CENTER FOR DRUG EVALUATION AND RESEARCH

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STATISTICAL REVIEW(S)

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

BLA/Serial Number:	125160/0
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Biometrics Division:	Division of Biometrics 3
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Keywords: clinical study, biological product, data quality, imputation, sensitivity analysis, single study

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1. EXECUTIVE SUMMARY

1.1 Conclusions and Recommendations

For Study CDP870-031, the sponsor's results for the co-primary endpoints, clinical response in the CRP $\geq$ 10 mg/L at baseline stratum at Week 6 and clinical response at both Weeks 6 and 26 were borderline with p-values of 0.037 and 0.045 for the Week 6 and Weeks 6 and 26 endpoints, respectively.

The treatment effect at Week 6 was small and ranged from 4.0% to 11.4 % depending on which analysis was performed. P-values for the various sensitivity analyses ranged from 0.037 to 0.547.

The proportion of subjects where at least one of the subtotals for the CDAI score was imputed was high (19.5%, 59/302) in the CRP $\geq$ 10 mg/L stratum at baseline for all visits. With such a high percentage of subjects with CDAI imputation, the results derived from the imputed scores should be interpreted with caution. .

From this reviewer's findings from a post-hoc exploratory analysis of clinical response at Week 6 by baseline CDAI, it was found that certolizumab pegol might be efficacious for subjects with baseline CDAI score above 300. However this would require confirmation by a new, well-controlled clinical study.

In summary, this reviewer finds the strength of evidence from Study CDP870-031 to support an induction claim is not substantial, as the efficacy results are both marginally significant and sensitive to data assumptions. However, the results from study CDP870-031 are statistically significant according to the sponsor's pre-specified analysis.

1.2 Statistical Issues and Findings

For Study CDP870-031, the sponsor's results for the co-primary endpoints, clinical response in the CRP $\geq$ 10 mg/L at baseline stratum at Week 6 and clinical response at both Weeks 6 and 26 are marginally significant with p-values of 0.037 and 0.045, at Week 6 and at Weeks 6 and 26, respectively.

Per this reviewer's request, the sponsor supplied additional information regarding subject disposition and clinical response through Week 6 and Week 26.

From these data, it is observed that there was a disproportionate number of subjects who discontinued prior to Week 6 (34 (22%) for placebo and 16 (11%) for certolizumab pegol, p=0.0113). The major reason for discontinuation prior to Week 6 was lack of improvement (31 for placebo and 10 for certolizumab pegol). The numbers of subjects who remained in study at Week 6 who were not in clinical response at Week 6 are similar between treatment groups (82 (53%) for placebo and 76 (52%) for certolizumab pegol).

There were also disproportionate numbers of discontinuations prior to Week 26 (85 (55%) for placebo and 62 (43%) for certolizumab pegol, p=0.0367). Numbers of subjects who remained in study at Week 26 who were not in clinical response at Week 26 are similar between treatment groups (82 (53%) for placebo and 76 (52%) for certolizumab pegol).

The treatment difference based on point estimate of prevalence was 8.7% at Week 6 (32.8% (40/122) for placebo and 41.5% (54/130) for certolizumab pegol).

Furthermore, the treatment effect at Week 6 is small and ranges from 4.0% to 11.4 %, depending on which analyses is performed; p-values range from 0.037 to 0.5472.

If one of the disputed placebo subjects were considered as a responder at Week 6 and one of the disputed placebo subjects were considered as a responder at Weeks 6 and 26, the p-value resulting from an ITT analyses would be 0.065 for both Week 6 and Weeks 6 and 26 endpoints, using Fisher's exact test. This sensitivity of the p-value indicates a lack of robustness of the sponsor's conclusion.

The sponsor's imputation rules for handling missing data in calculating subtotals for CDAI calculation were not pre-specified in the protocol but were pre-specified in the SAP. The imputation was complicated with the carried forward and carried back rules applied patient's diary card data for the 7 consecutive days prior to each scheduled assessment at which the CDAI score was calculated and was recorded on the CRF. The sponsor provided only seven examples (among $2^7 = 128$ possible examples) to demonstrate how the carried forward and carried back rules would be applied.

The proportion of subjects where at least one of the subtotals for the CDAI score was imputed was high (19.5%, 59/302) in the CRP $\geq$ 10 mg/L stratum at baseline for all visits. With such as high percentage of subjects with imputation, the results derived from the imputed CDAI score should be interpreted with caution.

Furthermore, it is observed that there were some differences in the numbers of subjects in clinical response at Week 6, and at Weeks 6 and 26 in the CRP$\geq$10 mg/L at baseline stratum resulting from analyses with imputation and without imputation (observed case) for the CDP870 400 mg treatment group. No differences however are observed for the placebo group.

Six subjects in CDP870 400 mg group with missing observations were considered to be in clinical response at Week 6 in the sponsor's analysis with their imputation methods. Among those six, four subjects were considered to be in clinical response at Weeks 6 and 26 in the sponsor's analysis. If these six subjects were considered to be non-responders, the resulting p-values from Fisher's exact test would be: 0.2050 at Week 6; and 0.15 at Weeks 6 and 26. These p-values would be much higher than the sponsor's reported values of .037 and .045, respectively.

Thus the superiority of CDP870 400 mg over placebo in terms of the co-primary efficacy endpoints (clinical response at Week 6, and clinical response at Weeks 6 and 26) in the stratum defined by CRP $\geq$ 10 mg /L at baseline is sensitive to the outcomes assumed for these six subjects.

However, from this reviewer's findings from post-hoc exploratory analyses of clinical response at Week 6 by baseline CDAI, it was found that certolizumab pegol might be efficacious for subjects with baseline CDAI score above 300. But, a second, well-controlled clinical study would be required to confirm this hypothesis..

2. INTRODUCTION

2.1 Background

CDP870 is an anti-Tumor Necrosis Factor (TNF), humanized antibody (Fragment Antigen Binding) Fab" fragment-polyethylene glycol (PEG) conjugate presented as lyophilized power.

The sponsor submitted the original BLA on February 28, 2006 to obtain an indication for certolizumab pegol for the [redacted]. The statistical review and evaluation was performed and was documented on December 21, 2006. This review should be reference for a more complete discussion of study design and analysis issues.

A Complete Response letter was issued by the Agency on December 21, 2006 stating that the sponsor's studies did not show substantial evidence of efficacy for inducing or maintaining clinical response in patients with moderately to severely active Crohn's disease. The principal statistical concern was that Study CDP870-031 showed a small treatment effect, and its statistical significance was sensitive to missing data assumptions. Although the maintenance study (CDP870-032) showed positive results, its interpretation was not clear given the weak results from study CDP870-031.

At key meetings (March 8, 2007, May 30, 2007) the sponsor maintained that two studies were designed to demonstrate effectiveness for chronic treatment of Crohn's disease, and, in particular, study 031 was not designed to show substantial evidence of induction. Moreover, the sponsor claimed agreements to their clinical program and statistical analysis plans were understood based on their pre-BLA interactions with CBER.

The sponsor submitted their complete response on April 30, 2007. The Division issued an information request (IR) letter, dated June 27, 2007, for additional statistical analyses. On July 20, 2007, the sponsor submitted their reply in the form of two attachments:

Attachment 1 provided responses to the IR letter; and
Attachment 2 provided an amendment to the Complete Response; this amendment consisted mainly of re-analyses conducted by independent statisticians commissioned by the sponsor. This re-analysis was suggested by the sponsor at the May 30, 2007 meeting

with OND and the Division, but it is not considered informative by this reviewer, as the sponsor's analysis had already been replicated during the original statistical review.

This review mainly addresses the material from the original April 30, 2007 Complete Response and the additional information provided in the July 20, 2007 Attachment 1, above. It should be noted that the focus of Agency-Sponsor interactions has been mainly on validating the results from study CDP870-031, which is the focus of this review.

2.2 Data Sources

All data were submitted in electronic format to the FDA CBER EDR at **\\Cbsap58\M\EDR Submissions\2006 BLA\DCC60002565.**

3. STATISTICAL EVALUATION

3.1 Evaluation of Efficacy

3.1.1 Clinical Response at Week 2 and Week 4

At the May 30, 2007 meeting, the medical division agreed that the Week 4 results from Study CDP870-031 could be submitted and considered as additional evidence of effectiveness of certolizumab pegol. For completeness, the results at Week 2 were also provided.

The Sponsor's results at Week 2, Week 4, and Week 6 for the CRP $\geq$ 10 mg/L at baseline and overall population for response and remission is Study CDP870-031 are given below.

Clinical Response at Week 2, 4, and 6
Study CDP870-031

	CRP ≥10mg/L Group (ITT)		Overall Population (ITT)	
	Placebo N=156	certolizumab pegol N=146	Placebo N=328	certolizumab pegol N=331
Week 2 Frequency Number (%) (95% CI)	n=155 26 (16.8%) (10.9%, 22.7%)	n=144 47 (32.6%) (25.0%, 40.3%)	n=326 46 (14.1%) (10.3%, 17.9%)	n=328 82 (25.0%) (20.3%, 29.7%)
Odds Ratio (95%CI)		2.47 (1.42, 4.31)		2.08 (1.39, 3.11)
Week 4 Frequency Number (%) (95% CI)	n=155 32 (20.6%) (14.3%, 27.0%)	n=143 47 (32.9%) (25.2%, 40.6%)	n=326 71 (21.8%) (17.3%, 26.3%)	n=327 94 (28.7%) (23.8%, 33.7%)
Odds Ratio (95%CI)		1.92 (1.13, 3.26)		1.46 (1.02, 2.09)
Week 6 Frequency Number (%) (95% CI)	n=154 40 (26.0%) (19%, 32.9%)	n=145 54 (37.2%) (29.4%, 45.1%)	n=325 87 (26.8%) (22.0%, 31.6%)	n=327 115 (35.2%) (30.0%, 40.3%)
Odds Ratio (95%CI)		1.70 (1.03%, 2.80%)		1.51 (1.08, 2.11)

Remission at Week 2, 4, and 6
Study CDP870-031

	CRP ≥10mg/L Group (ITT)		Overall Population (ITT)	
	Placebo N=156	certolizumab pegol N=146	Placebo N=328	certolizumab pegol N=331
Week 2 Frequency Number (%) (95% CI)	n=155 14 (9.0%) (4.5%, 13.5%)	n=145 24 (16.6%) (10.5%, 22.6%)	n=327 27 (8.3%) (5.3%, 11.2%)	n=330 44 (13.3%) (9.7%, 17.0%)
Odds Ratio (95%CI)		1.99 (0.98, 4.03)		1.75 (1.05, 2.91)
Week 4 Frequency Number (%) (95% CI)	n=155 15 (9.7%) (5.0%, 14.3%)	n=144 29 (20.1%) (13.6%, 26.7%)	n=327 37 (11.3%) (7.9%, 14.7%)	n=329 64 (19.5%) (15.2%, 23.7%)
Odds Ratio (95%CI)		2.49 (1.26, 4.93)		1.92 (1.24, 2.99)
Week 6 Frequency Number (%) (95% CI)	n=154 26 (16.9%) (11.0%, 22.8%)	n=146 32 (21.9%) (15.2%, 28.6%)	n=326 56 (17.2%) (13.1%, 21.3%)	n=329 71 (21.6%) (17.1%, 26.0%)
Odds Ratio (95%CI)		1.37 (0.76, 2.46)		1.34 (0.91, 1.99)

3.1.2 Reviewer's Comments and Evaluation

3.1.2.1 Reviewer's Comments on Sponsor's Results at Week 2 and Week 4

The sponsor's analysis of results at Week 2 and Week 4 are post-hoc analyses and should be considered exploratory.

As seen from sponsor's results at Week 2 and Week 4 for the CRP≥ 10 mg/L at the baseline, for those subjects treated with certolizumab pegol the number of subjects with complete response at Week 4 was the same as the number of subjects with response at Week 2 (47 both at Week 2 and Week 4). The odds ratio for response decreased from 2.47 at Week 2 to 1.92 at Week 4, then to 1.70 at Week 6. The odds ratio for remission increased from 1.99 at Week 2 to 2.49 at Week 4 then decreased to 1.37 at Week 6. It is observed that among Week 2, 4, and 6, the results are contradictory for complete response and remission; the odds ratio for remission was at the highest at Week 4, but for response, the odds ratio was at the highest at Week 2.

3.1.2.2. Subject Disposition and Clinical Response Status through Week 6 and Week 26

Per this reviewer's request, the sponsor supplied subject disposition and clinical response through Week 6 and Week 26 (See Appendix Tables 1 and 2).

It is observed that there are disproportionate numbers of subjects who discontinued prior to Week 6 (34 (22%) for placebo and 16 (11%) for certolizumab pegol, p=0.0113). The major reason for discontinuations prior to week 6 was lack of improvement (31 for

placebo and 10 for certolizumab pegol). Numbers of subjects who remained in study at Week 6 and were not in clinical response at Week 6 were similar between treatment groups (82 (53%) for placebo and 76 (52%) for certolizumab pegol).

There are disproportionate numbers of subjects who discontinued prior to Week 26 (85 (55%) for placebo and 62 (43%) for certolizumab pegol, p=0.0367). Numbers of subjects who remained in study at Week 26 who were not in clinical response at Week 26 were similar between treatment groups (82 (53%) for placebo and 76 (52%) for certolizumab pegol).

The estimated treatment difference at Week 6 was 8.7% (32.8% (40/122) for placebo and 41.5% (54/130) for certolizumab pegol).

3.1.2.3 Treatment Effect at Week 6

The sponsor's results for the primary endpoints, clinical response in the CRP ≥10 mg/L at baseline stratum at Week 6 and at Weeks 6 and 26 for Study 31 are borderline with p = 0.037 for Week 6 and p = 0.045, at Weeks 6 and 26. .

The treatment effect at Week 6 was small and ranged from 4.0% to 11.4 %, depending on which analysis was performed. P-values ranged from 0.037 to 0.5472 (see Appendix Table 3).

3.1.2.4 Data Quality and Data Discrepancies

Dr. Marcelo Mangalindan, FDA site investigator found data errors in Study CDP870-31 in two sites (Dr. P. Honiball, 39006 and Dr. J. Chojnacki, 33012), Observations at these clinical sites included issues with transcription of data related to CDAI scores for study CD870-031.

3.1.2.4.1 Data Discrepancies

This reviewer found that two placebo subjects had discrepancy in status of clinical response at Week 6.

Subject no.	Country	Completed	MRESP6	CLINRSP	NCLINRSP	ORESP6
401	Germany	Yes	No	Yes	Yes	No
525	Germany	No	No			Yes

Complied by this reviewer.

Where MRESP6 – Missing set to non-response
CLINRSP- Clinical response
NCLINRSP – Clinical response – no imputation
ORESP6 – Clinical response - observed data only

The sponsor's explanations were:

Subject 401 received rescue therapy at Week 2. Thus from this time point onwards the subject would be classified as a non-responder. As mentioned above, in the dataset created on 6 January 2006 this would need to be taken into consideration during any programming – hence *CLINRSP* and *NCLINRSP* still stating "Yes". However, the data submitted on 15 June 2006 this was already taken into consideration – hence *MRESP6* and *ORESP6* stating "No".

Subject 525. The apparent discrepancy where *MRESP6* (missing set to non-response at Week 6) states "No" whilst *ORESP6* (observed data only response at Week 6) states "Yes" is due to the definitions of the sensitivity analyses being considered. Subject 525 withdrew at Week 6 and thus would be considered a non-responder in the various analyses except for the observed data only analysis.

In their Complete response, the sponsor gave more detailed explanations on disputed subjects (401and 525).

However, for subject 401, it seems to this reviewer that this subject completed the study, CLINRSP and NCLINRSP which were created on 6 January 2006 were based on the observed CDAI score. Both CLINRSP and NCLINRSP were "Yes." The MRESP6 and ORESP6 were created post-hoc on 15 June 2006. Both MRESP6 and ORESP6 were 'No." For this subject, the consideration of rescue therapy might be made post-hoc. So, subject 401 should be considered to be a responder at Week 6 based on values on CLINRSP and NCLINRSP. Furthermore, it was found that this subject had similar discrepancy in status of clinical response at Weeks 6 and 26.

Subject 525 had clinical response at Week 6 (ORESP6) but, the sponsor stated that his subject was withdrawn at Week 6. This subject had data at Week 6. So, this subject should not be considered as missing. The value for MRESP6 for this subject should be "Yes".

If one of the disputed placebo subjects were considered as a responder at Week 6 and one of disputed placebo subjects were considered as a responder at Weeks 6 and 6, the p-value resulting from an ITT analyses would be 0.065 both at Week 6 and at Weeks 6 and 26 from Fisher's exact test.

3.1.2.5. Sponsor's Imputation Method

The sponsor's imputation rules for handling missing data in calculating subtotals for CDAI calculation were not pre-specified in the protocol but were pre-specified in the SAP. The imputation algorithm was complicated with "carried forward" and "carried back" rules applied to the patient's diary card data for the 7 consecutive days prior to each scheduled assessment at which the CDAI score was calculated and was recorded on the CRF. The sponsor provided only seven examples (among 2^7 =128 possible examples) to demonstrate how the carried forward and carried back rules were applied.

For CDAI, there is not a commonly acceptable imputation method to handling missing observations or missing index sub-scores.

The "observed data only" sensitivity analysis was conducted on subjects where no imputation techniques had to be applied when deriving the total CDAI score. Using the data set C87031 and variable ORESP6 for the stratum CRP≥ 10 mg /L at baseline there are 27 CDP870 and 43 placebo subjects for whom imputation techniques were applied at Week 6.

Per this reviewer request, the sponsor provided the tabulation of subjects where at least one of the subtotals for the CDAI score was imputed in the CRP ≥ 10 mg/L strata at baseline for all visits. It was observed that proportion of subjects where at least one of the subtotals for the CDAI score was imputed was high (19.5%, 59/302) in the CRP ≥ 10 mg/L strata at baseline for all visits. With such a high percentage of subjects with imputation, the results derived from the imputed CDAI score should be interpreted with caution. .

Furthermore, it is observed that there were some differences in the numbers of subjects in clinical response at Week 6, and at Weeks 6 and 26 in the CRP≥10 mg/L at baseline stratum resulting from analyses with imputation and without imputation (observed case) for the CDP870 400 mg treatment group. No differences however are observed for the placebo group. (See table below.)

Number of Subject in Clinical Response at Week 6, and Weeks 6 and 26 in the CRP≥10 mg/L at Baseline Stratum
Study CDP870-031

	Clinical Response at Week 6		Clinical Response at Weeks 6 and 26	
Analysis	CDP870 400 mg	Placebo	CDP870 400 mg	Placebo
With Imputation	54	40	31	19
Observed (No Imputation)	48	40	27	19

Complied by this reviewer.

Six subjects in CDP870 400 mg group with missing observations were considered to be in clinical response at Week 6 in the sponsor's analysis with imputation. Among those 6 subjects in CDP870 400 mg group with missing observations at Week 6, 4 subjects were considered to be in clinical response at Weeks 6 and 26 in the sponsor's analysis.
If six subjects in CDP870 400 mg group with missing observations were considered to be non-responders, then resulting p-values from Fisher's exact test would be much higher (0.2050 vs. reported 0.037 as reported at Week 6; 0.1499 vs. 0.045 as reported at Weeks 6 and 26) as seen from table below. In this analysis, subjects with missing observation were considered to be non-responders.

Number of Subjects with Clinical Response at Week 6, and Weeks 6 and 26 in the CRP≥10 mg/L at Baseline Stratum
Study CDP870-031
(Reviewer's ITT Analysis)

Week	CDP870 400 mg	Placebo	Difference	P-value
6	48/146 (32.9%)	40/156 (25.6%)	7.3%	0.2050
6 and 26	27/146 (18.5%)	19/156 (12.2%)	6.3%	0.1499

Compiled by this reviewer.
P-value was obtained using Fisher's exact test.

Thus, the superiority of CDP870 400 mg over placebo in terms of co-primary efficacy endpoints (clinical responses at Week 6, and at Weeks 6 and 26) in the stratum defined by CRP ≥ 10 mg /L at baseline is sensitive to the outcomes for those six subjects in the treatment group who had missing observations.

3.1.2.6 Reviewer's Additional Analyses

3.1.2.6.1. Treatment Effect at Week 6 for Overall Population

The sponsor's results for secondary efficacy endpoints, clinical response at Week 6 and at Weeks 6 and 26, for overall population for Study 31 were statistically significant with p-values of 0.016 and 0.024, at Week 6 and at Weeks 6 and 26, respectively.

For overall population, the treatment differences at Week 6 were moderate and ranged from 5.0% to 8.2 %, which was dependent on which analyses were performed with p-values ranged from 0.0228 to 0.2042 (see Appendix Table 4).

3.1.2.6.2. Subgroup Analyses of Clinical Responses at Week 6 and Clinical Response at Weeks 6 and 26 for the Overall Population

This reviewer performed subgroup analyses of number of subjects in clinical response at Week 6, and at Weeks 6 and 26 for the overall population by treatment group and by subgroups: country, gender, smoking, use of immunosuppressant and use of corticosteroid for the reviewer's ITT population. The results for these subgroup analyses are given in Appendix Table 5.

As seen from Appendix Table 5, proportion of subjects in clinical response at Week 6, and at Weeks 6 and 26 for the overall population are consistent for subgroups of gender, use of immunosurppressant, and use of corticosteroids. But, they are not consistent for subgroups of country and smoking.

3.1.2.6.3 Clinical Response by Visit

3.1.2.6.3.1 Available Data

This reviewer performed a exploratory analyses of clinical response by visit for Study 31 using the sponsor's raw data set with imputation and without imputation for available (observed case) data for the CRP ≥10 subgroup and for the overall population. The tabulations are given in Appendix Tables 6 and 7.

As seen from these tables, the treatment difference decreases from 14% (CR ≥10) and 11% (overall) at Week 2 to -5% (CRP ≥10) and -1% (overall) at Week 12 then increases from less than 0% at Week 12 to about 11% at Week 26. The treatment difference is not consistent among visits for both CRP ≥10 and overall populations. At Week 12, certolizumab was worse than placebo by about 5% for CRP ≥10 population and 1% for overall population.

3.1.2.6.3.2 Reviewer's ITT Analysis

Per request from the clinical team, this reviewer performed an exploratory analysis of clinical response by visit for Study 031 using sponsor's raw data set with imputation and without imputation for reviewer's ITT analysis for CRP ≥10 and overall population. The tabulations are given in Appendix Tables 8 and 9.

As seen from these tables, results are similar to those results based on available data in terms of treatment difference. The change of treatment difference is less dramatic. The treatment difference decreases from 15% (CRP ≥10) and 11% (overall) at Week 2 to 5% (CRP ≥10) and 5% (overall) at Week 12 then increases from 5% at Week 12 to about 12% at Week 26.

3.1.2.6.4 Analysis of Clinical Response at Week 6 by Baseline CDAI Score

Per request from the clinical team, this reviewer performed an exploratory analysis of clinical response at Week 6 using a logistic regression method. The model included treatment, geographic region, immunosuppressant status, corticosteroids use status, CRP strata, and baseline CDAI for subjects in the CRP ≥10 mg/L strata and overall population, P-values for treatment effect are 0.0348 and 0.0168 for subjects in the CRP ≥10 mg/L strata and overall population, respectively. P-values for baseline CDAI effect are 0.3730 and 0.0784 for subjects in the CRP ≥10 mg/L strata and overall population, respectively

The descriptive statistics for baseline CDAI score for overall population are:

Mean 298.68
Median 286
Q3 340.62
Q1 248.281

This reviewer also performed post-hoc and exploratory analyses of clinical response at Week 6 by baseline CDAI. In these analyses, baseline CDAI scores are split at quantiles Q1, median, and Q3 into four equal parts (≤250, 251-300, 301-350, and > 350) or at median into two equal parts (≤300 and > 300). The results from these analyses are given in Appendix Table 10.

As seen from Appendix Table 10, treatment differences in clinical response at Week 6 are 17% and 15% for subjects who had baseline CDAI above mean (300) in the CRP ≥10 mg/L stratum and overall population, respectively with p-values of 0.0305 and 0.0077, respectively. But, for subjects who had baseline CDAI less or equal to 300, the treatment differences are much less at 6% and 3% for subjects in the CRP ≥10 mg/L stratum and overall population, respectively.

These findings are from post-hoc exploratory analyses. Certolizumab pegol might or might not be efficacious for subjects with baseline CDAI score above 300. Confirmation of results would need to come from a new clinical study.

3.1.2.8 Clinical Response (70 Point Decrease in CDAI) by Visit

3.1.2.8.1 Available Data

This reviewer performed a post-hoc exploratory analysis of clinical response (70 points decrease in CDAI) by visit for Study CDP870-031 using sponsor's raw data set with imputation for available data for CRP≥10 and overall populations. The tabulation is given in Appendix Table 11.

As seen from this table, the treatment difference decreases from 18% (CR≥10 mg/L at baseline stratum) and 10% (overall) at Week 2 to 0% (CRP≥10 mg/L at baseline stratum) and -2% (overall) at Week 8 then increases from less than 0% at Week 8 to about 18% at Week 26. The treatment difference is not consistent among visits for both CRP≥10 mg/L at baseline stratum and overall populations. At Week 8, Cimzia is worse than placebo by 2% for overall population; no difference is observed for CR≥10 mg/L at baseline stratum population.

3.1.2.8.2 Reviewer's ITT Analysis

This reviewer also performed a post-hoc exploratory analysis of clinical response (70 points decrease in CDAI) by visit for Study CDP870-031 using sponsor's raw data set with imputation for reviewer's ITT analysis for CRP≥10 mg/L at baseline stratum and overall populations. In this analysis, a patient with missing data is assumed to be "failure." The tabulation is given in Appendix Table1 2.

As seen from this table, results are similar to those results based on available data in terms of treatment difference. The change of treatment difference is less dramatic. The treatment difference decreases from 18% (CRP≥10 mg/L at baseline stratum) and 10% (overall) at Week 2 to 8% (CRP≥10 mg/L at baseline stratum) and 4% (overall) at Week

8 then increases from 8% and 4% at Week 8 to about 17% and 14% at Week 26 for CRP≥10 mg/L at baseline stratum and overall populations, respectively.

4. SUMMARY AND CONCLUSION

4.1 Statistical Issues and Collective Evidence

For Study CDP870-031, the sponsor's results for the co-primary endpoints, clinical response in the CRP ≥ 10 mg/L at baseline stratum at Week 6 and clinical response at both Weeks 6 and 26 are marginally significant with p-values of 0.037 and 0.045, at Week 6 and at Weeks 6 and 26, respectively.

Per this reviewer's request, the sponsor supplied additional information regarding subject disposition and clinical response through Week 6 and Week 26.

From these data, it is observed that there was a disproportionate number of subjects who discontinued prior to Week 6 (34 (22%) for placebo and 16 (11%) for certolizumab pegol, p=0.0113). The major reason for discontinuation prior to Week 6 was lack of improvement (31 for placebo and 10 for certolizumab pegol). The numbers of subjects who remained in study at Week 6 who were not in clinical response at Week 6 are similar between treatment groups (82 (53%) for placebo and 76 (52%) for certolizumab pegol).

There were also disproportionate numbers of discontinuations prior to Week 26 (85 (55%) for placebo and 62 (43%) for certolizumab pegol, p=0.0367). Numbers of subjects who remained in study at Week 26 who were not in clinical response at Week 26 are similar between treatment groups (82 (53%) for placebo and 76 (52%) for certolizumab pegol).

The treatment difference based on point estimate of prevalence was 8.7% at Week 6 (32.8% (40/122) for placebo and 41.5% (54/130) for certolizumab pegol).

Furthermore, the treatment effect at Week 6 is small and ranges from 4.0% to 11.4 %, depending on which analyses is performed; p-values range from 0.037 to 0.5472.

If one of the disputed placebo subjects were considered as a responder at Week 6 and one of the disputed placebo subjects were considered as a responder at Weeks 6 and 26, the p-value resulting from an ITT analyses would be 0.065 for both Week 6 and Weeks 6 and 26 endpoints, using Fisher's exact test. This sensitivity of the p-value indicates a lack of robustness of the sponsor's conclusion.

The sponsor's imputation rules for handling missing data in calculating subtotals for CDAI calculation were not pre-specified in the protocol but were pre-specified in the SAP. The imputation was complicated with the carried forward and carried back rules applied patient's diary card data for the 7 consecutive days prior to each scheduled assessment at which the CDAI score was calculated and was recorded on the CRF. The

sponsor provided only seven examples (among $2^7 = 128$ possible examples) to demonstrate how the carried forward and carried back rules would be applied.

The proportion of subjects where at least one of the subtotals for the CDAI score was imputed was high (19.5%, 59/302) in the CRP ≥ 10 mg/L stratum at baseline for all visits. With such as high percentage of subjects with imputation, the results derived from the imputed CDAI score should be interpreted with caution.

Furthermore, it is observed that there were some differences in the numbers of subjects in clinical response at Week 6, and at Weeks 6 and 26 in the CRP≥10 mg/L at baseline stratum resulting from analyses with imputation and without imputation (observed case) for the CDP870 400 mg treatment group. No differences however are observed for the placebo group.

Six subjects in CDP870 400 mg group with missing observations were considered to be in clinical response at Week 6 in the sponsor's analysis with their imputation methods. Among those six, four subjects were considered to be in clinical response at Weeks 6 and 26 in the sponsor's analysis. If these six subjects were considered to be non-responders, the resulting p-values from Fisher's exact test would be: 0.2050 at Week 6; and 0.15 at Weeks 6 and 26. These p-values would be much higher than the sponsor's reported values of .037 and .045, respectively.

Thus the superiority of CDP870 400 mg over placebo in terms of the co-primary efficacy endpoints (clinical response at Week 6, and clinical response at Weeks 6 and 26) in the stratum defined by CRP ≥ 10 mg /L at baseline is sensitive to the outcomes assumed for these six subjects.

However, from this reviewer's findings from post-hoc exploratory analyses of clinical response at Week 6 by baseline CDAI, it was found that certolizumab pegol might be efficacious for subjects with baseline CDAI score above 300. But, a second, well-controlled clinical study would be required to confirm this hypothesis..

4.2 Conclusion and Recommendations

For Study CDP870-031, the sponsor's results for the co-primary endpoints, clinical response in the CRP ≥ 10 mg/L at baseline stratum at Week 6 and at Weeks 6 and 26 were borderline with p-values of 0.037 and 0.045 for the Week 6 and Weeks 6 and 26 endpoints, respectively.

The treatment effect at Week 6 was small and ranged from 4.0% to 11.4 % depending on which analysis was performed. P-values for the various sensitivity analyses ranged from 0.037 to 0.547. .

The proportion of subjects where at least one of the subtotals for the CDAI score was imputed was high (19.5%, 59/302) in the CRP ≥ 10 mg/L stratum at baseline for all

visits. With such a high percentage of subjects with CDAI imputation, the results derived from the imputed scores should be interpreted with caution. .

From this reviewer's findings from a post-hoc exploratory analysis of clinical response at Week 6 by baseline CDAI, it was found that certolizumab pegol might be efficacious for subjects with baseline CDAI score above 300. However this would require confirmation by a new, well-controlled clinical study.

In summary, this reviewer finds the strength of evidence from Study CDP870-031 to support an induction claim is not substantial, as the efficacy results are both marginally significant and sensitive to data assumptions. However, the results from study CDP870-031 can be deemed statistically significant according to the sponsor's pre-specified analysis.

SINATURES/DISTRIBUTION LIST

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5. APPENDIX

Table 1 Subject Disposition and Clinical Response through Week 6 – ITT

Table 1.1 Subject disposition and clinical response status through Week 6 - Intention to Treat Population
Study: CDP870-031
Stratum: CRP>=10 mg/L

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Accountability		Placebo (N=156)	CDP870 400 mg (N=146)	Total Patients (N=302)
Week 6	Received any double-blind treatment	156	146	302
	Subjects who discontinued prior to Week 6	34 (21.8%)	16 (11.0%)	50 (16.6%)
	Subjects who remained in study at Week 6	122 (78.2%)	130 (89.0%)	252 (83.4%)
	Subjects in clinical response at Week 6	40 (25.6%)	54 (37.0%)	94 (31.1%)
	Subjects not in clinical response at Week 6	82 (52.6%)	76 (52.1%)	158 (52.3%)
	Reason not in clinical response at Week 6 (a)			
	Insufficient data (no CDAI score at Week 6)	2 (2.4%)	2 (2.6%)	4 (2.5%)
	Received rescue therapy at or prior to Week 6	3 (3.7%)	2 (2.6%)	5 (3.2%)
	CDAI score did not meet criteria for clinical response	78 (95.1%)	74 (97.4%)	152 (96.2%)
	Withdrew at Week 6	12 (14.6%)	7 (9.2%)	19 (12.0%)

Subjects may have more than one reason for not being in clinical response.
(a) Percentages are calculated using the number of subjects not in clinical response as denominator.

Table 2 Subject Disposition and Clinical Response through Week 26 – ITT

Table 1.2 Subject disposition and clinical response status through Week 26 - Intention to Treat Population
Study: CDP870-031
Stratum: CRP>=10 mg/L

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Accountability		Placebo (N=156)	CDP870 400 mg (N=146)	Total Patients (N=302)
Week 26	Received any double-blind treatment	156	146	302
	Subjects who discontinued prior to Week 26	85 (54.5%)	62 (42.5%)	147 (48.7%)
	Subjects who remained in study at Week 26	71 (45.5%)	84 (57.5%)	155 (51.3%)
	Subjects in clinical response at Week 26	30 (19.2%)	47 (32.2%)	77 (25.5%)
	Subjects not in clinical response at Week 26	41 (26.3%)	37 (25.3%)	78 (25.8%)
	Reason not in clinical response at Week 26 (a)			
	Insufficient data (no CDAI score at Week 26)	0	1 (2.7%)	1 (1.3%)
	Received rescue therapy at or prior to Week 26	5 (12.2%)	4 (10.8%)	9 (11.5%)
	CDAI score did not meet criteria for clinical response	39 (95.1%)	35 (94.6%)	74 (94.9%)
	Withdrew at Week 26	2 (4.9%)	1 (2.7%)	3 (3.8%)

Subjects may have more than one reason for not being in clinical response.
(a) Percentages are calculated using the number of subjects not in clinical response as denominator.

Table 3 Analyses of Clinical Response at Week 6 in the CRP≥10 mg/L Stratum at Baseline

Study CDP870-031

Analysis	CDP870	Placebo	Diff (CDP870-Placebo)	p-value
Worst	54/146 (37.0%)	40/156 (25.6%)	11.4%	0.0354
Per Protocol	40/107 (37.4%)	33/117 (28.2%)	9.2%	0.1556
No Imputation	48/113 (42.5%)	40/104 (38.5%)	4.0%	0.5816
Observed case	48/119 (40.3%)	40/113 (35.4%)	4.9%	0.4990

In worst case, subject with miss observation was considered to be non-responder.
p-value was obtained by this reviewer using Fisher's exact test.

Table 4 Analyses of Clinical Response at Week 6 for Overall Population

Study CDP870-031

Analysis	CDP870	Placebo	Diff (CDP870-Placebo)	p-value
Worst	115/331 (34.7%)	87/328 (26.5%)	8.2%	0.0228
Per Protocol	83/230 (36.1%)	68/277 (28.7%)	7.4%	0.0876
No Imputation	108/262 (41.2%)	84/232 (36.2%)	5.0%	0.2680
Observed case	108/275 (39.3%)	84/249 (33.7%)	5.6%	0.2042

In worst case, subject with miss observation was considered to be non-responder.
p-value was obtained by this reviewer using Fisher's exact test.

Table 5 Subgroup Analyses of Clinical Responses at Week 6 and Weeks 6 and 26 for Overall Population

Overall Population
Reviewer's ITT Population – Study CDP870-031
Clinical Response at Week 6

Category	CDP870 400 mg	Placebo	Difference	95% C. I.
Country				
Australia	10/28 (35.7%)	7/28 (25.0%)	10.7%	(-13.2%, 34.6%)
Austria	4/13 (30.8%)	0/6 (0.0%)	30.8%	(5.7%, 55.9%)
Belarus	2/10 (20.0%)	1/8 (12.5%)	7.5%	(-26.3%, 41.3%)
Belgium	2/7 (28.6%)	4/11 (36.4%)	-7.8%	(-51.7%, 36.1%)
Bulgaria	3/11 (27.3%)	4/16 (25.0%)	2.3%	(-31.5%, 36.1%)
Canada	1/3 (100%)	1/1 (100%)	0.0%	
Czech Republic	8/34 (23.5%)	8/35 (22.9%)	0.6%	(-19.3%, 20.6%)
Estonia	1/3 (33.3%)	0/6 (0.0%)	33.3%	(-20.0%, 86.7%)
Georgia		1/1 (100%)		
Germany	3/15 (20.0%)	5/26 (19.2%)	0.8%	(-24.5%, 26.1%)
Hong Kong	0/1 (0.0%)	0/1 (0.0%)		
Hungary	7/15 (46.7%)	6/15 (40.0%)	6.7%	(-28.7%, 42.1%)
Italy	2/10 (20.0%)	3/11 (27.3%)	-7.3%	(-43.4%, 28.9%)
Latvia	0/2 (0.0%)	0/2 (0.0%)	0.0%	
Norway	0 /1 (0.0%)			
Poland	20/35 (57.1%)	12/35 (34.3%)	22.8%	(0.1%, 45.6%)
Russia	14/31 (45.2%)	3/27 (11.1%)	34.1%	(12.9%, 55.2%)
S. Africa	9/20 (45.0%)	12/25 (48.0%)	-3.0%	(-42.8%, 44.8%)
Slovenia	4/12 (33.3%)	3/9 (33.3%)	0.0%	(-40.8%, 40.8%)
Sweden	4/4 (100.0%)			
Ukraine	1/3 (33.3%)	1/3 (33.3%)	0.0%	(-75.5%, 75.5%)
U.S.	20/73 (27.4%)	16/62 (25.8%)	1.6%	(-13.4%, 16.5%)
Gender				
Male	55/157 (35.0%)	39/131 (29.8%)	5.2%	(-5.6%, 16.1%)
Female	60/176 (34.1%)	48/198 (24.2%)	9.9%	(10.6%, 19.1%)
Smoking				
Current smoker	43/106 (40.6%)	33/107 (30.8%)	9.8%	(-3.1%, 22.5%)
Never smoked	51/156 (32.7%)	36/150 (24.0%)	8.7%	(-1.4%, 18.7%)
Stopped after diagnosis of Crohn's disease	11/39 (28.2%)	10/35 (28.6%)	-0.4%	(-20.9%, 20.2%)
Stopped before diagnosis of Crohn's disease	10/32 (31.3%)	8/37 (21.6%)	9.7%	(-11.2%, 30.5%)
Immunosuppressants				
Current therapy				
Yes	45/126 (35.7%)	30/121 (24.8%)	10.9%	(-4.5%, 22.3%)
No	70/207 (33.8%)	57/208 (27.4%)	6.4%	(-2.4%, 15.3%)
Corticosteroids				
Current therapy				
Yes	43/129 (33.3%)	38/131 (29.0%)	4.3%	(-6.9%, 15.6%)
No	72/204 (35.3%)	49/198 (24.7%)	10.6%	(1.6%, 19.4%)

Compiled by reviewer.

Table 5 (Cont'd) Clinical Response at Weeks 6 and 26

Category	CDP870 400 mg	Placebo	Difference	95% C. I
Country				
Australia	5/28 (17.9%)	3/28 (10.7%)	7.2%	(-11.1%, 25.4%)
Austria	2/13 (15.4%)	0/6 (0.0%)	15.4%	(-4.2%, 35.0%)
Belarus	1/10 (10.0%)	1/8 (12.5%)	-2.5%	(-32.0%, 27.0%)
Belgium	1/7 (14.3%)	2/11 (18.2%)	-3.9%	(-38.4%, 30.6%)
Bulgaria	2/11 (18.2%)	3/16 (18.8%)	-0.6%	(-34.3%, 29.2%)
Canada	0/3 (0.0%)	0/1 (0.0%)	0.0%	
Czech Republic	8/34 (23.5%)	5/35 (14.3%)	9.2%	(-9.1%, 27.6%)
Estonia	0/3 (0.0%)	0/6 (0.0%)	0.0%	
Georgia		0/1 (0.0%)		
Germany	0/15 (0.0%)	1/26 (3.8%)	-3.8%	(11.2%, 3.5%)
Hong Kong	0/1 (0.0%)	0/1 (0.0%)	0.0%	
Hungary	3/15 (20.0%)	4/15 (26.7%)	-6.7%	(-36.8%, 23.5%)
Italy	2/10 (20.0%)	1/11 (9.1%)	10.9%	(-19.2%, 41.0%)
Latvia	0/2 (0.0%)	0/2 (0.0%)	0.0%	
Norway	0/1 (0.0%)			
Poland	17/35 (48.6%)	8/35 (22.9%)	25.7%	(4.1%, 47.3%)
Russia	10/31 (32.3%)	2/27 (7.4%)	24.9%	(5.7%, 44.0%)
S. Africa	6/20 (30.0%)	8/25 (32.0%)	-2.0%	(-29.2%, 25.2%)
Slovenia	3/12 (25.0%)	1/9 (11.1%)	13.9%	(-18.1%, 45.9%)
Sweden	3/4 (75.0%)			
Ukraine	0/3 (0.0%)	0/3 (0.0%)	0.0%	
U.S.	12/73 (16.4%)	13/62 (21.0%)	-4.6%	(-17.8%, 8.7%)
Gender				
Male	36/157 (22.9%)	22/131 (16.8%)	6.1%	(-3.0%, 15.3%)
Female	39/176 (22.2%)	30/198 (15.2%)	7.0%	(-0.9%, 14.9%)
Smoking				
Current smoker	29/106 (27.4%)	18/107 (16.8%)	10.6%	(-0.5%, 21.6%)
Never smoked	32/156 (20.5%)	21/150 (14.0%)	6.5%	(-1.9%, 14.9%)
Stopped after diagnosis of Crohn's disease	8/39 (20.5%)	7/35 (20.0%)	0.5%	(-17.8%, 18.9%)
Stopped before diagnosis of Crohn's disease	6/32 (18.8%)	6/37 (16.2%)	2.6%	(-15.5%, 20.5%)
Immunosuppressants				
Current therapy				
Yes	28/126 (22.2%)	19/121 (15.7%)	6.5%	(-3.2%, 16.3%)
No	47/207 (22.7%)	33/208 (15.9%)	6.8%	(-0.7%, 14.4%)
Corticosteroids				
Current therapy				
Yes	29/129 (22.5%)	19/131 (14.5%)	8.0%	(-1.4%, 17.4%)
No	46/204 (22.5%)	33/198 (16.7%)	5.8%	(-1.9%, 13.6%)

Compiled by reviewer.

Table 6 Clinical Response by Visit for Available Data

Clinical Response by Visit
Available Data
Study CDP870-031

	CRP ≥ 10 mg/L at Baseline Stratum				Overall Population			
Visit	Placebo N=156	Cimzia N=146	Diff	p-value	Placebo N=328	Cimizia N=331	Diff	p-value
2	27/141 (19%)	47/138 (34%)	15%	0.0048	47/308 (15%)	82/317 (26%)	11%	0.0011
4	34/121 (28%)	48/127 (38%)	10%	0.1047	73/271 (27%)	95/297 (32%)	5%	0.1878
6	41/108 (38%)	54/122 (44%)	6%	0.3329	88/250 (35%)	115/279 (41%)	6%	0.1553
8	43/99 (43%)	52/114 (46%)	3%	0.7496	96/229 (42%)	115/267 (43%)	1%	0.7963
12	42/84 (50%)	46/101 (45%)	-5%	0.5457	103/206 (50%)	119/244 (49%)	-1%	0.7949
16	39/80 (49%)	47/88 (53%)	4%	0.5463	97/197 (49%)	124/225 (55%)	6%	0.2282
20	33/73 (45%)	47/83 (57%)	12%	0.1544	89/183 (49%)	110/204 (54%)	5%	0.2988
24	33/71 (46%)	43/83 (52%)	5%	0.5097	87/177 (49%)	114/201 (57%)	8%	0.1414
26	32/69 (46%)	48/82 (59%)	13%	0.1359	90/175 (51%)	123/199 (62%)	11%	0.0431

Prepared by reviewer.
P-values were obtained by Chi-square test

Table 7 Clinical Response by Visit with No Imputation for Available Data

Clinical Response by Visit
With No Imputation
Available Data
Study CD870-031

	CRP ≥ 10 mg/L at Baseline Stratum				Overall Population			
Visit	Placebo N=156	Cimzia N=146	Diff	p-value	Placebo N=328	Cimizia N=331	Diff	p-value
2	25/132 (19%)	42/129 (33%)	14%	0.0118	44/288 (15%)	76/295 (26%)	11%	0.0017
4	31/114 (27%)	44/118 (37%)	10%	0.1003	69/256 (27%)	89/280 (32%)	5%	0.2203
6	40/104 (38%)	48/113 (42%)	4%	0.5472	84/232 (36%)	108/262 (41%)	5%	0.2538
8	41/94 (44%)	48/107 (45%)	1%	0.8595	93/214 (43%)	106/251 (42%)	-1%	0.7899
12	42/81 (52%)	42/94 (45%)	-7%	0.3438	99/195 (51%)	109/224 (49%)	-2%	0.6668
16	39/77 (51%)	44/82 (54%)	3%	0.7042	92/186 (49%)	112/206 (54%)	5%	0.3316
20	32/71 (45%)	42/78 (54%)	9%	0.2846	85/169 (50%)	101/192 (53%)	3%	0.6615
24	33/69 (48%)	39/77 (51%)	3%	0.7334	84/169 (50%)	105/187 (56%)	6%	0.2236
26	31/65 (48%)	43/73 (59%)	11%	0.1874	86/164 (52%)	111/180 (62%)	10%	0.0840

Prepared by reviewer.
P-values were obtained by Chi-square test

Table 8 Clinical Response by Visit for Reviewer's ITT Analysis

Clinical Response by Visit
Reviewer's ITT Analysis
Study CD870-031

	CRP ≥ 10 mg/L at Baseline Stratum				Overall Population			
Visit	Placebo N=156	Cimzia N=146	Diff	p-value	Placebo N=328	Cimizia N=331	Diff	p-value
2	27/156 (17%)	47/146 (32%)	15%	0.0027	47/328 (14%)	82/331 (25%)	11%	0.0007
4	34/156 (22%)	48/146 (33%)	11%	0.0305	73/328 (22%)	95/331 (29%)	7%	0.0577
6	41/156 (26%)	54/146 (37%)	11%	0.0453	88/328 (27%)	115/331 (35%)	8%	0.0278
8	43/156 (28%)	52/146 (36%)	8%	0.1321	96/328 (29%)	115/331 (35%)	6%	0.1320
12	42/156 (27%)	46/146 (32%)	5%	0.3810	103/328 (31%)	119/331 (36%)	5%	0.2167
16	39/156 (25%)	47/146 (32%)	7%	0.1664	97/328 (30%)	124/331 (37%)	7%	0.0320
20	33/156 (21%)	47/146 (32%)	11%	0.0298	89/328 (27%)	110/331 (33%)	6%	0.0882
24	33/156 (21%)	43/146 (29%)	8%	0.0968	87/328 (27%)	114/331 (34%)	7%	0.0273
26	32/156 (21%)	48/146 (33%)	12%	0.0150	90/328 (27%)	123/331 (37%)	10%	0.0076

Prepared by reviewer.
Reviewer's ITT analysis included all randomized subjects. In this analysis, subjects with missing data were considered to be "No" responders.
P-values were obtained by Chi-square test

Table 9 Clinical Response by Visit with No Imputation for Reviewer's ITT Analysis

Clinical Response by Visit
With No Imputation
Reviewer's ITT Analysis
Study CD870-031

	CRP ≥ 10 mg/L at Baseline Stratum				Overall Population			
Visit	Placebo N=156	Cimzia N=146	Diff	p-value	Placebo N=328	Cimizia N=331	Diff	p-value
2	25/156 (16%)	42/146 (29%)	13%	0.0077	44/328 (13%)	76/331 (23%)	10%	0.0015
4	31/156 (20%)	44/146 (30%)	10%	0.0391	69/328 (21%)	89/331 (27%)	6%	0.0785
6	40/156 (26%)	48/146 (33%)	7%	0.1667	84/328 (26%)	108/331 (33%)	7%	0.0474
8	41/156 (26%)	48/146 (33%)	7%	0.2091	93/328 (28%)	106/331 (32%)	4%	0.3048
12	42/156 (27%)	42/146 (29%)	2%	0.7208	99/328 (30%)	109/331 (33%)	3%	0.4802
16	39/156 (25%)	44/146 (30%)	5%	0.3177	92/328 (28%)	112/331 (34%)	6%	0.1083
20	32/156 (21%)	42/146 (29%)	8%	0.0956	85/328 (26%)	101/331 (31%)	5%	0.1897
24	33/156 (21%)	39/146 (27%)	6%	0.2573	84/328 (26%)	105/331 (32%)	6%	0.0828
26	31/156 (20%)	43/146 (29%)	9%	0.0531	86/328 (26%)	111/331 (34%)	8%	0.0403

Prepared by reviewer.
Reviewer's ITT analysis included all randomized subjects. In this analysis, subjects with missing data were considered to be "No" responders.
P-values were obtained by Chi-square test

Table 10 Clinical Response at Week 6 by Baseline CDAI Score

Clinical Response at Week 6 by Baseline CDAI Score
Study CD870-031

Baseline CDAI	CRP ≥ 10 mg/L at Baseline Stratum Placebo N=156	Cimzia N=146	Diff	p-value	Overall Population Placebo N=328	Cimizia N=331	Diff	p-value
≤ 250	10/44 (23%)	11/28 (39%)	16%	0.1318	22/91 (24%)	27/86 (31%)	7%	0.2833
251- 300	10/38 (26%)	10/43 (23%)	-3%	0.1047	27/97 (28%)	28/101 (27%)	-1%	0.9859
301 -350	8/31 (26%)	17/36 (47%)	21%	0.0707	18/70 (26%)	29/72 (40%)	14%	0.0652
> 350	12/43 (27%)	16/39 (41%)	14%	0.2109	20/70 (29%)	31/70 (44%)	15%	0.0534
≤ 300	20/82 (24%)	21/71 (30%)	6%	0.4700	49/188 (26%)	55/187 (29%)	3%	0.4690
> 300	20/74 (27%)	33/75 (44%)	17%	0.0305	38/140 (27%)	60/142 (42%)	15%	0.0077

Prepared by reviewer.
P-values were obtained by Chi-square test

Table 11 Clinical Responder (70 Points Decrease) by Visit for Available Date

Clinical Response (70 points Decrease) by Visit
Available Data
Study CD870-031

	CRP ≥ 10 mg/L at Baseline Stratum				Overall Population			
Visit	Placebo N=156	Cimzia N=146	Diff	p-value	Placebo N=328	Cimizia N=331	Diff	p-value
2	39/141 (28%)	63/138 (46%)	18%	0.0018	83/308 (27%)	117/317 (37%)	10%	0.0076
4	49/121 (41%)	73/127 (57%)	16%	0.0075	112/271 (41%)	145/297 (49%)	8%	0.0731
6	52/108 (48%)	70/122 (57%)	9%	0.1616	124/250 (50%)	153/279 (55%)	5%	0.2284
8	53/99 (54%)	61/114 (54%)	0%	0.9969	129/229 (56%)	143/267 (54%)	-2%	0.5360
12	46/84 (55%)	65/101 (64%)	9%	0.1847	122/206 (59%)	153/244 (63%)	4%	0.4504
16	48/80 (60%)	59/88 (67%)	7%	0.3429	122/197 (62%)	154/225 (68%)	6%	0.1604
20	40/73 (55%)	58/83 (70%)	15%	0.0517	105/183 (57%)	138/204 (68%)	9%	0.0369
24	38/71 (54%)	55/83 (66%)	12%	0.1070	105/177 (59%)	139/201 (69%)	10%	0.0461
26	35/69 (51%)	57/82 (70%)	19%	0.0184	97/175 (55%)	145/199 (73%)	18%	0.0004

Prepared by reviewer.
P-values were obtained by Chi-square test

Table 12 Clinical Responder (70 Points Decrease) by Visit for Reviewer's ITT Analysis

Clinical Response (70 Points Decrease) by Visit
Reviewer's ITT Analysis
Study CD870-031

	CRP ≥ 10 mg/L at Baseline Stratum				Overall Population			
Visit	Placebo N=156	Cimzia N=146	Diff	p-value	Placebo N=328	Cimizia N=331	Diff	p-value
2	39/156 (25%)	63/146 (43%)	18%	0.0009	83/328 (25%)	117/331 (35%)	10%	0.0051
4	49/156 (31%)	73/146 (50%)	19%	0.0010	112/328 (34%)	145/331 (44%)	10%	0.0110
6	52/156 (33%)	70/146 (48%)	15%	0.0097	124/328 (38%)	153/331 (46%)	8%	0.0339
8	53/156 (34%)	61/146 (42%)	8%	0.1620	129/328 (39%)	143/331 (43%)	4%	0.3126
12	46/156 (29%)	65/146 (44%)	15%	0.0068	122/328 (37%)	153/331 (46%)	9%	0.0188
16	48/156 (31%)	59/146 (40%)	9%	0.0800	122/328 (37%)	154/331 (47%)	10%	0.0152
20	40/156 (26%)	58/146 (40%)	14%	0.0090	105/328 (32%)	138/331 (42%)	10%	0.00100
24	38/156 (24%)	55/146 (38%)	14%	0.0123	105/328 (32%)	139/331 (42%)	10%	0.0080
26	35/156 (22%)	57/146 (39%)	17%	0.0017	97/328 (30%)	145/331 (44%)	14%	0.0002

Prepared by reviewer.
P-values were obtained by Chi-square test

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Pharmacoepidemiology and Statistical Science
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

BLA/Serial Number:	125160/0
Drug Name:	CIMZIA (Certolizumab pegol (lyophilized 200 mg/ml)
Indication(s):	[redacted]
Applicant:	UCB, Inc.
Received Date(s):	Received February 28, 2006 PDUFA: December 28, 2006
Review Priority:	Standard
Biometrics Division:	Division of Biometrics 3
Statistical Reviewer:	Milton C. Fan, Ph.D.
Concurring Reviewers:	Mike Welch, Ph.D.
	Steve Wilson, Ph.D.
Medical Division:	Gastroenterology Products (HFD-180)
Clinical Team:	Shewit Bezabeh, M.D. (HFD-180)
Project Manager:	Marlene Swider (HFD-180)

Keywords: clinical study, biological product, logistic regression, LOCF, sensitivity analysis, single study

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1. EXECUTIVE SUMMARY

1.1 Conclusions and Recommendations

The sponsor has submitted two Phase III studies (CDP870-031 and CDP870-032) for the claim. Study CDP870-031 was designed to evaluate the treatment in patients with active Crohn's disease. Study CDP870-032 was designed to evaluate the treatment of patients with active Crohn's disease who had responded to open induction therapy with CDP870 400 mg.

For Study CDP870-31, the co-primary efficacy endpoints (clinical responses at Week 6, and Weeks 6 and Week 26) in the stratum defined by CRP $\geq$ 10 mg /L at baseline showed borderline statistical significance compared to placebo (p=0.037 and 0.045 at Week 6, and Weeks 6 and Week 26, respectively). However, the sponsor's intent-to-treat analysis excluded two placebo subjects and one CDP870 400 mg subject. Furthermore, it was found that two placebo subjects had discrepancies in status of clinical complete response at Week 6 and one placebo subject had discrepancy in status of clinical complete response at Weeks 6 and 26. The superiority of CDP870 400 mg group over placebo was dependent on outcomes for those two placebo subjects who had discrepancies in status of clinical complete responses at Week 6 and Weeks 6 and 26. If one placebo subject was assumed to be a responder at Week 6 and other one placebo subject was assumed to be a responder at Week 6 and at Weeks 6 and 26, results from the ITT analyses would provide p-values of 0.065 at Week 6 and Weeks 6 and 26. This sensitivity of the p-value indicates a lack of robustness of the sponsor's conclusion.

For the secondary efficacy endpoints, both clinical remission at Week 6, and Weeks 6 and 26 in both the CRP$\geq$10 mg/L at baseline stratum and the overall population failed to achieve statistical significance. Clinical responses at Week 6, and Weeks 6 and 26 in the overall population achieved statistical significance for sponsor's ITT population, but they failed for the Per Protocol Population. Treatment differences on IBDQ were not statistically significant at Week 6, and Weeks 6 and 26 in both the CRP$\geq$10 mg/L at baseline stratum and the overall population. The strength of evidence from Study CDP870-31 was not statistically persuasive.

Study CDP870-032 showed that for the primary efficacy endpoint, the percentage of subjects with clinical response at Week 26, in the stratum defined by CRP$\geq$ 10 mg/L at baseline was statistically significantly higher in the CDP870 400 mg group compared with the placebo group in the ITT population.

However, for the U.S., the proportion of subjects in clinical response at Week 26 in the CRP $\geq$10 mg/L at baseline stratum for the CDP870 400 mg group was similar to that for the placebo group. Overall, the positive efficacy results were largely shown by countries other than the U.S.

For 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

≥10 mg/L at baseline stratum and overall population, and clinical response at Week 26 in overall population, the CDP870 400 mg group showed superiority over placebo.

In conclusion, the strength of evidence for this claim for maintenance was demonstrated for one single study, Study CDP870-032; however, it should be noted that results were driven by countries other than the U.S.

1.2 Brief Overview of Clinical Studies

1.1.1 Study CDP870-031

This study was a randomized, multinational, multicenter, double-blind placebo-controlled parallel group study to evaluate the safety and efficacy of CDP870 in treatment of active Crohn's disease. The duration of this study was 26 weeks.

The primary objective of this study was to compare the efficacy of subcutaneous CDP870 (400 mg) administered at 0, 2, and 4 weeks then 4-weekly to Week 24 versus placebo in the treatment of signs and symptoms of active Crohn's disease (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) over a 26-week period.

The secondary objectives of this study were to evaluate the safety of CDP870 with 4-weekly dosing over a 26 week period, to obtain data on the plasma concentrations of CDP870 and anti-CDP870 antibodies, and to evaluate the efficacy of CDP870 irrespective of baseline CRP levels.

Patients were randomized within strata, with 3 stratification factors:

1. CRP<10 mg/L or CRP≥10 mg/L at Week 0
2. Receiving corticosteroids at Week 0 or not
3. Receiving immunosuppressants (azathiprine/6-MP/ methotrexate) at Week 0 or not.

Subjects should have had Crohn's disease for a minimum of 3 months duration with CDAI score between 220 and 450, scored over the 7 days prior to the first dose of study drug.

Each patient received CDP870 (400 mg) or placebo via subcutaneous injection on eight occasions (Weeks 0, 2, 4, 8, 12, 16, 20 and 24).

A diary card was completed daily by the patient throughout the study for subsequent CDAI calculation by the Investigator. Diary card was issued at study entry, also at Weeks 0 through to 24. Diary data to be collected included the following:

1. Number of liquid or very soft stools.
2. Abdominal pain [none, mild, moderate, severe].

3. General well-being [generally well, slightly under par, poor, very poor or terrible].
4. Evening oral temperature (if the patient considered this elevated).
5. Use of loperamide, diphenoxylate/atropine or codeine phosphate for diarrhea.

Data from the patient diary card collected over the 7 days prior to the visit together with data from the clinical Crohn's disease assessment were used to calculate the patient's CDAI score.

The co-primary efficacy endpoints were:

1. The percentage of patients with clinical response at Week 6 in strata defined by CRP≥10 mg/L at baseline.
2. The percentage of patients with clinical response at both Weeks 6 and 26 in strata defined by CRP≥10 mg/L at baseline.

The clinical response was defined at least a 100 point decrease from the Week 0 CDAI score.

The major secondary efficacy endpoints included:

In the population with CRP≥ 10 mg/L at baseline
1. (i) Percentage of patients in clinical remission at Week 6
   (ii) Percentage of patients in clinical remission at both Weeks 6 and 26
   Clinical remission was defined as a total CDAI score of 150 or less.
2. (i) Percentage of patients with IBDQ response at Week 6
   (ii) Percentage of patients with IBDQ response at both Weeks 6 and 26.
   IBDQ response was defined as at least a 16 point increase from Week 0 IBDQ score.

In the overall irrespective of baseline CRP,
1. (i) Percentage of patients in clinical response at Week 6
   (ii) Percentage of patients in clinical response at both Weeks 6 and 26
2. (i) Percentage of patients in clinical remission at Week 6
   (ii) Percentage of patients in clinical remission at both Weeks 6 and 26
3 (i) Percentage of patients with IBDQ response at Week 6
   (ii) Percentage of patients with IBDQ response at both Weeks 6 and 26.

A total of 976 subjects were screened. A total of 662 subjects were randomized (329 for placebo and 333 for CDP870 400 mg).

1.1.2 Study CDP870-032

This study was a multi-national, multicenter, double-blind placebo-controlled study to assess the maintenance of clinical response to humanized anti-TNF PEG conjugate, CDP870 400 mg sc, (dosed 4-weekly from Weeks 8 to 24), in the treatment of patients

with active Crohn's disease who had responded to open induction therapy (dosed at Weeks 0, 2, and 4) with CDP870. The duration of the study was 26 weeks.

The study design for this study was similar to Study CDP870-031 with some exceptions listed below.

The primary objective was to compare efficacy of repeated 4-weekly treatment with CDP870 versus placebo, following successful open induction therapy, in the maintenance of clinical response in patients with active Crohn's disease over 26 weeks.

The secondary objectives were:

a) To evaluate the safety of CDP870 with 4-weekly dosing over a 26 week period.
b) To obtain data on the plasma concentrations of CDP870 and antibodies to CDP870.
c) To evaluate the duration of response to open induction therapy with CDP870.

Patients who demonstrated a clinical response (100 point decrease in Week 0 CDAI) at Week 6 following open induction therapy, with CDP870 400mg sc at Weeks 0, 2 and 4, were randomized to blinded 4-weekly dosing with CDP870) 400 mg or placebo for 24 weeks.

Patients were randomized within strata, with 3 stratification factors:

a) CRP<10 mg/L or CRP≥10 mg/L at Week 0
b) Receiving corticosteroids, at Week 0 or not
c) Receiving immunosuppressants (azathiprine/6-MP/methotrexate) at Week 0 or not.

Subjects should have had Crohn's disease for a minimum of 3 months duration with CDAI score between 220 and 450, scored over the 7 days prior to the first dose of study drug.

The primary efficacy endpoint was the proportion of patients with clinical response at Week 26 in strata defined by CRP≥10 mg/L at baseline. The clinical complete response was defined as at least a 100 point decrease in the Week 0 CDAI score.

The major secondary efficacy endpoints included:

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

a) Time to disease progression up to and including Week 26.
   Time to disease progression was defined as the earliest event, in Week 6 responders, or either an increase of ≥100 pts above Week 6 CDAI, absolute CDAI≥ 175 pts, for at least 2 consecutive visits (14 days or longer) or the use of rescue therapy.
b) Proportion of patients in clinical remission at Week 26
   Clinical remission was defined as a total CDAI score of 150 or less.

c) Proportion of patients with IBDQ response at Week 26
IBDQ response was defined as at least a 16 point increase from Week 0 IBDQ score.

In the overall irrespective of baseline CRP,

a) Proportion of patients in clinical response at Week 26
b) Time to disease progression up to and including Week 26
c) Proportion of patients in clinical remission at Week 26
d) Proportion of patients with IBDQ response at Week 26

Of 930 subjects screened for eligibility for the study, 668 subjects 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 (66.6%) had clinical response (a decrease in CDAI score of $\geq$ 100 points from baseline) at Week 6 and were randomized to the double-blind phase of study.

1.3 STATISTICAL ISSUES AND FINDINGS

The sponsor has submitted two Phase III studies (CDP870-031 and CDP870-032) for the claim. Study CDP870-031 was designed to evaluate the treatment in patients with active Crohn's disease. Study CDP870-032 was designed to evaluate the treatment of patients with active Crohn's disease who had responded to open induction therapy with CDP870 400 mg.

In Study DCP870-031, the co-primary efficacy endpoints were the percentage of subjects with clinical response (a decrease in CDAI score of $\geq$100 points from baseline) at Week 6 and at both Weeks 6 and 26 in the stratum defined by CRP$\geq$10 mg/L at baseline.

In the sponsor's analysis of co-primary efficacy endpoints, the sponsor's ITT population did not include all randomized patients. It included all patients randomized who received at least one injection of study treatment and who had at least one efficacy measurement after the first injection.

This reviewer performed "true" ITT analyses which included all randomized patients. In these analyses, patients with missing data were considered to be non-responders. To be conservative, Fisher's exact test was performed. Based on the reviewer's ITT analyses, contrary to sponsor's finding, the treatment difference for clinical response at Weeks 6 and 26 in the stratum defined by CRP$\geq$10 mg/L at baseline failed to achieve statistical significance.

Furthermore, it was found that two placebo subjects had discrepancies in status of clinical complete response at Week 6 and one placebo subject had discrepancy in status of clinical complete response at Weeks 6 and 26. The superiority of CDP870 400 mg group over placebo was dependent on outcomes for those two placebo subjects who had discrepancies in status of clinical complete responses at Week 6 and Weeks 6 and 26. If one placebo subject was assumed to be a responder at Week 6 and other one placebo subject was assumed to be a responder at Week 6 and at Weeks 6 and 26, results from the

ITT analyses would provide p-values of 0.0647 at Week 6 and Weeks 6 and 26. This sensitivity of the p-value indicates a lack of robustness of the sponsor's conclusion.

There was a slightly disproportion in gender for overall population (p=0.0572). Even in the CRP ≥10 mg/L at baseline stratum, slightly more females than males in the placebo group (57.7% vs. 42.3%) were observed, but males and females in CDP870 400 mg group were even.

This reviewer performed a post-stratification analysis of primary efficacy endpoints adjusted for gender. The resulting p-values were 0.0636 and 0.0647 at Week 6, and Weeks 6 and 26, respectively.

This reviewer also performed sensitivity analyses to find out how many changes in complete response status at Week 6, and Weeks 6 and 26 would change the 2-sided p-value from the observed p-value to greater than 0.05, keeping sample size fixed.

Results indicated that changes in the responder status of 2 subjects in CDP870 400 mg group or 2 subjects in the placebo group (i.e., from responder to non-responder in CDP870 400 mg group or from non-responder to responder in the placebo group) could change the observed 2-sided p-value <0.05 to greater than 0.05.

Results also indicated that a change in the responder status of just 1 placebo subject from non-responder to responder and when there was a change of 1 subject in CDP870 400 mg group from responder to non-responder would cause a shift in the 2-sided p-value from <0.05 to a p-value of greater than 0.05.

Furthermore, the superiority of CDP870 400 mg over placebo in terms of co-primary efficacy endpoints (clinical responses at Week 6, and Weeks 6 and Week 26) in the stratum defined by CRP ≥ 10 mg /L at baseline was dependent on outcomes for those 6 subjects in CDP870 400 mg group who had missing observations. So, resulted from sponsor's analysis with LOCF might not be robust.

In summary, the superiority of CDP870 400 mg over placebo in terms of co-primary efficacy endpoints (clinical responses at Week 6, and Weeks 6 and Week 26) in the stratum defined by CRP ≥ 10 mg /L at baseline was not robust.

For the secondary efficacy endpoints, both clinical remission at Week 6, and Weeks 6 and 26 in both the CRP≥10 mg/L at baseline stratum and the overall population failed to achieve statistical significance. Clinical responses at Week 6, and Weeks 6 and 26 in the overall population achieved statistical significance for sponsor's ITT population, but they failed for the Per Protocol Population. Treatment differences on IBDQ were not statistically significant at Week 6, and Weeks 6 and 26 in both the CRP≥10 mg/L at baseline stratum and the overall population. So, the strength of evidence from Study CD870-31 was not statistically persuasive.

Study CDP870-032 showed that for the primary efficacy endpoint, the percentage of subjects with clinical response at Week 26, in the stratum defined by CRP≥ 10 mg/L at baseline was statistically significantly higher in the CDP870 400 mg group compared with the placebo group in the ITT population.

However, for the U.S., the proportion of subjects with a clinical response at Week 26 in the CRP ≥10 mg/L at baseline stratum for the CDP870 400 mg group was similar to that for the placebo group. Overall, it appears the results were driven by data from sites outside the U.S.

For 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, the CDP870 400 mg group showed superiority over placebo.

2. INTRODUCTION

2.1 Overview

CDP870 is an anti-Tumour Necrosis Factor (TNF), humanized antibody (Fragment Antigen Binding) Fab" fragment-polyethylene glycol (PEG) conjugate presented as lyophilized power.

The sponsor has submitted this BLA to obtain a indication for certolizumab pegol for the

2.2 Data Sources

This BLA included two pivotal Phase III studies (CDP870-031 and CDP870-032) in patients with moderate to severe Crohn's disease. In addition, a population PK study (CDP-039) was performed to determine the effects of covariates such as age, gender, renal function and concomitant medications. Two Phase III studies were:

CDP870-031: A Phase III multi-national, multicenter, double-blind placebo-controlled parallel group, 26 week study to assess the safety and efficacy of the humanized anti-TNF PEG conjugate, CDP870 400 mg sc, (dosed at Weeks 0, 2, 4 then 4-week to Week 24) in the treatment of patients with active Crohn's disease.

CDP870-032: A Phase III multi-national, multicenter, 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 at 4-weekly from Week 8 to Week 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.

The sponsor submitted a Response to a Request for Information dated September 12, 2006 for population analysis in Report 40001559 and 40001548.

Dr. Marcelo Mangalindan, FDA site investigator found data errors in Study CDP870-31 in two sites (Dr. P. Honiball, 39006 and Dr. J. Chojnacki, 33012). Observations at these clinical sites included issues with transcription of data related to CDAI scores for study CD870-031. The sponsor submitted a proposal for correcting the databases and re-analyzing the primary and key secondary efficacy endpoints with the corrected CDAI data in General Correspondences dated October 2, 2006. The sponsor submitted the results of those re-analyses in General Correspondences dated October 13, 2006.

The sponsor submitted a Response to a Request for Information dated October 26, 2006 for the Information Request by this reviewer dated September 9, 2006.

The sponsor submitted Complete Response to Information Request Letter dated November 10, 2006 for the information request letter dated October 11, 2006.
The sponsor submitted Response to Request for Information dated November 29, 2006 for the information requests dated September 9, 2006 and November 6, 2006.

This submission provided updated response to Question 1 and the analyses requested in Question 3. The sponsor's updated response to Question 1 is given in Appendix A. The sponsor's analyses requested in Question 3 are given in Appendix B.

All data were submitted in electronic format to the FDA CBER EDR.

3. STATISTICAL EVALUATION

3.1 Evaluation of Efficacy

3.1.1 Study CDP870-031

3.1.1.1 Study Design

This study was a randomized, multinational, multicenter, double-blind placebo-controlled parallel group study to evaluate the safety and efficacy of CDP870 for treatment of active Crohn's disease. The duration of this study was 26 weeks.

The primary objective of this study was to compare the efficacy of subcutaneous CDP870 (400 mg) administered at 0, 2, and 4 weeks then 4-weekly to Week 24 versus placebo in the treatment of signs and symptoms of active Crohn's disease (CDAI between 220 and 450 scored over the 7 days prior to the first dose of study drug and C-Reactive Protein (CRP$\geq$ 10 mg/L at baseline) over a 26-week period.

The secondary objectives of this study were to evaluate the safety of CDP870 with 4-weekly dosing over a 26 week period, to obtain data on the plasma concentrations of CDP870 and anti-CDP870 antibodies, and to evaluate the efficacy of CDP870 irrespective of baseline CRP levels.

Patients were randomized within strata, with 3 stratification factors:

1. CRP<10 mg/L or CRP≥10 mg/L at Week 0
2. Receiving corticosteroids, at Week 0 or not
3. Receiving immunosuppressants (azathiprine/6-MP/ methotrexate) at Week 0 or not.

Subjects should have had Crohn's disease for a minimum of 3 months duration with CDAI score between 220 and 450, scored over the 7 days prior to the first dose of study drug.

Each patient received CDP870 (400 mg) or placebo via subcutaneous injection on eight occasions (Weeks 0, 2, 4, 8, 12, 16, 20 and 24).

Eligible baseline concomitant medication for Crohn's disease were: 5-ASA's or antibiotics (stable for 4 weeks prior to screening); corticosteroids equivalent to or less than 30 mg prednisone per day (stable dose for 2 weeks); azathioprine and 6-mercaptonpurine or methotrexate (stable dose for 8 weeks).

Following the injection at Week 8 (starting no later than Week 12), patients who in the investigator's opinion were clinically responding might at the investigator's discretion reduce the dose of any concomitant corticosteroids.

A diary card was completed daily by the patient throughout the study for subsequent CDAI calculation by the Investigator. A diary card was issued at study entry, also at Weeks 0 through to 24. Diary data collected included the following:

1. Number of liquid or very soft stools.
2. Abdominal pain [none, mild, moderate, severe].
3. General well-being [generally well, slightly under par, poor, very poor or terrible].
4. Evening oral temperature (if the patient considered this elevated).
5. Use of loperamide, diphenoxylate/atropine or codeine phosphate for diarrhea.

Data from the patient diary card collected over the 7 days prior to the visit together with data from the clinical Crohn's disease assessment were used to calculate the patient's CDAI score.

If the patient was withdrawn due to exacerbration of his/her Crohn's disease, the CDAI calculation would be made using the diary data for the 7 days prior to the withdrawal visit.

Patients were asked to answer 32 questions relating to the condition for their Crohn's disease over the 2 weeks prior to their study visit using the Inflammatory Bowel Disease Questionnaire (IBDQ).

The co-primary efficacy endpoints were:

1. The percentage of patients with clinical response at Week 6 in strata defined by CRP≥10 mg/L at baseline.
2. The percentage of patients with clinical response at both Weeks 6 and 26 in strata defined by CRP≥10 mg/L at baseline.

The clinical response was defined as at least a 100 point decrease from the Week 0 CDAI score.

The major secondary efficacy endpoints included:

In the population with CRP≥ 10 mg/L at baseline
1. (i) Percentage of patients in clinical remission at Week 6
   (ii) Percentage of patients in clinical remission at both Weeks 6 and 26
   Clinical remission was defined as a total CDAI score of 150 or less.
2. (i) Percentage of patients with IBDQ response at Week 6
   (ii) Percentage of patients with IBDQ response at both Weeks 6 and 26.
   IBDQ response was defined as at least a 16 point increase from Week 0 IBDQ score.

In the overall irrespective of baseline CRP,
1. (i) Percentage of patients in clinical response at Week 6
   (ii) Percentage of patients in clinical response at both Weeks 6 and 26
2. (i) Percentage of patients in clinical remission at Week 6
   (ii) Percentage of patients in clinical remission at both Weeks 6 and 26
3. (i) Percentage of patients with IBDQ response at Week 6
   (ii) Percentage of patients with IBDQ response at both Weeks 6 and 26.

No hypothesis testing was performed and only descriptive statistics were presented for CDAI, IBDQ, HBI, and CRP, Faecal Calprotectin, and Fistulae.

The sample size was determined on the basis of anticipated difference between CDP870 400 mg and placebo in the percentage of patients with clinical response (defined as at least a 100 point decrease in CDAI score from baseline) at Week 6 and both Weeks 6 and 24.

Sample Size Determination:

For clinical response at Week 6, the observed placebo response rate in elevated CRP subgroup at Week 6 was 28.6%. A placebo rate of 30% was assumed and a difference between CDP870 400 mg and placebo of 25% was considered clinical relevant. To detect a difference of 25% (30% placebo, 55% CDP870 400 mg) at a two-sided significance level of 5% for a 1:1 ratio with 85% power, 77 patients per treatment within the elevated CRP subgroup (CRP<10 mg/L, CRP≥ 10 mg/L), and therefore total sample size is 4 x 77= 308 patients.

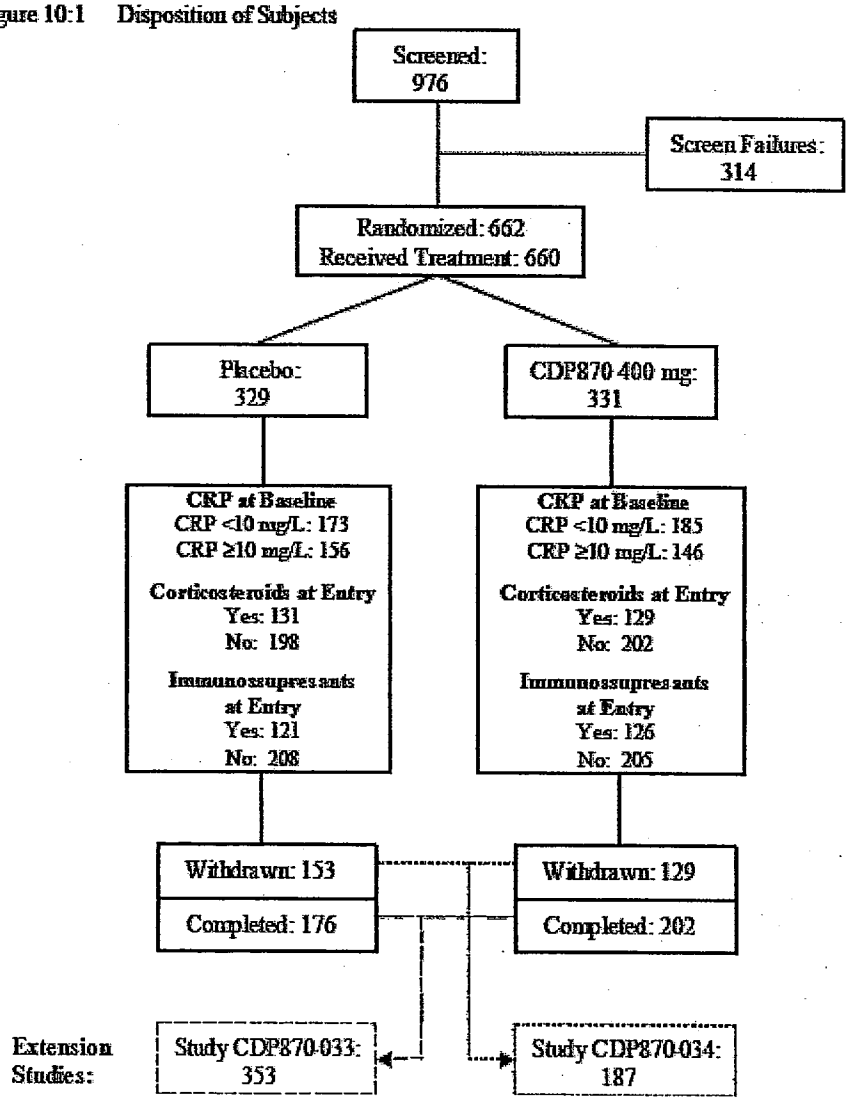
For clinical response at Week 6 and Week 26, a placebo rate of 15% was assumed and a difference between CDP870 400 mg and placebo of 15% was considered clinical relevant. To detect a difference of 15% (15% placebo, 30% CDP870 400 mg) at a two-sided significance level of 5% for a 1:1 ratio with 85% power, 151 patients per treatment within the elevated CRP subgroup were required. It was planned to recruit equal number into each CRP subgroup (CRP<10 mg/L, CRP≥ 10 mg/L), and therefore total sample size is 4 x 151= 604 patients.

The sample size was based on the larger of the two estimates so as to control the Type I error. The significance level of 5% had not been adjusted to account for co-primary variables, as both were required to be significant in this study.

3.1.1.2 Sponsor's Analysis

The disposition of subjects through Week 26 is shown below.

Figure 10:1 Disposition of Subjects



A total of 976 subjects were screened. A total of 662 subjects were randomized (329 for placebo and 333 for CDP870 400 mg). Two subjects were randomized to the CDP870 400 mg group but did not receive treatment. Subject 18009/0928 was withdrawn due to CRP <10 mg/L (after enrollment to CRP<10 mg/L arm was closed) and Subject 39018/0293 withdrew due to subject decision. A higher proportion of subjects withdrew from the study in the placebo group compared with CDP870 400 mg group (46.5% vs. 39.0%). The most common reason for withdrawal was "lack of improvement or disease deterioration" (34.4% for placebo and 23.9% for CDP870 400 mg).

The ITT population was the primary population for analysis of efficacy. The ITT population included 659 subjects (331 in CDP870 400 mg and 328 in placebo). 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 of total number of subjects with efficacy protocol deviation exceeded 15% of the ITT population (115 subjects, or 17.5% of the ITT population), efficacy analyses were also performed using the PP population. The PP population included 544 subjects (267 in CDP870 400 mg and 277 in placebo).

3.1.1.2.1 Planned Analysis

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

The intent to treat (ITT) population was the primary population for analysis of efficacy.

All patients eligible for the ITT population, who did not have any major efficacy protocol deviation were included in the per-protocol population.

The purpose of this study was to demonstrate significant effects on both co-primary endpoints and therefore, there was no adjustment for Type I error.

In order to investigate the impact of certain characteristics on efficacy, the co-primary endpoints (percentage of responders at Week 6 and at both Weeks 6 and 26) were examined by the following subgroups:

- Use of immunosuppressants at entry
- Use of steroids at entry
- Smoking status at entry
- Previous surgery for Crohn's disease
- Duration of Crohn's disease
- Patients with antibodies to CDP870
- CDAI score at entry.

For exploratory purpose, the impact of the subgroups on the co-primary endpoints was examined using logistic regression, including a factor for the subgroup of interest plus the interaction term with treatment, as well as the other stratification factors stated in the main analysis.

Tests for two-factor interactions between treatment and "subgroup of interest" were assessed for statistical significance at the 0.10 level.

A Closed Test procedure (Koch) was used to control for multiple comparisons across the secondary efficacy endpoints. Hypothesis testing was performed on the major secondary variables at a 5% significance level, only if both co-primary endpoints were significant.

All patients eligible for the ITT population, who did not have any major efficacy protocol deviation, were included in the per-protocol (PP) population. The PP population was only be defined if more than 15% of patients in the ITT population were classified as major protocol deviators.

If the date of this visit fell within a scheduled visit window, these data were also included in summaries of that visit unless a visit had already occurred. In order to fall within a visit window, the visit should be:

- ± 3 days of Weeks 2, 4, 6 or 26
- ± 7 days of Weeks 8, 12, 16, 20 or 24.

The detailed calculation of Crohn's disease activity index score in given in Appendix A.

Imputation rules for the handling of missing data in the calculation of CDAI score are given in Appendix B.

The detailed method used in the calculation of Inflammatory Bowel Disease Questionnaire (IBDQ) score is given in Appendix C.

For all responder analyses (clinical response, remission, and IBDQ response), patients who withdrew for any reason were considered as non-responders from that timepoint onwards.

Any missing data during the trial prior to study completion/withdrawal remained as missing at that timepoint. This included CDAI, IBDQ, SF-36, WPAI and EQ-5D scores, if after imputation the scores was still set to missing.

The handling of missing data (caused by prematurely discontinued patients or otherwise) was managed according to a last observation carried forward (LOCF) principle whereby missing values were replaced with the last previous non-missing value.

If there were more than 5% of observations with missing data (after imputation techniques had been applied and withdrawals had been taken into consideration) at

Weeks 6 and 26 for clinical response, remission and IBDQ response, then a sensitivity analysis would be performed on the respective endpoint.

For the primary endpoints only, three sensitivity analyses were performed were:

a) Observed case- only observed data were included in the analysis and no imputations were made both regards to the imputation techniques and withdrawals.
b) Worst case- a patient was classified as a 'non-responder' at any visit with missing data prior to study completion/withdrawal.
c) Best/Worst case - Any patients with missing data who was randomized to active treatment was classified as 'non-responder' and any patient with missing data who was randomized to placebo was classified as a 'responder'.

Logistic regression was used in all categorical analyses with the statistical output including odds ratios and 95% confidence intervals for the odds ratios. The confidence interval was based on the normal distribution (Wald inference).

For the CRP≥10 mg/L population and the overall population, the analyses were adjusted for the stratification factors, corticosteroid use at entry and immunosuppressant use at entry and CRP strata (CRP<10 mg/L, CRP≥10 mg/L), plus geographical region.

For all responder analyses, patients who withdrew for any reason were considered as non-responder from that timepoint onwards.

If patients received rescue therapy during the 26-week double-blind period, they were considered as treatment failures from the timepoint of administration of first rescue therapy onwards.

3.1.1.2.2 Treatment Group Comparability

A summary of the demographic characteristics at baseline, baseline Crohn's disease characteristics, and medical history and current diagnoses of treatment subjects by randomized treatment are presented in Appendix Table 1.

As seen from Appendix Table 1, overall, demographic characteristics at baseline were generally similar across the two treatment groups with the exception of gender (p=0.0572).

3.1.1.2.3 Sponsor's Analysis of Primary Efficacy Parameter

The co-primary endpoints were the percentage of subjects with clinical response (a decrease in CDAI score of ≥100 points from baseline) at Week 6 and at both Weeks 6 and 26 in the stratum defined by CRP≥10 mg/L at baseline.

A summary of subjects with clinical response at Week 6, and at both Weeks 6 and 26 in the CRP≥10 mg/L at baseline stratum is given below.

Summary of Subjects with Clinical Response at Week 6 in the CRP ≥10 mg/L Stratum at Baseline – ITT Population

Week 6	Placebo (N=156)	CDP870 400 mg (N=146)
Number of Subjects	154	145
Frequency	40 (26.0%)	54 (37.2%)
95% CI for Percentage Response	19.0%, 32.9%	29.4%, 45.1%
Odds Ratio		1.70
95% CI for Odds Ratio		1.03, 2.80
p-value [a]		0.037

[a] P-values have been calculated using Logistic regression with factors for treatment, steroid use at entry, immunosuppressant use at entry and geographical region.
Source: Table 14.2.2:1

Summary of Subjects with Clinical Response at Weeks 6 and 26 in the CRP ≥10 mg/L Stratum at Baseline - ITT Population

Weeks 6 and 26	Placebo (N=156)	CDP870 400 mg (N=146)
Number of Subjects	154	144
Frequency	19 (12.3%)	31 (21.5%)
95% CI for Percentage Response	7.1%, 17.5%	14.8%, 28.2%
Odds Ratio		1.91
95% CI for Odds Ratio		1.02, 3.57
p-value [a]		0.045

[a] P-values have been calculated using Logistic regression with factors for treatment, steroid use at entry, immunosuppressant use at entry and geographical region.
Source: Table 14.2.2:1

As seen from tables above, both endpoints were statistically significantly higher in the CDP870 400 mg group compared with the placebo group for the ITT population.

However, for the PP population, the treatment differences were not statistically significant at Week 6, and Weeks 6 and 26 in the CPR≥10 mg/L at baseline or in the overall population (see Appendix Table 2).

3.1.1.2.3.1 Sensitivity Analyses

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

- Observed case – using only observed data
- Worst case – subjects with missing data were set to non-responders (after imputation techniques were applied and withdrawals were taken into consideration)

Summaries of the clinical response calculated with observed data are given in Appendix Tables 3- 4.

As seen from Appendix Tables 3-4, the results from the " observed case" analysis revealed that the treatment differences at both Week 6 and Weeks 6 and 26 failed to achieve statistical significance (p=0.434 and 0.456, respectively for Week 6, and Weeks 6

and 26). The results from the "worst case" analysis showed that the treatment differences at both Week 6, and Weeks 6 and 26 were statistically significant (p=0.035 and 0.047, respectively for Week 6, and Weeks 6 and 26).

3.1.1.2.4 Sponsor's Analysis of Secondary Efficacy Endpoints

3.1.1.2.4.1 Clinical Remission at Week 6, and Weeks 6 and 26

A summary of subjects with clinical remission at Week 6, and Weeks 6 and 26 in the CRP≥10 mg/L at baseline stratum and the overall population for ITT population is given below.

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 at Baseline Stratum		Overall Population	
	Placebo N=156	CDP870 400 mg N=146	Placebo N=328	CDP870 400 mg N=331
Week 6				
n	154	146	326	329
Frequency	26 (16.9%)	32 (21.9%)	56 (17.2%)	71 (21.6%)
95% CI for Percentage Response	(11.0%, 22.8%)	(15.2%, 28.6%)	(13.1%, 21.3%)	(17.1%, 26.0%)
Odds Ratio		1.37		1.34
95% CI for Odds Ratio		(0.76, 2.46)		(0.91, 1.99)
p-value [a]		0.294		0.142
Weeks 6 and 26				
n	154	145	326	327
Frequency	13 (8.4%)	19 (13.1%)	32 (9.8%)	47 (14.4%)
95% CI for Percentage Response	(4.1%, 12.8%)	(7.6%, 18.6%)	(6.6%, 13.0%)	(10.6%, 18.2%)
Odds Ratio		1.58		1.56
95% CI for Odds Ratio		(0.73, 3.38)		(0.96, 2.52)
p-value [a]		0.243		0.072

[a] P-value has been calculated using Logistic regression with factors for treatment, steroid use at entry, immunosuppressant use at entry and geographical region. In the Overall Population, CRP strata was also included as a factor in the model.
Source: Table 14.2.3.1 and Table 14.2.3.3

As seen from table above, in both the CRP≥10 mg/L at baseline stratum and the overall population, irrespective of baseline CRP, treatment difference in the proportion of subjects with clinical remission (CDAI score ≤150 points) between the two treatment group were not statistically significant at Week 6, and Weeks 6 and 26.

3.1.1.2.4.2 Clinical Response in the Overall Population

A summary of subjects with clinical response (decrease in CDAI score of ≥100 points from baseline) at Week 6, and Weeks 6 and 26 for overall population for ITT population is given below.

Summary of Subjects with Clinical Response at Week 6 and Weeks 6 and 26 in the Overall Population – ITT Population

Time-point	Placebo (N=328)	CDP870 400 mg (N=331)
Week 6		
N	325	327
Frequency	87 (26.8%)	115 (35.2%)
95% CI for Percentage Response	(22.0%, 31.6%)	(30.0%, 40.3%)
Odds Ratio		1.51
95% CI for Odds Ratio		(1.08, 2.11)
p-value[a]		0.016
Weeks 6 and 26		
N	325	325
Frequency	52 (16.0%)	75 (23.1%)
95% CI for Percentage Response	(12.0%, 20.0%)	(18.5%, 27.7%)
Odds Ratio		1.58
95% CI for Odds Ratio		(1.06, 2.35)
p-value[a]		0.024

[a] p-values have been calculated using Logistic regression with factors for treatment, CRP strata, steroid use at entry, immunosuppressant use at entry and geographical region.
Source: Table 14.2.2.26

As seen from the table above, in the overall populatión, the proportion of subjects with clinical response was also statistically significant higher in the CDP870 400 mg group compared with the placebo group at Week 6, and Weeks 6 and 26 in the ITT population.

However, for the PP population, the treatment differences were not statistically significant at Week 6, and Weeks 6 and 26 in the CPR≥10 mg/L at baseline or in the overall population (see Appendix Table 5).

3.1.1.2.4.3 IBDQ

In order to assess the effect of study medication on Quality of Life (QoL), IBDQ response and IBDQ global scores were compared between CDP870 400 mg and placebo treatment groups. IBDQ response was defined as an increase in IBDQ global score of ≥16 points from baseline, and analyzed at Week 6, and Weeks 6 and 26.

Summaries of subjects with a increase IBDQ global score of ≥16 points from baseline at Week 6, and Weeks 6 and 26 in the CRP≥10 mg/L at baseline stratum and overall population are given Appendix Table 6 and Table 7, respectively.

As seen from Appendix Tables 6 and 7, differences between the two treatment groups were not statistically significant at Week 6, and Weeks 6 and 26 in both the CRP≥10 mg/L at baseline stratum and the overall population.

3.1.1.2.5 **Re-analyses**

Dr. Marcelo Mangalindan, FDA site investigator found data errors in Study CDP870-31 in two sites (Dr. P. Honiball, 39006 and Dr. J. Chojnacki, 33012), Observations at these clinical sites included issues with transcription of data related to CDAI scores for study

CD870-031. The sponsor submitted a proposal for correcting the databases and re-analyzing the primary and key secondary efficacy endpoints with the corrected CDAI data in General Correspondences dated October 2, 2006. The sponsor submitted the results of those re-analyses in General Correspondences dated October 13, 2006.

The sponsor stated that the results demonstrated that the updated CDAI data did not change the overall outcome of the study.

3.1.1.3 Reviewer's Comments and Evaluation

3.1.1.3.1 Logistic Regression Method

The sponsor used the logistic regression method to analyze all categorical data. Logistic regression method involves statistical models. Koch, G and Gansky, S (1996) stated these methods are advantageous in explaining the role of treatment differences in the variation of response variables. These methods, however, usually require additional nonstatistical arguments to justify assumptions that the data under study are like a statistically random sample; since centers and patients in most studies are selected for inclusion by convenience, the fundamental assumptions for modeling methods are debatable.

On the basis of randomization, the design approach methods have the advantage of requiring minimal assumption about homogeneity of treatment difference across center or other factors or about sample sizes for centers. So, Fisher's exact test and chi-square test are more appropriate statistical methods for analyzing binary data without stratification in a clinical study. The Mantel-Haenszel test is a more appropriate statistical test for analyzing binary data with stratification.

3.1.1.3.2 Reviewer's Comments on Sponsor's Primary Endpoint Analysis

3.1.1.3.2.1 LOCF (Last Observation Carried Forward) Analyses

It was observed that there were some differences in the number of subjects in clinical response at Week 6, and Weeks 6 and 26 in the CRP≥10 mg/L at baseline stratum from resulted from analyses with LOCF and without LOCF (observed case) for CDP870 400 mg treatment group as seen below. No difference was observed for the placebo group.

Number of Subject in Clinical Response at Week 6, and Weeks 6 and 26 in the CRP≥10 mg/L at Baseline Stratum
Study CDP870-031

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

Complied by this reviewer.

Six subjects in CDP870 400 mg group with missing observations were considered to be in clinical response at Week 6 in the sponsor's analysis with LOCF. Among those 6 subjects in CDP870 400 mg group with missing observations at Week 6, 4 subjects were considered to be in clinical response at Weeks 6 and 26 in the sponsor's analysis.
If six subjects in CDP870 400 mg group with missing observations were considered to be non-responders, then resulting p-values from Fisher's exact test would be much higher (0.2050 vs. reported 0.037 as reported at Week 6; 0.1499 vs. 0.045 as reported at Weeks 6 and 26) as seen from table below. In this analysis, subjects with missing observation were considered to be non-responders.

Number of Subjects with Clinical Response at Week 6, and Weeks 6 and 26 in the CRP≥10 mg/L at Baseline Stratum
Study CDP870-031
(Reviewer's ITT Analysis)

Week	CDP870 400 mg	Placebo	Difference	P-value
6	48/146 (32.9%)	40/156 (25.6%)	7.3%	0.2050
6 and 26	27/146 (18.5%)	19/156 (12.2%)	6.3%	0.1499

Compiled by this reviewer.
P-value was obtained using Fisher's exact test.

The superiority of CDP870 400 mg over placebo in terms of co-primary efficacy endpoints (clinical responses at Week 6, and Weeks 6 and Week 26) in the stratum defined by CRP ≥ 10 mg /L at baseline was dependent on outcomes for those 6 subjects in CDP870 400 mg group who had missing observations. So, results from sponsor's analysis with LOCF might not be robust.

3.1.1.3.2.2 Intent-to-Treat Analysis

Sponsor's ITT population did not include all randomized patients. It included all patients randomized who received at least one injection of study treatment and who had at least one efficacy measurement after the first injection. It excluded 3 patients (2 in placebo and 1 in CDP870 400 mg) at Week 6 and 4 patients (2 in placebo and 2 in CDP870 400 mg) at Weeks 6 and 26. The sponsor's ITT analysis was not the "true" ITT analysis.

This reviewer performed the "true" ITT analyses which included all randomized patients using the raw dataset provided by the sponsor. It was found that some discrepancy between the raw dataset and the study report on the number of subjects with clinical response at Week 6 and Week 6 and 26 in the stratum CRP≥10 mg/L at baseline stratum for placebo. Table 14.2.2.7 gave 40 and 19 for week 6 and Weeks 6 and 26, respectively. But, from sponsor's raw dataset, the numbers were 41 and 20 for Week 6 and Weeks 6 and 26, respectively.

In reviewer's analyses, patients with missing data were considered to be non-responders. To be conservative, Fisher's exact test was performed. The results from analyses are given below.

Summary of Subjects with Clinical Response at Week 6, and Weeks 6 and 26 In the CRP ≥10 mg/L at Baseline Stratum (Reviewer's Intent-to-Treat Population) Study CDP870-031

	CDP870 400mg (N=146)		placebo (N=156)			
Week	n	(%)	n	(%)	Difference	p-value
6	54	(37.0%)	41	(26.3%)	10.7%	0.0482
6 and 26	31	(21.2%)	20	(12.8%)	8.4%	0.0647

Compiled by this reviewer.
P-value was obtained by the Fisher's exact test.

As seen from table above, contrary to sponsor's finding, treatment difference for clinical response at Weeks 6 and 26 in the CRP ≥10 mg/L at baseline stratum failed to achieve statistical significance.

This reviewer found that two placebo subjects (401 and 525) had discrepancy in status of complete response at Week 6 and one placebo subject (525) had discrepancy in status of complete response at Weeks 6 and 26. The detailed discussion of these discrepancies is given in Section 3.1.1.3.4.1 and 3.1.1.3.4.2. If both subjects 401 and 525 were assumed to be responders at Week 6 and subject 401 was assumed to be a responder at Weeks 6 and 26. The results from analyses are given below.

Summary of Subjects with Clinical Response at Week 6, and Weeks 6 and 26 In the CRP ≥10 mg/L at Baseline Stratum (Modified Reviewer's Intent-to-Treat Population)[†] Study CDP870-031

	CDP870 400mg (N=146)		placebo (N=156)			
Week	n	(%)	n	(%)	Difference	p-value
6	54	(37.0%)	42	(26.9%)	10.1%	0.0647
6 and 26	31	(21.2%)	20	(12.8%)	8.4%	0.0647

Compiled by this reviewer.
[†]If both subjects 401 and 525 were assumed to be responders at Week 6 and subject 401 was assumed to be a responder at Weeks 6 and 26.
P-value was obtained by the Fisher's exact test.

As seen from table above, contrary to sponsor's finding, both treatment differences for clinical responses at Week 6 and at Weeks 6 and 26 in the CRP ≥10 mg/L at baseline stratum failed to achieve statistical significance.

3.1.1.3.2.3 Disproportion in Gender

There was a slight disproportion in gender for overall population (p=0.0572). Even in the CRP ≥10 mg/L at baseline stratum, slightly more females than males in the placebo group (57.7% vs. 42.3%) but males and females in the CDP870 400 mg group were even.

This reviewer performed post-stratification analyses of primary efficacy endpoints adjusted for gender for the reviewer's intent-to-treat population. The resulting p-values were 0.0636 and 0.0647 at Week 6, and Weeks 6 and 26, respectively.

3.1.1.3.2.4 Sensitivity Analysis

This reviewer performed the following sensitivity analyses to find out how many switches in complete response status at Week 6 in the CRP ≥10 mg/L at baseline stratum would change the 2-sided p-value from the observed p-value to greater than 0.05, keeping sample size fixed in the reviewer's ITT analysis.

(1) In Case 1, CDP870 400 mg complete response rate was varied, keep the placebo complete response rate fixed at 26.3% at Week 6.

(2) In Case 2, placebo complete response rate was varied, keep CDP870 400 mg complete response rate fixed at 37.0% at Week 6.

(3) In Case 3, both placebo and CDP870 400 mg rate were varied.

The result for Study CDP870-031 is given in Appendix Tables 8-10.

As seen from Appendix Table 8, Case 1 results indicated that a change of 0.7% (37.0% to 36.3%) at Week 6 from the observed CDP870 400 mg responder rate, changes the 2-sided p-values (by Fisher's exact test) from 0.0482 (less than 5%) to 0.0635 (greater 5%) at Week 6. This difference of 0.7% is numerically equivalent to one responder in CDP870 400 mg group in the numerator of the responder rate when given that the size of CDP870 400 mg and placebo are 146 and 156, respectively, and the placebo responder rate was 26.3% at Week 6.

As seen from Appendix Table 9, Case 2 results indicated that a change of 0.6% (26.3% to 26.9%) at Week 6 changes the 2-sided p-values (by Fisher's exact test) from 0.0482 (less than 5%) to 0.0647 (greater 5%) at Week 6. This difference of 0.6% is numerically equivalent to one responder in placebo group in the numerator of the responder rate when given that the size of CDP870 400 mg and placebo are 146 and 156, respectively, and the CDP870 400 mg responder rate was 37.0% at Week 6.

Case 1 and Case 2 results also indicate that for complete response at Week 6 in the CRP ≥10 mg/L at baseline stratum, changes in the responder status of one subject in CDP870 400 mg group or 1 subject in the placebo group (i.e., from responder to non-responder in

CDP870 400 mg group or from non-responder to responder in the placebo group) could change the observed 2-sided p-value from less than 0.05 to greater than 0.05.

As seen from Appendix Table 10, Case 3 results indicated that a change in the responder status of just one placebo subject from non-responder to responder or when there was a change of one subject in CDP870 400 mg group from responder to non-responder would cause a shift in the 2-sided p-value from less than 0.05 to greater than 0.05.

3.1.1.3.2.5 Subgroup Analysis

This reviewer performed subgroup analyses of number of subjects in clinical response at Week 6, and Weeks 6 and 26 in the CRP ≥10 mg/L at baseline stratum by treatment group and by subgroups: country, gender, smoking, use of immunosuppressant and use of corticosteroid for reviewer's ITT population. The results for these subgroup analyses are given below

In the CRP ≥10 mg/L Stratum at Baseline
(Reviewer's Intent-to-Treat Population)
Study CDP870-031

Clinical Response at Week 6

Category	CDP870 400 mg	Placebo	Difference	95% C. I.
Country				
Austria	4/11 (36.4%)	0/5 (0.0%)	36.4%	(7.9%, 64.8%)
Australia	7/20 (35.0%)	4/16 (25.0%)	10.0%	(-19.8%, 39.8%)
Belarus	1/4 (25.0%)	0/2 (0.0%)	25.0%	(-17.4%, 67.4%)
Belgium	1/4 (25.0%)	3/8 (37.5%)	-12.5%	(-66.0%, 41.6%)
Bulgaria	0/2 (0.0%)	0/4 (0.0%)	0.0%	
Canada	1/1 (100%)	1/1 (100%)	0.0%	
Czech Republic	3/12 (25.0%)	3/10 (30.0%)	-5.0%	(-42.5%, 32.5%)
Estonia	1/2 (50.0%)	0/4 (0.0%)	50.0%	(-19.3%, 100%)
Germany	2/9 (22.2%)	4/18 (22.2%)	0.0%	
Hong Kong	0/1 (0.0%)			
Hungary	3/7 (42.9%)	4/10 (40.0%)	2.9%	(-44.8%, 50.5%)
Italy	2/3 (66.7%)	3/9 (33.3%)	33.3%	(-28.3%, 95.0%)
Latvia	0/2 (0.0%)	0/1 (0.0%)	0.0%	
Poland	8/17 (47.1%)	5/16 (31.3%)	15.8%	(-17.0%, 48.7%)
Russia	3/4 (75.0%)	2/5 (40.0%)	35.0%	(-25.4%, 95.4%)
S. Africa	5/9 (55.6%)	6/11 (54.5%)	1.1%	(-42.8%, 44.8%)
Slovenia	1/3 (33.3%)	1/2 (50.0%)	-16.7%	(-100.0%, 70.8%)
Sweden	2/2 (100.0%)			
Ukraine	1/1 (100%)	1/2 (50.0%)	50.0%	(-19.3%, 100.0%)
U.S.	9/32 (28.1%)	4/32 (12.5%)	15.6%	(-3.7%, 35.0%)
Gender				
Male	31/73 (42.5%)	21/66 (31.8%)	10.7%	(-5.3%, 26.6%)
Female	23/73 (31.5%)	20/90 (22.2%)	9.3%	(-4.4%, 23.0%)
Smoking				
Current smoker	25/52 (48.1%)	17/52 (32.7%)	15.4%	(-3.2%, 34.0%)
Never smoked	22/60 (36.7%)	17/70 (24.3%)	12.4%	(-3.4%, 28.2%)
Stopped after	4/22 (18.2%)	3/14 (21.4%)	-3.2%	(-30.1%, 23.6%)

diagnosis of Crohn's disease				
Stopped before diagnosis of Crohn's disease	3/12 (25.0%)	4/20 (20.0%)	5.0%	(-25.1%, 35.1%)
Immunosuppressants				
Current therapy				
Yes	18/55 (32.7%)	13/57 (22.8%)	9.9%	(-6.6%, 26.4%)
No	36/91 (39.6%)	28/99 (28.3%)	11.3%	(-2.1%, 24.7%)
Corticosteroids				
Current therapy				
Yes	21/57 (36.8%)	18/63 (28.6%)	8.2%	(-8.5%, 25.0%)
No	33/89 (37.1%)	23/93 (24.7%)	12.4%	(-9.8%, 25.7%)

Compiled by this reviewer.

Clinical Response at Weeks 6 and 26

Category	CDP870 400 mg	Placebo	Difference	95% C. I
Country				
Australia	4/20 (20.0%)	1/16 (6.3%)	13.7%	(-7.4%, 34.9%)
Austria	2/11 (18.2%)	0/5 (0.0%)	18.2%	(-4.6%, 41.0%)
Belarus	0/4 (0.0%)	0/2 (0.0%)	0.0%	
Belgium	0/4 (0.0%)	1/8 (12.5%)	-12.5%	(-35.4%, 10.4%)
Bulgaria	0/2 (0.0%)	0/4 (0.0%)	0.0%	
Canada	0/1 (0.0)	0/1 (0.0%)	0.0%	
Czech Republic	3/12 (25.0%)	1/10 (10.0%)	15.0%	(-15.8%, 45.8%)
Estonia	0/2 (0.0%)	0/4 (0.0%)	0.0%	
Germany	0/9 (0.0%)	1/18 (5.6%)	-5.6%	(-16.1%, 5.0%)
Hong Kong	0/1 (0.0%)			
Hungary	1/7 (14.3%)	3/10 (30.0%)	-15.7%	(-54.2%, 22.7%)
Italy	2/3 (66.7%)	1/9 (11.1%)	55.8%	(-1.6%, 100.0%)
Latvia	0/2 (0.0%)	0/1 (0.0%)	0.0%	
Poland	6/17 (35.3%)	3/16 (18.8%)	16.5%	(-13.2%, 46.2%)
Russia	3/4 (75.0%)	1/5 (20.0%)	55.0%	(-0.06%, 100.0%)
S. Africa	3/9 (33.3%)	5/11 (45.5%)	-12.2%	(-54.7%, 30.5%)
Slovenia	0/3 (0.0%)	0/2 (0.0%)	0.0%	
Sweden	2/2 (100.0%)			
Ukraine	0/1 (0.0%)	0/2 (0.0%)	0.0%	
U.S.	5/32 (15.6%)	3/32 (9.4%)	6.2%	(-9.9%, 22.4%)
Gender				
Male	18/73 (24.7%)	10/66 (15.2%)	9.5%	(-3.6%, 22.6%)
Female	13/73 (17.8%)	10/90 (11.1%)	6.7%	(-4.2%, 17.6%)
Smoking				
Current smoker	15/52 (28.8%)	6/52 (11.5%)	17.3%	(2.2%, 32.4%)
Never smoked	12/60 (20.0%)	8/70 (11.4%)	8.6%	(-4.0%, 21.1%)
Stopped after diagnosis of Crohn's disease	3/22 (13.6%)	3/14 (21.4%)	-7.8%	(-33.6%, 18.1%)
Stopped before diagnosis of Crohn's disease	1/12 (8.3%)	3/20 (15.0%)	-6.7%	(-28.8%, 15.5%)

Immunosuppressants				
Current therapy				
Yes	12/55 (21.8%)	7/57 (12.3%)	9.5%	(-4.3%, 23.4%)
No	19/91 (20.9%)	13/99 (13.1%)	7.8%	(-2.9%, 18.4%)
Corticosteroids				
Current therapy				
Yes	13/57 (22.8%)	6/63 (9.5%)	13.3%	(0.2%, 26.4%)
No	18/89 (20.2%)	14/93 (15.1%)	5.1%	(-5.9%, 16.2%)

Compiled by this reviewer.

As seen from tables above, proportions of subjects in clinical response at Week 6, and Weeks 6 and 26 in the CRP ≥10 mg/L at baseline stratum were consistent for subgroups of gender, use of immunosurppressant, and use corticosteroids. But, they were not consistent for subgroups of country and smoking.

3.1.1.3.3. Reviewer's Comments on Sponsor's Analysis of Secondary Endpoints

3.1.1.3.3.1 Intent-to-Treat Analysis for Clinical Response in the Overall Population

Sponsor's ITT population did not include all randomized patients. It included all patients randomized who received at least one injection of study treatment and who had at least one efficacy measurement after the first injection. It excluded 10 patients (6 in placebo and 4 in CDP870 400 mg) at Week 6 and 12 patients (8 in placebo and 4 in CDP870 400 mg) at Weeks 6 and 26. The sponsor's ITT analysis was not the "true" ITT analysis.

This reviewer performed the "true" ITT analyses which included all randomized patients. In these analyses, patients with missing data were considered to be non-responders. To be conservative, Fisher's exact test was performed. The results from analyses are given below.

Summary of Subjects with Clinical Response at Week 6, and Weeks 6 and 26
Overall Population
(Reviewer's Intent-to-Treat Population)
Study CDP870-031

	CDP870 400mg (N=333)		placebo (N=329)			
Week	n	(%)	n	(%)	Difference	p-value
6	115	(34.5%)	88	(26.7%)	7.8%	0.0350
6 and 26	75	(22.5%)	54	(16.4%)	6.1%	0.0501

Compiled by this reviewer.
P-value was obtained by the Fisher's exact test.

As seen from table above, contrary to sponsor's finding, treatment difference for clinical response at weeks 6 and 26 for overall population was closed to achieve statistical significance.

3.1.1.3.4 Information Requests

This reviewer issued an information request dated September 9, 2006. On November 29, the sponsor submitted the updated response to Question 1 and the analyses requested in Question 3. The sponsor failed to respond Questions 2 and 4. The information request included the following items:

1) There is some discrepancy between the data set and the study report on the number of subjects with clinical response at Week 6 and Weeks 6 and 26 in the stratum CRP >= 10 mg /L at Baseline stratum for placebo group. Table 14.2.2.7 gave 40 and 19 for Week 6 and Weeks 6 and 26, respectively. But, from sponsor's data set, the numbers are 41 and 20, for Week 6 and Weeks 6 and 26, respectively. Please explain.

2) Please provide summary of subtotal for each subtotal of CDAI at baseline, at Week 6, and at Week 26 in the stratum CRP >= 10 mg /L at Baseline stratum and overall population by treatment group with imputation and without imputation.

3) Please provide summary of subjects disposition and clinical response through Week 26 in the stratum CRP >= 10 mg /L at Baseline stratum and overall population for all randomized subjects by treatment group

4) For best/worst case analysis for Study 031, there were assumed that 3 subjects (2 placebo and 1 CDP870) had missing data. But, from sponsor's data set, it was found 24 CDP870 and 48 placebo subjects had missing data. Please explain.

3.1.1.3.4.1 Comments on Sponsor's Response to Question 1

The sponsor's detailed response to Question 1 is given Appendix A.

This reviewer found that two placebo subjects had discrepancy in status of complete response at Week 6.

Subject no.	Country	Completed	MRESP6	CLINRSP	NCLINRSP	ORESP6
401	Germany	Yes	No	Yes	Yes	No
525	Germany	No	No			Yes

Complied by this reviewer.

Where MRESP6 – Missing set to non-response
CLINRSP- Clinical response
NCLINRSP – Clinical response – no imputation
ORESP6 – Clinical response - observed data only

The sponsor's explanations were:

Subject 401 received rescue therapy at Week 2. Thus from this time point onwards the subject would be classified as a non-responder. As mentioned above, in the dataset created on 6 January 2006 this would need to be taken into consideration during any programming – hence *CLINRSP* and *NCLINRSP* still stating "Yes". However, the data submitted on 15 June 2006 this was already taken into consideration – hence *MRESP6* and *ORESP6* stating "No".

Subject 525. The apparent discrepancy where *MRESP6* (missing set to non-response at Week 6) states "No" whilst *ORESP6* (observed data only response at Week 6) states "Yes" is due to the definitions of the sensitivity analyses being considered. Subject 525 withdrew at Week 6 and thus would be considered a non-responder in the various analyses except for the observed data only analysis.

For subject 401, it seems to this reviewer that this subject completed the study, CLINRSP and NCLINRSP which were created on 6 January 2006 were based on the observed CDAI score. Both CLINRSP and NCLINRSP were "Yes." The MRESP6 and ORESP6 were created post-hoc on 15 June 2006. Both MRESP6 and ORESP6 were 'No." For this subject, the consideration of rescue therapy might be made post-hoc. So, subject 401 should be considered to be a responder at Week 6 based on values on CLINRSP and NCLINRSP. Furthermore, it was found that this subject had similar discrepancy in status of complete response at Weeks 6 and 26 (See Section 3.1.13.5).

Subject 525 had complete response at Week 6 (ORESP6) but, the sponsor stated that this subject was withdrawn at Week 6. This subject had data at Week 6. So, this subject should not be considered as missing. The value for MRESP6 for this subject should be "Yes". It was also found that this subject had complete response at Weeks and

3.1.1.3.4.2 Comments on Sponsor's Response to Question 3

Subject disposition and clinical response status through week 26 was summarized in Appendix B.

It was found that number of subject in clinical response and number of subject not in clinical response did not add up to number of subject remained in the study.

3.1.1.3.5 Discrepancy in Status of Complete Response at Weeks 6 and 26

Per request from Dr. Hyde, this reviewer found that one placebo subject had discrepancy in status of complete response at Weeks 6 and 26.

Subject no.	Country	Completed	MRESP626	CLIN626	NCLIN626	ORESP626
401	Germany	Yes	No	Yes	Yes	No

Complied by this reviewer.

Where MRESP626 – Missing set to non-response
CLIN626- Clinical response

NCLIN626 – Clinical response – no imputation
ORESP626 – Clinical response - observed data only

It seems to this reviewer that this subject completed the study. CLIN626 and NCLIN626 which were created on 6 January 2006 were based on the observed CDAI score. The MRESP626 and ORESP626 were created post-hoc on 15 June 2006. For this subject, the consideration of rescue therapy might be made post-hoc. So, subject 401 should be considered to be a responder at Weeks 6 and 26 based on values on CLIN626 and NCLIN626.

3.1.2 Study CDP870-032

3.1.2.1 Study Design

This study was a multi-national, multicenter, double-blind placebo-controlled study to assess the maintenance of clinical response to humanized anti-TNF PEG conjugate, CDP870 400 mg sc, (dosed 4-weekly from Weeks 8 to 24), in the treatment of patients with active Crohn's disease who had responded to open induction therapy (dosed at Weeks 0, 2, and 4) with CDP870. The duration of study was 26 weeks.

The study design for this study was similar to Study CDP870-031 with some exceptions listed below.

The primary objective was to compare efficacy of repeated 4-weekly treatment with CDP870 versus placebo, following successful open induction therapy, in the maintenance of clinical response in patients with active Crohn's disease over 26 weeks.

The secondary objectives were:
a) To evaluate the safety of CDP870 with 4-weekly dosing over a 26 week period.
b) To obtain data on the plasma concentrations of CDP870 and antibodies to CDP870.
b) To evaluate the duration of response to open induction therapy with CDP870.

Patients who demonstrated a clinical response (100 point decrease in Week 0 CDAI) at Week 6 following open induction therapy, with CDP870 400mg sc at Weeks 0, 2 and 4, were randomized to blinded 4-weekly dosing with CDP870 400 mg or placebo for 24 weeks.

Patients were randomized within strata, with 3 stratification factors:

a) CRP<10 mg/L or CRP≥10 mg/L at Week 0
b) Receiving corticosteroids, at Week 0 or not
c) Receiving immunosuppressants (azathiprine/6-MP/methotrexate) at Week 0 or not.

Subjects should have had Crohn's disease for a minimum of 3 months duration with CDAI score between 220 and 450, scored over the 7 days prior to the first dose of study drug.

The primary efficacy endpoint was the proportion of patients with clinical response at Week 26 in stratum defined by CRP≥10 mg/L at baseline. The complete response was defined as at least a 100 point decrease in the Week 0 CDAI score.

The major secondary efficacy endpoints included:

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

a) Time to disease progression up to and including Week 26.
   Time to disease progression was defined as the earliest event, in Week 6 responders, or either an increase of ≥100 pts above Week 6 CDAI, absolute CDAI≥ 175 pts, for at least 2 consecutive visits (14 days or longer) or the use of rescue therapy.
b) Proportion of patients in clinical remission at both Week 26
   Clinical remission was defined as a total CDAI score of 150 or less.
c) Proportion of patients with IBDQ response at Week 26
   IBDQ response was defined as at least a 16 point increase from Week 0 IBDQ score.

In the overall irrespective of baseline CRP,

a) Proportion of patients in clinical response at Week 26
b) Time to disease progression up to and including Week 26
c) Proportion of patients in clinical remission at Week 26
d) Proportion of patients with IBDQ response at Week 26

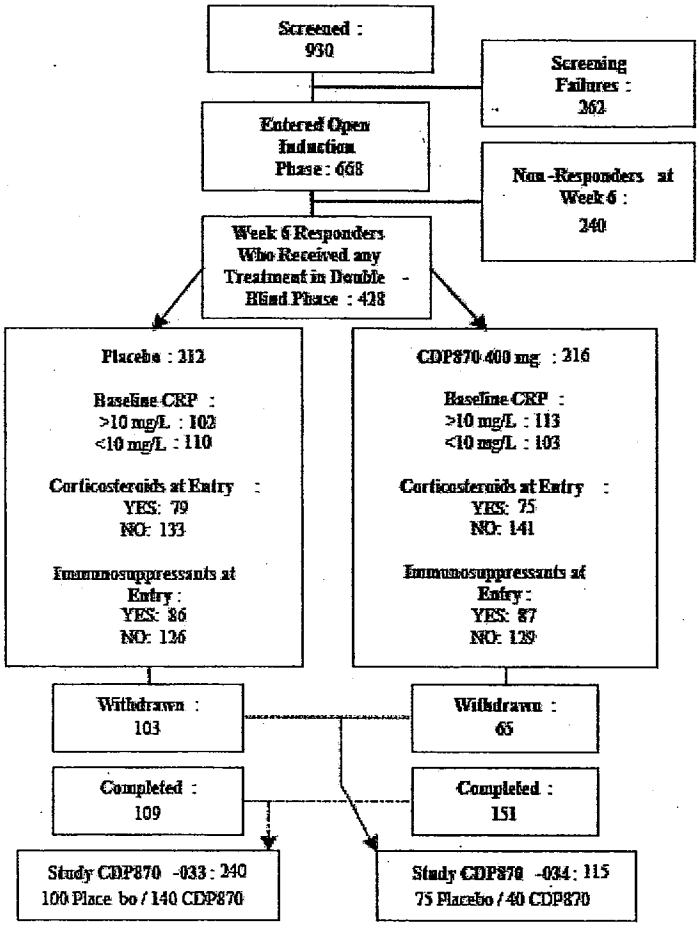
Based on a 20% treatment difference (25% placebo, 45% active) to be detected at Week 26, at a two-sided significance level of 5% for a 1:1 ratio with 80% power, 98 patients per treatment arm within elevated CRP subgroup were required. It was planned to recruit equal numbers into each CRP subgroup (CRP < 10 mg/L, CRP≥ 10 mg/L), therefore total sample size was 4 x 98=392 patients.

To account for the expected 25% screen failure rate and the predicted 60:40 split in the population with CRP< 10 mg/L and CRP ≥ 10 mg/L, approximately 1186 patients were needed to be screened.

3.1.2.2 Sponsor's Analysis

The disposition of subjects through Week 26 is shown below.

Figure 10:1 Disposition of Subjects



Of 930 subjects screened for eligibility for the study, 668 subjects 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 (66.6%) had clinical response (a decrease in CDAI score of $\geq$ 100 points from baseline) at Week 6 and were randomized to the double-blind phase of study.

However, 17 (10 in placebo and 7 in CDP870) of 445 subjects randomized never received double-blind therapy. For the purpose of Safety Population, these subjects were characterized as non-responders and only considered in the open-label phase of the study.

Of the 428 subjects randomized, 216 subjects received CDP870 400 mg and 212 subjects received placebo in the maintenance phase. A total of 260 subjects (60.7%) completed the maintenance phase of the study. A greater percentage of subjects in the CDP870 400 mg treatment group (151 subjects, 69.9%) than in placebo group (109 subjects, 51.4%) completed the study.

The most common reason for withdrawal during the maintenance phase of the study was lack of improvement/disease deterioration (75 subjects, 35.4% in placebo vs. 46 subjects,

21.3% in CDP870 400 mg), followed by AE (29 subjects, 13.7% in placebo vs. 21 subjects, 9.7% in CDP870 400 mg).

Three randomized subjects were excluded from the ITT population (Subject 45035/2934 in CDP870; Subject 45035/2046 and Subject 45035/2710 in placebo) due to possible unblinding of their treatment assignment to the study Investigator during the study. A total of 425 subjects were included in ITT population. A total of 85 subjects (38 in placebo and 47 in CDP870) were excluded from the PP population.

Because of total number of subjects with efficacy protocol deviation exceeded 15% of the ITT population (85 subjects, or 20.0% of the ITT population), efficacy analyses were also performed using the PP population. The PP population included 340 subjects (168 in CDP870 400 mg and 172 in placebo).

3.1.2.2.1 Planned Analysis

Time to disease progression, in the strata defined by CRP≥ 10 mg/L at baseline, was analyzed using a Cox proportional hazard model with indicator variables for treatment, steroid use at entry, immunosuppressant use at entry and country/region.

A patient who had not progressed by Week 26 or time of withdrawal was censored in the analysis.

If the assumption of proportionality of hazards was not met, then a log-rank test would be used.

No hypothesis testing was performed and only descriptive statistics were presented for CDAI, IBDQ, HBI, CRP, Faecal Calprotectin, and Fistulae.

3.1.2.2.2 Treatment Group Comparability

A summary of the demographic characteristics at baseline, baseline Crohn's disease characteristics, and medical history and current diagnoses of treatment subjects by randomized treatment are presented in Appendix Table 11.

As seen from Appendix Table 11, overall, demographic characteristics at baseline were generally similar across the two maintenance treatment groups with exception of gender (p=0.0517) and smoking status (0.0325).

3.1.2.2.3 Sponsor's Analysis of Primary Efficacy Endpoint

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

A summary of subjects with clinical response at Week 26 in the CRP≥10 mg/L at baseline stratum for the ITT population is given below.

Summary of Subjects in the CRP ≥10 mg/L Strata at Baseline with a Clinical Response at Week 26 – ITT Population

Time-point	Placebo (N=101)	CDP870 400 mg (N=112)
Week 26		
n	101	112
Frequency	34 (33.7%)	69 (61.6%)
95% CI for Percentage Response	(24.4%, 42.9%)	(52.6%, 70.6%)
Odds Ratio		3.30
95% CI for Odds Ratio		(1.83, 5.97)
p-value [a]		<0.001

[a] p-values have been calculated using Logistic regression with factors for treatment, CRP stratum, steroid use at entry, immunosuppressant use at entry and geographical region.
Source: Table 14.2.2:1

As seen from table above, the percentage of subjects with clinical response at Week 26 in the stratum defined by CRP≥ 10 mg/L at baseline was statistically significantly higher in the CDP870 400 mg group compared with the placebo group in the ITT population.

A summary of subjects with clinical response at Week 26 in the CRP≥10 mg/L at baseline stratum for PP Population is given in Appendix Table 12.

As seen from Appendix Table 12, the percentage of subjects with clinical response at Week 26 in the stratum defined by CRP≥ 10 mg/L at baseline was statistically significantly higher in the CDP870 400 mg group compared with the placebo group in the PP population.

3.1.2.2.3.1 Sensitivity Analyses

Three sensitivity analyses of the primary efficacy endpoint were performed, using different methods to classify subjects with missing data.

These three sensitivity analyses were:

- Observed case – using only observed data
- Worst case – subjects with missing data were set to non-responders (after imputation techniques were applied and withdrawals were taken into consideration)

Summaries of the clinical response calculated with observed data are given in Appendix Tables 13-14.

As seen from Appendix Tables 13-14, the results from the " observed case" analysis revealed that the treatment differences at Week 26 failed to achieve statistical significance (p=0.088). The result from both "worst case" analysis showed that the treatment difference at Week 26 was statistically significant (p<0.001).

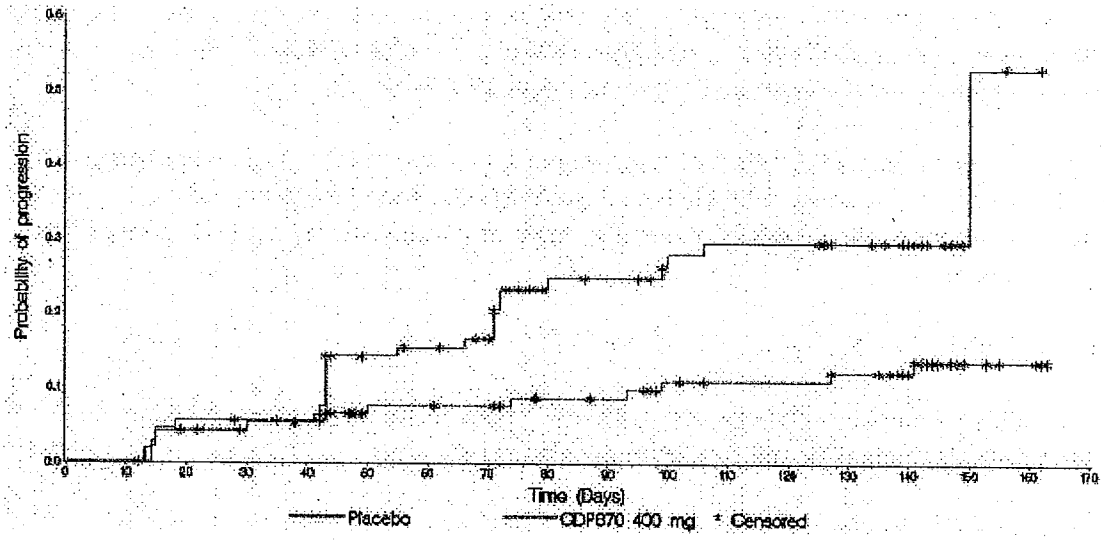
3.1.2.2.4 Sponsor's Analysis of Secondary Efficacy Endpoints

3.1.2.2.4.1 Time to Disease Progression

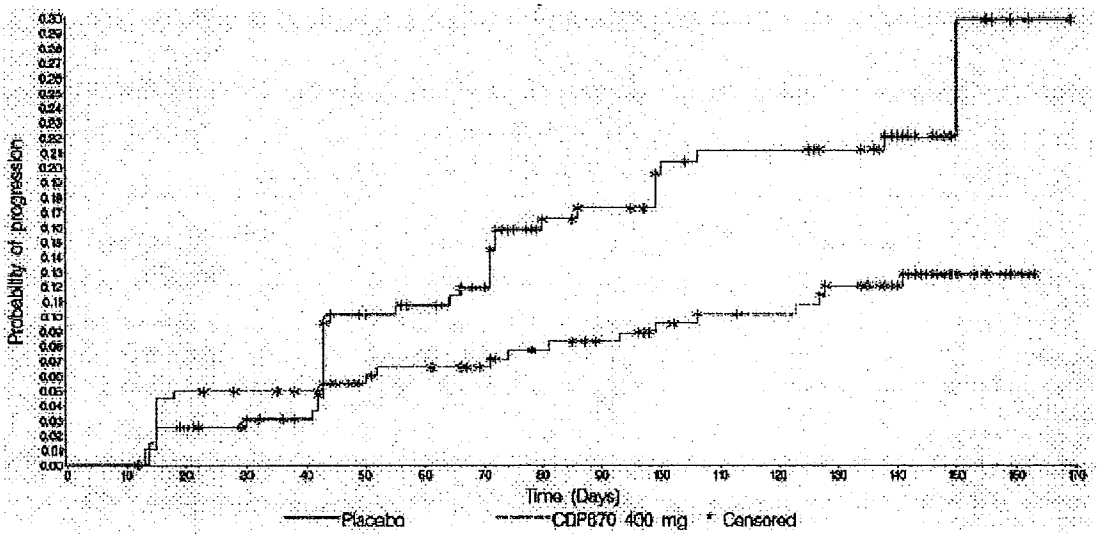
In this study, the time to disease progression (up to and including Week 26) was defined as the earliest of the following 2 events in subjects who were randomized to CDP870 400 mg or placebo at Week 6: an increase of ≥ 100 points in Week 6 CDAI score and an absolute CDAI score ≥ 175 points for at least 2 consecutive visits (i.e., 14 days or longer), where the earlier visit was used for defining the time to loss of response, or the use of rescue therapy.

Plot of the Kaplan Meier survival curve for time to disease progression in the CRP≥ 10 mg/L at baseline stratum and plot for the overall population are given below. The upper curves represents the placebo group.

Kaplan Meier Survival Curve for Time to Disease Progression in the CRP≥ 10 mg/L at Baseline Strata --- ITT Population Study CDP870-032



Kaplan Meier Survival Curve for Time to Disease Progression in the Overall Population --- ITT Population Study CDP870-032



In both the CRP≥ 10 mg/L at baseline and overall populations, over the course of the study period, the probability of disease progression was lower in subjects receiving CDP870 400 mg compared with subjects receiving placebo. In the CRP≥ 10 mg/L at baseline stratum, this difference was statistically significant (p=0.034).

3.1.2.2.4.2 Clinical Remission at Week 26

A summary of subjects with clinical remission at Week 26 in the CRP≥10 mg/L at baseline stratum and the overall population for ITT population is given below.

Summary of Subjects with Clinical Remission at Week 26 in the CRP≥ 10 mg/L at Baseline Strata and Overall Population --- ITT Population Study CDP 870-032

Time-point	CRP ≥10 mg/L at Baseline Strata		Overall Population	
	Placebo (N=101)	CDP870 400 mg (N=112)	Placebo (N=210)	CDP870 400 mg (N=215)
Week 26				
n	101	112	210	215
Frequency	26 (25.7%)	47 (42.0%)	60 (28.6%)	103 (47.9%)
95% CI for Percentage Remission	(17.2%, 34.3%)	(32.8%, 51.1%)	(22.5%, 34.7%)	(41.2%, 54.6%)
Odds Ratio		2.23		2.44
95% CI for Odds Ratio		(1.22, 4.07)		(1.61, 3.70)
p-value		0.010		<0.001

Source: Table 14.2.4:1 and Table 14.2.4:4

As seen from table above, in both the CRP≥10 mg/L at baseline stratum and the overall population, irrespective of baseline CRP, treatment difference in the proportion of subjects with clinical remission (CDAI score ≤150 points) between the two treatment group were statistically significant at Week 26.

3.1.2.2.4.3 Clinical Response in the Overall Population

A summary of subjects with clinical response (decrease in CDAI score of ≥100 points from baseline) at Week 26 for overall population for ITT population is given below.

Summary of Subjects with Clinical Response at Week 26 in the Overall Population
ITT Population
Study CDP 870-032

Time-point	Placebo (N=210)	CDP870 400 mg (N=215)
Week 26		
n	210	215
Frequency	76 (36.2%)	135 (62.8%)
95% CI for Percentage Response	(29.7%, 42.7%)	(56.3%, 69.3%)
Odds Ratio		3.12
95% CI for Odds Ratio		(2.07, 4.69)
p-value [a]		<0.001

[a] p-values have been calculated using Logistic regression with factors for treatment, CRP stratum, steroid use at entry, immunosuppressant use at entry and geographical region.
Source: Table 14.2.2.26

As seen from the table above, in the overall population, the proportion of subjects who with maintained clinical response was also statistically significant higher in the CDP870 400 mg group compared with the placebo group at Week 26 in the ITT population.

For the PP population, the treatment differences were statistically significant at Week 26 in the CPR≥10 mg/L at baseline or in the overall population (see Appendix Table 15).

3.1.2.2.4.4 IBDQ

In order to assess the effect of study medication on Quality of Life (QoL), IBDQ global scores were compared between CDP870 400 mg and placebo treatment groups. IBDQ response was defined as an increase in IBDQ global score of ≥16 points from baseline, and analyzed at Week 6, Week 16 and Week 26.

The summary of subjects with a increase IBDQ global score of ≥16 points from baseline at Week 6, Week 16 and Week 26 in the CRP≥10 mg/L at baseline stratum and overall population is given Appendix Table 16.

As seen from Appendix Table 16, treatment differences between the two treatment groups were statistically significant at Week 26 in both the CRP≥10 mg/L at baseline stratum and the overall population.

3.1.2.3 Reviewer's Comments and Evaluation

3.1.2..3.1 Reviewer's Comments on Sponsor's Primary Endpoint Analysis

3.1.2.3.1.1 Subgroup Analyses

This reviewer performed subgroup analyses of number of subjects in clinical response at Week 26 by treatment group and by subgroups: country, gender, smoking, use of immunosuppressant and use of corticosteroid for reviewer's ITT population. In these analyses, all randomized patients were included and patients with missing data were considered to be non-responders. The results for these subgroup analyses are given below.

In the CRP ≥10 mg/L Stratum at Baseline
(Reviewer's Intent-to-Treat Population)
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 this reviewer.

As seen from table above, the proportion of subjects in clinical response at Week 26 was consistent for subgroups of gender, smoking, use of immunosuppressant, and use corticosteroids. It was consistent for subgroups of country with exception of U.S. But, the width of confidence interval by country was so large. For U.S., the proportion of subjects in clinical response at Week 26 for CDP870 400 mg was similar to that for placebo. Overall results were driven by data from sites outside the U.S.

3.2 Evaluation of Safety

3.2.1 Study CDP870-031

Two hundred and sixty nine of 331 subjects (81.3%) experienced a total of 1124 AEs in the CDP870 400 mg group compared with 260 of 329 subjects (79.0%) who experienced a total of 1095 AEs in the placebo group. The most common adverse event was headache (18.1% and 16.4%), followed by abdominal pain (11.2% and 11.2%), nasopharyngitis (13.3% and 8.2%), and Cohn's disease (10.0% and 11.2%) in the CDP870 400 mg group and the placebo group, respectively.

The incidence of SAEs was 10.3% in the CDP870 400 mg and 7.0% in the placebo group. Three SAEs (ie, acute myocardial infarction, hypertensive heart disease and metastatic lung cancer) were reported with outcome death of a subject in the CDP870 400 mg group, but none of the events were considered by the Investigators to be related to study drug.

The overall incidence of AEs in the Infections and Infestations System Organ Class (SOC) was higher (42.0% vs. 31.0%) in the CDP870 400 mg when compared with the placebo group.

3.2.2 Study CDP870-032

In the double-blind maintenance phase of the study, the incidence of treatment-emergent AEs was similar between the CDP870 400 mg group and the placebo group. However, the overall incidence of AEs in the Infections and Infestations SOC was higher (32.9% vs. 25.9%) in the CDP870 400 mg group when compared with the placebo group. The most frequent AEs reported in the CDP870 400 mg group were headache,

nasopharyngitis, and cough. The most frequent AEs reported in the placebo group were Crohn's disease, headache, and injection site pain.

The incidence of SAEs was similar in the two treatment groups. The incidence of SAEs was 5.6% in the CDP870 400 mg and 6.6% in the placebo group.

A single death was reported in the open-label phase due to a fentanyl overdose. No deaths occurred in the double-blind phase of the study.

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Race and Age

4.1.1 Study CDP870-031

The results for these subgroup analyses are given below

In the CRP ≥10 mg/L Stratum at Baseline
(Reviewer's Intent-to-Treat Population)
Study CDP870-031

Clinical Response at Week 6

Category	CDP870 400 mg	Placebo	Difference	95% C. I.
Gender				
Male	31/73 (42.5%)	21/66 (31.8%)	10.7%	(-5.3%, 26.6%)
Female	23/73 (31.5%)	20/90 (22.2%)	9.3%	(-4.4%, 23.0%)

Clinical Response at Weeks 6 and 26

Category	CDP870 400 mg	Placebo	Difference	95% C. I
Gender				
Male	18/73 (24.7%)	10/66 (15.2%)	9.5%	(-3.6%, 22.6%)
Female	13/73 (17.8%)	10/90 (11.1%)	6.7%	(-4.2%, 17.6%)

As seen from table above, proportions of subjects in clinical responses at Week 6 and Weeks 6 and 26 were consistent for subgroups of gender.

4.1.2 Study CDP870-032

The results for these subgroup analyses are given below

In the CRP ≥10 mg/L Stratum at Baseline
(Reviewer's Intent-to-Treat Population)
Study CDP870-032

Clinical Response at Week 26

Category	CDP870 400 mg	Placebo	Difference	95% C. I.
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%)

As seen from table above, proportion of subjects in clinical response at Week 26 was consistent for subgroups of gender.

No conclusion on race and age can be drawn due to limited sample size.

4.2 Other Special/Subgroup populations

4.2.1 Study CDP870-031

This reviewer performed subgroup analyses of number of subjects in clinical response at Week 6, and Weeks 6 and 26 by treatment group and by subgroups: country, smoking, use of immunosuppressant and use of corticosteroid for reviewer's ITT population. The results for these subgroup analyses are given below

In the CRP ≥10 mg/L Stratum at Baseline
(Reviewer's Intent-to-Treat Population)
Study CDP870-031

Clinical Response at Week 6

Category	CDP870 400 mg	Placebo	Difference	95% C. I.
Country				
Australia	7/20 (35.0%)	4/16 (25.0%)	10.0%	(-19.8%, 39.8%)
Austria	4/11 (36.4%)	0/5 (0.0%)	36.4%	(7.9%, 64.8%)
Belarus	1/4 (25.0%)	0/2 (0.0%)	25.0%	(-17.4%, 67.4%)
Belgium	1/4 (25.0%)	3/8 (37.5%)	-12.5%	(-66.0%, 41.6%)
Bulgaria	0/2 (0.0%)	0/4 (0.0%)	0.0%	
Canada	1/1 (100%)	1/1 (100%)	0.0%	
Czech Republic	3/12 (25.0%)	3/10 (30.0%)	-5.0%	(-42.5%, 32.5%)
Estonia	1/2 (50.0%)	0/4 (0.0%)	50.0%	(-19.3%, 100%)
Germany	2/9 (22.2%)	4/18 (22.2%)	0.0%	
Hong Kong	0/1 (0.0%)			
Hungary	3/7 (42.9%)	4/10 (40.0%)	2.9%	(-44.8%, 50.5%)
Italy	2/3 (66.7%)	3/9 (33.3%)	33.3%	(-28.3%, 95.0%)
Latvia	0/2 (0.0%)	0/1 (0.0%)	0.0%	
Poland	8/17 (47.1%)	5/16 (31.3%)	15.8%	(-17.0%, 48.7%)
Russia	3/4 (75.0%)	2/5 (40.0%)	35.0%	(-25.4%, 95.4%)
S. Africa	5/9 (55.6%)	6/11 (54.5%)	1.1%	(-42.8%, 44.8%)

Slovenia	1/3 (33.3%)	1/2 (50.0%)	-16.7%	(-100.0%, 70.8%)
Sweden	2/2 (100.0%)			
Ukraine	1/1 (100%)	1/2 (50.0%)	50.0%	(-19.3%, 100.0%)
U.S.	9/32 (28.1%)	4/32 (12.5%)	15.6%	(-3.7%, 35.0%)
Smoking				
Current smoker	25/52 (48.1%)	17/52 (32.7%)	15.4%	(-3.2%, 34.0%)
Never smoked	22/60 (36.7%)	17/70 (24.3%)	12.4%	(-3.4%, 28.2%)
Stopped after diagnosis of Crohn's disease	4/22 (18.2%)	3/14 (21.4%)	-3.2%	(-30.1%, 23.6%)
Stopped before diagnosis of Crohn's disease	3/12 (25.0%)	4/20 (20.0%)	5.0%	(-25.1%, 35.1%)
Immunosuppressants				
Current therapy				
Yes	18/55 (32.7%)	13/57 (22.8%)	9.9%	(-6.6%, 26.4%)
No	36/91 (39.6%)	28/99 (28.3%)	11.3%	(-2.1%, 24.7%)
Corticosteroids				
Current therapy				
Yes	21/57 (36.8%)	18/63 (28.6%)	8.2%	(-8.5%, 25.0%)
No	33/89 (37.1%)	23/93 (24.7%)	12.4%	(-9.8%, 25.7%)

Compiled by this reviewer.

Clinical Response at Weeks 6 and 26

Category	CDP870 400 mg	Placebo	Difference	95% C. I
Country				
Australia	4/20 (20.0%)	1/16 (6.3%)	13.7%	(-7.4%, 34.9%)
Austria	2/11 (18.2%)	0/5 (0.0%)	18.2%	(-4.6%, 41.0%)
Belarus	0/4 (0.0%)	0/2 (0.0%)	0.0%	
Belgium	0/4 (0.0%)	1/8 (12.5%)	-12.5%	(-35.4%, 10.4%)
Bulgaria	0/2 (0.0%)	0/4 (0.0%)	0.0%	
Canada	0/1 (0.0)	0/1 (0.0%)	0.0%	
Czech Republic	3/12 (25.0%)	1/10 (10.0%)	15.0%	(-15.8%, 45.8%)
Estonia	0/2 (0.0%)	0/4 (0.0%)	0.0%	
Germany	0/9 (0.0%)	1/18 (5.6%)	-5.6%	(-16.1%, 5.0%)
Hong Kong	0/1 (0.0%)			
Hungary	1/7 (14.3%)	3/10 (30.0%)	-15.7%	(-54.2%, 22.7%)
Italy	2/3 (66.7%)	1/9 (11.1%)	55.8%	(-1.6%, 100.0%)
Latvia	0/2 (0.0%)	0/1 (0.0%)	0.0%	
Poland	6/17 (35.3%)	3/16 (18.8%)	16.5%	(-13.2%, 46.2%)
Russia	3/4 (75.0%)	1/5 (20.0%)	55.0%	(-0.06%, 100.0%)
S. Africa	3/9 (33.3%)	5/11 (45.5%)	-12.2%	(-54.7%, 30.5%)
Slovenia	0/3 (0.0%)	0/2 (0.0%)	0.0%	
Sweden	2/2 (100.0%)			
Ukraine	0/1 (0.0%)	0/2 (0.0%)	0.0%	
U.S.	5/32 (15.6%)	3/32 (9.4%)	6.2%	(-9.9%, 22.4%)
Smoking				
Current smoker	15/52 (28.8%)	6/52 (11.5%)	17.3%	(2.2%, 32.4%)
Never smoked	12/60 (20.0%)	8/70 (11.4%)	8.6%	(-4.0%, 21.1%)

Stopped after diagnosis of Crohn's disease	3/22 (13.6%)	3/14 (21.4%)	-7.8%	(-33.6%, 18.1%)
Stopped before diagnosis of Crohn's disease	1/12 (8.3%)	3/20 (15.0%)	-6.7%	(-28.8%, 15.5%)
Immunosuppressants				
Current therapy				
Yes	12/55 (21.8%)	7/57 (12.3%)	9.5%	(-4.3%, 23.4%)
No	19/91 (20.9%)	13/99 (13.1%)	7.8%	(-2.9%, 18.4%)
Corticosteroids				
Current therapy				
Yes	13/57 (22.8%)	6/63 (9.5%)	13.3%	(0.2%, 26.4%)
No	18/89 (20.2%)	14/93 (15.1%)	5.1%	(-5.9%, 16.2%)

Compiled by this reviewer.

As seen from table above, proportions of subjects in clinical responses at Week 6 and Weeks 6 and 26 were consistent for subgroups of use of immunosurppressant, and use of corticosteroids. But, it was not consistent for subgroups of country and smoking.

4.2.2 Study CDP870-032

This reviewer performed subgroup analyses of number of subjects in clinical response at Week 26 by treatment group and by subgroups: country, smoking, use of immunosuppressant and use of corticosteroid for reviewer's ITT population. In these analyses, all randomized patients were included and patients with missing data were considered to be non-responders. The results for these subgroup analyses are given below.

In the CRP ≥10 mg/L Stratum at Baseline
(Reviewer's Intent-to-Treat Population)
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 this reviewer.

As seen from table above, proportion of subjects in clinical response at Week 26 was consistent for subgroups of smoking, use of immunosurppressant, and use corticosteroids. For U.S., proportion of subjects in clinical response at Week 26 for CDP870 400 mg was similar to that for placebo. Overall results were driven by data from sites outside the U.S.

5. SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

The sponsor has submitted two Phase III studies (CDP870-031 and CDP870-032) for the claim. Study CDP870-031 was designed to evaluate the treatment in patients with active Crohn's disease. Study CDP870-032 was designed to evaluate the treatment of patients with active Crohn's disease who had responded to open induction therapy with CDP870 400 mg.

In Study DCP870-031, the co-primary efficacy endpoints were the percentage of subjects with clinical response (a decrease in CDAI score of $\geq$100 points from baseline) at Week 6 and at both Weeks 6 and 26 in the stratum defined by CRP$\geq$10 mg/L at baseline.

In the sponsor's analysis of co-primary efficacy endpoints, the sponsor's ITT population did not include all randomized patients. It included all patients randomized who received

at least one injection of study treatment and who had at least one efficacy measurement after the first injection.

This reviewer performed "true" ITT analyses which included all randomized patients. In these analyses, patients with missing data were considered to be non-responders. To be conservative, Fisher's exact test was performed. Based on the reviewer's ITT analyses, contrary to sponsor's finding, the treatment difference for clinical response at Weeks 6 and 26 in the stratum defined by CRP≥10 mg/L at baseline failed to achieve statistical significance.

Furthermore, it was found that two placebo subjects had discrepancies in status of clinical complete response at Week 6 and one placebo subject had discrepancy in status of clinical complete response at Weeks 6 and 26. The superiority of CDP870 400 mg group over placebo was dependent on outcomes for those two placebo subjects who had discrepancies in status of clinical complete responses at Week 6 and Weeks 6 and 26. If one placebo subject was assumed to be a responder at Week 6 and other one placebo subject was assumed to be a responder at Week 6 and at Weeks 6 and 26, results from the ITT analyses would provide p-values of 0.0647 at Week 6 and Weeks 6 and 26. This sensitivity of the p-value indicates a lack of robustness of the sponsor's conclusions.

There was a slightly disproportion in gender for overall population (p=0.0572). Even in the CRP ≥10 mg/L at baseline stratum, slightly more females than males in the placebo group (57.7% vs. 42.3%) were observed, but males and females in CDP870 400 mg group were even.

This reviewer performed a post-stratification analysis of primary efficacy endpoints adjusted for gender. The resulting p-values were 0.0636 and 0.0647 at Week 6, and Weeks 6 and 26, respectively.

This reviewer also performed sensitivity analyses to find out how many changes in complete response status at Week 6, and Weeks 6 and 26 would change the 2-sided p-value from the observed p-value to greater than 0.05, keeping sample size fixed.

Results indicated that changes in the responder status of 2 subjects in CDP870 400 mg group or 2 subjects in the placebo group (i.e., from responder to non-responder in CDP870 400 mg group or from non-responder to responder in the placebo group) could change the observed 2-sided p-value <0.05 to greater than 0.05.

Results also indicated that a change in the responder status of just 1 placebo subject from non-responder to responder and when there was a change of 1 subject in CDP870 400 mg group from responder to non-responder would cause a shift in the 2-sided p-value from <0.05 to a p-value of greater than 0.05.

Furthermore, the superiority of CDP870 400 mg over placebo in terms of co-primary efficacy endpoints (clinical responses at Week 6, and Weeks 6 and Week 26) in the stratum defined by CRP ≥ 10 mg /L at baseline was dependent on outcomes for those 6

subjects in CDP870 400 mg group who had missing observations. So, resulted from sponsor's analysis with LOCF might not be robust.

In summary, the superiority of CDP870 400 mg over placebo in terms of co-primary efficacy endpoints (clinical responses at Week 6, and Weeks 6 and Week 26) in the stratum defined by CRP ≥ 10 mg /L at baseline was not robust.

For the secondary efficacy endpoints, both clinical remission at Week 6, and Weeks 6 and 26 in both the CRP≥10 mg/L at baseline stratum and the overall population failed to achieve statistical significance. Clinical responses at Week 6, and Weeks 6 and 26 in the overall population achieved statistical significance for sponsor's ITT population, but they failed for the Per Protocol Population. Treatment differences on IBDQ were not statistically significant at Week 6, and Weeks 6 and 26 in both the CRP≥10 mg/L at baseline stratum and the overall population. So, the strength of evidence from Study CDP870-31 was not statistically persuasive.

Study CDP870-032 showed that for the primary efficacy endpoint, the percentage of subjects with clinical response at Week 26, in the stratum defined by CRP≥ 10 mg/L at baseline was statistically significantly higher in the CDP870 400 mg group compared with the placebo group in the ITT population.

This percentage was consistent for subgroups of country with the exception of the U.S. But, the width of confidence interval by country was so large. For the U.S., the proportion of subjects in clinical response at Week 26 in the CRP ≥10 mg/L at baseline stratum for the CDP870 400 mg group was similar to that for the placebo group. Overall results were driven by countries other than the U.S.

Finding of efficacy was also supported by results from 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.

Finally, efficacy results from Study CDP870-032 were driven by countries except the U.S. For the U.S., proportion of subjects in clinical response at Week 26 in the CRP ≥10 mg/L at baseline stratum for the CDP870 400 mg group was similar to that for the placebo group for primary efficacy endpoint, the percentage of subjects with clinical response at Week 26.

5.2 Conclusions and Recommendations

The sponsor has submitted two Phase III studies (CDP870-031 and CDP870-032) for the claim. Study CDP870-031 was designed to evaluate the treatment in patients with active Crohn's disease. Study CDP870-032 was designed to evaluate the treatment of patients with active Crohn's disease who had responded to open induction therapy with CDP870 400 mg.

For Study CDP870-31, the co-primary efficacy endpoints (clinical responses at Week 6, and Weeks 6 and Week 26) in the stratum defined by CRP ≥ 10 mg /L at baseline showed borderline statistical significance compared to placebo (p=0.037 and 0.045 at Week 6, and Weeks 6 and Week 26, respectively). However, the sponsor's intent-to-treat analysis excluded two placebo subjects and one CDP870 400 mg subject. Furthermore, it was found that two placebo subjects had discrepancies in status of clinical complete response at Week 6 and one placebo subject had discrepancy in status of clinical complete response at Weeks 6 and 26. The superiority of CDP870 400 mg group over placebo was dependent on outcomes for those two placebo subjects who had discrepancies in status of clinical complete responses at Week 6 and Weeks 6 and 26. If one placebo subject was assumed to be a responder at Week 6 and other one placebo subject was assumed to be a responder at Week 6 and at Weeks 6 and 26, results from the ITT analyses would provide p-values of 0.065 at Week 6 and Weeks 6 and 26. This sensitivity of the p-value indicates a lack of robustness of the sponsor's conclusion.

For the secondary efficacy endpoints, both clinical remission at Week 6, and Weeks 6 and 26 in both the CRP≥10 mg/L at baseline stratum and the overall population failed to achieve statistical significance. Clinical responses at Week 6, and Weeks 6 and 26 in the overall population achieved statistical significance for sponsor's ITT population, but they failed for the Per Protocol Population. Treatment differences on IBDQ were not statistically significant at Week 6, and Weeks 6 and 26 in both the CRP≥10 mg/L at baseline stratum and the overall population. The strength of evidence from Study CDP870-31 was not statistically persuasive.

Study CDP870-032 showed that for the primary efficacy endpoint, the percentage of subjects with clinical response at Week 26, in the stratum defined by CRP≥ 10 mg/L at baseline was statistically significantly higher in the CDP870 400 mg group compared with the placebo group in the ITT population.

However, for the U.S., the proportion of subjects in clinical response at Week 26 in the CRP ≥10 mg/L at baseline stratum for the CDP870 400 mg group was similar to that for the placebo group. Overall, the positive efficacy results were largely shown by countries other than the U.S.

For 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, the CDP870 400 mg group showed superiority over placebo.

In conclusion, the strength of evidence for this claim for maintenance was demonstrated for one single study, Study CDP870-032; however, it should be noted that results were driven by countries other than the U.S.

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6. Appendix

Appendix A Sponsor's Updated Response to Question 1

In response to FDA email dated 9 September 2006 regarding additional information for study CDP870-031 for BLA 125160, the sponsor has the proposals listed below for complying with the requests (which are restated in bold followed by sponsor's responses) and then followed by FDA responses in *Italic*.

1) There is some discrepancy between the data set and the study report on the number of subjects with clinical response at Week 6 and Weeks 6 and 26 in the stratum CRP >= 10 mg /L at Baseline stratum for placebo group. Table 14.2.2.7 gave 40 and 19 for Week 6 and Weeks 6 and 26, respectively. But, from sponsor's data set, the numbers are 41 and 20, for Week 6 and Weeks 6 and 26, respectively. Please explain.

In the CDP870-031 Clinical Study Report, Table 14.2.2.7 gives a Summary of Patients with a Decrease in CDAI Score of >= 100 Points from Baseline (Clinical Response) in the CRP >= 10 mg/L Strata at Baseline - Missing Set to Non-Response - Intention to Treat Population.

Using the data set that was sent to the Reviewers on 15 June 2006 the corresponding variables that would be used to re-create this table would be as follows:

Data set	=	C87031
Variables	=	MRESP6 and MRESP626
Stratum	=	1, 2, 3 and 4 (in order to select the CRP >= 10 mg/L Strata at Baseline subgroup)

Using the data set and variables described above, the numbers from the report (40 and 19) are repeated and it has not been possible to reproduce the alternative numbers of 41 and 20. To understand this discrepancy, please indicate which data set and variables were used to arrive at the numbers 41 and 20, for Week 6 and Weeks 6 and 26, respectively.

The FDA responds:

Using the data sets dated Jan 06, 2006 the corresponding variables that was used to create a table in which number of subjects with clinical response at Week 6 and in the stratum CRP >= 10 mg /L at Baseline stratum for placebo group. The table gives 41 for number of subjects with clinical response at Week 6 for placebo group.

Data set	=	*EFFCDAI*
Variables	=	*CLINRSP*
Visit	=	*6*
Stratum	=	*1, 2, 3 and 4 (in order to select the CRP >= 10 mg/L Strata at Baseline subgroup)*

Merging VISIT= 6 and VISIT=26 data from EFFCDAI, for strata 1 to 4 for same variables as described above were used to create a table in which number of subjects with clinical response at Weeks 6 and 26 and in the stratum CRP >= 10 mg /L at Baseline stratum for placebo group. The table gives 20 for number of subjects with clinical response at Weeks 6 and 26 for placebo group.

Merging C87031 data set and VISIT=6 data from EFFCDAI data set, for strata 1 to 4 for MRESP6, CLINRSP, NCLINRSP, and ORESP6 by treatment group, it was found two placebo subjects had discrepancy in status of complete response at Week 6.

Subject no.	*Country*	*Completed*	*MRESP6*	*CLINRSP*	*NCLINRSP*	*ORESP6*
401	*Germany*	*Yes*	*No*	*Yes*	*Yes*	*No*
525	*Germany*	*No*	*No*			*Yes*

Please explain the discrepancy for Subjects 401 and 525.

UCB updated response (23 November 2006)

In order to try and adequately respond to the reviewers' concerns with regards to both questions "1)" and "4)" of this document, the following response is given.

In general terms the discrepancies arise due to how the different data sets submitted to the BLA were created. The data sets dated 6 January 2006 (and included in the initial BLA submitted on 28 February 2006) did not take into account the use of rescue therapy and handling subjects who withdrew, while the data sets submitted to the BLA on 15 June 2006 (as part of the complete response to FDA's letter dated 28 April 2006) accounted for rescue therapy and subjects who withdrew.

The analyses of the clinical response rates (and clinical remission rates) were conducted using the following considerations:

For all responder analyses, subjects who withdrew for any reason were considered as non-responders from that timepoint onwards. For example, if a subject withdrew at Week 20, the subject would be considered a non-responder for Weeks, 20, 24 and 26. The exception to this consideration was with regards to the sensitivity analysis using "observed data only" (see below).

For study CDP870-031 if after derivation of the total CDAI score using the imputation techniques (as described in section 6.8.1 of the Integrated Summary of Efficacy Statistical Analysis Plan in the BLA), a subject had a missing total CDAI score at Week 6 or Week 26, the subject would be excluded from the relevant co-primary efficacy analysis. This was done in order to avoid making any assumptions about complete data not being present.

If a subject received rescue therapy, they were considered as treatment failures from the timepoint of administration of first rescue therapy onwards.

As part of the pre-planned analyses and in order to further investigate the robustness of the response rates, three sensitivity analyses were performed:

- Only observed data was included in the analysis and no imputations were made both with regards to missing CDAI scores and withdrawals. This sensitivity analysis would indicate that the imputation techniques used (as detailed in section 6.8.1 of the Integrated Summary of Efficacy Statistical Analysis Plan as well as the imputation regarding withdrawals) are robust and valid and makes no assumptions about the nature of or reason for the missing data.

- A subject was classified as a 'non-responder' at any visit with missing data prior to study completion/withdrawal. This would also indicate that the imputation techniques used (as detailed in section 6.8.1 of the Integrated Summary of Efficacy Statistical Analysis Plan) are robust and valid.

- Any subject with missing data (after imputation techniques had been applied and withdrawals had been taken into consideration) who was randomized to active treatment was classified as a 'non-responder' and any subject with missing data who was randomized to placebo was classified as a 'responder'. This sensitivity analysis would treat the handling of missing data with a conservative approach.

Using the *EFFCDAI* data set dated 6 January 2006 and included in the BLA, the above considerations including the use of rescue therapy would need to be taken into consideration during any programming work.

Points of note:

The rescue therapy visit data are found in variable *RSVISIT*. This should be compared to the variable *VISIT*.
VISRCD is the nominal visit variable (recoded visit) used in the various analyses. The reason for this anomaly (*VISIT* and *VISRCD*) is due to the fact that the decision on whether a subject received rescue therapy and from which visit was made at the "blind review" meeting prior to the treatment code being broken in order not to influence any decisions, at which time the recoded visit variable (*VISRCD*) was not finalised.

Using the *C87031* data submitted to the BLA on 15 June 2006, the above considerations including the use of rescue therapy were already taken into account.

Response to specific discrepancies noted:

1)
Subject 401 received rescue therapy at Week 2. Thus from this time point onwards the subject would be classified as a non-responder. As mentioned above, in the dataset created on 6 January 2006 this would need to be taken into consideration during any programming – hence *CLINRSP* and *NCLINRSP* still stating "Yes". However, the data submitted on 15 June 2006 this was already taken into consideration – hence *MRESP6* and *ORESP6* stating "No".

Subject 525. The apparent discrepancy where *MRESP6* (missing set to non-response at Week 6) states "No" whilst *ORESP6* (observed data only response at Week 6) states "Yes" is due to the definitions of the sensitivity analyses being considered. Subject 525 withdrew at Week 6 and thus would be considered a non-responder in the various analyses except for the observed data only analysis.

4)
By applying the considerations stated above this would account for the discrepancies noted by the reviewers.

Appendix B Summary of Subject Disposition and Clinical Response Status through Week 26

Table 1 Subject Disposition and Clinical Response Status through Week 26 - Intention to Treat Population

Stratum: CRP >= 10mg/L

Page 1 of 4 — Final (original data) - Study CDP870-031 — 23NOV2006 at 14:43

Accountability	Placebo (N=156)	CDP870 400 mg (N=146)	Total Patients (N=302)
Received any double-blind treatment	156	146	302
Week 6			
Subjects who discontinued prior to or at Week 6	46 (29.5%)	21 (14.4%)	67 (22.2%)
Subjects who remained in study at Week 6	110 (70.5%)	125 (85.6%)	235 (77.8%)
Subjects in clinical response at Week 6	40 (26.0%)	54 (37.2%)	94 (31.4%)
Subjects not in clinical response at Week 6	114 (74.0%)	91 (62.8%)	205 (68.6%)
Reason not in clinical response at Week 6:			
Insufficient data (no CDAI score at Week 6)	2 (1.3%)	1 (0.7%)	3 (1.0%)
Received rescue therapy at or prior to Week 6	5 (3.2%)	5 (3.4%)	10 (3.3%)
Reason for discontinuation (a):			
Adverse Event	8 (5.1%)	6 (4.1%)	14 (4.6%)
Protocol non-compliance	0	0	0
Patient decision	2 (1.3%)	2 (1.4%)	4 (1.3%)
Clinical Decision	4 (2.6%)	2 (1.4%)	6 (2.0%)
Lost to follow-up	0	0	0
Lack of improvement/disease deterioration	41 (26.3%)	15 (10.3%)	56 (18.5%)
Other	0	0	0

APPEARS THIS WAY
ON ORIGINAL

Table 1 Subject Disposition and Clinical Response Status through Week 26 - Intention to Treat Population

Stratum: CRP >= 10mg/L
Final (original data) - Study CDP870-031

Accountability	Placebo (N=156)	CDP870 400 mg (N=146)	Total Patients (N=302)
Received any double-blind treatment	156	146	302
Week 26			
Subjects who discontinued after Week 6 but prior to Week 26	41 (26.3%)	42 (28.8%)	83 (27.5%)
Subjects who remained in study at Week 26	69 (44.2%)	83 (56.8%)	152 (50.3%)
Subjects in clinical response at Week 26	30 (19.2%)	47 (32.4%)	77 (25.6%)
Subjects not in clinical response at Week 26	126 (80.8%)	98 (67.6%)	224 (74.4%)
Reason not in clinical response at Week 26:			
Insufficient data (no CDAI score at Week 26)	0	1 (0.7%)	1 (0.3%)
Received rescue therapy at or prior to Week 26	11 (7.1%)	15 (10.3%)	26 (8.6%)
Reason for discontinuation (a):			
Adverse Event	14 (9.0%)	20 (13.7%)	34 (11.3%)
Protocol non-compliance	1 (0.6%)	1 (0.7%)	2 (0.7%)
Patient decision	3 (1.9%)	3 (2.1%)	6 (2.0%)
Clinical Decision	6 (3.8%)	5 (3.4%)	11 (3.6%)
Lost to follow-up	0	0	0
Lack of improvement/disease deterioration	26 (16.7%)	28 (19.2%)	54 (17.9%)
Other	2 (1.3%)	1 (0.7%)	3 (1.0%)

APPEARS THIS WAY
ON ORIGINAL

Table 1 Subject Disposition and Clinical Response Status through Week 26 - Intention to Treat Population

Stratum: Overall

Final (original data) - Study CDP870-031

23NOV2006 at 14:43

Accountability	Placebo (N=328)	CDP870 400 mg (N=331)	Total Patients (N=659)
Received any double-blind treatment	328	331	659
Week 6			
Subjects who discontinued prior to or at Week 6	75 (22.9%)	47 (14.2%)	122 (18.5%)
Subjects who remained in study at Week 6	253 (77.1%)	284 (85.8%)	537 (81.5%)
Subjects in clinical response at Week 6	87 (26.8%)	115 (35.2%)	202 (31.0%)
Subjects not in clinical response at Week 6	238 (73.2%)	212 (64.8%)	450 (69.0%)
Reason not in clinical response at Week 6:			
Insufficient data (no CDAI score at Week 6)	3 (0.9%)	4 (1.2%)	7 (1.1%)
Received rescue therapy at or prior to Week 6	7 (2.1%)	6 (1.8%)	13 (2.0%)
Reason for discontinuation (a):			
Adverse Event	13 (4.0%)	10 (3.0%)	23 (3.5%)
Protocol non-compliance	0	0	0
Patient decision	3 (0.9%)	4 (1.2%)	7 (1.1%)
Clinical Decision	6 (1.8%)	2 (0.6%)	8 (1.2%)
Lost to follow-up	0	1 (0.3%)	1 (0.2%)
Lack of improvement/disease deterioration	61 (18.6%)	32 (9.7%)	93 (14.1%)
Other	3 (0.9%)	4 (1.2%)	7 (1.1%)

APPEARS THIS WAY
ON ORIGINAL

Table 1 Subject Disposition and Clinical Response Status through Week 26 - Intention to Treat Population

Stratum: Overall
Final (original data) - Study CDP870-031

Accountability	Placebo (N=328)	CDP870 400 mg (N=331)	Total Patients (N=659)
Received any double-blind treatment	328	331	659
Week 26			
Subjects who discontinued after Week 6 but prior to Week 26	77 (23.5%)	82 (24.8%)	159 (24.1%)
Subjects who remained in study at Week 26	176 (53.7%)	202 (61.0%)	378 (57.4%)
Subjects in clinical response at Week 26	87 (26.6%)	122 (37.2%)	209 (31.9%)
Subjects not in clinical response at Week 26	240 (73.4%)	206 (62.8%)	446 (68.1%)
Reason not in clinical response at Week 26:			
Insufficient data (no CDAI score at Week 26)	1 (0.3%)	3 (0.9%)	4 (0.6%)
Received rescue therapy at or prior to Week 26	18 (5.5%)	24 (7.3%)	42 (6.4%)
Reason for discontinuation (a):			
Adverse Event	26 (7.9%)	27 (8.2%)	53 (8.0%)
Protocol non-compliance	1 (0.3%)	3 (0.9%)	4 (0.6%)
Patient decision	6 (1.8%)	19 (5.7%)	25 (3.8%)
Clinical Decision	13 (4.0%)	11 (3.3%)	24 (3.6%)
Lost to follow-up	0	1 (0.3%)	1 (0.2%)
Lack of improvement/disease deterioration	52 (15.9%)	47 (14.2%)	99 (15.0%)
Other	3 (0.9%)	1 (0.3%)	4 (0.6%)

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Appendix C Calculation of Crohn's Disease Activity Index Score

The method as detailed (by Best et al, 1976) [5] will be used in the calculation of the Crohn's Disease Activity Index (CDAI).

The CDAI score will be derived for each scheduled assessment as described below. The CDAI score will also be derived, where data are available, for the withdrawal visit (note that the withdrawal visit CRF pages are only completed for patients who do not complete the study period and there is the possibility of overlap in the 7 day diary card data between the withdrawal visit and the previous scheduled assessment).
The CDAI score will be calculated at each scheduled assessment as the sum of the eight subtotal scores listed below. Where applicable (i.e. where the subtotal scores are not whole numbers by definition), the subtotal scores will not be rounded prior to derivation of the CDAI score. The derived CDAI score will not be rounded prior to use in summaries and analysis, but will be rounded for presentation in patient data listings.

SUBTOTAL 1: The total number of liquid or very soft stools over the 7 days prior to the scheduled assessment will be obtained from patient diary card data, and multiplied by 2. If a patient does not have 7 days' data (after the rules specified below for dealing with missing data have been applied), then this subtotal will be set to missing.

SUBTOTAL 2: The sum of abdominal pain scores (0=none, 1=mild, 2=moderate, 3=severe) over the 7 days prior to the scheduled assessment will be obtained from patient diary card data, and multiplied by 5. If a patient does not have 7 days' data (after the rules specified below for dealing with missing data have been applied), then this subtotal will be set to missing.

SUBTOTAL 3: The sum of general well-being scores (0=generally well, 1=slightly under par, 2=poor, 3=very poor, 4=terrible) over the 7 days prior to the scheduled assessment will be obtained from patient diary card data, and multiplied by 7. If a patient does not have 7 days' data (after the rules specified below for dealing with missing data have been applied), then this subtotal will be set to missing.

SUBTOTAL 4: The number of the following six categories that applies to the patient will be obtained, and multiplied by 20:

1. Arthritis/arthralgia
2. Iritis/uveitis
3. Erythema nodosum/pyoderma gangrenosum/aphthous stomatitis
4. Anal fissure, fistula or abscess
5. Other fistula
6. Fever over 100°F (37.8°C) during previous 7 days.

Data in categories 1 to 5 will be reviewed at the scheduled assessment. Data for 6 will be obtained from patient diary card data.

As an example, a patient who has arthritis and an anal fistula and a temperature of over 100°F will score 3 x 20 = 60 for this subtotal.

Note that missing temperatures over the 7-day diary card period will be assumed to represent normal temperatures (i.e. below 100°F), since it is possible that only abnormal temperatures are recorded.

SUBTOTAL 5: The score for whether the patient was taking loperamide, diphenoxylate/atropine or codeine phosphate for diarrhoea (0=no, 1=yes) over the 7 days prior to the scheduled assessment will be obtained from patient diary card data, and multiplied by 30. To achieve a score of 30, a patient will have taken one or more of these medications over some or all of the 7-day period (regardless of whether complete data were recorded for the 7 days). Otherwise, if none of these medications was recorded, this subtotal will be set to zero.

SUBTOTAL 6: The score for presence of abdominal mass at the scheduled assessment (0=none, 2=questionable, 5=definite) will be multiplied by 10.

SUBTOTAL 7: For male patients, the haematocrit score will be defined as 47 minus the most recent haematocrit (%) value (unrounded) and then multiplied by 6.

For female patients, the haematocrit score will be defined as 42 minus the most recent haematocrit (%) value (unrounded) and then multiplied by 6.

It should be noted that this subtotal could be zero or negative.

SUBTOTAL 8: Percentage below standard weight [6] will be calculated using 100 x [1−{Body Weight at Assessment (kg) / Standard Weight (kg)}] and not further multiplied to obtain the subtotal.
It should be noted that this subtotal could be zero or negative.
To avoid this subtotal excessively lowering the calculated CDAI score, if the calculated subtotal is less than (i.e. more negative than) -10 it will be set to -10.

If one or more of the above subtotals cannot be calculated at a particular scheduled assessment (after the rules specified below for dealing with missing data have been applied), then the CDAI score will be set to missing at that scheduled assessment.

Appendix D Rules for Handling Missing Data in Calculating Subtotals for CDAI Calculation

Rules for Handling Missing Data in Calculating Subtotals for CDAI Calculation

Missing data in the above calculation will be handled as follows:

Patient Diary Card Data (SUBTOTALS 1-3, 4(6), 5)

Patient diary card data for the 7 consecutive days prior to each scheduled assessment at which the CDAI score is to be calculated will be recorded on the CRF.

If patient diary card data are completely missing for one or more of the 7 consecutive days prior to the scheduled assessment, diary card data immediately prior to this 7-day period (up to a maximum of 14 days) may be transcribed onto the CRF and used in the derivation of the CDAI score.

If diary card data are partially missing at one or more of the 7 days to be used in the calculation (usually the 7 consecutive days prior to the scheduled assessment, except as provided for above), the following approach will be used:

1) For SUBTOTAL 4 part (6) and SUBTOTAL 5, missing data will be assumed to correspond to "normal" measurements (i.e. temperature below 100°F or no loperamide, diphenoxylate/atropine or codeine phosphate medication taken). This includes the situation in which all of the 7 days' diary card data are missing. Therefore no imputation will be carried out.
2) For SUBTOTALS 1-3, the last non-missing observation will be carried forward and imputed in place of the missing value (or missing values if there is more than one consecutive missing value). If this is not possible because the first scheduled observation on the diary card is missing, then the first available non-missing observation will be carried back and imputed in place of the missing value (or missing values if there is more than one consecutive missing value).

The following examples demonstrate further how the carried forward and carried back rules will be applied (for SUBTOTALS 1-3), where "x" denotes a non-missing and "." denotes a missing value:

Example 1

Day	-7	-6	-5	-4	-3	-2	-1
Variable	.	.	.	.	.	.	.

If there are no data at all for a particular variable (SUBTOTALS 1-3) from the 7 days of diary card data, then the relevant subtotal (and hence the CDAI score at that scheduled assessment) will be set to missing.

Example 2

Day	-7	-6	-5	-4	-3	-2	-1
Variable	x	x	x	.	x	x	x

The value at day -5 will be carried forward for use at day -4.

Example 3

Day	-7	-6	-5	-4	-3	-2	-1
Variable	x	x	x	.	.	.	.

The value at day -5 will be carried forward for use at days -4, -3, -2 and -1.

Example 4

Day	-7	-6	-5	-4	-3	-2	-1
Variable	x	.	.	x	.	.	.

The value at day -7 will be carried forward for use at days -6 and -5; the value at day -4 is carried forward for use at days -3, -2 and -1.

Example 5

Day	-7	-6	-5	-4	-3	-2	-1
Variable	.	x	x	x	x	x	x

The value at day -6 will be carried back for use at day -7.

Example 6

Day	-7	-6	-5	-4	-3	-2	-1
Variable	.	.	.	x	x	x	x

The value at day -4 will be carried back for use at days -7, -6 and -5.

Example 7

Day	-7	-6	-5	-4	-3	-2	-1
Variable	.	x	.	x	.	.	x

The value at day -4 will be carried forward for use at days -3 and -2. The value at day -6 will be carried forward for use at day -5. The value at day -6 will be carried back for use at day -7.

Data Recorded at Scheduled Assessments (SUBTOTALS 4 (1-5), 6-8)

If any of the data required for SUBTOTAL 4 (1-5) or SUBTOTAL 6 are missing at the scheduled assessment at which the CDAI score is to be calculated, then the CDAI score will be set to missing at that scheduled assessment. No imputation will be carried out. However, prior to final database lock, it may be necessary to revise this proposed course of action following blinded review of patient data listings by the Medical Advisor at UCB Pharma.

If haematocrit (required for SUBTOTAL 7) or body weight (required for SUBTOTAL 8) are missing at the scheduled assessment at which the CDAI score is to be calculated, then the value of haematocrit or body weight from the previous scheduled assessment will be carried forward and imputed in place of the missing haematocrit or body weight value to enable these subtotals to be calculated. If haematocrit or body weight is also missing at the previous assessment, then the relevant subtotal, and hence the CDAI score, will be set to missing at that scheduled assessment.

Appendix E Inflammatory Bowel Disease Questionnaire

The method as detailed (by Guyatt et al, 1989) [7] will be used in the calculation of the Inflammatory Bowel Disease Questionnaire (IBDQ) score.
The total IBDQ global score will be derived as the sum of the responses (from 1 to 7) to all 32 questions on the IBDQ and can therefore range from 32 to 224. The IBDQ score for each of the four categories (bowel symptoms, systemic symptoms, emotional function and social function) will be defined as the sum of the responses of the subset of questions of the IBDQ as specified below:

- Bowel Symptoms Questions 1, 5, 9, 13, 17, 20, 22, 24, 26, 29
- Systemic Symptoms Questions 2, 6, 10, 14, 18
- Emotional Function Questions 3, 7, 11, 15, 19, 21, 23, 25, 27, 30, 31, 32
- Social Function Questions 4, 8, 12, 16, 28.

Rules for Handling Missing Data

The following approach will be applied in the case of partially completed questionnaires. If sixteen or fewer of the 32 responses are missing, the mean of the available responses (rounded to nearest whole number) will be imputed for the missing responses so that a total IBDQ score can be calculated. If more than sixteen of the 32 responses are missing, the total IBDQ score will be set to missing.

Similarly, the IBDQ score for the four categories (bowel symptoms, systemic symptoms, emotional function and social function) will be calculated if 50% or more of the items within the category are answered. The mean of the available responses within the category (rounded to the nearest whole number) will be imputed for the missing responses. If more than 50% of the responses within a category are missing, the score for this category will be set to missing.

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Table 1 Summary of Demographic and Baseline Characteristics --- Randomized Population--- Protocol CDP870-031

Characteristics	Placebo (N=329)	CDP870 400 mg (N=333)	p-value
Sex			0.0572
Male	131 (39.8%)	157 (47.2%)	
Female	198 (60.2%)	176 (52.8%)	
Race			0.2195
Caucasian	314 (95.4%)	315 (94.6%)	
Afro-Caribbean	0 (0.0%)	5 (1.5%)	
Asian (Indian)	1 (0.3%)	2 (0.6%)	
Asian (Oriental)	2 (0.6%)	2 (0.6%)	
Other Races	12 (3.7%)	9 (2.7%)	
Age (months)			0.2728
Mean (SD)	37.9 (12.0)	36.9 (11.8)	
Age			0.7952
<65 years	319 (97.0%)	324 (97.3%)	
≥65 years	10 (3.0%)	9 (2.7%)	
Height (m)			0.4950
Mean (SD)	1.69 (0.096)	1.70 (0.096)	
Weight (kg)			0.8599
n	329	331	
Mean (SD)	68.5 (17.7)	68.8 (17.2)	
Body Mass Index (kg/m^2)			0.9693
n	329	331	
Mean (SD)	23.7 (5.3)	23.8 (5.4)	
Smoking Status			0.8787
Never Smoked	150 (45.6%)	156 (46.9%)	
Stopped Before Diagnosis of Crohn's Disease	37 (11.3%)	32 (9.6%)	
Stopped After Diagnosis of Crohn's Disease	35 (10.6%)	39 (11.7%)	
Current Smoker	107 (32.5%)	106 (31.8%)	
Duration of Crohn's disease (years)			
Mean (SD)			
Location of Crohn's disease at screening			
L1-Terminal ileum			
L2-Colon			
L3-Hecolon			
L4- Upper GI			

Compiled by this reviewer.

Table 1 Summary of Demographic and Baseline Characteristics --- Randomized Population--- Protocol CDP870-031 (Continued)

Characteristics	Placebo (N=329)	CDP870 400 mg (N=333)	p-value
Behavior of Crohn's disease at screening			
B1- Inflammatory disease			
B2- Stricturing disease			
B3- Penetrating disease			
Resection Performed at Screening			0.7482
Yes	114 (34.7%)	119 (35.8%)	
No	215 (65.3%)	213 (64.2%)	
CDAI score at baseline			0.4710
n	328	330	
Mean (SD)	296.9 (61.7)	300.4 (64.5)	
CRP Level at baseline			0.3561
<10 mg/L	173 (52.6%)	187 (56.2%)	
≥10 mg/L	156 (47.4%)	146 (43.8%)	
Immunosuppressants Current therapy			0.7780
Yes	121 (36.8%)	126 (37.8%)	
No	208 (63.2%)	207 (62.2%)	
Corticosteroids			0.7763
Current therapy			
Yes	131 (39.8%)	129 (38.8%)	
No	198 (60.2%)	204 (67.3%)	

Compiled by this reviewer.

Table 2 Summary of Patients with Clinical Response at Week 6, and Weeks 6 and 26

Summary of Patients with Clinical Response
In the CRP≥10 mg/L Strata at Baseline
(PP Population)
Study CDP870-031

Scheduled visit	Placebo (N=134)	CDP870 400 mg (N=122)
Week 6		
n	117	107
Frequency	33 (28.2%)	40 (37.4%)
95% CI for Percentage Response	(20.1%, 36.4%)	(28.2%, 46.6%)
Odds Ratio		1.53
95% CI for Odds Ratio		(0.86, 2.70)
p-value (a)		0.146
Week 6 and 26		
n	105	89
Frequency	15 (14.3%)	21 (23.6%)
95% CI for Percentage Response	(7.6%, 21.0%)	(14.8%, 32.4%)
Odds Ratio		1.73
95% CI for Odds Ratio		(0.82, 3.66)
p-value (a)		0.149

Data Source: Listing 16.2.6:4 Crohn's Disease Activity Index (CDAI) Score.
Note: Change from baseline = Post baseline visit - baseline.
(a) p-value has been calculated using Logistic regression with factors for treatment, steroid use at entry, immunosuppressant use at entry and geographical region
SAS Program: KEF_02.sas

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Table 3 Sensitivity Analyses for Clinical Response at Week 6, and Weeks 6 and 26 ---- Observed Case

Summary of Patients with Clinical Response In the CRP≥10 mg/L Strata at Baseline (Observed Case) Study CDP870-031

Scheduled visit	Placebo (N=156)	CDP870 400 mg (N=146)
Week 6		
n	113	119
Frequency	40 (35.4%)	48 (40.3%)
95% CI for Percentage Response	(26.6%, 44.2%)	(31.5%, 49.2%)
Odds Ratio		1.24
95% CI for Odds Ratio		(0.72, 2.14)
p-value (a)		0.434
Week 6 and 26		
n	64	73
Frequency	19 (29.7%)	27 (37.0%)
95% CI for Percentage Response	(18.5%, 40.9%)	(25.9%, 48.1%)
Odds Ratio		1.33
95% CI for Odds Ratio		(0.63, 2.84)
p-value (a)		0.456

Data Source: Listing 16.2.6:4 Crohn's Disease Activity Index (CDAI) Score.
Note: Change from baseline = Post baseline visit - baseline.
(a) p-value has been calculated using Logistic regression with factors for treatment, steroid use at entry, immunosuppressant use at entry and geographical region
SAS Program: KEF_02.sas

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Table 4 Sensitivity Analyses for Clinical Response at Week 6, and Weeks 6 and 26 ---Worst Case

Summary of Patients with Clinical Response In the CRP≥10 mg/L Strata at Baseline (Worst Case: Missing Set to Non-Response) Study CDP870-031

Scheduled visit	Placebo (N=156)	CDP870 400 mg (N=146)
Week 6		
n	156	146
Frequency	40 (25.6%)	54 (37.0%)
95% CI for Percentage Response	(18.8%, 32.5%)	(29.2%, 44.8%)
Odds Ratio		1.71
95% CI for Odds Ratio		(1.04, 2.81)
p-value (a)		0.035
Week 6 and 26		
n	156	146
Frequency	19 (12.2%)	31 (21.2%)
95% CI for Percentage Response	(7.0%, 17.3%)	(14.6%, 27.9%)
Odds Ratio		1.89
95% CI for Odds Ratio		(1.01, 3.55)
p-value (a)		0.047

Data Source: Listing 16.2.6:4 Crohn's Disease Activity Index (CDAI) Score.
Note: Change from baseline = Post baseline visit - baseline.
(a) p-value has been calculated using Logistic regression with factors for treatment, steroid use at entry, immunosuppressant use at entry and geographical region
SAS Program: KEF_02.sas

Table 5 Summary of Patients with Clinical Response at Week 6, and Weeks 6 and 26 -- Overall Population --- PP Population

Summary of Patients with Clinical Response
(PP Population)
Study CDP870-031

Scheduled visit	Placebo (N=277)	CDP870 400 mg (N=267)
Week 6		
n	237	230
Frequency	68 (28.7%)	83 (36.1%)
95% CI for Percentage Response	(22.9%, 34.5%)	(29.9%, 42.3%)
Odds Ratio		1.45
95% CI for Odds Ratio		(0.98, 2.15)
p-value (a)		0.066
Week 6 and 26		
n	209	199
Frequency	36 (17.2%)	50 (25.1%)
95% CI for Percentage Response	(12.1%, 22.3%)	(19.1%, 31.2%)
Odds Ratio		1.59
95% CI for Odds Ratio		(0.98, 2.60)
p-value (a)		0.062

Data Source: Listing 16.2.6:4 Crohn's Disease Activity Index (CDAI) Score.
Note: Change from baseline = Post baseline visit - baseline.
(a) p-value has been calculated using Logistic regression with factors for treatment, CRP strata, steroid use at entry, immunosuppressant use at entry and geographical region
SAS Program: KEF_02.sas

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Table 6 Summary of Patients with an Increase in IBDQ Global Score of ≥ 16 Points from Baseline at Week 6, and Weeks 6 and 26

Summary of Patients with an Increase in IBDQ Global Score of ≥ 16 Points from Baseline
In the CRP≥10 mg/L Strata at Baseline
(ITT Population)
Study CDP870-031

Scheduled visit	Placebo (N=156)	CDP870 400 mg (N=146)
Week 6		
n	156	144
Frequency	58 (37.2%)	71 (49.3%)
95% CI for Percentage Response	(29.6%, 44.8%)	(41.1%, 57.5%)
Odds Ratio		1.62
95% CI for Odds Ratio		(1.02, 2.58)
p-value (a)		0.041
Week 6 and 26		
n	156	144
Frequency	34 (21.8%)	42 (29.2%)
95% CI for Percentage Response	(15.3%, 28.3%)	(21.7%, 36.6%)
Odds Ratio		1.47
95% CI for Odds Ratio		(0.86, 2.48)
p-value (a)		0.156

Data Source: Listing 16.2.6:8 IBDQ Global Scores and Sub-Scores.
(a) p-value estimating the difference between treatment groups has been calculated using Logistic regression with factors for treatment, steroid use at entry, immunosuppressant use at entry and geographical region
SAS Program: EFF_27.SAS

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Table 7 Summary of Patients with an Increase in IBDQ Global Score of ≥ 16 Points from Baseline at Week 6, and Weeks 6 and 26

Summary of Patients with an Increase in IBDQ Global Score of ≥ 16 Points from Baseline
Overall Population
(ITT Population)
Study CDP870-031

Scheduled visit	Placebo (N=328)	CDP870 400 mg (N=331)
Week 6		
n	328	327
Frequency	139 (42.4%)	151 (46.2%)
95% CI for Percentage Response	(37.0%, 47.7%)	(40.8%, 51.6%)
Odds Ratio		1.17
95% CI for Odds Ratio		(0.86, 1.59)
p-value (a)		0.329
Week 6 and 26		
n	328	327
Frequency	84 (25.6%)	101 (30.9%)
95% CI for Percentage Response	(20.9%, 30.3%)	(25.9%, 35.9%)
Odds Ratio		1.30
95% CI for Odds Ratio		(0.92, 1.83)
p-value (a)		0.139

Data Source: Listing 16.2.6:8 IBDQ Global Scores and Sub-Scores.
(a) p-value estimating the difference between treatment groups has been calculated using Logistic regression with factors for treatment, CRP strata, steroid use at entry, immunosuppressant use at entry and geographical region
SAS Program: EFF_27.SAS

Table 8 Case 1 Sensitivity Analysis for Study CDP870-031 --- Reviewer's Intent-to-Treat Analysis

Case 1: Placebo complete response rate fixed at the observed of rate of 26.3% at Week 6 (41 subjects with complete response over the total of 156).

Number of CDP870 subjects: 146
Number of Placebo subjects: 156

Complete Response at Week 6

Number of Subjects who were Complete Response in the Numerator of rates		Responder Rate			
CDP 870 400 mg	Placebo	CDP 870 400 mg	Placebo	Difference	p-value
54[†]	41[†]	37.0%	26.3%	10.7%	0.0482
53	41[†]	36.3%	26.3%	10.0%	0.0635

[†] Observed number of subjects with complete response for this trial

Table 9 Case 2 Sensitivity Analysis for Study CDP870-031 --- Reviewer's Intent-to-Treat Analysis

Case 2: CDP870 400 mg complete response rate fixed at the observed of rate of 37.0% at Week 6

(54 subjects with complete response over the total of 146).

Number of CDP870 subjects: 146
Number of Placebo subjects: 156

Complete Response at Week 6

Number of Subjects who were Complete Response in the Numerator of rates		Responder Rate			
CDP 870 400 mg	Placebo	CDP 870 400 mg	Placebo	Difference	p-value
54[†]	41[†]	37.0%	26.3%	10.7%	0.0482
54[†]	42	37.0%	26.9%	10.1%	0.0647

[†] Observed number of subjects with complete response for this trial

Table 10 Case 3 Sensitivity Analysis for Study CDP870-031 --- Reviewer's Intent-to-Treat Analysis

Case 3: CDP870 400 mg complete response rate varied; Placebo complete response rate varied.

Number of CDP870 subjects: 146
Number of Placebo subjects: 156

Complete Response at Week 6

Number of Subjects who were Complete Response in the Numerator of rates		Responder Rate			
CDP 870 400 mg	Placebo	CDP 870 400 mg	Placebo	Difference	p-value
54†	41†	37.0%	26.3%	10.7%	0.0482
54†	42	37.0%	26.9%	10.1%	0.0647
53	41†	36.3%	26.3%	10.0%	0.0635

† Observed number of subjects with complete response for this trial

Table 11 Summary of Demographic and Baseline Characteristics --- Randomized Population--- Protocol CDP870-032

Characteristics	Placebo (N=222)	CDP870 400 mg (N=223)	p-value
Sex			0.0517
Male	113 (50.9%)	93 (41.7%)	
Female	109 (49.1%)	130 (58.3%)	
Race			0.5088
Caucasian	203 (91.4%)	210 (94.2%)	
Afro-Caribbean	3 (1.4%)	2 (0.9%)	
American (Indian)	1 (0.5%)	0 (0.0%)	
Asian (Indian)	4 (1.8%)	6 (2.7%)	
Asian (Oriental)	1 (0.5%)	1 (0.5%)	
Other Races	10 (4.5%)	4 (1.8%)	
Age (months)			0.7830
Mean (SD)	37.7 (12.0)	37.4 (11.2)	
Age			0.4079
<65 years	218 (98.2%)	221 (99.1%)	
≥65 years	4 (1.8%)	2 (0.9%)	
Height (m)			0.0967
Mean (SD)	1.71 (0.10)	1.70 (0.09)	
Weight (kg)			0.0388
Mean (SD)	71.9 (17.3)	68.5 (16.8)	
Body Mass Index (kg/m^2)			0.1479
Mean (SD)	24.5 (5.5)	23.7 (5.4)	
Smoking Status			0.0325
Never Smoked	103 (46.4%)	94 (42.2%)	
Stopped Before Diagnosis of Crohn's Disease	22 (9.9%)	42 (19.3%)	
Stopped After Diagnosis of Crohn's Disease	15 (6.8%)	18 (8.1%)	
Current Smoker	82 (36.9%)	68 (30.5%)	

Table 11 Summary of Demographic and Baseline Characteristics --- Randomized Population--- Protocol CDP870-032 (Continued)

Characteristics	Placebo (N=222)	CDP870 400 mg (N=223)	p-value
Resection Performed at Screening			0.7482
Yes	114 (34.7%)	119 (35.8%)	
No	215 (65.3%)	213 (64.2%)	
CDAI score at baseline			0.4710
n	328	330	
Mean (SD)	296.9 (61.7)	300.4 (64.5)	
CRP Level at baseline			0.3197
<10 mg/L	115 (51.8%)	105 (47.1%)	
≥10 mg/L	107 (48.2%)	118 (53.9%)	
Immunosuppressants Current therapy			0.8775
Yes	89 (40.1%)	91 (40.8%)	
No	133 (59.9%)	132 (59.2%)	
Corticosteroids Current therapy			0.4686
Yes	85 (38.3%)	78 (35.0%)	
No	137 (61.7%)	145 (65.0%)	

Compiled by this reviewer.

Table 12 Summary of Patients with a Decrease in CDAI Score of ≥ 100 Points from Baseline (Clinical Response) in the CRP ≥ 10 mg/L Strata at Baseline – Per Protocol Population

Study CDP870-032

Scheduled visit	Double-Blind Phase	
	Placebo (N=84)	CDP870 400 mg (N=87)
Week 26		
n	66	76
Frequency	19 (28.8%)	47 (61.8%)
95% CI for Percentage Response	(17.9%, 39.7%)	(50.9%, 72.8%)
Odds Ratio		5.04
95% CI for Odds Ratio		(2.28, 11.17)
p-value (a)		<0.001

Data Source: Listing 16.2.6:4 Crohn's Disease Activity Index (CDAI) Score.
Note: Change from baseline = Post baseline visit - baseline.
(a) p-value has been calculated using Logistic regression with factors for treatment, steroid use at entry, immunosuppressant use at entry and geographical region
SAS Program: KEF_02.sas

Table 13 Sensitivity Analyses for Clinical Response at Week 26 --- Observed Case

Summary of Patients with Clinical Response
In the CRP≥10 mg/L Strata at Baseline
(Observed Case)
Study CDP870-032

Scheduled visit	Double-Blind Phase	
	Placebo (N=101)	CDP870 400 mg (N=112)
Week 26		
n	45	70
Frequency	33 (73.3%)	62 (88.6%)
95% CI for Percentage Response	(60.4%, 86.3%)	(81.1%, 95.0%)
Odds Ratio		2.52
95% CI for Odds Ratio		(0.87, 7.28)
p-value (a)		0.088

Data Source: Listing 16.2.6:4 Crohn's Disease Activity Index (CDAI) Score.
Note: Change from baseline = Post baseline visit - baseline.
(a) p-value has been calculated using Logistic regression with factors for treatment, steroid use at entry, immunosuppressant use at entry and geographical region
SAS Program: KEP_02.sas

Table 14 Sensitivity Analyses for Clinical Response Week 26 --- Worst Case

Summary of Patients with Clinical Response
In the CRP≥10 mg/L Strata at Baseline
(Worst Case: Missing Set to Non-Response)
Study CDP870-032

 Final - Study CDP870-032 08SEP2005 at 12:35

Scheduled visit	Double-Blind Phase	
	Placebo (N=101)	CDP870 400 mg (N=112)
Week 26		
n	101	112
Frequency	34 (33.7%)	69 (61.6%)
95% CI for Percentage Response	(24.4%, 42.9%)	(52.6%, 70.6%)
Odds Ratio		3.30
95% CI for Odds Ratio		(1.83, 5.97)
p-value (a)		<0.001

Data Source: Listing 16.2.6:4 Crohn's Disease Activity Index (CDAI) Score.
Note: Change from baseline - Post baseline visit - baseline.
(a) p-value has been calculated using Logistic regression with factors for treatment, steroid use at entry, immunosuppressant use at entry and geographical region
SAS Program: KEF_02.sas

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Table 15 Summary of Patients with Clinical Response at Week 26, -- Overall Population --- PP Population

Summary of Patients with Clinical Response
(PP Population)
Study CDP870-032

Scheduled visit	Double-Blind Phase	
	Placebo (N=168)	CDP870 400 mg (N=172)
Week 26		
n	139	150
Frequency	46 (33.1%)	93 (61.3%)
95% CI for Percentage Response	(25.5%, 41.2%)	(53.5%, 69.1%)
Odds Ratio		3.70
95% CI for Odds Ratio		(2.18, 6.26)
p-value (a)		<0.001

Data Source: Listing 16.3.6:4 Crohn's Disease Activity Index (CDAI) Score.
Note: Change from baseline = Post baseline visit - baseline.
(a) p-value has been calculated using Logistic regression with factors for treatment, CRP strata, steroid use at entry, immunosuppressant use at entry and geographical region
SAS Program: KEF_02.sas

Table 16 Summary of Subjects with an IBDQ Response at Week 6, 16 and 26 --- ITT Population

Summary of Subjects with an IBDQ Response at Week 6, 16 and 26 In the CRP≥10 mg/L Strata at Baseline and Overall Population (ITT Population) Study CDP870-032

Time-point	CRP ≥10 mg/L at Baseline Strata		Overall Population	
	Placebo (N=101)	CDP870 400 mg (N=112)	Placebo (N=210)	CDP870 400 mg (N=215)
Week 6				
n	101	110	210	212
Frequency	92 (91.1%)	100 (90.9%)	192 (91.4%)	192 (90.6%)
Week 16				
n	101	112	210	214
Frequency	44 (43.6%)	74 (66.1%)	107 (51.0%)	147 (68.7%)
Week 26				
n	101	112	210	214
Frequency	37 (36.6%)	66 (58.9%)	90 (42.9%)	129 (60.3%)
Odds ratio		2.62		2.16
p-value [a]		<0.001		<0.001

[a] p-value estimating the difference between treatment groups was calculated using Logistic regression with factors for treatment, CRP stratum (for Overall Population only), use of corticosteroids at entry, use of immmunosuppressants at entry and geographical region.

Source: Table 14.2.5.21, Table 14.2.5.22, Table 14.2.5.23 and Table 14.2.5.24