Overall, no clear relationship between clinical remission and anti-CDP870 antibody status was observed. In the CRP ≥10 mg/L at Baseline stratum, the rate of clinical remission in subjects 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.

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 subgroups at Weeks 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).

10.4.2 Applicant's Analysis of Secondary Efficacy Endpoints:

10.4.2.1 Clinical Remission

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

Table 37: Summary of Subjects with Clinical Remission at Weeks 6 and 26 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 ≥ mg/L at baseline stratum and the overall population, irrespective of CRP, showed that treatment differences between the two groups were not statically significant at both time points of Week 6 and Weeks 6 and 26.

10.4.2.2 Clinical Response in the Overall ITT and PP Populations

Table 38. Summary of Subjects with Clinical Response at Weeks 6 and 26 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
Weeks 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 38,** 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 Weeks 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 Weeks 6 and Weeks 6 and 26 with respective p-values of 0.066 and 0.062.

In addition, the applicant performed 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 Weeks 6 and 26 with p-values of 0.146 and 0.149 respectively.

10.4.2.3 IBDQ

The IBDQ is a disease-specific self-administered questionnaire to assess health-related quality of life (QoL). 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 poorest quality of life) of 224 (highest quality of life). Scores < 170 indicate clinically active disease, scores ≥ 170 points indicate clinically inactive disease.

In order to assess the effect of study treatment on QoL, IBDQ response and IBDQ global scores were compared between the CDP870 400 mg and placebo treatment groups. IBDQ response was

defined as an increase in IBDQ global score ≥16 points from baseline, and was analyzed at Weeks 6 and 26.

Table 39. Summary of patients with an increase in IBDQ Global Score ≥16 from baseline in the CRP≥ 10mg/L Strata at baseline –ITT population

Scheduled visit	Placebo (N= 156)	CDP870 400 mg (N=146)	p-value
Week 6			
n	156	144	
Frequency (%)	58(37.2)	71 (49.3)	0.041
Weeks 6 and 26			
n	156	144	
Frequency (%)	34(21.8)	42(29.	0.156

The proportion of subjects with IBDQ response in the ITT Population higher in the CDP870 400 mg group compared to the placebo group, the treatment difference was not statistically significant at Weeks 6 and 26 and in both the CRP ≥ 10 mg/L at baseline stratum and the over all population. However, differences between the two treatment groups were not statistically significant at Weeks 6 and 26, and in both the CRP≥10 mg/L at baseline stratum and overall population. The only statistically significant difference was at Weeks 6 and 26 in the CRP ≥10 mg/L at baseline stratum. These results indicate a non significant treatment effect on the QoL of study subjects.

Table 40: Summary of patients with an Increase in IBDQ Global Score of ≥ 16 from baseline (IBDQ Response) in the overall Population- ITT Population

Scheduled Visit	Placebo (N= 328)	CDP870 400 mg (N=331)	p-value
Week 6			
n	328	327	
Frequency	139 (42.4)	151(46.2)	0.329
Weeks 6 and 26			
n	328	327	
Frequency	84(25.6)	101(30.9)	0.139

As seen from the above table, differences between the two treatment groups were not statistically significant at Weeks 6 and 26, in the Overall population. The pre-specified criteria were not met.

10.2.4.4 Short From Health Survey 36-item (SF-36)

The SF-36 is a generic health related quality of life questionnaire composed of 6 scales (physical functioning, role-physical, body pain, general health, vitality, social functioning, role-emotional, and mental health) which are grouped into a physical component summary score or a mental component summary score. Bodily pain and role physical scales of the SF-36 were examined in more detail than other scales since they were likely to be impacted by Crohn's disease and, therefore, expected to respond to treatment. For bodily pain, the adjusted mean sub-score was not statistically significantly ($p<.05$) different at Weeks 6 and 26 in both the CRP≥10 mg/L at baseline stratum and the overall population. The adjusted mean sub score was statistically significant for CDP 870 400 mg group compared to placebo at Week 6 and, Weeks 6 and 26.

Changes from baseline in sub-scores of the different scales and components of SF-36 were always positive in both treatment groups and tended to increase in magnitude overtime. However, the changes from baseline were similar for both treatment groups.

10.2. 4.5 Harvey Bradshaw Index (HBI)

The HBI is an instrument used to assess health-related quality of life based on a number of variables such as symptoms of the previous day for general well being, pain and number stools. In addition, the HBI also assesses abdominal mass and complications. HBI was assessed in the current study because it is used as a measure of efficacy in the extension studies CDP870-033 and CDP870-034. For the CRP≥10 mg/L at baseline stratum, mean HBI score at baseline was 9.9 (SD=3.37, n=145) in the CDP870 400 mg group and 10.1 (SD3.57, n=155) in the placebo group. Changes from baseline at week 26 were 4.5 (SD=4.22, n=79) and -3.5(SD+4.12, n=63) respectively. For the overall population, the mean HBI score at baseline was 9.8 (SD=3.3), n=330) in the CDP870 400 mg group and 9.7 (SD+3.24, n=325) in the placebo group. Changes from baseline at week 26 were -4.4 (SD+3.8, n=198) and -3.6 (SD=3.93, n=166), respectively.

10.4.3.1 FDA's Review of Efficacy Endpoints

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 41**) 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 CDP870 400 mg group (see table below). No difference was observed for the placebo group.

Table 41:

Analysis	Clinical Response at Week 6		Clinical Response at Weeks 6 and 26	
	CDP870 400 mg	Placebo	CDP870 400 mg	Placebo
LOCF	54	40	31	19
Observed	48	40	27	19

As seen from the above table, six subjects in the CDP870 400 mg 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 Week 6 and 26 in the applicant's analysis. If the six subjects in CDP870 400 mg group with missing observation were imputed as non-responders, then resultant the p-value will be as follows:

Table 42. 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 CDP870 400 mg 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 CDP870 400 mg group with missing observations. However, as seen on the above table, the reported applicant analysis with LOCF might not be robust.

10. 4.3.2 Intent to Treat Analysis

The 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) at Weeks 6 and 26. 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 the "true" ITT population, where the above subjects were included.

Table 43. Number of Subjects with Clinical Response at Week 6 and Weeks 6 and 26 in the CRP≥10 mg/ L at baseline Stratum (FDA's ITT Population Analysis)

Scheduled Visit	Placebo N=156	CDP870 400 mg 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.

Please refer to review by FDA statistician for detailed analysis.

10.4.3.3 Additional FDA Analysis for secondary efficacy endpoints

FDA statistician performed a number of analyses for sensitivity, disproportionate in gender and subgroup.

Table 44. Summary of Subjects with Clinical Response at Week 6 and Weeks 6and 26 Over all Population

Scheduled Visit	Placebo N= 329	CDP 870 400 mg N=333	p-value
Week 6			
Frequency (%)	88(26.7)	115(34.5)	**0.0350**
Week 6 and 26			
Frequency	54(16.4)	75(22.5)	**0.0501**

For the Overall ITT population, contrary to the applicant's analysis, FDA's analysis for clinical response at Week 6 showed statistical significance at Week 6 only but failed to achieve at Weeks 6 and 26 failed to show a treatment difference.

10.1.8 Reviewer's Efficacy Summary

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 in divergent 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 CDP870 400 mg treatment group and 26% of 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.

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 statistical Reviewer 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 37% and 26.3% for the CDP870 400 mg and placebo groups respectively. For Weeks 6 and 26, the rate was 21.2% and 8.4 % 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 significance for a 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 clinical response 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 imputed using the technique of LOCF which raises serious concern of the robustness of the data. If the missing data were considered as non-responders to be conservative, then the re-analysis of efficacy endpoints failed to achieve statistically significant results.

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 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.

10.1.9 Safety

10.1.9.1. 0 Methods and Findings

Safety was assessed by types and incidence of Adverse Events (AEs), discontinuations due to AEs, and drug–related serious and severe AEs, clinical laboratory assessments. Other safety variables include CDP870 and anti-CDP870 plasma levels, auto- antibodies, and fecal calprotectin.

10.1.9.1.1 Exposure.

The safety population was the population of all subjects randomized who received at least one injection of study treatment. The safety population included 660 subjects, 331 randomized to CDP870 400 mg and 329 randomized to placebo. The extent of exposure to study medication as assessed by number of injections ranged from 1 to 8 with mean injection of 5.8 for placebo and 6.4 for CDP870 400 mg treatment group. 6.4% of placebo and 3.3% of the treatment group received a single injection while 54.1% of placebo and 61.3% of the treatment group were administered the maximum 8 injections.

Table 45. Displays the number of injections for study

Number of Injections	Placebo (N=329)	CDP870 400 mg (N= 331)	Total (N= 660)
Number of injections (%)			
1	21(6.4%)	11(3.3%)	32(4.8%)
2	36(10.9%)	19(5.7%)	55(8.3%)
3	41(12.5%)	32(9.7%)	73 (11.1%)
4	24 (7.3%)	21(6.3%)	45(6.8%)
5	10(3.0%)	20(6.0%)	30(4.5%)
6	13(4.0%)	17(5/1%)	30(4.5%)
7	6(1.8%)	8(2.4%)	14(2.1%)
8	178(54.1%)	203(61.3%)	381(57.7%)
N	329	331	660
Mean(SD	5.8(2.6)	6.4(2.3)	6.1(2.5)
Median	8	8	8
Minimum	1	1	1
Maximum	8	8	8

The median number of injections of 8 and with a mean ragging from 5.8 for the placebo group to 6.1 for all subjects. In addition, the number of subjects that received 8 injections (that completed the study) as reported is 203, where as the number completed for analysis is 202.

10.1.9.2 Adverse Events (AEs)

AEs were recorded at Weeks 0, 2, 4, 6, 8, 12, 16, 20, 24 and 26/withdrwal visits. AEs (excluding SAEs) reported between Screening and first injection at week 0 was recorded as past medical history. In the CIMZIA group 269 of 331 subjects (81.3%) experienced a total of 1124 AEs compared with 260 of 329 subjects (79.0%) who experienced a total of 1095 AEs in the placebo group.

10.1.9.3 Deaths

There was one death during study CDP870-031.

- Patient 45102/0017, 22 year old while male randomized to CDP870 400 mg, received two injections of study medication on Feb-03-2004 and Feb-17-2004. Treatment regimen was discontinued due to grand mall seizure. Patient was found dead on ——— , 10 months after last injection. Death certificate listed acute myocardial infraction, hypertensive heart disease and metastatic lung disease. On note: patient had received 19 injections of infliximab prior to enrollment into study.

Reviewer's Comment: Subject's death seems unrelated to study medication. Subjects with a number risk factors that may have contributed to his death.

10.1.9.4 Other Serious Adverse Events

10.1.9.4.1 Malignancies

A total of nine malignancies were diagnosed during the trial. Of these, 4 were diagnosed in the placebo group and 5 in the CDP870 400 mg group. The neoplasms diagnosed in the CDP870 400 mg group are, one each of the following: dysplastic naevus syndrome, metastatic lung cancer, rectal cancer, tongue neoplasm and skin papilloma. The four neoplasms diagnosed in the placebo group are as follows: tongue neoplasm, an angiomyolipoma, cervical cancer stage 0 and a Hodgkin's disease. The malignancies in the CDP870 400 mg group were considered possibly related to study medication. The metastatic lung cancer was diagnosed 10 months after withdrawal and subject has a normal baseline chest x-ray.

10.1.9.4.2 Serious Adverse events (SAEs)

The number of patients with serious adverse events for the study is presented in the **Table 46 below.** In the CIMZIA group 34 of the 331 subjects (10.3%) randomized to the CDP870 400 mg group experienced a total of 49 SAEs. In the placebo group, 23 of 329 (7%) subjects experienced a total of 30 SAEs.

Table 46. Incidence of all SAEs by organ Class and Preferred Term

Primary System Organ Class	Placebo (N=329) n (%)	CIMZIA (N= 331) n (%)
Total number of SAEs	**30**	**49**
Total patients having SAEs	**23(7.0)**	**34(10.3)**
GI system disorders	13(4.0)	20(6.0)
Infections and infestations	3(0.9)	7(2.1)
Renal and Urinary disorder	1(0.3)	3(0.9)
Neoplasms benign & malignant	2(0.6)	2(0.6)
Injury, poisoning and procedural complications	2(0.6)	7(2.1)
Musculoskeletal and connective tissue	2(0.6)	1(0.3)
Cardiac disorders	1(0.3)	1(0.3)
Endocrine disorders	0	1(0.3)
Eye disorders	0	1(0.3)
CNS	0	1(0.3)
Vascular disorders	0	1(0.3)
Skin and subcutaneous tissue	1(0.3)	0
Blood and lymphatic disorder	1(0.3)	0
General disorders & administration site	1(0.3)	0
Hepatobiliary	1(0.3)	0

The incidences of SAEs between the two treatment groups were similar except for GI system disorders and infections, which were higher in the CDP870 400 mg group.

10.1.9.4.3 Serious Infection

Serious infection AEs that were observed in the study are listed in the table below. SAEs in the infection and infestations SOC occurred in 7 of 331 subjects (2.1%) who experienced a total of 9 SAEs in the CDP870 400 mg group compared with 3 of 329 subjects (0.9%) who experienced a total of 3 SAEs in the placebo group.

Table 47. Incidence of All serious infections and infestations AEs by Preferred Term

Preferred Term	Placebo (N= 329) n (%)	CIMZIA (N=331) n (%)
Total Number of AEs	3	7
Pneumonia	0	1(0.3%)
Perianal abscess	2	4(0.3%)
Abscess Limb	0	1(0.3%)
Sinusitis	1(0.3%)	0
UTI	0	1(0.3%)
Viral infection	0	0

10.1.9.4.4 Tuberculosis and Opportunistic Infections

There were no cases of tuberculosis or other opportunistic infections reported in the study.

10.5.1.4.5 Viral and other Infections of Interest

In the CIMZIA group 12of 331 subjects (3.6%) experienced a total of 13 AEs of herpes simplex, as compared to none in the placebo group. Eight of these AEs were classified as mild, 5 as moderate, and none as severe. Four subjects (1.2%) in the placebo group experienced a total of 4 AEs of herpes zoster and none in the placebo group.

10.1.9.4.6 Demyelinating Diseases

The following symptoms were observed and reported in the Nervous System Disorders that could represent signs or symptoms of a demyelinating disease: in the CDP870 400 mg group; hypoesthesia 0.6% (2/331), extrapyramidal disorder, ageusia, hypogeusia, and grandma convulsions in 0.3% (1/331), trigeminal nerve disorder in 0.3% (1/331) and paresthesia in 0.6% (2/331). The reported signs and symptoms in the placebo group include: Trigeminal nerve disorder in 0.3% (1/329), hypotonia in 0.3% (1/329) and paresthesia in 1.5% (5/329). However, no demyelinating disease AE diagnosis was reported.

10.1.9.5 Dropouts and Other Significant Adverse Events

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. A total of 76 (11.5%) subjects withdrew from the study due to AEs. Of these, 39 (11.9%) subjects were from the placebo group and whereas the remaining 37(11.2%) subjects were from the CDP870 400 mg group. Most AEs leading to withdrawal were associated with gastrointestinal disorders in both the placebo and CDP870 400 mg treatment groups. Most AEs

leading to withdrawal were associated with gastrointestinal disorders (7.9% for placebo and 8.9% for the CDP870 400 mg treatment group).

Table 48. Summary of AEs Leading to Withdrawal and Occurring in ≥1% of subjects

Preferred term	Placebo (N= 329)	CIMZIA (N= 331)
Total # of AEs leading to withdrawal	51	45
GI disorders	29(7.9)	28(8.5)
Crohn's disease	24(7.3)	19(5.7)
Abdominal pain	2(0.6)	4(1.2)

10.1.9.5.1 Overall profile of dropouts

Subjects who prematurely terminated the study were reviewed and are summarized in the table below. The major cause of withdrawal is lack of efficacy. The number of subjects that did not complete the study due to AEs was 39 for the placebo and 37 for the CDP870 400 mg group respectively. In addition, 23 (6.9%) subjects in the CDP 870 mg group withdrew from the study due "subject decision" compared to 9 (2.7%) in the placebo group.

Table 49. Summary of Subjects withdrawing by reason

Reason for withdrawal	Placebo (N=329) (%)	CIMZIA (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)

10.1.9.5.2 Adverse Events associated with dropouts

Table 50: Summary of All Adverse Events Leading to Withdrawal by System Organ Class and Preferred Term- Safety Population

System Organ Class Preferred Term	Placebo (N=329)	CIMZIA (N=331)
Total # of AEs Leading to Withdrawal	*51 (39, 11.9%	45 (36, 10.9%)
GI Disorders	**30 (26, 7.9%)**	**34 (19, 5.7%)**
Crohn's Disease	24 (24, 7.3%)	19 (19, 5.7%)
Abdominal pain	2 (2, 0.6%)	4 (4, 1.2%)
Diarrhea	1 (1, 0.3%)	2 (2, 1.2%)
Intestinal Obstruction	0	2 (2, 0.6%)
Nausea	1 (1, 0.3%)	2 (2, 0.6%)
Abdominal Distention	0	1 (1, 0.3%)
Acute Diverticulitis	0	1 (1, 0.3%)
Intestinal Fistula	0	1 (1, 0.3%)
Small Intestinal obstruction	0	1 (1, 0.3%)
Vomiting	0	1 (1, 0.3%)
Abdominal mass	1 (1, 0.3%)	0
Ileus	1 (1, 0.3%)	0
Infections and Infestations	**6 (6, 1.8%)**	**4 (4, 1.2%)**
Perianal Abscess	2 (2, 0.6%)	(2, 2, 0.6%)
Abscess Limb	2 (2, 0.6%)	1 (1, 0.3%)
Muscle Abscess	0	1 (1, 0.3%)
Herpes Zoster	2 (2, 0.6%)	0
Viral Infection	1(1, 0.3%)	0
Viral URI	1 (1, 0.3%)	0
Investigations	**1 (1, 0.3%)**	**3 (2, 0.6%)**
ALT increase	0	1 (1, 0.3%)
AST	0	1 (1, 0.3%)
Hepatic Enzyme increase	1 (1, 0.3%)	0
Endocrine Disorder	**0**	**1 (1, 0.3%)**
Goitre	0	1 (1, 0.3%)
Musculoskeletal & Connective Tissue	**1 (1, 0.3%)**	**1 (1, 0.3%)**
Arthralgia	0	1 (1, 0.3%)
Back pain	1 (1, 0.3%)	0
Nervous System Disorders	**1 (1, 0.3%)**	**1 (1, 0.3%)**
Grand Mal Convulsion	0	1 (1, 0.3%)
Dizziness	1 (1, 0.3%)	0
Skin & Subcutaneous Tissue	**1 (1, 0.3%)**	**1 (1, 0.3%)**
Hyperhidrosis	0	1 (1, 0.3%)
Pyoderma Gangrenosum	1 (1, 0.3%)	0

Blood and Lymphatic disorders	**2 (2, 0.6%)**	**0**
Anemia	1 (1, 0.3%)	0
Leukocytosis	1 (1, 0.3%)	0
Cardiac Disorders	**1 (1, 0.3%)**	**0**
Bradycardia	1 (1, 0.3%)	0
Congenital, Familial and Genetic disorders	1 (1, 0.3%)	0
Dermoid Cyst	1 (1, 0.3%)	0
General Disorder & administration Site Conditions	**4 (2, 0.6%**	**0**
Chest discomfort	1 (1, 0.3%)	0
Chest pain	1 (1, 0.3%)	0
Feeling Hot	1 (1, 0.3%)	0
Malaise	1 (1, 0.3%)	0
Injury, poisoning and Procedural complications	**1 (1, 0.3%)**	**0**
Femur Fracture	1 (1, 0.3%)	0
Neoplasms	1 (1, 0.3%)	0
Hodgkin's disease	1 (1, 0.3%)	0
Psychiatric	**1 (1, 0.3%)**	**0**
Depression	1 (1, 0.3%)	0

** Number of AEs, (number of patients, percentage of patients)*

No pattern was observed in the adverse events leading to withdrawal between the two groups.

10.1.9.5.3 Incidence of GI disorders AEs Occurring in > 1% of subjects

Table 51. Incidence of GI disorders AEs Occurring in > 1% of subjects by preferred Term-Safety Population

Preferred Term	Placebo (N=329) n = (%)	CIMZIA (N= 331) n (%)
Total number of AEs	291	277
Total Incidence of AEs	140(42.6)	139(42.0)
Abdominal pain	37(11.2)	37(11.2)
Crohn's disease	37(11.2)	33(10.0)
Nausea	27(8.2)	26(7.9)
Vomiting	11(3.3)	18(5.4)
Abdominal mass	11(3.3)	9(2.7)
Diarrhea	16(4.9)	9(2.7)
Abdominal pain upper	6(1.8)	8(2.4)
Hemorrhoids	2(0.6)	8(2.4)
Dyspepsia	11(3.3)	7(2.1)
GERD	3(0.9)	5(1.5)
Abdominal Distension	2(0.6)	5(1.5)

No pattern was observed between the two treatment groups.

Table 52: Incidence of Severe GI Disorders AEs by Preferred Term-

Preferred Term	Placebo (N=329) n %	CIMZIA (N=331) n (%)
Total number of AEs	37	34
Total incidence of AEs	25(7.6)	25(7.6)
Crohn's Disease	10(3.0)	8(2.4)
Abdominal pain/tenderness	9(2.7)	10(3.0)
Intestinal obstruction	1(0.3)	2(0.6)
Vomiting	1(0.3)	2(0.6)
Nausea	2(0.6)	1(0.3)
Intestinal Fistula	1(0.3)	1(0.3)
Abdominal adhesions	0	1(0.3)
Acute diverticulitis	0	1(0.3)
Anal Fistula	0	1(0.3)
Fecal incontinence	0	1(0.3)
Diarrhea/ Frequent BM	4(1.2)	1(0.3)
Small bowel obstruction	0	1(0.3)
Dysphagia	1(0.3)	0
GI motility disorder	1(0.3)	0
Ileus	1(0.3)	0
Esophagitis	1(0.3)	0

The incidence of AEs in the Gastrointestinal Disorders regardless of intensity and severity was similar between the CDP870 400 mg and the placebo groups. There was a 2.2% difference for any gastrointestinal AE with the CDP 870 400 mg group of 6.2% and placebo group 4%.

10.1.9.5.4 Other Significant AEs

10.5.1.5.1 AEs by Anti-CDP870 antibodies

In the CIMZIA group 305 / 331 (92.1%) tested negative to anti-CDP870 antibodies and 26/331 (7.9%) had a positive anti-CDP 870 antibody result. Of the subjects that tested negative for the anti-CDP 870 antibody, 246 of 305 subjects (80.7%) experienced a total of 10036 AEs compared to 23 of 26 subjects (88.5%) who tested positive. A single AE in the antibody positive subject led withdrawal from study compared to 35/ 305 (11.5%) antibody negative subgroups. The rate of reported incidences of Crohn's disease was 10.8 5 in the antibody negative subgroup as compared to no reported incidence in the antibody positive subgroup. The overall incidence was comparable between the two subgroups except for some incidences such headache

and abdominal pain which was higher in the antibody negative subgroup. The table below lists the summary of all AEs by organ class and anti-CDP870 antibody status.

Reviewer's comment: Antibody level detection in presence of certolizumab raises concerns of accuracy and interpretation of antibody indeterminate results.

Table 53: Summary of all AEs by Organ Class, Preferred Term and Anti-CDP870 Antibody Status

Organ Class	CIMZIA	
	Anti-CDP 870 antibody Negative (N= 305)	Anti-CDP 870 antibody Positive (N= 26)
Total Number of AEs	**1036 (246, 80.7%)**	**88 (23, 88.5%)**
GI Disorders	263 (129, 42.3%)	14 (10, 38.5%)
Infections and Infestation	194 (126, 41.3%)	20 (13, 50.0%)
Nervous system disorders	130 (70, 23.0%)	7 (6, 23.1%)
General disorder & administration site	82 (54, 17.7%)	14 (5, 19.2%)
Musculoskeletal & Connective tissue	68 (42, 13.8%)	6(4, 15.4%)
Skin and Subcutaneous tissue	50 (41, 13.4%)	4 (4, 15.4%)
Investigations	45 (31, 10.2%)	5 (4, 15.4%)
Psychiatric disorders	40 (26, 8.5%)	1 (1, 3.8%)
Respiratory, Thoracic & Mediastinal	45 (26, 8.5%)	6 (1, 3.8%)
Blood and Lymphatic system	22 (20, 6.6%)	1 (1, 3.8%)
Eye	20 (16, 5.2%)	1 (1, 3.8%)
Injury, poisoning and Procedural	16 (12, 3.9%)	3 (3, 11.5%)
Renal and Urinary	13 (12, 3.9%)	1 (1, 3.8%)
Reproductive and Breast	12 (10, 3.3%)	0
Vascular	2 (1, 0.3%)	0
Metabolic and Nutrition	6 (6, 2.0%)	0
Cardiac	7 (5, 1.6%)	0
ENT	7 (5, 1.6%)	0
Neoplasms	5 (5, 1/.6%)	0
Endocrine	2 (2, 0.7%)	1 (1, 3.8%)
Immune system	2 (2, 0.7%)	2 (1, 3.8%)

10.1.9.5.2 AEs Occurring within 30 minutes of Injection

There were a total of 148 AEs in the placebo group and 56 in the CDP 870 400 mg group occurring within 30 minutes of injection. Most of these AEs were observed in the placebo group, except for headache which had a higher incidence in the CDP 870 400 mg group. Incidence of AEs occurring within 30 minutes of injection in ≥1% of subjects for the safety population is presented in the table below.

Table 54. A summary of all AEs occurring within 30 minutes of injection in ≥1% of subjects

Preferred Term	Placebo (N=329) n (%)	CIMZIA (N= 331) n (%)
Total number of AEs	148	56
Total incidence of AEs	78(23.7)	36(10.9)
Headache	6(1.8)	10(3.0)
Injection site pain	20(6.1)	3(0.9)
Abdominal pain	6(1.8)	3(0.9)
Nausea	6(1.8)	3(0.9)
Injection site reaction	8(2.4)	0
Application site pain	7 (2.1)	0
Arthralgia	4(1.2)	0
Injection site burning	4(1.2)	0

10.1.9.5.3 Injection Reactions

Both the total number and total incidence of Local and Systemic Injection Reactions AEs of any intensity and severe intensity were lower in the CDP870 400 mg group compared with placebo group. Most of the Local and Systemic Injection Reaction AEs of any intensity occurred only in subjects from the placebo group with the most common AE being injection site pain. Among the common local and systemic injection reactions AEs, all but headache had a lower incidence in the CDP870 400 mg group compared with the placebo group. The tables below summarized the incidence of AEs in Local and Systemic Injection Reactions occurring in ≥1% of subjects and incidence of severe AEs in General Disorders and Administration Site Conditions for safety population.

Table 55.: Incidence of Local and Systemic Injection Reactions AEs Occurring in ≥1% of Subjects

Preferred Term	Placebo (N=329) n (%)	CDP870 400 mg (N=331) n (%)
Total number of AEs	157	64
Total incidence of AEs	84(25.5)	39(11.8)
Headache	6(1.8)	11(3.3)
Nausea	6(1.8)	4(1.2)
Injection site pain	21(6.4)	3(0.9)
Abdominal pain	6(1.8)	3(0.9)
Injection site erythema	4(1.2)	3(0.9)
Injection site reaction	9(2.7)	1(0.3)
Fatigue	4(1.2)	1(0.3)
Application site pain	7(2.1)	0
Injection site burning	4(1.2)	0
Arthralgia	5(1.2)	0

Table 56: Incidence of Severe General Disorders and Administration Site Conditions

Preferred term	Placebo (N=329) n (%)	CIMZIA (N=331) n (%)
Total number of AEs	21	4
Total incidence of AEs	10(3.0)	4(1.2)
Fatigue	4(1.2)	2(0.6)
Pyrexia	1(0.3)	1(0.3)
Asthenia	0	1(0.3)
Injection site pain	5(1.5)	0
Application site pain	1(0.3)	0
Injection site reaction	1(0.3)	0

10.1.9.8 Laboratory Findings

10.5.1.8.1 Overview of laboratory testing in the development program
General laboratory testing was performed according to the schedule outline in section 10.1.3

10.5.1.8.2 Selection of studies and analyses for drug-control comparisons of values

Study CDP870-031 was a randomized, blinded, placebo-controlled trial which allowed for direct comparison of drug vs. control in subjects with active Crohn's disease.

10.1.9.8.3 Standard analyses and exploration of laboratory values

The numbers of subjects with markedly abnormal values, and changes from baseline were examined in the study. No noticeable differences were observed between CDP870 400mg and placebo treatment groups in the number of subjects with markedly abnormal hematology value. However, mean absolute values of lymphocytes were consistently higher in the CDP870 400 mg group compared with the placebo group. Platelet and WBC values showed a small decrease in CDP 870 400 mg compared with placebo group.

Despite some changes in the mean values from baseline for RBCs, hemoglobin, hematocrit, basophils and eosinophils, no important trends across visits or differences between the two treatment groups were observed.

Fluctuations in the mean absolute values for total calcium, creatinine, glucose, potassium, sodium, total protein and urea were noted. However, no important trends or change across visits or differences between the two treatment groups were observed. In addition, no important trends in markedly abnormal biochemistry values were observed except for the higher number of subjects in the placebo group compared with the CDP870 400 mg group with markedly abnormal total calcium, potassium, ALT and AST.

10.1.9.8.4 Special assessments

Data were collected for the presence of auto-antibodies. Five of 188 subjects (2.7%) in the CDP870 400 mg group and 1 of 160 (0.6%) subjects in the placebo group who had a negative ANA at week 0 had a positive result at Week 26. For anti-dsDNA antibodies, 2 of 188 subjects (1.1%) in the CDP870 400 mg were negative at Week 0 and positive at Week 26 compared with 1 of 160 subjects (0.6%) in the placebo group. None of the subjects who withdrew before Week 26 had anti-nuclear or anti-dsDNA antibodies at withdrawal that were not present at Week 0.

10.1.9.9 Vital signs

Vital signs were collected according to the scheduled outlined on section 10.1.3. No patterns of abnormal vital signs were observed.

10.1.9.10 Electrocardiograms (ECGs)

No significant ECG changes were noted from baseline.

10.2 Study CDP870-32 (PRECiSE II)

Title: A Phase III muti-national, multi-center, double-blind placebo-controlled parallel group, 26 week study to assess the maintenance of clinical response to humanized anti- TNF PEG conjugate CDP870 400 mg sc, (dosed every 4weeks from 8-24), in the treatment of patients with active Crohn's disease who have responded to open induction therapy (dosed at Weeks 0, 2 and 4) with CDP870

10.2.1 Objectives

The primary objective was to compare efficacy of repeated every 4 weeks treatment with CDP870 versus placebo, following successful open induction therapy in subjects with active CD (CDAI between 220 and 450) scored over the 7 days prior to the first dose of study drug and C-Reactive Protein [CRP] ≥ 10 mg/ L at Baseline), in the maintenance of clinical response over 26 weeks.

The secondary objectives were

1. To evaluate the safety of CDP870 with every 4 weeks dosing over a 26 week period
2. To obtain data on the plasma concentrations of CDP870 and antibodies to CDP870
3. To evaluate the duration of response to open induction therapy with CDP870

10.2.2 Study Endpoints:

The evaluation of efficacy for study CDP870-032 was based on the following

Primary Endpoint: The proportion of subjects with clinical response at Week 26 (CDP870 vs Placebo) in the stratum defined by CRP ≥ 10 mg/ L at baseline. Clinical Response was defined at least a 100 point decrease in the week 26 CDAI score.

10.2.2.1 Secondary Endpoints:

In the population with CRP≥10 mg/L at baseline:

1. Time to disease progression up to week 26 (CDP870 vs Placebo). Time to disease progression is defined as the earliest event, in Week 6 responders of either an increase of ≥100 points above Week 6 CDAI, or an absolute CDAI≥175 points, for at least 2 consecutive visits or use of rescue therapy.

2. Proportion of subjects with clinical remission at Week 26, with Clinical Remission defined as CDAI score of 150 or less
3. Proportion of subjects with IBDQ response at Week 26, as defined as at least a 16 point increase from Week 0 IBDQ score.

In the overall population:

4. Clinical response of overall population

5. Time to disease progression up to and including Week 26
6. Proportion of patients in clinical remission at Week 26
7. Proportion of patients with IBDQ response at Week 26.

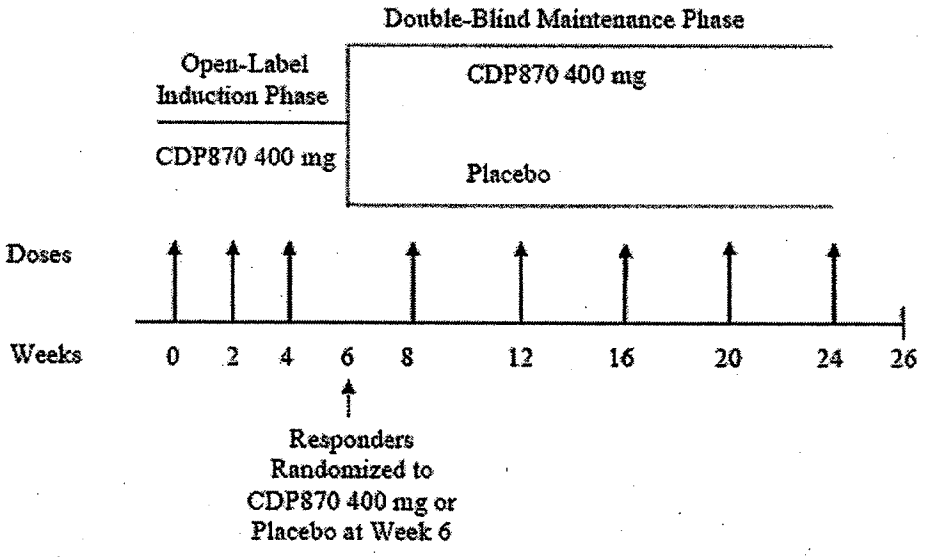
10.2.3 Study design overview:

Patients who demonstrate a clinical response (100 point decrease from Week 0 CDAI) at Week 6 following open induction therapy were randomized to blinded every 4 weeks dosing with 400 mg CDP870 or placebo for a total duration of 24 weeks.

This was a multicenter, double-blind, placebo-controlled, randomized within strata, parallel group with three 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.

The treatment and schedules are presented in **Tables 57 and 58**



10.2.3.1 Clinical assessments:

The clinical assessment conducted for study CDP870-032 was very similar to that of PRECiSE I and focused on measurements of CDAI, CRP, IBDQ and other parameters as scheduled in the table below.

Table 58: 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		X									X

And ds-DNA)											
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

10.2.4 Study population

Of note: The study population, the criteria use for inclusion and exclusion were similar to that of the PRECiSE I study.

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 entry) either by radiological, endoscopic or histological evidence, affecting the terminal ileum (L1), colon (L2) or ileo colon (L3) according to the Vienna Classification (1998)

3. Had active Crohn's disease (CDAI 220 and 450) 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.

Reviewer's comment: The following medications were allowed, no requirements were made for subjects who have failed conventional therapy.

Table 50: 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 51: 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

Medical History Exclusion

11. had current or recent history of severe, progressive, and 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 (AIDS) 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

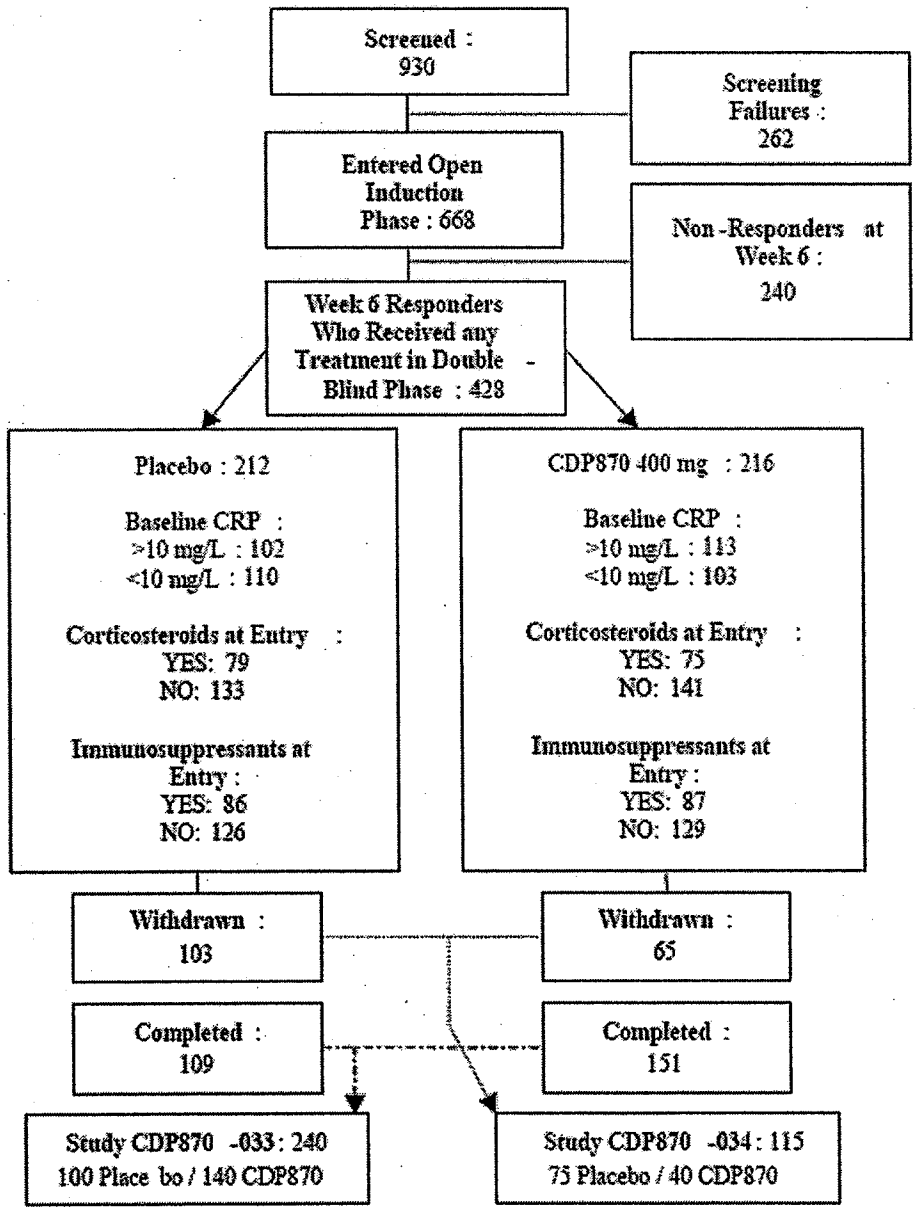
3. Any safety issues arose during the course of the study
4. The subject required defined rescue therapy to treat an exacerbation of their Crohn's disease.

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

10.2.5 Results:

Table 52: Subject Disposition



Of 930 subjects screened for the study, 668 entered the open-label induction phase and were treated with CDP870 400 mg at Weeks 0, 2 and 4. At Week 6, all subjects remaining in the study were assessed for clinical response. A total of 445 subjects (64.1%) had a decrease in CDAI score of $\geq$ 100 points from baseline at Week 6 and were randomized to the double –blind phase of the study. The submission states that 17 subjects of these never received double blind therapy

with CDP870 or placebo. These subjects were considered as non-responders for purpose of safety population and only considered in the open-label phase of the study. A total of 240 subjects (33.4%) were withdrawn during the induction phase. Rates of withdrawal during the induction phase were similar in the CRP > 10 mg/L, CRP< 10 mg/L and overall population (336.6%, 33.1% and 33.4% of subjects withdrew respectively). The most common reason for withdrawal during induction was lack of improvement or disease progression.

Table 53: Summary of subject Accountability- Open-label Induction Phase

Accountability	Open-Label CDP870 400 mg (N= 660) n (%)
Received Any Treatment	**668 (100%)**
Response at Week 6	
Number who responded	428 (64.1%)
Number of non-responders	240(35.9%)
Withdrawn During induction	**223 (33.4%)**
Reason for Withdrawal	
AE	44 (6.6%)
Protocol non-compliance	6(0.9%)
Subject decision	21(3.1%)
Clinical decision	19(2.8%)
Lost to follow up	4(0.6%)
Lack of improvement	159(23.8%)
Other	20(3.0%)

Table 54: Summary of Subject Accountability- Maintenance Phase

Accountability	Placebo (N=212) n= (%)	CDP870 400 mg (N= 216) n= (%)	Total Subjects (N=428) n= (%)
Received any treatment	212	216	428
Completed study	109 (51)	151(70)	260 (61)
Withdrawn during Maintenance	103(49)	65(30)	168(39)
Reason for Withdrawal			
AE	29(14)	21(10)	50(12)
Protocol non-compliance	0	1(0.5)	1(0.2)
Subject decision	13(6.0)	14(7)	27(6.0)
Clinical decision	13(6.0)	7(3.0)	20(5)
Lost to follow up	2(1.0)	1(0.5)	3(1)
Lack of improvement	75(35)	46(21)	121(28)
Other	6(3.0)	1(0.5)	7(2)

The most common reason for withdrawal during the maintenance phase of the study was lack of improvement/disease deterioration, followed by AE.

10.2.6 Protocol Deviations

There were 277 protocol deviations involving 233 subjects. In the double-blind phase of the study, 151 subjects who received double blind treatment had a total of 182 protocol deviations. In the treatment group, 73 subjects had a total of 88 deviations and in the placebo group, 78 subjects experienced 94 deviation. Nine subjects who were randomized to double-blind treatment, but did not receive any double-blind treatment had a total of 14 protocol deviations, 6 subjects randomized to placebo group and 3 subjects randomized to CDP870 400 mg.

Reviewer's comment: Most of these deviations were felt to be minor

10.2.7 Demographics and Other Baseline Characteristics

Baseline Demographics:

There were slight gender disparity between the treatment and the placebo groups. The open-label CIMZIA enrolled 43% male compared to 52% males in the placebo group. Overall the smoking history was similar. Subjects randomized to the treatment group had a lower mean weight and BMI than those randomized to placebo.

The history of CD among randomized patients was similar between the treatment and placebo groups. However, the median duration of disease was longer for subjects in the treatment group (6.7 years) compared to the placebo group (4.5 years).

The following table is a summary of subject demographic characteristics by treatment group for the Safety population:

Table 55: Summary of Demographic Characteristics at Screening

Characteristics	Open-label phase Non-responders	Open Label Phase Responders		Total subjects
	CDP870 (N=240)	Placebo N= 212	CDP870 N= 216	N= 665
Age				
Median	36	36	36	36
Sex				
Male (%)	114(48)	110(52)	92(43)	316(47)
Race				
Caucasian	229(95)	193(91)	203(94)	625(94)
Afro-Caribbean	3(1)	3(1)	2(1)	8(1)
Asian	1(0.4)	6(3)	7(3)	14(2)
Other	7(3)	10(5)	4(2)	21(3)
Weight (Kg)				
Mean(SD)	70.0(15.5)	72.3(17.40)	68.85(16.817)	70.38(17.442)
Body Mass Index ($Kg/M^{2)}$				
Mean (SD)	24.11(5.508)	24.56(5.49)	23.81(5.43)	24.16(5.48)
Smoking Status				
Never	107 (45)	99(47)	91(42)	297(45)
Stopped before CD	21(9)	15(7)	18(8)	54(8)
Stopped after CD	28(12)	21(10)	42(19)	91(14)
Current smoker	84(35)	77(36)	65(30)	226(34)
CRP level				
> 10 mg/ L		101	111	212
CDAI Score				
Mean		314	317	306

10.2.7 Efficacy Findings:

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.

10.2.7.1 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 56: Clinical Response in CRP≥ 10 mg/ L Strata at baseline with response at Week 26

Time Point	Placebo (N= 101)(%)	CDP870 400 mg (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 Stratum defined by CRP ≥ 10 mg/L at baseline was 62% 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
- Subjects with missing data were set to as non-responders (after imputation technique has been applied and withdrawal were taken into consideration)
- Subjects with missing data who were randomized to active treatment were set to non-responders and subjects with missing data who 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.

10.2.7.2 Secondary Efficacy analysis

10.2.7.2.1 Time to Disease progression:

Time to disease progression was defined as the earlier of the following two events in subjects who were randomized to CDP870 400 mg or placebo at Week 6:

- An increase of ≥ 100 points in the Week 6 CDAI score
- An absolute CDAI score ≥175 points for at least two consecutive visits

In the CRP ≥10 mg/L at baseline and overall population, the probability of disease progression was lower in subjects in subjects receiving CDP870 400 mg compared with subjects receiving placebo. The Kaplan Meier survival curves below present the results for both the Stratum CRP ≥10 mg/L and overall population.

Table 57 : Kaplan Meier Survival Curve for Time to Disease Progression in the in the CRP ≥10 mg/L at baseline : ITT population

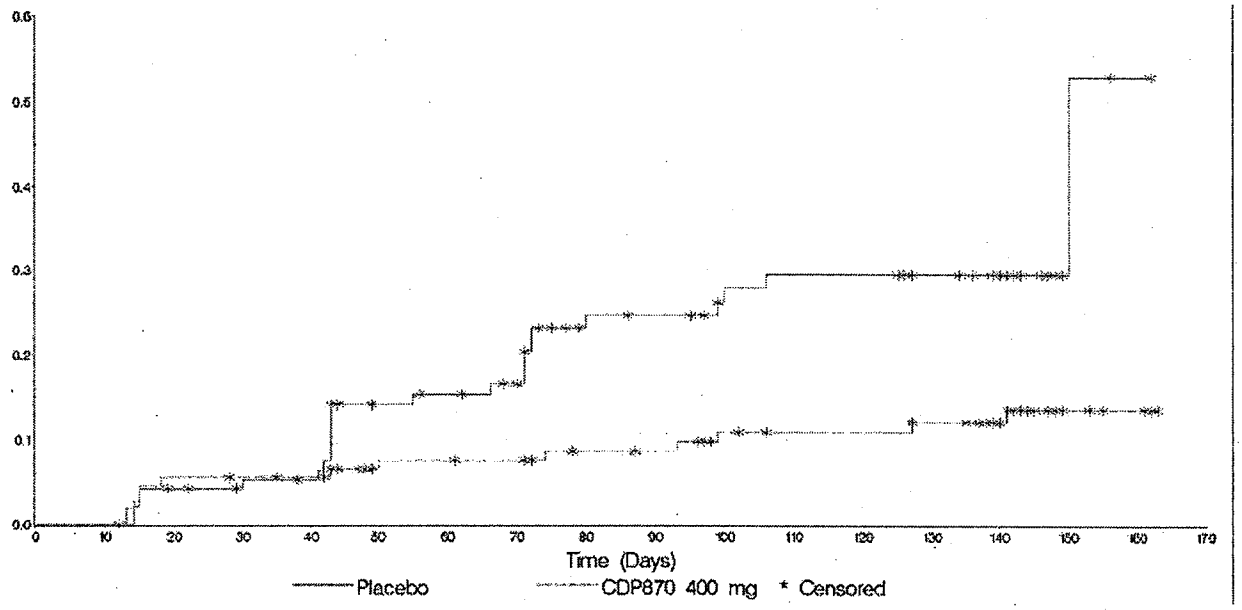
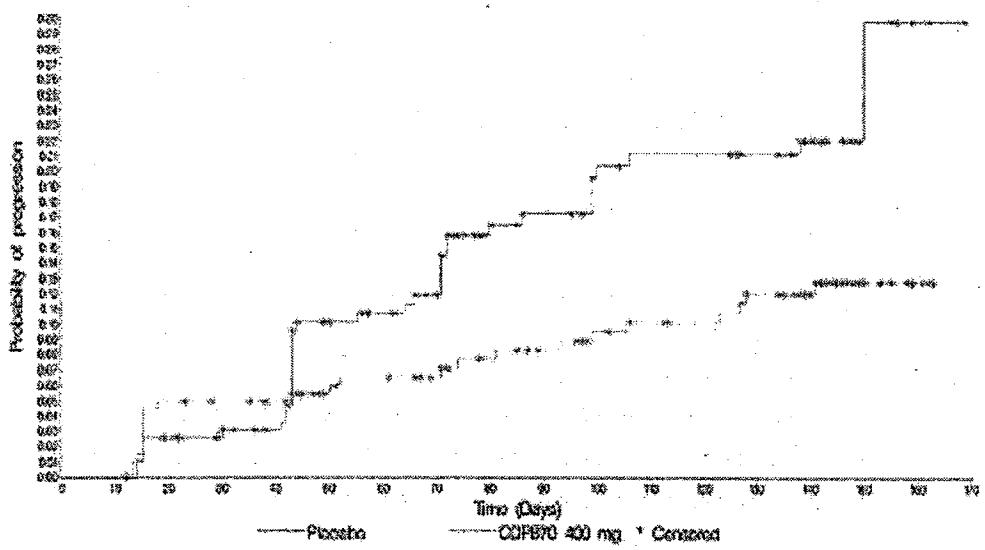


Table 58: Kaplan Meier Survival Curve for Time to Disease Progression in the Overall Population –ITT population.



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 (p=0.034).

10.2.7.2.2 Clinical Remission:

In the CRP ≥ 10 mg/ L at baseline stratum, 47 of 112 subjects (42%) randomized to CDP870 400 mg , 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 CDP870 400 mg treatment group was also statistically significant (48% vs 29%) compared to that of placebo group.

Table 59: 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.

10.2.7.2.3 Clinical Response

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

Table 60. 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.

10.2.7.2.4 IBDQ

IBDQ response and IBDQ global scores were measured in order to assess study treatment on Qol. IBDQ response was defined as in increase in IBDQ global score ≥16 points from baseline and was analyzed at Week 6, Week 16 and Week 26. The following table shows a summary of IBDQ response at weeks 6, 16 and 26 for the ITT population.

Table 61: Summary of Subjects with an IBDQ Response in the CRP≥10mg/ L at Baseline and Overall pollution: ITT

Time-point	CRP≥10 mg/L at Baseline		Overall population	
	Placebo N= 101	CDP870 N= 112	Placebo N= 210	CDP870 N=215
Week 6 Frequency	92(91%)	100(91%)	192(91%)	192(91%)
Week 16 Frequency	44(44%)	74(66%)	107(51%)	147(69%)
Week 26 Frequency	37(37%)	66(59%)	90(43%)	129(60%)
p-value		**<0.001**		**<0.001**

As seen from the above table, treatment differences between the two groups were statistically significant at Week 26.

10.2.7.2.5 Subgroup Analysis

The FDA statistician performed subgroup analysis of number of subjects in clinical response at Week 26 by treatment group and by subgroups for: country, gender, smoking, use of immunosuppressants and use of corticosteroids for the ITT population. The subgroup analysis results showed that the proportion of subjects in clinical response at week 26 was consistent for the subgroups of gender, smoking, use of immunosuppressant, and use of corticosteroids. It was also consistent for subgroups of country with the exception of U.S. For the U.S population, the proportions of subjects in clinical response at week 26 for the CDP870 group were similar to that of the placebo. It was inferred from this analysis that the overall efficacy results were driven from countries other than the U.S.

Table 62: In the CRP ≥10 mg/L Stratum at Baseline: (*Statistical Reviewer's ITT) Study CDP870-032 Clinical Response at Week 26

Category	CDP870 400 mg	Placebo	Difference	95% C. I.
Country				
Australia	4/5 (80.0%)	2/4 (50.0%)	30.0%	(-30.3%, 90.3%)
Canada	3/5 (60.0%)	2/7 (28.6%)	31.4%	(-23.0%, 85.9%)
Denmark	10/14 (71.4%)	6/14 (42.9%)		28.5% (-6.5%, 63.7%)
Germany	2/9 (22.2%)			
Hungary	8/10 (80.0%)	6/12 (50.0%)		30.0% (-7.6%, 67.6%)
Ireland	0/1 (0.0%)	1/3 (33.3%)	-33.3%	(-86.7%, 20.0%)
Israel	3/7 (42.9%)			
Lithuania	1/1 (100%)			
New Zealand	3/6 (50%)			
Norway	3/9 (33.3%)			
Poland	5/6 (83.3%)	1/9 (11.1%)	72.2%	(36.0%, 100.0%)
S. Africa	8/11 (72.7%)	2/7 (28.6%)	44.1%	(1.6%, 86.7%)
Serbia	12/16 (75.0%)	5/10 (50.0%)		25.0% (-12.6%, 62.6%)
Singapore	2/3 (66.7%)			
Ukraine	2/2 (100.0%)	1/3 (33.3%)	66.7%	(13.3%, 100.0%)
U.S.	5/12 (41.7)	9/21 (42.9%)		-1.2% (-36.2%, 33.8%)
Gender				
Male	38/55 (69.1%)	17/55 (30.9%)	38.2%	(20.9%, 55.5%)
Female	33/63 (52.4%)	18/52 (34.6%)	17.8%	(-0.1%, 35.6%)
Smoking				
Current smoker	22/40 (55.0%)	17/44 (38.6%)	16.4%	(-4.7%, 37.4%)
Never smoked	26/46 (56.5%)	15/48 (31.3%)	25.2%	(5.8%, 44.7%)
Stopped after diagnosis of Crohn's disease	13/20 (65.0%)	2/12 (16.7%)	48.3%	(18.6%, 78.0%)
Stopped before diagnosis of Crohn's disease	10/12 (83.3%)	1/3 (33.3%)	50.0%	(27.4%, 100.0%)
Immunosuppressants				
Current therapy				
Yes	29/48 (60.4%)	11/43 (25.6%)	34.8%	(15.9%, 53.8%)
No	42/70 (60.0%)	24/64 (37.5%)	22.5%	(6.0%, 39.0%)

Corticosteroids				
Current therapy				
Yes	22/44 (50.0%)	14/45 (31.1%)	18.9%	(-1.1%, 38.9%)
No	49/74 (66.2%)	21/62 (33.9%)	32.3%	(16.4%, 48.3%)

*Compiled by FDA statistical reviewer.

10.2.7.6 Reviewer's Efficacy Summary

The primary objective of study CDP870-032 was to compare efficacy of repeated 4-weekly treatment with CDP870 versus placebo in subjects with active Crohn's Disease with CRP $\geq$ 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 met the stated primary efficacy endpoints in that the percentage of subjects with clinical response at Week 26, in the stratum defined by CRP $\geq$ 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 $\geq$ 10 mg/ L at Baseline stratum and overall population, clinical remission at week 26 in both the CRP $\geq$ 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.

10.2.8 Evaluation of Safety

10. 2.8.0. Methods and Findings

All subjects received CDP870 400 mg at weeks 0, 2 and 4 results in three doses of therapy to the placebo group. Safety was assessed by types and incidence of AEs, discontinuations due to AEs, and drug-related serious and severe AEs, clinical laboratory assessment. Other safety variables include circulating CDP870 and anti-CDP870 plasma levels, and auto antibodies, and fecal calprotectin.

10. 2.8.1 Exposure

Study subjects received open-label induction with CDP870 400 mg at Weeks 0, 2 and 4. Responders were then randomized in a 1:1 ratio at Week 6 either to receive CDP870 400 mg or placebo at 4 weekly intervals from Week 8 to Week 24.

Table 63 : Extent of Exposure – Double Blind Maintenance Phase

Number of Injections	Placebo N= 212	CDP870 N= 216	Total N= 428
Number (%) 1 injection	36 (17)	26(12)	62(15)
Number (%) 2 injections	37(18)	17(8)	54(13)
Number (%) 3 injections	21(10)	17(8)	38(9)
Number (%) 4 injections	7(3)	6(3)	13(3)
Number (%) 5 injections	111(52)	150(69)	261(61)
Mean	3.6	4.1	3.8
Median	5	5	5
Minimum	1	1	1
Maximum	5	5	5

In the open-label induction phase of the study, 668 subjects received at least 1dose of CDP870 400 mg. The majority of subjects (93%) received three doses of the CDP870 400 mg. In the double –blind maintenance phase of the study, 216 subjects received at least one dose of CDP870 400 mg and 212 subjects received at least one dose of placebo. Of subjects randomized to CDP870 treatment arm 96.4% received all five injections.

10. 2.8.2 AEs

AEs were recorded at Weeks 0, 2, 4, 6, 8, 12, 16, 20, 24 and 26. During the open-label phase of the study, 392 of 668 subjects (59%) experienced a total of 1094 AEs. Of these, 163 were from the 240 subjects (68%) who were non-responders to the open-label induction, and 229 were from the 428 subjects (54%) who responded to the open-label induction.

10.2.8.3 Deaths

Only one death was reported during the study period. The report stated that a 36 year old male subject with past medical history for depression was found dead from fentanyl overdose. The subject had received a single dose of CDP870 at Week 0. Death was confirmed by autopsy. The cause of death was deemed not study drug related. No death occurred during the double blind phase of the study.

10.2.8.4 Other Serious AEs

10.2.8.4.1 Malignancies

No malignancies were reported during the study period.

10.2.8.4.2 Serious Adverse Events (SAEs)

The number of subjects with SAEs for both the induction and maintenance phases of the study is presented in the **Tables 64 and 66** below.

Primary System Organ Class	Open label Induction Phase		
	Non Responders N=240 (%)	Responders N= 428(%)	Total N= 668(5)
Total number of SAEs **Total patients having SAEs**	**51** **42(18)**	**5** **5(1.2)**	**56** **47(7)**
GI system disorders	28(12.0)	1(0.2)	29(4.0)
Infections and infestations	11(5)	1(0.2)	12(2.0)
Respiratory	1(0.4)	0	1(0.1)
Injury, poisoning and procedural complications	1(0.4)	0	1(0.1)
Endocrine disorders	0	1(0.2)	1(0.1)
Skin and subcutaneous tissue	1(0.3)		0
Blood and lymphatic disorder	1(0.4)	0	1(0.1)
General disorders & administration	2(0.8)	1(0.2)	3(0.4)

Primary System Organ Class	Double blind Maintenance Phase	
	Placebo N=212 (%)	CDP 870 N=216 (%)
Total number of SAEs **Total incidence of SAEs**	**19** **14 (7)**	**19** **12 (7)**
Infections	**2**	**6(3)**
Perineal abscess	0	2(1)
Perianal abscess	0	1(0.5)
Pneumonia	0	1(0.5)
TB	0	1(0.5)
Abdominal abscess	1(0.5)	1(0.5)
Bacteremia	1(0.5)	0
General disorders	9(4)	4(2)
Renal and Urinary	0	2(1.0)
Respiratory	0	2(0.9)
Blood and Lymphatics	0	1(0.5)

Metabolism	2(1)	1(0.5)
Immune System	1(0.5)	0

During the open-label induction phase of the study, 47 of 668 (7%) subjects experienced a total of 56 SAEs. Most of these were in 42 of 240 (18%) non-responders who experienced a total of 51 SAEs. The difference of SAEs between the responders and non-responders were mainly due to higher incidence of GI system disorders.

In the double-blind maintenance phase, the incidence of SAEs was similar between the treatment and the placebo groups.

10.2.8.4.3 Serious Infections

The incidence of serious infections is summarized in the following table.

Table 65 : Summary of Serious infections in both the open label and double blind phases

Infections and Infestations	Open label Phase		Double Blind Phase	
	Non Responders N= 240 (%)	Responders N= 428(%)	Placebo N= 121	CDP870 N=216
Total incidence	**11(5)**	**1(0.2)**	**2(1)**	**6(3)**
Perianal abscess	4(2)	0	0	3(2)
Abdominal abscess	4(2)	0	1(0.5)	0
Viral GI	0	1(0.2)	0	0
Pneumonia	1(0.4)	0	0	1(0.5)
TB	**0**	**0**	**0**	**1(0.5)**
PID	1(0.4)	0	0	0
Bacteremia	0	0	1(0.5)	1(0.5)
Pyelonephritis	1(0.4)	0	0	0

In both the induction and maintenance phases, the most common serious infection was perianal / abdominal abscess. There was only one case of TB reported during the duration of the study, which was in the CIMZIA group.

10.2.8.4. 4 Dropouts and other Significant AEs
The table below presents dropouts and other significant AEs in both the open-label and double-blind phases. In the open-label phase the dropout and AEs rates are compared between responders and non-responders. In the double-blind phase, the responders from the open-label phase are compared after randomization to either placebo or CIMZIA treatment group.

Table 66: Summary of AEs leading to Withdrawals by System Organ Class and Preferred Term

Primary System Organ Class Preferred Term	Open label Phase		Double Blind Phase	
	Non Responders N=240 (%)	Responders N=428(%)	Placebo N=212	CDP870 N=216
Total # of AEs	61, 47 (20)	4, 4 (1)	34, 28 (13)	25, 18 (8)
GI	18 , 17 (8)	25, 10 (5)	18, 17 (8)	11, 10 (5)
Infections	6, 5 (2)	5, 5 (2)	6, 5 (2)	5, 5 (2)
Skin & subcutaneous	1, 1 (0.4)	0	0	4, 3 (1.4)

In both the open-label induction and double-blind maintenance phases of the study, CD under GI disorders was the leading cause of study withdrawal. Twenty four of 668 (3.6%) subjects in the induction phase and 10 of 216 (4%) of the CDP870 phase of the double blind phase withdrew due to GI AEs. There is no significant difference in AEs leading to withdrawal between the phases or the groups.

10.2.8.5. Other significant AEs

10.2.8.5.1 AEs by Anti-CDP870 antibodies

As with study CDP870-032, a positive anti-CDP870 status was defined as a subject who had an anti-CDP870 antibody level of > 2.4 U/ L at one or more visits.

In the open induction phase of the study, 58 of 668 subjects (8.7%) tested positive for anti-CDP870 antibodies and 603 of 668 subjects (90.3%) were negative. In the antibody positive group 33 of 58 subjects (57%) experienced AEs, compared with 356 of 603 (59%) subjects in the antibody negative group. The incidence , intensity and relationship to study drug was similar in both groups.

During the double-blind maintenance phase of the study, 18 of 216 subjects (8.3%) in the CDP870 mg treatment group tested positive for antibodies to CDP870 and 196 subjects (91%) were antibody negative. Thirteen subjects (72%) in the antibody positive group experienced AEs,

compared with 125 subjects (64%) in the antibody negative group. The relationship of AEs to the study medication was similar in both antibody groups. A higher percentage of subjects in the antibody positive group experienced severe AEs (4 of 18, 22%) compared with the antibody-negative group (11 of 196 , 6%).

10.2.8.6 Safety Conclusions:

There were no differences in incidence of malignancies between the treatment groups. There were no cases of demyelinating disease reported during the study period.

The incidence of SAEs was similar for both treatment groups. One death occurred during the study period that was attributed to fentanyl overdose.

Although all subjects were screened at baseline for TB with a PPD skin test and Chest X-ray, one subject receiving CDP870 in the double blind phase was diagnosed with pneumonia and pleural effusion secondary to TB.

The most frequent AEs in the open-label phase were headache, CD, urinary tract infections and abdominal pain. The most common AEs in the double blind phase were headache, nasopharyngitis in the CDP870 group, and CD , headache, and abdominal pain in the placebo group.

In the double-blind phase, the total incidence of AEs in the infections and infestations SOC was higher in CDP870 group (33% vs. 26%) compared in the placebo group.

The total incidence of AEs and SAEs in anti-CDP870 antibody positive subjects was lower when compared to antibody- negative subjects in the open-label phase of the study. However, in subjects randomized to CDP870 group in the double-blind phase, the incidence of AEs (72% vs 64%) and SAEs (11% vs 5%) was greater in the anti-CDP870 antibody positive subjects compared with antibody negative subjects. In the double-blind phase a greater number of antibody-positive subjects withdrew due to AEs (2 of 18 , 11%) compared to with antibody-negative subject (16 of 169 , 8%).

There were no significant trends in the laboratory or vital signs data suggestive of a significant safety signal for CDP870.

10.3 III. Study CDP870-005 (Phase 2)

Title: A phase 2, multi-center, double blind, placebo-controlled, parallel group, dose-response study to assess the safety and efficacy of CDP870 dosed subcutaneously in patients with active Crohn's disease.

Objectives:
Primary objective:

To evaluate CDP870 (100, 200, and 400 mg) compared to placebo in achieving a clinical response at 12 Weeks, following dosing at 0, 4, and 8 Weeks.

Secondary objectives:

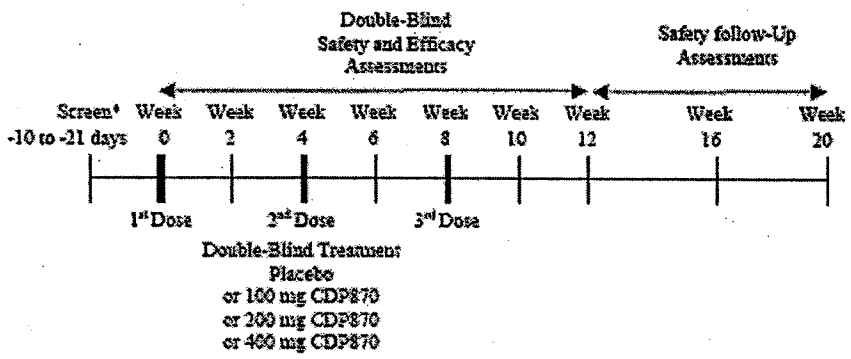
- To evaluate a single dose of CDP870 (100, 200 or 400 mg) compared to placebo in achieving a clinical response within 4 weeks of treatment.
- To evaluate the tolerability and safety of CDP870 in patients with active CD
- To obtain data on the plasma concentrations of CDP870 and anti-CDP870 antibody levels up to 20 weeks following dosing at 0, 4 and 8 weeks.

Study Design:

In this study three CDP870 treatment groups (100, 200 and 400 mg) were compared to placebo over a 20 week period. Patients were randomized in a ratio of 1:1:1:1 and stratified according to whether or not they were receiving steroids, immunosuppressants or long term anti-infectives at screening. Patients received a total of 3 doses SQ at Weeks 0, 4 and 8. Double blind assessments were conducted at weeks 0, 2, 4, 6, 8, 10 and 12. Efficacy and safety assessments were continued to week 20.

A total of 260 eligible patients were randomized, 65 to each of the 4 treatment groups.

Table 67: Treatment scheme



Study Endpoints:

Primary Endpoint:
The primary analysis was the comparison of subjects with clinical remission who received 400 mg CIMZIA to that of placebo. Clinical remission as defined the percentage of patients with decrease in CDAI≥100 points from pre-injection or who achieve remission (CDAI score ≤150) at 12 weeks.
Secondary Endpoints:

1. CDAI, actual change from baseline at Weeks 2, 4, 6, 10 and 12
2. The percentage of patients with a decrease in CDAI of ≥100 points or who achieved remission (CDAI≤150) at week 2,4,6, 8 and 10
3. Time to first decrease in CDAI of ≥100 points or to remission measured from baseline.
4. The percentage of patients with a decrease in CDAI of ≥70 points at Weeks 2, 4, 6, 8, 10 and 12.
5. Time to first decrease in CDAI of ≥70 points measured from baseline.
6. The percentage of patients in remission at Weeks 2, 4, 6, 8, 10 and 12.
7. Time to first remission measured from baseline.
8. The percentage of patients with a ≥30% reduction from baseline in CDAI at Weeks 2, 4, 6, 8, 10 and 12.
9. Percentage reduction in CDAI from baseline at Weeks 2, 4, 6, 8, 10 and 12.
10. Disease activity, measured as AUC of CDAI scores and change in CDAI scores from pre-first dose (using LOCF).
11. The percentage of patients showing a closure of at least 50% of fistula(e) on any 2 consecutive visits, for the subgroup of patients with fistula (e).
12. IBDQ and IBDQ categories, actual and change from baseline at Weeks 2, 4, 6, 8,
13. CRP, actual and change from baseline at Weeks 2, 4, 6, 8, 10, 12, 16 and 20.

14. Time to rescue medication/hospitalization for exacerbation of Crohn's disease assessed during the study (Weeks 0 to 20).

15. Patient diar y card information, fistula(e) assessment

SELECTION OF STUDY POPULATION

A. Inclusion Criteria

Patients recruited to the study conformed to the following criteria:

(i) Patients were to be able to understand the information provided to them and give written informed consent.

(ii) Clinical diagnosis of Crohn's disease confirmed either by radiological, endoscopic or histological evidence.

(iii) Active Crohn's disease (CDAI $\geq$220 and $\leq$450) scored over the week prior to the first study dose, in order to ascertain the current level of disease.

(iv) Patients aged 18 years or above at Screening.

(v) Sexually active females of childbearing potential (not surgically sterile or post-menopausal) who could become pregnant, had to be using effective birth control (combination hormonal oral contraception; injectable or implantable hormonal contraception, intrauterine contraceptive device with spermicide [barrier methods were not acceptable]) and be willing to continue precautions for six months after the final dose of CDP870. The patient was to report any signs of pregnancy during the study period and for six months after the final injection to the investigator. A blood or urine pregnancy test was to be completed prior to each dose for all women of childbearing potential.

(vi) Patients had to meet all concomitant medication criteria. For all drugs being taken at Screening, the patient had to remain on a stable dose throughout the duration of the double-blind phase of the study (12 weeks).

Table 68: Concomitant Medication - Inclusion Criteria

Drug class	Drug	Dose	Stable treatment required prior to Screening	Additional comments
Steroids	Prednisone or prednisolone	≤30 mg/day	2 weeks	Total duration of steroid treatment must have been ≥4 weeks
	Budesonide	≤9 mg/day	2 weeks	
	Methylprednisolone	≤24 mg/day	2 weeks	
Other immuno-suppressants	Azathioprine 6-mercaptopurine	Stable dose	8 weeks	Total duration of therapy must have been ≥3 months
	Methotrexate	≥12.5 mg/week	8 weeks	Total duration of therapy must have been ≥3 months
Anti-infectives	Antibiotics (long-term)	Stable dose	4 weeks	Short additional course for acute infection allowed.
5-Amino-salicyclic acid (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	Treatment was not to be commenced during the study before Week 12

B. Exclusion Criteria

Patients were not eligible for enrolment into the study if any of the following exclusion criteria applied:

(i) Acute suppurative infection of a fistula (abscess) present at Screening.

(ii) Ulcerative colitis.

(iii) Bowel perforation or evidence of non-inflammatory obstruction (for example, fixed stenosis seen at endoscopy or radiographically) within 6 months prior to screening.

(iv) History of obstructive symptoms (e.g. post-prandial abdominal pain, nausea and vomiting) within 3 months prior to Screening. Patients must have had a small bowel X-ray series to rule out significant mechanical obstruction. Any patient showing a narrowed bowel segment with proximal dilations (indicating a significant and fixed bowel obstruction) was to be excluded.

(v) Extensive bowel resection (greater than 100 cm of small bowel and/or more than the right side of the colon resected).

(vi) Functional colostomy or ileostomy note: patients who had a temporary stoma in

the past, which had been reversed, were eligible to enter the study).

(vii) Positive stool laboratory results for enteric pathogens.

(viii) Did not meet any of the concomitant medication criteria in T-Table 2.

Table 69: Concomitant Medication – Exclusion Criteria

Drug Class	Exclusion Criteria
Steroid/corticotroplin	Any therapy for indications other than Crohn's disease (Note: sparing use of topical hydrocortisone for skin disease or not more than 800 µg/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, long-term anti-infectives	Discontinuation within 4 weeks of Screening
Sodium cromoglycate, cyclosporin, mycophenolate	Regular treatment for Crohn's disease within 4 weeks of Screening
Opioid-containing analgesics (including codeine). Non-steroidal anti-inflammatory drugs (including all cyclo-oxygenase inhibitors)	Treatment with more than 4 doses within 2 weeks of Screening (including self-medication) (Note: This did not include permitted opioids when taken for the control of diarrhoea, i.e. loperamide, diphenoxylate/atropine, codeine phosphate)

Previous Clinical Trials and Anti-TNFα Therapy Exclusion

(ix) Participation in a clinical trial of antibody, cytokine or other immunomodulatory therapy within 12 weeks of Screening or in any other clinical drug trial within four weeks prior to Screening.

(x) Treatment with another biological anti-TNFα therapy within 12 weeks of screening.

(xi) Previous participation in a clinical trial with CDP870.

(xii) Previous treatment with any anti-TNFα therapy resulting in an infusion reaction which was suspected or confirmed to be associated with an immune response? (e.g. human anti-chimeric antibody).

(xiii) Previous treatment with an y anti-TNFα therapy where there was a lack of clinical response to the first dose.

Medical History Exclusion Criteria

(xiv) Current or recent history of severe, progressive, uncontrolled renal, hepatic, hematological, gastrointestinal, endocrine, pulmonary, cardiac, neurological, or cerebral disease.

(xv) Any patients with a history of either current, recurrent, chronic, recent (minimum three months prior to Screening) serious infection (including, but not limited to, opportunistic infections such as cytomegalovirus [CMV], *Pseudomonas carinii*, atypical mycobacterium, herpes zoster) or patients who has ever had a life-threatening infection; these patients would be excluded due to the potential immunosuppressant effects of anti-TNFα therapy.

(xvi) History of TB or evidence of previous infection with TB on a chest X-ray (X-ray must have been taken within three months prior to Screening); these patients would be excluded in view of a potential link between TB and anti-TNFα therapy.

(xvii) Known history of or concurrent hepatitis or Human Immunodeficiency Virus (HIV) infection.

(xviii) Concurrent malignancy or a history of malignancy (other than carcinoma of the cervix or basal cell carcinoma successfully treated more than 5 years prior to Screening); these patients would be excluded due to safety concerns related to potential progression of the malignancy.

(xix) Concurrent bowel dysplasia or a history of bowel dysplasia in the five years prior to Screening.

(xx) History of a lymphoproliferative disorder including lymphoma or signs and symptoms suggestive of lymphoproliferative disease at any time.

(xxi) Pregnant (to be tested in any woman who was potentially fertile at Screening and prior to each dose of study drug) or lactating females.

(xxii) Known recent drug or alcohol abuse.

(xxiii) History of clinically important allergies or multiple drug allergy.

(xxiv) Any other condition which made the patient 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 anaemia) or demyelinating disease (e.g., multiple sclerosis, myelitis, optic neuritis).

Laboratory Parameter Exclusion Criteria

(xxv) Clinically significant abnormal hematology or biochemistry values at Screening unless abnormalities considered by the investigator to be related to Crohn's disease. In particular

- Hemoglobin <10 g/dL or hematocrit <30%
- White blood cells (WBC) <3 × 10^9/L (<3,000/mm^3)
- Platelets <100 × 10 g/L (<100,000 mm^3)
- Serum creatinine >1.5 × upper limit of normal (ULN) for the patient's age and sex
- Plasma bilirubin >35 μ mol/L
- >3 × ULN of the following liver enzymes:
  Plasma aspartate aminotransferase (AST)
  Alanine aminotransferase (ALT)
  Alkaline phosphatase

Other Exclusion Criteria

(xxvi) Non co-operation or unable to comply with the study procedures.

Results:

The study was conducted between February 15 2001 and March 12, 2002 at 58 centers in a total of 10 countries. Of the 292 patients who were randomized and received study medication, 207 completed the study (week 20 visit).

Table 70: Number of subjects per study arm

Population	Number of patients (%) [a]				
	Placebo (N=73)	CDP870			Total (N=292)
		100 mg (N=74)	200 mg (N=72)	400 mg (N=73)	
All Patients	73 (100.0)	74 (100.0)	72 (100.0)	73 (100.0)	292 (100.0)
Safety	73 (100.0)	74 (100.0)	72 (100.0)	73 (100.0)	292 (100.0)
ITT	73 (100.0)	74 (100.0)	72 (100.0)	72 (98.6)	291 (99.7)
PP	61 (83.6)	59 (79.7)	56 (77.8)	61 (83.6)	237 (81.2)

Demographic and Baseline Characteristics:

Demographic characteristics for the safety, ITT and PP populations are presented in the following **table 71**:

Table 71

Characteristic	Placebo N=61	CDP870 100 mg mg N=59	CDP870 200 mg N=56	CDP870 400 N= 61	Total patients N= 237
Age					
Median	36	33	40	35	36.6
Gender					
Male	20	29	18	25	92
Duration CD					
Mean (year)	7.95	7.73	8.84	8.60	
Anti-TNF Therapy?					
Yes	16	18	17	13	
No	57	56	55	60	

Efficacy results

Table 72: Summary of responders at Weeks 6 and 12

Time	Placebo (N=73)	CDP870 400mg (n=72)	p-value
Week 6	**24 (32%)**	**34 (47%)**	**0.078**
Week 12	**26 (36%)**	**32(44%)**	**0.278**

10.1.10 Conclusions:

As can be seen from the above results the primacy efficacy endpoints for the phase II study failed to achieve statistically results for stated time period of 12 weeks. In addition, clinical response assessment for Week 6 also was not statistically significant.

Study CDP870-005 had a different dosing scheduled that the pivotal studies, subjects were dosed at Weeks 0, 4, and 8 as opposed to the pivotal study dosing schedule of Weeks 0, 2 and 4. In addition, efficacy analysis was conducted at Week 12 as opposed to Week 6 clinical response analysis of the pivotal studies. Because of the differences in dosing schedule, time for efficacy analysis and endpoints, data from the study was not pooled with that of the pivotal studies.

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