Pharmacokinetics parameters in Japanese subjects were similar to those in Caucasian subjects following SC dosing at three dose levels in a biocomparability study.

No clinical studies were conducted to special population. CIMZIA has not studied in the population with renal, hepatic impairment and in the pediatric geriatric populations. Specific clinical studies have not been performed to asses the effect of gender on the pharmacokinetics of CIMZIA.

2 INTRODUCTION AND BACKGROUND

CD is an idiopathic, immunologically mediated, chronic inflammatory disease of the Gastrointestinal (GI) tract. CD may affect any portion of the GI tract; however, few Characteristic patterns of involvement account for most cases. Approximately 40-50% of patients have involvement of both the terminal ileum and cecum, 30 % have isolated terminal ileum disease, and 20% have disease confined to the colon. Overall, 75% of patients have small bowel involvement and about 90% of these patients have a terminal ileal involvement. Typically, the rectum is spared and the pattern of involvement is often discontinuous with intervening normal regions.

Characteristic signs and symptoms of CD include abdominal pain, diarrhea, rectal bleeding and fever. Typical secondary symptoms are weight loss, abscesses, fistulas, and anemia. Extraintestinal complications may include systemic symptoms such as arthralgias, malnutrition, dermatologic disorders, kidney stones and gallstones, inflammation of the eyes, mouth and liver disturbances. Along with the chronic nature of CD, there is often an unpredictable pattern of disease relapse and remission which can be extremely distressing to the affected patient.

Although CD is not usually fatal, it can progress to serious life-threatening GI complications such as obstruction, perforation, abscess, peritonitis, and hemorrhage. Such complications often result in surgery, life-long medical care, substantial impact of daily functioning and reduced quality of life.

Currently, there is no medical or surgical cure for the disease. The goal of therapy is to suppress the inflammatory response and maintain symptomatic control and health related quality of life while minimizing short-and long-term side effects of therapy.

2.1 Product Information

Certolizumab (cimzia) pegol is a recombinant, humanized, antibody Fab fragment with specificity for human TNFα. The Fab fragment is manufactured in *E Coli*, purified, and conjugated ——— to a polyethylene glycol (PEG) to extend the plasma half life. This is a new molecular entity (NME) with proposed indication for moderate to severely active CD population both for ——— maintenance of disease. The proposed dosing regimen is CIMZIA 400 mg to be administered SC at weeks 0, 2, 4 and followed by 4-weekly dosing.

2.2 Currently Available Treatment for Indications

Currently approved treatment indications include Budesonide and infliximab. Budesonide is a synthetic corticosteroid that is approved for mild and moderate active CD involving the ileum and /or the ascending colon. Infliximab is a chimeric monoclonal antibody against TNFα

approved for long-term treatment of CD in patients with moderate to severe disease that had inadequate response to conventional therapy.

In addition to the above FDA approved therapy, a number of unapproved agents are used to treat the disease condition. Some of these unapproved but routinely used medications include aminosalicylates, antibiotics, thiopurine agents and methotrexate.

2.3 Availability of Proposed Active Ingredient in the United States

This product is under review for marketing approval. No product with the active ingredient is currently approved in the US.

2.4 Important Issues With Pharmacologically Related Products

An increased risk of serious infections including TB, and lymphoma is associated with currently approved TNF-antagonist. A higher risk of lymphoma has been observed in patients receiving TNF blockers compared to the general U.S. Population.

2.5 Presubmission Regulatory Activity

The clinical development program for CIMZIA was initially submitted under IND 11197 for the study of CD population in 2001, by then applicant GD Searle (Pharmacia/ Monsanto). After the IND submission and prior to the End of Phase 2 meeting, ownership of the company has changed from Searle to Celltech. The following datelines are to highlight the important presubmission regulatory activities:

- On April 15, 2003, an End of Phase 2 meeting was held between FDA and Celltech in which a number of issues were discussed and agreed upon. During the meeting, the applicant had planned to discuss and conduct two induction studies (studies 009 and 010) and a safety study (study 011). According the reviewed meeting minutes, applicant's proposal for two induction studies were not discussed due to lack of time. It's not clear from the meeting minutes if agreement was reached on how many studies were planned for the clinical development program.

- May, 2003, the applicant submitted 4 protocols under IND 11197 for review. These protocols included CDP870-031 (PRECiSE I) an induction and maintenance study, CDP870-032 (PRECiSE II) a maintenance only study and protocols CDP870-033 and 034, an open-label extension studies. It is not clear to this Reviewer why the FDA accepted to review only one induction and maintenance study and not the required "two well controlled studies".

- On September 22, 2003, a teleconference was held between FDA and Pfizer (the new owner of the IND). The applicant agreed to use the nonresponder imputation technique

to evaluate missing data as opposed to the initially proposed Last Observation Carried Forward (LOCF) imputation technique.

- On September 27, 2005, a type B meeting to discuss the pre-BLA was held between FDA and UCB Pharma, Inc, the new owner for the BLA. During this meeting the clinical studies for the BLA were deemed adequate for review of marketing application.
- The BLA was submitted for review on February 2006.

2.6 Other Relevant Background Information

CIMZIA is not approved in any foreign country.

3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

3.1 CMC (and Product Microbiology, if Applicable)

The CDP870 drug substance is produced in a [redacted] production process [redacted]

The filling and storage of the bulk drug substance are adequately described. The bulk is [redacted] and is stored frozen. Adequate stability studies have been conducted to support the container closure system. [redacted] test are conducted after a filling process occurs. No review issues *noted.*

Conclusion
The drug substance section of the application as it relates to microbiology product quality is deemed acceptable. This application is recommended for approval.

3.2 Animal Pharmacology/Toxicology

CDP870 binds to human TNFα with high affinity and weakly cross-reacts with TNFα from non-human primates. However, CDP870 does not recognize TNFα from rodents. So, toxicity studies with CDP870 were conducted in cynomolgus monkeys. In repeat dose toxicity studies in monkeys, slight hematological changes (decreased hemoglobin, RBC and packed cell volume, increased WBC) were observed and these changes were reversible. In addition, vacuolation of several tissues, particularly hemolymphoreticular tissues were observed in animals receiving high doses. This may be related to the pharmacological actions of the drug. About 5% of the animals receiving i.v. or subcutaneous doses of CDP870, developed anti-CDP870 antibodies. CDP870 was not genotoxic in a battery of genotoxicity assays. As CDP870 does not cross-react with TNFα from rodents, reproductive toxicity studies (Segment I fertility and early embryonic development, Segment II teratogenicity and Segment III pre- and post- natal development) were conducted in rats using a [redacted] anti-TNF antibody (cTN3 [redacted]. cTN3 had no effects on the fertility and early embryonic development, it was not teratogenic and had no effects on pre- and post- natal development in rats. Thus, the preclinical studies with CDP870 suggest that the applicant's proposed dose of the product appears to be safe for the treatment of patients with Crohn's disease.

The applicant conducted adequate preclinical studies with CDP870 to determine the safety of the drug, and the applicant's proposed dose appears to be safe for the proposed indication. Thus, from a preclinical standpoint, the BLA application is approvable.

4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

4.1 Sources of Clinical Data

The source of clinical data for this review consisted of two phase II and two randomized, controlled, multinational clinical trials and a 120 day safety update of pooled data from the two ongoing extension studies. All studies were supported by the applicant.

4.2 Tables of Clinical Studies

Table 1: Completed Phase II and III studies

Protocol	Study Description	Number of patients	
		CIMZIA	Placebo
CDP870-004 Phase II	12 week, multiple dose, parallel group in Crohn's patients	219	73
CDP870-005 Phase II	4 wk single dose, parallel group	68	24
Phase III studies			
CDP870-031 (PRECISE I) Induction and Maintenance	26 week, multiple dose, parallel group, placebo controlled	331	329
CDP870-032 (PRECISE II) Maintenance	26 week, multiple dose, parallel group to assess maintenance of response	216	212

Table 2: Ongoing Long-term Safety Follow-up studies:

Protocol	Study Description	Number of patients	Duration
CDP870-033	Open-label Safety Study of patients completing studies 031 or 032	595	2 years
CDP870-034	Open-label Safety Study of patients withdrawing from 031 or 032	310	3 years

4.3 Review Strategy

The medical reviewer thoroughly reviewed the phase II and Phase III clinical trials both individually and together as pooled data. The additional 120 day safety data was also reviewed.

4.4 Data Quality and Integrity

Clinical investigator (CI) inspections were conducted at three international sites that enrolled a large number of subjects. According to the report filed by Division of Scientific Investigation, Good Clinical Practice Branch, " the studies at the sites appear to have been well conducted. With two exceptions, the regulatory deficiencies appear to have been minor and inadvertent. One subject was entered into the study who did not meet inclusion criteria. At one site the CDAI data was from the wrong reporting periods for 13 of 14 subjects. The applicant corrected the information following the inspection and forwarded the correct information to the agency." Re-analysis of these protocol deviations did not affect the outcome results. Data from these inspected sites were deemed acceptable for use in support of the BLA.

4.5 Compliance with Good Clinical Practices

The applicant stated that the study was carried out in accordance with Good Clinical Practice (GCP) regulations and guidelines.

4.6 Financial Disclosures

As required in 21 CFR 54.4, the applicant submitted a Food and Drug Administration Form 3454 and disclosure form (Form 3455) certifying that no investigator participated in any of the clinical studies had any financial interests to disclose.

5 CLINICAL PHARMACOLOGY

The Office of Clinical Pharmacology finds that the BLA is non-acceptable due to the lack of evidence that the applicant has identified the right dose yet for the treatment of active Crohn's disease, especially in the induction phase. The Office of Clinical Pharmacology recommends evaluation of higher doses for demonstrating efficacy during the induction phase. Further, the applicant should substantiate the design of the future trail using clinical trial simulation based on current data.

5.1 Pharmacokinetics

The single- and multiple-dose pharmacokinetics (PK) of certolizumab were characterized following administration of I.V. and S.C. doses of certolizumab pegol encompassing the proposed clinical dosage to healthy subjects and patients with Crohn's disease. Mean Cmax and AUC values increase in a linear manner with dose. Mean peak plasma levels occurred around 4 days post-dose, while mean terminal half-life of certolizumab was estimated at 13 days following S.C. administration.

Therapeutic biologics are not CYP450 substrates and as such, they are generally unlikely to be associated with PK drug-drug interactions. A drug-drug interaction study was conducted to evaluate the effect of administration of a single dose of CIMZIA on the steady-state PK of methotrexate. The study demonstrated the lack of a significant drug interaction between certolizumab pegol and methotrexate.

Considerable variability in the exposure levels has been observed for a fixed dose of 400 mg where the CDP870 concentration range is between 0.5 and 80 mcg/mL. As exposure is highly variable and there is a dependence of response on exposure, it may be important to individualize each patient's dose in order to attain the full potential for efficacy.

Future studies should explore higher doses. Since there is no concentration-safety relationship for serious adverse events, serious infection rates, urinary infection rates, and herpes viral infections rate, it seems reasonable to increase the dose frequency and/or amount.

The applicant should perform clinical trial simulations before the next trial to explore the impact of different analyses techniques on various drug effect sizes and dropout rates. To investigate dose titration value, dose should be increased for non-responders.

5.2 Pharmacodynamics

The Clinical Pharmacology studies include three healthy volunteer studies (CDP870-001, CDP870-003 and PHA-024), one study of the pharmacokinetics (PK) of certolizumab pegol in subjects with RA receiving methotrexate (MTX) (PHA-001), two phase II studies (CDP870-005 and CDP870-008) in patients with Crohn's disease and two pivotal phase III studies (CDP870-031 and CDP870-032) in patients with moderate to severe Crohn's disease. Furthermore, a population PK study (CDP870-039) was included to investigate the covariate effect on CDP870 pharmacokinetics.

Cross-study analyses are summarized from PK and PK/Pharmacodynamic (PD) modeling studies, which include a population PK study. Since the clinical pharmacology development program has concentrated on investigations of the PK and immunogenicity of certolizumab pegol, a detailed summary of investigations undertaken to determine the impact of antibodies to certolizumab pegol on PK and PD is also included.

Single intravenous (iv) and subcutaneous (sc) doses of certolizumab pegol have been shown to have predictable dose-related exposure with an approximately linear relationship between the dose administered and the maximum certolizumab pegol concentration (Cmax) and the area under the certolizumab pegol plasma concentration versus time curve (AUC) in both healthy volunteers and patients. The terminal elimination phase half-life (t1/2) was approximately 14 days for all dosage levels tested.

Certolizumab pegol has also been demonstrated to have a bioavailability of approximately 80 % when given by the sc route (CDP870-003). The dosing schedule used in the Phase III clinical development program was selected from the Applicant's PK modeling and simulation using data from Phase I and Phase II Crohn's disease and RA studies (CDP870-001, CDP870-002, CDP870-003, CDP870-004, CDP870-005 and CDP870-008). Based upon this dose-response modeling, the majority of improvement in efficacy over placebo was observed at doses of up to 400mg with smaller additional improvements at higher doses. PK modeling was also performed by the Applicant using data only from Study CDP870-003 and Study CDP870-005 to determine the optimum induction dose of certolizumab pegol in Crohn's disease. This simulation predicted that a regimen of 400 mg certolizumab pegol every two weeks during induction would maximize exposure to certolizumab pegol and maintain more consistent plasma levels.

Plasma concentration-time curves from the pivotal Studies CDP870-031 and CDP870-032 were consistent with predictions derived from these PK models and simulations. The population PK of certolizumab pegol were characterized at the end of the Phase III program using data from four studies in Crohn's disease (Studies CD870-005, CDP870-008, CDP870-031 and CDP870-032), three studies in healthy volunteers (Studies CDP870-001, CDP870-003 and PHA-024) and one study in RA (CDP870-004). This modeling (Study CDP870-039) was performed to estimate the inter-subject variability in the main pharmacokinetic parameters, and to identify important demographic and physiologic determinants of certolizumab pegol disposition. Demographic parameters investigated included age, body weight, gender, ethnicity, and body surface area. Health measures included creatinine clearance as a function of renal status, and liver function. The effect of ethnicity on PK was also investigated in a specific study (PHA-024) in which single sc doses of 100, 400 and 800 mg were given to healthy Japanese and Caucasian subjects. The PK profile was similar in both ethnic groups at all doses tested. The presence of antibodies to certolizumab pegol was assessed in all clinical studies except the MTX interaction study in subjects with RA (PHA-001). Antibodies have been detected in some subjects (Crohn's and RA) in all dose groups of certolizumab pegol tested to date. The percentage of subjects testing positive for antibodies appears to decrease with increasing dose level but increases with continued dosing, while the incidence of antibodies also appears to be lower with co-administration of immunosuppressants. In the clinical studies, presence of antibody was shown to have a significant effect on pharmacokinetics, with increased clearance of certolizumab pegol. This outcome was verified in the population PK analysis.

Certolizumab pegol is a PEGylated ——— protein Fab' fragment and as such is not expected to exhibit the same potential for drug-drug interactions as small molecule pharmaceutical agents. Formal drug-drug interaction studies have not been performed other than the potential for a PK drug-drug interaction between MTX and certolizumab pegol, which was examined in subjects with RA in Study PHA-001. Concurrent administration of a single 400 mg sc dose of certolizumab pegol with weekly, individualized, oral doses of 5 mg to 17.5 mg MTX did not have a statistically or clinically meaningful effect on the overall extent of plasma exposure (AUC) or Cmax of MTX. The potential for other drug-drug interactions was examined in the population PK analysis, CDP870-039, which showed that concomitant drug treatment such as steroids, aminosalicylic acid and analogues, or anti-infectives did not affect the pharmacokinetics of certolizumab pegol. Concomitant immunosuppressant treatment had a small

but statistically significant effect on certolizumab pegol pharmacokinetics, possibly indirectly by reducing the incidence of anti-certolizumab pegol antibody production.

5.3 Exposure-Response Relationships

The BLA includes two phase II studies (CDP870-005 and CDP870-008) in patients with Crohn's disease and two pivotal phase III studies (CDP870-031 and CDP870-032) in patients with moderate to severe Crohn's disease. Furthermore, a population PK study (CDP870-039) was included to investigate the covariate effect on CDP870 pharmacokinetics.

The key points to consider are:

- The primary analysis using baseline observation carried forward (BOCF) or last observation carried forward (LOCF) imputation technique needs to be revisited since the dropouts are not missing completely at random but depend on worsening of symptoms. Future studies should have an elaborate sensitivity analysis to address this issue. Further discussions between FDA and applicant are necessary, especially including the statistics groups.

- The probability of clinical response (defined as □CDAI $\leq$ -100) is clearly dependent upon the CDP870 concentration in study CDP870-005 at Week 6 where patients having lower concentrations (e.g., less than 10 mcg/mL) exhibit lower response rates.

- The relationship between the probability of response and the CDP870 concentration is not as clear for studies CDP870-031 and -032 at week 26, which might be due US vs. non-US sites, i.e. there is no significant exposure-response for US sites but it is significant for non-US sites which might be due to different background treatment received. The reason for observing a flat exposure-response relationship might be due to the observed exposures fall on the lower flat part of the exposure-response curve. Future studies should enroll considerable US patients and analyses should be stratified to address these issues.

- Considerable variability in the exposure levels is observed for a fixed dose of 400 mg where the CDP870 concentration range is between 0.5 and 80 mcg/mL. When exposure is highly variable and there is a dependence of response on exposure, then it could be important to individualize each patient's dose in order to attain the full potential for efficacy.

- Future studies should investigate higher doses. Since there is no concentration-safety relationship for serious adverse events, serious infection rates, urinary infection rates, and herpes viral infections rate, it seems reasonable to increase the dose frequency and/or amount.

- The applicant should perform clinical trial simulations before the next trial to explore the impact of different analyses techniques on various drug effect sizes and dropout rates. To

learn the titration value, increase dose for non-responders. Please discuss with Office of Clinical Pharmacology/Pharmacometrics group.

6 INTEGRATED REVIEW OF EFFICACY

6.1 Indication:

Treatment of active Crohn's disease

The applicant's proposed wording:

[redacted]

6.1.1 Methods

The clinical program to support the application for marketing the biologic included three Phase 1 clinical studies in healthy volunteers, two Phase 2 studies, two pivotal Phase 3 studies (CDP870-031 and CDP870-032) and two ongoing extension safety studies (CDP870-033 and CDP870-034). The clinical data from both randomized clinical Phase 3 trials was analyzed to evaluate the clinical benefit for subjects with active Crohn's disease who received Certolizumab. The FDA statistical reviewer confirmed the major efficacy analyses and performed sensitivity analyses to corroborate the findings of the applicant.

6.1.2 General Discussion of Endpoints

Study CDP870-031 (PRECiSE 1) was designed to assess induction and maintenance of clinical response, while study CDP870-032 (PRECiSE 2) examined maintenance of clinical response in subjects who responded to open-label induction therapy. In both the PRECiSE 1 and PRECiSE 2 studies, the percentage of patients with clinical response was measured based on a change from baseline of Crohn's Disease Activity Index (CDAI). A clinical response was defined as a patient having a decrease from baseline score of at least 100 points. A clinical remission was defined as a CDAI score of 150 points or less. CDAI is a universally accepted and validated measure of disease activity and has been used in a number of clinical trials. In addition, Inflammatory Bowel Disease Questionnaire (IBDQ) as defined by as a patient having an increase from baseline in overall IBDQ scores of at least 16 and the Harvey Bradshaw Index (HBI) as were collected.

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

3. The percentage of subjects with clinical response at Week 6 in the stratum defined by CRP ≥ 10 mg/ L at Baseline.
4. The percentage of subjects with clinical response at both Weeks 6 and 26 in the stratum defined by CRP ≥ 10 mg/L at Base line.

Clinical response was defined as ≥ 100 point decrease from Week 0 CDAI score.

The secondary endpoints for PRECiSE 1 study will allow evaluation in all patients irrespective of baseline CRP levels.

Secondary Endpoints:

The major secondary variables were In patients with CRP ≥ 10 mg/ L at baseline

- Clinical remission in the stratum defined by CRP ≥10 mg/L at Baseline
  - The percentage of subjects in clinical remission at Week 6
  - The percentage of subjects in clinical remission at both Weeks 6 and 26
- IBDQ response in the stratum defined by CRP ≥10 mg/L at Baseline
  - The percentage of subjects with IBDQ response at Week 6
  - The percentage of subjects with IBDQ response at both Weeks 6 and 26
- SF-36 sub scores for bodily pain and role physical in the stratum defined by CRP ≥10 mg/L at Baseline
- Clinical response in the Overall Population
  - The percentage of subjects with clinical response at Week 6
  - The percentage of subjects with clinical response at both Weeks 6 and 26
- Clinical remission in the Overall Population
  - The percentage of subjects in clinical remission at Week 6
  - The percentage of subjects in clinical remission at both Weeks 6 and 26
- IBDQ response in the Overall Population
  - The percentage of subjects with IBDQ response at Week 6
  - The percentage of subjects with IBDQ response at both Weeks 6 and 26
- SF-36 sub scores for bodily pain and role physical in the Overall Population

The evaluation of the primary efficacy for PRECiSE II was based on :

- The percentage of subjects with clinical response at Week 26 is the stratum defined by CRP≥10mg/L at Baseline (clinical response defined as a ≥ 100- point decrease from Week 0 CDAI score)

Secondary Efficacy Endpoints : PRECiSE II

The major secondary efficacy variables were:

- Time to disease progression in the stratum defined by CRP ≥10 mg/L at Baseline
- Clinical remission in the stratum defined by CRP ≥10 mg/L at Baseline (clinical remission defined as CDAI score of ≤ 150 points)
- IBDQ response (defined as an increase of ≥ 16 points from baseline) in the stratum defined by CRP ≥10 mg/L at Baseline
- SF-36 sub-scores for bodily pain and role physical in the stratum defined by CRP ≥10 mg/L at Baseline
- Clinical response in the Overall Population
- Time to disease progression in the Overall Population
- Clinical remission in the Overall Population
- IBDQ response in the Overall Population
- SF-36 sub-scores for bodily pain and role physical in the over all population

Reviewer's comments: The CDAI is a validated, weighted index for measuring disease activity based on a number of signs and symptoms of CD, physical examination and hematocrit measurement. CDAI has been utilized in a number pivotal clinical studies to assess the therapeutic efficacy of a number of drugs and biologics in the CD population. For both pivotal studies CDAI calculations were done at week 0 and at each subsequent follow-up visits. The following variables are components of in CDAI used for calculation.

Patient diary

- Number of liquid or very soft stools per day
- Abdominal pain rating (none, mild, moderate, severe)
- General well-being rating (general well, slightly under par, poor, very poor, terrible)
- Use of diphenoxylate, loperamide or other opioids for diarrhea

Clinical Examination

- Existence of complications including: arthritis or arthralgia, iritis or uveitis, erythema nodosum, pyoderma gangrenosum, aphthous stomatitis, anal fissure, fistula or abscess, other fistula, fever over 37.8 °C (100°F) during the past week
- Presence of abdominal mass (absent, questionable, definite)
- Body weight

Blood Sample

- Hematocrit value

The **Inflammatory Bowel Disease Questionnaire (IBDQ)** is a disease-specific self-administered questionnaire that was to assess health-related quality of life. The IBQD is a previously validated instrument with four parts based on 32 questions: 10 questions related to bowel movement, 5 to systemic symptoms, 12 to emotional functions, and 5 to social functions. Each question is scored by the patient from 1 to 7, where 7 represent the most favorable. Sub-

score is calculated for each set of questions, and missing values are replaced by the average of the other answers in the same sub-score. The total score is made up of the sum of the 4 sub-scores, and may thus range from 32 to 224. Scores < 170 indicate clinically active disease, scores ≥ 170 points indicate clinically inactive disease.

Reviewer's comment: Clinical interpretation of IBDQ measurements and meaningfulness as such these measurements are used as supportive data.

The **Harvey-Bradshaw Index (HBI)** is a validated instrument used to assess health-related quality of life based upon the following variables:

- General well-being the previous day (generally well, slightly under par, poor, very poor, terrible)
- Abdominal pain the previous day (none, mild, moderate, severe)
- Number of liquid or very soft stools the previous day
- Abdominal mass (none, questionable, definite and tender)
- Complications (arthralgia, uveitis, erythema nodosum, aphthous ulcera, pyoderma gangrenosum, anal fissure, new fistula, abscess)

6.1.3 Study Design

The first pivotal study, PRECiSE I, is a multi-center, double-blind, placebo-controlled, randomized within strata, parallel group study to assess the safety and efficacy of CDP870 in subjects with active Crohn's disease as defined by a Baseline CDAI score between 220 and 450 inclusive. The study was designed to assess the safety and efficacy of CIMIZIA in inducing clinical response and maintaining clinical remission over 26 week period. Following screening at Week-2, eligible subjects were randomized in a 1:1 ratio to receive either the study medication or placebo sc at Weeks, 0, 2, 4, 8, 12, 16, 20 and 24. Treatment groups were stratified at randomization according to three factors:

- CRP < 10 mg/ L or ≥ 10 mg/ L at Week 0
- Corticosteroid use at Week 0 or not
- Receiving immunosuppressant use at Week 0 or not

The second pivotal study, PRECiSE II, was a randomized withdrawal study to assess the effectiveness of CIMIZIA in maintaining clinical remission in subjects who demonstrate a clinical response (100 point decrease in Week 0 CDAI) at Week 6 following open induction. Responders to the open induction therapy were randomized to blinded 4 weekly dosing with 400 mg CDP870 or placebo 24 weeks. This was a multicenter, double-blind, placebo-controlled, randomized within strata, parallel group with 3 stratification factors:

- CRP< 10 mg/L or > 10 mg/L at Week 0
- Receiving corticosteroids at Week 0 or not
- Receiving immunosuppressants at Week 0 or not

Reviewer's Comment: Both pivotal studies were designed to evaluate the stated endpoints. The selected study duration is appropriate to assess safety and efficacy of chronic disease condition.

6.1.4 Efficacy Findings

Primary Efficacy Endpoints: PRECiSE I

The co-primary efficacy endpoints for the study were: **In the population with CRP≥10mg/L at baseline:**

- the percentage of patients with clinical response (at least 100-point decrease from Week 0 CDAI) at Week 6
- The percentage of patients with clinical response at both Weeks 6 and 26.

All patients randomized who received at least one injection of study medication and who had at least one efficacy measurement after the first medication administration, irrespective of any major protocol deviations were included in the intent to treat(ITT) population.

The ITT population was the primary population for analysis of efficacy.

All patients eligible for ITT population, who did not have any major efficacy protocol deviation, were included in the per-protocol (PP) population. The ITT population included 659 subjects with 331 randomized to treatment and 328 randomized to placebo groups respectively. One subject in the placebo group was dosed but had no post-baseline measurement of efficacy and therefore was excluded from the ITT population.

Primary endpoint: Clinical Response at Week 6 and Weeks 6 and 26 (applicant analysis):

The proportion of subjects in clinical response at Week 6 and Weeks 6 and 26 is presented in Table 3. At Week 6, 37% of subjects randomized to the CIMZIA group were in clinical response compared to 26% subjects that were randomized to the placebo arm, resulting in a p-value of 0.037. At Weeks 6 and 26, 21.5% of subject enrolled in the CIMZIA group and 12.3 % of subjects enrolled in the placebo group were in clinical response with a resultant p-value of 0.045.

Table3. Summary of subjects with Clinical Response at Week 6 and Weeks 6 and 26 in the CRP ≥ mg/ L Stratum at Baseline-ITT Population:

Week 6	Placebo (N=156)	CIMZIA (N=146)	p-value
Number of subjects	154	145	
Frequency (%)	40 (26)	54 (37)	0.037
Weeks 6 and 26	**Placebo (N=156)**	**CIMZIA (N=146)**	**p-value**
Number of subjects	154	144	
Frequency (%)	19(12.3)	31(21.5)	0.045

According to the applicant's analysis, both endpoints were statistically significantly higher in the CIMZIA group compared with the placebo group for the ITT population.

FDA's Review of Primary Efficacy Endpoints: PRECiSE I

The FDA statistical reviewer performed major efficacy and sensitivity analyses to corroborate the findings of the applicant as follows.

Of Note: An agreement was reached between the FDA and the applicant on November, 2003, to change the imputation techniques from Last Observation Carried Forward (LOCF) to nonresponder imputation for missing data caused by dropouts.

Based on the review of FDA statistician, some discrepancies (**table 4**) were noted between the applicant's analyses of clinical response at Week 6 , and Weeks 6 and 26 in the CRP≥10 mg/L at baseline stratum. The differences were noted when the analysis was performed with LOCF and without LOCF for the observed case in the CIMZIA group (see table below). No difference was observed for the placebo group.

Table 4:

Analysis	CR* at Week 6		CR at Weeks 6 and 26	
	CIMZIA	Placebo	CIMZIA	Placebo
LOCF	54	40	31	19
Observed	48	40	27	19

CR: Clinical Response

As seen from the above table, six subjects in the CIMZIA with missing observations were considered to be clinical response at Week 6 in the applicant's analysis with LOCF. Of these six subjects, four were considered to be in clinical response at Weeks 6 and 26 in the applicant's analysis. If the six subjects in CIMZIA group with missing observation were imputed as non-responders, then resultant the p-value will be as follows:

Table 5. Number of Subjects with Clinical Response at Week 6 , and Weeks 6 and 26 in the CRP≥10mg/L at baseline stratum: ITT population

Scheduled Visit	Placebo N= 156	CDP870 N=146	p-value
Week 6			
Frequency (%)	40(25.6)	48(32.9)	**0.2050**
Week 6 and 26			
Frequency	19(12.2)	27(18.5)	**0.1499**

As seen from the above table, changing the imputation from LOCF to non-responders resulted in p-value of 0.2050 and 0.1499 for Week 6 and Weeks 6 and 26 respectively. These p-values are much higher than the p-values of 0.037 and 0.045 reported by the applicant.

The applicant's superiority finding of CIMZIA treatment group compared to the placebo group for the co-primary efficacy endpoints of clinical response at Week 6 and Weeks 6 and 26 in the stratum defined by CRP≥10 mg/ L was dependent of the six subjects in the CIMZIA group with missing observation. However, as seen on the above table, the reported applicant analysis with LOCF might not be robust.

Intent to Treat Analysis

FDA statistical reviewer also performed ITT analysis. According to the reviewer, "the applicant's ITT did not include all randomized patients". The applicant's analysis included all randomized patients who received at least one injection of study treatment and who had at least one efficacy measurement after the first injection. The analysis excluded three subjects (2 in placebo and 1 in treatment group) at Week 6 and four subjects (2 in placebo and 2 in treatment group). FDA's analysis included all randomized patients and was deemed "true" ITT analysis. In these analyses, patients with missing data were considered to be non-responders.

The following table shows analysis performed by FDA statistical review based on "true" ITT population, where the above subjects were included.

Table 6. Number of Subjects with Clinical Response at Week 6 and Week 6 and 26 in the CRP≥10 mg/ L at baseline Stratum (FDA's ITT Population Analysis)

Scheduled Visit	Placebo N=156	CIMZIA N= 146	p-value
Week 6			
Frequency (%)	41(26.3)	54(37)	0.0482
Weeks 6 and 26			
Frequency (%)	20(12.8)	31(21.2)	0.0647

As opposed to the applicant's finding of statistical significance of the ITT population, FDA's "true" ITT population analysis failed to show statistical significant finding at the co-primary efficacy analysis of Weeks 6 and 26, while the clinical response at Week 6 was significant between the two treatment arms.

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Applicant's Analysis of Secondary Efficacy Endpoints, PRECiSE I:

Clinical Remission

Clinical remission was evaluated for both CRP ≥10 mg/L at base line stratum and the overall population at Week 6 and Weeks 6 and 26 for ITT population.

Table 7: Summary of Subjects with Clinical Remission at Week 6 and Weeks 6 and 26 in the CRP≥10 mg/L at baseline Stratum and overall population –ITT population

Time-point	CRP ≥10 mg/ L		Overall Population	
	Placebo	CDP870	Placebo	CDP870
Week 6				
N	156	146	326	329
Frequency (%)	26(17)	32(22)	56(17)	71(22)
p-value		**0.294**		**0.142**
Weeks 6 and 26				
N	154	145	326	327
Frequency (%)	13(8)	19(13)	32(10)	47(14)
p-value		**0.243**		**0.072**

The secondary efficacy analysis for clinical remission (as defined by CDAI score ≤150 points) in both the CPR ≥ 10 mg/L at Baseline stratum and the overall population, irrespective of CRP, showed that the treatment difference between the two groups were not statistically significant at both time points of Week 6 and Weeks 6 and 26.

Clinical Response in the Overall ITT and PP Populations

Table 8. Summary of Subjects with Clinical Response at Week 6 and Weeks 6 and 26 in the Overall population-ITT and PP population

Time point	ITT		PP	
	Placebo	CDP870	Placebo	CDP870
Week 6				
N	**325**	**327**	**277**	**267**
Frequency (%)	87(27)	115(35)	68(28)	83(36)
p-value		0.016		0.066
Week 6 and 26				
N	**325**	**325**	**209**	**199**
Frequency (%)	52(16)	75(23)	36(17)	50(25)
P-value		0.024		0.062

As seen from **table 8**, evaluation of clinical response (decrease of CDAI score ≥100 from base line for both the ITT and PP populations reveals different results. In the overall population, the proportion of subjects with clinical response was statistically significantly higher in the CDP 870 group compared to placebo in both time points of Week 6 and Weeks 6 and 26 in the ITT population. However, for the PP population, the treatment difference was not statistically significant for both time points of Week 6 and Weeks 6 and 26 with respective p-values of 0.066 and 0.062.

In addition, the applicant performed additional clinical response analyses for the CRP ≥10mg/L stratum at baseline for the PP population. The analysis showed that the treatment difference for CDP870 and placebo groups were not statically significance (p>.05) at Week 6 and Weeks 6 and 26 with p-values of 0.146 and 0.149 respectively.

Applicant's Sensitivity Analysis:

Sensitivity analyses were performed on the respective co-primary endpoints in the CRP≥ 10 mg/L at the baseline stratum. The applicant performed three sensitivity analysis using three different methods to handle missing data. These methods include:

1. Observed data:
2. Missing data set to non-responders (Worst case), after imputation techniques were applied and withdrawals were taken into consideration

3. Missing data randomized to active treatments were set to non-responders and subjects with missing data were data that were randomized to placebo were set to responders (best/ worst case- most conservative approach).

Tables 9, 10 and 11 below present sensitivity analysis performed by the applicant.

Table 9: Clinical Response in the CRP ≥10 mg/ L Strata at Baseline- Observed case

Scheduled visit	Placebo (N=156)	CIMZIA (N=146)	p-value
Week 6			
n	113	119	
Frequency (%)	40(35.4)	48(40.3)	0.434
Week 6 and 26			
n	64	73	
Frequency (%)	19 (29.7)	27(37)	0.456

Sensitivity analysis on both co-primary endpoints for the CRP≥10 mg/L baseline stratum on only observed cases revealed that treatment differences at both Week 6 and Weeks 6 and 26 failed to achieve statistical significance (p>0.05)with p-values of 0.434 and 0.456 respectively.

Table 10: Clinical Response in the CRP ≥10 mg/ L Strata at Baseline- Missing Set to Non-Response (Worst case)-ITT population

Scheduled Visit	Placebo (N=156)	CIMZIA (N=146)	p-value
Week 6			
n	156	146	
Frequency (%)	40(25.6)	54(37)	0.035
Weeks 6 and 26			
n	156	146	
Frequency (%)	19(12.2)	31(21.2)	0.047

Results from worst case, where missing data were set to non-responders after imputation techniques were applied and withdrawals were taken into consideration showed the treatment difference at both Week 6 and Weeks 6 and 26 were statistically significant (p>0.05) with respective p-values of 0.035 and 0.047

Table 11: Clinical Response in the CRP ≥10 mg/ L Strata at Baseline- Missing Set to Best/Worst case ITT population

Scheduled visit	Placebo (N=156)	CIMZIA (N=146)	p-value
Week 6			
n	156	146	
Frequency (%)	42 (26.9)	54(37)	0.061
Weeks 6 and 26			
n	156	146	
Frequency	20 (12.9)	31(21.2)	0.068

Sensitivity analysis where subjects with missing data were randomized to active treatment were set to non-responders and subjects with missing data who were randomized to placebo were set to responders (best/worst case) showed that the treatment differences at both week and Weeks 6 and 26 were not statistically significant (p.0.05).

As observed from the tables above, two of the three sensitivity analysis performed by the applicant showed that the treatment differences at Week 6 and Weeks 6 and 26 failed to achieve statistical significance.

Examination of Subgroups

The impact of different subgroups on the co-primary efficacy endpoints in the CRP≥10 mg/ L at baseline stratum tests for two-factor interactions between treatment and the subgroups. Statistical significance was assessed at 0.10 level.

Use of Immunosuppressant at Study Entry

The analysis of the co-primary efficacy endpoints (CDAI≥100 points from baseline at Week 6 and Week 6 and Weeks 6 and 26 in the CRP ≥ 10mg/L at baseline stratum) by use of immunosuppressants at study entry showed that the interaction between treatment effect showed 13 /57 (22.8%) and 18/55 (32.7%) response rate, respectively for the placebo and treatment group, with a p-value of 0.228 which was not significant at p (>0.10) level. The analyses by subjects using and not using immunosuppressants at baseline showed that the difference on the clinical response between the two treatment groups was not statistically significant (p>0.05) at Week 6, and Weeks 6 and 26.

Use of Corticosteroids at Study Entry

The analysis of the co-primary efficacy endpoints by use of corticosteroids at study entry and at Week 6, and Weeks 6 and 26 showed that the clinical response rate of 6/63 (9.5%) for the

placebo group and 13/56 (23.2%) for CDP870 group which a p-value of 0.039, which was statistically significant (p>0.05). Where as corticosteroid use at Week 6 was not statistically significant with a p-value of 0.105. The impact long-term use of corticosteroids with CIMZIA on clinical response may need further consideration. Analysis of the subgroup of subjects who were not using corticosteroids showed that the difference in clinical response between the two treatment groups were not statistically significant (p>0.05) at both Week 6, and Weeks 6 and 26.

Smoking status at Study Entry

The analysis of the co-primary efficacy endpoints by smoking status showed that interaction between treatment and smoking status was not statistically significant at (p>0.10). However, of the subjects in the subgroup of current smoker, 15 of 52 subjects (28.8%) had clinical response at Week 6 and Weeks 6 and 26 in the CIMZIA group compared with 6 of 52 subjects (11.5%) in the placebo group (p=0.030). The analysis performed at Week 6 for this subgroup showed no statistically significant (p>0.05) difference between the two treatment groups.

Previous Surgery for Crohn's Disease

The analysis of the co-primary efficacy endpoints by previous surgery for Crohn's disease showed that the interaction between treatment and previous surgery for Crohn's disease was not statistically significant (p>0.10). The treatment effect was still significant ($p \leq 0.05$) at Week 6 , and Weeks 6 and 26. The analyses in the subgroups showed that the difference in clinical response between the 2 treatment groups was not statistically significant (p>0.05) in the subgroup with previous surgery for Crohn's disease at both Week 6 , and Weeks 6 and 26. However, of the subjects in the subgroup with no previous surgery, 25 of 102 subjects (24.5%) had clinical response at Week 6 and Weeks 6 and 26 in the CIMZIA group compared with 15 of 111 subjects (13.5%) in the placebo group (odds ratio=2.06, p=0.049). The analysis performed at Week 6 for this subgroup showed no statistically significant (p>0.05) difference between the 2 treatment groups.

Duration of Crohn's Disease

The analysis of the co-primary efficacy endpoints by duration of Crohn's disease at Baseline showed that the interaction between treatment and duration of Crohn's disease was not statistically significant (p>0.10). The treatment effect was not significant (p>0.05) at Week 6 , and Weeks 6 and 26. The analysis of the subgroup of subjects with longer than or equal to Baseline mean Crohn's disease duration showed that the difference in clinical response between the 2 treatment groups was not statistically significant (p>0.05) at both Week 6 , and Weeks 6 and 26. In the analysis of the subgroup of subjects with less than Baseline mean Crohn's disease duration, the difference at Week 6 was statistically significant; 42 of 104 subjects (40.4%) had clinical response in the CIMZIA group compared with 21 of 81 subjects (25.9%) in the placebo group (p=0.043).
However, there was no statistically significant difference at Weeks 6 and 26.

Antibodies to CDP870

Analyses of clinical response and clinical remission by anti-CDP870 antibody status assessed the effect of these antibodies on the clinical efficacy of CDP870. Due to the continuous dosing in the study design, the antibody assays were conducted in the presence of CDP870,

which could result in false-negative results, therefore the most conservative approach was used. Subjects were considered to be anti-CDP870 antibody positive if they tested positive for antibody (>2.4 U/mL) on at least 1 study visit and negative if they tested negative for antibody (≤2.4 U/mL) at all visits.

In the CRP ≥10 mg/L at Baseline stratum, a total of 130 of 146 subjects (89.0%) were antibody-negative and 16 of 146 subjects (11.0%) were antibody-positive among subjects in the CIMZIA group. In the Overall Population, a total of 305 of 331 subjects (92.1%) were antibody-negative and 26 of 331 subjects (7.9%) were antibody-positive among subjects in the CIMZIA group.

Overall, no clear relationship between clinical response and anti-CDP870 antibody status was observed. In the CRP ≥10 mg/L at Baseline stratum, the proportion of subjects with clinical response who were antibody-negative ranged across visits from 28.7% to 38.0% compared with a range of 12.5% to 37.5% in those who were antibody-positive. Differences were not statistically significant (p>0.05) at Week 6 or Weeks 6 and 26. In the Overall Population, the proportion of subjects with clinical response who were antibody-negative ranged across visits from 25.8% to 37.0% compared with a range of 15.4% to 50.0% in those who were antibody-positive. Differences were not statistically significant (p>0.05) at Week 6 , and Weeks 6 and 26.

Overall, no clear relationship between clinical remission and anti-CDP870 antibody status was observed. In the CRP ≥10 mg/L at Baseline stratum, the proportion of subjects with clinical remission who were antibody-negative ranged across visits from 17.8% to 24.0% compared with a range of 6.3% to 37.5% in those who were antibody-positive (P-value not calculated). In the Overall Population, the proportion of subjects with clinical remission who were antibody-negative ranged across visits from 14.1% to 28.4% compared with a range of 3.8% to 42.3% in those who were antibody-positive (P-value not calculated).

It is worth noting that the small number of subjects who were antibody-positive compared with antibody-negative (approximately 10-fold) may have contributed to the large variability observed in the proportions of subjects with clinical response and clinical remission in the antibody-positive group, and could have hindered the ability to detect the relationship between efficacy and anti-CDP870 antibody status.

*The validity of antibody assay, antibody level cut off points with potentially introducing false positive results.

CDAI Score at Entry
The applicant conducted an analysis for CDAI score at entry with a subgroup analysis. The two subgroup categories were baseline CDAI of <335 and baseline CDAI score of ≥335. The analyses of the subgroup showed the difference in clinical response between the 2 treatment groups was not statistically significant (p>0.50) in either subgroup at Week 6 and Weeks 6 or 26. Additional analysis of the co-primary efficacy endpoint by CDAI score at entry showed that the interaction between treatment and CDAI score was not statistically significant (p>0.10).

Efficacy Findings: PRECiSE II

The ITT Population was the primary population for all assessments of efficacy. Because the number of subjects with major efficacy protocol deviations exceeded 15% of study subjects, the PP population was identified and key analysis were repeated for the PP population.

Primary Efficacy Results:

The primary objective of the study was the percentage of subjects with clinical response (a decrease in CDAI Score ≥ 100 points from baseline) at Week 26 in the stratum defined by CRP ≥ 10 mg/L from baseline.

A summary of clinical response in the CRP≥ 10 mg/L strata at baseline by treatment group is presented in the table below.

Table 12: Clinical Response in CRP≥ 10 mg/ L Strata at baseline with response at Week 26

Time Point	Placebo (N= 101)(%)	CIMZIA (N= 112)(%)	p-Value
Week 26			
N	101	112	
Frequency	34 (34)	69(62)	<0.001

The percentage of subjects with clinical response at week 26 in the Strata defined by CRP ≥ 10 mg/L at baseline was 69% which was statistically significantly higher compared to that of placebo which was 34%. Similar higher significant result was also observed in PP population.

The applicant performed the following three different sensitivity analysis for the above primary efficacy endpoint.

- Observed data with no imputation
- Missing data prior to classified as non-responders (after imputation technique has been applied)
- Subjects with missing data randomized to treatment classified as non-responders and subjects randomized to placebo classified as responders (Best / Worst Case)

Sensitivity analysis performed by applicant revealed that the results from the "observed case" revealed that the treatment difference at Week 26 was not statistically significant. The results from other two (worst case and best/ worst) sensitivity analysis showed that the treatment difference between the two groups was statistically significant. These results were confirmed by FDA statistician.

Secondary Efficacy Analysis: PRECiSE II

Time to Disease progression:

Time to disease progression was defined as the earlier of the following two events in subjects who were randomized to CIMZIA or placebo at Week 6 :

- An increase of $\geq$ 100 points in the Week 6 CDAI score
- An absolute CDAI score $\geq$175 points for at least 2 consecutive visits

In the CRP $\geq$10 mg/L at baseline and overall population, the probability of disease progression was lower in subjects in subjects receiving CIMZIA compared with subjects receiving placebo. The Kaplan Meier survival curves below present the results for both the Strata CRP $\geq$10 mg/L and overall population.

Table 13 : Kaplan Meier Survival Curve for Time to Disease Progression in the in the CRP ≥10 mg/L at baseline : ITT population

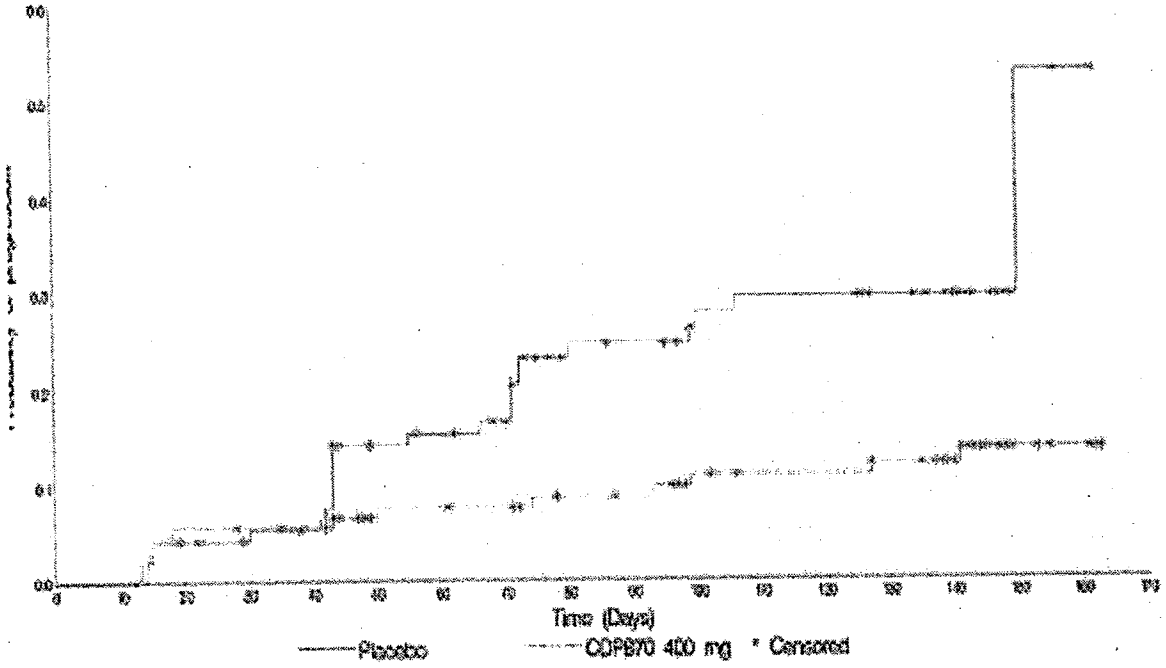
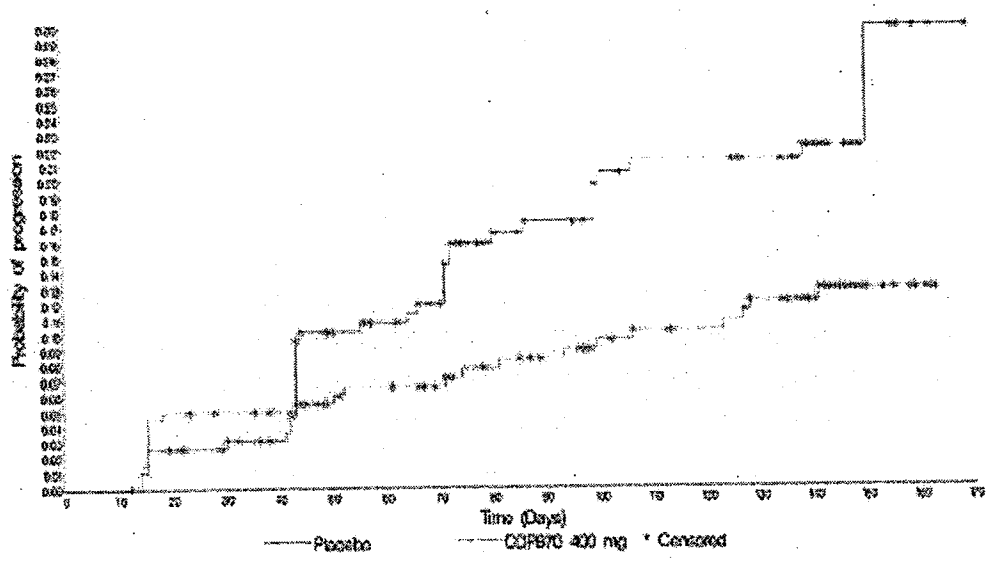


Table 14: Kaplan Meier Survival Curve for Time to Disease Progression in the Overall Population –ITT population.



As seen from the above two Kaplan Meier Survival curves, in both the CRP ≥ 100mg/L and overall population, the probability of disease progression was lower for the treatment group compared to the placebo group through out the study period.

Clinical Remission:

In the CRP ≥ 10 mg/ L at baseline stratum, 47 of 112 subjects (42%) randomized to CIMZIA , compared with 26 of 101 subjects (25. 7%) randomized to placebo were in clinical remission as defined by a CDAI score of ≤ 150 , at Week 26. In the overall population, the proportion of subjects in clinical remission in the CIMZIA treatment group was also statistically significant (48% vs 29%) compared to that of placebo group.

Table 15: Summary of Subjects with Clinical Remission at Week 26 in the CRP ≥10 mg/L at Baseline Strata and Overall Population: ITT population

Time-point	CRP≥ mg/L 10 mg/L		Overall Population		p-value
	Placebo	CDP870	Placebo	CDP870	
Week 26					
n	101	112	210	215	
Frequency	26(26%)	47(42%)	60(29%)	103(48%)	<0.001

Statistically significant clinical remission was achieved for both the CRP ≥10mg/L and the overall population for the CRP870 mg treatment group compared to the placebo group at Week 26.

Clinical Response

Clinical response for the overall population was conducted as secondary efficacy endpoint analysis.

Table 16: Summary of subjects in the overall population with clinical response at Week 26

Time-point	Placebo N= 210	CDP870 N= 215	p-value
Week 26			
n	210	215	
Frequency	76 (36%)	135 (63%)	<0.001

In the overall population at week 26, 135 of 215 (63%) subjects in the CDP870 group were in clinical response compared to 76 of 210 (36%) of the placebo treated group. The difference was statistically significant.

6.1.5 Clinical Microbiology

N/A

6.1.6 Efficacy Conclusions

PRECiSE I:

The primary objective of study PRECiSE I was to evaluate the efficacy and safety of sub-cutaneously administered CIMZIA in the reduction of signs and symptoms of subjects with Crohn's Disease when compared with placebo. The co-primary endpoints were prespecified to be the proportion of subjects who achieved a clinical response (a decrease in CDAI score≥100) at Week 6 and Week 6 and Weeks 6 and 26 in subjects with the stratum defined by CRP ≥ 10 mg/ L at Baseline.

Analysis of the primary efficacy endpoint revealed in divergent results between the analyses performed by the applicant and that of the FDA. 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% of the CIMZIA treatment group and 26% of the placebo group with a p-value of 0.037. For Weeks 6 and 26and 26, the proportion of responders was 21.5 % for the CIMZIA treatment group and 12.3% for the placebo group, resulting in a p-value of 0.045.

The applicant's analysis of the co-primary efficacy endpoints the intent to treat population all randomized subjects were not included. The intent to treat population included randomized patients who received at least one injection of study treatment and who had at least one efficacy measurement.

FDA's performed analysis of the co-primary efficacy endpoints, where all randomized subjects were included and subjects with missing data were considered as non-responders (as previously agreed between the FDA and the applicant). The results of the analysis showed that the proportion of responders at Week 6 was 32.9% and 25.6% for the CIMZIA and placebo groups respectively. For Weeks 6 and 26and 26, the rate was 18.5% and 12.2% for CP870 400 mg and placebo group respectively. Based of this analysis, the treatment difference for the co-primary efficacy evaluation in the stratum defined by CRP≥ 10 mg/ L at Baseline did not meet the primary endpoint.

Sensitivity analyses on the respective co-primary 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 significant for treatment difference between the CDP 870 400 mg group and placebo. Only the analysis where subjects with missing data were set to non-responders showed that the applicant's results were statistically significant for treatment difference, while that of the FDA revealed a statistically non-significant result.

The statistically significant result obtained by the applicant for the co-primary efficacy endpoint for the stratum defined by CRP≥ 10 mg/ L at Baseline, was dependent on outcomes of six subjects in the CIMZIA group with missing observation, which raises serious concern of the robustness of the data. The results failed to show substantial evidence for efficacy.

Analysis of secondary efficacy for clinical remission at Week 6 and Weeks 6 and 26and 26for the CRP≥ 10 mg/ L at Baseline stratum and the overall population irrespective of baseline CRP, differences in the proportion of subjects with clinical remission (CDAI score ≤150) between the two treatment groups were not statistically significant.

The single pivotal study designed to evaluate the efficacy of CIMZIA in inducing clinical response and maintaining clinical remission failed to show substantial evidence for efficacy. The limitation of the single induction study data is that the results are not robust enough. A second induction study with positive results is needed to support the proposed indication by the applicant.

PRECiSE II

The primary objective of study PRECiSE II was to compare efficacy of repeated 4-weekly treatment with CIMZIA versus placebo in subjects with active Crohn's Disease with CRP ≥ 10 mg/ L at Baseline, following successful open induction therapy with CIMZIA, in the maintenance of clinical response over 26 weeks.

The results of PRECiSE II study met the stated primary efficacy endpoints in that the percentage of subjects with clinical response at Week 26, in the stratum defined by CRP ≥ 10 mg/ L at Baseline was statistically higher in the CIMZIA treatment group compared with the placebo treatment group.

Analysis of results for the major 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, were also statistically significant, supporting the findings from the primary efficacy analysis.

As pointed out from the subgroup analysis performed by FDA statistician, the overall efficacy results were driven from subjects enrolled outside U.S

7 INTEGRATED REVIEW OF SAFETY

7.1 Methods and Findings

The data source for the review of safety data for CD is comprised from the following groups:

- 426 subjects from the placebo group
- 1350 subjects that received Certolizumab 400 mg
- 212 subjects who received placebo following open-label induction with Certolizumab 400 mg in study CDP870-032

□f the 1350 subjects who had received 400 mg CIMZIA, the safety data base for CD includes 1350 subjects dosed with CIMIZA 400 mg, 498 had been dosed for 6 months and 220 dosed for 12 months.

In addition the source of safety data included 650 subjects from rheumatoid arthritis studies
The cutoff for the clinical database used to generate the pooled summaries was August 19, 2005.

Table 17: Duration of subject Exposure CD population

Exposure in Months (%)	Placebo	CIMZIA 400 mg
≤ 3 (34)	218	410
> 3 to ≤ 6 (20)	31	227
> 6 to ≤12 (36)	177	485
> 12 to ≤18 (11)	0	220
> 18 (1)	0	8

7.1.1 Deaths

In the CD studies to date, six deaths occurred in subjects exposed to CIMZI.

Reviewer's Comment: The following three deaths were deemed possibly related to the study drug.

- **Subject 35/119:** A 60 year old female with history of small bowel ileus, received 3 doses of cimzia 200 mg. About two months after the of last dose, hospitalized with complications of small bowel ileus and steroid induced myopathy. Patient underwent resection of terminal ileum and roof of bladder on [redacted]. Post-operative course was complicated with Staphylococcus aures (MRSA) and Adult Respiratory Distress Syndrome (ARDS) resulting in respiratory failure and death. It was felt by the investigators that the ileus could

be possibly related to study medication, while the complications are unrelated to study drug.

Reviewer's Comment: The Reviewer agrees with the assessment of the investigator that the cause of death could be possible attributed to the study drug. The study drug, as immune suppressant can predispose the patient to infections that may lead to ileus. In addition, the study drug could have contributed to the post-operative complications of MRSA and ARDS.

- **Subject 33006/610:** A 58 year old female with medical history significant for only CD enrolled in study CDP870-033 after completing a 26-week enrollment in study CDP870-031. Patient died due to intestinal obstruction. Cause of death was felt to possibly related to study medication.

Reviewer's Comment: Similar to the above subject, the study drug could have contributed to subject's death. Intestinal obstruction could be a result of a number of factors such infection, abscess, mass effect or others. The study drug can attribute to the cause of death by altering the host's immune function or by lack of efficacy and worsening of disease condition that may have resulted in intestinal obstruction.

- **Subject 39018/0487**: A 51 year old Caucasian female received one dose of Certolizumab 400 mg, following withdrawal(due to worsening symptoms) from study CDP870-031 in study in which she received placebo and subsequently enrolled and in study CDP870-034. She withdrew after receiving parenteral prednisone for exacerbation of CD. She was diagnosed with bleeding duodenal ulcer and received a number of therapies including MTX, infliximab, azathioprine and increased prednisone dose. At 18 weeks after withdrawal from study CDP870-034 she was diagnosed with Pneumocystis carinii and died due to Pneumocystis carinii alveolitis.

Reviewer's Comment: The reviewer is in agreement with the investigator's possibly drug related attribution for the cause of death. CIMIZA and other TNF antagonist interfere with the host's immune function and some times predispose the subject to a number of infections, including opportunistic infections such Pneumocystis carinii.

Reviewer's Comment: The following three deaths listed below were assessed as unrelated to the study medications.

- **Subject 45102/0017:** A 22 year old while male experienced grand mal seizure AE after receiving two doses of study medication. Ten months after withdrawing from study, subject died with acute myocardial infraction and metastatic lung cancer listed as the cause of his death in his death certificate.

- **Subject 45093/2815:** A 36 year old male with past medical history of depression, was found dead after receiving a single dose of study medication. An autopsy showed fentanyl overdose as the cause of death.
- **Subject 43006/2231:** A 50 year old male with CD completed study CDP870-032 and was enrolled in study CDP870-033 receiving 11 doses of cimzia. Subject died of mechanical

asphyxiation due to a piece of meat blocking trachea.

Table 18. Listing of death from the clinical development program

Study #	Subject	Dose	AE	Days on Treatment	Investigator attribution
870-005	35/119	200 mg	Small bowel ileus , Sepsis, MRSA	9/20/01- 11/16/01	Possible
870-031	45102/0017	400 mg	Acute MI , Lung CA with Mets	2/3/04- 2/17/04	Unrelated
870-032	45093/2815	400 mg	Fentanyl overdose	Single dose on 10/28/04	Unrelated
870-033	33006/610	400 mg	Intestinal obstruction	275 days on treatment	Possible
870-034	39018/0487	400 mg	Pneumocystis carinii	One dose	Possible
870-032	43006/2231	400 mg	Mechanical asphyxiation	11 doses	Unrelated

Reviewer's Comment: As mentioned above consistent with the mechanism of action of TNF blocking agents, treatment such CIMIZIA can possibly contribute to the three death by interfering with the subject immune system that can predispose the patient to opportunistic infections. In addition, lack of efficacy can result in disease deterioration that can manifest as ileus or small bowel obstruction.

Deaths in studies of subjects with Rheumatoid Arthritis ;

The applicant has also submitted a preliminary listing of AEs leading to death for the pooled ongoing studies for the RA population. The applicant reports that in RA studies, studies CDP870-015 and CDP870-027, to date 13 subjects have experienced fatal AEs. Of these, seven are from open-label, three from ongoing double-blind in which the treatment allocation is unknown and one from an ongoing blinded study in which the treatment code was broken and the patient was found to be assigned to placebo. The submitted listings are not complete as some of the studies are still ongoing. According to the submitted listing of the 13 deaths reported, 7 were from open-label, 4 deaths were from blinded studies later assigned to placebo group, one death due to bronchopneumonia was assigned to possibly attributed to study medication and one was reported with incomplete summary after the cut off date.

The fatal events for the other 12 subjects were assessed by the Investigators as unlikely related or unrelated to the study medication.

Reviewer's comments: The clinical development programs for CIMZIA RA have over 650 subjects randomized with various exposure durations. To date, 13 subjects have experienced fatal AEs. Of these, 5 were assigned to placebo group or to subjects with single exposure. Thirteen deaths in 650 exposed subjects of which 5 were from placebo. For the seven fatalities appear have a cardiac origin (MI, Cardiac arrest, pericardiac effusion). Patients with rheumatoid arthritis are also predispose to pericardiac disease. The number of deaths observed

in the RA population appears high. At this time, it's difficult to conduct a complete assessment due to ongoing studies, incomplete data and due to unknown randomization. However, the excess death rate warrants further evaluation.

7.1.2 Other Serious Adverse Events

Malignancies

In the clinical studies for CD studies, 7 (0.5%) subjects randomized to CIMZIA and 3 (0.7%) subjects randomized to placebo reported a malignancy. Malignancies reported in the Certolizumab group included tongue neoplasms (n=2), basal cell carcinoma, small intestine carcinoma, dysplastic nevus syndrome, and a Bowen's disease. The malignancies reported in the placebo-treated group were tongue neoplasms, cervical carcinoma, and Hodgkin's disease.

In addition, there were 4 malignancies reported in subjects exposed to CIMZIA in RA clinical studies. These included tongue neoplasm, ovarian carcinoma, squamous cell carcinoma and non-Hodgkin's disease. The subject with non-Hodgkin's disease received three doses of CIMIZIA 200 mg sc during the phase and during open label study. The etiology of non-Hodgkin's lymphoma is deemed possibly related to study medication.

Reviewer's comments: TNFα has reportedly a significant role in immune function, which means that patients receiving anti- TNFα treatment may be an increased risk for malignancy, particularly the potential for lymphoma. In the overall population exposed to CIMZIA 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 etiology of non-Hodgkin's lymphoma deemed possibly related to the study drug. It should be noted that there is a higher risk of lymphomas with RA.

Serious Adverse Events:

The number of subjects with serious adverse events is presented in the table below. The CD treatment group had 17% of subjects who had one or more SAEs compared to 10% in the placebo group. By system-organ class, the greatest number of SAEs occurred in the GI system disorders class, due to worsening of colitis and its associated symptoms. The system-organ class of those SAEs that occurred in greater numbers in the treatment group compared to placebo was: GI (10 % vs 5.4%), Pyrexia (0.4 vs 0.2), infections and infestations (4% vs 1.4), perianal abscess (1.3% vs 1.2) and renal and urinary system (1% vs 0.2). Most these SAEs occurred in greater than 1% of the treatment group.

Table 19: Summary of serious AEs by System Organ Class and Preferred Term (MedDRA Classification) Adult Crohn's Disease –safety population

Primary Sytem Organ Class	Placebo (N=426) (n %)	CIMZIA (N=1350) (%)
Total SAEs	**54 (9.6)**	**337 (17)**
Blood and Lymphatics	1 (0.2)	9 (0.7)
Cardiac Disorders	1 (0.2)	0
Congenital (dermoid)	1 (0.2)	0
Ear and Labyrinth	0	1 (0.1)
Endocrine (goitre)	0	1 (0.1)
Eye	1 (0.2)	2 (0.1)
Gastrointestinal	**28 (5.4)**	**173 (10.0)**
Crohn's Disease	**16 (3.3)**	**90 (6.0)**
Intestinal obstruction	**2 (0.5)**	**8 (0.6)**
Perirectal abscess	**1 (0.2)**	**5 (0.4)**
Small intestinal obstruction	**0**	**10 (0.7)**
General & administration site	3(2, 0.5)	10 (0.7)
Hepatobiliary	1 (0.2)	2 (0.1)
Immune system	0	2(2, 0.1)
Infections & infestations	**6 (1.4)**	**65 (4.3)**
Perianal abscess	**3 (0.7)**	**18 (1.3)**
Injury, poisoning, Procedural	1 (0.2)	12 (0.7)
Metabolism and Nutrition	0	8 (0.5)
Musculoskeletal & Connective tissue	3 (0.7)	8 (0.5)
Neoplasms	2 (0.5)	3 (0.2)
Nervous System	0	4 (0.3)
Pregnancy and Perinatal	0	5 (0.3)
Psychiatric	1 (0.2)	1 (0.1)
Renal and Urinary	**1 (0.2)**	**14 (1.0)**
Nephrolithiasis	**1 (0.2)**	**6 (0.4)**
Reproductive and Breast	0	2 (0.1)
Respiratory, thoracic mediastinal	0	6 (0.4)
Skin and subcutaneous tissue	2 (0.5)	2 (0.1)
Social circumstances	0	1 (0.1)
Surgical & medical procedure	1(0.2)	0
Vascular	0	2 (0.1)

The high number of SAEs, particularly the GI SAEs in the overall population compared to the controlled studies is mainly from subjects enrolled in the open-label extension studies CDP870-033 and CDP870-034. There were 105 events in 76 patients (N=310) in study 870-033 and 59 events in 35 subjects for study 870-034. This was felt due to the number of subjects who failed the controlled studies and then enrolled into the open-label extension study.

Reviewer's Comments: For comparison between of placebo and treatment group and incidence of serious adverse events, please see appendix 10 of each pivotal study's safety assessment.

In RA population, 11% of subjects in the treatment group, and 6.8% of subjects in the placebo group experienced SAEs. SAEs occurring in the greatest percentage of subjects in the CIMZIA 400 mg group were in the musculoskeletal and connective tissue disorder (1.8%), surgical and medical procedure (1.8%), infections and infestations and Nervous system (1.5% each) and included RA (1.2%), and rash (0.6%). In the placebo group, SAEs occurring in greatest percentage of subjects were in the musculoskeletal and connective tissue disorder (1.5%), nervous system disorders (1.2%) , and GI and general disorders and administration site conditions (0.9%) and included RA (0.9%) , chest pain and vomiting (0.6% each).

Serious infectious Adverse Events:

In the overall CD population, infections SAEs were 4.4% in the treatment group as compared to 1.4% of the placebo group. The most frequent infections SAEs were perianal abscess (1.3 % vs 0.7%), abdominal abscess (0.5% vs 0%) and intestinal abscess (0.3% vs 0%) in the treatment and placebo group respectively. The table below presents the summary of serious infections in the CD safety population.

In the controlled studies, infections SAEs were reported in a comparable percentage of subjects in the treatment group and the placebo group, although the percentage was higher in the overall population. This is due to the longer exposure and in addition, some subjects who received only three doses in the PRECiSE II study and did not respond were then enrolled into the ongoing extension studies.

Table 20: Summary of serious infections: Crohn's Disease Population

Preferred Term	Placebo (N=426)(%)	CIMZIA (N=1350)(%)
Any serious infection	**6 (1.4)**	**66 (4.4)**
Perianal abscess	**3 (0.7)**	**18 (1.3)**
Abdominal abscess	**0**	**7 (0.5)**
Intestinal abscess	**0**	**4 (0.3)**
Staph infection	**0**	**3 (0.2)**
UTI	**0**	**3 (0.2)**
Gastroenteritis	**0**	**2(0.1)**
Perineal abscess	**0**	**2(0.1)**
Pneumonia	**0**	**3(0.2)**

Reviewer's comment: Many of the infections in SAE were in GI serious, which is expected in the population of subjects with active CD. However, the higher percentage observed in the treatment group compared to the placebo group, especially with regard to abscess is of a concern. If some of these abscesses are due to fistulas, then one would question possible lack of therapeutic benefit from the biologic agent..

Tuberculosis (TB) and Opportunistic infections:

Patients treated with approved anti-TNF α agents are at increased risk for infections and it recommended that patients receiving such biologic agents be screened and monitored closely for the development of latent TB. Patients participating in the CIMZIA clinical program were screened for latent or active TB. A total of 13 CIMZIA treated cases of TB have been reported as June 06, 2006. Of these, three cases were from CD population, one case from the psoriasis and nine cases from the RA trials.

In addition, two subjects (one from CD and one from RA) were diagnosed with Pneumocystis carinii pneumonia (PCP). The patient with CD withdrew from the study, due to disease deterioration, was subsequently treated with methotrexate, azathioprine, infliximab and steroids before diagnosis of PCP which was proven fatal.

Reviewer's comments. Although expected with such kind of immunologic therapy, the incidence of TB 0f 13/ 2000 exposed appears in excess than what would be expected after pre- screening of subjects prior to therapy. In the future, more stringent screening methods such chest CT should be considered.

7.1.3 Dropouts and Other Significant Adverse Events

7.1.3.1 Overall profile of dropouts

Of 1350 subjects in the CD population who started a study and received at least one dose of Certolizumab 400 mg, 38% completed at least one study and 52% withdrew from at least one study. The most common reasons for withdrawal in the treatment group were lack of improvement/disease deterioration (33%), AEs (19%) and patient decision (10%). The most common reasons for withdrawal in the placebo group were lack of improvement / disease deterioration (31%), AEs (11%) and clinical decision (5%).

Table 19 : Summary of subject accountability: CD population

	Placebo (N= 426)	**CIMZIA (N= 1350) (%)**	**All CDP870 dose (N= 1564)(%)**
Commenced at least 1 study	**426**	**1350**	**1564**
Completed at least 1 study	250 (59)	513 (38.0)	665(43)
Ongoing in studies 033 & 034	0	668 (50)	668 (43)
Withdrawn from at least 1 study	179 (42.0)	699 (52)	761(49)
Reason for withdrawal			
AE	**48(11)**	**257(19)**	**275(18)**
Protocol Non-compliance	2 (0.5)	18(1)	18(1)
Subject decision	16 (4)	137 (10)	152(10)
Clinical decision	**22(5)**	**89 (7)**	**99 (6)**
Lost to F/U	0	17 (1)	18(1)
Lack of improvement	**133 (31)**	**439 (33)**	**486 (31)**
Other	7(1.6)	48 (4)	48(3)

7.1.3.2 Adverse events associated with dropouts

In the overall CD population, 223 of 1277 subjects (17.5%) in the treatment group experienced AEs leading to withdrawal, compared with 21 of 329 subjects (6.4%) in the placebo group. The most frequent AE that led to withdrawal were GI disorders (11.5% vs 2.7%) and infections and infestations (3% vs 1.5%) in the Certolizumab group vs placebo group respectively. AEs leading to withdrawal that were reported in at least 0.5% of subjects in the Certolizumab 400 mg group were CD (8.5% vs 2.1%), perianal abscess (0.8% vs 0.3%), abdominal pain (0.5% vs 0.3%),

anemia (0.5% vs 0%), small intestinal obstruction (0.5% vs 0%) and abdominal abscess (0.5% vs 0%) in the treatment group vs placebo group respectively.

The rate of AEs leading to withdrawal was 6.4% in the controlled group compared to 17.5% in the overall CD population. The AE CD was the most common AE leading to withdrawal for subjects in the Certolizumab 400 mg group in both the controlled studies (18 of 759 subjects, 2.4%) and overall population (109 of 1277 subjects, 8.5%), and was lower in the controlled studies, compared with the overall population. *This difference is attribute to the inclusion of non-responders to the overall population from study CDP870-032 who withdrew due to CD AEs during the open-label stage of the study (24 of 668, 3.6%) and data from the open-label extension studies , CDP870-033 (18 of 583, 3.1%) and CDP870-034 (49 of 310, 15.7%)*

7.1.3.3 Other significant adverse events

Overall, 555 of 1350 subjects (41.1%) in the CIMZIA group reported infection AEs, as compared to 129 of 426 subjects (30.3%) in the placebo group. The most frequent infection AEs in CIMZIA vs placebo group, were nasopharyngitis (9.4 % vs 7.7%), and urinary tract infections (UTI) (7.4% vs 5.2%). The most common viral infections were Influenza (4.8% vs 4.5%), Herpes simplex (2.4% vs 0.2%), other viral infections(1.3% vs 2.8%), and gastroenteritis (0.4% vs 0.9%).

Table 20: Summary of infections in the Crohn's Disease population

Preferred Term	Placebo (N=426)(%)	CIMZIA (N=1350) (%)
Any infections	**159 (30.3)**	**1088 (41.1)**
Any serious infection	**6 (1.4)**	**66 (4.4)**
Nasopharyngitis	40 (7.7)	164 (9.4)
UTI	32 (5.2)	133 (7.4)
URI	10 (2.3)	93 (5.3)
Influenza	19 (14.5)	81 (, 4.8)
Sinusitis	13 (2.6)	62 3.4)
Herpes Simplex	1 (0.2)	48 (2.4)
Pharyngitis	1(0.2)	35 (2.3)
Perianal abscess	4(0.9)	30(2.1)
Bronchitis	4(0.9)	26(1.9)
Gastroenteritis	6 (1.4)	28 (23, 1.7)
Viral infections	13(2.8)	20(1.3)
Lower respiratory	0	12 (0.8)
Candidiasis	0	10(0.7)
Gastroenteritis viral	2 (0.5)	11(0.7)
Pharyngitis Strep	1 0.2)	13(0.7)
Fungal infection	0	10 (0.7)
Tooth abscess	1 (0.2)	10 (0.7)

Adverse Events by Anti-Certolizumab pegol Antibody Status in Studies of subjects with CD

For purpose of analysis, subjects were considered antibody positive if they had at least one antibody level of >2.4 units/mL measured at any visit. Subjects with all antibody levels recorded at <2.4 units /mL are considered antibody negative. (The applicant states that "due to long half-life of Certolizumab pegol and the continued dosing in the pooled studies, plasma collected in these studies contained levels of Certolizumab that may interfere with the assay, resulting in false negative results). Of subjects that received CIMZIA 100 of 1342 (7.5%) became antibody positive ,while 92.5% of subjects who remained antibody negative.

Table 21: Summary of Overall AEs by anti-CDP870 antibody status: CD

Any AEs	CIMZIA: Antibody status	
	Negative N=1242	Positive N= 100
Any AEs	5087 (77.4%)	515 (85%)
Intensity		
Mild	2781 (61.0%)	247(69.0%)
Moderate	1949 (53.0%)	60 (60.0%)
Severe	257 (18%)	22, (22.0%)
Relationship to study drug		
Unrelated	2398(56%)	265(64%)
Unlikely	1427(42%)	132(47%)
Possible	962 (32%)	67 (36%)
Probable	189 (8.0%)	22(9%)
Definite	**111 (4.0%)**	**29 (8.0%)**

As seen from the above table, 85 of 100 (85%) antibody positive subjects who received the certolizumab 400 mg reported 515 AEs, as compared to 961 of 1242 (77.4%) antibody negative subjects that reported 5087 AEs. Severe AEs were reported in 22% of antibody positive subjects compared to 18% of the antibody negative subjects. Of the AEs in the antibody positive subjects, 50% were deemed possible, probable or definitely related to the treatment drug, compared to 44% of the antibody negative subjects.

Table 22: Antibody positive subjects with of AEs that were at least 3% higher than Antibody negative subjects:

AEs	Antibody Positive (%)	Antibody negative (%)
Infections & Infestations	51	42
General Disorder and Administration	28	21
Musculoskeletal & Connective Tissue	21	16
Investigation	16	10
Metabolism & nutrition	9	4

The rates of the GI disorder SOC (47% vs 46.5%) and Neoplasms (1.0% vs 1.6%) were comparable between antibody positive and negative subgroups.

AEs leading to withdrawal were evaluated by antibody status for subjects in studies CDP870-031 and CDP870-032. AEs leading to withdrawal were reported by 17 of 84 (20%) antibody positive subjects as compared to 205 of 1185 (17%) who were antibody negative.

Hypersensitivity reactions following injection were not collected in the CD studies. Reviews of events reported within two hours of injection by antibody status were comparable between the two subgroups.

Interpretation of the data by antibody status may be limited due to sensitivity of assay methods, cut off antibody measures and the disparity (13 fold difference) in subgroup size. The incidence AEs of infections, general disorders, musculoskeletal and connective tissue and metabolisms are higher in the antibody positive subjects compared to antibody negatives.

Treatment emergent Adverse events:

The following table (**Table 23**) presents treatment emergent comparison between the placebo and CIMZIA treated group. The placebo group had a higher (77%) incident of any AE compared to the CIMZIA treated group (73%). This is because, sorbitol was used as a placebo agent resulting in higher AEs.

Table 23: Overview of Treatment Emergent AES

AE	Placebo N=426	CIMZIA N= 1350
Any AE (%)	76.5	73
SAEs (%)	9.6	9.3
Injection Reactions (%)	21.6	13.6
Acute hypersensitivity (%)	19.6	14.8
Delayed reactions (%)	4.8	3.0

Reviewer's Comment: As seen from the above table, while the rate of SAEs appear comparable between the two groups (9.6% vs 9.3%), any AE (76.5% vs 73%), injections reactions (22% vs 14%), acute hypersensitivity reactions (20% vs 15%) and delayed reactions (5% vs 3%)were higher in the placebo group vs the CIMZIA group respectively.

7.1.4 Other Search Strategies

7.1.5 Common Adverse Events

7.1.5.1 Eliciting adverse events data in the development program

AE data are focused on subjects who received the 400 mg dose of Certolizumab pegol, administered sc., which is the dose and route planned for licensure. Certain AE data were also summarized for controlled and uncontrolled studies. The safety review primary focus is on

placebo- controlled studies data. In addition, AEs occurring after the first dose of placebo in study CDP870-032 are presented separately.

7.1.5.2 Appropriateness of adverse event categorization and preferred terms

The adverse event categorization and preferred terms were deemed to be appropriate. Treatment emergent AEs were reported using MEDRA system-organ/preferred term classification. Individual AEs were summarized by system-organ, preferred term and relationship to study drug as determined by the Investigators.

7.1.5.3 Incidence of common adverse events

The incidence of all AEs occurring in > 1% of the CD population was comparable between placebo, CIMZIA and all CDP870 groups. In the controlled studies, 73% of subjects in the Certolizumab 400 mg group and 76.5% of subjects in the placebo group experienced at least one AE. In overall population 77.9% of subjects experienced at least one AE. The incidence of AEs between placebo, the controlled CD and the overall CD population was comparable.

7.1.5.4 Common adverse event tables

The most frequently reported treatment-emergent AEs, defined as those occurring in ≥ 2% of CIMZIA treated subjects are presented in the table below. In the CIMZIA treatment group 77.9% subjects experienced one or more AEs compared to 76.5% of the placebo group. Crohn's disease was the most number of AEs with 16% in the Certolizumab group compared to 11% of the placebo. In addition, a higher number of subjects in the Certolizumab 400 mg group experienced URI, pharyngitis and herpes simplex infections compared to the placebo group.

Table 24: Summary of AEs by Incidence > 2% (MedDRA Classification) CD population

Preferred Term	**Placebo (N= 426)**	**CIMZIA (N=1350)**	**All CDP870 doses (N=1564)**
Total # AES	**1423 (76.5%)**	**5615 (77.9%)**	**6393 (77.6%)**
Crohn's Disease	52 (11%)	251 (16%)	276 (15%)
Headache	145 (17%)	358 (16%)	440 (16%)
Abdominal pain	76 (10%)	219 (12%)	250 (12%)
Nasopharyngitis	58 (12%)	219 (13%)	259 (14%)

UTI	32 (5%)	133 (7%)	144 (7%)
Nausea	48 (9%)	123 (7%)	153 (8%)
Arthralgia	24 (5%)	118 (7%)	134 (7%)
Pyrexia	44(7%)	121 (6%)	139(6%)
Vomiting	22 (3%)	92 (5%)	104 5%)
Diarrhea	27 (5%)	87(5%)	96 (5%)
URI	10 (2%)	93 (5%)	94 (5%)
Influenza	29(7%)	147 (7%)	140 (8%)
Rash	11 (3%)	64 (4%)	74 (4%)
Insomnia	14 (3%)	63 (4%)	69 (4%)
Back pain	27 (5%)	62 (4%)	67 (4%)
Cough	11 (13%)	51 (4%)	61 (4%)
Fatigue	24 (5%)	54 (4%)	64 (4%)
Sinusitis	13 (3%)	62 (3%)	70 (3%)
Anemia	13 (3%)	47(3%)	51 (3%)
Dyspepsia	16 (3%)	48 (3%)	53 (3%)
Abdominal pain upper	9 (2%)	41 (2%)	48 (2%)
Anxiety	5 (1%)	45 (2%)	49 (2%)
Herpes Simplex	1(0.2%)	48 (2%)	50(2%)
Dizziness	15 (3%)	36 (2%)	45 (3%)
Depression	11(2%)	35 (2%)	40 (2%)
Injection site reaction	55(7%)	88 (4%)	89 (4%)
Pharyngitis	1 (0.2%)	35 (2%)	36 (2%)
Pain in extremity	6 (1%)	36 (2%)	41 (2%)
Abdominal distension	5 (1%)	29 (2%)	33 (2%)
Perianal abscess	4 (1%)	30 (2%)	33 (2%)
Constipation	9 (2%)	31 (2%)	31 (2%)
Hemorrhoids	3 (1%)	30 (2%)	30 (2%)
Peripheral Edema	7(1%)	35 (2%)	39(2%)
Bronchitis	4 (1%)	26 (2%)	30(2%)
Aphthous stomatitis	3 (1%)	31 (2%)	38 (2%)
Gastroenteritis	6 (1%)	28 (2%)	29 (2%)
Rectal hemorrhage	2 (1%)	25 (2%)	28 (2%)
Conjunctivitis	2 (1%)	30 (2%)	31 (1%)
Anal fissure	2 (1%)	30 (2%)	38 (2%)
Myalgia	6 (1%)	23 (2%)	28 (2%)
Muscle cramps	7 (1%)	20(1%)	22 (1%)
Pruritus	4 (1%)	17 (1%)	31 (2%)

7.1.5.5 Identifying common and drug-related adverse events

The event rates of AE categories do not indicate that receiving Certolizumab treatment increased the rate of common AEs compared to placebo. The higher incidence observed with infection is consistent with the mechanism of action for this class of treatment modalities than suppress the immune system. No new adverse events by group classification or by preferred term were identified.

7.1.5.6 Additional analyses and explorations

7.1.6 Less Common Adverse Events

Less common but clinically significant adverse events are discussed in section 7.1.2 of this review

7.1.7 Laboratory Findings

7.1.7.1 Overview of laboratory testing in the development program

General laboratory testing was dose according to the schedule outline in Appendix 10.
For the CD population, data used to calculate changes from baseline in laboratory values for subjects in studies CDP870-033 and CDP870-034 were calculated using subject's actual baseline value from the pivotal studies (CDP870-031 and CDP870-032). For subjects who received placebo in study CDP870-032, after receiving the first three doses of Certolizumab 400 mg, all data are presented in the CIMZIA column.

7.1.7.2 Standard analyses and explorations of laboratory data

The number of subjects with markedly abnormal post baseline lab values was analyzed in both pivotal studies. In the Certolizumab group, an upward shift in hemoglobin and hematocrit values, particularly from values below, to values within normal limits was noted. For platelets and neutrophil values, a downward shift, particularly from values above to values within normal limits was noted. For subjects in the treatment group, the mean hemoglobin value at baseline was 128.4 g/L (SD=17.16 g/L) and for subjects in placebo group, the mean baseline value was 128.0 g/L (SD = 17.03 g/L). The median value for subjects in both groups at baseline was 129 g/L. The mean hematocrit value for subjects in the Certolizumab group at baseline was 0.39 (SD= 0.046) and for the placebo group, the mean value was 0.39 (SD=0.045). The mean median value

for subjects in both groups was 0.390. For subjects in the Certolizumab group, hematocrit values fluctuated close to the Week 0 values during study visits up to Week 26.

For biochemistry evaluation, no clinically significant trend was observed for the majority of biochemistry parameters for either treatment group. At baseline, mean and median values for the biochemistry parameters were comparable for subjects in the Certolizumab and placebo groups. Other anti-TNFα agents have been reported to increase risk for cardiovascular (particularly, cardiac failure), hepatobiliary, and hematologic events. Review of the biochemistry data showed that the incidence of increased hepatic enzymes were slightly higher with Certolizumab 400 mg treatment group compared to placebo. There was one report each of hepatitis, hepatotoxicity, and jaundice in patients with CD who received Certolizumab compared to three cases of hepatitis in the placebo group (one CD and two RA).

7.1.7.2.1 Analyses focused on measures of central tendency

See above section

7.1.7.2.2 Analyses focused on outliers or shifts from normal to abnormal

See above section

7.1.7.2.3 Marked outliers and dropouts for laboratory abnormalities

See above section

7.1.7.3 Additional analyses and explorations

In the CD population, the proportion of subjects with normal (negative) anti-nuclear and anti-dsDNA antibody values at baseline was similar in the two treatment groups. There was a shift noted (from 0.5% to 10.2%) in the Certolizumab 400 mg group from normal (negative) baseline anti-nuclear antibody values to positive ant-nuclear antibody values at the end of the study. No trend in anti-dsDNA antibody values from baseline to end of study was noted for the Certolizumab 400 or the placebo group.

Table 25: Summary of Changes from Baseline in Auto-Antibody Assays at End of Study

Auto-antibody Week 0	Placebo (N=426)		CIMZIA (N=1072)	
Anti-nuclear	**Normal**	**AB Present**	**Normal**	**AB Present**
Normal	294 (86.5%)	5 (1.5%)	705 (86.0%)	27 (3.3%)
AB Present	4 (1.2%)	37 (10.9%)	4 (0.5%)	84 (10.2%)
Anti-dsDNA (IU/ml)	**Negative**	**Positive**	**Negative**	**Positive**
Negative	322(94.7%)	6 (1.8%)	794 (96. 8%)	10 (1.2%)
Positive	3(0.9%)	9 (2.6%)	6(0.7%)	10 (1.2%)

7.1.7.4 Special assessments

No special assessments were performed for Studies CDP870-031 and CDP870-032.

7.1.8 Vital Signs

Vital signs were collected according to the outlined schedule

7.1.8.1 Overview of vital signs testing in the development program

The only study in which vital signs, including ECGs formally analyzed was study PHA-024 , a randomized, double-blind, placebo-controlled, two-center, single dose study designed to evaluate three single dose levels of Certolizumab pegol (100, 400 and 800 mg) given sc. in subjects of Caucasian and Japanese descent. The submission reports that there were no clinically significant findings in vital signs measurements or in results of physical examination during the study period.

7.1.8.2 Selection of studies and analyses for overall drug-control comparisons

The table below represents the studies selected in the CD database by study and treatment group

Table 26 : Summary of Studies in the CD safety Data base by study and treatment group

Population	Study	Placebo	CIMZIA 400 mg	CIMZIA all doses
	Total	426	1350	1564
Controlled IV	Sub-total	24 (5.6%)	N/A	68(4.3%)
	CDP870-008	24(5.6%)	N/A	68 (4.3%)
Controlled SC	Sub-total	402 (94.4%)	832 (61.6%)	978 (62.5%)
	CDP870-005	73(17.1%)	73 (5.4%)	219(14.0%)
	CDP870-031	329(77.2%)	331(24.5%)	331(21.2%)
	CDP870-032	N/A	668(49.5%)	428(27.4%)
Uncontrolled SC	Sub-total	3(0.7%)	1205 (89.3%)	902(57.7%)
	CDP870-032	N/A	668(49.5%)	668 (42.7%)
	CDP870-033	3(0.7%)	592(43.9%)	592(37.9%)
	CDP870-034	N/A	310(23.0%)	310(19.8%)

7.1.8.3 Standard analyses and explorations of vital signs data

Please see above section 7.1.1.14

7.1.9 Electrocardiograms (ECGs)

7.1.9.1 Overview of ECG testing in the development program, including brief review of preclinical results

ECGs were evaluated for the following studies at screening CDP870-001, CDP870-002, CDP870-003, CDP870-004, PHA-001 and PHA-024. In addition, in study PHA-024 12 lead serial ECG was conducted to assess QTc. There was no clinically significant ECG changed in study PHA-024. There were no ECG monitoring for studies PRECiSE 1, PRECiSE 2, CDP870-033 and CDP870-034.

7.1.10 Immunogenicity

Data from Study CDP870-004 in subjects with RA were used to set a baseline for the screening ELISA so that a positive antibody response could be defined. The baseline was set at twice the mean of pre-infusion from all subjects entering CDP870-004. Subject plasma samples were considered positive for antibodies to Certolizumab if they showed a greater that tow fold increase over the baseline. This resulted in a definition of an antibody positive (Ab+) subject being one in which the anti-certolizumab antibody concentration exceeded 2.4 units/ml at any time point. This definition was retained for subsequent studies for consistency.

In study CDP870-031, 26 of 331 subjects (7.9%) developed anti-certolizumab antibodies during the course of study. For study CDP870-032, 17 of 213 (7.9%) of subjects developed anti-certolizumab antibodies. Antibody formation was lower in those subjects using concomitant immunosuppressants (3.3%) compared to those who were not (11.2%).

To assess antibody formation status to re-exposure, antibody levels were measured in subjects enrolled in studies CDP870-033 and CDP870-034. Of the 81 subjects who entered study CDP870-033 after a fixed treatment free period of 24 weeks, 19 (23%) were antibody negative in the pivotal study, and developed antibodies during the study. Of 66 subjects who entered study

CDP870-034 and who had a variable treatment free period (2-21 weeks), 2(3.0%), were antibody negative, and developed antibodies in the safety population of study CRP870-034.

The population PK study(CDP870-039) explored the effects on anti-certolizumab antibodies and immunosuppressants on plasma levels of certolizumab pegol. The conclusions were that there was a statistically significant and clinically relevant impact of anti-certolizumab pegol antibodies on certolizumab PK and a statistically significant but not clinically relevant impact of immunosuppressants.

The overall incidence of neutralizing antibodies among those who generated antibodies was approximately 80%. In addition, the incidences of anti-certolizumab antibodies and neutralizing anti—certolizumab antibodies appear to be inversely proportional to Certolizumab dose.

Table 27: Neutralizing anti-certolizumab antibodies titers in CD by plasma concentration of certolizumab

Study	Plasma concentration	n	Neutralizing anti-certolizumab antibody titers			
CDP870-031			< 30	30	300	3000
	<0.41 µg/Ml	14	0	3	6	5
	>0.41 µg/Ml	11	4	3	2	2
CDP870-032	<0.41 µg/Ml	40	4	16	12	9
	>0.41 µg/Ml	12	5	5	1	1

In conclusion, the incidence of anti-certolizumab and neutralizing ant-certolizumab antibodies appear to be inversely proportional to certolizumab dose. These observations are complicated by the known interference of certolizumab in the plasma with the anti-certolizumab antibody assay.

7.1.11 Human Carcinogenicity

The potential role of TNF-blocker therapy in the development of malignancies in not known. Certain malignancies, such as lymphomas have been observed with other TNFα blockers. There is no lymphoma cases observed in Certolizumab treated subjects yet. Malignancies occurring in Certolizumab studies are discussed in section 7.1

7.1.12 Special Safety Studies

The effect of receiving prior infliximab therapy was evaluated in studies PRECiSE 1, 2, CDP870-033 and CDP870-034. In the CIMZIA group, 360 of 1276 (28%) subjects reported prior infliximab exposure as compared to 916 of 1276 (72%) who did not.

Subjects reporting prior infliximab use had a higher rale of AEs than those subjects who did not in the CIMZIA group (84% vs 76% , respectively), but a comparable rate in the placebo group (78% vs 78%, respectively). Subjects with prior infliximab had a higher rate of AEs leading to withdrawal than those without prior exposure in the CIMZIA group (21% vs 16% respectively) and the placebo group (9% vs 5% respectively). However, the differences between the CIMZIA group and the placebo group were similar in those reporting prior infliximab use (11%) and those who did not (11%).

Subjects reporting use of prior infliximab had a higher rate of local and systemic injection AEs reported within 2 hours of injection than those who did not in the CIMZIA group (20% vs 13% respectively) and in the placebo group (33% vs 22% respectively).

Subjects with prior infliximab use had a higher rate of SAEs than those subjects who did not in the CIMZIA group (20% vs 16% respectively) but a lower rate in the placebo group (5% vs 8% respectively).

Reviewer's Comment: The prior infliximab subjects in both the placebo and CIMZIA group are not well characterized with regard to length of exposure, reason for stopping infliximab use, documentation of prior AEs with Infliximab use and efficacy of infliximab. The observed incidence of AEs, SAEs, withdrawals and systemic and local reactions is higher in the prior infliximab exposed subjects than those non-exposed. However, the study was not designed to evaluate the incidence of AEs between those with prior infliximab use vs non users. Therefore, more data is needed to further understanding of these observations. The data should be collected on subjects where their prior infliximab exposure is where documented with regard to previous AEs, number of exposure, reason for stopping infliximab use and efficacy of infliximab.

7.1.13 Withdrawal Phenomena and/or Abuse Potential

There are no withdrawal phenomena and/or abuse potential issues identified with this product to date.

7.1.14 Human Reproduction and Pregnancy Data

No formal studies have been conducted with Certolizumab in pregnant women. Eight subjects reported pregnancies in the CD population receiving CIMZIA. Of these eight pregnancies, two

were ongoing at the time of BLA submission, three resulted in term in full term healthy babies, two were elective abortions and one resulted in miscarriage. In addition, two male subjects reported of their partner's pregnancy and delivery of healthy babies.

7.1.15 Assessment of Effect on Growth

There were no pediatric patients in the clinical studies.

7.1.16 Overdose Experience

Doses of certolizumab pegol up to 800 mg sc and 20 mg/Kg IV have been administered without any known safety issues identified. No information on signs or symptoms on overdose were available during the clinical development program.

7.1.17 Postmarketing Experience

There is no post marketing experience since no certolizumab formulation has been approved in any country.

7.2 Adequacy of Patient Exposure and Safety Assessments

7.2.1 Description of Primary Clinical Data Sources (Populations Exposed and Extent of Exposure) Used to Evaluate Safety

The applicant provided primary source data with data collected from studies under the Applicant's IND # 11197. The IND described the protocols of the clinical development program. These protocols include for studies CDP870-031 (PRECiSE 1), CDP870-032 (PRECiSE 2), CDP870-033 and 034 ongoing open label studies.

Please refer to section 4.2 for listing of all studies.

7.2.1.1 Demographics

Refer to sections 10.1.5 and 10.2.5 for subject demographics .

7.2.1.2 Extent of exposure (dose/duration)

See section 7.1 table 17
The safety database included information on about 2200 subjects that received certolizumab and about 426 placebo subjects. Of the certolizumab recipients, 1350 received the 400 mg dose SC, while 210 had received certolizumab either through IV administration or doses other than 400 mg. In addition, the data base included about 650 subjects in rheumatoid arthritis trials. The

duration of exposure ranges from less than three months for about 410 subjects that received the 400 mg to greater than 12 months (220 subjects). The majority of subjects 55% had exposure between greater than 3 to less than 12 months.

7.2.2 Description of Secondary Clinical Data Sources Used to Evaluate Safety

CIMZIA is also underdevelopment for RA under study protocols CDP870-002, PHA-001, PHA-011, PHA-014 and PHA-015. Data from RA studies have been included in the discussion an analysis of safety data.

7.2.2.1 Other studies

CIMZIA is also underdevelopment for RA under study protocols CDP870-002, PHA-001, PHA-011, PHA-014 and PHA-015. Data from RA studies have been included in the discussion an analysis of safety data.

7.2.2.2 Postmarketing experience

There is no approved formulation of CIMZIA, so no postmarketing experience is available.

7.2.2.3 Literature

The applicant submitted 44 literature references. The submitted literature covered topics for inflammatory bowel disease in general and the currently available therapies. Specific issues discussed included risk/ benefit of TNF blocking agents and risk benefit assessment of infliximab therapy. There were no literature dealing with safety data or signal for CIMZIA, as this biologic is not approved in any country.

7.2.3 Adequacy of Overall Clinical Experience

Please above section extent of exposure. The applicant has a large database that existed for over 2200 subjects in controlled trials for both CD and RA. The applicant has adequate number of moderately to severely active CD in both pivotal studies.

7.2.4 Adequacy of Special Animal and/or In Vitro Testing

See section 3.2

7.2.5 Adequacy of Routine Clinical Testing

The clinical testing provided to study subjects was adequate.

7.2.6 Adequacy of Metabolic, Clearance, and Interaction Workup

See section 5.0, 5.1 and 5.2

7.2.7 Adequacy of Evaluation for Potential Adverse Events for Any New Drug and Particularly for Drugs in the Class Represented by the New Drug; Recommendations for Further Study

No significant AEs in addition to the already known for anti TNF agents were identified and there are no new recommendations for further studies for safety.

7.2.8 Assessment of Quality and Completeness of Data

The primary safety data source provided was complete and of good quality.

7.2.9 Additional Submissions, Including Safety Update

The applicant submitted a 120 day safety update on June 27, 2006. The major safety data from that update was reviewed and incorporated with the safety review.

7.3 Summary of Selected Drug-Related Adverse Events, Important Limitations of Data, and Conclusions

Based on prior experience of use of TNFα blocking agents is associated with a number of adverse events that appear drug related. These adverse events were highlighted in the applicant's proposed package insert. These adverse events include high incidence of TB, risk of Lymphomas, Cardiac related and drug administration reactions. The safety review has revealed that there were 13 cases of TB in both populations. There was no lymphoma cases observed in subjects that received the treatment. However, it is difficult to draw conclusions from these data alone because the small number subjects.

8 ADDITIONAL CLINICAL ISSUES

8.1 Dosing Regimen and Administration

The proposed dosage regimen is 400 mg given as a S.C. injection at 0, 2, and 4 weeks followed by a maintenance regimen of 400 mg every 4 weeks thereafter. The single- and multiple-dose pharmacokinetics (PK) of certolizumab were characterized following administration of I.V. and S.C. doses of certolizumab pegol encompassing the proposed clinical dosage to healthy subjects and patients with Crohn's disease. Mean Cmax and AUC values increase in a linear manner with

dose. Mean peak plasma levels occurred around 4 days post-dose, while mean terminal half-life of certolizumab was estimated at 13 days following S.C. administration.

Considerable variability in the exposure levels has been observed for a fixed dose of 400 mg where the CDP870 concentration range is between 0.5 and 80 mcg/mL. As exposure is highly variable and there is a strong dependence of response on exposure, it may be important to individualize each patient's dose in order to attain the full potential for efficacy.

The incidences of anti-certolizumab pegol antibodies and neutralizing anti-certolizumab pegol antibodies appear to be inversely proportional to certolizumab pegol dose. When antibodies occur, they have a significant effect on the pharmacokinetics. This is reflected in the population PK analysis, which showed that antibodies to certolizumab pegol increased the clearance of certolizumab pegol by approximately four-fold as determined by covariate analysis. Increased clearance in antibody positive subjects can be expected to result in a 52 % reduction in C_{max}, 86 % reduction in C_{trough} and 72 % reduction in AUC_{τ} in a typical 70 kg Caucasian subject with Crohn's disease administered 400 mg certolizumab pegol every four weeks.

8.2 Drug-Drug Interactions

A drug-drug interaction study was conducted to evaluate the effect of administration of a single dose of Certolizumab pegol 400 mg on the steady-state PK of methotrexate. The study demonstrated the lack of a significant drug interaction between certolizumab pegol and methotrexate.

8.3 Special Populations

No clinical studies were conducted to special population. CIMZIA has not studied in the population with renal, hepatic impairment and in the pediatric geriatric populations. Specific clinical studies have not been performed to asses the effect of gender on the pharmacokinetics of CIMZIA. Population pharmacokinetic analysis showed that Caucasians had typical clearance value approximately 15% higher than non-Caucasians, which is clinically significant. Pharmacokinetics parameters in Japanese subjects were similar to those in Caucasian subjects following SC dosing at three dose levels in a biocomparability study.

8.4 Pediatrics

As per the Pediatric Research Equity Act of 2003 (PREA), the applicant plans to conduct studies in pediatric population after registration for marketing is completed.

8.5 Advisory Committee Meeting

No advisory committee meeting was held to discuss this application

8.6 Literature Review

The applicant submitted the appropriate literature references for the TNFα blocking agents and other immune modifiers as well as literature for CD.

8.7 Postmarketing Risk Management Plan

No Risk management plan was proposed

8.8 Other Relevant Materials

N/A

9 OVERALL ASSESSMENT

9.1 Conclusions

Safety Conclusions:

Safety data submitted to this BLA included safety assessments from studies PRECiSE I and II and a 120 day safety update with additional pooled data from the two ongoing open-label studies of the clinical development program. In addition, safety data from ongoing RA studies was also submitted. The overall safety profile reported from the pivotal studies and the 120-day safety update were as expected given what has been seen in clinical trials and the post-marketing use of TNF antagonists. The incidence of malignancy reported in the CD studies was low during the clinical development program. Consistent with the mechanism of action, subjects treated with CIMZIA were at slightly increased risk infections compared to placebo. 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. No PML cases were

observed during the study period. The overall number of antibody positive subjects was 7.6% and no apparent correlation between antibody development and adverse events or reduction in efficacy was observed.

This Reviewer is in agreement with the safety conclusions of the applicant that no new safety signals, compared to other TNF blockers, were observed on review of the submitted safety information.

Efficacy conclusion:

The primary objective of study CDP870-031 was to evaluate the efficacy and safety of sub-cutaneously administered CDP870 in the reduction of signs and symptoms of subjects with Crohn's Disease when compared with placebo. The co-primary endpoints were prespecified to be the proportion of subjects who achieved a clinical response (a decrease in CDAI score≥100) at Week 6 and Weeks 6 and 26 in subjects with the stratum defined by CRP ≥ 10 mg/ L at Baseline.

Analysis of the primary efficacy endpoint revealed a divergence between the analyses performed by the applicant and that of the FDA. The applicant's analysis of the co-primary efficacy endpoints using the intent-to-treat (ITT) population showed that the Week 6 clinical response rate was 37.2 % in the CDP870 400 mg treatment group and 26.0% in the placebo group with a p-value of 0.037. For Weeks 6 and 26, the proportion of responders was 21.5 % for the CDP870 400 mg treatment group and 12.3% for the placebo group, resulting in a p-value of 0.045.

In the applicant's analysis of the co-primary efficacy endpoints the true ITT population of all randomized subjects was not included. The ITT population included only randomized patients who received at least one injection of study treatment and who had at least one efficacy measurement.

FDA performed an analysis of the co-primary efficacy endpoints, in which all randomized subjects were included and subjects with missing data were considered as non-responders (as previously agreed between the FDA and the applicant). The results of the analysis showed that the proportion of responders at Week 6 was 32.9% and 25.6% (p=0.205)for the CDP870 400 mg and placebo groups respectively For weeks 6 and 26, the rate was 18.5% and 12.2% (p=0.1499) for CP870 400 mg and placebo group respectively(FDA statistician analysis). Based of this analysis, the treatment difference for the co-primary efficacy evaluation in the stratum defined by CRP≥ 10 mg/ L at Baseline did not meet the primary endpoint. As seen from these results, while the applicant's p-value achieved statistical significance, FDA's > .05 p-values are of the co-primary endpoints did not confirm applicant's analysis.

Sensitivity analyses on the respective co-primary endpoints were conducted by both the applicant and FDA. Analysis using observed data and best/ worst case were consistent in that both analyses performed by the FDA and the applicant failed to show statistical significance for treatment difference between the CDP 870 400 mg group and placebo. Only the analysis where subjects with missing data were set to non-responders showed that the applicant's results were

statistically significant for treatment difference, while that of the FDA revealed a statistically non-significant result.

The statistically significant result obtained by the applicant for the co-primary efficacy endpoint for the stratum defined by CRP≥ 10 mg/L at Baseline, was dependent on outcomes of six subjects in the CDP870 400 mg group with missing observation, which raises serious concern of the robustness of the data.

In the analysis of secondary efficacy for clinical remission at Week 6 and Weeks 6 and 26 for the CRP≥ 10 mg/ L at Baseline stratum and for the overall population irrespective of baseline CRP, differences in the proportion of subjects with clinical remission (CDAI score ≤150) between the two treatment groups were not statistically significant by the applicant's analysis.

The primary objective of study CDP870-032 was to compare efficacy of every four weeks treatment with CDP870 versus placebo in subjects with active Crohn's Disease with CRP ≥ 10 mg/ L at Baseline, following successful open induction therapy with CDP870, in the maintenance of clinical response over 26 weeks.

The results of study CDP 870-032 showed that the clinical response rate in the CRP> 10 mg/ L stratum was 62% compared to 34 % in the placebo, with treatment effect of 28% and p-value <0.001. Study CDP870-032 met the stated primary efficacy endpoints in that the percentage of subjects with clinical response at Week 26, in the stratum defined by CRP ≥ 10 mg/ L at Baseline was statistically higher in the CDP870 400 mg treatment group compared with the placebo treatment group.

Analysis of results for the major 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, were also statistically significant, supporting the findings from the primary efficacy analysis.

As pointed out from the subgroup analysis performed by FDA statistician, the overall efficacy results were driven from subjects enrolled outside U.S.

In conclusion, the efficacy results of the induction of maintenance study (CDP870-031) failed to achieve statistical significance. In addition, the observed treatment difference of about 9% was less than the expected treatment difference of 15-25% for clinical relevance. The second pivotal study for maintenance (CDP870-032) achieved the stated endpoints with clinically meaningful treatment effect of 28%. Based on these findings, CIMZIA can be approved for maintenance of remission in CD population only. However, since induction of clinical response was not achieved by CIMZIA, more data is needed to provide clear direction for use. Some of these data may include smaller studies where induction is attained using other agents such as steroids and subjects are transitioned to CIMZIA for maintenance.

9.2 Recommendation on Regulatory Action

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

- The clinical development program consisted of a single induction and a maintenance study, and lacks a second induction study.
- 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.
- 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, [redacted] there is 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

9.3 Recommendation on Postmarketing Actions

N/A

9.3.1 Risk Management Activity

N/A

9.3.2 Required Phase 4 Commitments

N/A

9.3.3 Other Phase 4 Requests

N/A

9.4 Labeling Review

N/A

9.5 Comments to Applicant

A complete response (CR) letter will be sent to the applicant.

APPEARS THIS WAY
ON ORIGINAL

10 APPENDICES

10.1 Review of Individual Study Reports

10.1 CDP870-031(PRECiSE I)

Title: A Phase 3 multi-national, multi-center, double blind placebo-controlled parallel group, 26 week study to assess the safety and efficacy of the humanized ant-TNF PEG conjugate, CDP870 400 mg SC, (dosed at 0, 2, 4 then every 4 weeks to Week 24) in the treatment of patients with active Crohn's disease

10.1.1 Objectives

The primary objectives of the study was to compare the efficacy of subcutaneous CDP870 400 mg administered at Weeks 0, 2, 4 and then every 4 weeks to Week 24 compared with placebo in the reduction of signs and symptoms of active Crohn's disease.

The secondary objectives of this study were:

- Evaluate the safety of CDP870 with 4-weekly dosing over a 26-week period
- Obtain data on the plasma concentrations of CDP870 and anti-CDP870 antibodies
- Evaluate the efficacy of CDP870 irrespective of Baseline CRP levels
- Compare the effect of CDP870 versus placebo on subject reported outcome scores

10.1.2 Study Endpoints:

The evaluation of efficacy for study CDP870-031 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 Base line.

Clinical response was defined as $\geq$ 100 point decrease from Week 0 CDAI score.

10.1.2.1 Secondary Endpoints:

The major secondary variables were:

Clinical remission in the stratum defined by CRP $\geq$10 mg/L at Baseline

- The percentage of subjects in clinical remission at Week 6
- The percentage of subjects in clinical remission at both Weeks 6 and 26

2. IBDQ response in the stratum defined by CRP ≥10 mg/L at Baseline
   - The percentage of subjects with IBDQ response at Week 6
   - The percentage of subjects with IBDQ response at both Weeks 6 and 26
5. SF-36 sub scores for bodily pain and role physical in the stratum defined by CRP ≥10 Mg/L at Baseline
6. Clinical response in the Overall Population
   - The percentage of subjects with clinical response at Week 6
   - The percentage of subjects with clinical response at both Weeks 6 and 26
7. Clinical remission in the Overall Population
   - The percentage of subjects in clinical remission at Week 6
   - The percentage of subjects in clinical remission at both Weeks 6 and 26
8. IBDQ response in the Overall Population
   - The percentage of subjects with IBDQ response at Week 6
   - The percentage of subjects with IBDQ response at both Weeks 6 and 26
9. SF-36 sub scores for bodily pain and role physical in the Overall Population

The **CDAI** is a validated, weighted index for measuring disease activity based on a number of signs and symptoms of CD, physical examination and hematocrit measurement. For the pivotal study, CDAI calculations were done at week 0 and at each subsequent follow-up visits. The following variables are components of CDAI used for calculation:

Patient diary
- Number of liquid or very soft stools per day
- Abdominal pain rating (none, mild, moderate, severe)
- General well-being rating (general well, slightly under par, poor, very poor, terrible)
- Use of diphenoxylate, loperamide or other opioids for diarrhea

Clinical Examination
- Existence of complications including: arthritis or arthralgia, iritis or uveitis, erythema nodosum, pyoderma gangrenosum, aphthous stomatitis, anal fissure, fistula or abscess, other fistula, fever over 37.8 °C (100°F) during the past week
- Presence of abdominal mass (absent, questionable, definite)
- Body weight-

Blood Sample
- Hematocrit value

The **Inflammatory Bowel Disease Questionnaire (IBDQ)** is a disease-specific self-administered questionnaire that was to assess health-related quality of life. The IBQD is a previously validated instrument with four parts based on 32 questions: 10 questions related to bowel movement, 5 to systemic symptoms, 12 to emotional functions, and 5 to social functions. Each question is scored by the patient from 1 to 7, where 7 represent the most favorable. A sub-score is calculated for each set of questions, and missing values are replaced by the average of

the other answers in the same sub-score. The total score is made up of the sum of the 4 sub-scores, and may thus range from 32 to 224. Scores < 170 indicate clinically active disease, scores ≥ 170 points indicate clinically inactive disease.

The **Harvey-Bradshaw Index (HBI)** is a validated instrument used to assess health-related quality of life based upon the following variables:

- General well-being the previous day (generally well, slightly under par, poor, very poor, terrible)
- Abdominal pain the previous day (none, mild, moderate, severe)
- Number of liquid or very soft stools the previous day
- Abdominal mass (none, questionable, definite and tender)

Complications (arthralgia, uveitis, erythema nodosum, aphthous ulcera, pyoderma gangrenosum, anal fissure, new fistula, abscess)

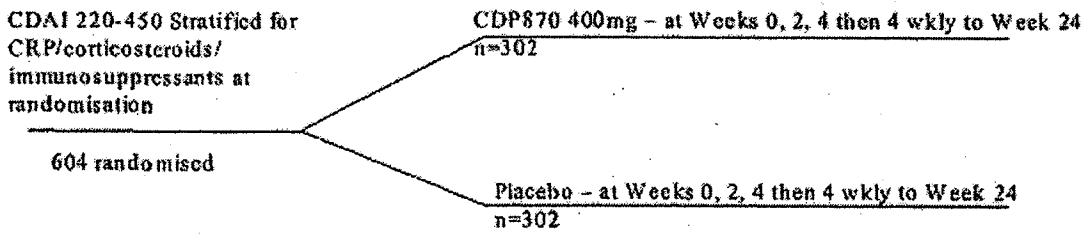
10.1.3 Study design overview

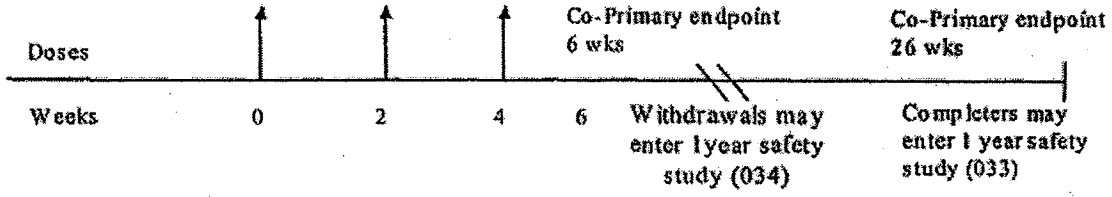
This was a multi-center, double-blind, placebo-controlled, randomized within strata, parallel group study to assess the safety and efficacy of CDP870 in subjects with active Crohn's disease as defined by a Baseline CDAI score between 220 and 450 inclusive. The study was conducted between December 10, 2003, and May 31, 2005, in 171 international sites in the following countries; Australia, Austria, Belgium, Bulgaria, Canada, Czech Republic, Estonia, Georgia, Germany, Hong Kong, Hungary, Italy, Latvia, Norway, Poland, Slovenia, South Africa, Sweden, Ukraine and USA.

Following screening at Week- 2, eligible subjects were randomized in a 1:1 ratio to receive either the study medication or placebo sc at Weeks 0, 2, 4, 8, 12, 16, 20 and 24. Treatment groups were stratified at randomization according to three factors:

- CRP < 10 mg/ L or ≥ 10 mg/ L at Week 0
- Corticosteroid use at Week 0 or not
- Receiving immunosuppressant use at Week 0 or not

The treatment and schedules are presented in **Figures 1 and 2.**





Injections were administered by qualified personnel at each center.

10.1.3.1 Clinical Assessments:

Crohn's disease

- Crohn's disease history, clinical Crohn's disease assessment,
- CDAI, IBDQ.

General

- Demographic data -~ including sex, height, race and smoking status
- Physical examination, vital signs, concomitant diseases, concomitant medications.

Measurements:
CDAI: Weeks 0, 2, 4, 6, 8, 12, 14, 20, 24 and 26/Withdrawal

CRP: Screening, Weeks 0, 2, 4, 6, 8, 12, 16, 20, 24, and 26/Withdrawal

IBDQ: Weeks 0, 6, 16 and 26/Withdrawal.

Faecal Calprotectin: Weeks 0, 6, and 26 / Withdrawal. With samples collected at other time points to be stored for future analysis if necessary.

Safety: Adverse events were monitored throughout the study. All patients completing or withdrawing from the study but not entering a follow-on study were followed up for safety issues for 12 weeks following their final dose.

10.1.4 Study population

Inclusion Criteria

Subjects were eligible to participate in the study if all of the following criteria were fulfilled at the Screening Visit:

1. Were able to understand the information provided to them and give written informed Consent

2. Had definitive diagnosis of Crohn's disease confirmed (at least 3 months prior to study entr y) either by radiological, endoscopic or histological evidence, affecting the terminal leum (L1), colon (L2) or ileo colon (L3) according to the Vienna Classification (1998)

3. Had active Crohn's disease (between CDAI 220 and 450 inclusive) scored over the seven days prior to the first dose of study drug

4. Aged 18 years or above at Screening

5. Met all concomitant medication criteria in the following table. For all drugs being taken at Screening, the subject had to be able to remain on a stable dose throughout the duration of the study, although steroids were allowed to be tapered starting at Weeks 8 to 12. However, there was no specific requirement to have had or to have any prior therapy.

Table 28: Concomitant medication inclusion criteria

Drug class	Drug	Dose	Stable treatment required prior to screening	Additional comments
Corticosteroids	Prednisone or Prednisolone	≤30 mg/day	2 weeks	Total duration of steroid treatment must be ≥ 4 weeks
	Budesonide	≤9 mg/day	2 weeks	
	Methylprednisolone	≤24 mg/day	2 weeks	
Immunosuppressants	Azathioprine 6-mercaptopurine	Stable dose	8 weeks	Total duration of therapy must be ≥ 3 months
	Methotrexate	Stable dose	8 weeks	
Antibiotics	E.g. Ciprofloxacin, metronidazole	Stable dose	4 weeks	Short additional course for acute infection allowed
5-ASA analogues	Sulphasalazine, mesalazine, olsalazine, pentasa or similar	Stable dose	4 weeks	
Topical ano-rectal treatments	Steroids, 5-ASA analogues (creams, suppositories, ointments, enemas)	Stable dose	2 weeks	
Anti-diarrhoeals	Any including opioids	Stable dose	4 weeks	
Analgesics	NSAIDS/Cox inhibitors	Stable dose	4 weeks	

Exclusion Criteria

Subjects were not eligible to participate in the study if any of the following criteria was present at the Screening Visit:

Crohn's Disease Related

1. Had fistula abscess present at Screening
2. Had stricturing type disease with symptoms or signs of non-inflammatory mechanical obstruction or bowel perforation in last 3 months
3. Had short bowel syndrome

4. Had functional colostomy or ileostomy (note: patients who have had a temporary stoma in the past, which has been reversed, are eligible to enter the study).

5. Had positive stool laboratory results for enteric pathogens.

Concomitant medication Exclusion

6. Met any of the concomitant medication criteria in the table below

Table 29. Concomitant medication exclusion criteria

Drug Class	Exclusion Criteria
Corticosteroid/Corticotrophin	• Any therapy for indications other than Crohn's disease (note: sparing use of topical hydrocortisone for skin disease or not more than 800 µg per day inhaled beclomethasone, or equivalent, for asthma was permitted). • Parenteral therapy within 4 Weeks of Screening • Discontinuation within 2 Weeks of Screening
Azathioprine, 6-mercaptopurine, methotrexate, chronic (>4 Weeks) antibiotic therapy	Discontinuation within 4 Weeks of Screening
Cyclosporin, mycophenolate, thalidomide	Regular treatment for Crohn's disease within 4 Weeks of Screening

Previous Clinical Trials and anti-TNF Therapy Exclusion

7. Had received any experimental unregistered therapy or biological therapies (within or outside a clinical trial) within 12 Weeks prior to study entry (Screening) or had been dosed in any clinical trial within the 4 Weeks prior to Screening

8. Had previous treatment with any anti-TNF therapy resulting in a severe hypersensitivity or an anaphylactic reaction

9. Had previously participated in a clinical trial where they received CDP870

10. Had previous treatment with any anti-TNF therapy where there was no clinical response to the first dose

Reviewer's comment: It appears that some anti-TNF non-responders may have been excluded from the study.

Medical History Exclusion

11. had current or recent history of severe, progressive, uncontrolled renal, hepatic, Hematological, gastrointestinal, endocrine, pulmonary, cardiac, neurological, or cerebral disease

12. Had a history of chronic infection, recent serious (within 6 months, including herpes zoster) or life threatening infection, or any current sign or symptom, which may have indicated an infection (egg, fever, cough)

13. Had history of tuberculosis or positive chest X-ray for tuberculosis or positive (defined as positive induration per local medical practice) purified protein derivative (PPD) skin test. Subjects with a positive PPD skin test who had received Bacille Calmette Guérin (BCG) vaccination and had a negative chest X-ray for tuberculosis were allowed to be enrolled

14. Had known concurrent viral hepatitis or known positivity to Hepatitis B-e Antigen (HBeAg), Hepatitis B Virus (HBV) Deoxyribonucleic Acid (DNA), HBV DNA polymerase, Hepatitis C Virus Ribonucleic Acid (HCVRNA), anti-HCV antibodies with decompensated liver function or had Acquired Immunodeficiency Disease Syndrome (A IDS) or known Human Immunodeficiency Virus (HIV) infection

15. Had concurrent malignancy or a history of malignancy (other than carcinoma of the cervix or basal cell carcinoma successfully treated more than five years prior to Screening)

16. Had concurrent bowel dysplasia or a history of bowel dysplasia in the 5 years prior to Screening

17. Had history of a lymphoproliferative disorder including lymphoma or signs and symptoms suggestive of lymphoproliferative disease at any time

18. Were pregnant (had to be tested in any woman who was of child-bearing potential at screening and prior to each dose of study drug) or lactating females

19. Were women of child-bearing age NOT practicing (in the Investigator's opinion) effective birth control. All women had to test negative on a serum pregnancy test before study entry and immediately prior to dosing (urine test)

20. Had known recent drug (including cannabis) or alcohol abuse

21. Had any other condition that made the subject unsuitable for inclusion into the study, e.g., significant active or quiescent infectious disease, ongoing or previous history of blood dyscrasia (e.g., pancytopenia, aplastic anemia), demyelinating disease (e.g., multiple sclerosis, myelitis, optic neuritis) or ischemic heart disease

Other Exclusion

22. Were non co-operative or unable to comply with the study procedures.

Removal of subjects from therapy or assessment

The Investigator had to withdraw a subject from the study if in the opinion of the Investigator:

1. The subject's clinical condition warranted the subject's withdrawal
2. The subject failed to comply with the protocol
3. Any safety issues arose during the course of the study
4. The subject required defined rescue therapy to treat an exacerbation of their Crohn's disease.

Rescue therapy was defined as the subject needing to be treated for an exacerbation of their Crohn's disease with any of the following:

- Infliximab
- Corticosteroids
- Immunosuppressants (azathioprine/ 6-mercaptopurine, methotrexate)
- Surgery
- Hospitalization

Table 30. Study assessments and examination outline

	Screen 14 to 10 Days	Weeks									
		0	2	4	6	8	12	16	20	24	26
Inclusion / exclusion	X										
Consent	X										
Demography	X										
Issue diary	X	X	X	X	X	X	X	X	X	X	
Crohn's disease history	X										
Relevant Past Medical History and Concomitant diseases	X	X									
Physical examination	X										X
Chest X ray	X										X
PPD test	X										
Weight	X	X	X	X	X	X	X	X	X	X	X
Concomitant medication	X	X	X	X	X	X	X	X	X	X	X
AEs		X	X	X	X	X	X	X	X	X	X
Clinical Crohn's disease Assessment		X	X	X	X	X	X	X	X	X	X
CDAI		X	X	X	X	X	X	X	X	X	X
Hematology/biochem/ Urine/CRP	X	X	X	X	X	X	X	X	X	X	X
Stool microbiology	X										
Pregnancy test	X	X	X	X	X	X	X	X	X	X	X
CDP870 & anti-CDP870 Plasma levels		X	X	X	X	X	X	X	X	X	X
Auto-antibodies (ANA And ds-DNA)		X									X
Fecal calprotectin		X	X	X	X	X	X	X	X	X	X
Vital signs	X	X									X
Subject status	X	X	X	X	X	X	X	X	X	X	X
CDP870 or placebo		X	X	X		X	X	X	X	X	
IBDQ		X			X			X			X
Harvey Bradshaw Index		X									X
Health Outcome Questionnaires (SF-36, WPAI)		X			X			X			X
Heath outcome Questionnaires EQ-5D Healthcare RUS		X	X	X	X	X	X	X	X	X	X

10.1.5 Results

Subject Disposition:

Nine hundred seventy six (976) patients were screened for the study. Of these, 662 met the inclusion criteria and were enrolled in the study. Two subjects that were randomized to the CDP879 400 mg group but did not receive treatment. The most common reason for withdrawal was lack of improvement or disease deterioration and AE.

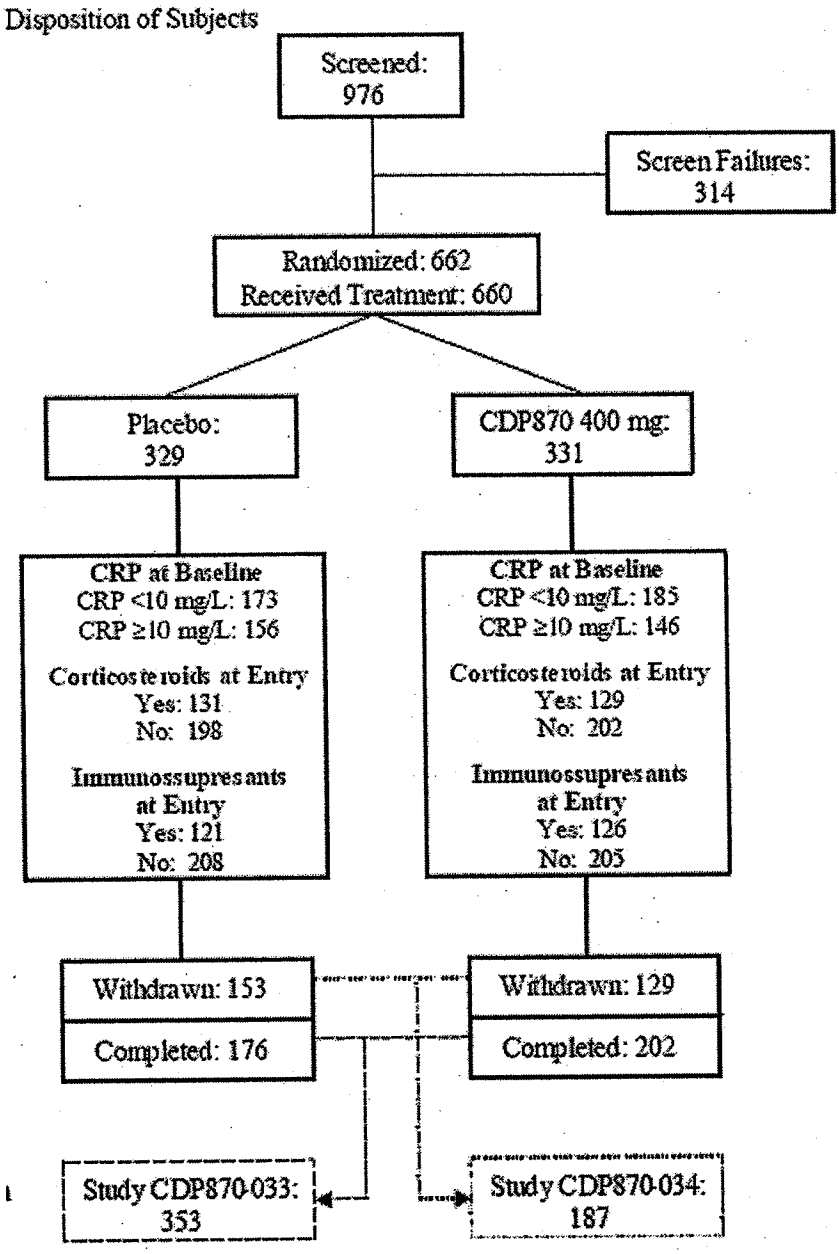


Figure 3: Displays Subject Disposition Scheme.

Demographics

Baseline Demographics

A total of 660 patients were enrolled in this study to receive CDP870 400mg or placebo. The baseline demographics and disease characteristics of study subjects are presented below. Of the enrolled subjects 44% were male, and 95% were Caucasian, with a median age of 36 years and median weight of 68.7 Kg. No baseline demographic imbalance was seen across the two treatment groups except for gender with about 40% male in the placebo group as opposed to 47% males in the CIMZIA group.

Tables: 31 and 32 Baseline Characteristics:

Characteristic	Placebo	CDP870 400 mg	Total subjects
Subjects Randomized	**329 (%)**	**331 (%)**	**660(%)**
Sex			
Male (%)	131 (40)	157 (47)	288 (44)
Age			
Median	36	36	36
Race			
Caucasian	314 (95)	313(95)	627(95)
Afro-Caribbean	0	5 (2)	5 (0. 8)
Asian (Indian)	1	2	3
Other	12 (14)	9(3)	21(3)
Weight (Kg)			
Mean (SD)	68.5 (18)	68.9 (17)	68.7 (17)
Body Mass Index (Kg/M^2)			
Mean (SD)	23.8 (5)	23.8(5)	23.8 (5)
Smoking Status			
Never	150 (46)	156 (47)	306 (46)
Stopped before CD	37 (11)	32 (10)	69(11)
Stopped after CD	35 (11)	39 (12)	74 (11)
Current Smoker	107(33)	104(31)	211(32)

History	Placebo N=329(%)	CDP870 400 mg N=331 (%)	Total N=660(%)
Duration CD (yrs.)			
N	328	331	659
Median	5.5	4.8	5.1
Location of CD			
Terminal ileum	83(25)	91(28)	174(26)
Colon	71(22)	87(26)	158(24)
Ileo colon	158(48)	138(42)	296(45)
Upper GI	17(5)	4(1)	9(1)
Behavior of CD			
Inflammatory	214(65)	226(68)	440(67)
Stricture	45(14)	42(13)	87(13)
Penetrating	70(21)	63(19)	133(20)
Resection at screening			
Yes	114(35)	118(36)	232(35)
No	215(65)	213(65)	482(65)
Number of resections			
0	215(65)	213(64)	428(65)
1	76(23)	79(24)	155(24)
2	29(9)	25(8)	54(8)
3	6(2)	8(2)	14(2)
>3	3(1)	6(2)	9(1)
CDAI score baseline			
Mean (SD)	297(62)	300.2 (64)	298(63)
Median	285	287.7	286
Minimum	161	149	149
Maximum	513	491	513
CRP level			
<10 mg/L	173(53)	185(56)	358(54)
> 10mg/L	156(47)	146(44)	302(46)

Baseline Disease Characteristics

Baseline disease characteristics are shown above . For all enrolled subjects, the median duration of CD was 5.1 years, the median CDAI score was 298, and 54% of subjects had a CRP ≥10 mg/L. The location of CD was comparable between the two treatment groups. No significant imbalances were seen among the two treatment arms.

Past Therapy for Crohn's Disease

The proportion of subjects who received prior infliximab for CD was slightly higher in the CDP870 400 mg group (30.2%) compared with the placebo group (25.8%). Total number of

infusions, and hypersensitivity reactions were similar between the 2 treatment groups. Current and prior use of immunosuppressants, corticosteroids and 5-ASAs was similar between the two treatment groups.

Table 33 . Summary of Prior Infliximab Therapy and Medication for CD

Medication	Placebo (N= 329)(%)	CDP870 400 mg (N= 331)(%)	Total Subjects (N=660)(%)
Infliximab Prior therapy			
Yes (%)	85(25.8)	100(30.2)	185(28)
No (%)	244(74.2)	231(69.8)	475(72)
Immunosuppressants			
Current Therapy			
Yes	124(37.7)	128(38.7)	252(38.2)
No	205(62.3)	203(61.3)	408(61.8)
Prior therapy			
Yes	70(21.3)	72(21.8)	142(21.5)
No	135(41.0)	131(39.6)	266(40.3)
Corticosteroids			
Current therapy			
Yes	130(39.5)	130(39.3)	260(39.4)
No	199(60.5)	201(60.7)	400(60.6)
Prior Therapy			
Yes	152(46.2)	143(43.2)	295(44.7)
No	47(14.3)	58(17.5)	105(15.9)
5-ASAs			
Current therapy			
Yes	188(57.1)	189(57.1)	377(57.1)
No	141(42.9)	142(42.9)	283(42.9)
Prior therapy			
Yes	117(35.6)	116(35.0)	233(35.3)
No	24(7.3)	26(7.9)	50(7.6)

* Prior and current therapy as outline in the exclusion and inclusion criteria for medical therapy

10.1.6 Withdrawals, Compliance, and Protocol Violations:

Withdrawals:
Out of 660 total randomized patients, 282 (42.7%) did not complete the study. The majority of these patients (129, 29%) withdrew from the study due to lack of improvement or disease deterioration. The proportions of subject were 46.5% for placebo and 39.0 % for the treatment group. The following table displays withdrawing subjects by reason.

Table 34: Summary of Subjects Withdrawing by Reason

Reason for withdrawal	Placebo (N=329) (%)	CDP870 400 mg (N=331) (%)	Total Subjects (N=660) (%)
Total # of subjects withdrawn	153 (47.5)	129 (39)	282 (42.7)
Lack of improvement	113(34.3)	79 (23.9)	192 (29.1)
AE	39 (11.9)	37(11.2)	76 (11.5)
Subject decision	9 (2.7)	23(6.9)	32(4.8)
Clinical decision	19 (5.8)	13(3.9)	32(4.8)
Other	6(1.8)	5(1.5)	11(1.7)
Protocol non-compliance	2(0.6)	3(0.9)	5(0.8)
Lost to follow up	0	2(0.6)	2(0.3)

Compliance:
Protocol deviations:
The most common protocol deviation was of "non-compliance with schedule visit". The occurrence of scheduled visit non compliance was 56 of 329 subjects (17%) in the placebo group and 50 of 333 subjects (15%) in the treatment group. In addition 27 of 329 (8.2%) of placebo group and 33 of 333 (10%) of CDP870 group had protocol deviation due concomitant medications. Other deviations include re-calculated CDAI outside range (220-450) at week 0 and rescue therapy. A total of 118 subjects were excluded from per protocol (PP) population.

10.1.7 Efficacy Findings

Primary Efficacy Endpoints:

The co-primary efficacy endpoints for the study were: **In the population with CRP≥10mg/L at baseline:**

- the percentage of patients with clinical response (at least 100-point decrease from Week 0 CDAI) at Week 6
- The percentage of patients with clinical response at both Weeks 6 and 26.

All patients randomized who received at least one injection of study medication and who had at least one efficacy measurement after the first medication administration, irrespective of any major protocol deviations were included in the intent to treat(ITT) population.

The ITT population was the primary population for analysis of efficacy.

All patients eligible for ITT population, who did not have any major efficacy protocol deviation, were included in the per-protocol (PP) population. The ITT population included 659 subjects with 331 randomized to treatment and 328 randomized to placebo groups respectively. One subject in the placebo group was dosed but had no post-baseline measurement of efficacy and therefore was excluded from the ITT population.

Because the total number of subjects with efficacy protocol deviations exceeded 15% of the ITT Population (115 subjects, or 17.5% of the ITT Population), efficacy analyses were also performed using PP Population. The PP population, identified when study was blinded, included 544 subjects. 267 subjects randomized to CDP870 400 mg and 277 subjects randomized to placebo.

Primary endpoint: Clinical Response at Week 6 and Weeks 6 and 26 (sponsor analysis)

The proportion of subjects in clinical response at Week 6 and at Weeks 6 and 26 is presented in **Table 11**. At Week 6 , 37% of subjects randomized to the CDP870 400 mg group were in clinical response compared to 26% subjects that were randomized to the placebo arm, resulting in a p-value of 0.037. At weeks 6 and 26, 21.5% of subject enrolled in the CDP870 400 mg group and 12.3 % of subjects enrolled in the placebo group were in clinical response with a resultant p-value of 0.045.
Missing observations were handled by the Last Observation Carried Forward method, which was different than the agreed upon analysis plan of using of the non-responder imputation technique.

Table 3: Summary of subjects with Clinical Response at Week 6 and Weeks 6 and 26

Week 6	Placebo (N=156)	CDP870 400 mg (N=146)	p-value
Number of subjects	154	145	
Frequency (%)	40 (26)	54 (37)	0.037
Weeks 6 and 26	**Placebo (N=156)**	**CDP870 400 mg (N=146)**	**p-value**
Number of subjects	154	144	
Frequency (%)	19(12.3)	31(21.5)	0.045

According to the applicant's analysis, both endpoints were statistically significantly higher in the CDP870 400 mg group compared with the placebo group for the ITT population.

10.1.7.2 Applicant's Sensitivity Analysis:

Sensitivity analyses were performed on the respective co-primary endpoints in the CRP≥ 10 mg/L at the baseline stratum. The applicant performed three sensitivity analysis using three different methods to handle missing data. These methods include:

4. Observed data: excluding the missing data and using only observed data
5. Missing data set to non-responders, (Worst case) after imputation techniques were applied and withdrawals were taken into consideration
6. Missing data randomized to active treatments were set to non-responders and subjects with missing data were data that were randomized to placebo were set to responders (best/ worst case- most conservative approach).

Tables 33, 34 and 35 below present sensitivity analysis performed by the applicant.

Table 34: Clinical Response in the CRP ≥10 mg/ L Strata at Baseline- Observed case

Scheduled visit	Placebo (N=156)	CDP870 400 mg (N= 146)	p-value
Week 6			
n	113	119	
Frequency (%)	40(35.4)	48(40.3)	0.434
Weeks 6 and 26			
n	64	73	
Frequency (%)	19 (29.7)	27(37)	0.456

Sensitivity analysis on both co-primary endpoints for the CRP≥10 mg/L baseline stratum on only observed cases revealed that treatment differences at both Weeks 6 and 26 and Weeks 6 and 26 and 26 failed to achieve statistical significance (p>0.05)with p-values of 0.434 and 0.456 respectively.

Table 35: Clinical Response in the CRP ≥10 mg/ L Strata at Baseline- Missing Set to Non-Response (Worst case)-ITT population

Scheduled Visit	Placebo (N=156)	CDP870 400 mg (N=146)	p-value
Week 6			
n	156	146	
Frequency (%)	40(25.6)	54(37)	0.035
Weeks 6 and 26			
n	156	146	
Frequency (%)	19(12.2)	31(21.2)	0.047

Results from worst case, where missing dat were set to non-responders after imputation techniques were applied and withdrawals were taken into consideration showed the treatment difference at both Weeks 6 and 26 and Weeks 6 and 26 were statistically significant (p>0.05) with respective p-values of 0.035 and 0.047

Table 36: Clinical Response in the CRP ≥10 mg/ L Strata at Baseline- Missing Set to Best/Worst case ITT population

Scheduled visit	Placebo (N=156)	CDP870 400 mg (N=146)	p-value
Week 6			
n	156	146	
Frequency (%)	42 (26.9)	54(37)	0.061
Weeks 6 and 26			
n	156	146	
Frequency	20 (12.9)	31(21.2)	0.068

Sensitivity analysis where subjects with missing data were randomized to active treatment were set to non-responders and subjects with missing data who were randomized to placebo were set to responders (best/worst case) showed that the treatment differences at both Week and Weeks 6 and 26 were not statistically significant (p.0.05).

As observed from the tables above, two of the three sensitivity analysis performed by the applicant showed that the treatment differences at Weeks 6 and 26 and weeks 6 and 26 failed to achieve statistical significance.

10.1.7.3 Examination of Subgroups

The impact of different subgroups on the co-primary efficacy endpoints in the CRP≥10 mg/ L at baseline stratum tests for two-factor interactions between treatment and the subgroups. Statistical significance was assessed at 0.10 level.

Use of Immunosuppressant at Study Entry

The analysis of the co-primary efficacy endpoints (CDAI≥100 points from baseline at Weeks 6 and 26 and weeks 6 and 26 in the CRP ≥ 10mg/L at baseline stratum) by use of immunosuppressants at study entry showed that the interaction between treatment effect showed 13 /57 (22.8%) and 18/55 (32.7%) response rate, respectively for the placebo and treatment group, with a p-value of 0.228 which was not significant at p (>0.10) level.

Use of Corticosteroids at Study Entry

The analysis of the co-primary efficacy endpoints by use of corticosteroids at study entry and at Weeks 6 and 26, and weeks 6 and 26 showed that the clinical response rate of 6/63 (9.5%) for the placebo group and 13/56 (23.2%) for CDP870 group which a p-value of 0.039, which was statistically significant (p>0.05). Where as corticosteroid use at Weeks 6 and 26 was not statistically significant with a p-value of 0.105. The impact long-term use of corticosteroids with CIMZIA on clinical response may need further consideration. Analysis of the subgroup of subjects who were not using corticosteroids showed that the difference in clinical response between the two treatment groups were not statistically significant (p>0.05) at both Weeks 6 and 26, and weeks 6 and 26.

Smoking status at Study Entry

The analysis of the co-primary efficacy endpoints by smoking status showed that interaction between treatment and smoking status was not statistically significant at (p>0.10). However, of the subjects in the subgroup of current smoker, 15 of 52 subjects (28.8%) had clinical response at Weeks 6 and 26 in the CDP870 400 mg group compared with 6 of 52 subjects (11.5%) in the placebo group (p=0.030). The analysis performed at Weeks 6 and 26 for this subgroup showed no statistically significant (p>0.05) difference between the 2 treatment groups.

Previous Surgery for Crohn's Disease

The analysis of the co-primary efficacy endpoints by previous surgery for Crohn's disease showed that the interaction between treatment and previous surgery for Crohn's disease was not statistically significant (p>0.10). The treatment effect was still significant (p≤0.05) at Weeks 6 and 26, and Weeks 6 and 26. The analyses in the subgroups showed that the difference in clinical response between the 2 treatment groups was not statistically significant (p>0.05) in the subgroup with previous surgery for Crohn's disease at both Weeks 6 and 26, and Weeks 6 and 26.However, of the subjects in the subgroup with no previous surgery, 25 of 102 subjects(24.5%) had clinical response at Weeks 6 and 26 in the CDP870 400 mg group compared with 15 of 111 subjects (13.5%) in the placebo group (odds ratio=2.06, p=0.049). The analysis performed at Weeks 6 and 26 for this subgroup showed no statistically significant (p>0.05) difference between the 2 treatment groups.

Duration of Crohn's Disease

The analysis of the co-primary efficacy endpoints by duration of Crohn's disease at Baseline showed that the interaction between treatment and duration of Crohn's disease was not statistically significant ($p>0.10$). The treatment effect was not significant ($p>0.05$) at Weeks 6 and 26, and Weeks 6 and 26. The analysis of the subgroup of subjects with longer than or equal to Baseline mean Crohn's disease duration showed that the difference in clinical response between the 2 treatment groups was not statistically significant ($p>0.05$) at both Weeks 6 and 26, and Weeks 6 and 26. In the analysis of the subgroup of subjects with less than Baseline mean Crohn's disease duration, the difference at Weeks 6 and 26 was statistically significant; 42 of 104 subjects (40.4%) had clinical response in the CDP870 400 mg group compared with 21 of 81 subjects (25.9%) in the placebo group ($p=0.043$). However, there was no statistically significant difference at Weeks 6 and 26.

Antibodies to CDP870

*The validity of antibody assay, antibody level cut off points with potentially introducing false positive results.

Analyses of clinical response and clinical remission by anti-CDP870 antibody status assessed the effect of these antibodies on the clinical efficacy of CDP870. Due to the continuous dosing in the study design, the antibody assays were conducted in the presence of CDP870, which could result in false-negative results, therefore the most conservative approach was used. Subjects were considered to be anti-CDP870 antibody positive if they tested positive for antibody (>2.4 U/mL) on at least 1 study visit and negative if they tested negative for antibody (≤2.4 U/mL) at all visits.

In the CRP ≥10 mg/L at Baseline stratum, a total of 130 of 146 subjects (89.0%) were antibody-negative and 16 of 146 subjects (11.0%) were antibody-positive among subjects in the CDP870 400 mg group. In the Overall Population, a total of 305 of 331 subjects (92.1%) were antibody-negative and 26 of 331 subjects (7.9%) were antibody-positive among subjects in the CDP870 400 mg group.

Overall, no clear relationship between clinical response and anti-CDP870 antibody status was observed. In the CRP ≥10 mg/L at Baseline stratum, the rate of clinical response in subjects who were antibody-negative ranged across visits from 28.7% to 38.0% compared with a range of 12.5% to 37.5% in clinical response rate in those who were antibody-positive. Differences were not statistically significant ($p>0.05$) at Weeks 6 and 26 or Weeks 6 and 26. In the Overall Population, the rate of clinical response in subjects who were antibody-negative ranged across visits from 25.8% to 37.0% compared with a range of 15.4% to 50.0% in those who were antibody-positive. Differences were not statistically significant ($p>0.05$) at Weeks 6 and 26, and Weeks 6 and 26.