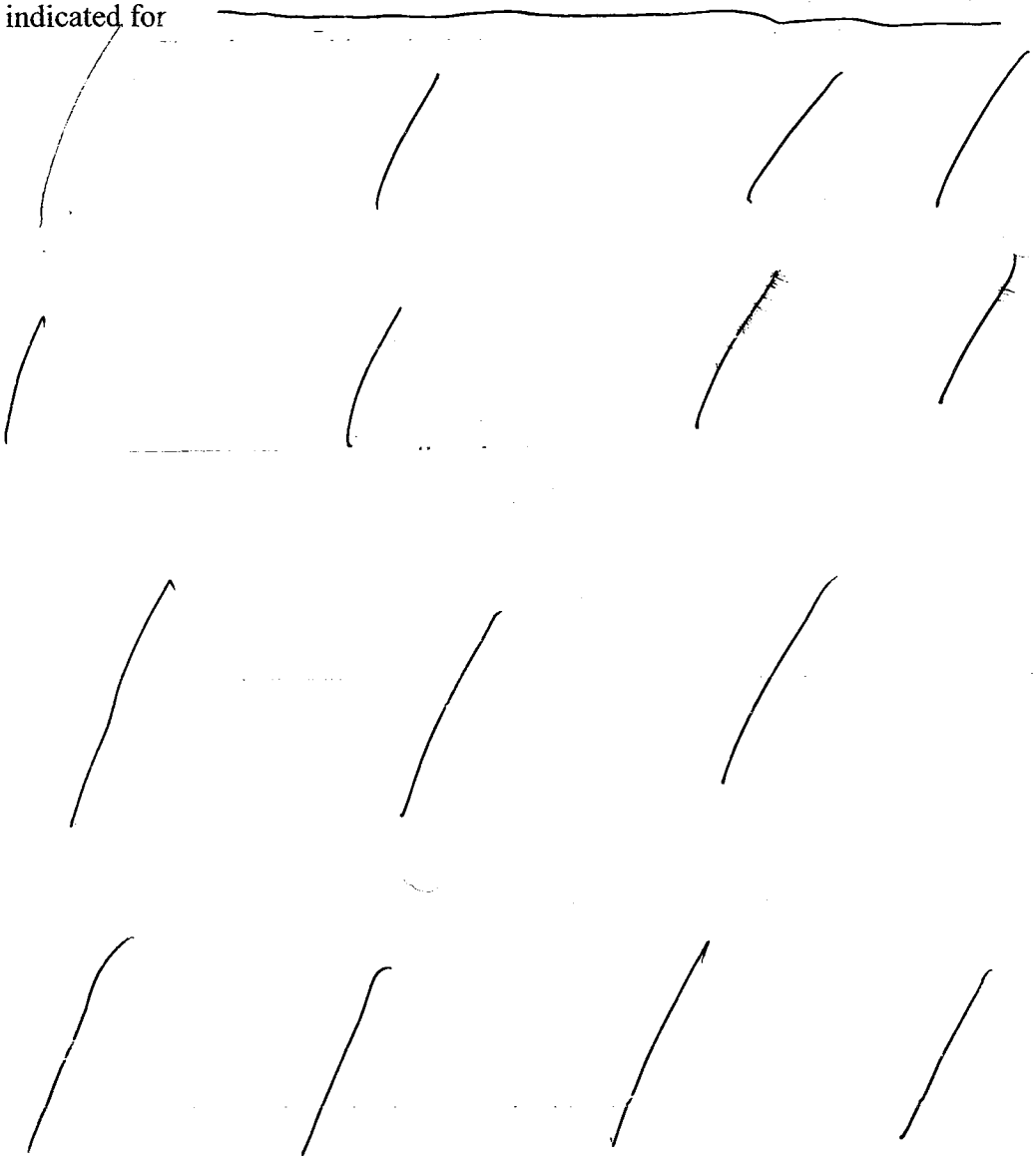
regimen of 400 mg at day 0, week 2, and 4 and then every 4 weeks is adequate. My review of study results suggest that there may be potential for improved efficacy of study drug at higher dose levels in particular for demonstrating efficacy during the induction phase, however, given the Applicant reiterates that there is no need for further dose ranging studies, this issue will remain unresolved.

Re-analysis by the statistical team of the Complete Response Resubmission and subsequent additional responses by the Applicant *continue to show that the strength of evidence of Study CDP 870-031 is not statistically persuasive.* The following are the main points taken from Dr. Milton Fan's review:

> For Study CDP870-031, the sponsor's results for primary endpoint, clinical response in the CRP $\geq$ 10 mg/L at baseline stratum at Week 6 and Weeks 6 and 26 for Study 31 were borderline with p-values of 0.037 and 0.045, at Week 6 and Weeks 6 and 26, respectively.
>
> Per this reviewer's request, the sponsor supplied subject disposition and clinical response through Week 6 and Week 26. It was observed that there was disproportionate discontinued prior to Week 6 (34 (22%) for placebo and 16 (11%) for certolizumab pegol, p=0.0113). The major reason for discontinued prior to week 6 was lack of improvement (31 for placebo and 10 for certolizumab pegol). Number of subjects who remained in study at Week 6 were not in clinical response at Week 6 was similar between treatment groups (82 (53%) for placebo and 76 (52%) for certolizumab pegol).
>
> There was disproportionate discontinued prior to Week 26 (85 (55%) for placebo and 62 (43%) for certolizumab pegol, p=0.0367). Number of subjects who remained in study at Week 26 were not in clinical response at Week 26 was similar between treatment groups (82 (53%) for placebo and 76 (52%) for certolizumab pegol).
>
> The treatment difference based on point prevalence was 8.7% at Week 6 (32.8% (40/122) for placebo and 41.5% (54/130) for certolizumab pegol). Furthermore, the treatment effect at Week 6 was small and ranged from 4.0% to 11.4 %, which is dependent on which analyses were performed with p-values ranged from 0.037 to 0.5472.
>
> If one of disputed placebo subjects were considered as a responder at Week 6 and one of disputed placebo subjects were considered as a responder at Weeks 6 and 6, p-value resulted from true "ITT" analyses were 0.065 both at Week 6 and at Weeks 6 and 26 from Fisher's exact test. This sensitivity of the p-value indicates a lack of robustness of the sponsor's conclusion.
>
> The sponsor's imputation rules for handling missing data in calculating subtotals for CDAI calculation was not pre-specified in the protocol but was pre-specified in SAP. The imputation was complicated with the carried forward and carried back rules applied patient's diary card data for the 7 consecutive days prior to each scheduled assessment at which the CDAI score was calculated and was recorded on the CRF. The sponsor provided only 7 examples among 2^7 (128) possible examples to demonstrate how the carried forward and carried back rules were applied.
>
> Proportion of subjects where at least one of the subtotals for the CDAI score was imputed was high (19.5%, 59/302) in the CRP $\geq$ 10 mg/L stratum at baseline for all visits. With so

(placebo vs treatment, percentage completing study, concomitant medications, age, weight, sex, history of CD, etc). However, overall the results of the various analyses did not identify a unique characteristic that differentiates the subjects except for the fact that the US subgroup constitutes a small sample size and there is a relative imbalance to randomization to placebo in this subgroup.

Based as a whole, studies CDP870-031, CDP870-032 and support from phase 2 CDP870-005 show that Cimzia has a positive response for patients with active CD, and Cimzia may be indicated for



In summary, the clinical issues that were raised in the December 2006 Complete Response remain unchanged. Thus, I do not feel there is sufficient justification to overturn the original recommendation to deny approval for market release of Cimzia in the United States. Primarily, the efficacy data are not adequate to support appropriate use of Cimzia in CD that includes both inducing and maintaining response.

B. Updated Safety Analysis

1. Methods and Findings

As of July 15, 2007, it is estimated that a total of 2629 CD patients have received at least one dose of Cimzia (1564 in pooled studies, 1065 in non-pooled studies). Of 1564 pooled patients who received Cimzia, 1350 received the 400 mg dose. The mean number of days for which subjects have been exposed to 400 mg Cimzia has increased from 291 to 370 days, with 286 subjects having been on drug for at least 24 months. Duration of exposure of the 1065 patients in the non-pooled studies has not been calculated.

The Applicant states that for the pooled CD population studies, additional seven months of exposure did not reveal additional Cimzia toxicities and that there were no reports of events not previously seen in studies of Cimzia in patients with CD. For the non-pooled data, the Global Drug Safety database was reviewed for SAEs, including deaths.

The definitions of adverse events, serious adverse events, and pooling conventions have not changed from those described in the 120 Day safety update.

1.1 Deaths

As of July 15, 2007, in all completed and ongoing studies in patients with CD, a total of 12 subjects died. **All had received Cimzia**. Six of these deaths were reported previously as part of the original BLA and 120-Day safety update. More recently, on Sept 14, 2007 another death was reported in study -042. The patient deceased on ——— but was not reported to the Applicant until September 2007. For the eight deaths not previously reported, brief narratives follow:

1) Study -033, Subject 39004/2484: A 50-year-old female in South Africa developed **disseminated tuberculosis.** Computed tomography (CT) scans of the chest, abdomen and pelvis revealed nodular changes consistent with miliary tuberculosis. Treatment for these events included hyperalimentation, intravenous rifampicin, ciprofloxacin and gentamycin. Despite intensive treatment, the subject died. The Investigator assessed the event Crohn's disease as unlikely related to study treatment and the event disseminated tuberculosis as definitely related.

Comment: This is the first fatal case of TB reported for a Cimzia treated patient. Cimzia and other TNF-α antagonists interfere with the host immune function and may predispose the subject to infections. TB is a recognized risk factor with TNF-α antagonist and ten cases of TB have been reported in the CD program to date. Many patients who developed TB had negative PPD and normal CXR at baseline, thus closer vigilance is warranted for signs and symptoms of TB in patients taking Cimzia so early identification and treatment can be initiated.

2) Study -033, Subject 45071/116: A 43-year-old female developed pelvic pain. Patient had remained in the study for 496 days and the last dose had been administered 24 days prior to the event. Evaluation revealed a rectal/pelvic mass. Diagnosis of **metastatic rectal tumor** was made. Subject died from complications related to chemotherapy. Death considered by Investigator to not be related to Cimzia.

Comment: Malignancy is a recognized safety concern with treatment of TNF-α antagonists. GI tract malignancies are known to occur more often in patients with CD. Continued long term observation is required for better understanding of the relationship between risk of study medication and development of malignancies.

3) Study -034, Subject 43003/2529: A 47-year-old female with long history of CD was on Cimzia for almost 2 years. Subject developed worsening of CD and **refused intervention with medications or hospitalization**. Patient had remained in the study for 701 days and the last dose had been administered three days prior to the event. Subject also refused any nutritional support. The subject's condition continued to deteriorate and she died from complications of her CD. Death considered by Investigator to not be related to study.

Comment: Cimzia is not effective for many patients with CD. Deterioration of CD in this patient may be related to the study drug and to the eventual death of the patient. There are numerous mislabeled sections in this CRF and the conclusion made by the investigator is questionable.

4) Study -034, Subject 45141/2558: A 41-year-old female died of **poisoning secondary to multiple drug intoxication**. Patient had remained in the study for 221 days and the last dose had been administered 320 days prior to the event. Death considered by Investigator to unlikely to be related to study medication.

Comment: Given cause of death and last dose of study medication administered almost one year prior to death, I agree with the investigator that death is unlikely related to study medication.

5) Study -031/034, Subject 12001/420: A 44-year-old male was on Cimzia for 30 days. Subject noted to have worsening of Crohn's disease and admitted to hospital for evaluation. Patient had remained in the study for 30 days and the last dose had been administered 11 days prior to the event. Evaluation revealed a **rectal cancer** with metastatic disease. Death considered by Investigator to be possibly related to study medication however the short time on Cimzia makes it unlikely to be related to study drug.

Comment: CD patients are at higher risk of developing GI tract malignancies. I agree with investigator that the timing and short duration of exposure to study drug makes it unlikely that Cimzia is related to cause of death.

6) Study -042, Subject 048/61: A 43-year old male enrolled in open label infliximab failure study had worsening of underlying CD. Patient had remained in the study for 14 days. One month after the last dose of Cimzia, the patient died suddenly. Exact cause of **sudden cardiac death is unknown**. Death considered by Investigator to be possibly related to study medication.

Comment: Cases of new onset or worsening congestive heart failure have been reported with TNF-α antagonists, however, few serious cardiac events have been reported with Cimzia to date. The short duration of exposure to the study drug and other medications taken near time of death, make it difficult to assess relationship of study drug to death.

7) Study -042, Subject 031/0223: A 47-year old male was enrolled in open-label infliximab failure study. Patient had been in the study from December 2006 to March 2007 and had been administered five doses of Cimzia. In June 2007, patient experienced **hemolysis which progressed to acute respiratory distress syndrome** (ARDS) and died on [redacted] despite care in the intensive care unit. The investigator in this event rated the death as unlikely related to the study drug.

Comment: The source of sudden onset hemolysis and ARDS is unknown and concerning. Patient was also on flagyl, ciprofloxacin, Ambien CR, Tinidazole and celebrex. The close timing of administration of study drug to the death event makes for a plausible causal relation.

8) Study -042, Subject 113/0487: This safety report was received on November 22, 2007, concerning a 36-year old male who developed abdominal high grade malignant metastatic tumor, sepsis with E. coli and Klebsiella, and subsequently died in the hospital on [redacted] He received three doses of Cimzia from May through June 2007; the patient was previously on infliximab with prior loss of response. The investigator judged the death as unlikely to be related to study medication.

Comment: Although the investigator stated the study drug is unlikely related to the death, the patient was previously treated with another TNF –α antagonist. Even though the short duration of treatment on Cimzia makes this study drug unlikely to be the cause of death, it is possible that treatment on a TNF-α agonist did predispose the patient to malignancy and infection.

Table 1: Summary of frequency and incidence rates of Death for all indications in the placebo controlled and safety population studies provided by Applicant:

	PBO CONTROLLED STUDIES		CZP CONTROLLED STUDIES		ALL CZP DOSES	
	%	100 pt-yrs	%	100 pt-yrs	%	100 pt-yrs
CD	***0/436=0***	***0***	***1/832=0.1***	***0.3***	***9/2166=0.4***	***0.4***
RA	***1/647=0.2***	***0.4***	***8/1774=0.5***	***0.8***	***31/2367=1.3***	***0.8***
Psoriasis	*0/58=0*	*0*	*0/117=0*	*0*	*0/117=0*	*0*

In summary, there is an increased incidence of 0.4 per 100 pt-years of death in the CD treatment population compared to placebo as well as an approximately two fold increased incidence of death for the RA Cimzia treatment population. Definitive causality can not be made at this time between administration of study drug and death in each case reported, however, given the mechanism of action of this class of drug, careful monitoring of patients is necessary for infections and malignancy in particular.

Other Serious Adverse Events

As of March 28, 2006, 438 SAEs had been reported in 290 subjects (21.5%), compared with 337 SAEs in 228 subjects (16.9%) in the original Summary of Clinical Safety. This is a difference of 62 subjects (4.6%). The most recent safety update information as of October 26, 2006 shows 328 subjects reporting SAEs (24.3%), which is another 3% increase from the March 28, 2006 data collection. In the updated safety analysis, the most common SAE was related to exacerbation of CD.

1.2.1 Malignancies

As of July 15, 2007, a total of 12 malignancy events had been reported for subjects in the pooled and non-pooled CD Populations. Ten events occurred in subjects receiving Cimzia 400 mg and two events occurred in subjects receiving placebo. Five of the ten malignancies in the Cimzia-treated patients and the two malignancies in placebo treated patients were previously reported. The five previously unreported malignancies are: prostate cancer, fatal rectal cancer, breast cancer, basal cell carcinoma and metastatic malignant melanoma. In addition, one subject in the compassionate use study, -092, experienced a small intestine carcinoma. No new cases of lymphomas have been reported. The Applicant states that the incidence of malignancies remained constant through seven additional months of drug exposure. Continued long-term monitoring is planned in the Risk Management Protocol.

Table 2: Summary of frequency and incidence rates for malignancy (solid tumor, excludes non-melanoma skin cancers) for all indications in the placebo controlled and safety population studies provided by Applicant:

	PBO CONTROLLED STUDIES		CZP CONTROLLED STUDIES		ALL CZP DOSES	
	%	100 pt-yrs	%	100 pt-yrs	%	100 pt-yrs
CD	*2/436=0.5*	*1.3*	*1/832=0.1*	*0.3*	*7/2166=0.3*	*0.3*
RA	***1/647=0.2***	***0.4***	***9/1774=0.5***	***0.9***	***31/2367=1.3***	***0.8***
Psoriasis	*0*	*0*	*0*	*0*	*0*	*0*

A two-fold increased incidence of malignancy appears to be limited to the RA treated population as compared to those subjects in the CD or Psoriasis trials. Reasons for this are not clear at this time, however, it is likely that longer period of observation will be required prior to better understanding of potential development of malignancy as related to Cimzia as well as other TNF-α antagonists.

1.2.2 Infections

There was an overall slight increase of 1% (5.9% to 6.9%) in the number of serious infection AEs noted after seven additional months of Cimzia exposure in the pooled CD population. The most common SAE in the Infections and Infestations were GI related abscesses, which is not unexpected for patients with CD. No new GI toxicities were found in the updated safety profile. Given that Cimzia has immunosuppressive actions, it is likely to see an increase in infections in the treatment populations, thus continued monitoring is required by all health care providers.

1.2.2.1 Tuberculosis

As of July 15, 2007, there are a total of ten subjects who have been diagnosed with TB in the pooled and non-pooled CD population studies, compared to three cases reported at the time of the previous 120 day safety update. Six subjects were diagnosed with pulmonary TB and four had extra-pulmonary disease. There was one fatality among the cases. Most of the subjects had normal PPD and CXR results at baseline.

The increase in number of pulmonary and disseminated TB is concerning. TNF-α antagonists are known to be associated with the reactivation of latent TB and boxed warnings have been included for labels of such drugs currently on the market. Physician and patient education is vital to limiting such adverse events. Improved and continued monitoring for TB will be critical for patients on Cimzia. It is to be noted that there are no cases of TB in the placebo group as compared to incidences of 0.4 to 1 per 100 pt-years in the treatment groups among all studies with Cimzia.

Table 3: Summary of frequency and incidence rates for TB for all indications in the placebo controlled and safety population studies provided by Applicant:

	PBO CONTROLLED STUDIES		CZP CONTROLLED STUDIES		ALL CZP DOSES	
	%	100 pt-yrs	%	100 pt-yrs	%	100 pt-yrs
CD	***0/436=0***	***0***	***1/832=0.1***	***0.3***	***9/2166=0.4***	***0.4***
RA	***0/647=0***	***0***	***10/1774=0.6***	***1***	***26/2367=1.1***	***0.7***
Psoriasis	***0/58=0***	***0***	***1/117=0.9***	***1.6***	***1/117=0.9***	***1.0***

1.2.2.2 Other opportunistic infections

There were twenty additional cases of the following opportunistic infections in the additional seven months of Cimzia exposure in the pooled and non-pooled CD population: Herpes Simplex and Zoster, Varicella, and fungal. Of these, five were serious AEs: optic Herpes Zoster neuritis, fatal PCP, systemic candida, disseminated zoster, and oral candida/CMV colitis. Opportunistic infections seem to be emergent only in subjects treated with Cimzia, which is likely due to the immune suppression associated with TNF-α antagonists. Patients will need to be carefully monitored while on this class of drugs.

Table 4: Summary of frequency and incidence rates for opportunistic infection SAE for all indications in PBO controlled and safety population studies provided by Applicant:

	PBO CONTROLLED STUDIES		CZP CONTROLLED STUDIES		ALL CZP DOSES	
	%	100 pt-yrs	%	100 pt-yrs	%	100 pt-yrs
CD	*0*	*0*	*0*	*0*	*5/2166=0.2*	*0.2*
RA	*0*	*0*	*1/1774=0.1*	*0.1*	*5/2367=0.2*	*0.1*
Psoriasis	*0*	*0*	*0*	*0*	*0*	*0*

1.2.3 Abnormalities of Hematology Parameters

Non-bleeding events:

Two possibly clinically significant abnormalities in hematology parameters were identified from information contained in adverse event reports, the first of which was previously reported and the second is a new report since the 120 Day safety update:

1) Study CDP870-005; a 39-year-old Caucasian female subject receiving Cimzia 200 mg subcutaneously, experienced two episodes of **thrombocytopenia**. The first event was serious, requiring hospitalization. Both events resolved. Patient was also on azathioprine which was discontinued on August 21, 2001.

2) Study CDP870-033; a 43-year-old Caucasian female receiving Cimzia 400 mg subcutaneously, experienced **pancytopenia**. At the time of the event, the subject was receiving chemotherapy for rectal carcinoma. The Investigator assessed this event as **chemotherapy induced** and unrelated to Cimzia.

Table 5: Summary of frequency and incidence rates for serious non-bleeding event for all indications in the placebo controlled and safety population studies provided by Applicant:

	PBO CONTROLLED STUDIES		CZP CONTROLLED STUDIES		ALL CZP DOSES	
	%	100 pt-yrs	%	100 pt-yrs	%	100 pt-yrs
CD	***0***	***0***	***0***	***0***	***5/2166=0.2***	***0.2***
RA	***0***	***0***	***2/1774=0.2***	***0.2***	***5/2367=0.2***	***0.1***
Psoriasis	*0*	*0*	*0*	*0*	*0*	*0*

Bleeding events:

In the placebo controlled studies for CD and RA, the overall rate of treatment emergent adverse events (TEAEs) of bleeding was similar for the Cimzia group compared to placebo from the information submitted by the Applicant. When the ISS data set was analyzed by combining preferred terms to evaluate for overall bleeding events, there was approximately slightly over 4% difference between Cimzia treated and placebo patients. There were a total of 93 bleeding AEs (80 in treated and 13 in placebo) in comparison to the 66 reported from the Applicant as described in the chart below. The following terms were analyzed as a group: bleeding tendency, bloody discharge, conjunctival hemorrhage, diarrhea hemorrhagic, ecchymosis, epistaxis, fecal blood, gingival bleeding, hematemesis, hematoma, hematuria, hemorrhoidal hemorrhage, increased INR, menometrorrhagia, menorrhagia, rectal hemorrhage, retinal hemorrhage, and vaginal hemmorhage. Injection site reactions were not included for this analysis.

Table 6: Number and percentage of patients with TEAEs of Bleeding in controlled studies for CD as provided by the Applicant:

Primary System Organ Class Preferred Term	Placebo (N=426)		All CZP Doses (N=1046)	
Bleeding Events	19	(4.5%)	47	(4.5%)
Bleeding tendency	1	(0.2%)	0	
Blood in stool (combined)	8	(1.9%)	6	(0.6%)
Blood in urine (combined)	2	(0.5%)	8	(0.8%)
Blood discharge	0		1	(0.1%)
Conjunctival haemorrhage (combined)	0		1	(0.1%)
Contusion	3	(0.7%)	3	(0.3%)
Diarrhoea hemorrhagic (combined)	0		1	(0.1%)
Dysfunctional Uterine bleeding (combined)	0		3	(0.3%)
Ecchymosis (combined)	1	(0.2%)	4	(0.4%)
Epistaxis	0		3	(0.3%)
Injection site bruising (combined)	4	(0.9%)	7	(0.7%)
Petechiae	0		1	(0.1%)
Rectal haemorrhage (combined)	3	(0.7%)	9	(0.9%)

Note: Data displayed as number of subjects (% of subjects).

Table 7: Number and percentage of patients with TEAEs of bleeding in controlled studies for RA as provided by the Applicant:

Combined term	Placebo N=647		All CZP Doses (PBO-Controlled) N=1774		All CZP Doses (All Studies) N=2367	
	n (%)	100 p-y	n (%)	100 p-y	n (%)	100 p-y
Total Number of Bleeding Events	23 (3.6%)	9.59	99 (5.6%)	10.96	163 (6.9%)	5.25
Blood urine	10 (1.5%)	4.12	25 (1.4%)	2.67	43 (1.8%)	1.32
Injection site bruising	3 (0.5%)	1.23	27 (1.5%)	2.89	39 (1.6%)	1.21
Dysfunctional uterine bleeding	3 (0.5%)	1.23	16 (0.9%)	1.70	34 (1.4%)	1.05
Ecchymosis	2 (0.3%)	0.82	18 (1.0%)	1.92	33 (1.4%)	1.02
Gastrointestinal haemorrhage	3 (0.5%)	1.23	12 (0.7%)	1.27	18 (0.8%)	0.55
Conjunctival haemorrhage	1 (0.2%)	0.41	2 (0.1%)	0.21	5 (0.2%)	0.15
Other haemorrhage	0	0	1 (0.1%)	0.11	4 (0.2%)	0.12
Purpura	1 (0.2%)	0.41	2 (0.1%)	0.21	4 (0.2%)	0.12

Notes: CZP = certolizumab pegol; PBO = placebo; p-y = patient-years.

For bleeding SAEs, there were no subjects in the placebo group as compared to the increased incidence of 0.7 per 100 pt-years found in the CD-Cimzia treatment group. In pre-clinical studies, there was an increase in the aPTT observed in monkeys receiving 50 and 100 mg doses of Cimzia. A similar increase was observed in an *ex vivo* study with monkey blood. However, no effects on aPTT were observed in animals receiving the study drug up to 26 weeks.

Table 8: Summary of frequency and incidence rates for serious bleeding event for all indications in the placebo controlled and safety population studies provided by Applicant:

	PBO CONTROLLED STUDIES		CZP CONTROLLED STUDIES		ALL CZP DOSES	
	%	100 pt-yrs	%	100 pt-yrs	%	100 pt-yrs
CD	***0***	***0***	***1/832=0.1***	***0.3***	***16/2166=0.7***	***0.7***
*RA**	*1/648=0.2*	*0.4*	*5/1774=0.3*	*0.5*	*9/2367=0.4*	*0.2*
Psoriasis	*1/58=1.7*	*4.1*	*1/117=0.9*	*1.6*	*1/117=0.9*	*1.0*

*NOTE: EMEA report states in RA studies there were *seven* SAEs reflecting bleeding events and none in placebo as stated below:

Rheumatoid Arthritis Population

SAE's suggestive of bleeding events: For the completeness the RA clinical trial, SAE safety databases were also searched for events of bleeding and/or increased bleeding.

In a total safety SAE database of 1898 subjects who received CDP870 in all RA studies (i.e. controlled, open-label extension and treatment studies), there were 7 (0.37%) SAEs, reflecting bleeding events (one case each of melena, hematoma, hematuria and two cases each of menorrhagia and metrorrhagia). Five of these events occurred in the placebo controlled studies and two events in the open label extension studies. There were no serious bleeding events in subjects receiving placebo in these studies.

Following public report from the EMEA that Cimzia was not authorized for marketing due to concerns of a new safety signal of increased bleeding in subjects administered Cimzia, the data sets were re-analyzed for bleeding adverse events.

The following discrepancies were found:

1] UCB states in correspondence dated Dec 21, 2007, that originally **four** bleeding SAEs occurred in Cimzia treated subjects in placebo controlled studies, of which three were removed for various reasons. The integrated studies summary (ISS) contains AEs for trials -005, -008, -031 and -032. Reviewing the ISS dataset, there were 93 AEs related to bleeding, of these 13 occurred in PBO, 79 in Cimzia treated (4.8% difference CZP-PBO). The following terms were consolidated to search for generalized bleeding events: bleeding tendency, bloody discharge, conjunctival hemorrhage, diarrhea hemorrhagic, ecchymosis, epistaxis, fecal occult blood, gingival bleeding, hematemesis, hematochezia,

hematoma, hematuria, hemorrhoidal hemorrhage, menometrorrhagia, menorrhagia, metorrhagia, rectal hemorrhage, retinal hemorrhage, and vaginal hemorrhage.

Table 9: A total of eight subjects were found listed with bleeding SAEs vs none in PBO:

PATIENT #	PROTOCOL	CENTER #	REASON
2302	-032	45119	Melena --> Transfusion
487	-031	39018	Duodenal Ulcer Bld
193	-031	13002	DUB
595	-031	18004	GI bleed
2802	-032	19010	Metrorhagia/IUD (event prior to CZP)
87	-005	55	Rectal bleed --> Surgery required
856	-031	33007	Retinal bleed --> Hospitalized
744	-031	34008	Rectal bleed

Furthermore, of the above eight listed patients as having SAEs in the ISS dataset, the following four patients do not have corresponding SAEs documented in their CRF:

1. Pt 487
2. Pt 193
3. Pt 595
4. Pt 744

2] Table 10: From the ISS dataset, the following patients all have rectal bleeding related AEs for which there is no center folder in the BLAMAIN CRF file:

PATIENT #	PROTOCOL	CENTER #
286 and 299	-031	45009
2150	-032	45136
2315 and 2398	-032	39011
2622	-032	45131
2708	-032	22007
2739	-032	16001

3] Table 11: From the ISS dataset, the following patients with bleeding AEs do not have CRFs:

PATIENT #	PROTOCOL	CENTER #	REASON
15	-031	45009	Vaginal bleed
144	-031	45009	Rectal bleed
306	-031	45109	Rectal bleed
371	-008	11	Rectal bleed
492	-008	52	Rectal bleed
2844	-032	39014	Rectal bleed

4] Table 12: From the ISS dataset, the following patients have CRFs but do not have corresponding AEs documented in the CRF:

PATIENT #	PROTOCOL	CENTER #	REASON
63	-031	45113	Rectal bleed
195	-031	39006	Vaginal bleed
288	-031	39003	Bleeding tendency
377	-031	45083	Inc rectal bleeding
2030	-032	45117	Rectal bleed
2326	-032	31001	Rectal bleed
2400	-032	31001	Rectal bleed
2547	-032	11010	Rectal bleed
2742	-032	39019	Rectal bleed
2820	-032	32005	Vaginal bleed

5] Individual datasets for trials -033 and -034 were reviewed for bleeding AEs. In trial -033, there were 21 AEs found related to bleeding, of which three were SAEs: dysfunctional uterine bleeding (hospitalized for surgery), rectal bleed (hospitalized), and increase INR (hospitalized and required blood transfusion). Of the 21 reported AEs, only six had matching case reports documented. In trial -034, 25 AEs were identified related to bleeding, of which two were SAES: GI bleed and duodenal ulcer bleed (hospitalized). Of the 25 reported AEs, 16 had matching case reports documented.

Table 13: On January 15, 2008, the Applicant submitted a response to the above inquiry of discrepancies in regards to SAEs:

Patient Number	**Event**	**Event occurring during Placebo Controlled study**	**Location of event in 21 Dec 07 submission**
2302	Rectal Bleeding	No	SAE occurred in open label induction phase of study -032. Included in Listing 1 and Table 7.5.
487	Duodenal Ulcer Bleed	No	SAE occurred in LTFU Study CDP870-034 (patient was originally enrolled into study -031). Included in Listing 1 and Table 7.5
193	DUB/Dysfunctional Uterine Bleeding	No	SAE occurred in LTFU Study CDP-870-033 (patient was enrolled into study -031). This event was inadvertently excluded from the 21 Dec 07 submission because it was entered into the GDS database under the MedDRA term "UTERINE POLYP". When the analysis was performed data was pulled based upon MedDRA terms rather than the reported term ("DYSFUNCTIONAL UTERINE BLEEDING DUE TO MULTIPLE UTERUS POLYPS")
595	GI Bleed	No	SAE occurred in LTFU Study CDP870-034 (patient was originally enrolled into study -031). Included in Listing 1 and Table 7.5
2802	Metrorrhagia/IUD	No	SAE occurred prior to study drug administration

			(not TEAE) and therefore was not including in the 21 Dec 07 submission.
87	Rectal Bleed	Yes	Patient received 100mg in study CDP870-005. included in Listing 1 and Table 7.2, and Table 7.5.
856	Retinal Bleed	Yes	Patient received 400mg in study CDP870-031. Included in Listing 1, Table 7.1, Table 7.2 and Table 7.5.
744	Rectal Bleed	No	SAE occurred in LTFU Study CDP870-033 (patient was originally enrolled into study -031). This event was inadvertently excluded from the 21 Dec 07 submission because it was entered into the GDS database under the MedDRA term "WORSENING OF CD". The narrative submitted with the original BLA listed "CROHN'S DISEASE DETERIORATED" as the MedDRA term, while the title of the narrative in electronic structure of the BLA was "RECTAL BLEEDING". When the analysis was performed data was pulled based upon MedDRA terms rather than the reported term ("RECTAL BLEED AS A SYMPTOM OF WORSENING OF CD"). This event is now included using the preferred term "RECTAL HEMMORHAGE".

As above, two of the patients were inadvertently excluded from the analysis and the other subjects are accounted for. Mishandling of data, especially for serious adverse events, is a concern. A safety analysis can not be completely reliable given any discrepancies.

Problems with Coagulation Assays:

On January 28, 2008, the Applicant submitted documentation regarding a commissioned study with researchers from the [redacted] This study was to investigate the possible interference of Cimzia, the Fab' fragment, and PEG in coagulation tests (including aPTT and PT assays). This additional study was performed after coagulation assays were performed in RA study CDP870-050 and results from the groups treated with Cimzia had more subjects with prolonged aPTT when compared to the placebo group, a three to four fold increase, and to a lesser extent prolonged PT. **During the CD studies for certolizumab pegol coagulation testing (aPTT, PT, TT) were not performed during study visits.**

In the three RA Phase 3 studies analyzed, of subjects with normal Screening and Baseline values, 83 subjects in the All CZP Doses group had Grade 3 elevated aPTT values (11.4% treated vs. 6.4% PBO) and 13 subjects had Grade 3 elevated PT values (1.8% treated vs. 0.6% PBO). Grade 3 was defined as ≥ 2 x ULN for aPTT. No Cimzia-treated subject with a Grade 3 abnormality of a clotting parameter were reported to experience an SAE related to bleeding at the time of the abnormality. With the exception of three subjects who participated in Study CDP870-014, all prolonged aPTT and PT values occurred in subjects in Study CDP870-050.

(0.6% vs. 0.7%), abscess intestinal (0.3% vs. 0.3%) and gastroenteritis (0.1% vs. 0.2%) for the March 28 and October 27, 2006, cut-off dates, respectively.

Other serious gastrointestinal tract infection and abscess events that occurred in the pooled and non-pooled CD Population in patients receiving Cimzia through July 15, 2007, included perianal abscess (9 subjects), abdominal abscess (4 subjects), peritonitis (3 subjects), perirectal abscess (2 subjects), intestinal abscess, pelvic abscess, rectal abscess, anal abscess, abdominal wall abscess, subcutaneous abscess, post-operative abscess, gastroenteritis, gastroenteritis viral, gastroenteritis clostridial, gastrointestinal infection (one subject for each event).

The gastrointestinal tract infection and abscess TEAEs that led to withdrawal with the highest frequency in the Cimzia 400 mg group were perianal abscess (3.9%, 5%) abdominal abscess (0.5%, 0.5%) and perirectal abscess (0.5% vs. 0.5%), in the previous and updated CD pooled population, respectively. After seven additional months of therapy, the pattern and frequency of gastrointestinal infection adverse events was similar to that previously reported. No new Cimzia-related toxicity was noted.

Table 14: Summary of GI disorders SAEs Occurring in ≥0.3% of Subjects in Pooled CD data:

Serious Adverse Events	28-Mar-06 400mg CZP Dose (N=1350) n (%)	27-Oct-06 400mg CZP Dose (N=1350) n (%)
Gastrointestinal disorders	165 (12.2%)	186 (13.8%)
Crohn's disease	97 (7.2%)	115 (8.5%)
Abdominal pain	20 (1.5%)	21(1.6%)
Intestinal obstruction	10 (0.7%)	12 (0.9%)
Small intestinal obstruction	12 (0.9%)	13 (1.0%)
Diarrhea	5 (0.4%)	6 (0.4%)
Ileal stenosis	3 (0.2%)	4 (0.3%)

Source: 120 Day safety update and Table 4.4:6

Table 15: Summary of frequency and incidence rates for serious GI events for all indications in the placebo controlled and safety population studies provided by Applicant:

	PBO CONTROLLED STUDIES		CZP CONTROLLED STUDIES		ALL CZP DOSES	
	%	100 pt-yrs	%	100 pt-yrs	%	100 pt-yrs
CD	*6.3*	*18.1*	*6*	*14.2*	*354/2166=16*	*17.4*
RA	*0.8*	*2*	*1.6*	*2.8*	*72/2367=3*	*1.8*
Psoriasis	*2*	*4.1*	*1.7*	*3.1*	*2/117=1.7*	*2.1*

Of note: events occurring ≥ 12 weeks after the last dose are excluded from analyses

No new serious hepatobiliary toxicity has been noted in the updated safety data.

1.2.6 Cardiovascular Disorders

New cases of SAEs in this category from both pooled and non-pooled CD data are one case each of: myocardial ischemia, thrombophlebitis, sudden cardiac death, angina, vena cava embolism, supraventricular tachycardia, and hypotension. Six of seven reported new SAEs have occurred in the non-pooled ongoing studies. No definitive evidence of cardiac Cimzia-related toxicity is noted.

Review of the ISS data set show that there were three SAEs in this SOC. One event was bradycardia that resolved in a placebo subject, the other two SAEs occurred in the same patient (hypertensive heart disease and myocardial infarction leading to death). Thus, in the CD controlled trials the incidence of SAE for Cardiac disorders for Cimzia vs PBO is 0.1 vs 0.2% respectively. For vascular disorders, there were also three SAEs, however, all occurred in three separate Cimzia-treated subjects. One event was hypertension responsive to therapy and the other two were DVTs that resolved with treatment.

Review of the RA study update show a prevalence of cardiac related deaths. From inception through January 31, 2007, a total of 29 deaths have occurred in the Cimzia RA studies according to the Applicant. These include ten deaths (nine Cimzia treated=0.5% and one PBO=0.2%) in the PBO-controlled studies and 19 deaths in the open-label studies. In the controlled studies, seven of the nine deaths were cardiac related (one in PBO). In the open-label studies, 10 of 19 deaths were cardiac related.

The Applicant reports in the October 25, 2007, RA Safety Update submission that the estimated standardized mortality ratio for subjects receiving Cimzia is 1.02, and that the literature estimates the RA population SMR to range from 1.3 to 5.6. Although the overall mortality rate in the Cimzia studies was similar to the expected rate, the proportion of cause of death for cardiac events is higher than that observed in the general population, but similar to that seen in other biologically-treated RA patient populations.

Cardiovascular SAEs in the RA studies indicate an incidence of 0.5% in placebo, 1% in all Cimzia doses done in placebo-controlled trials, and 2.4% for all CZP doses in all studies.

Table 16: Summary of frequency and incidence rates for serious CV events for all indications in the placebo controlled and safety population studies provided by Applicant:

	PBO CONTROLLED STUDIES		CZP CONTROLLED STUDIES		ALL CZP DOSES	
	%	100 pt-yrs	%	100 pt-yrs	%	100 pt-yrs
CD	*0*	*0*	*0*	*0*	*4/2166=0.2*	*0.2*
RA	*0.5*	*1.2*	*1*	*1.6*	*57/2367=2.4*	*1.4*
Psoriasis	*0*	*0*	*0*	*0*	*0*	*0*

Of note: events occurring ≥ 12 weeks after the last dose are excluded from analyses

Overall, there does not appear to be increased cardiovascular adverse events in Cimzia treated subjects in the CD and Psoriasis population. Patients with RA are at baseline increased risk for heart disease. The rate of CV SAEs in the Cimzia treated RA population appears to be consistent with what is seen in RA subjects treated with other TNF antagonists.

1.2.7 Nervous System Disorders

One new case of a recovered cerebral vascular accident with possible relation to Cimzia is reported from pooled and non-pooled CD data. Also, there was one previously new case of parasthesia from which the subject has not recovered at time of reporting.

Table 17: Summary of frequency and incidence rates of cerebrovascular accidents for all indications in the placebo controlled and safety population studies provided by Applicant:

	PBO CONTROLLED STUDIES		CZP CONTROLLED STUDIES		ALL CZP DOSES	
	n=	%	n=	%	n=	%
CD	***0***	***0***	***0***	***0***	***2/1350***	***0.1***
RA	***1/647***	***0.2***	***4/1774***	***0.2***	***9/2367***	***0.4***
Psoriasis	*0*	*0*	*0*	*0*	*0*	*0*

1.2.8 Serious Skin Reactions

Due to the recent TNF blocker post marketing reports of serious skin reactions (such as Stevens-Johnson Syndrome, toxic epidermal necrolysis, and erythema multiforme), the division requested the Applicant review their safety database for all indications used and submit an analysis. On March 27, 2008, correspondence from the Applicant indicated that there are no reports of these types of reactions to date seen with Cimzia.

Table 18: Summary of SAEs Occurring in ≥ 0.3% in the 400 mg Cimzia dose group for Pooled CD pts

Primary System Organ Class Preferred Term	28-Mar-06 400mg CZP Dose (N=1350)	27-Oct-06 400mg CZP Dose (N=1350)
	n (%)	n (%)
Total Number of SAEs	290 (21.5%)	328 (24.3%)
Blood and lymphatic system disorders	14 (1.0%)	16 (1.2%)
Anemia	7 (0.5%)	9 (0.7%)
Iron deficiency anemia	4 (0.3%)	4 (0.3%)
Gastrointestinal disorders	165 (12.2%)	186 (13.8%)
Crohn's disease	97 (7.2%)	115 (8.5%)
Abdominal pain	20 (1.5%)	21(1.6%)
Intestinal obstruction	10 (0.7%)	12 (0.9%)
Small intestinal obstruction	12 (0.9%)	13 (1.0%)
Diarrhea	5 (0.4%)	6 (0.4%)
Ileal stenosis	3 (0.2%)	4 (0.3%)
General disorders and administration site conditions	11 (0.8%)	13 (1.0%)
Pyrexia	7 (0.5%)	8 (0.6%)
Infections and Infestations	78 (5.8%)	93 (6.9%)
Perianal abscess	22 (1.6%)	25(1.9%)
Abdominal abscess	8 (0.6%)	9 (0.7%)
Perirectal abscess	3 (0.7%)	5 (0.4%)
Pneumonia	4 (0.3%)	5 (0.4%)
Urinary tract infection	5 (0.4%)	5 (0.4%)
Abscess intestinal	4 (0.3%)	4 (0.3%)
Sepsis	1 (0.1%)	4 (0.3%)
Metabolism and nutrition disorders	9 (0.7%)	10 (0.7%)
Dehydration	3 (0.2%)	4 (0.3%)
Hypoalbuminaemia	4 (0.3%)	4 (0.3%)
Musculoskeletal and connective tissue disorders	11(0.8%)	16 (1.2%)
Fistula	2 (0.1%)	4 (0.3%)
Renal and urinary disorders	14 (1.0%)	16 (1.2%)
Nephrolithiasis	6 (0.4%)	8 (0.6%)

1.3 Dropouts and other significant adverse events

Table 19:

Number of Subjects	28-Mar-06 400mg CZP Dose N=1350		27-Oct-06 400mg CZP Dose N=1350	
	n	%	n	%
Commenced at least one study	1350		1350	
Completed at least one study	513	(38.0%)	513	(38.0%)
Ongoing in Study CDP870-033 or Study CDP870-034	545	(40.4%)	475	(35.2%)
Withdrawn from at least one study	805	(59.6%)	858	(63.6%)
Reason for withdrawal:				
Adverse event	319	(23.6%)	354	(26.2%)
Protocol non-compliance	22	(1.6%)	22	(1.6%)
Patient decision	180	(13.3%)	198	(14.7%)
Clinical decision	102	(7.6%)	116	(8.6%)
Lost to follow-up	22	(1.6%)	24	(1.8%)
Lack of improvement/disease deterioration	466	(34.5%)	479	(35.5%)
Other	51	(3.8%)	57	(4.2%)

1.4 Common adverse events

Common TEAEs such as those occurring in ≥2% of subjects in the 400 mg Cimzia dose group are listed in Table 20. In the pooled CD Population for both cut-off dates, the TEAEs by preferred term that occurred in the greatest percentage of subjects in the 400 mg Cimzia dose treatment group were in the Gastrointestinal disorders and Nervous system disorders SOCs and included CD, headache, and abdominal pain. Overall, there was a small increase of 2% in total number of AEs, and there was no substantial change in the pattern/types of AEs reported in the seven months of increased drug exposure.

Table 20: Common Adverse Events

Primary System Organ Class Preferred Term	28-Mar-06 400mg CZP Dose (N=1350)	27-Oct-06 400mg CZP Dose (N=1350)
	n (%)	n (%)
Total number of adverse events	1112 (82.4%)	1141 (84.5%)
Blood and lymphatic system disorders	107 (7.9%)	122 (9.0%)
Anemia	47 (3.5%)	58 (4.3%)
Eye disorders	93 (6.9%)	109 (8.1%)
Conjunctival infections	39(2.1%)	32 (2.4%)
Gastrointestinal disorders	705 (52.2%)	736 (54.5%)
Crohn's disease	278 (20.6%)	316 (23.4%)
Abdominal pain	180 (13.3%)	191(14.1%)
Nausea	109 (8.1%)	119 (8.8%)
Diarrhea	84 (6.2%)	97 (7.2%)
Vomiting	76 (5.6%)	95 (6.3%)
Dyspepsia	51 (3.8%)	51 (3.8%)
Constipation	41 (3.0%)	46 (3.4%)
Abdominal pain upper	41 (3.0%)	42 (3.1%)
Abdominal distension	33 (2.4%)	36 (2.7%)
Hemorrhoids	31 (2.3%)	36 (2.7%)
Anal fissure	29 (2.1%)	32 (2.4%)
Aphthous stomatitis	30 (2.2%)	31 (2.3%)
General disorders and administration site conditions	322 (22.9%)	344 (25.5%)
Pyrexia	105 (7.8%)	115 (8.5%)
Fatigue	54 (4.0%)	58 (4.3%)
Influenza like illness	40(3.0%)	45 (3.3%)
Injection site reaction	32 (2.4%)	32 (2.4%)
Edema peripheral	28(2.1%)	29 (2.1%)
Injection site pain	26 (1.9%)	27 (2.0%)
Infections and infestations	644 (47.7%)	684 (50.7%)
Nasopharyngitis	157 (11.6%)	170 (12.6%)
Urinary tract infection	114 (8.4%)	130 (9.6%)
Upper respiratory tract infection	89 (6.6%)	99 (7.3%)
Influenza	76 (5.6%)	86 (6.4%)
Sinusitis	61 (4.5%)	69 (5.1%)
Bronchitis	37 (2.7%)	44 (3.3%)
Perianal abscess	37 (2.7%)	43 (3.2%)
Gastroenteritis	35 (2.6%)	42 (3.1%)
Pharyngitis	37 (2.7%)	40 (3.0%)
Herpes simplex	36 (2.7%)	34 (2.5%)
Viral infection	28 (2.1%)	32 (2.4%)
Musculoskeletal and connective tissue disorders	290 (21.5%)	315 (23.3%)
Arthralgia	119 (8.8%)	123 (9.1%)
Back pain	64 (4.7%)	66 (4.9%)
Pain in extremity	31 (2.3%)	34 (2.5%)
Muscle spasms	4 (0.3%)	32 (2.4%)
Nervous system disorders	309 (22.9%)	324 (24.0%)
Headache	230 (17.0%)	234 (17.3%)
Dizziness	34 (2.5%)	36 (2.7%)
Psychiatric disorders	145 (10.7%)	155 (11.5%)
Insomnia	61 (4.5%)	66 (4.9%)
Anxiety	42(3.1%)	46 (3.4%)
Depression	41 (3.0%)	47 (3.5%)

Primary System Organ Class Preferred Term	28-Mar-06 400mg CZP Dose (N=1350)	27-Oct-06 400mg CZP Dose (N=1350)
Respiratory, thoracic and mediastinal disorders	187 (13.9%)	194 (14.4%)
Pharyngolaryngeal pain	55 (4.1%)	58 (4.3%)
Cough	56 (4.1%)	58 (4.3%)
Skin and subcutaneous tissue disorders	265 (19.6%)	281 (20.8%)
Rash	66 (4.9%)	76 (5.5%)
Vascular disorders	59 (4.4%)	69 (5.1%)
Hypertension	20 (1.5%)	27 (2.0%)

1.5 Hypersensitivity reactions

The CD safety population was searched for events occurring within two hours of Cimzia injection that are commonly associated with acute hypersensitivity. A total of 35 subjects in the pooled CD population experienced events that fit in this category. Of those, most were previously reported except for three (two cases of dizziness and one case of rash).

1.6 Withdrawal phenomena and/or potential abuse

A total of 212 subjects randomized to placebo in the maintenance phase of Study -032 initially received three doses of open-label Cimzia 400 mg sc. For these subjects Cimzia was withdrawn following active therapy. Safety data for these subjects revealed no rebound of Crohn's disease symptoms following withdrawal of the study drug.

Abuse and dependence potential of Cimzia has not been evaluated. However, there are no abuse potential issues identified with this product to date.

1.7 Human reproduction and pregnancy data

As of July 15, 2007, a total of 18 subjects reported becoming pregnant while enrolled in clinical studies of Cimzia (all indications), four of which were in RA studies. One subject in psoriasis Study CPD870-040 became pregnant twice. Of the 19 pregnancies reported, three pregnancies are ongoing. Of the 15 pregnancies with a known outcome, six resulted in live births (five full-term, one premature), seven were terminated by elective abortion, one resulted in a spontaneous abortion, and one resulted in fetal death requiring a therapeutic abortion. No congenital anomalies have been reported in any of the infants born to female subjects receiving Cimzia who became pregnant while enrolled in a Cimzia study. No elective abortions were reported to be the result of a congenital anomaly.

In addition, nine female partners of male study subjects who received Cimzia were reported to have become pregnant while the male subject was enrolled in a clinical study of CZP (all indications). Eight resulted in a live birth. One was ongoing at the time of data reporting (last menstrual period May 26, 2007).

The use of Cimzia in pregnant or lactating women has not been evaluated in clinical trials. Continued birth control precaution while on study medication is warranted.

1.8 Overdose experience

No information on overdose has become available during the clinical development of Cimzia. There is no antidote for Cimzia. Doses of Cimzia up to 800 mg sc have been administered without any additional safety issues identified.

1.9 Post-marketing data

Cimzia was approved for use in CD in Switzerland September, 2007. There are no post-marketing safety data at this time as the drug has not yet been distributed.

2 Summary of drug-related adverse events

The overall numbers of AEs, SAEs, and AEs leading to death or withdrawal have not changed substantially since the last safety update.

Table 21:

	28-Mar-06 400mg CZP Dose N=1350	27-Oct-06 400mg CZP Dose N=1350
	n (%)	n (%)
Any Adverse Events	1112 (82.4%)	1141 (84.5%)
Intensity:[a]		
Mild	888 (65.8%)	919 (68.1%)
Moderate	801 (59.3%)	838 (62.1%)
Severe	283 (21.0%)	305 (22.6%)
Relationship to Study Drug:[b]		
Unrelated	843 (62.4%)	873 (64.7%)
Unlikely	628 (46.5%)	655 (48.5%)
Possible	478(35.4%)	502 (37.2%)
Probable	119 (8.8%)	126 (9.3%)
Definite	58(4.3%)	62 (4.6%)
Related to Study Drug[c]	538 (39.9%)	565 (41.9%)
Serious Adverse Events	290 (21.5%)	328 (24.3%)
Adverse Events Leading to Death	3 (0.2%)	4 (0.3%)
Adverse Events Leading to Withdrawal[d]	288 (21.3%)	328 (25.7%)

C. Conclusion

The Applicant states: "the data in this safety update confirms the previous conclusions in the original BLA and subsequent 120 Day safety update, with the majority of new events occurring in the Gastrointestinal Disorders SOC and the Infections and Infestations SOC. No new safety signals have emerged, and the safety profile of CZP is overall similar to that seen with the other anti-TNF therapies. The Risk Management Plan submitted with the BLA and update within the Complete Response submitted on 30-Apr-2007 will continue to monitor the safety of CZP."

I agree that overall there is not a significant increase in the total numbers of AEs/SAEs, that the overall pattern of events remain relatively consistent, and the safety profile is relatively similar to other TNF-α antagonists. However, I do not concur that there are no safety signals. Of concern, there are seven additional cases of TB (including one fatality), numerous additional cases of serious infections (Herpes, candidal, and fungal infections as well as increase in bacterial abscesses), five additional cases of malignancy, and two new cases of unresolved Alopecia totalis. There appears to be a potential increased risk of bleeding for subjects exposed to Cimzia. Of particular note, there have been discrepancies between the datasets provided, the corresponding patient case report forms, and analysis of data. The quality and reliability of data presented is not complete. Despite the discrepancies, the data overall likely provide a baseline understanding of safety for this TNF-α antagonist.

There is continued need for development of treatments for patients with CD which can be a chronic and unrelenting disease process. Therapy with TNF-α antagonists have shown potential in improving treatment of disease. However, as these drugs have impact on the immune system, there are significant side effects that physicians and patients alike must be aware in particular in areas of infection and malignancy.

Cimzia appears to have some efficacy in treating the maintenance of remission in a number of patients with CD. Cimzia, as a subcutaneous medication, improves the ease of administration and there have been relatively few problems reported with injection site reactions. Given the overall safety profile is similar to other drugs in this category, I feel there may be a place in the market for this study medication in the future with appropriate warning of the significant potentials adverse events that have been reported to date. However, at this time more statistically robust data with [redacted] nduction, improved integrity in the data presented, and continued investigation on the risks of increased bleeding would be warranted prior to release on the market.

Currently, there already exist two other TNF-α antagonists both of which have indications for induction and maintenance of remission in CD. To maintain consistency across the drug class, Cimzia should also meet the standards to which the other TNF-α antagonists were approved.

1 Page(s) Withheld

_____ Trade Secret / Confidential

_____ Draft Labeling

_____ Deliberative Process

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: December 21, 2006

FROM: Julie Beitz, MD

SUBJECT: Office Director Memo

TO: BLA STN 125160 Cimzia (certolizumab pegol); UCB, Inc.

Excessive tumor necrosis alpha (TNFα) activity is believed to be involved in the pathogenesis of inflammatory bowel disease, including Crohn's disease. Certolizumab pegol is a recombinant humanized antibody Fab' fragment which binds with high affinity to and neutralizes the biologic activity of human TNFα *in vivo*. The Fab' fragment is synthesized in *E. coli*, purified, and conjugated to polyethylene glycol which extends its plasma half-life to approximately 14 days. Certolizumab pegol has been evaluated in patients with moderately to severely active Crohn's disease. This memo documents my concurrence with the Division of Gastroenterology Product's complete response action for certolizumab pegol, administered subcutaneously on Weeks 0, 2, and 4 followed by maintenance dosing every 4 weeks to reduce signs and symptoms and maintain clinical response in patients with moderately to severely active Crohn's disease.

Efficacy

On February 28, 2006, UCB, Inc. submitted BLA STN 125160 which included two phase 3 studies evaluating the efficacy of certolizumab pegol 400 mg in patients with moderately to severely active Crohn's disease. Study CDP870-031 was a multicenter, randomized, double-blind, placebo-controlled clinical trial of 6 months duration in 662 patients. There were two co-primary endpoints: clinical response at Week 6 following SC treatment at Weeks 0, 2, and 4, and clinical response at both Weeks 6 and 26. These endpoints were to be assessed in the patient stratum defined by a baseline C-reactive protein or CRP $\geq$ 10 mg/L. Study CDP870-032 was a randomized withdrawal study in which 428 patients who responded at Week 6 to open label certolizumab pegol 400 mg administered SC at Weeks 0, 2, and 4 were randomized to either certolizumab pegol or placebo administered every 4 weeks through Week 24. The primary endpoint was a comparison between the treatment groups of the percentage of patients in clinical response at Week 26. This endpoint was to be assessed in the patient stratum defined by a baseline CRP $\geq$ 10 mg/L. In both studies, clinical response was defined as $\geq$ 100 point reduction from baseline in the Crohn's Disease Activity Index or CDAI score; clinical remission was defined as a CDAI score $\leq$ 150.

For Study CDP870-031, the sponsor's analysis found the co-primary endpoints to be statistically significantly higher for certolizumab pegol 400 mg compared to placebo treatment in patients with a baseline CRP $\geq$ 10 mg/L. At Week 6, clinical responses were noted in 37% of certolizumab pegol-treated patients vs. 26% of placebo-treated patients (p=0.037). Clinical responses in patients at both Weeks 6 and 26 were noted in 22% of certolizumab pegol-treated patients vs. 12% of placebo-treated patients (p=0.045). For this analysis, the sponsor defined the intent-to-treat population as the number of patients randomized who received at least one dose of study medication and had one efficacy assessment. The FDA statistician performed several additional analyses to assess the robustness of the sponsor's results. If the true intent-to-treat population is used (i.e., all patients randomized) and patients with missing information are counted as non-responders (i.e., not using a last observation carried forward or LOCF approach) the difference between certolizumab pegol and placebo was not significant at either Week 6 or at Weeks 6 and 26. Regarding secondary endpoints, there was no difference between certolizumab pegol and placebo treatment in the percentage of patients who achieved a clinical remission at Week 6 or at Weeks 6 and 26 in the sponsor's analysis.

For Study CDP870-032, the clinical response rate to induction therapy with open label certolizumab pegol 400 mg SC was 64%, much higher than that observed at Week 6 in Study CDP870-031. The sponsor's analysis found that among patients with a baseline CRP $\geq$ 10 mg/L who had responded to certolizumab pegol and who were then randomized at Week 6 to receive additional treatment with certolizumab pegol, the percentage of patients with clinical responses at Week 26 was 62%. Among such patients randomized to placebo treatment at Week 6, the response rate at Week 26 was only 34% ($p< 0.001$). FDA accepts this analysis as it was based on the true ITT population and LOCF was not an issue, however, analysis of efficacy by country revealed that the positive finding at Week 26 in this study was driven primarily by countries other than the US. For patients with a baseline CRP $\geq$ 10 mg/L, the clinical response rates at Week 26 in the US were 42% for certolizumab pegol and 43% for placebo treatment, whereas, clinical response rates in countries outside the US were 64% and 31%, respectively. The reason for the difference in response rates observed at US vs. non-US sites is unclear but might be explained by differences in host factors (see pharmacokinetics discussion below). Regarding secondary endpoints, the probability of disease progression was significantly lower and clinical remission rates at Week 26 were significantly higher in patients with a baseline CRP $\geq$ 10 mg/L randomized to receive maintenance therapy with certolizumab pegol compared to placebo treatment.

Safety

In the clinical development program for Crohn's disease, a total of 1564 patients received certolizumab pegol, of which 1350 received dosing with 400 mg, and 426 received placebo treatment. The most common serious adverse events on certolizumab pegol treatment were infections and manifestations or exacerbations of Crohn's disease.

In studies of Crohn's disease, the incidence of infection (all severities) on certolizumab pegol treatment was higher compared to placebo treatment (41% vs. 30%). The most common infections were nasopharyngitis, urinary tract and upper respiratory tract infections. Serious infections occurred in 4.4% of certolizumab pegol-treated patients as compared to 1.4% of patients on placebo treatment. This finding is consistent with the known risk of serious infections with other anti-TNFα agents. The most common serious infections on certolizumab pegol were perianal, abdominal, and intestinal abscesses.

Patients enrolled in clinical trials of certolizumab pegol were screened for latent or active tuberculosis. To date, there have been 13 reports of tuberculosis on certolizumab pegol in clinical trials: 3 in trials of Crohn's disease, 1 in a psoriasis trial, and 9 in rheumatoid arthritis trials. In addition, there were two reports of *Pneumocystis carinii* pneumonia on certolizumab pegol treatment, one in a patient with Crohn's disease and the other in a rheumatoid arthritis patient.

In studies of Crohn's disease, seven malignancies were diagnosed in certolizumab pegol-treated patients and three in placebo-treated patients, including one case of Hodgkin's disease. In clinical studies of rheumatoid arthritis, there were three reports of malignancies in certolizumab pegol-treated patients and one malignancy in a placebo-treated patient, a case of non-Hodgkin's lymphoma.

Rat studies using a homologous anti-TNF antibody revealed no effects on fertility or early embryonic development, no evidence for teratogenicity, and no effects on pre-natal or post-natal development. The antibody was excreted in rat milk. The preclinical reviewer concurred with the sponsor's proposed Pregnancy Category B.

Certolizumab pegol was not found to be genotoxic in the Ames test, the human lymphocyte chromosomal aberration test, or the mouse micronuclear test. No carcinogenicity studies were conducted.

Note that the acceptability of the clinical laboratory data for the phase 3 studies submitted in this application has not been determined pending resolution of data integrity issues involving the MDS Pharma Canadian site.

In addition to routine postmarketing surveillance, the sponsor has proposed to extend to three years the duration of two ongoing open label extension studies in Crohn's disease, maintain a patient registry, and

conduct a claims database study to estimate the rate of adverse events of interest in patients treated with certolizumab pegol and other anti-TNFα agents.

Pharmacokinetic Considerations

Study CDP870-005 was a randomized placebo-controlled study evaluating 100, 200, or 400 mg doses of certolizumab pegol administered subcutaneously at Weeks 0, 4, and 8. The primary endpoint was a comparison between the treatment groups of the percentage of patients in clinical response or remission at Week 12. This study differed from the phase 3 trials in dosing regimen and the time of response evaluation but served as the basis for two important features of the subsequent phase 3 clinical development of certolizumab pegol: selection of the 400 mg dose and the decision to evaluate efficacy in the subpopulation of Crohn's disease patients with baseline elevated CRP levels.

FDA's analysis of the phase 3 studies (CDP870-031 and CDP870-032) suggests that there does not appear to be an exposure-response relationship for certolizumab pegol 400 mg at Week 6 or Week 26 for patients with a baseline CRP $\geq$ 10 mg/L. In addition, at Week 26, there does not appear to be an exposure-response relationship for certolizumab pegol in patients enrolled at US sites in Study CDP870-032 whereas there was a fairly defined trend at non-US sites. With US and non-US sites combined, the overall trend at Week 26 in this study was driven by the non-US sites. Since the exposure at US and non-US sites is similar, the reason for the lack of an exposure-response relationship for US patients is not known, but might be due to differences in host factors that could make them either less sensitive to certolizumab pegol treatment or more responsive to placebo treatment.

There does not appear to be a relationship between exposure to certolizumab pegol and rates of serious adverse events, serious infections, urinary tract infection or herpes viral infection. Thus, evaluation of higher or more frequent doses of certolizumab pegol in future studies should be feasible from a safety perspective.

Eight percent of patients exposed to certolizumab pegol in Studies CDP870-031 and CDP870-032 developed anti-certolizumab pegol antibodies, of which 80% were neutralizing *in vitro*. Antibody formation was lower in patients using concomitant immunosuppressants compared to those who were not. The presence of antibodies increased the clearance of certolizumab pegol four-fold. Therefore, dose adjustment is recommended for antibody positive patients. No other dose adjustments are recommended at the present time. No definitive conclusions can be drawn regarding the effect of liver dysfunction on the pharmacokinetics of certolizumab pegol because of the limited number of patients with liver function abnormalities studied.

Tradename Review

The tradename "Cimzia" is acceptable.

Labeling

The product labeling remains unresolved at this time.

Conclusions

I agree with the conclusions of the review team regarding certolizumab pegol for the treatment of moderately to severely active Crohn's disease, namely that:

1) the effects of certolizumab pegol treatment relative to placebo as noted in Study CDP870-031 do not provide substantial evidence to support a claim for either induction or maintenance of clinical response;

2) the positive effects of certolizumab pegol relative to placebo as noted in Study CDP870-032 as maintenance therapy for patients in whom clinical response had been previously induced are compelling

but are driven primarily by responses in patients enrolled at non-US sites; the reasons for this observation should be further explored;

3) further efforts to identify a more efficacious certolizumab pegol dose or regimen in US patients should be pursued before embarking on additional phase 3 safety and efficacy studies;

4) the safety profile of certolizumab pegol as presented in this application appears to be acceptable and is consistent with known risks of other anti-TNFα agents; and

5) there is no safety information presented on the use of certolizumab pegol as maintenance therapy following induction with other agents.

The deficiencies in this application will be conveyed to the sponsor in a Complete Response letter. The sponsor could address these deficiencies by refining the dose and regimen of certolizumab pegol and conducting another safety and efficacy study to evaluate the product as induction therapy in patients with moderately to severely active Crohn's disease. Alternatively, the sponsor may wish to perform a second maintenance study evaluating the safety and efficacy of certolizumab pegol following induction with another agent.

Julie Beitz MD 12/21/06

Julie Beitz, MD
Office Director,
Office of Drug Evaluation III
CDER, FDA

DEPARTMENT OF HEALTH AND HUMAN SERVICES — PUBLIC HEALTH SERVICE

Food and Drug Administration

Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Silver Spring, MD 20993

Division of Gastroenterology Products
HFD-180

John E Hyde 12-19-06

Date: December 19, 2006

From: John Hyde, Ph.D., M.D., Clinical Team Leader, DGP

Subject: Clinical Team Leader Summary Review of BLA/STN 125160/0
CIMZIA for Crohn's Disease

I concur with both the review and proposed regulatory action.

John E Hyde 12/19/06

To: BLA 125160/0 File
Brian Harvey, M.D., Ph.D., Division Director, DGP
Julie Beitz, M.D., Office Director, ODE 3

Identifying information

BLA/STN#:	125160
Applicant:	UCB, Inc.
Biologic name:	Certolizumab Pegol
Proposed trade name:	CIMZIA
Submission date:	February 28, 2006
Stamp date:	March 1, 2006
PDUFA goal date:	December 29, 2006
Formulation:	200 mg certolizumab, lyophylized, in 5 mL glass vial, for reconstitution with 1 mL sterile water for subcutaneous administration.
Proposed indication:	[redacted]
Proposed regimen:	400 mg subcutaneous injection at Weeks 0, 2, and 4, followed by 400 mg subcutaneous injection every four weeks.

Recommended regulatory action: Complete Response.

Introduction and Regulatory Background

General Background

This BLA is for the new molecular entity Cimzia (certolizumab pegol), a humanized antibody Fab' fragment targeting human tumor necrosis factor alpha (TNFα). The antibody fragment is manufactured using recombinant technology in E. coli. The fragment is conjugated to polyethylene glycol to extend its plasma half-life. The product is lyophylized and provided in

glass vials for reconstitution with sterile water. Cimzia is to be administered at a dose of 400 mg as a subcutaneous (SC) injection every two weeks for the first four weeks, then every four weeks.

Cimzia is proposed as [redacted] The Applicant has proposed labeling that includes a boxed warning for TB risk, warnings for risk of infection, heart failure, use with anakinra, neurological events, hematologic events, and malignancies. The proposed labeling also includes precautions regarding hypersensitivity reactions, autoimmunity, immunosuppression, and immunizations. These warnings and precautions are similar to those found in the labeling of other approved anti-TNFα agents.

Cimzia is not currently approved in any foreign country.

The [redacted] clinical investigations of certolizumab pegol [redacted] were for rheumatoid arthritis (RA), and they were conducted [redacted] During the development for RA the product was reformulated into its current lyophylized form. The Phase 2 studies in Crohn's disease were conducted in 2001 to 2002 outside of the U.S., and they were not done under an IND. The Phase 3 clinical studies were conducted under BB-IND 11,197, which was initially received on 7/31/03. Sponsorship of the IND has changed several times during the development program. The original sponsor was GD Searle LLC (a subsidiary of Pharmacia). Sponsorship was transferred on 2/16/04 to Celltech R&D Ltd., which had been a partner in the development. On 3/24/05 sponsorship was transferred to UCB Pharma, which on 12/21/05 changed its name to UCB, Inc.

Presubmission Communications between FDA and the IND Sponsors

Before the Crohn's disease IND was submitted, a pre-IND/End-of-Phase-2 meeting between FDA and GD Searle was held on April 15, 2003. As presented at that meeting, the IND Sponsor was planning two short induction studies, and one study of re-induction. [redacted] The FDA minutes from that meeting reflect that:

- The FDA felt that the existing and planned preclinical studies looked adequate, but FDA was unwilling to provide a definitive answer without reviewing the data.
- FDA felt the data from the two Phase 2 dose-ranging studies supported using the proposed dosing scheme of 400 mg at Weeks 0, 2, and 4 in Phase 3.
- The FDA agreed that improvement in CDAI by at least 100 points was an acceptable definition for a primary endpoint of clinical response.
- The FDA did not concur that the Sponsor's proposed development plan would be adequate to support a BLA submission. In particular, FDA did not agree with the proposed Week 6 timepoint. FDA said that the clinical trials needed to reflect the chronic nature of the disease and that data out to six months would be required. [redacted] . The FDA stated "Two pivotal studies that support the proposed use would be required to support the BLA at the time of submission."

- FDA questioned why the product would only work in the subset of patients with CRP ≥ 10.

The meeting agreements identified explicitly at the end of the FDA minutes as sent to the Sponsor were:

> *Searle and CBER (Drs. Liang and Siegel) will hold informal teleconferences to reach agreement on a clinical development approach that may include two randomized, controlled studies in patients with high and low CRP, with dual endpoints and require safety data collection out to at least 6 months. The proposed indication will be discussed further at a future time.*

The Sponsor's version of the minutes from that meeting reflect the understanding that the preclinical package was appropriate, that the dose selection was acceptable, and that the primary endpoint of CDAI decline of at least 100 was an acceptable definition. The Sponsor minutes also show that the Sponsor understood that FDA did not consider the proposed clinical program to be acceptable. Their minutes show an understanding that a six-week efficacy endpoint alone was not acceptable, and that a six-month chronic efficacy endpoint was acceptable, but it could be coupled with earlier response points. The Sponsor minutes state FDA indicated that two pivotal, placebo-controlled trials would be acceptable and that the safety database requirements were undetermined but would need to include some 52-week data. The Sponsor minutes state that FDA wanted information on all patients regardless of baseline CRP, but that stratification by CRP would be acceptable.

In a submission dated May 22, 2003, Pharmacia provided a Revised Clinical Plan that included Phase 3 studies generally like those that eventually were conducted. On June 16, 19, and 23, 2003, there were a series of discussions about study designs between the sponsor and the Medical Officer, as documented in internal Sponsor E-mails (but for which FDA appears to have no record). Pharmacia submitted protocol revisions resulting from those discussions in a fax on July 29, 2003.

BB-IND 11,197 for Crohn's disease was received on July 31, 2003. Over the next three months there were several documented telecons between the Sponsor and the Medical Officer discussing some technical refinements of the protocol. Of note, in the telecon of September 22, 2003, the sponsor explicitly agreed to use a non-responder imputation for missing data. There was no follow-up End-of-Phase-2 meeting, and the sponsor did not submit an SPA request for any of the clinical protocols, although that procedure was available at the time (the SPA guidance was published in May 2002). The FDA telecon minutes indicate that only the Medical Officer was involved in the telecons discussing the clinical protocols; in particular, there is no record of Division Director participation in those telecons.

On 8/26/05 there was a telecon to put the Sponsor on partial hold when it had been found that there was a [redacted] contamination problem with manufacturing campaigns [redacted] That hold was removed shortly thereafter, on 9/2/05, when further information revealed that the [redacted] were within acceptable levels according to [redacted] (see CMC issues below and CMC reviews for details).

Chemistry, Manufacturing, and Controls Issues

The reader is referred to the Drug Product Reviews by K. Brorson, the PEG-linker and Immunogenicity Assay Review by G. Gill-Sangha, and the Immunogenicity Assay Review by K. Brorson.

Certolizumab pegol is a pegylated humanized anti-TNFα Fab' antibody fragment. [redacted]. The Fab' fragment is expressed in E. coli, purified, and pegylated by conjugation with PEG2MAL40K, [redacted] to produce the final drug product. For administration, the product is to be reconstituted in 1 mL sterile water. The product is supplied in packs containing two vials of Cimzia, two vials of water for injection, two syringes, needles, and alcohol swabs.

The drug substance is manufactured at [redacted] and the product is manufactured by [redacted] Release testing is done at [redacted] at UCB Manufacturing in Rochester, NY, and at contract sites.

The product from the commercial process has shown adequate stability for [redacted] months, and the clinical product has shown adequate stability for [redacted] months. The reviewer recommended that the Applicant's request for 18 months expiry at the recommended storage temperature of 2 to 8 °C was reasonable.

Inspection of the drug substance and drug product manufacturing facilities uncovered issues as identified in the 483's, but these have been resolved (see Drug Product Reviews for details). There are no remaining facilities issues that would preclude approval.

Minor CMC issues were raised late in the review cycle (FDA communication of 11/29/06 and submissions of 12/4/06 and 12/6/06) regarding an [redacted] in-process control level and a question about the need for a process change comparability protocol (see [redacted] Review). These issues were not fully resolved, and the reviewer proposed requests to be included in a letter to the Applicant.

A [redacted] contamination problem was reported to the FDA on 8/25/05 for campaigns [redacted] which resulted in the IND being placed briefly on partial hold. The [redacted] were determined to be at acceptable levels under [redacted] and [redacted], so the IND was allowed to proceed. However, affected lots were put on special stability monitoring. The reviewer did not feel that the [redacted] contamination issue should preclude licensure of the product, because the problem impacted a limited number of lots, and [redacted] fell within the [redacted] criteria. The reviewer felt that the [redacted] changes [redacted] would be likely to remove the possibility of future [redacted] contamination, and that that could be verified during inspection. Each batch will be monitored at lot release for the [redacted]

The immunogenicity review noted modest levels of anti-certolizumab pegol develop directed at [redacted] and mainly impact clearance. The reviewer also cited an internal Pfizer/Celltech committee report identified as ARLE05M0622 – 40001531 "Final Report of CDP870 antibody subgroup on CDP870 immunogenicity." The major conclusions were:

- About 40% of patients chronically dosed SC develop HAHA.
- HAHA increases clearance of certolizumab pegol
- Lower doses (0.3 mg/kg) result it higher rates of HAHA than higher doses (3-10 mg/kg)
- Certolizumab pegol is more immunogenic in RA patients than Crohn's disease patients.
- Certolizumab pegol is more immunogenic when administered SC than IV
- There is no consistent trend towards increases in adverse events in $HAHA^+$ patients.

The reviewer commented that all of these observations were consistent with current understandings of antibody responses to proteins.

The anti-certolizumab pegol assay has been qualified and is adequate. However, the reviewer did note that under current assay procedure the [redacted]

Conclusions and Recommendations

The reviewer felt an 18 month expiration date was reasonable based on available stability data. The CMC team concluded that only two minor issues need to be resolved prior to approval, and wording to be conveyed to the Applicant was proposed in the Chemistry Executive Summary.

The reviewers recommended that any eventual approval letter should include [redacted] No Phase 4 commitments were recommended.

Pre-clinical Pharmacology and Toxicology Issues

The reader is referred to the Pharmacology/Toxicology Review and Evaluation by S. Chakder.

Certolizumab has high affinity for human TNFα and weakly cross-reacts with TNFα from non-human primates, but it does not bind rodent TNFα. The affinity for human TNFα is estimated to be about 40-fold greater than for cynomolgus monkey TNFα. The affinity of certolizumab for human TNFα was estimated to be less than of etanercept, but greater than that of adalimumab and infliximab. Certolizumab was not found to bind to normal human tissue in a battery of 37 human tissues types.

The ability of certolizumab to neutralize human TNFα was demonstrated by the ability of certolizumab to reduce the pyrogenic effect of human TNFα in a rabbit model. In *in vitro* testing, certolizumab did not mediate cell killing by either complement-mediated cytotoxicity or antibody-dependent cellular cytotoxicity, whereas both types of cytotoxicity were seen with etanercept, adalimumab, and infliximab (although etanercept had lower ADCC), findings that are

consistent with the lack of an Fc region in certolizumab. Also, certolizumab did not induce human lymphocyte apoptosis or cause neutrophil degranulation, whereas concentration-dependent effects were seen with etanercept, adalimumab, and infliximab.

Due to the lack of affinity of certolizumab for rodent TNFα, toxicology studies were performed in cynomolgus monkeys, but high doses were still required to overcome the low cross-reactivity. The studies included single- and repeated-dose studies using both intravenous and subcutaneous routes of administration. Slight hematologic changes (decreased RBC and increased WBC) were observed, which were reversible. Vacuolation in hemolymphoreticular tissues was observed after a month at high doses (400 mg/kg), and foamy macrophages were observed in several tissues after various durations of treatment at 100 mg/kg. Elevated aPTT was seen with dosing of 50 and 100 mg/kg, and the effect on aPTT was also produced *in vitro*. Anti-certolizumab pegol antibodies developed in about 5% of animals.

Reproduction studies were conducted in rats using a homologous anti-TNF antibody. It had no effect on fertility or early embryonic development, was not teratogenic, and had no effect on pre- or post-natal development. The [redacted] anti-TNF antibody was found to be excreted in rat milk. The reviewer concurred with the Applicant's proposed pregnancy category of B.

Pharmacokinetic studies found plasma concentration to be dose-proportional following SC administration. The half-life was 8.4 days in cynomolgus monkeys following SC administration and 6.1 days after IV administration. There were no apparent gender differences in animals. Clearance was increased in animals that developed antibodies to certolizumab.

Studies in rats found the biodistribution of certolizumab pegol was similar to that of IgG. The highest concentration following a single IV dose was in the kidney.

Certolizumab was not found to be genotoxic in the Ames test, the human lymphocyte chromosomal aberration test, or the mouse micronuclear test. No carcinogenicity studies were conducted.

Conclusions and Recommendations

The pre-clinical reviewer concluded that the product was approvable. He recommended that the pregnancy category should be B, as the Applicant proposed, and that the labeling should mention [redacted] He did not recommend any additional preclinical studies to be conducted in Phase 4.

Clinical Pharmacology Issues

The reader is referred to the Clinical Pharmacology Review by T. Ghosh, S. Al-Fayoumi, and C. Tornoe.

Single- and repeated-dose pharmacokinetic (PK) studies were done in healthy subjects and Crohn's patients, and as part of the Phase 3 studies (see Clinical Pharmacology Review for descriptions of the various studies). Studies also compared Cimzia to two liquid formulations

used in Phase 2. Certolizumab pegol concentrations were measured with a —— ELISA assay that the reviewers found to be acceptably validated.

Basic PK analysis showed that with SC administration, mean C_{max} and AUC were linear with dose, peak levels occurred around four days after dosing, and the terminal half-life was about 13 days. In the two Phase 3 studies, the certolizumab pegol trough levels achieved two weeks after the initial dose were similar on average to the steady state trough levels with every four week dosing, confirming the Applicant's estimated optimum induction regimen that had been based on PK modeling. No pediatric PK data were provided.

The reviewers concluded that Cimzia and the IV formulations used in Phase 2 were comparable. The bioavailability for subcutaneous Cimzia is about 80% compared to IV formulations.

A drug-drug interaction study with methotrexate in RA patients found no significant interaction. No other interaction studies were performed, but the reviewers felt any interactions would be unlikely, because therapeutic biologics are not CYP450 substrates.

In a study comparing healthy Caucasian subjects and healthy subjects of Japanese descent, the PK parameters were found to be comparable in the two groups at the proposed therapeutic dose. Based on the Applicant's population PK analyses using pooled clinical trials, the data did not show any significant effect of age, gender, or creatinine clearance on PK. No conclusions could be drawn about the affect of liver dysfunction because of the limited number of patients. Repeated administration, weight, monocyte count, immunosuppressant intake, and ethnicity showed statistically significant effects, but they were not considered to be of a magnitude that would warrant dose adjustment. Only the presence of antibodies had more than a 30% effect on PK parameters. In the reviewer's population PK modeling, only weight and presence of antibodies appeared to have any clinically significant impact on clearance. The reviewer recommended ——————————————————

The probability of developing antibodies appeared to be inversely related to Cimzia dose. The reviewers noted that such an observation could be complicated by the interference of certolizumab pegol in the anti-certolizumab pegol assay, but the relationship was still seen after certolizumab pegol concentrations became undetectable after cessation of dosing. The percentage of subjects with antibodies increased with continued dosing. The presence of antibodies effects the pharmacokinetics; from population PK analysis the clearance was estimated to increase by about four fold when antibodies were present, producing an estimated 86% reduction in trough levels and 72% reduction in AUC_{τ}.

The reviewers noted a wide range in the certolizumab pegol levels in the clinical efficacy studies. They felt there was evidence, most clearly seen in the Phase 2 SC study (Study 005), of an exposure-response relationship. From pharmacometric modeling of exposure-response in the Phase 3 studies, the reviewers felt that higher doses should be investigated for induction. The reviewers also noted that the exposure-response relationship was not seen when the analysis was restricted to U.S. study sites. No reason for the difference was identified.

Conclusions and Recommendations
The reviewers did not believe that the Applicant had fully explored the appropriate dose range and had not yet determined the proper dose for either induction or maintenance of remission. The reviewers recommend that the Applicant redefine the dose-response relationship and use simulations based on current data for future clinical trial design to support product approval.

Clinical/Statistical Issues

The reader is referred to the Clinical Review by S. Bezabeh and to the Statistical Review by M. Fan.

Phase 2 Studies

The Applicant conducted two Phase 2 dose-ranging studies to investigate the efficacy of certolizumab pegol. One was a single-dose IV study; the other a repeated-dose study by the SC route. The IV study was started first, but the study periods overlapped. These studies were conducted outside of the U.S. and were not under IND.

Phase 2 Intravenous Study (008)

This was a randomized, double-blind, placebo-controlled, parallel dose-response study of three different doses of an intravenous formulation of certolizumab pegol in 92 patients with active Crohn's disease.

The study enrolled patients with moderately to severely active Crohn's disease, as defined by Crohn's disease activity index (CDAI) in the range of 220 to 450 inclusive. Patients were allowed to be taking corticosteroids, 5-ASA's, or immunomodulators (i.e., any of conventional therapy) at the time of entry, provided dosing was stable; however, there was no requirement that patients had failed conventional therapy.

Patients were randomized with equal probability to receive placebo, or one of three doses of certolizumab pegol IV. Initially the three doses to be tested were 1.25 mg/kg, 5 mg/kg, and 20 mg/kg. After two patients received the 1.25 mg/kg dose, the protocol was modified to replace that dose with 10 mg/kg. Assigned treatment was administered one time only, at Week 0, as an IV infusion over about 30 minutes. At Weeks 0, 2, 4, 8, 10, 12 there were assessments that included CDAI, IBDQ, AE's, and various laboratory measurements, including CRP and samples for PK evaluation. There we additional safety assessments at Weeks 16 and 20.

The primary efficacy endpoint was the fraction of patients that had achieved success, which was either clinical response (defined as CDAI decrease of at least 100) or clinical remission (CDAI $\leq$ 150) at Week 4 (the Applicant referred to this combined endpoint as "response," but to avoid confusion with "clinical response" as used in the Phase 3 studies, this review will use the term "success" here). Efficacy analyses were exploratory. Secondary endpoints included success rates at the other assessment timepoints, success rates in the stratum defined by baseline CRP $\geq$

10 mg/L, IBDQ changes, fistula response, AE's, and PK. Results for the primary endpoint are shown in table below:

Week 4 Success Rates in Study 008

	Placebo	Certolizumab 5 mg/kg IV	Certolizumab 10 mg/kg IV	Certolizumab 20 mg/kg IV
Week 4 Success	56% (14/25)	60% (12/25)	59% (10/17)	48% (11/23)

The two patients who received 1.25 are not included in the table.
Results are shown for patients as treated (one patient assigned to placebo received 5 mg/kg).

An analysis stratified on patients receiving steroids, immunomodulators, or anti-infectives (S/I/A-I), suggested that there was a better response to Cimzia 5 and 10 mg/kg in those patients taking S/I/A-I, but for 20 mg/kg that subgroup did not show a better success rate. No significant safety issues were identified. In this study, 15% of patients were positive for anti-certolizumab pegol antibodies, but this antibody formation was not associated with AE's.

Phase 2 Subcutaneous Study (005)

This was a randomized, double-blind, placebo-controlled, parallel, dose-response study of three different doses of Cimzia in 292 patients with active Crohn's disease.

The study enrolled patients with moderately to severely active Crohn's disease, as defined by CDAI in the range of 220 to 450 inclusive. Patients were allowed to be taking corticosteroids, 5-ASA's, or immunomodulators (i.e., any of "conventional therapy") at the time of entry, provided dosing was stable; however, there was no requirement that patients had failed conventional therapy. Patients were excluded if they had complicated Crohn's disease (obstruction, extensive surgery), additional intestinal diseases, prior TB, or significant other diseases (see Clinical Review for details of eligibility criteria).

Patients were randomized with equal probability to receive placebo, Cimzia 100 mg, Cimzia 200 mg, or Cimzia 400 mg. Assigned treatment was administered SC at Weeks 0, 4, and 8. At Weeks 0, 2, 4, 6, 8, 10, 12 there were assessments that included CDAI, IBDQ, fistula response, AE's, and various laboratory measurements, including CRP and samples for PK evaluation. There we additional safety assessments at Weeks 16 and 20.

The primary efficacy endpoint was the fraction of patients who had achieved success, which was either clinical response (defined as CDAI decrease of at least 100) or clinical remission (CDAI $\leq$ 150) at Week 12. A closed statistical analysis procedure was proposed in which the 400 mg dose would be compared to placebo first, followed by simultaneous comparisons for the other two Cimzia groups. Secondary endpoints included success rates at the other assessment timepoints, success rates in the stratum defined by baseline CRP $\geq$ 10 mg/L, IBDQ changes, AE's, and PK.

The mean age was 26 years, 39% were males, 97% were Caucasian. The mean duration of Crohn's disease ranged across groups from 7.7 to 8.8 years, the mean baseline CDAI ranged

from 292 to 311, and the mean CRP ranged from 6.2 to 7.7 mg/L; 41% had baseline CRP ≥ 10. Results of the success rate are shown in table below:

Success Rates in Study 005

	Placebo	Cimzia 100 mg	Cimzia 200 mg	Cimzia 400 mg
N =	73	74	72	72
Week 6				
All Patients	33%[2] (24/73)	42% (31/74)	38% (27/72)	47%[2] (34/72)
Week 12				
All Patients	**36%**[1] (26/73)	36% (27/74)	36% (26/72)	**44%**[1] (32/72)
CRP ≥ 10	18%[3] (5/28)	35% (11/31)	32% (9/28)	53%[3] (17/32)
CRP < 10	47% (21/45)	38% (16/42)	39% (17/44)	38% (15/40)

[1] The primary analysis endpoint involved first comparing 400 mg to placebo, p = .0.360 (Fisher's exact test, the Applicant's reported p-value of 0.278 used an uncorrected chi-square).
[2] At Week 6, a post-hoc comparison of 400 mg vs. placebo had nominal p = 0.111 (Fisher's exact test, the Applicant's reported p-value of 0.078 used an uncorrected chi-square).
[3] Post-hoc analysis of 400 mg vs. placebo in subset with Baseline CRP ≥ 10 mg/L had nominal p = 0.0094.

The primary analysis showed some trend toward a higher success rate at the highest dose, but the results fell well short of statistical significance (p=0.36 using an exact method). There was a more striking apparent effect of Cimzia in the subset with Baseline CRP ≥ 10, which presumably provided encouragement for designing the primary analysis of the Phase 3 studies to focus on that subset of patients. Examination of the time course of CDAI scores suggested a pattern in which all groups trended toward improvement, but in which all three active arms showed a similar trend toward greater improvement at Weeks 2 and 4, then stabilizing, although with 400 remaining slightly higher; placebo CDAI scores rose more gradually, but essentially caught up with the treatment arms between Weeks 8 and 12.

There were no marked differences in adverse experience across the groups. Anti-certolizumab pegol antibodies were found on at least one occasion in 32%, 32%, and 23% of the patients in the 100, 200 and 400 mg groups, respectively, but there was no apparent clinical significance to antibody development.

Phase 3 Studies

There were two pivotal Phase 3 efficacy studies. The first involved placebo-controlled induction and maintenance phases, and had both short-term (Week 6) and long-term (Weeks 6 and 26)

efficacy endpoints. The second study employed open-label induction and had a randomized control only for the maintenance phase, with efficacy evaluated long-term (Week 26).

Phase 3 Induction Study (031, PRECiSE I)

This was a randomized, double-blind, placebo-controlled, international multicenter study of the effect of Cimzia in adult patients with moderately to severely active Crohn's disease. The study randomized 662 patients to placebo or Cimzia 400 mg, administered SC. The study had an induction period lasting six weeks, followed by a maintenance period through Week 24.

Eligibility, Treatment, and Assessments

To be eligible, patients needed to be adults with a confirmed diagnosis of Crohn's disease for at least the past three months, and they were required to have a CDAI between 220 and 450 inclusive scored over the week before entry. Providing they had been at stable doses for the time periods specified in the protocol, patients were allowed have current treatment with 5-ASA's, chronic antibiotic therapy, oral corticosteroids up to the equivalent of prednisone 30 mg/day, immunomodulators, or topical agents. Patients who had been treated with other anti-TNFα agents could enter the study, but only if they had not had a severe hypersensitivity reaction to it and only if they had responded to the first dose. Patients were excluded if they had complicated Crohn's disease (obstruction, extensive surgery), additional intestinal diseases, prior TB, or significant other diseases. Details of the eligibility criteria can be found in the Clinical Review.

Patients were randomized with equal probability to Cimzia or placebo. Randomization was stratified based on the three factors of baseline CRP (≥ 10 mg/L vs. < 10 mg/L), use of corticosteroids at Baseline, and use of immunosuppressants at Baseline. All patients were treated at Weeks 0, 2, and 4 with either placebo or Cimzia 400 mg SC. Because Cimzia is supplied in vials of 200 mg each to be reconstituted in 1 mL water, each treatment was given as two SC injections of a 1 mL volume. Following Week 4, patients were given the assigned therapy at the same dose every four weeks. Dosing continued through Week 24. Concomitant Crohn's disease medications could be continued, but were to be kept stable unless toxicity required dose reduction. Oral corticosteroids could be continued, but investigators were encouraged to taper steroids according to guidelines in the protocol, starting between Weeks 8 and 12.

Major assessments that included CDAI, CRP, AE's, and basic laboratory testing, were performed at Weeks 0, 2, 4, 6, 8, 12, 16, 24, and 26. The IBDQ and SF-36 were done at Weeks 0, 6, 16, and 26. Further details are given in the Clinical Review.

Endpoints

The study was designed with two co-primary endpoints of clinical response at Week 6 and clinical response at both Weeks 6 and 26, in the stratum defined by Baseline CRP ≥ 10 mg/L. Analysis was to be done using the "ITT" population, with logistic regression adjustment for baseline corticosteroid use, baseline immunosuppressant use, and geographic region. Clinical response was defined as a decrease of at least 100 in CDAI compared to Baseline; subjects who withdrew or who had missing data at a given timepoint were considered non-responders from

that time onwards. The "ITT" population was defined by the Applicant as all patients who received at least one treatment and had at least one post-randomization observation.

Protocol-specified major secondary endpoints were: clinical remission and IBDQ response at Week 6 and at Weeks 6 and 26, with clinical remission defined as a CDAI ≤ 150 and IBDQ response defined as increase of at least 16 points in IBDQ compared to baseline. Analysis of these secondary endpoints was subject to a closed procedure conditioned the significance of the co-primary endpoints. Additional secondary endpoints listed in the protocol included corticosteroid tapering, fistula response, CRP, fecal calprotectin, and other patient-reported outcomes.

Results

A total of 976 patients were screened, and 662 were randomized. Two patients did not receive treatment, and the Applicant did not consider them further in any efficacy analyses. Of the remaining 660 patients, 329 were randomized to placebo, and 331 to Cimzia. The median age was 36 years, the percent male was 44%, and percent Caucasian was 95%. The median duration of disease was 5.1 years, 35% had previous resection, median Baseline CDAI was 286, 67% were considered inflammatory CD, and the fraction with Baseline CRP ≥ 10 was 46%. Almost all patients were currently on one or more "conventional therapy" agents; 39% were taking corticosteroids, 57% were taking 5-ASA's, and 38% were taking immunosuppressants. Overall, 28% of patients had had prior infliximab therapy, but information about response or tolerance to infliximab was not recorded.

Only 57% of patients completed the study, this was mainly the result of withdrawals due to lack of improvement or disease deterioration. The withdrawal rate was slightly higher in the placebo group (47%, vs. 39% for Cimzia). The major protocol deviations were non-compliance with scheduled visit for 16% of patients; 9% had deviations due to concomitant medications.

The table below presents the principal efficacy results of the study from the Applicant's analysis, together with some major secondary endpoint results:

Response and Remission in Study 031

	CRP ≥ 10			Overall		
	Placebo N=156	Cimzia N=146	p*	Placebo N=328	Cimzia N=331	p*
Response[1]						
Week 6	**26.0%** (40/154)	**37.2%** (54/145)	**.037**[3]	26.8% (87/325)	35.2% (115/327)	.016
Weeks 6 & 26	**12.3%** (19/154)	**21.5%** (31/145)	**.045**[3]	16.0% (52/325)	23.1% (75/327)	.024
Remission[2]						
Week 6	16.9% (26/154)	21.9% (32/145)	.294	17.2% (56/325)	21.6% (71/325)	.142
Weeks 6 & 26	8.4% (13/154)	13.1% (19/145)	.243	9.8% (32/325)	14.4% (47/325)	.072

*P-values as computed by Applicant using logistic regression including covariates of baseline corticosteroids, baseline immunosuppressants, and geographic region.
[1] Defined as a decrease from baseline in the CDAI by ≥ 100 points
[2] Defined as a CDAI ≤ 150 points.
[3] Specified co-primary endpoints were response rates at Week 6 and Week 6 and 26 in the CRP ≥ 10 stratum.

By this analysis the co-primary endpoints, clinical response at Week 6 and at Weeks 6 and 26 in the stratum defined by Baseline CRP ≥ 10, were both statistically significant. The difference in response rates between Cimzia and placebo at Week 6 was 11.2% in the CRP ≥ 10 stratum, and the difference was 9.2% for the Weeks 6 and 26 endpoint. In the overall group, the differences in response rates were 8.4% at Week 6, and 7.1% at Weeks 6 and 26. Although the treatment effect for the overall group appeared smaller, the statistical significance was stronger due to the larger number of patients.

For the secondary endpoint of clinical remission, the differences in rates were smaller (generally around 5% higher for Cimzia than for placebo), and none is statistically significant.

The Statistical Reviewer noted that the "ITT" analysis presented by the Applicant was not a true ITT analysis because it excluded three patients at Week 6 and four patients at Week 26. In addition, he found in the raw data an additional placebo patient that was listed as showing a response at Week 6. A re-analysis is given in the table below:

FDA Re-analysis of Primary Endpoints in Study 031

	CRP ≥ 10		
	Placebo N=156	Cimzia N=146	p*
Response			
Week 6	26.3% (41/156)	37.0% (54/146)	.0603
Weeks 6 & 26	12.3% (20/156)	21.5% (31/146)	.0721

*P-values computed by FDA as twice the one-sided p-value from Fisher's exact test (without stratification).

In the process of investigation of reasons for the discrepancy between the two analyses, patient 525 from site 22025 in Germany came to attention. This patient was in the placebo group, and the data recorded for Week 6 indicated a clinical response. In the 11/29/06 submission, the Applicant explained that this was a patient who was withdrawn "at Week 6" and therefore imputed as a non-responder. Examination of the CRF's showed that efficacy data were recorded for Week 6, but that he was also found to have elevated liver enzymes at that time, and he was then withdrawn from the study. There is no indication he received any rescue therapy before the efficacy evaluation. In this reviewer's assessment, that patient provided a reasonable representation of the placebo response through Week 6, and it would be appropriate to include him as a placebo responder in the Week 6 analysis. An additional observation on that patient was that his CRF's record a baseline CRP of 3, although he was recorded in the datasets as having baseline CRP ≥ 10. Thus, this case raised concerns about the quality of the datasets in addition to the problems that were uncovered at two of the four inspected clinical sites (see Clinical Site Inspections, below).

A second patient, 401, was identified by the Statistical Reviewer as showing discrepancies in the dataset regarding response. This patient received rescue medication at Week 2, and in this reviewer's opinion, the Applicant's case is stronger for imputing a non-response for that patient.

Results for the secondary endpoint of clinical remission (CDAI ≤ 150) were presented above. Analyses of the other major secondary endpoint of IBDQ response showed a (statistically significant) difference of 12% at Week 6 in the subgroup with Baseline CRP ≥ 10, but the differences in the rates at Weeks 6 and 26, and the differences in the overall population, either for Week 6 or for Weeks 6 and 26, were smaller and not statistically significant. Examination of the co-primary endpoints by various clinical subgroups is presented in the Clinical Review. Of note, the presence of antibodies did not show any clear relationship to efficacy.

Phase 3 Maintenance Study (Study 032, PRECiSE II)

This was a randomized, double-blind, placebo-controlled, international multicenter study of the effect of Cimzia in maintaining response in adult patients with moderately to severely active Crohn's disease. In this study 448 patients who had responded to Cimzia SC induction therapy

included, corticosteroid tapering, fistula response, CRP, fecal calprotectin, and pre-specified patient-reported outcomes.

Results

A total of 930 patients were screened and 668 patients participated in the open-label induction, and 428 were randomized. For the placebo and Cimzia groups, the median ages were 36 years in both, percentage of males were 52% and 43%, and percentages of Caucasians were 91% and 94%. The median durations of disease were 4.5 and 6.7 years, the median baseline CDAI scores were 314 and 317, and the percentages with CRP ≥ 10 were 48% and 51%.

The response rate to the open-label induction was 64 % (428/668). This was much higher than the Week 6 clinical response rates seen in either group for Study 031; however, this study had no control group during induction for comparison. The table below presents the principal efficacy results of the study at Week 26 from the Applicant's analysis, together with some major secondary endpoint results:

Response and Remission in Study 032

	CRP ≥ 10			Overall		
	Placebo N=101	Cimzia N=112	p*	Placebo N=210	Cimzia N=215	p*
Response[1]						
Week 26	**34%** (34/101)	**62%** (69/112)	**<.001**[3]	36% (76/210)	63% (135/215)	<.001
Remission[2]						
Week 26	26% (26/101)	42% (47/112)	.018	29% (60/210)	48% (103/215)	<.001

*P-values as computed by Applicant using logistic regression including covariates of baseline corticosteroids, baseline immunosuppressants, and geographic region.

[1] Defined as a decrease from baseline in the CDAI by ≥ 100 points

[2] Defined as a CDAI ≤ 150 points.

[3] Specified primary endpoint was response at Week 26 in the CRP ≥ 10 stratum.

In this study the primary analysis endpoint was highly statistically significant. Sensitivity analyses conducted by the Applicant supported the primary efficacy analysis conclusions.

The results for the major secondary endpoint of clinical remission and overall clinical response are included in the table above. For time to disease progression, analysis of Kaplan-Meier curves showed slower progression in the both the CRP ≥ 10 stratum and overall. The rates of IBDQ response were also statistically significant both in the CRP ≥ 10 stratum and overall, with a 22% difference in the CRP ≥ 10 stratum, and a 17% difference overall.

The Statistical Reviewer confirmed the statistical significance of the primary analysis and of the secondary efficacy endpoints as well. However, he noted that the efficacy findings were driven by the results in countries other than the U.S.; viz., for the CRP ≥ 10 stratum, the response rates

in the U.S. were 41% (5/12) for Cimzia and 42% (9/21) for placebo, while the rates outside the U.S. were 64% and 31%, respectively. He also commented that the evidence for the maintenance claim was mainly supported by this single study.

Ongoing Studies

The Applicant is also conducting two open-label extension studies, for which the primary objective is to obtain additional and longer-term follow-up safety data. Preliminary safety results from these studies were included in the safety database for this application.

Study 033 was designed to accept patients who had successfully completed either of the pivotal Phase 3 efficacy studies. Patients are continued on treatment with Cimzia 400 mg SC every four weeks. The duration was planned for ——— as part of the risk management plan presented in the application, the Applicant is proposing to continue treatment under this study for up to ——— The Applicant reports that 595 patients have been enrolled in the study.

Study 034 is also an open-label extension, but it is designed to enroll patients who withdrew from either of the pivotal Phase 3 efficacy studies due to an exacerbation of Crohn's disease. After a variable period of being off Cimzia, patients are re-induced with Cimzia using the same induction regimen as used in the pivotal efficacy studies, and then are maintained on Cimzia 400 mg SC every four weeks. The duration was planned for ———, as part of the risk management plan presented in the application, the Applicant is proposing to continue treatment under this study for up to ——— also. As of the clinical database cutoff date, 310 patients had been enrolled.

The sponsor also is developing Cimzia for RA ——— Efficacy studies are ongoing; however, safety data from that development program were included in this application. In particular, several of the cases of TB noted in the Clinical Review have come from the RA studies.

Clinical Site Inspections

Three clinical sites were inspected: Krakow, Poland (Dr. Hebzda, Study 033); Lodz, Poland (Dr. Chojnacki, Study 31); Warsaw, Poland (Dr. Petryka, Study 032); and Pretoria, South Africa (Dr. Honiball, Study 031). The inspections did not reveal any significant issues regarding the conduct of the study at the Krakow and Warsaw sites, and the DSI Reviewer recommended that data from these sites appeared acceptable for use in support of the BLA. The inspector at the Lodz site noted that one subject was entered who did not meet study criteria due to incorrect calculation of the CDAI score. At the site in Pretoria, the inspector uncovered errors in the transcription of information from patient diaries to the case report forms, such that the CDAI information was incorrect. The Applicant worked with the investigators to correct the information and submit updated data to the BLA. The inspectors recommended that the corrective actions were adequate. In the October 13, 2006, submission, the Applicant provided re-analyses for Study 031 using the corrected data from the Pretoria and Lodz sites.

The Agency (not this Division directly) has become aware of information that has raised concerns about the integrity of laboratory testing conducted by [redacted] and the testing done at their [redacted] site in particular. The [redacted] site conducted some of the laboratory testing for the Phase 3 studies for Cimzia. As of the date of this review, the Agency had not made a public statement regarding [redacted]. Thus, the acceptability of the clinical laboratory data for the clinical studies in this application is undetermined pending resolution of the potential problems with [redacted]

Safety

The reader is referred to the Clinical Review for full details of the safety analysis. The safety database consisted of safety information on 1350 subjects that received Certolizumab 400 mg, 212 patients that received induction doses of Cimzia followed by placebo in the Maintenance Study (Study 032), and 426 patients that received placebo in clinical studies.

Identification of drug-related toxicity in these studies is somewhat challenging, because patients with Crohn's disease would be expected to experience GI AE's over the course of several months observation, and the majority of patients did have AE's in these studies. Dr. Bezabeh reviewed reports of deaths and non-fatal SAE's, and he performed analyses of all adverse events reported in the clinical studies.

Six deaths in Crohn's disease studies were reported in this application. Three were assessed as possibly drug-related: small bowel ileus complicated with sepsis, intestinal obstruction, and Pneumocystis carinii pneumonia. The applicant also reported 13 additional deaths in ongoing RA studies. In the 12 cases with complete information, four were in the placebo group, and all were assessed as unlikely related, or unrelated, to study medication.

In the Crohn's disease studies there have been seven malignancies in patients receiving certolizumab pegol vs. three with placebo. The seven cases were two tongue neoplasms, basal cell carcinoma, small intestine carcinoma, dysplastic nevus syndrome, and Bowen's disease. In RA trials there have been four malignancies: tongue neoplasm, ovarian carcinoma, squamous cell carcinoma and non-Hodgkin's lymphoma.

Of the 1564 patients exposed to Cimzia, 255 patients had a total of 275 SAE's. The crude rate of 16% of patients was greater that the 9.6% rate in placebo patient, but exposure duration has been longer in Cimzia-treated patients. The majority of SAE's are referable to the GI tract, and most of these probably reflect underlying disease. However, another important category was serious infections, which were reported in about 4% of Cimzia-treated patients and 1.4% of the placebo group. This is consistent with the known risk of serious infections with other anti-TNFα agents. Of note, 13 cases of TB had been reported in the CD and RA development programs as of June 2006. The Clinical Reviewer observed slightly higher rates of AE's and SAE's in the subgroup with prior infliximab exposure.

The Clinical Reviewer did not identify a particular problem with hypersensitivity reactions. The rate of antibody formation was estimated at 7.6%. Formation of anti-certolizumab pegol antibodies did not have any evident correlation with adverse events.

Although approved anti-TNFα agents include warnings for cardiovascular, hematologic, and neurological AE's, the Clinical Reviewer did not find evidence of significantly increased risk for these events with Cimzia in the clinical trial database. The Clinical Reviewer did note that there was a slightly higher risk of increased liver enzymes with Cimzia compared to placebo, that that the overall rate was low.

The size of the clinical study patient population was felt to be adequate for safety evaluation.

Clinical Conclusions and Recommendations

The Clinical Reviewer concluded that the application did not provide substantial evidence that Cimzia had efficacy for reducing signs and symptoms of active Crohn's disease (i.e., inducing a response). The reviewer felt that the Maintenance Study (Study 032) had a strong outcome. However, without sufficient evidence that Cimzia could be used to induce the response to be maintained, and without clinical experience maintaining the response achieved by any other approved therapy, he did not feel there was sufficient information to be able to write adequate instructions for use. The Clinical Reviewer concluded that there was insufficient clinical efficacy data to approve the product, and that the Applicant should be sent a Complete Response letter describing the deficiencies in the clinical data.

The Clinical Reviewer concluded that the safety profile of Cimzia was reasonably consistent with that of other anti-TNFα agents, and there were no new safety signals beyond what has been seen for that class. The predominant safety finding was increased risk of infections, including serious infections, and increased risk of TB in particular. There was a higher observed rate of SAE's in the subgroup with prior infliximab exposure.

The Statistical reviewer concluded that the superiority of Cimzia over placebo in the Induction Study (Study 031), in the stratum defined by CRP ≥ 10, was not robust, and further, the evidence of an effect on the major secondary endpoints was not statistically persuasive. He concluded that the Maintenance Study (Study 032) had a statistically significant difference favoring Cimzia for the response rate at Week 26 in the stratum defined by CRP ≥ 10. The efficacy results in Study 032 were supported by the results for the secondary efficacy endpoints. However, the Statistical Reviewer was concerned that the results in Study 032 were driven by countries other than the U.S., and that the claim for maintenance was supported mainly by that single study; he considered the strength of evidence in support of a maintenance claim not statistically persuasive.

Advisory Committee

This application was not presented to an Advisory Committee.

Office of Surveillance and Epidemiology Consults

Review of the trade name "Cimzia" by DMETS identified some similarity to the approved products Amicar, Omacor, and Zenvia when scripted, and similarity in sound to Zenvia. However, DMETS concluded that the potential for confusion was minimal and that the name Cimzia was acceptable. DMETS also reported that DDMAC found the name acceptable from the promotional standpoint.

The Applicant's proposed postmarketing risk management activities , in addition to the usual routine pharmacovigilance. No RiskMAP was proposed. The OSE RMP Team felt that insufficient detail was provided concerning the proposed additional pharmacovigilance activities, and they provided recommendations regarding those plans to be conveyed to the Applicant (see OSE/RMP Team memo).

Pediatrics

No pediatric data were provided in this application. The Applicant requested a deferral of pediatric studies for patients aged 6 to 17 years and stated the Crohn's disease is uncommon in children less than 6 years of age. The Applicant also presented an outline of a proposed pediatric studies aimed at evaluating efficacy, safety, and PK of Cimzia in that pediatric population.

Regulatory Conclusions

This reviewer concurs with the recommendation of the Clinical Reviewer, that the efficacy data in this application are not sufficient to support approval. The Applicant should be sent a Complete Response (CR) Letter citing the deficiencies that need to be addressed.

In describing the clinical deficiencies, the CR Letter should include the following points:

1) There is not substantial evidence to support the use of Cimzia for inducing response in active Crohn's disease in the intended population, because Study 031 is only a single study that showed a small effect that is not statistically strong enough to provide substantial evidence by itself, and because the ability to maintain a response once it has been achieved, as shown in Study 032, is not viewed as sufficient to contribute substantial evidence of ability to accomplish the more significant task of inducing a response by reducing symptoms in patients who still have active disease.
2) We are not able to concur with the conclusions that Study 031 was a positive study for its primary objective, because we feel there was inadequate justification for excluding patient 525 from Site 22025 from the Week 6 results. Further, that patient appeared to have his baseline CRP results entered incorrectly in the database. Thus, we continue to have concerns about the reliability of the datasets, despite the corrective actions taken in response to the clinical site inspections.

3) Although Study 032 met its objective of showing the ability of Cimzia to maintain patients who have been brought into clinical response, there is insufficient information to provide adequate instructions for use based only on that result. This is because, in the absence of a finding that Cimzia is able to induce a clinical response, there is no information on the safety and efficacy of using Cimzia in conjunction with agents that are able to induce the response that Cimzia might maintain.
4) We are concerned that Study 032 showed no effect of Cimzia in the subgroup of U.S. patients. The Applicant should be asked to investigate if possible causes can be identified, such as patient characteristics, concomitant therapy practices, lots used, or other factors, that might explain the apparent differences between U.S. and non U.S. sites.

Because the best means to address these deficiencies will depend in part on the prospects the Applicant sees for being able to demonstrate acceptable efficacy for inducing a response, and because the issues involved are complex, the CR Letter should recommend that the Applicant meet with the Division to discuss the different possibilities for supplementing the product development program to provide an approvable application.

The two CMC concerns described in the Chemistry Executive Summary should be conveyed to the Applicant in the CR Letter. Also, the OSE RMP Team comments on the risk management plans should be conveyed to the Applicant.

Any specific comments on labeling should be deferred until the Applicant has provided an application that is otherwise approvable. The Applicant should be so advised.

Action on the pediatric deferral request can be delayed until the Agency is in a position to take an approval action for this product. The Applicant apparently did not request a waiver for children ages five and under. It is likely that such a waiver request could be justified, and it would be reasonable to grant such a waiver if the Applicant submits a request for it with adequate justification.

Safety findings will need to be updated with any subsequent submission, and the Applicant should be so advised in the CR Letter.

Because the Agency has not come to a conclusion regarding the specific actions to be taken in response to concerns about the integrity of data from ——— , no comment on this matter should be conveyed to the Applicant in the CR Letter. However, the Division will need to stay abreast of this issue, because it may have implications for any resubmissions by the Applicant in response to the CR letter.

CLINICAL REVIEW

Application Type	BLA
Submission Number	STN 125160/0
Letter Date	February 28, 2006
Stamp Date	March 1, 2006
PDUFA Goal Date:	December 29, 2006
Reviewer Name:	Shewit Bezabeh MD, MPH
Review Completion Date:	December 19, 2006
Established Name	Certolizumab pegol
(Proposed) Trade Name	CIMZIA
Therapeutic Class	TNF antagonist
Applicant	UCB, Inc.
Priority Designation	Standard
Formulation:	Aqueous solution
Dosing Regimen:	400 mg SQ at 0, 2 and 4 week followed by — — dosing
Indication:	Crohn's disease
Intended Population:	Moderate to severely active Crohn's disease

12/19/06

John E Hyde 12-19-06

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1 EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

It the recommendation of this Reviewer that the BLA receive a Complete Response (CR) letter for the following reasons.

1. The clinical development program consisted of a single induction and maintenance study, and a single maintenance study. The clinical development program lacks a second induction study.
2. The efficacy results of the single induction study CDP870-031 (PRECiSE I), failed to show substantial evidence of effectiveness to support approval of the application.
3. The single maintenance study (PRECiSE II) achieved its primary endpoint. There was substantial evidence of effectiveness to support CIMZIA for the maintenance of clinical remission in moderately to severely active Crohn's disease patients. However, if CIMZIA is approved for maintenance of clinical remission only, there is a lack of adequate data to provide directions of use for maintenance of quiescent Crohn's disease where induction may have been achieved by other treatment regimens.

The applicant should consider conducting a second induction study with possible higher doses and /or conduct other smaller studies that may provide data to guide the direction of use for maintenance of quiescent Crohn's disease.

1.2 Recommendation on Post marketing Actions

None warranted at this time

1.2.1 Risk Management Activity

None warranted at this moment

1.2.2 Required Phase 4 Commitments

None are warranted at this moment

1.2.3 Other Phase 4 Requests

None are warranted at this moment

1.3 Summary of Clinical Findings

1.3.1 Brief Overview of Clinical Program

The clinical development program for the submission includes two Phase 2 studies, two pivotal Phase 3 studies(PRECiSE I and II) in subjects with moderate to severe Crohn's disease (CD) and two ongoing long term extension safety studies (CDP870-033 and CDP870-034). The two pivotal Phase 3 studies constituted one single study each to assess induction and maintenance in subjects with moderately to severely active CD. The submission includes the safety and efficacy results from the two pivotal studies.

The primary objective of the two pivotal studies was to determine the efficacy and safety of CIMZIA 400 mg in moderately to severely active CD, when administered at weeks 0, 2, and 4 then every 4 weeks to week 24. The first pivotal study (PRECiSE I) is an induction and maintenance study, with primary objective of treating the signs and symptoms of active CD over a 26 week period. The co-primary efficacy endpoints of the study were the percentage of subjects with clinical response at Week 6 and Weeks 6 and 26 in the population strata defined by CRP $\geq$10 mg/ L at baseline.

The second pivotal study (PRECiSE II) was a randomized treatment withdrawal study. All subjects who entered the study were dosed with CIMZIA 400 mg at Weeks 0, 2 and 4, and assessed for clinical response at Week 6. Responders were then randomized to either CIMZIA 400 mg or placebo every 4 weeks as maintenance therapy to Week 24. Week 6 non-responders were withdrawn from the study. The primary efficacy endpoint was clinical response at Week 26.

1.3.2 Efficacy

The evaluation of efficacy for PRECiSE 1 Pivotal study was based on the following **co-primary efficacy endpoints:**

1. The percentage of subjects with clinical response at Week 6 in the stratum defined by CRP $\geq$ 10 mg/ L at Baseline.
2. The percentage of subjects with clinical response at both Weeks 6 and 26 in the stratum defined by CRP $\geq$ 10 mg/L at Baseline.

Review of data from the single induction and maintenance study (PRECiSE I) failed to show substantial evidence of effectiveness to support approval. The results obtained by FDA and applicant were divergent. In addition, applicant's marginally positive results for the co-primary efficacy endpoints were not supported by sensitivity analysis.

The applicant's analysis of the co-primary efficacy endpoints using the intent to treat population showed that the Week 6 clinical response rate was 37% for the CIMIZIA treatment group and 26% for the placebo group with a p-value of 0.037. For Weeks 6 and 26, the proportion of responders was 21.5% for the CIMIZIA treated group compared to 12.3% of the placebo group, resulting in a p-value of 0.045.

FDA performed analysis of the co-primary efficacy endpoints, where all randomized subjects were included and subjects with missing data were considered as non-responders. The results of the re- analysis showed that the proportion of responders at Week 6 was 32.9% and 25.6% (p = 0.205) for the CIMZIA and placebo group respectively. For Weeks 6 and 26, the rate was 18.5% and 12.2% (p= 0.149) for the CIMZIA and placebo group respectively.

A treatment difference of more 10% is usually considered clinically meaningful. The applicant had anticipated a treatment difference of 15-25%, and this treatment difference range was a factor in calculating the sample size of the study. The observed treatment difference of less than 10% during the induction and maintenance study is less that the accepted treatment difference to be considered clinically relevant.

In addition, sensitivity analyses on the respective co-primary efficacy endpoints were conducted by both the applicant and FDA. Analysis using observed data and best/worst case performed by the FDA and the applicant were consistent in that both analyses failed to show statistical significance for treatment difference between the CIMZIA group and placebo. The applicant's sensitivity analysis, where subjects with missing data were set to non-responders showed statistical significance for treatment difference, whereas the same analysis performed by FDA revealed a statistically non-significant result.

Based of the analysis, the treatment difference for the co-primary efficacy evaluation in the stratum defined by CRP≥ 10 mg/ L at Baseline failed to show superiority over placebo.

Analysis of the major secondary efficacy endpoints included clinical remission in the stratum defined by CRP ≥ 10 mg /L at baseline at Week 6 and Weeks 6 and 26, clinical response in the overall population, clinical remission in the overall population and IBDQ response in the stratum defined by CRP ≥ 10 mg /L at baseline. Analysis of the results showed that clinical remission at Week 6, and Weeks 6 and 26 in both in the stratum defined by CRP ≥ 10 mg /L at baseline and overall population failed to achieve results of statistical significance. The clinical remission results for the CRP≥ 10 mg/L stratum at Week 6 were 22% and 17% for the treatment and placebo groups respectively with a p-value of 0.294. Clinical remission for Weeks 6 and 26 in the CRP≥ 10 mg/L strata revealed response rates of 13% and 8% with a resultant p-value of 0.243 for treatment and placebo groups respectively. Clinical remission for the overall population also failed to achieve statistical significance with p-values of 0.142 (22% vs 17%) and 0.072 (14% vs 10%) for Week 6 and Weeks 6 and 26 respectively.

Analysis for clinical response at Week 6, Weeks 6 and 26 in the overall population was statistically significant for applicant's ITT population, but failed when re-analyzed for the Per Protocol population. Treatment differences on IBDQ was statistically significant at Week 6 (p=

0.041), but failed to achieve statistical significance for Weeks 6 and 26 in both in the stratum defined by CRP ≥ 10 mg /L at baseline with p-value of 0.156. For the overall population, IBDQ score results did not achieve the stated statistical significance at Week 6 and Weeks 6 and 26 with resultant p-values of 0.329 and 0.139 respectively.

Of Note: According to the FDA Statistical Reviewer, review of raw data has revealed that they may have discrepancies on two subjects' outcome response classification. Subject 401 from Germany received rescue therapy and should have been classified as a non-responder. Subject 525 from clinical site 22025 in Germany was in a placebo group. In the 11/29/06 submission, the Applicant explained that this was a subject who was withdrawn "at week 6" and therefore imputed as non-responder. Examination of CFR showed that efficacy data were recorded for Week 6, but subject was withdrawn from study due to elevated liver enzyme. Further CFR review showed that the subject CRP was 3, while subject was on subset on subjects with CRP> 10. This subject should be imputed as a placebo responder at Week 6. The data discrepancy noted also raises further concern about the quality of the data set.

Review of the maintenance CDP870032 (PRECiSE II) study demonstrated that subjects in the stratum defined by CRP ≥ 10 mg /L at baseline, who initially responded to open-label induction with CIMZIA had a statistically significant increase in the proportion of subjects attaining clinical response at Week 26 compared to placebo. The clinical response rate was 62% for the treatment group compared to 34% of the placebo group with a p-value of <0.001.

Analysis of the secondary efficacy endpoints: time to disease progression in both the CRP ≥ 10 mg /L at baseline stratum and overall population, clinical remission at Week 26 in both the CRP ≥ 10 mg /L at baseline stratum and overall population, and clinical response at week 26 in overall population, achieved statistical significant results supporting the findings of the primary efficacy. The results of the secondary efficacy endpoint for clinical remission for subjects in the stratum defined by CRP ≥ 10 mg /L at baseline and the overall population was as follows. For subjects in the stratum defined by CRP ≥ 10 mg /L at baseline the clinical remission rate was 42% and 26% in the treatment and placebo groups respectively (p= <0.001). For the overall population clinical response rate was 48% for the treatment group compared to 29% of the placebo group (p=<0.001).

1.3.3 Safety

Safety data submitted to this BLA included safety assessments from the Phase II, PRECiSE I and II studies, and a 120 day safety update with additional pooled data from the two ongoing open-label studies of the clinical development program for CD. Additional safety data from ongoing rheumatoid arthritis (RA) trials were also submitted for review. The overall safety profile reported from the pivotal studies and the 120 day safety update were as expected to that seen in other clinical trials and the post-marketing use of approved TNF antagonists. TNFα has a significant role in immune function, which means that patients receiving anti-TNFα treatment may be increased risk for malignancy, particularly lymphomas. In the overall population exposed to certolizumab there were only two incidences of lymphomas. A Hodgkin's lymphoma was diagnosed in a placebo group of the CD program and a non-Hodgkin's observed in RA

population. The overall incidence of malignancy reported in the CD studies was low. Serious infections, opportunistic infections, demyelinating diseases and infusion reactions have also been reported in patients treated with TNF blockers. Consis tent with the mechanism of action, subjects treated with CIMZIA were at slightly increased risk infections compared to placebo. Out of 2200 patients in the CD, rheumatoid arthritis, and psoriasis clinical studies, a total of 13 cases of TB have been reported. Other anti-TNF antagonists have been reported to increase risk for cardiovascular, hepatobiliary, hematologic and neurologic events. Review of cardiovascular, hematologic, and neurologic events in the clinical studies safety database did not indicate an increased risk for these events with CIMZIA treatment. The incidence of increased hepatic enzymes was slightly higher with CIMZIA treatment compared to placebo but the overall incidence was low (< 1%). Specifically, no PML cases were observed during the study period. The overall number of antibody-positive subjects was small and no apparent correlation between antibody development and adverse events or reduction in efficacy was observed.

The incidence of adverse events in a small subset of subjects with prior infliximab exposure was 84% compared to 76% rate in the subjects with no prior exposure. In addition, the incidence of serious adverse events in the prior infliximab exposed group was 20% compared to 15% of non-exposed group. The reasons for the observed higher adverse events in subjects with prior infliximab exposure are not clear and would require further evaluation.

This Reviewer is in agreement with the safety conclusions of the applicant in that the adverse events observed during the clinical development program have been seen with other TNF antagonist. No new safety signals, other than those observed with the treatment of anti-TNF agents, were observed on review of the submitted safety information.

1.3.4 Dosing Regimen and Administration

Both studies, PRECiSE I and II, used the currently proposed dosing regimen, which is CIMIZIA 400 mg Sub Cutaneously (SC) at Weeks 0, 2 and 4 followed by 4-weekly dosing. Review by the clinical pharmacology team has raised some concern about dose exposure and response that may need to be addressed by the applicant prior to final approval of the biologic.

1.3.5 Drug-Drug Interactions

The population PK analysis study (CDP870-039) showed that concomitant administration of corticosteroids, amino-salicylic acid analogs, or anti-infectives did not impact the pharmacokinetics of CIMZIA. Concomitant use of immunosuppressants had no clinically relevant impact of pharmacokinetics of CIMZIA.

1.3.6 Special Populations

Population pharmacokinetic analysis showed that Caucasians had typical clearance value approximately 15% higher than non-Caucasians, which is clinically significant.