CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

BLA 125160/0

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

Clinical Pharmacology Review

STN: 125160/0

Letter Date: 3/1/06, 11/13/06

Brand Name: Cimzia®

Generic Name: Certolizumab Pegol

Reviewers: Tapash K. Ghosh, Ph. D. 11/8/07

Team Leader: Sue Chih Lee, Ph. D. 11/8/07

PM Reviewers: Christoffer W. Tornoe, Ph.D. 11/8/07

PM Team Leader: Joga Gobburu, Ph. D. 11/8/07

ORM Division: Gastroenterology Products

OCPB Division: Division of Clinical Pharmacology 3

Sponsor: UCB, Inc.

Submission Type: Complete response

Formulation, Strength(s): Lyophilized powder for S.C. Injection, 200 mg/vial

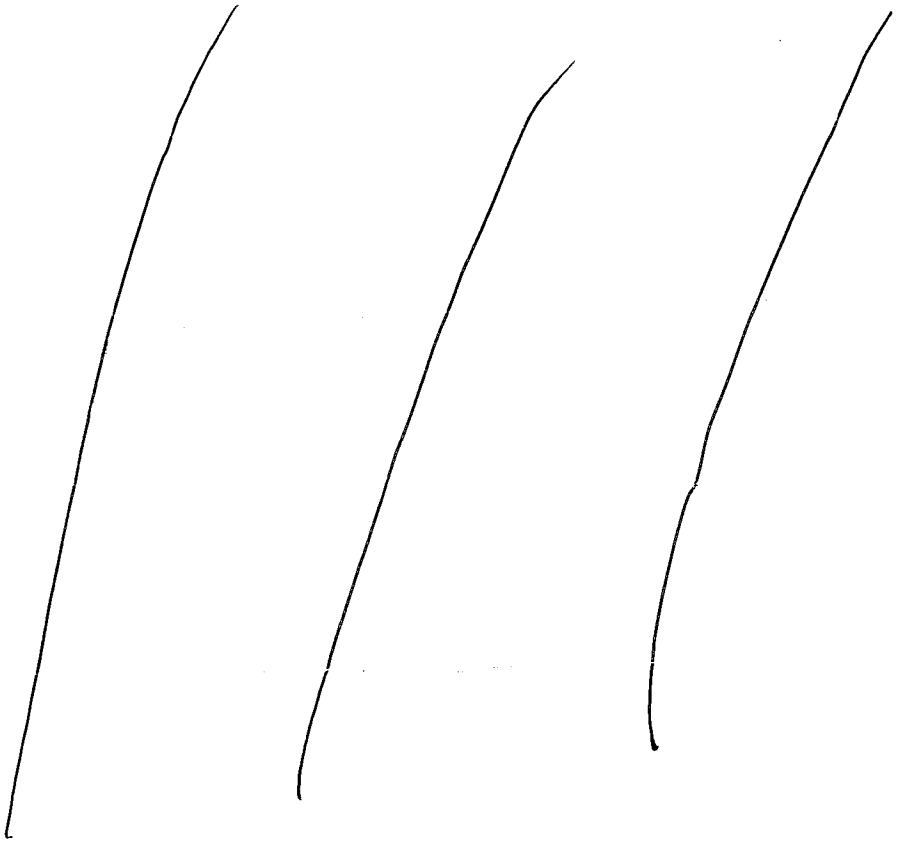
Proposed Indication: [redacted]

Proposed Dosage Regimen: 400 mg given as a S.C. injection at 0, 2, and 4 weeks followed by a maintenance regimen of 400 mg every 4 weeks thereafter.

The office of clinical pharmacology finds the Cimzia Chrohn's Disease Pharmacometric analysis presented by UCB, Inc. in their complete response generally acceptable.

The sponsor found, similar to the FDA reviewer, that the change in CDAI score is correlated with CDP870 concentrations. However, the sponsor believes increasing the dose leads to higher dropout rates thus not increasing the overall response rate. This could not be confirmed by the FDA reviewer.

Information from four phase III trials with Cimzia in RA patients



In conclusion, the sponsor is still recommended to investigate increasing the dose and/or the frequency of dosing in future Crohn's Disease trials.

Clinical Pharmacology Review

STN: 125160/0

Letter Date: 3/1/06, 11/13/06

Brand Name: Cimzia®

Generic Name: Certolizumab Pegol

Reviewers: Tapash K. Ghosh, Ph. D.

Suliman I. Al-Fayoumi, Ph.D.

Acting Team Leader: Abimbola O. Adebowale, Ph. D.

PM Reviewers: Christoffer W. Tornoe, Ph.D.

Tapash K. Ghosh, Ph. D.

PM Team Leader: Joga Gobburu, Ph. D.

ORM Division: Gastroenterology Products

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Sponsor: UCB, Inc.

Submission Type: NME (1 S)

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Table of Contents

1 Executive Summary

Certolizumab pegol (aka CDP870) is a recombinant, humanized, antibody Fab' fragment with specificity for human TNFα. The Fab' fragment is manufactured in *E. coli*, purified, and _____ to polyethylene glycol (PEG) in order to extend its plasma half-life.

Certolizumab pegol acts as a selective immunosuppressive agent through neutralizing the biological activity of TNFα by binding with high affinity to the soluble and transmembrane forms of TNFα and subsequently, inhibiting the binding of TNFα with its receptors. Biological activities attributed to TNFα include: induction of pro-inflammatory cytokines such as interleukins 1 and 6, enhancement of leukocyte migration by increasing endothelial layer permeability and expression of adhesion molecules by endothelial cells and leukocytes, activation of neutrophil and eosinophil functional activity, induction of acute phase reactants and other liver proteins, as well as tissue degrading enzymes produced by synoviocytes and/or chondrocytes.

Crohn's disease is a chronic inflammatory disease of the GIT. Currently, budesonide and infliximab are the only two therapies approved for the treatment of patients with Crohn's disease in the US. Budesonide is a corticosteroid with topical anti-inflammatory activity in the gut mucosa but low systemic activity due to rapid hepatic metabolism. Infliximab (Remicade®), is a chimeric monoclonal antibody to TNFα. Infliximab has a relatively rapid onset of efficacy with reduction in signs and symptoms by week 2 but response can diminish with continued treatment.

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

Therapeutic biologics are not CYP450 substrates and as such, they are generally unlikely to be associated with PK drug-drug interactions. A drug-drug interaction study was conducted to evaluate the effect of administration of a single dose of Certolizumab pegol 400 mg on the steady-state PK of methotrexate. The study demonstrated the lack of a significant drug interaction between certolizumab pegol and methotrexate.

Considerable variability in the exposure levels has been observed for a fixed dose of 400 mg where the CDP870 concentration range is between 0.5 and 80 mcg/mL. As exposure is highly variable and there is a dependence of response on exposure, it may be important to further explore higher doses and the titration value for non-responders in order to attain the full potential for efficacy.

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

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

The incidences of anti-certolizumab pegol antibodies and neutralizing anti-certolizumab pegol antibodies appear to be inversely proportional to certolizumab pegol dose. These observations are complicated by the known interference of certolizumab pegol in the plasma with the anti-certolizumab pegol antibody assay; however the lower rate of immunogenicity at high doses continued to be observed after plasma concentrations of certolizumab pegol had fallen below detectable levels following cessation of dosing.

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

An information request letter dated October 10, 2006 was sent to the sponsor encompassing issues from different disciplines including clinical pharmacology. The clinical pharmacology section requested the sponsor to provide justification for selection of a fixed dose rather than an individualized dose. OCP also suggested that the sponsor should use the *maximum Bayesian a posteriori* estimates to impute the CDAI scores at 6 and 26 weeks to determine responder status.

In the complete response received from the sponsor on November 13, 2006, the sponsor responded that the disadvantages in terms of cost and inconvenience to the patient and physician associated with an individualized dose regimen based on plasma concentration monitoring would not be justified by potential to improve response in a subset of the quartile of patients with the lowest plasma exposure. They insisted that a fixed dose regimen provides the optimal treatment for patients. They also concluded that the sensitivity analyses (with different imputation methods for missing data) do not allow the detection of any clear relationship between response status and exposure (concentration).

OCP's position on the clinical pharmacology issues communicated to the sponsor in the information request letter dated October 10, 2006 has been addressed in the OCP review. However, the sponsor's response on November 13, 2006 could not be reviewed and incorporated in this review due to time limitation. Further discussion is warranted in this area. Therefore, a complete review of the sponsor's response on November 13, 2006 has been deferred to a later date.

1.1 Recommendation

The Office of Clinical Pharmacology does not believe that the sponsor has fully determined the proper dose for either induction or maintenance based on the observed exposure-response data generated in this BLA. The sponsor should redefine the dose – response relationship. Further, the sponsor should substantiate the design and analysis of the future trial using clinical trial simulation based on current data.

1.2 Phase 4 Commitments

None

Primary Reviewers:

Tapash K. Ghosh, Ph.D. 12/11/06
Clinical Pharmacology
Division of Clinical Pharmacology III

Christoffer W. Tornoe, Ph.D. 12/11/06
Pharmacometrics

Acting Clinical Pharmacology Team Leader: Abimbola O. Adebowale, Ph. D. 12/11/06

PM Team Leader: Joga Gobburu, Ph. D. 12/11/06

DCP3 Division Director: Edward D. Bashaw, Pharm. D. 12/12/06

2 Summary of OCP Findings

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

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

- The single- and multiple-dose pharmacokinetics (PK) of certolizumab were characterized following administration of I.V. and S.C. doses of certolizumab pegol encompassing the proposed clinical dosage to healthy subjects and patients with Crohn's disease. Mean Cmax and AUC values increase in a linear manner with dose. Mean peak plasma levels occurred around 4 days post-dose, while mean terminal half-life of certolizumab was estimated at 13 days following S.C. administration.
- Therapeutic biologics are not CYP450 substrates and as such, they are generally unlikely to be associated with PK drug-drug interactions. A drug-drug interaction study was conducted to evaluate the effect of administration of a single dose of Certolizumab pegol 400 mg on the steady-state PK of methotrexate. The study demonstrated the lack of a significant drug interaction between certolizumab pegol and methotrexate.
- Considerable variability in the exposure levels has been observed for a fixed dose of 400 mg where the CDP870 concentration range is between 0.5 and 80 mcg/mL. As exposure is highly variable and there is a dependence of response on exposure, it may be important to individualize each patient's dose in order to attain the full potential for efficacy.
- Future studies should explore higher doses. Since there is no concentration-safety relationship for serious adverse events, serious infection rates, urinary infection rates, and herpes viral infections rate, it seems reasonable to increase the dose frequency and/or amount.
- The primary analysis using baseline observation carried forward (BOCF) or last observation carried forward (LOCF) imputation technique needs to be revisited since the dropouts are not missing completely at random but depending on worsening of symptoms. Future studies should have an

elaborate sensitivity analysis to address this issue. Further discussions between FDA and sponsor are necessary, especially including the statistics groups.

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

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

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

- The incidences of anti-certolizumab pegol antibodies and neutralizing anti-certolizumab pegol antibodies appear to be inversely proportional to certolizumab pegol dose. These observations are complicated by the known interference of certolizumab pegol in the plasma with the anti-certolizumab pegol antibody assay; however the lower rate of immunogenicity at high doses continued to be observed after plasma concentrations of certolizumab pegol had fallen below detectable levels following cessation of dosing.

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

3 Question-Based Review

3.1 General Attributes

Certolizumab pegol (CDP870) is an engineered, humanized, antibody Fab' fragment with specificity for human TNFα, which is manufactured in E. coli. The Fab' fragment is subsequently purified and conjugated to polyethylene glycol (PEG). Studies to date have demonstrated that certolizumab pegol is an effective inhibitor of TNFα, a polypeptide cytokine known to mediate the up-regulation of cellular adhesion molecules and chemokines, up-regulation of major histocompatibility complex (MHC) class I and class II molecules, and direct leukocyte activation, in rheumatoid arthritis (RA). Similarly, there is considerable evidence that excessive TNFα activity is involved in the pathogenesis of Crohn's disease. In man, TNFα is strongly expressed in the bowel wall of areas affected by Crohn's disease and fecal concentrations of TNFα in Crohn's disease have been shown to reflect clinical severity of the disease. Certolizumab pegol is therefore a candidate medicinal product for the reatment of inflammatory diseases such as Crohn's disease and RA, but this license application is concerned only with the target indication of Crohn's disease. Studies in RA are described only where they provide background information relevant to this application for Crohn's disease.

CIMZIA® (proposed brand name for Certolizumab pegol) is supplied as a sterile, white, lyophilized powder for reconstitution and then subcutaneous administration. After reconstitution with 1 mL of sterile Water for Injection, USP, the resulting pH is approximately 5.2. Each single-use vial contains approximately 200 mg certolizumab pegol, 100 mg sucrose, 0.9 mg lactic acid, and 0.1 mg polysorbate. No preservatives are present.

The recommended dose of CIMZIA is 400 mg (two 200 mg injections) every two weeks for the first three doses, followed by a dose every four weeks.

3.2 General Clinical Pharmacology

Certolizumab pegol (aka CDP870) is a recombinant, humanized, antibody Fab' fragment with specificity for human TNFα. The Fab' fragment is manufactured in *E. coli*, purified, and [redacted] to polyethylene glycol (PEG) in order to extend its plasma half-life.

Certolizumab pegol acts as a selective immunosuppressive agent through neutralizing the biological activity of TNFα by binding with high affinity to the soluble and transmembrane forms of TNFα and subsequently, inhibiting the binding of TNFα with its receptors. Biological activities attributed to TNFα include: induction of pro-inflammatory cytokines such as interleukins 1 and 6, enhancement of leukocyte migration by increasing endothelial layer permeability and expression of adhesion molecules by endothelial cells and leukocytes, activation of neutrophil and eosinophil functional activity, induction of acute phase reactants and other liver proteins, as well as tissue degrading enzymes produced by synoviocytes and/or chondrocytes.

Crohn's disease is a chronic inflammatory disease of the GIT. Currently, budesonide and infliximab are the only two therapies approved for the treatment of patients with Crohn's disease in the US. Budesonide is a corticosteroid with topical anti-inflammatory activity in the gut mucosa but low systemic activity due to rapid hepatic metabolism. Infliximab (Remicade®), is a chimeric monoclonal antibody to TNFα. Infliximab has a relatively rapid onset of efficacy with reduction in signs and symptoms by week 2 but response can diminish with continued treatment.

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

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

Single intravenous (iv) and subcutaneous (sc) doses of certolizumab pegol have been shown to have predictable dose-related exposure with an approximately linear relationship between the dose administered and the maximum certolizumab pegol concentration (C_{max}) and the area under the certolizumab pegol plasma concentration versus time curve (AUC) in both healthy volunteers and patients. The terminal elimination phase half-life ($t_{1/2}$) was approximately 14 days for all dosage levels tested. Certolizumab pegol has also been demonstrated to have a bioavailability of approximately 80 % when given by the sc route (CDP870-003). The dosing schedule used in the Phase III clinical development program was selected from the Sponsor's PK modeling and simulation using data from Phase I and Phase II Crohn's disease and RA studies (CDP870-001, CDP870-002, CDP870-003, CDP870-004, CDP870-005 and CDP870-008). Based upon this dose-response modeling, the majority of improvement in efficacy over placebo was observed at doses of up to 400mg with smaller additional improvements at higher doses. PK modeling was also performed by the Sponsor using data only from Study CDP870-003 and Study CDP870-005 to determine the optimum induction dose of certolizumab pegol in Crohn's disease. This simulation predicted that a regimen of 400 mg certolizumab pegol every two weeks during induction would maximize exposure to certolizumab pegol and maintain more consistent plasma levels.

Plasma concentration-time curves from the pivotal Studies CDP870-031 and CDP870-032 were consistent with predictions derived from these PK models and simulations. The population PK of certolizumab pegol were characterized at the end of the Phase III program using data from four studies in Crohn's disease (Studies CD870-005, CDP870-008, CDP870-031 and CDP870-032), three studies in healthy volunteers (Studies

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

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

3.2.1 Is there evidence from clinical trials supporting one fixed dose for all patients?

Considerable variability in the exposure levels is observed for a fixed dose of 400 mg. The CDP870 concentration range following a dose of 400 mg is between 0.5 and 80 mcg/mL (see Figure 1 below).

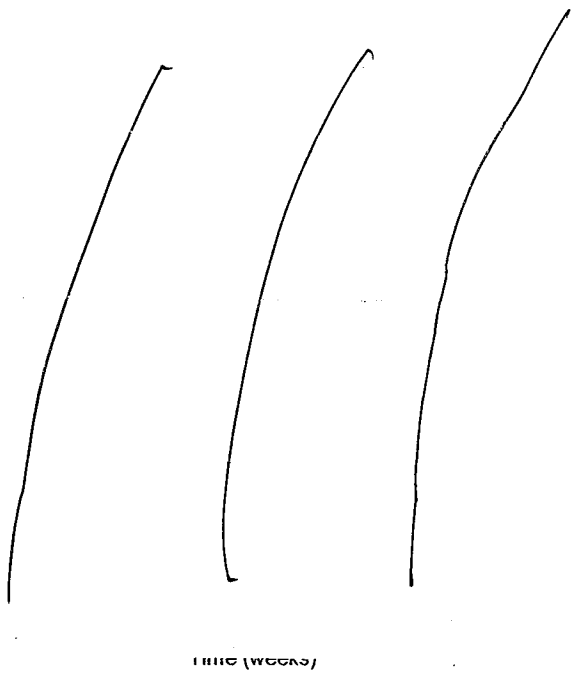

Figure 1 CDP870 plasma concentrations vs. time (solid red lines = median, dots = individual CDP870 concentration).

When exposure is highly variable and there seem to be a dependence of response on exposure, then it could be important to titrate each patient's dose to effect in order to attain the full potential for efficacy.

The probability of developing antibodies decreases with increasing CDP870 steady-state concentration, i.e. the lower the CDP870 steady-state concentration, the higher the probability of having CDP870 antibodies (see figure below). Therapeutic drug monitoring (TDM) might be considered to optimize the individual patient exposure based on the patient's antibody status.

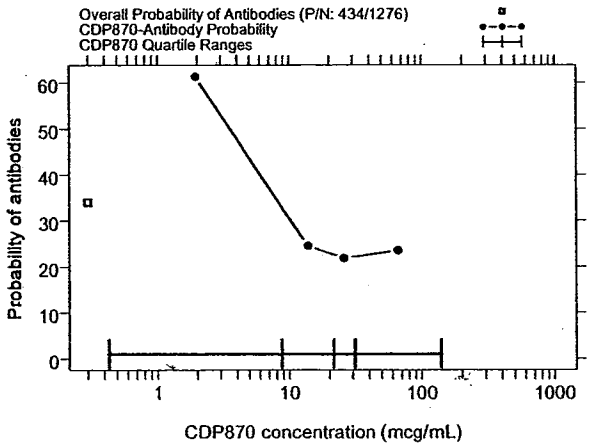

Figure 2 Probability of antibodies vs. CDP870 steady state concentration.

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3.2.2 Is there evidence of exposure-response at week 6 and week 26?

The probability of achieving clinical response (defined as $\Delta CDAI \leq -100$) is clearly dependent upon the CDP870 concentration in study CDP870-005 at week 6 where patients having lower concentrations (e.g., less than 10 mcg/mL) exhibit lower response rates (see Figure 3 below). The relationship between the probability of response and the CDP870 concentration is not as clear for studies CDP870-031 and -032 at week 26 due to unknown reasons.

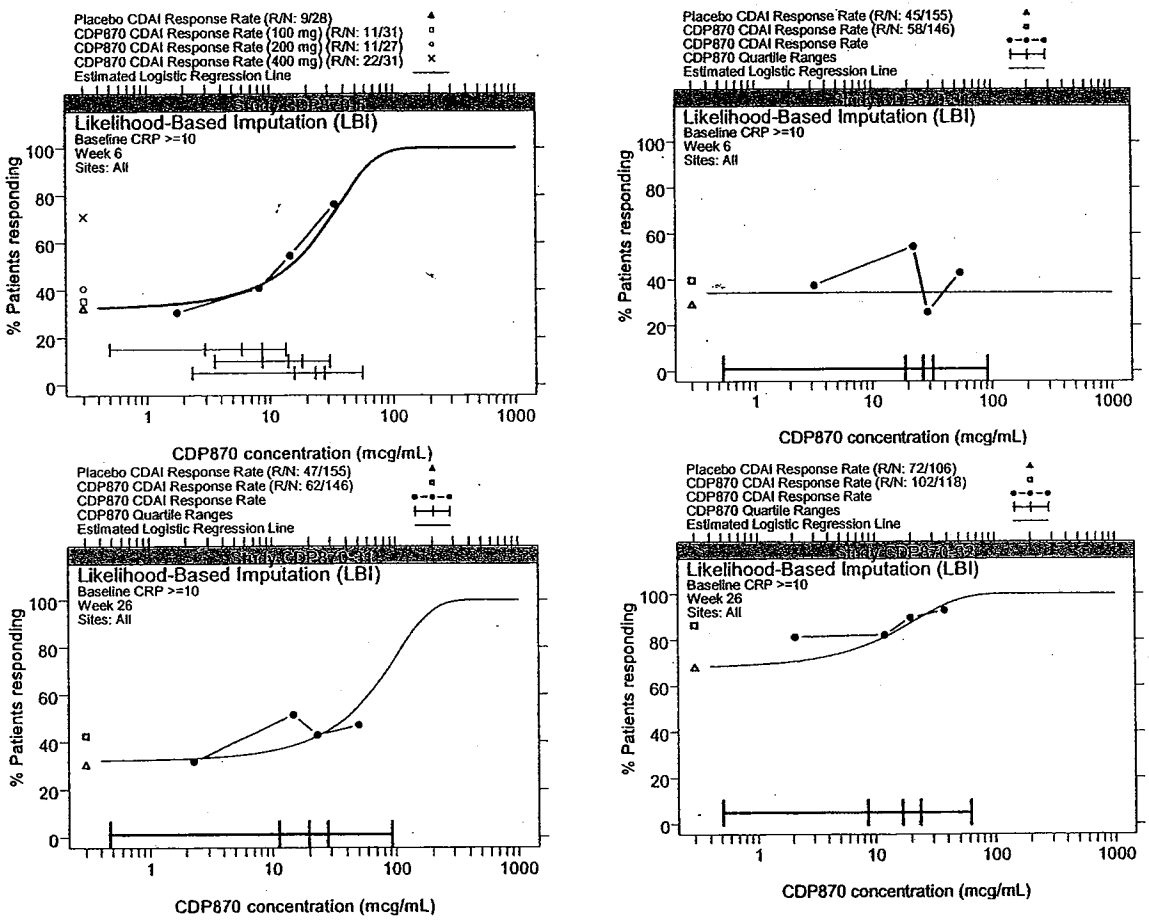

Figure 3 Exposure-response for studies CDP870-005 week 6 (top left), CDP870-031 week 6 (top right) and week 26 (bottom left), and CDP870-032 at week 26 (bottom right).

The least square (LS) mean predicted baseline corrected CDAI score at week 26 using mixed-model repeated measures (MMRM) analysis is approximately 30 points lower for active treatment compared to placebo for both phase III studies. However, there seems to be a significant difference in the change in baseline corrected CDAI scores over time for studies CDP870-031 and -032 where clinical response (i.e. ΔCDAI $\leq$ -100) for active treatment is achieved at week 24 for study CDP870-031 (double-blind) and at week 4 for study CDP870-032 (open-label until week 6). It is unclear what is causing this observed difference (Figure 4).

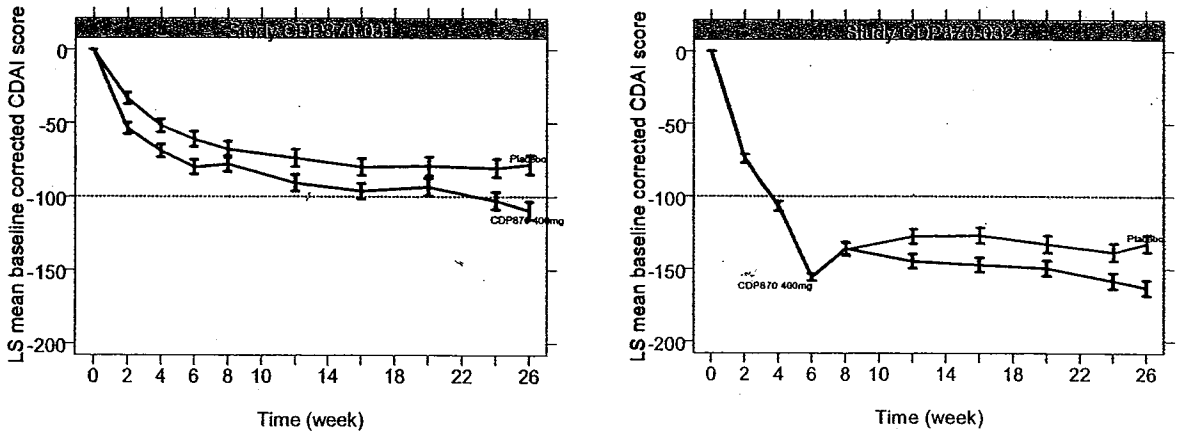

Figure 4 LS mean predicted (±SE) baseline corrected CDAI score for study CDP870-031 (left) and CDP870-032 (right).

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3.2.3 Is the exposure-response relationship consistent between US and non-US subgroups?

There does not seem to be a significant exposure-response relationship for the US sites in study CDP870-031 and CDP870-032 as opposed to a fairly defined trend in non-US sites (see Figure 5 below). With US and non-US sites combined, the overall trend is driven by the non-US sites (Refer to Figures 3 and 5).

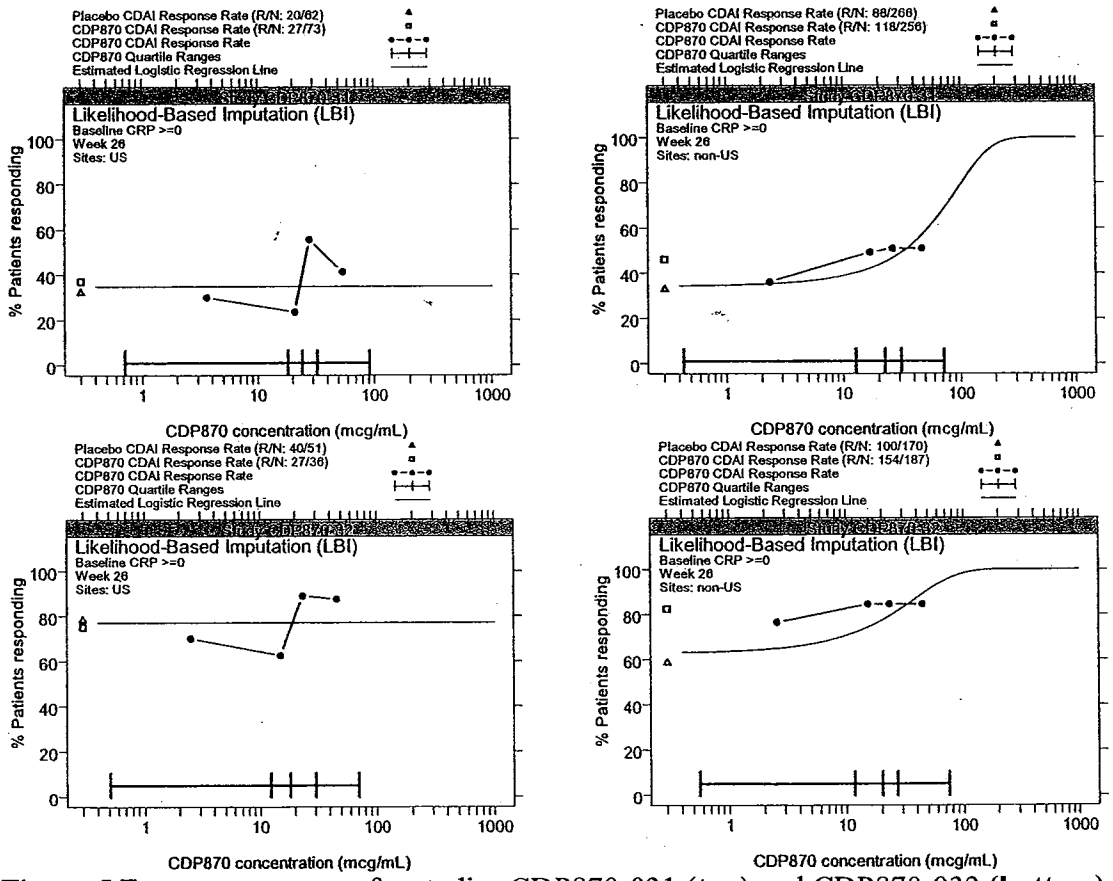

Figure 5 Exposure-response for studies CDP870-031 **(top)** and CDP870-032 **(bottom)** at week 26 for US **(left)** and non-US **(right)** sites.

Since the exposure is similar between non-US and US sites (i.e. between 0.5 and 80 mcg/mL), the reason for not seeing an exposure-response relationship for the US population might be due to lower sensitivity to CDP870 and/or a different background treatment resulting in a higher placebo response rate.

3.2.4 What is the mechanism for dropouts?

Patients seem to be dropping out of Study CDP870-031 and CDP870-032 due to worsening of symptoms.

The overall dropout rate is about 40%, and the dropouts are not missing completely at random, rather they are correlated with the ΔCDAI score. In particular, 90% of patients with ΔCDAI score above 54 drop out by Week 26 in study CDP870-031, whereas only 5% of those patients with ΔCDAI score below -135 drop out of the study by Week 26. Similar trend was observed in Study CDP870-032 as well (see Figure 6).

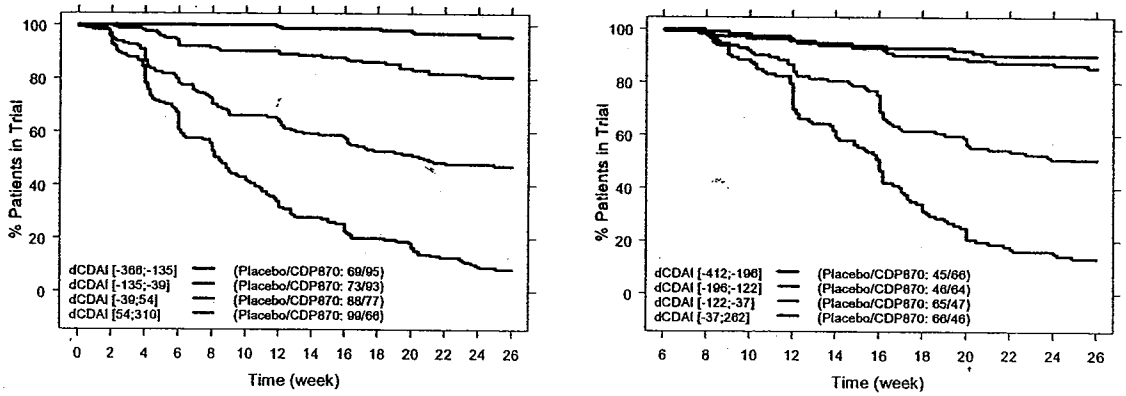

Figure 6 Dropout stratified on baseline corrected CDAI score at final visit for studies CDP870-031 (left) and CDP870-032 (right).

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3.2.5 Is there evidence of adequate safety data?

There does not seem to be a relationship between concentration and the serious adverse events, serious infections, urinary infection rates, and herpes viral infections rate (see figures below). It therefore seems reasonable to evaluate higher than 400 mg dose for future studies from both efficacy and safety point of view.

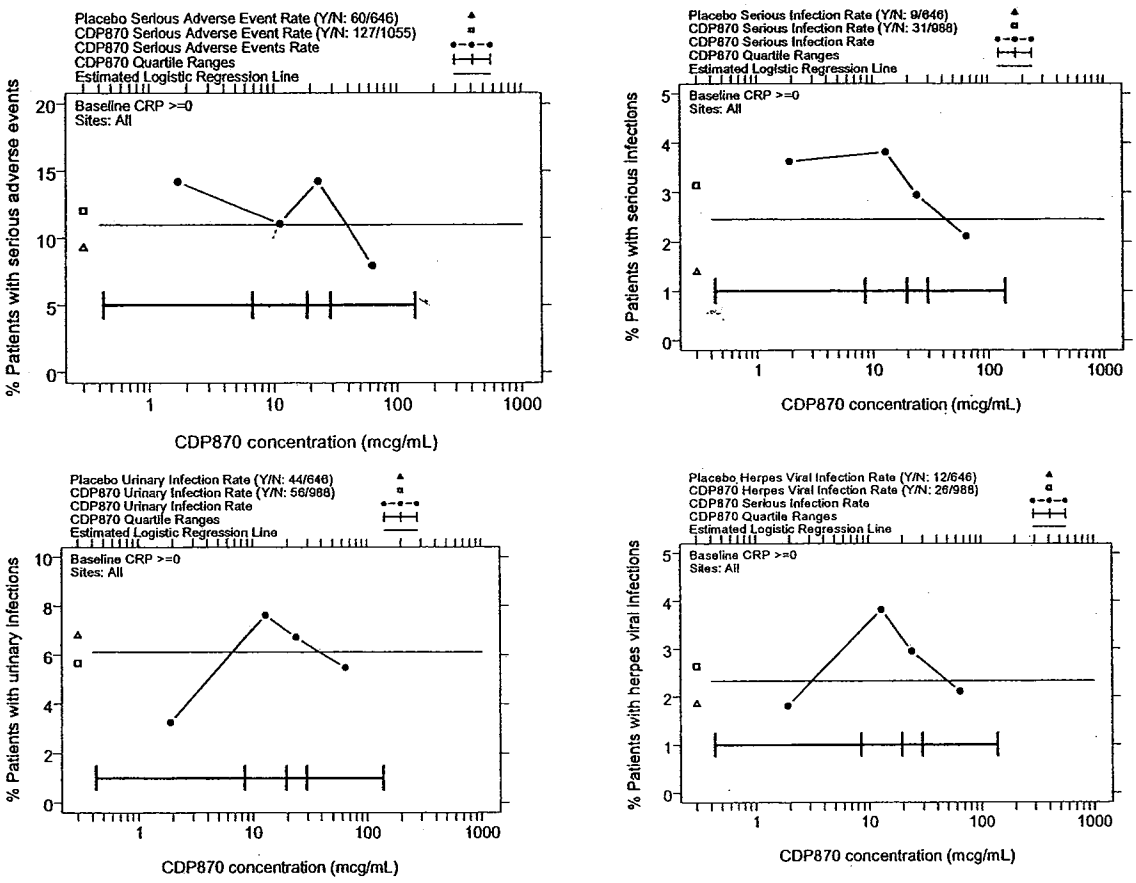

Figure 7 Concentration-safety relationship for serious adverse events (top left), serious infections (top right), urinary infections (bottom left), and herpes viral infections (bottom right).

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3.2.6 What is the Impact of Formation of Anti-Certolizumab Pegol Antibodies and Neutralizing Anti-Certolizumab Pegol Antibodies in Subjects with Crohn's Disease?

The incidences of anti-certolizumab pegol antibodies and neutralizing anti-certolizumab pegol antibodies appear to be inversely proportional to certolizumab pegol dose. These observations are complicated by the known interference of certolizumab pegol in the plasma with the anti-certolizumab pegol antibody assay; however the lower rate of immunogenicity at high doses continued to be observed after plasma concentrations of certolizumab pegol had fallen below detectable levels following cessation of dosing. When antibodies occur, they have a significant effect on the pharmacokinetics. This is reflected in the population PK analysis, which showed that antibodies to certolizumab pegol increased the clearance of certolizumab pegol by approximately four-fold as determined by covariate analysis. Increased clearance in antibody positive subjects can be expected to result in a 52 % reduction in Cmax, 86 % reduction in Ctrough and 72 % reduction in AUCτ in a typical 70 kg Caucasian subject with Crohn's disease administered 400 mg certolizumab pegol every four weeks.

3.2.7 Have the single and multiple dose pharmacokinetics of certolizumab pegol been adequately characterized?

The single- and multiple-dose pharmacokinetics (PK) of certolizumab were characterized following administration of I.V. and S.C. doses of certolizumab pegol encompassing the proposed clinical dosage to healthy subjects and patients with Crohn's disease. As the sought after route of administration under the current application is S.C. injection, this review will solely address PK data obtained following administration of S.C. formulations of certolizumab pegol.

Single Dose PK

Three studies evaluated the single dose PK of Certolizumab, namely studies CPD870-003, PHA-024 and PHA-001.

Study CPD870-003 was a double-blind, double-dummy, ascending dose group, phase 1 study evaluating the PK of certolizumab following administration of certolizumab pegol via I.V. and S.C. routes in 3 groups of 8 healthy male subjects/group. In each group, 6 subjects received CDP870 via the S.C. route while 2 subjects received CDP870 via the I.V. route. The I.V. dose of CDP870 remained the same at 1 mg/kg for each group and was administered as a 60 minute constant rate (100 ml/h) infusion. The S.C. doses were escalated in the order 20, 60, and 200 mg administered in volumes of 0.1, 0.3 and 1.0 ml, respectively. Blood and urine samples were collected up to 56 days post-dose for safety and PK analysis. The key PK findings of the study are summarized below in Table 1.

Table 1 The mean PK parameters of Certolizumab for each dose via IV & SC routes in healthy subjects (Study CPD870-003)

Parameter	IV Administration	SC Administration			
	1 mg/kg	20 mg (0.1 ml)	20 mg (1.0 ml)	60 mg (0.3 ml)	200 mg (1.0 ml)
C_{max} (µg/ml)	32.62 (6.45)	2.68 (0.33)	2.45 (0.17)	10.98 (1.5)	30.98 (4.31)
T_{max} (days)[a]	0.08 (0.04 - 0.25)	4.29 (1.50 - 7.02)	3.01 (2.00 - 10.00)	2.25 (1.50 - 4.00)	3.50 (1.50 – 14.02)
AUC_t (µg·day/ml)	295 (133)	27.0 (12.5)	29.9 (11.7)	154 (74.1)	647 (85.3)
λ_z (1/day)	0.0694 (0.0295)	-	0.0411 (0.0122)[d]	0.0620 (0.0166)[e]	0.0559 (0.0061)[f]
$T_{½z}$ (days)	12.02 (6.01)	-	18.48 (7.34)[d]	11.83 (3.68)[e]	12.53 (1.40)[f]
AUC (µg·day/ml)	342 (143)	-	74.5 (27.7)[d]	244 (50.2)[e]	699 (98.9)[f]
AUC extrap (%)	15 (11)	-	55 (2)[d]	14 (4)[e]	8 (4)[f]
V_z (ml)[b]	3722 (653)	-	7114 (287)[d]	4224 (1025)[e]	5265 (978)[f]
CL (ml/day)[c]	251 (104)	-	291 (80)[d]	254 (58.9)[e]	291 (43.9)[f]
MRT (days)	16.8 (8.19)	-	28.2 (11.1)[d]	19.6 (4.46)[e]	20.5 (1.31)[f]

Study PHA-024 was a randomized, double-blind, placebo-controlled, two-center, single dose study designed to evaluate three single dose levels of CDP870 (100, 400, and 800 mg) given by subcutaneous (SC) injections in subjects of Caucasian (n = 24) and Japanese (n = 24) descent. Twelve subjects (six Caucasian, six Japanese) were randomized to each of the four treatment groups: placebo, CDP870 100 mg, CDP870 400 mg, and CDP870 800 mg. Blood samples were collected up to 57 days post-dose for PK analysis. The key PK findings of the study are summarized below in Table 2.

Table 2 The mean PK parameters of Certolizumab for each dose in healthy subjects (Study PHA-024)

Pharmacokinetic Profile of CDP870 after Single SC Dose						
Pharmacokinetic Parameter	CDP870 Treatment Group					
	100 mg		400 mg		800 mg	
	Cauc (n=6)	Japan (n=6)	Cauc (n=6)	Japan (n=6)	Cauc (n=6)	Japan (n=4)†
$AUC_{0-t(last)}$ (µg*h/mL)						
Mean	6448	5495	27057	22780	49797	57558
SD	2077	1955	3830	2909	13976	6722
$AUC_{0-\infty}$ (µg*h/mL)						
Mean	7338	7088*	28752	23774	52597	61664
SD	1616	1942	4205	2784	14480	8638
C_{max} (µg/mL)						
Mean	21.1	18.4	49.5	46.3	105	102
SD	10.8	15.8	8.2	13.1	21.9	10.3
t_{max} (hour)						
Mean	96.1	130	144	116	129	171
SD	37.3	110	37.1	41.4	45.8	0.3
$t_{1/2,z}$ (hour)						
Mean	248	266*	312	257	295	316
SD	35.1	87.9	62.8	74.7	87.3	73

Study PHA-001 was an open-label, single-dose, multi-center, drug-drug interaction study conducted in 16 male and/or female patients who had Rheumatoid Arthritis (RA) for a minimum of 6 months. Subjects in this study were receiving chronic treatment with stable weekly methotrexate doses (5-17.5 mg/week, as a single dose) for a minimum of 3 months. The key objective of the study was to evaluate the effect of a single S.C. dose of CDP-870 400 mg (2 x 200 mg) on the steady-state plasma PK profile and renal clearance of methotrexate in subjects with RA. On Day 1 of the study, subjects received their weekly individualized methotrexate dose, on Day 2 subjects received a single subcutaneous 400 mg (2 x 200 mg) dose of CDP-870, and on Day 8, subjects received their weekly individualized methotrexate dose. Blood samples were collected for determination of Certolizumab levels up to 57 days post-dose. Summary of the key PK parameters for cetrolizumab is provided in Table 3.

Table 3 Mean PK parameters for Cetrolizumab in patients with RA

Pharmacokinetic Parameter	Methotrexate 5-17.5 mg Weekly + CDP-870 400 mg SD N = 16	
	Mean	(%CV)
AUC(0-55 days) (hr*µg/mL)	21187.32	(32%)
AUC (0-lqc) (hr*µg/mL)	21183.68	(32%)
AUC (0-∞) (hr*µg/mL)	22418.01	(33%)
Cmax (µg/mL)	46.55	(38%)
Tmax (hr)	131.99	(48%)
T1/2 (hr)	257.71	(42%)
CL/F (L/hr)	0.021	(50%)
Source: Table T6.2.		

Overall, the single dose PK data indicate that mean Cmax and AUC values increase in a linear manner with dose within a dose range of 20-800 mg following S.C. administration. Additionally, mean peak plasma levels occurred around 4 days post-dose, while mean terminal half-life of Certolizumab was estimated at 13 days following S.C. Also, coadministration of Certolizumab with methotrexate did not alter the PK of Certolizumab.

Multiple Dose PK

Multiple dose PK were collected from two Phase 2 studies (Study 004, 005) and two Phase 3 studies (Study 031 and 032) in RA and Crohn's patients. The results are combined in Pop-PK analysis (Study CDP870-039).

3.2.8 Does certolizumab pegol cause QT/QTc prolongation?

No studies have been conducted to assess the cardiac safety of certolizumab pegol.

3.2.9 What are the ADME characteristics of certolizumab pegol following oral administration?

Absorption: Systemic absorption from a sc injection site was evaluated in Studies CDP870-003, PHA-024 and PHA-001. Mean T_{max} ranged from 54 hours to 171 hours post-injection. The observed mean C_{max} following 400 mg sc doses was evaluated in Studies PHA-001 and PHA-024, ranging from 46.3 ± 13.1 µg/mL to 49.5 ± 8.2 µg/mL. C_{max} increased with dose in an approximately dose-proportional manner. Mean AUC extrapolated to infinity was evaluated following single 400 mg sc doses in Studies PHA-001 and PHA-024, ranging from 22, 419 ± 7, 398 µg.h/mL to 28,752 ± 4,205 µg.h/mL, respectively. AUC increased with dose in a dose-proportional manner. The absolute bioavailability (F) of 20 mg, 60 mg and 200 mg certolizumab pegol sc compared to 1 mg/kg certolizumab pegol iv was estimated in Study CDP870-003, and ranged from 76% at 200 mg/kg to 88 % at 60 mg/kg although these were estimated using mean AUC values from dose cohorts of different subjects rather than using within subject comparison. The population PK analysis CDP870-039 estimated absolute bioavailability to be 85 %. Pharmacokinetic modeling of combined data from healthy subject studies CDP870-001 and CDP870-003 suggested that the systemic bioavailability was approximately 100 % based upon comparison of clearance and volume of distribution values derived from iv versus sc dosing when corrected for individual subject weights.

Distribution: The central volume of distribution (Vc) was estimated in the population PK analysis, CDP870-039, as 4.0 L with an inter-subject variability (% CV) of 16.9 %.

Metabolism: No human studies of the metabolism of certolizumab pegol were performed. The Fab' fragment comprises protein components and is expected to be degraded to peptides and amino acids by proteolysis. Studies in rats indicate that a proportion of the PEG (11 - 21 %) is excreted as the 40 kDa PEG in urine.

Elimination: In human pharmacokinetic studies included in this application, plasma clearance (CL/F) was estimated by taking the ratio between the dose administered and the AUC extrapolated to infinity. In Study CDP870-001, during which certolizumab pegol was administered iv, mean clearance values ranged from 9.21 mL/h to 14.38 mL/h. In Study CDP870-003, clearance was estimated to be 10.46 mL/h following iv dosing and ranged from 10.58 mL/h to 12.13 mL/h following sc dosing.

The population PK analysis, Study CDP870-039, estimated clearance to be 17.25 mL/h in the overall population with an inter-subject variability of 38.3 % (CV) and an inter-occasion variability of 16.4 %. Certolizumab pegol has a long elimination half-life ($t_{½}$) of approximately 14 days, ranging from 10.33 days to 18.48 days in Studies CDP870-001, CDP870-003, PHA-024 and PHA-001.

Interactions: One study, PHA-001, investigated the interaction between certolizumab pegol and MTX in subjects with RA on a stable dose of MTX. This study showed that concurrent administration of certolizumab pegol had no statistically or clinically

significant effects on the overall exposure (AUC) or peak plasma concentration (C_{max}) of MTX. Furthermore, the similarity of the plasma concentration-time curves and PK parameters to those observed in healthy volunteer studies CDP870-003 and PHA-024 suggest that concurrent administration of MTX had no effect on the pharmacokinetics of a single dose of certolizumab pegol.

The population PK analysis, CDP870-039, showed that concomitant administration of steroids, amino-salicylic acid analogs or anti-infectives had no impact on the pharmacokinetics of certolizumab pegol. Chronic immunosuppresant administration had a statistically significant but not clinically relevant impact on the pharmacokinetics of certolizumab pegol in subjects with Crohn's disease included in the population PK analysis. For a typical 70 kg Caucasian subject with Crohn's disease, the predicted effect was a 6 % reduction in C_{max}, and 13% increase in C_{trough} with no effect on AUC. This finding may be an indirect effect consequent of reduced production of antibodies to certolizumab pegol in the presence of immunosuppressants.

In vitro cytochrome P450 inhibition studies with human microsomes were not performed because proteins and immunoglobulin antibodies do not compete for the cytochrome P450 mixed function oxidase drug metabolism system. An *in vitro* p-glycoprotein interaction study showed that neither certolizumab pegol nor its non-PEGylated Fab' fraction were inhibitors of p-glycoprotein mediated transport.

3.3 Intrinsic Factors

3.3.1 Is there a need for dosage adjustment in special populations?

Elderly

Specific clinical studies have not been performed in elderly subjects, however population pharmacokinetic analysis showed no effect of age (only 56 out of 1580 subjects were 65 years or older).

Gender

Specific clinical studies have not been performed to assess the effect of gender on the pharmacokinetics of certolizumab pegol, however a cross-study population pharmacokinetic analysis including 1580 subjects (688 male and 892 female) showed no effect on gender.

Ethnicity

The effect of ethnicity on the PK of cetrolizumab pegol was evaluated in study PHA-024. Study PHA-024 was a randomized, double-blind, placebo-controlled, two-center, single dose study designed to evaluate three single dose levels of CDP870 (100, 400, and 800 mg) given by subcutaneous (SC) injections in subjects of Caucasian (n = 24) and Japanese (n = 24) descent. Twelve subjects (six Caucasian, six Japanese) were randomized to each of the four treatment groups: placebo, CDP870 100 mg, CDP870 400

mg, and CDP870 800 mg. Blood samples were collected up to 57 days post-dose for PK analysis. The key PK findings of the study are summarized in Table 2.

The study findings indicate that the PK of cetrolizumab pegol is comparable between Caucasian and Japanese subjects at the proposed therapeutic dosage.

Pediatrics

No pediatric patient was studied in this submission as Crohn's disease is not likely to happen in this population.

Hepatic Impairment

Specific clinical studies have not been performed to assess the effect of hepatic impairment on the pharmacokinetics of certolizumab pegol. Population pharmacokinetic analysis did not allow any conclusion to be drawn on the effect of hepatic impairment because of the small number of patients (6 out of 1580 subjects) with significant liver dysfunction included in this analysis.

Renal Impairment

Specific clinical studies have not been performed to assess the effect of renal impairment on the pharmacokinetics of certolizumab pegol. However, population pharmacokinetic analysis showed no effect of creatinine clearance; hence renal impairment is unlikely to have significant impact in patients with mild to moderate renal impairment.

3.3.2 Is there a need for dosage adjustment based on immune response against Certolizumab Pegol ?

The incidences of anti-certolizumab pegol antibodies and neutralizing anti-certolizumab pegol antibodies appear to be inversely proportional to certolizumab pegol dose. These observations are complicated by the known interference of certolizumab pegol in the plasma with the anti-certolizumab pegol antibody assay; however the lower rate of immunogenicity at high doses continued to be observed after plasma concentrations of certolizumab pegol had fallen below detectable levels following cessation of dosing.

An inverse dose relationship with the incidence of anti-certolizumab pegol antibodies was also observed in healthy volunteers following single iv or sc administration of certolizumab pegol.

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

3.4 Extrinsic Factors

3.4.1 What extrinsic factors (drugs, herbal products, diet, smoking, and alcohol use) influence systemic exposure and/or response and what is the impact of any differences in exposure on response?

Therapeutic biologics are not CYP450 substrates and as such, they are generally unlikely to be associated with PK drug-drug interactions. A drug-drug interaction study was conducted to evaluate the effect of administration of a single dose of Certolizumab pegol 400 mg on the steady-state PK of methotrexate. The study demonstrated the lack of a significant drug interaction between certolizumab pegol and methotrexate.

Study PHA-001 was an open-label, single-dose, multi-center, drug-drug interaction study conducted in 16 male and/or female patients who had Rheumatoid Arthritis (RA) for a minimum of 6 months. Subjects in this study were receiving chronic treatment with stable weekly methotrexate doses (5-17.5 mg/week, as a single dose) for a minimum of 3 months. The key objective of the study was to evaluate the effect of a single S.C. dose of CDP-870 400 mg (2 x 200 mg) on the steady-state plasma PK profile and renal clearance of methotrexate in subjects with RA. On Day 1 of the study, subjects received their weekly individualized methotrexate dose, on Day 2 subjects received a single subcutaneous 400 mg (2 x 200 mg) dose of CDP-870, and on Day 8, subjects received their weekly individualized methotrexate dose. Blood samples were collected for determination of methotrexate levels up to 24 hrs post-dose on days 1 and 8. Moreover, urine samples were collected for 12 hrs prior to the methotrexate dose, and for 24 hrs post-dose on days 1 and 8. Summary of the key PK parameters for cetrolizumab is provided in Table 4.

Table 4 LSM ratios and 90% confidence intervals for Methotrexate PK parameters

Pharmacokinetic Parameter	Least Squares Means (a)				Ratio Ceadmin/ Methotrexate	90% Confidence Interval	p-value (b)
	Methotrexate 5-17.5 mg Weekly + CDP-870 400 mg SD		Methotrexate 5-17.5 mg Weekly				
	N	LSM	N	LSM			
AUC (0-24) (hr*ng/mL) (c)	14	102.16	16	105.98	0.964	(0.791, 1.175)	0.7478
AUC (0-lqc) (hr*ng/mL) (c)	16	98.98	16	99.18	0.978	(0.822, 1.163)	0.8232
AUC (0-∞) (hr*ng/mL) (c)	16	102.21	15	103.24	0.990	(0.833, 1.177)	0.9198
Cmax (ng/mL) (c)	16	25.66	16	28.21	0.909	(0.779, 1.062)	0.2992
XU (0-24) (µg/mL) (c)	15	459.45	16	659.46	0.697	(0.442, 1.097)	0.1828
CL/F (L/hr)	16	9.78	15	9.69	1.010	(0.850, 1.201)	0.9198
CLrenal (L/hr)	15	4.11	15	6.50	0.632	(0.394, 1.016)	0.1105
Tmax (hr)	16	1.39	16	1.20	--	--	0.0198
T1/2 (hr)	16	2.77	15	3.30	--	--	0.1308

The results of study PHA-001 indicate that concomitant administration of cetrolizumab pegol with methotrexate does not result in a significant effect on the PK of methotrexate.

3.5 General Biopharmaceutics

3.5.1 What is the composition of the commercial formulation?

Table 5 Composition of the commercial formulation of certolizumab pegol

Name of Ingredients	Reference to Quality Standards	Unit Quantity (including Overfill) Before Lyophilization
CDP870 Drug Substance	Company Standard	— mg
Sucrose	NF	— mg
Polysorbate	NF	— mg

3.5.2 Are the various formulations of certolizumab used throughout the clinical development adequately linked?

The clinical trial formulation is identical to the commercial formulation. Moreover, comparability was demonstrated between the commercial formulation and the various formulations utilized during clinical development

The commercial formulation of certolizumab pegol Injection (Lyophilized), 200 mg/vial is a lyophilized formulation with a dosage strength of 200 mg in — nominal capacity vial (Table 5). Each vial is intended for single use, following reconstitution with sterile Water for Injection. The clinical trial formulation is identical to the commercial formulation.

The pre-clinical, Phase 1 & 2 development programs for certolizumab pegol were originally initiated using a liquid formulation at 20 mg/mL for I.V. administration, which was then followed by a 200 mg/mL injection of a liquid formulation for S.C. administration. ——— eventually led to the development of a lyophilized formulation (200 mg /mL), which was utilized in the Phase 3 clinical program.

Over the course of product development, two formal comparability studies were performed to bridge the drug product presentations employed through the clinical program. Comparability studies, including pre-clinical and analytical comparability

assays, demonstrated comparability of the drug substance and drug product between the clinical trial formulation and the liquid formulations utilized in earlier clinical development.

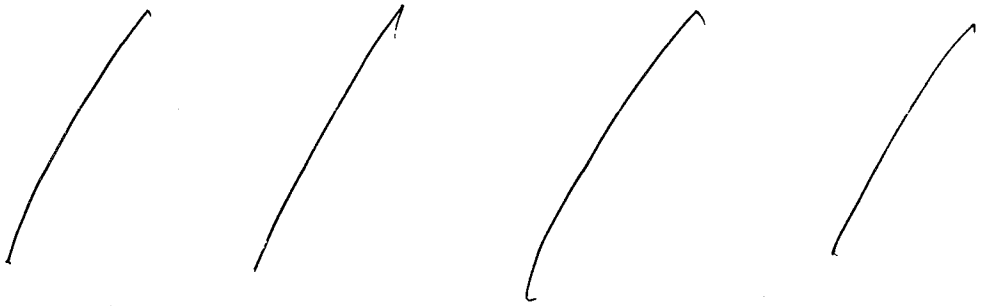
3.6 Analytical Section

3.6.1 Have the analytical methods been adequately validated?

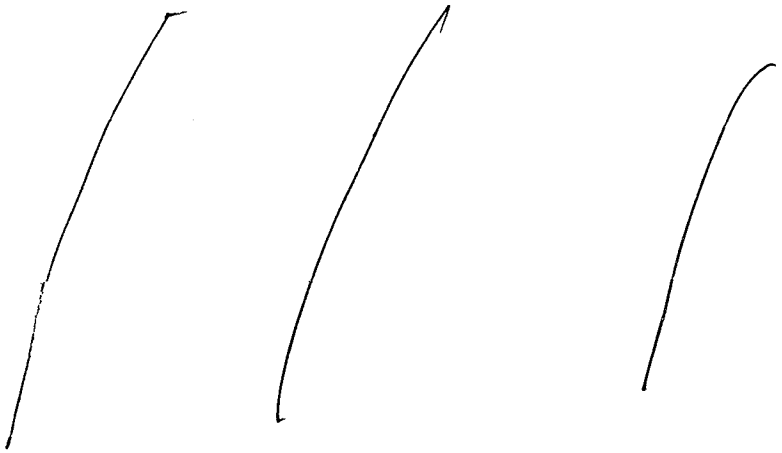
Serum concentrations of certolizumab pegol were determined using an enzyme-linked immunosorbent assay with a LLOQ of —µg/mL.

A validated method was developed for the determination of certolizumab pegol concentrations in human plasma using a —— enzyme-linked immunosorbent assay (ELISA).

As part of the method, ——————————————————



Details of the analytical assay method validation are as follows:



Overall, the analytical assay for quantitation of certolizumab pegol in human plasma is acceptable.

2 Page(s) Withheld

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_____ Deliberative Process

5 Individual Study Reports

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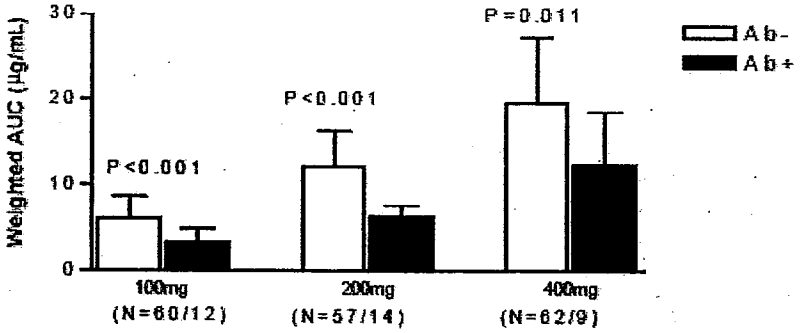
5.1 Immunogenicity

Incidence and Impact of Formation of Anti-Certolizumab Pegol Antibodies in Subjects with Crohn's Disease: Anti-certolizumab pegol antibodies were analyzed in six studies of subjects with Crohn's disease, one in which certolizumab pegol was administered iv (CDP870-008), and five in which certolizumab pegol was administered sc (CDP870-005, CDP870-031, CDP870-032, CDP870-033 and CDP870-034). In Study CDP870-008, no antibodies at a concentration >2.4 units/mL were noted at doses of 1.25 (n=2) and 10 mg/kg, while at 5 and 20 mg/kg the incidences were 32 and 9 % respectively. Sub-analyses of pharmacokinetics in Ab+ (Ab+ status is defined as those subject with anti-certolizumab pegol antibody concentration >2.4 units/mL at any time during the study) and antibody negative (Ab-) subjects were not performed for this study due to the low numbers of subjects.

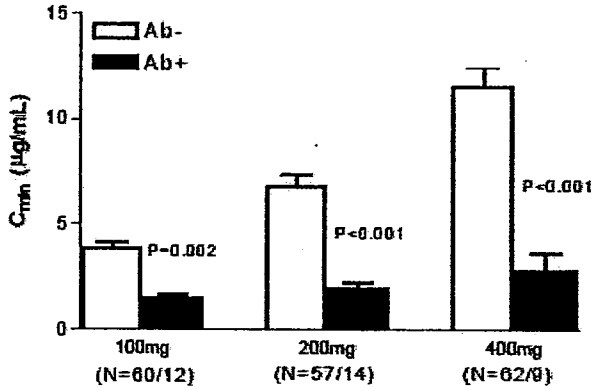
In Study CDP870-005, at doses of 100, 200 and 400 mg sc, the incidence of Ab+ subjects at the end of the double-blind treatment phase (Week 12) was 16, 19 and 12 %, respectively. Subjects were followed for 12 weeks after their last dose and the incidence of Ab+ subjects increased to 32, 32 and 23 %, respectively (Week 20). Certolizumab pegol pharmacokinetics were compared in Ab- and Ab+ subjects, as measured by AUC and C_{min} (Figure 8 and Figure 9). Both AUC and C_{min} were significantly reduced in Ab+ subjects.

Figure 8 Study CDP870-005: Comparison of AUC (weighted mean) in Ab- and Ab+ subjects with Crohn's disease



P-values compare antibody groups at each treatment using a two-sample t-test. AUC was calculated using available data from the first 12 weeks of treatment and then divided by weeks covered by this data to give an average AUC per week. Ab+ subjects were those with at least one positive result (>2.4 units/mL) up to and including Week 12.

Figure 9 Study CDP870-005: Comparison of mean Cmin in Ab- and Ab+ subjects with Crohn's disease



P values compare antibody groups at each treatment using a 2-sample t-test. Ab+ subjects were those with at least one positive result (>2.4 units/mL) up to and including Week 12. C_{min} was defined as the minimum certolizumab pegol plasma concentration after Week 0.

In the pivotal Study CDP870-031, 26 of 331 subjects who received certolizumab pegol (7.9%) developed anti-certolizumab pegol antibodies during the course of the study. Geometric mean certolizumab pegol plasma trough concentrations were substantially lower in the subgroup that tested positive to anti-certolizumab pegol antibodies compared with the subgroup that tested negative at all study visits from Weeks 2 to 26. Differences were particularly large, by approximately 10-fold, between Week 8 and Week 24 and apparent peak concentration occurred at Week 4 in the Ab+ subgroup compared with Week 6 in the Ab - subgroup.

A similar profile was observed in pivotal Study CDP870-032. Of the 215 subjects who received certolizumab pegol in the double-blind phase, 213 of whom provided plasma samples analyzable for anti-certolizumab pegol antibodies throughout the study, a total of 17 (7.9 %) developed anti-certolizumab pegol antibodies during the course of the study. When looking at the whole study population (668 subjects) who received certolizumab pegol in the open-label phase, 58 subjects (8.7%) developed anti-certolizumab pegol antibodies during the course of the study. Of these, four subjects developed antibodies during the open-label induction phase of the study. In the double-blind maintenance phase of the study, an additional 17 subjects in the 400 mg certolizumab pegol group developed anti-certolizumab pegol antibodies, compared with an additional 37 subjects in the placebo group. Subjects who were Ab+ had lower plasma trough concentrations of certolizumab pegol compared with Ab- subjects at all study visits.

Although reduced efficacy would be expected in Ab+ subjects, in the absence of a known minimum effective plasma concentration of certolizumab pegol, it is not possible to draw any firm conclusion based solely upon the PK data. Reliable assessment of the relationship between efficacy and antibody status is made difficult by the small number of Ab+ subjects, leading to greater variability and the large difference in group sizes.

The population PK study (CDP870-039) explored the effect of anti-certolizumab pegol antibodies and immunosuppressants on plasma levels of certolizumab pegol. The

conclusions were that there was a statistically significant and clinically relevant impact of anticertolizumab pegol antibodies on certolizumab pegol PK and a statistically significant but not clinically relevant impact of immunosuppressants (See PopPK report).

The influence of baseline immunosuppressant and corticosteroid use on the generation of antibodies to certolizumab pegol was explored for both pivotal studies. Antibody generation was lower in those using concomitant immunosuppressants (3.3% across both studies) compared to those who were not (11.2% across both studies) but was similar, irrespective of corticosteroid use (7.4% and 8.5% across both studies for those using and not using concomitant corticosteroids, respectively).

The Incidence of Neutralizing Anti-Certolizumab Pegol Antibodies in Crohn's Disease: In Study CDP870-031, 26 subjects were found to be positive for antibodies to certolizumab pegol in the screening ELISA, of which samples from 25 subjects were available for neutralizing bioassay. Overall, 21 of the 25 subjects tested had neutralizing antibodies. Samples from six subjects had titers of 30, eight had titers of 300 and seven had titers of 3,000. For Study CDP870-032, 58 subjects were positive for antibodies to certolizumab pegol in the screening ELISA. Of the 55 samples available for testing, 44 had neutralizing antibodies. Samples from 21 subjects had titers of 30, 13 had titers of 300 and 10 had titers of 3,000. Overall, the incidence of neutralizing antibodies amongst those who generated antibodies was approximately 80%. Neutralizing anti-certolizumab pegol antibody titers were generally higher in subjects with lower plasma concentrations of certolizumab pegol, as evidenced in Table 6.

Table 6 Distribution of neutralizing anti-certolizumab pegol antibody titers in subjects with Crohn's disease by plasma concentration of certolizumab pegol

Study	Plasma certolizumab pegol concentration	n		Neutralizing anti-certolizumab pegol antibody titer			
				<30	30	300	3000
CDP870-031	≤ µg/mL	14	n	0	3	6	5
	≥ µg/mL	11	n	4	3	2	2
CDP870-032	≤ µg/mL	40	n	4	16	12	9
	≥ µg/mL	12	n	5	5	1	1

Summary and Conclusions

The incidences of anti-certolizumab pegol antibodies and neutralizing anti-certolizumab pegol antibodies appear to be inversely proportional to certolizumab pegol dose. These observations are complicated by the known interference of certolizumab pegol in the plasma with the anti-certolizumab pegol antibody assay; however the lower rate of immunogenicity at high doses continued to be observed after plasma concentrations of certolizumab pegol had fallen below detectable levels following cessation of dosing.

An inverse dose relationship with the incidence of anti-certolizumab pegol antibodies was also observed in healthy volunteers following single iv or sc administration of certolizumab pegol.

In the pivotal studies of Crohn's disease where subjects received 400 mg sc (CDP870-031 and CDP870-032) the incidence of subjects testing positive for antibodies at any time during the studies was 7.9% in those randomized to certolizumab pegol. When an additional analysis was performed including subjects who tested negative for antibodies but showed increased clearance of drug (inferred Ab+), the rate increased to approximately 10%. The proportion of subjects developing antibodies is lower in those receiving concomitant immunosuppressants (3.3%).

In general, the incidences of antibodies were higher in subjects with RA than with Crohn's disease, and higher following sc than iv administration of certolizumab pegol. The incidence of subjects expressing anti-certolizumab pegol antibodies increased with continued administration of certolizumab pegol in subjects with both RA and Crohn's disease. Antibodies were directed entirely against the — the Fab'. No antibodies were detectable against the PEG moiety. There was no cross-reactivity of anti-certolizumab pegol antibodies with other commercially available anti-TNF agents, nor was certolizumab pegol recognized by antibodies to infliximab.

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

5.2 Pharmacometric Review

5.2.1 Executive Summary

Cimzia (Certolizumab pegol) is an anti-Tumour Necrosis Factor (TNF), genetically engineered humanized antigen binding fragment (Fab'), derived [redacted], manufactured by [redacted] using *E. Coli.*

The sponsor has submitted the BLA to seek the indication for [redacted]

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

The key points to consider are:

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

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

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

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

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

- The sponsor should perform clinical trial simulations before the next trial to explore the impact of different analyses techniques on various drug effect sizes and dropout rates. To learn the titration value, increase dose for non-responders. Please discuss with Office of Clinical Pharmacology/Pharmacometrics group.

5.2.2 Background

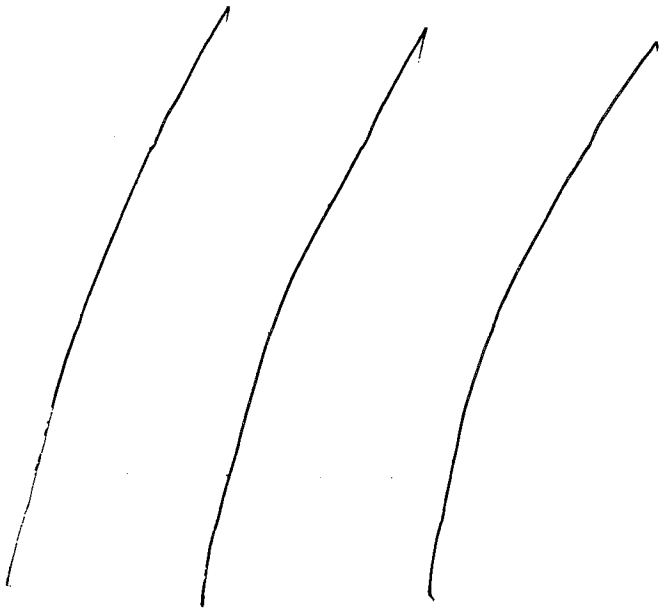
Cimzia (Certolizumab pegol) is an anti-Tumour Necrosis Factor (TNF), genetically engineered humanized antigen binding fragment (Fab'), derived [redacted], manufactured [redacted] using *E. Coli.*

The sponsor has submitted the BLA to seek the indication for [redacted]

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

5.2.3 Question Based Review

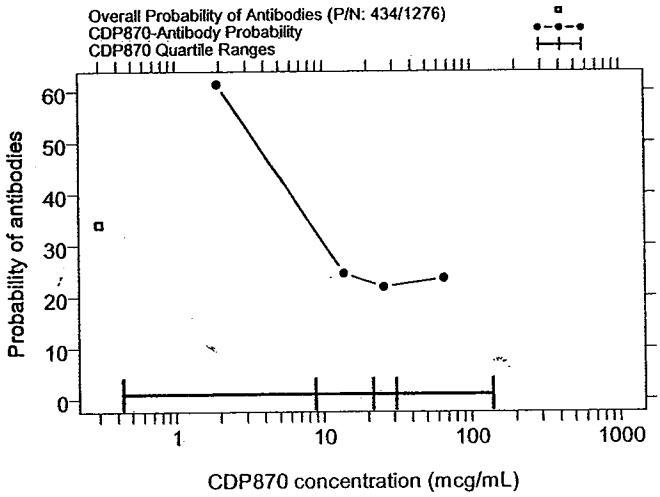
Is there evidence from clinical trials supporting one fixed dose for all patients?
Considerable variability in the exposure levels is observed for a fixed dose of 400 mg. The CDP870 concentration range following a dose of 400 mg is between 0.5 and 80 mcg/mL (see figure below).



CDP870 plasma concentrations vs. time (solid red lines = median, dots = individual CDP870 concentration).

When exposure is highly variable and there seem to be a dependence of response on exposure, then it could be important to titrate each patient's dose in order to attain the full potential for efficacy.

The probability of developing antibodies decreases with increasing CDP870 steady-state concentration, i.e. the lower the CDP870 steady-state concentration, the higher the probability of having CDP870 antibodies (see figure below). Therapeutic drug monitoring (TDM) might be considered to optimize the individual patient exposure based on the patient's antibody status.



Probability of antibodies vs. CDP870 steady state concentration.

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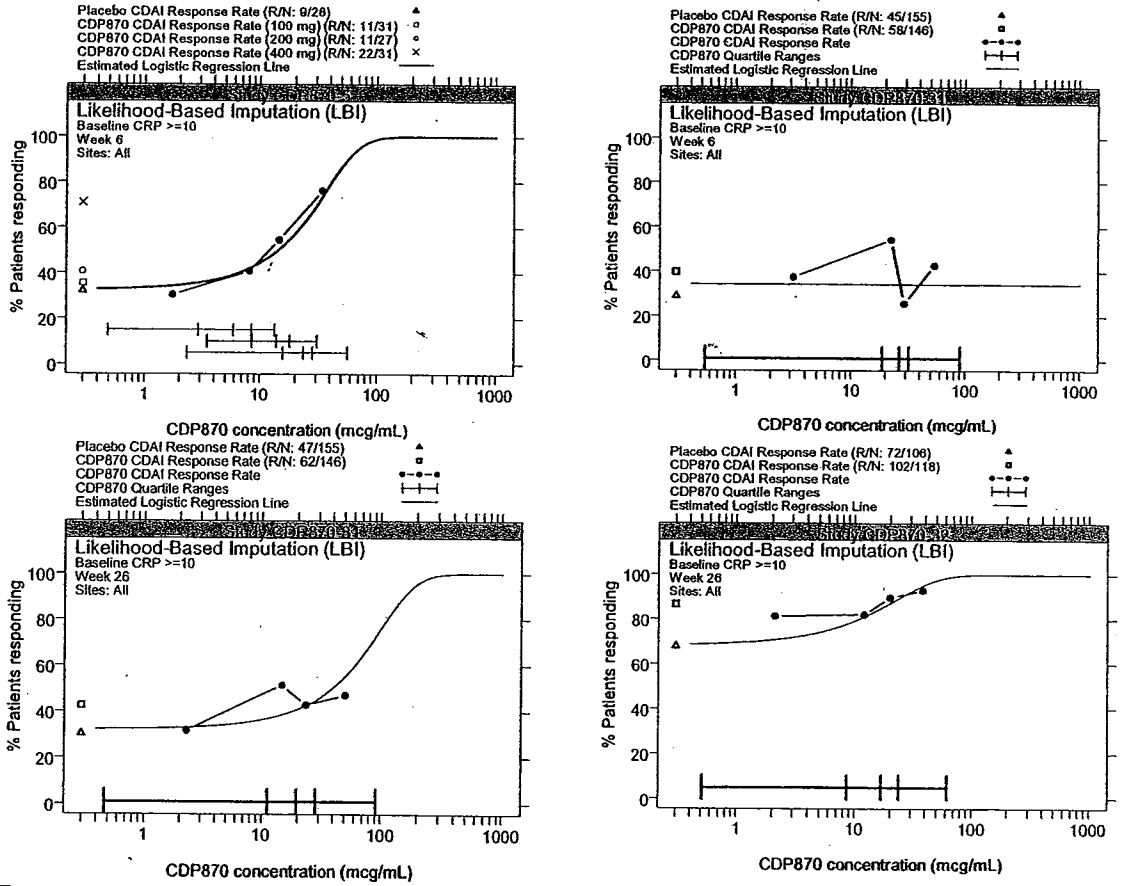
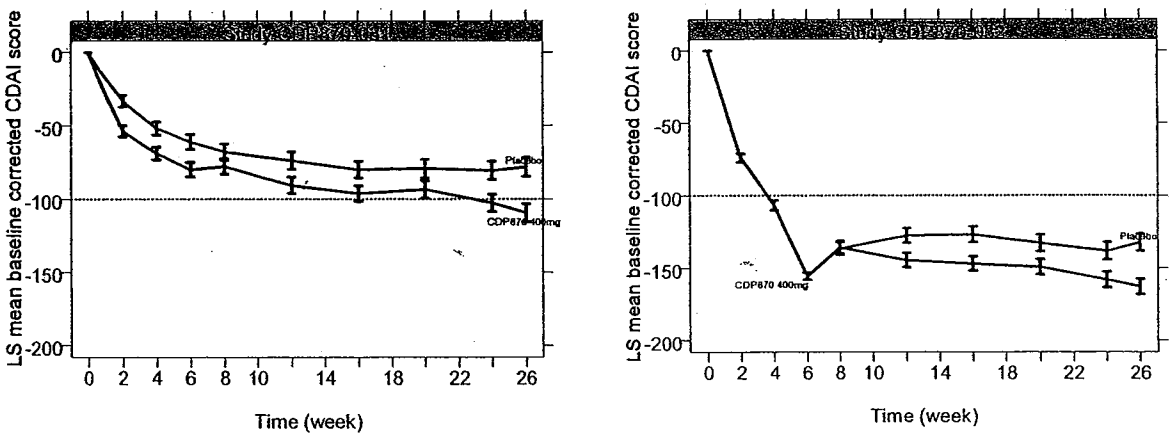
Is there evidence of exposure-response at week 6 and week 26?

The probability of achieving clinical response (defined as $\Delta CDAI \leq -100$) is clearly dependent upon the CDP870 concentration in study CDP870-005 at week 6 where patients having lower concentrations (e.g., less than 10 mcg/mL) exhibit lower response rates (see figure below). The relationship between the probability of response and the CDP870 concentration is not as clear for studies CDP870-031 and -032 at week 26 due to unknown reasons.



Exposure-response for studies CDP870-005 week 6 (**top left**), CDP870-031 week 6 (**top right**) and week 26 (**bottom left**), and CDP870-032 at week 26 (**bottom right**).

The least square (LS) mean predicted baseline corrected CDAI score at week 26 using mixed-model repeated measures (MMRM) analysis is approx. 30 points lower for active treatment compared to placebo for both phase III studies. However, there seems to be a significant difference in the change in baseline corrected CDAI scores over time for studies CDP870-031 and -032 where clinical response (i.e. DCDAI≤ -100) for active treatment is achieved at week 24 for study CDP870-031 (double-blind) and at week 4 for study CDP870-032 (open-label until week 6). It is unclear what is causing this observed difference.



LS mean predicted (±SE) baseline corrected CDAI score for study CDP870-031 **(left)** and CDP870-032 **(right)**.

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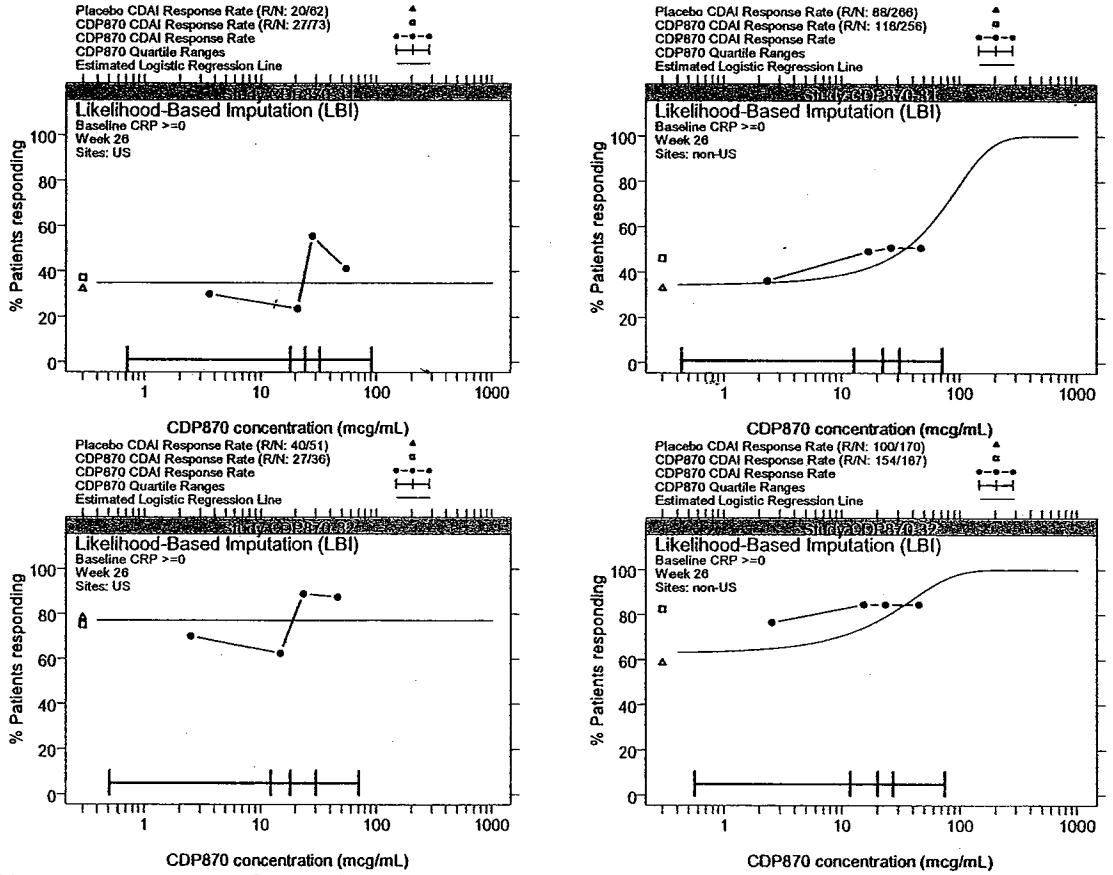
Is the exposure-response relationship consistent between US and non-US subgroups?

There does not seem to be a significant exposure-response relationship for the US sites in study CDP870-031 and CDP870-032 as opposed to a fairly defined trend in non-US sites (see figure below). With US and non-US sites combined, the overall trend is driven by the non-US sites.

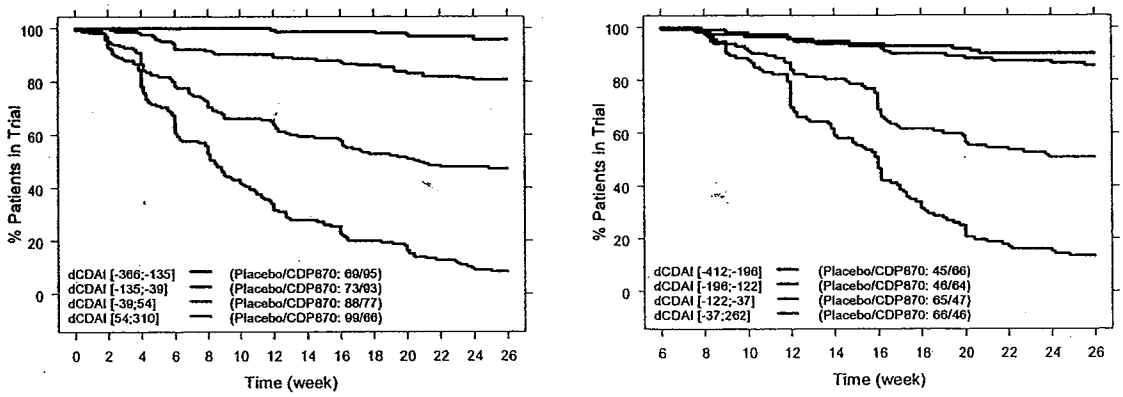


Exposure-response for studies CDP870-031 (**top**) and CDP870-032 (**bottom**) at week 26 for US (**left**) and non-US (**right**) sites.

Since the exposure is similar between non-US and US sites (i.e. between 0.5 and 80 mcg/mL), the reason for not seeing a exposure-response relationship for the US population might be due to lower sensitivity to CDP870 and/or a different background treatment resulting in a higher placebo response rate.

What is the mechanism for dropouts?
Patients seem to be dropping out of Study CDP870-031 and CDP870-032 due to worsening of symptoms.

The overall dropout rate is about 40%, and the dropouts are not missing completely at random, rather they are correlated with the ΔCDAI score. In particular, 90% of patients with ΔCDAI score above 54 drop out by Week 26 in study CDP870-031, whereas only 5% of those patients with ΔCDAI score below -135 drop out of the study by Week 26. Similar trend was observed in Study CDP870-032 as well.



Dropout stratified on baseline corrected CDAI score at final visit for studies CDP870-031 **(left)** and CDP870-032 **(right)**.

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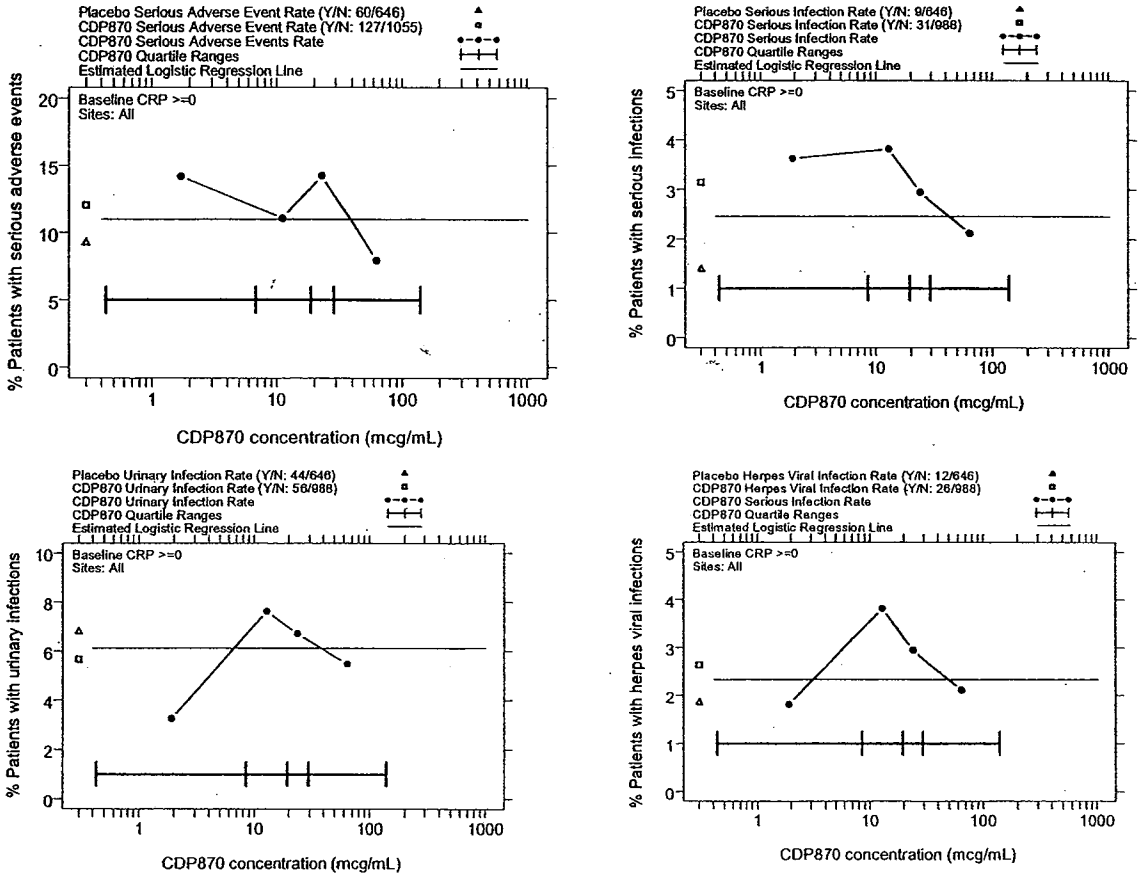
Is there evidence of adequate safety data?

There does not seem to be a relationship between concentration and the serious adverse events, serious infections, urinary infection rates, and herpes viral infections rate (see figures below). It is therefore reasonable to evaluate higher than 400 mg dose for future studies from both efficacy and safety point of view.



Concentration-safety relationship for serious adverse events **(top left)**, serious infections **(top right)**, urinary infections **(bottom left)**, and herpes viral infections **(bottom right)**.

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_____ Trade Secret / Confidential

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5.2.4 Sponsor Exposure-Response Modeling

Studies

Study CDP870-001: A placebo controlled, double blind, ascending single dose study, investigating the tolerability and pharmacokinetics of intravenously administered CDP870 in healthy male volunteers.

Study CDP870-002: A phase II double-blind, placebo-controlled, ascending dosage group (1, 5, 20 mg/kg), multi-centre study of the anti-TNF (Tumour Necrosis Factor) fab'- PEG conjugate CDP87O administered intravenously to patients with active rheumatoid arthritis, with 8 week follow-up and option for second dose in open fashion.

Study CDP870-003: Single ascending dose IV or subcutaneous (SC) administration to healthy subjects. Randomized, double blind, double dummy, parallel group study; doses of 1 mg/kg for IV and 20, 60, 200 mg for SC administration in volumes of 0.1, 0.3 and 1.0 mL respectively.

Study CDP870-004: A Phase II Multi-Center, Double-Blind, Placebo-Controlled, Two-Panel Study to Compare the Efficacy and Safety of Subcutaneous (SC) 50 mg, 100 mg, 200 mg, 400 mg, 600 mg, and 800 mg CDP-870 Versus Placebo Administered at 0, 4, and 8 Weeks With Assessments to Week 12 in the Treatment of the Signs and Symptoms of Patients With Rheumatoid Arthritis and Further Open Dosing With SC 400 mg CDP-870 4-Weekly With Three Safety Follow-Up Visits

Study CDP870-005: A Phase II, multi-centre, double-blind, placebo-controlled, parallel group, dose-response study to assess the safety and efficacy of the humanised anti-TNF PEG conjugate, CDP870, dosed subcutaneously in patients with active Crohn's disease.

Study CDP870-008: A Phase II, multi-centre, double-blind, placebo-controlled, parallel-group study to assess the safety and efficacy of a single intravenous infusion of the humanized anti-TNF PEG conjugate, CDP870 (1.25, 5, 10, 20 mg/kg) in patients with active Crohn's disease.

Methods

PK Model

Population pharmacokinetic (PK) models were used to fit data from the above mentioned CDP870 studies to gain an understanding of the impact of patient covariates, anti-CDP870 responses, and inter-patient variability.

CDAI Subcomponent Analysis

An analysis of the subcomponents that make up the Crohn's Disease activity index (CDAI) was performed to determine if certain subcomponents had a detrimental effect on the ability to detect a difference between placebo and treatment, either due to added variability or reduced magnitude of effect.

Exposure-CDAI Modeling

Dose-effect models were used to determine dose-response relationships using the full CDAI score using either dose or the individual concentrations predicted by the PK model as measures of exposure.

Longitudinal Modeling

Longitudinal models were developed to explore the change in placebo and treatment effect over time. The models considered using either concentration or dose as the measure of exposure, various forms of exposure-effect relationships, and different relationships between placebo and treatment effect. The models also considered the impact of patient covariates.

Results

PK Modeling

Body weight, sex, body mass index (BMI), and anti-CDP870 responses were found to have a significant impact on the PK observed.

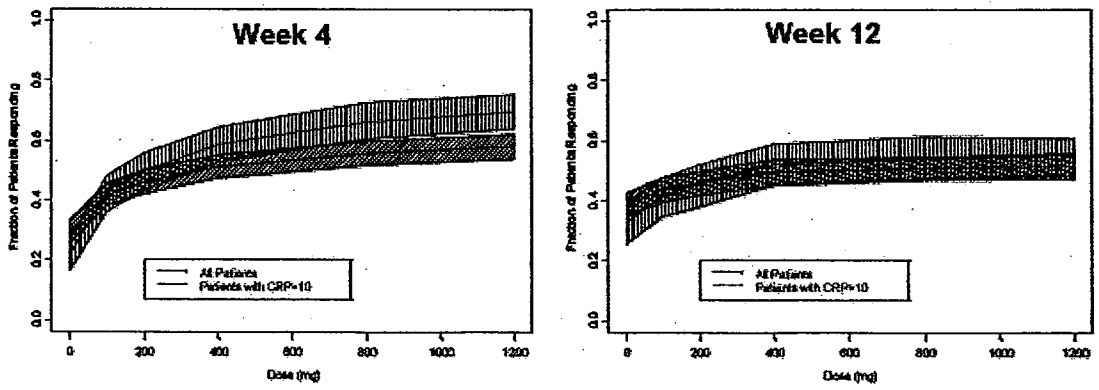
CDAI Subcomponent Analysis

Dose-response models were fit to the optimized set of subcomponents and compared to the fitting of the complete CDAI score. The optimized set of CDAI subcomponents resulted in a small improvement in the precision of the dose-response model, but it did not appear to markedly change the shape of the dose-response curve in terms of the maximum effect relative to placebo or the potency of CDP870.

Exposure-Effect Modeling

The concentration-effect and dose-effect models were equally effective in fitting the data. This suggested that the inter-patient variability in PK that is accounted for when using the individual concentrations predicted by the PK model did not contribute significantly to the variability observed in efficacy. For this reason subsequent modeling and simulation was performed using the dose response models.

Dose-response modeling at week 4 and week 12 predicted the dose-response shown in the following figures for a population of Crohn's patients similar to those enrolled in Study CDP870-005:



Model Predicted Population Response Rate at Week 4 and Week 12 (CDAI Change >70 and >25%)

Based on the dose-response modeling, it was found that the majority of the improvement in efficacy over placebo occurs at doses of up to 400 mg, with smaller additional improvements at higher doses. Patients with a baseline C-reactive protein (CRP) concentration of greater than 10 mg/L were found to have both a lower placebo response and higher response to CDP870. Only doses ≥400mg of CDP870 were found to result in a clinically relevant 30% difference in the percentage of responding patients (CDAI Change >70 and >25%) relative to placebo at week 4 and only in patients with CRP>10 at baseline. Doses of ≥400mg were also found to be required to achieve a clinically relevant difference in the percentage of patients achieving remission (CDAI < 150), and this was only achieved at week 4 and in patients with CRP>10 at baseline. A comparison of the response achieved with CDP870 to that achieved in earlier Remicade (infliximab) trials showed that Remicade produced a larger treatment response relative to placebo, both as a result of a lower placebo response and higher treatment response. The difference in the placebo response between the CDP870 and Remicade studies was thought to be the result of changes that occurred in the 6 years between these studies, such as changes in the Crohn's population available for treatment and/or changes in the standard of care.

Longitudinal Modeling

The final model that was found to best describe the longitudinal CDAI data in Study 005 was as follows:

$$CDAI = CDAI_{Placebo}\ (1 - E_{Drug})$$

$$CDAI_{Placebo} = CDAI_{t=0} + (CDAI_{\infty} - CDAI_{t=0})\ (1 - e^{-k_p \cdot time})$$

$$CDAI_{\infty} = e^{(\theta_1 + CRP>10\ \theta_7 + \eta_1)}$$

$$k_p = e^{(\theta_2 + \eta_2)}$$

$$E_{Drug} = \frac{E_{max}\ Dose}{ED_{50} + Dose}$$

$$ED_{50} = e^{(\theta_4 + \theta_5\ Immunop. + \eta_3)}$$

$$E_{Max} = \frac{X_{max}}{1 + X_{max}}$$

$$X_{max} = e^{(\theta_3 + \theta_6\ time + \theta_8\ CRP>10)}$$

In this model the placebo CDAI score decays exponentially over time and treatment with CDP870 results in a fractional change in the CDAI score relative to the placebo response. Two variations in this model were explored: in one case the fractional change was held constant over time, and in the second case the fractional change was allowed to change with time. The magnitude of the fractional change was determined by an Emax dose-response relationship.

Allowing the longitudinal model to account for a decline in the magnitude of the treatment response relative to placebo was found to significantly improve the fit to the data. The predicted reduction in efficacy relative to placebo over time agreed with the results found with the week 4 and week 12 dose-response models and observations from

Remicade studies and suggested that long term therapy with CDP870 would not likely be efficacious.

An important finding with this model was that the patients in the highest dose group (400 mg) that have the strongest treatment response are predicted to show a CDAI that increases with time following their maximum response shortly after treatment begins.

Sponsor's Exposure-Response Conclusions
The overall inferences and conclusions that can be made from the sponsor's modeling and simulation project are as follows:

- Based on concentration-response and dose-response modeling, inter-patient variability in PK does not contribute significantly to inter-patient variability in efficacy
- A subcomponent analysis of the CDAI did not result in a significantly improved concentration-response relationship or the ability to detect the maximum magnitude of response
- Doses >400 mg CDP870 will likely lead to some improvement in efficacy; however, most difference from placebo occurs at doses up to 400 mg
- A greater response to treatment with CDP870 relative to placebo is observed in patients with baseline CRP>10
- Only doses ≥400mg of CDP870 will result in a clinically relevant 30% difference in median percentage of responding patients relative to placebo at week 4 and only in patients with CRP>10
- No dose level of CDP870 will result in a 30% difference in responding patients at week 12, even in CRP>10 patients
- Improvement in response relative to placebo was higher with Remicade compared to CDP870 at weeks 4 and 12 mainly due to a lower placebo response in the Remicade trial
- Longitudinal modeling indicated that the treatment effect of CDP870 relative to placebo diminishes with time, suggesting that chronic therapy is not likely to be efficacious
- Trial simulations based on modeling of both Study 005 data and placebo data from CDP571 studies indicates that greater than 100 patients or 50 patients would be required to detect a significant and clinically relevant response at week 4 at 400 or 800 mg, respectively

5.2.5 Reviewer's Exposure-Response Comments

- *Sponsor's PK analysis, CDAI subcomponent analysis, exposure-effect, and longitudinal modeling are reasonable but the phase III data was not included in the analysis.*

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5.2.6 Reviewer's Exposure-Response Modeling

Studies

Studies CDP870-005 and CDP870-008 described under Sponsor's Methods in Section 0 were pooled with the two phase III studies (CDP870-031 and CDP870-032) for the reviewer's analysis.

Study CDP870-031

A Phase III multi-national, multi-centre, 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-weekly to Week 24), in the treatment of patients with active Crohn's disease.

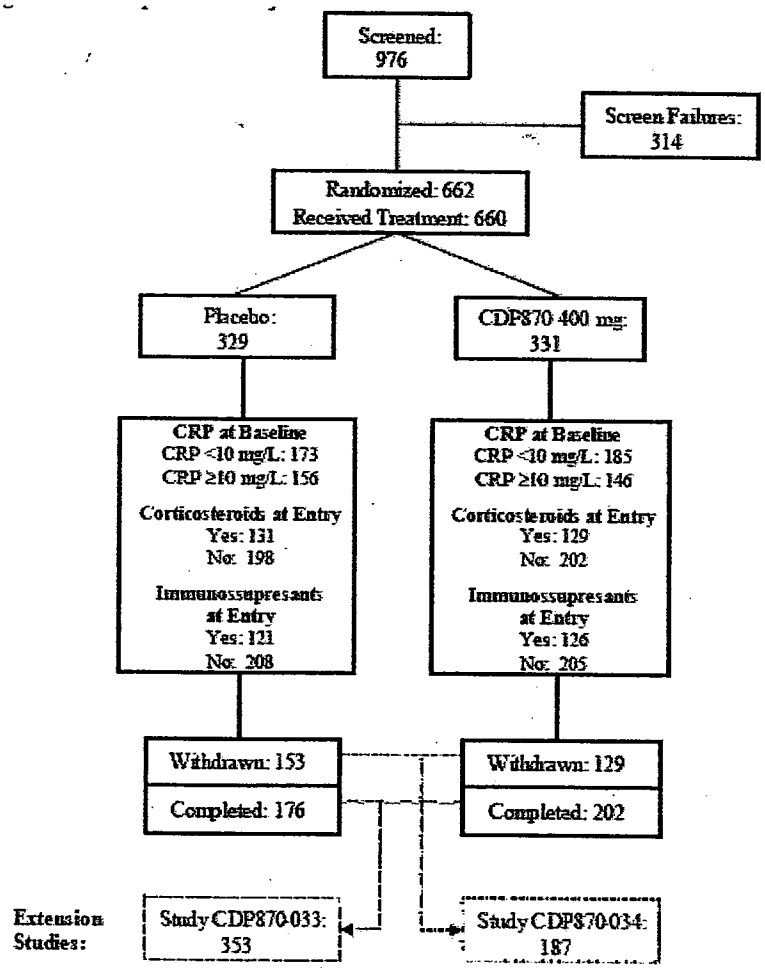

Figure 10 Disposition of subjects in Study CDP870-031 (Table 10.1 in CDP870-031 study report).

Study CDP870-032

A Phase III multi-national, multi-centre, 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 4-weekly from Weeks 8 to 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

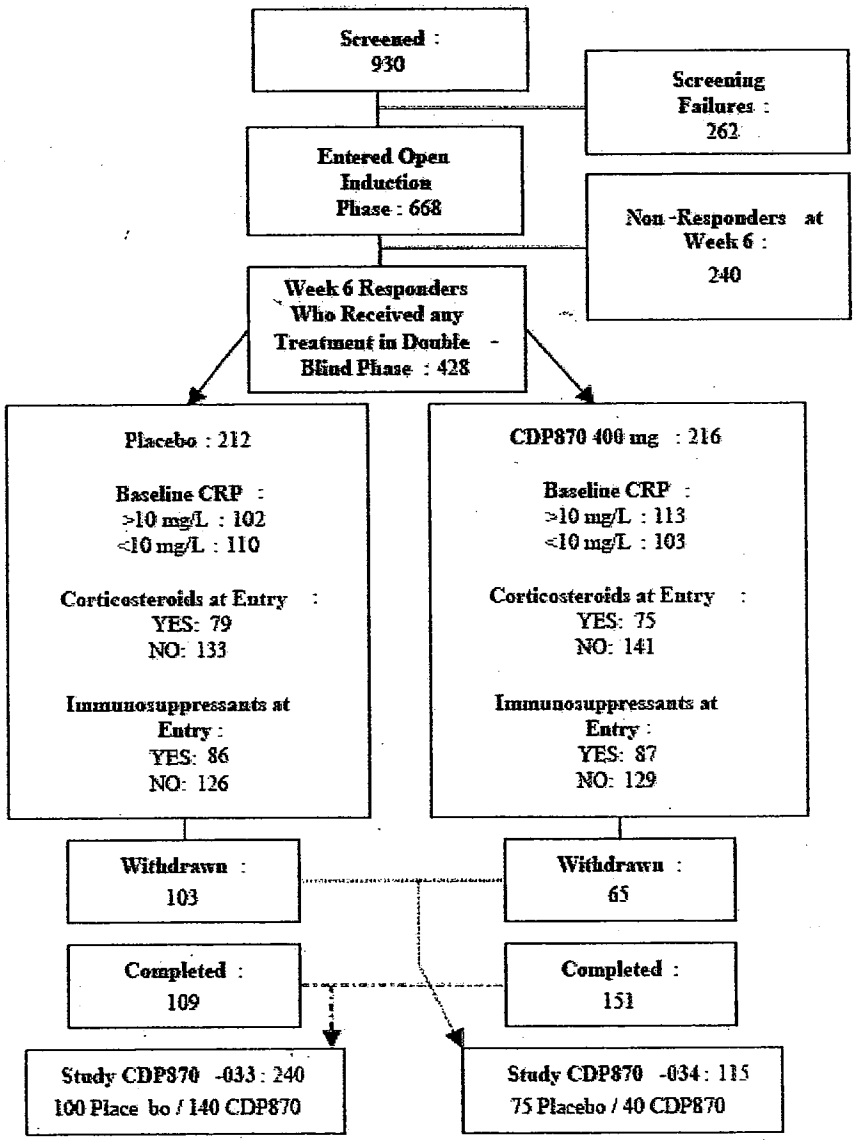

Figure 11 Disposition of subjects in Study CDP870-032 (Table 10.1 in CDP870-032 study report).

Data
The sponsor was requested to submit a pooled dataset with longitudinal PK, CDAI scores, and safety information from studies CDP870-005, -008, -031, and -032 for this analysis.

Methods
When considerable data are missing, especially mostly due to symptom worsening, it is important to analyze the data in multiple different ways to arrive at sound inferences about effectiveness.

Baseline observation carried forward (BOCF) (also referred to as non-responder imputation), and last observation carried forward (LOCF) for missing data can be inappropriate imputation techniques for these types of data when the dropouts are not occurring at random but rather due to lack of effectiveness.

Two alternative methods have therefore been investigated, i.e. longitudinal modeling and mixed-model repeated measures (MMRM) analyses which are briefly described in the following.

Longitudinal Model of Change in CDAI Score
Similar to the sponsor's analysis, a longitudinal model was developed to explore the change in CDAI score over time and to investigate the impact of patient covariates using non-linear mixed-effects modeling.

Mixed-Model Repeated Measures Analysis
Mixed-model repeated measures analysis is similar to the longitudinal model with the exemption that time is handled as a discrete and not continuous variable.

Exposure-Response Analysis
The model predictions from the longitudinal model were used to substitute the missing data and use observed data when available.

The logistic regression was performed using each patient's (active and placebo) response status and his/her last observed CDP870 concentration before visit 6 or 26, i.e.

$$p(\text{responder}) = \exp(x) / (1+\exp(x))$$

where p is the probability of responding, x = intercept + slope*PK concentration (when slope is significant different from 0) or x = intercept (if the PK concentration is not a significant covariate, i.e. no exposure-response relationship). The CDP870 concentration in placebo patients was set to 0 mcg/mL in the logistic regression estimation. The CDP870 concentration was only added as a covariate for the logistic regression when the p-value was 0.05 or below.

Results and Discussion

CDP870 Exposure Analysis

Considerable variability in the exposure levels is observed for a fixed dose of 400 mg. The trough CDP870 concentration range following a dose of 400 mg is between 0.5 and 90 mcg/mL (see **Figure 12**).

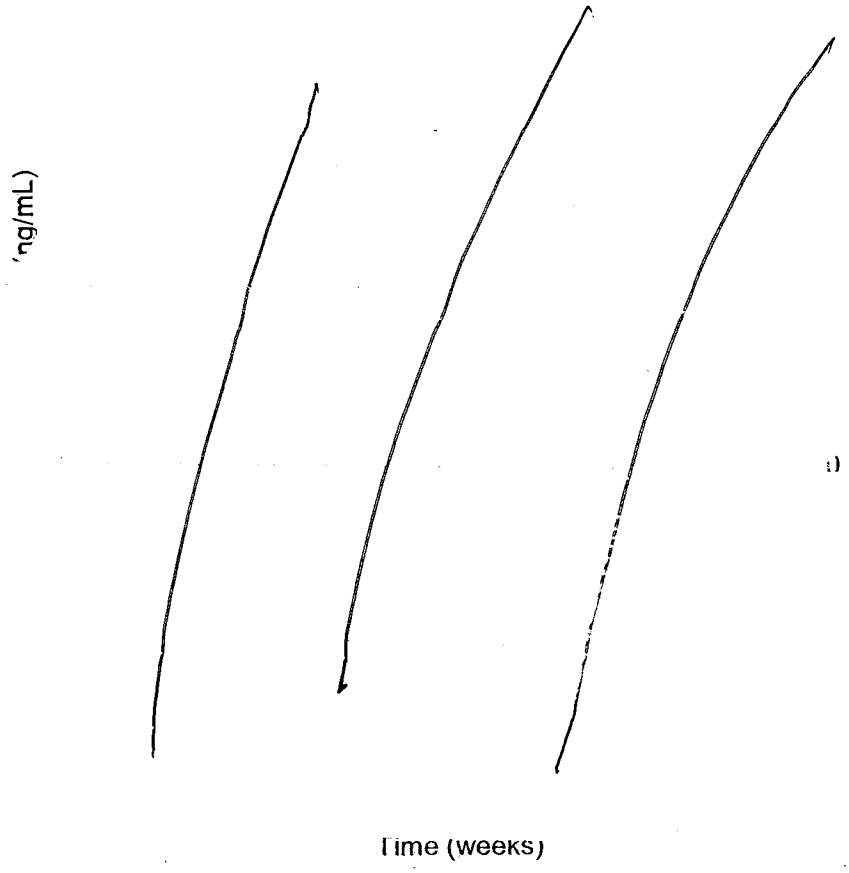

Figure 12 CDP870 plasma concentrations (solid lines = median, dots = individual CDP870 concentration) for studies CDP870-005, CDP870-008, CDP870-031, and CDP870-032.

The probability of developing antibodies decreases with increasing CDP870 steady-state concentration, i.e. the lower the CDP870 steady-state concentration, the higher the probability of having CDP870 antibodies (see **Figure 13**). Therapeutic drug monitoring (TDM) might be considered to optimize the individual patient exposure based on the patient's antibody status.

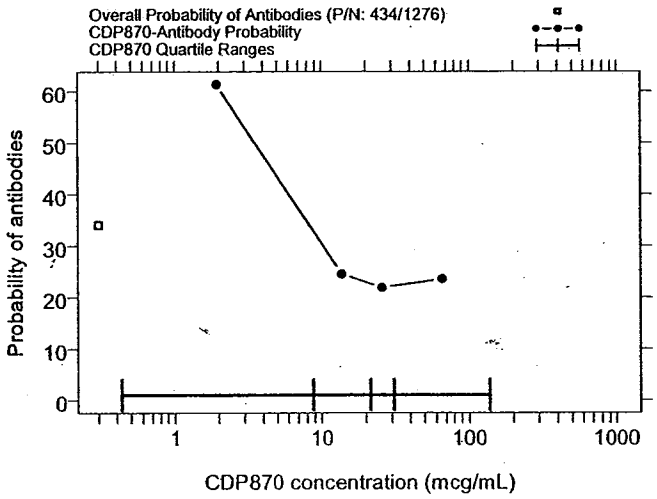

Figure 13 Probability of antibodies vs. CDP870 steady state concentration.

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Dropout Analysis

Longitudinal analysis of the CDAI data in the phase III studies (CDP870-031 and -032) is complicated by a significant dropout due to the lack of effectiveness, i.e. see **Figure 14)** where the percentage of patients remaining in the trial is plotted against time stratified on the ΔCDAI score at final visit.

Patients seem to be dropping out of studies CDP870-031 and CDP870-032 due to worsening of symptoms. The overall dropout rate is about 40%, and the dropouts are not missing completely at random, rather they are correlated with the ΔCDAI score. In particular, 90% of patients with ΔCDAI score > 54 drop out by Week 26 in study CDP870-031, whereas only 5% of those patients with ΔCDAI score < -135 drop out of the study by Week 26. Similar trend was observed in Study CDP870-032 as well.

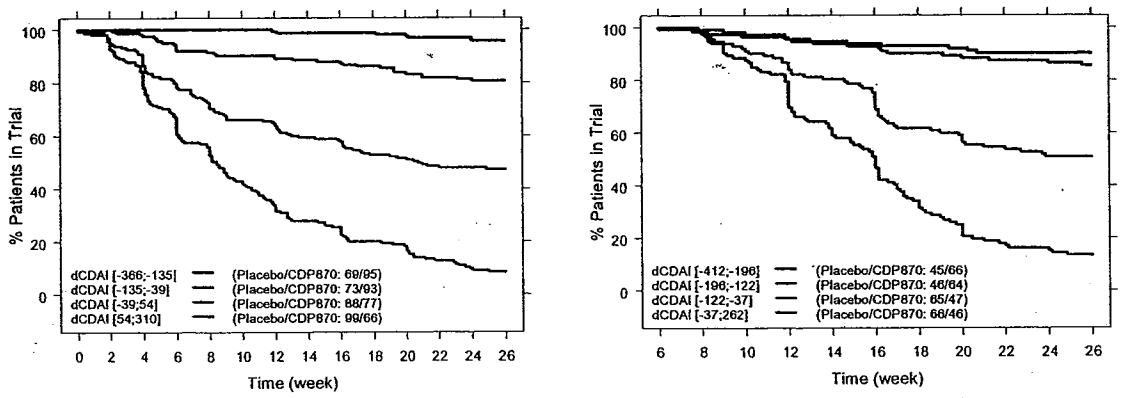

Figure 14 Dropout stratified on baseline corrected CDAI score at final visit for studies CDP870-031 (**left**) and CDP870-032 (**right**).

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Mixed Model Repeated Measures (MMRM) Analysis

The developed mixed-model repeated measures (MMRM) model is described by:

$$\Delta CDAI = Dose + Visit + Baseline + Dose*Visit$$

The Type 3 tests of fixed effects are shown in **Table 7** for study CDP870-031 and **Table 8** for study CDP870-032. The interaction term between dose and visit (Dose*Visit) is not significant in CDP870-031 while all other parameters are significant on a 5% significance level.

Table 7 Type 3 tests of fixed effects for mixed-model repeated measures (MMRM) analysis of study CDP870-031.

	DF	F value	Pr > F
Visit	8	20.73	<0.0001
Dose	1	8.95	<0.0029
Baseline	1	51.30	<0.0001
Dose*Visit	8	1.80	0.0755

Table 8 Type 3 tests of fixed effects for mixed-model repeated measures (MMRM) analysis of study CDP870-032.

	DF	F value	Pr > F
Visit	8	106.13	<0.0001
Dose	1	10.80	<0.0011
Baseline	1	128.35	<0.0001
Dose*Visit	8	3.34	0.0060

The median observed baseline corrected CDAI scores are shown in **Figure 15** (top) while the least squares (LS) mean estimates from the MMRM analysis are shown in **Figure 15** (bottom) for studies CDP870-031 (left) and CDP870-032 (right). There seems to be a significant difference in the change in baseline corrected CDAI scores over time for studies CDP870-031 and -032 where clinical response (i.e. DCDAI≤ -100) for active treatment is achieved at week 24 for study CDP870-031 (double-blind) and at week 4 for study CDP870-032 (open-label until week 6). It is unclear what is causing this observed difference.

The LS mean predicted baseline corrected CDAI score at week 26 is approx. 30 points lower for active treatment compared to placebo for both studies.

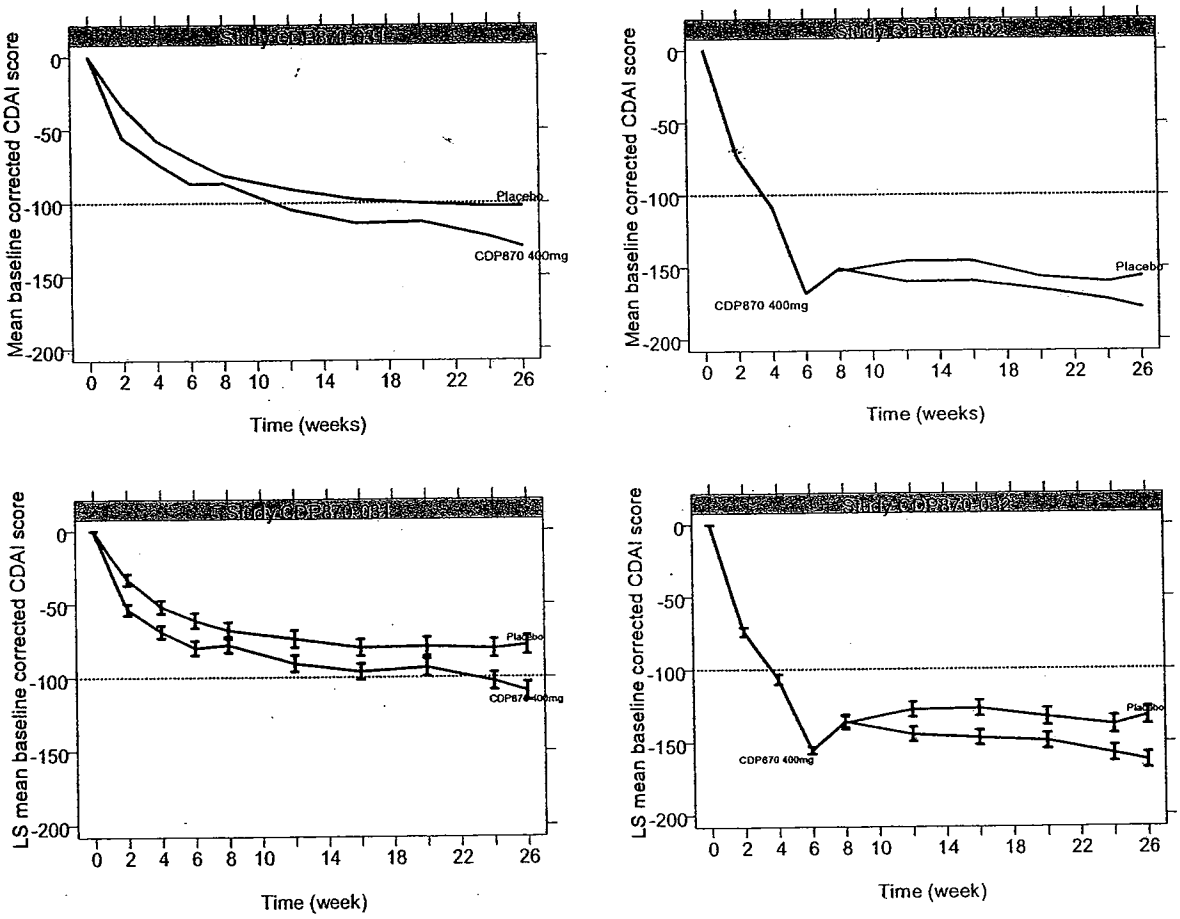

Figure 15 Observed median (**top**) and LS mean predicted (±SE) (**bottom**) baseline corrected CDAI score for study CDP870-031 (**left**) and CDP870-032 (**right**).

Longitudinal Model of Change in CDAI Score

The longitudinal modeling of change in CDAI score is used to impute the missing CDAI scores at final visit with likelihood-based predictions.

The developed longitudinal model for the change in baseline corrected CDAI score (ΔCDAI) over time is described by the equation below:

$$\Delta CDAI(t) = CDAI_{max,i} * (1 - \exp(-k_i * t)) + \varepsilon_{ij}$$

where

$$CDAI_{max,i} = CDAI_{max,Slope} * BSL_i + \eta_{CDAImax,i}$$

$$k_i = k * \exp(\eta_{k,i})$$

with BSL_i being the observed baseline CDAI score for subject i which was identified as the only significant covariate.

By this model, the baseline corrected CDAI score can increase or decrease over the time to reach the maximal effect, $CDAI_{max}$. The rate constant k is the first-order rate constant of baseline corrected CDAI score change over time. The inter-individual variability (IIV) for maximal CDAI effect ($CDAI_{max}$) and the residual variability were assumed to be normally distributed, whereas for rate of CDAI score changes from baseline (k) a log-normal distribution was assumed. Missing data were not imputed using last observation carry forward (LOCF) for estimation. The data was modeled by NONMEM VI and FOCE method was used (see section 0 for NONMEM control stream). The estimated parameters are presented in **Table 9** .

Table 9 Longitudinal model parameters to describe CDAI score change from baseline over time.

		Population Mean		**Inter-Individual Variability**	
Parameter	**Unit**	**Estimate**	**RSE (%)**	**Estimate**	**RSE(%)**
$CDAI_{max,Slope}$	[-]	-0.322	2.46	86.8 (SD)	4.16
k	[$Week^{-1}$]	0.441	4.26	86.6% (CV%)	8.03
Residual error (SD)	[-]	48.0	1.65	-	-

The maximum CDAI score ($CDAI_{max}$) is estimated to decrease by -0.32 by an increase of 1 in baseline CDAI score. The model thereby suggests that patients with high CDAI scores are more likely to get better than subjects with low CDAI scores. The time to reach the maximal effect is about 6 weeks, i.e. $4*t_{1/2}=4*\log(2)/0.441\ week^{-1}= 6.3$ weeks.

The goodness-of-fit plots in Appendix 0 (**Figure 29**) suggest that the model has a slight tendency to over predict the higher ΔCDAI scores.

The estimated relationship between $CDAI_{max}$ and baseline CDAI score is shown in **Figure 16**.

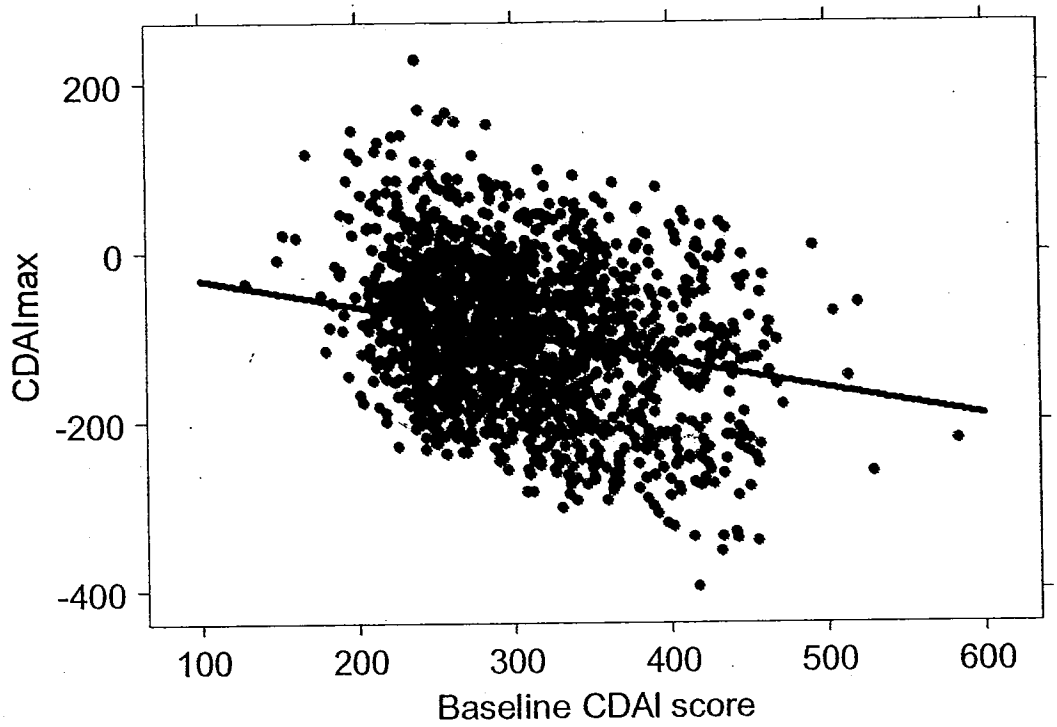

Figure 16 Estimated $CDAI_{max}$ (blue dots) and model predicted relationship between $CDAI_{max}$ and baseline CDAI score (solid red line).

For patients that dropped out before week 6/26, their CDAI score at week 6/26 is imputed with the individual estimated CDAI scores at week 6/26. This method is referred to as the likelihood-based imputation (LBI) method in the exposure-response analysis in the following section.

Exposure-Response Analysis

The probability of clinical response (defined as ΔCDAI < -100) is clearly dependent upon the CDP870 concentration. Patients having lower concentrations (e.g., less than 10 mcg/mL) exhibit lower response rates (see **Figure 17**). The exposure-response relationship using baseline observation carried forward (BOCF), last observation carried forward (LOCF), and likelihood-based imputation (LBI) methods are shown in Appendices.

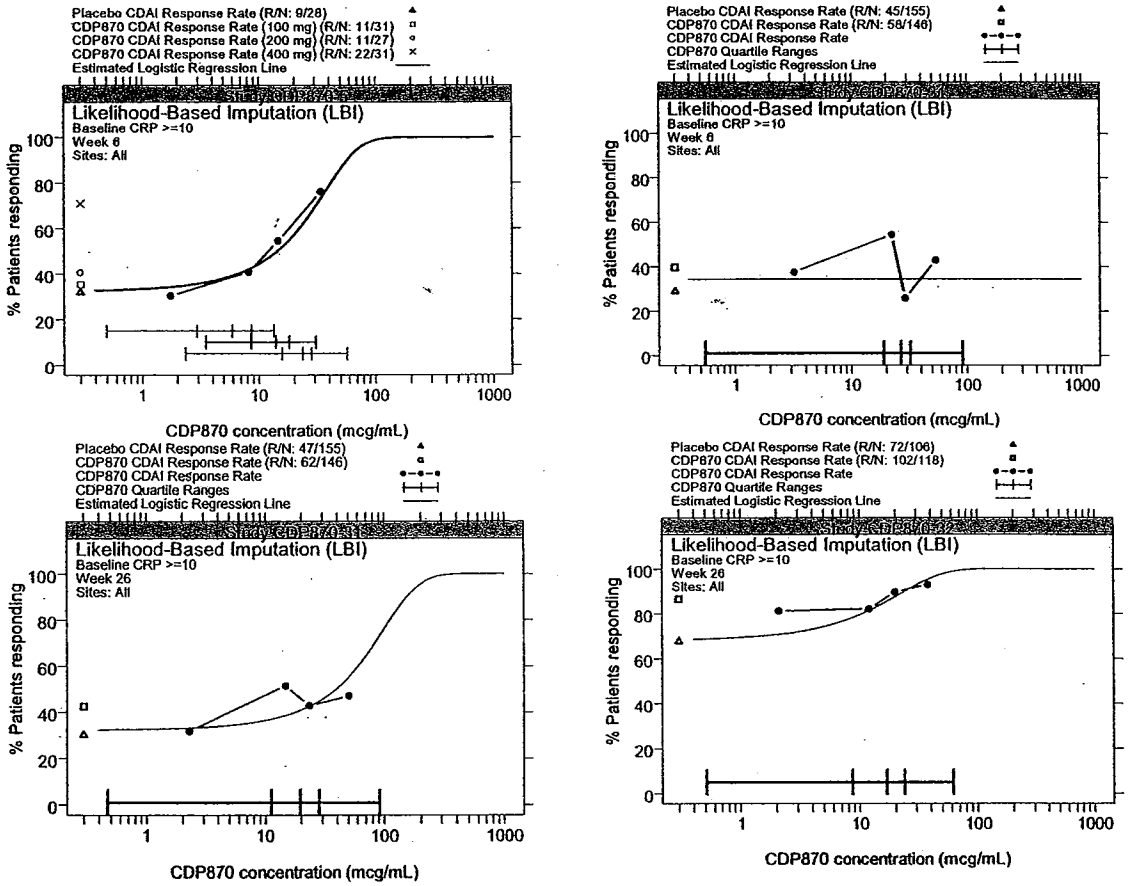

Figure 17 Exposure-response for studies CDP870-005 week 6 (**top left**), CDP870-031 week 6 (**top right**) and week 26 (**bottom left**), and CDP870-032 at week 26 (**bottom right**).

When exposure is highly variable and there is a dependence of response on exposure, then it is important to individualize each patient's dose in order to attain the full potential for efficacy.

There does not seem to be a significant exposure-response relationship for the US sites in study CDP870-031 and CDP870-032 (see **Figure 18**).

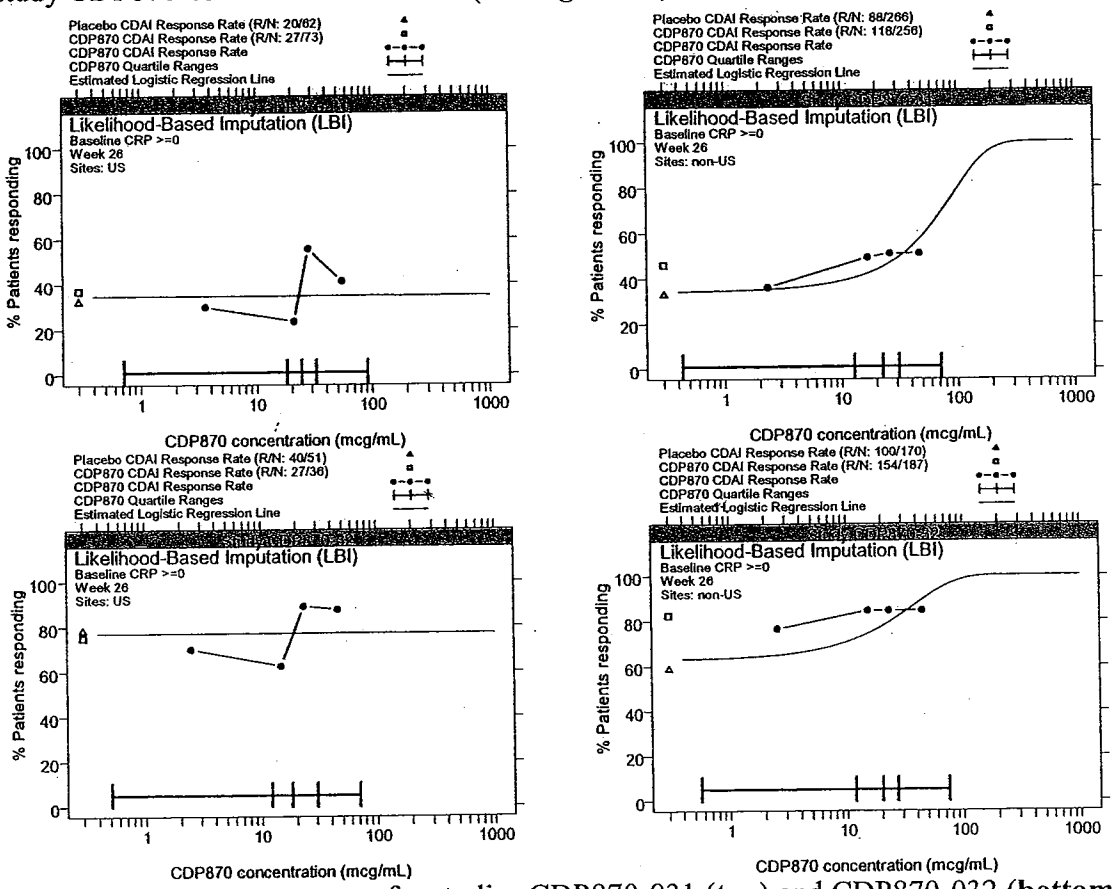

Figure 18 Exposure-response for studies CDP870-031 (**top**) and CDP870-032 (**bottom**) at week 26 for US (**left**) and non-US (**right**) sites.

Since the exposure is similar between non-US and US sites (i.e. between 0.5 and 80 mcg/mL), the reason for not seeing a exposure-response relationship for the US population might be due to lower sensitivity to CDP870 and/or a different background treatment resulting in a higher placebo response rate.

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Exposure-Safety Analysis

There does not seem to be a relationship between dose/concentration and the serious adverse events, serious infections, urinary infection rates, and herpes viral infections rate (see **Figure 19** and **Figure 20**). It therefore seems reasonable to evaluate higher than 400 mg dose for future studies from both efficacy and safety point of view.

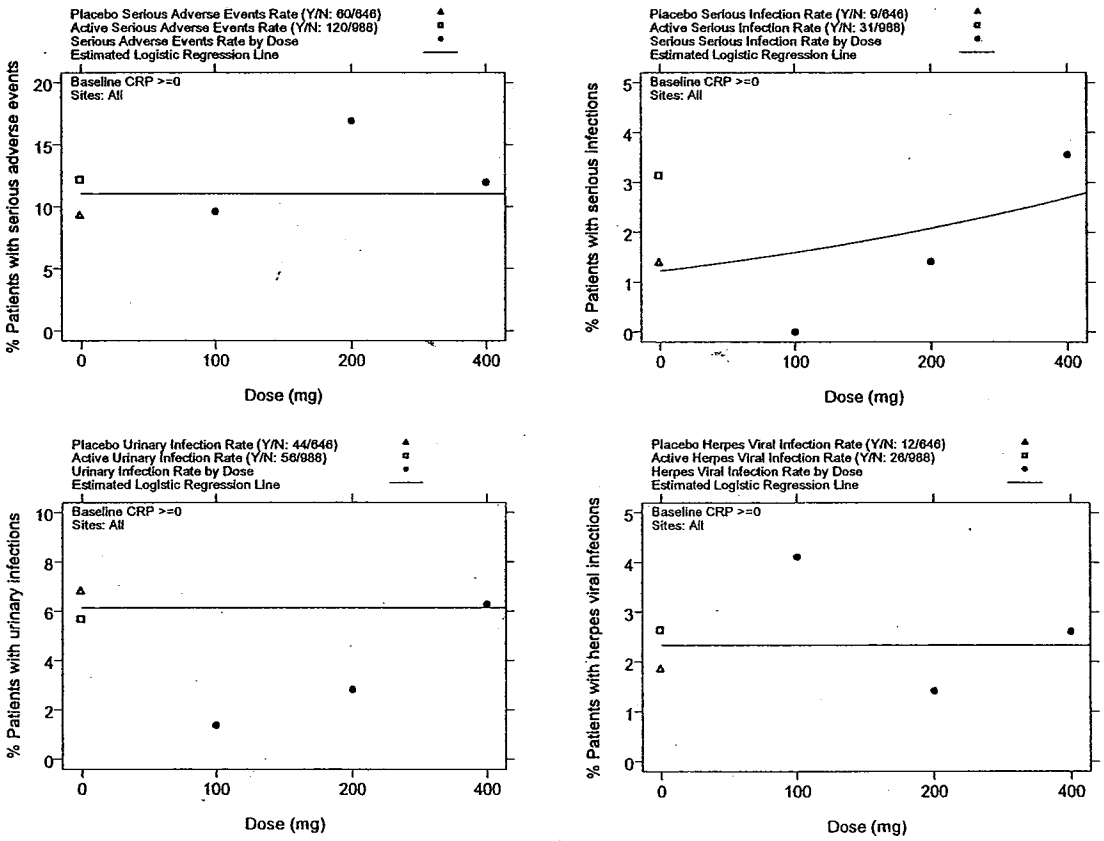

Figure 19 Dose-safety relationship for serious adverse events **(top left)**, serious infections **(top right)**, urinary infections **(bottom left)**, and herpes viral infections **(bottom right)**.

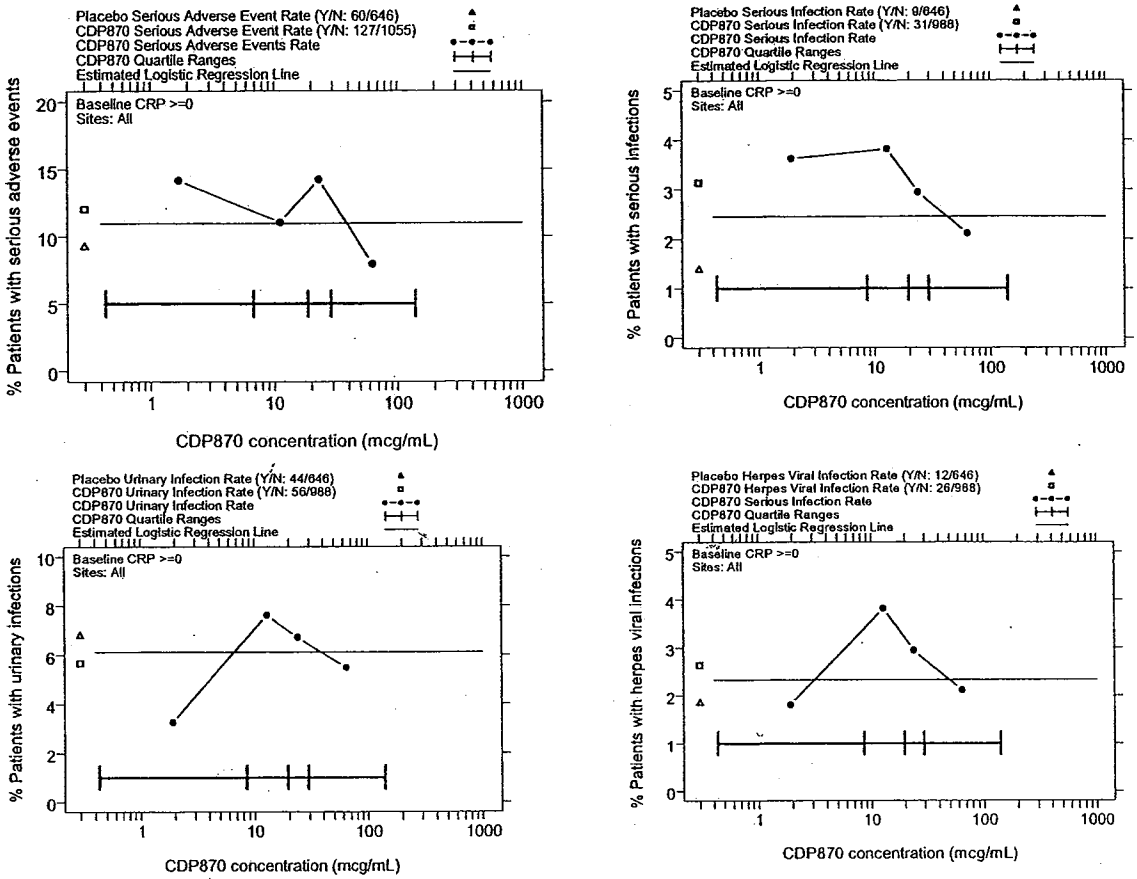

Figure 20 Concentration-safety relationship for serious adverse events (**top left**), serious infections (**top right**), urinary infections (**bottom left**), and herpes viral infections (**bottom right**).

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5.2.7 Sponsor's Population PK Modeling

Background

The Phase II dose finding study in Crohn's disease patients, Study CDP8700-005, confirmed 400 mg per month as the most appropriate dose for progression into Phase III. Analysis of the results from this study suggested that although a dose of 400 mg every 4 weeks was effective, additional response may be achievable. Two key considerations that can impact the efficacy of CDP870 are the attained plasma concentration and occurrence of anti-CDP870 antibody response. PK modeling and simulation was performed to evaluate alternate dosing regimen (s) to achieve increased exposure.

An initial model was developed to generate early exposure during weeks 0-8 utilizing PK data derived from a SC administration of CDP870 in volunteers. The model incorporated the expected modulators of exposure, i.e., immunogenicity and disease effects. Three dosing regimens were simulated in the proposed model – 400 mg 4 weekly (0 and 4 weeks), 400 mg 2 weekly (0, 2 and 4 weeks) and 400 mg 4 weekly with an 800 mg loading dose at week 0. The simulation showed that 400 mg 2 weekly and 800 mg loading dose regimens were predicted to result in higher PK exposure over the 28 and 56-day periods than that predicted for a 400 mg monthly dose regimen. CDP870 400 mg 2-weekly was predicted to achieve this without the large peak to trough ratio observed with the 800 mg dose, effectively "smoothing" drug levels over the 4-week period while retaining a large exposure. Two weekly dosing was also predicted to achieve higher Cmin values and so will be less susceptible to anti-CDP780 antibody effects, maintaining an exposure that may decrease the incidence of subjects mounting an antibody response in the induction period.

As a result of these simulations the following treatment regimens were chosen for the Phase III efficacy studies -031 and -032:

- CDP870 400 mg SC at Weeks 0, 2, 4 and every 4 weeks thereafter.
- Placebo SC at Weeks 0, 2, 4 and every 4 weeks thereafter.

Study objectives
The primary objectives of the retrospective population pharmacokinetic analysis were:

• To characterize the pharmacokinetics of certolizumab pegol in the CD population, including estimation of the inter-subject variability in the main pharmacokinetic parameters, using data pooled from 8 clinical trials (4 trials performed in Crohn's disease patients, 3 in healthy volunteers and 1 in RA patients).

• To identify important demographic and/or physiologic determinants of certolizumab pegol disposition, including, if possible, renal and hepatic function marker in CD population.

These objectives were achieved through population pharmacokinetic modeling of CDP870 concentration-time data, using a non-linear mixed-effects model.

Methods

Data

The different study designs are summarized in **Table 10**.

Table 10 Summary of Study Designs.

Study number	Type	Subject N° total/active Population	Route, Dose and Formulation	PK sampling scheme
001	Human pharmacology	16 /12 Healthy	IV: 0.3, 1, 3, 10 mg/kg Single dose, 20 mg/mL Sln	Rich
003	Human pharmacology	30/30 Healthy	IV: 1 mg/kg, 20 mg/mL Sln Sc: 20, 60, 200 mg Single dose, 200 mg/mL Sln	Rich
004	Therapeutic exploratory	322/242 RA	Sc: 50, 100, 200, 400, 600, 800 mg, 4-weekly dosing 200 mg/mL Sln	Sparse
005	Therapeutic exploratory	292/219 CD	Sc: 100, 200, 400 mg 4-weekly dosing 200 mg/mL Sln	Sparse
008	Therapeutic exploratory	92/68 CD	IV: 1.25, 5, 10, 20 mg/kg Single dose 200 mg/mL Sln	Rich
024	Human pharmacology	48/36 Healthy	Sc: 100, 400, 800 mg Single dose, Lyo. Powder	Rich
031	Therapeutic confirmatory	662/333 CD	Sc: 400 mg Week 0, 2, 4, then 4-weekly, Lyo. Powder	Sparse
032	Therapeutic confirmatory	668 CD	Sc: 400 mg Week 0, 2, 4, then 4-weekly, Lyo. Powder	Sparse
Total		**2130/1608**		

Methods for Data Evaluation:

The association between various covariates and pharmacokinetic parameters (CL, Vc, Ka and F) was examined.

CDP870 was administered subcutaneously from a lyophilized formulation (Studies 031, 032 and 024), a liquid formulation at 200 mg/mL (Studies 003, 004, 005 and 008) and intravenously from a liquid formulation at 20 mg/mL (Studies 001 and 003). Doses of 19.2 to 2176 mg were administered as single dose, every 4 weeks (Studies 004 and 005) or at week 0, 2, 4 then every 4 weeks (Studies 031 and 032).

The subjects received a single dose of CDP870 (Studies 001, 003, 008, 024) or multiple dosing regimens for 8 weeks (Studies 004 and 005) or 24 weeks (Studies 031 and 032).

Data from 1580 subjects were obtained and used in the population analysis. There were 1268 Crohn's disease, 78 healthy and 234 Rheumatoid Arthritis subjects, 688 males and

892 females with the following means (range) demographic covariates: 70 (36-151) kg, 24 (13-56) kg/m², 39 (18-73) years old.

CDP870 plasma concentration data from 1580 subjects were used for non linear mixed effects modeling by extended least squares regression using the NONMEM software with double precision and first-order (FO) estimation. A 2-compartment open model with infusion time in the depot compartment, first order absorption and elimination and a baseline concentration was fitted to the plasma profiles. Inter-individual variability was set on each structural parameter (absorption rate (ka), infusion time in depot compartment (D1), bioavailability (F), clearance (CL), central volume of distribution (Vc) inter-compartment microconstants (k23, k32) and baseline). Inter-occasion variability (IOV) was set on CL and a proportional error model for residual variability was used. Log-normal distribution of the pharmacokinetic parameters in the studied population was assumed. Inter-subject variability (% CV) in each pharmacokinetic parameter was calculated as the square root of the variance for the respective parameter × 100.

Analysis Strategy

The analysis strategy applied in the population pharmacokinetic analysis of CDP870 is illustrated in **Figure 21**.

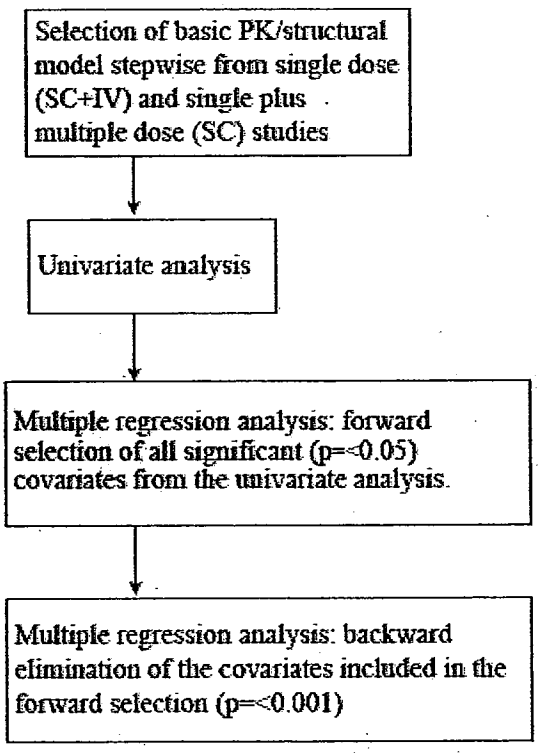


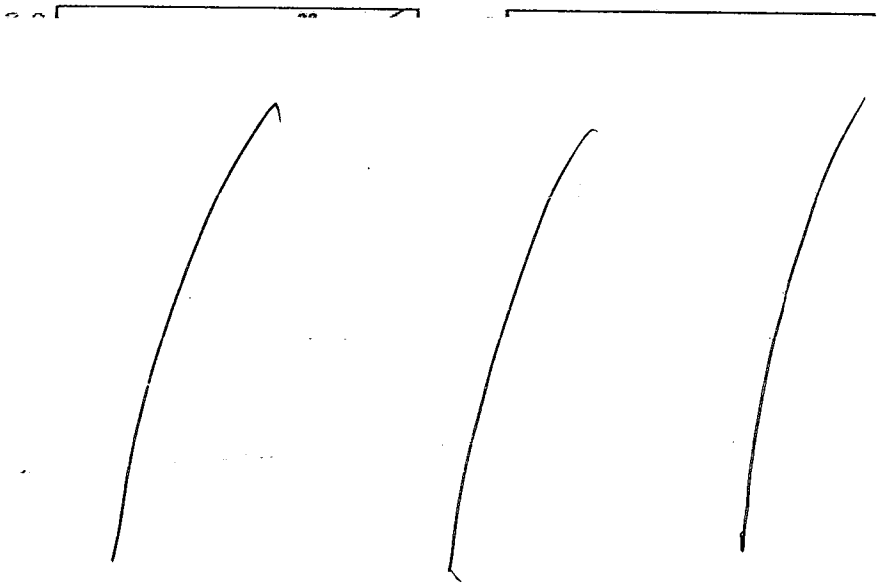
Figure 21 Population Pharmacokinetic Analysis Strategy.

Results

Selection of Basic/Structural Model

The basic model consisted of the pharmacokinetic parameters, inter-subject variability (ETA) in each parameter, inter-occasion variability on clearance for multiple dose studies and residual variability in drug concentrations (ERR), without any covariate.
Based on data available for CDP870 (mainly IV studies 001 and 003), a 2-compartment linear pharmacokinetic model with first order absorption (ka) was tested to establish the structural model:

The model was expressed in terms of Vc, CL, F, ka and inter-compartment rate constants. The initial analysis for the population pharmacokinetics of CDP870 conducted without including any subject covariates led to the BASE 1 model. The outliers (defined as data records giving weighted residuals >6 or <-6) were temporarily removed from the dataset at this stage. The resulting minimum value of the objective function (OBJ1) from this model was then used as the reference in the subsequent univariate analyses. The outliers were reintroduced in the dataset after the multiple regression analysis, for estimation of the parameters of the FINAL model. The main diagnostic plots are also shown in **Figure 22** and **Figure 23** and parameter estimates in **Table 11**.



(Lin-Lin and Log-Log scale, — unity line, — Loess smooth)

Figure 22 Observed CDP870 Concentrations vs Population Predicted Concentrations from the BASE 1 Model.

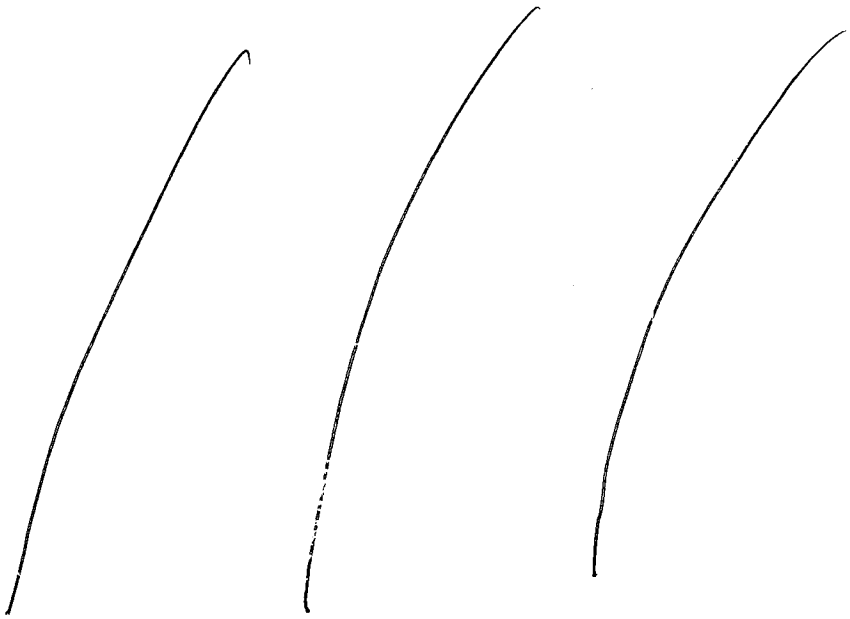


Figure 23 Weighted Residuals vs Population Predicted Concentrations of CDP870 Concentrations and vs Time after First Dose from the BASE 1 Model.

Table 11 Parameter Estimates from the BASE 1 Pharmacokinetic Model for CDP870

Parameter	Estimate[95% CI]	Precision (%CV)[a]
Θ_F	0.78 [0.70 – 0.85]	4.97
Θ_{ka}	0.326 [0.253 – 0.399]	11.4
Θ_{D1}	0.274 [0.224 – 0.324]	9.31
Θ_{CL}	0.443 [0.398 – 0.488]	5.19
Θ_{Vc}	3.48 [3.21 – 3.75]	3.97
Θ_{K23}	0.178 [0.116 – 0.240]	17.8
Θ_{K32}	0.328 [0.216 – 0.440]	17.4
Θ_{BAS}	1.02 [0.925 – 1.12]	4.76
Inter-subject variability in F (%CV)[b]	25.4	20.1
Inter-subject variability in k_a (%CV)[b]	48.6	44.1
Inter-subject variability in D1 (%CV)[b]	111	53.8
Inter-subject variability in CL (%CV)[b]	35.1	9.11
Inter-occasion variability in CL (%CV)[b]	22.0	12.0
Inter-subject variability in Vc (%CV)[b]	21.6	20.4
Inter-subject variability in k_{23} (%CV)[b]	0.09	1.4×10^{7}
Inter-subject variability in k_{32} (%CV)[b]	21.8	183
Inter-subject variability in BAS (%CV)[b]	67.8	11.8
Residual variability in concentration (%CV)[b]	28.4	6.53

[a] Precision was calculated as the s.e. divided by the parameter estimate × 100.
[b] The %CV for both inter-subject and residual variability is an approximation taken as the square root of the variance × 100.

Covariates Exploration of the Base Model

The correlations between the main pharmacokinetic parameters, CL, Vc, ka, F and the covariates were graphically explored (see **Figure 24**). The main correlations were those of CL and Vc with the anti-CDP870 antibodies. CL and Vc did not seem to be correlated with weight but the bioavailability parameter F clearly was. As these three parameters are correlated with each other, it was not possible at this stage to determine which one was the most correlated to the weight. No other major correlations appeared from this graphical analysis. Particularly, CL and Vc were not correlated to the dose.

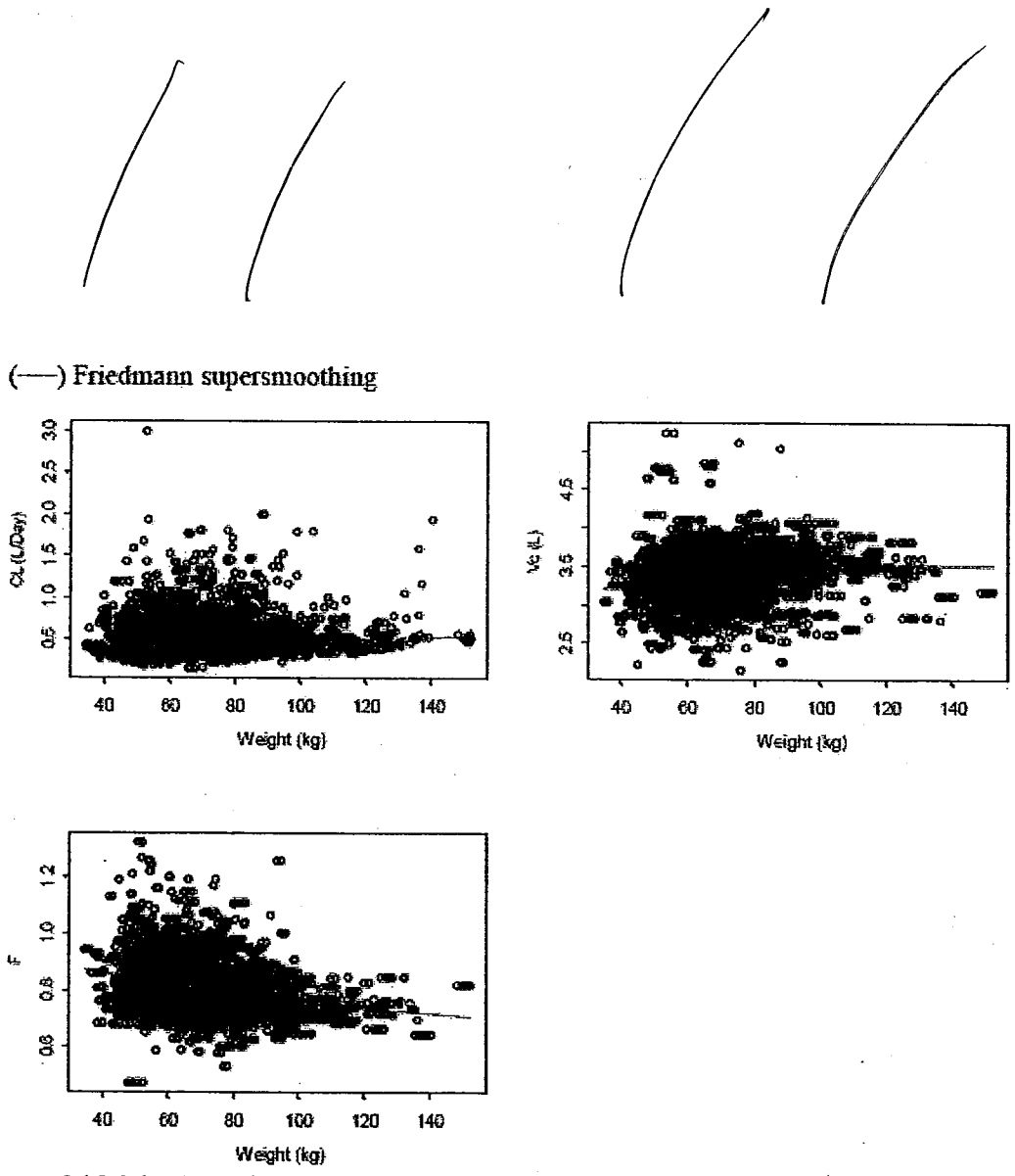


Figure 24 Main Covariates Correlated to the Pharmacokinetic Parameters in the BASE 1 Model

Univariate Analysis

The effects of the covariates age, weight, height, BSA, BMI, gender, ethnicity, CLcr, anti-CDP870 antibody on CL were evaluated through a power model and the effect of white blood cells and monocytes count through an additive model as some values of the monocytes count were at 0, hence not allowing a power model. For the categorical covariates such as liver dysfunction, concomitant medications, multiple dosing,, laboratory and health status the effect was evaluated through a multiplicative model as described hereunder.

The typical population values for CL, Vc, ka and F were centered for the typical adult covariate values, i.e. age = 40 years, weight = 70 kg, BSA = 1.73 m^2, BMI = 24 kg/m^2, white blood cells count = $7.5x10^9$/L, monocytes count = $0.4x10^9$/L and CLcr = 100 mL/min. These values were very close to the actual means/medians of the analysis dataset.

The effect of the covariates was considered statistically significant if they decreased the objective function value by more than 3.84 ($p \leq 0.05$) in comparison with the BASE 1 model and if the 95% confidence interval of their THETA estimate did not span over the null hypothesis value, e.g. the value of 1 for a multiplicative factor.

Multiple Linear Regression with Forward Selection and Backward Elimination

All significant covariates of the univariate analysis were added to the model one by one and an objective function value was obtained for each covariate (see **Table 12**). The Base model added with the covariate resulting in the most important decrease of the objective function was called the BASE 2 model and its objective function value OBJ2. All the remaining significant covariates of the univariate analysis were added to the BASE 2 model one by one and a new objective function was obtained for each of them. A BASE 3 model was selected in the same way as the BASE 2 model. The process was repeated until all covariates resulting in a significant decrease of the objective function ($\Delta OBJ > 3.84$, $p \leq 0.05$) were included in the model. This model was called the BASE X model.

Table 12 Summary of the Forward Covariate Selection in the Multiple Regression Analysis.

Test	ΔOBJF[a])	THETA value
BASE 1 + anti-CDP870 antibodies on CL	-1642.8	2.68
BASE 2 + dosing occasions on CL	-374.5	1.23
BASE 3 + health status on Vc (HV / RA)	-208.9	0.675/0.721
BASE 4 + weight on Vc	-70.6	0.394
BASE 5 + dosing occasions on Vc	-57.5	0.875
BASE 6 + laboratory on Vc	-81.5	1.27
BASE 7 + weight on CL	-46.9	0.322
BASE 8 + immunosuppressants on Vc	-34.1	1.14
BASE 9 + ethnicity on CL (Asian, Other)	-21.5	0.871/0.802
BASE 10 + health status (RA) on CL	-18.4	0.872
BASE 11 + form on k_a /D1	-15.8	1.54/0.28
BASE 12 + monocytes count on CL	-6.9	0.0133
BASE 13 + sex on F	-8.6	1.05

[a] Difference in objective function value from the previous BASE X model

The covariates were then removed from the BASE X model one at a time and the model run to get an objective function value. The model leading to the weakest deterioration in the regression fit, through the objective function, was declared the BASE X+1 model provided that the increase in the objective function compared to OBJX was smaller than 10.83 for THETA ($p \leq 0.001$), and the corresponding covariate was definitely withdrawn from the model. The remaining covariates were removed one at a time from the BASE X+1 similarly to the previous step. This process was repeated until the removal of each covariate from the BASE X+Y model led to an increase of the objective function value equal or greater to 10.83 ($p \leq 0.001$).

The log-Likelihood ratio was used to assess whether the difference in the objective function between the base model and the more complex model statistically improved the fit of the model to the data. A decrease in the objective function ($\Delta OBJF$) > 3.84 (based on the log-Likelihood ratio which is approximately χ^2 distributed) when compared to the BASE 1 model was considered significant ($p = 0.05$) for inclusion of the covariates from the univariate analysis into the BASE 2 model. An increase in the objective function ($\Delta OBJF$) > 10.83 when compared to the BASE X model was considered significant ($p \leq 0.001$) for keeping the covariate in the final model from the multiple regression analysis with backward deletion.

Final Pharmacokinetic Model

After all covariates had been removed from the model through the multiple regressions with backward deletion, the 95% CI of the THETAs for the remaining covariates were inspected to determine whether they significantly affected the model. The not significant covariates had to be removed one at a time starting with the one with the weakest effect on the objective function. When all the remaining THETAs were significant, the model was declared the FINAL model.

For the final estimation of parameters, the model was rerun on the full dataset after reintroducing the outlying data that had been excluded right before the univariate analysis step. The parameter estimates were very close to those obtained without the outliers. The main differences were observed for antibody effect on CL and for k23 and k32 estimates. The clearance increase in presence of antibody was 3.6-fold without and 4.1-fold with outliers (a 12% difference). The differences in k23 and k32 estimates were of 15% and 17% respectively but the difference in their ratio was only of 2%. The difference in all the other parameters was less than 6%.

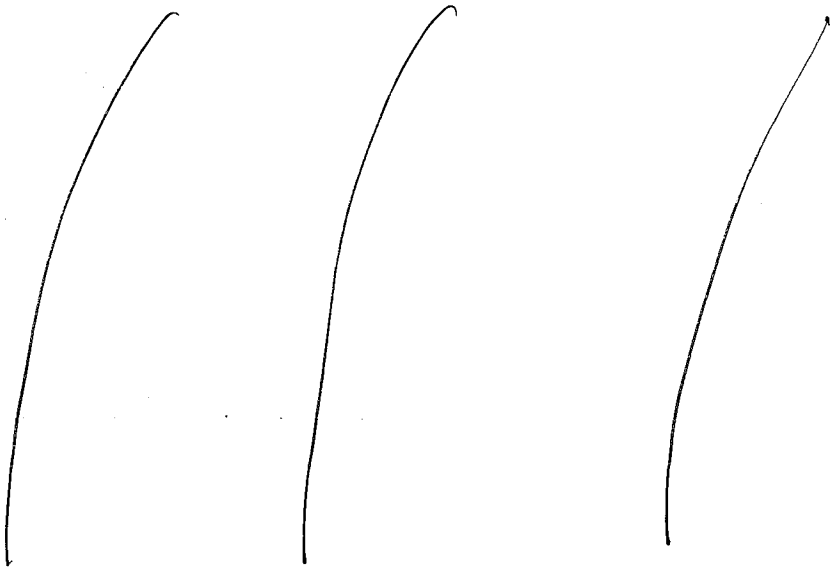


Figure 25 Observed vs Population and Individual predicted CDP870 Concentrations from the Final Model (Lin-Lin and Log-Log Scale)

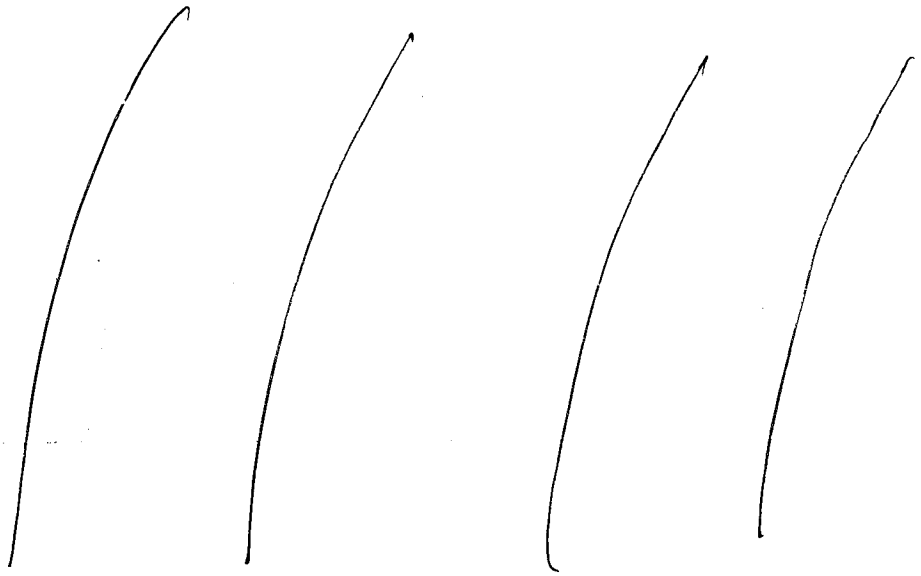


Figure 26 Weighted Residuals vs Population Predicted CDP870 Concentrations and vs Time after First Dose from the Final Model (Lin-Lin and semi-Log scale)

Overall, the fit of the observed individual concentration time profiles with the individual predicted concentration was good. **Table 13** presents the final parameter estimates from the final pharmacokinetic model for CDP870.

The reference population for CL is a Crohn's disease Caucasian subject with a weight of 70 kg and monocyte count of 0.4×10^9/L. The reference population for Vc is a Crohn's disease subject with a weight of 70 kg who did not receive an immunosuppressant therapy, and samples assayed by laboratory 1.

Table 13 Parameter Estimates from the Final Pharmacokinetic Model for CDP870

Parameter	Estimate[95% CI]	Precision (%CV)[a]
Θ_F	0.85 [0.78 – 0.93]	4.68
Θ_{ka}	0.256 [0.195 – 0.317]	12.1
Θ_{D1}	0.282 [0.215 – 0.349]	12.2
Clearance		
Θ_{CL}	0.414 [0.375 – 0.453]	4.86
$\Theta_{ABFL,CL}$	4.08 [3.36 – 4.80]	8.95
$\Theta_{MD,CL}$	1.35 [1.28 – 1.42]	2.50
$\Theta_{WT,CL}$	0.309 [0.176 – 0.442]	22.0
$\Theta_{OTHR,CL}$	0.842 [0.757 -0.927]	5.13
$\Theta_{RA,CL}$	0.862 [0.780 – 0.944]	4.84
$\Theta_{Mono,CL}$	0.014 [0.004 – 0.024]	35.6
Volume		
Θ_{Vc}	4.00 [3.68 – 4.32]	4.05
$\Theta_{WT,Vc}$	0.511 [0.379 – 0.643]	13.2
$\Theta_{RA,Vc}$	0.793 [0.712 – 0.874]	5.23
$\Theta_{HV,Vc}$	0.703 [0.641 – 0.765]	4.50
$\Theta_{MD,Vc}$	0.850 [0.810 – 0.890]	2.41
$\Theta_{CVAN,Vc}$	1.27 [1.17 – 1.37]	4.14
$\Theta_{IS,Vc}$	1.16 [1.09 – 1.23]	3.25
Other pharmacokinetic parameters		
Θ_{K23}	0.174 [0.092 – 0.256]	24.0
Θ_{K32}	0.296 [0.184 – 0.408]	19.3
Θ_{BAS}	1.02 [0.946 – 1.09]	3.71
Inter and intra-subject variability		
Inter-subject variability in F (%CV)[b]	15.6	45.5
Inter-subject variability in k_a (%CV)[b]	53.6	39.0
Inter-subject variability in D1 (%CV)[b]	120	52.6
Inter-subject variability in CL (%CV)[b]	38.3	9.52
Inter-occasion variability in CL (%CV)[b]	16.4	21.2
Inter-subject variability in CLAB (%CV)[b]	69.4	21.2
Inter-subject variability in Vc (%CV)[b]	16.9	24.0
Inter-subject variability in k_{32} (%CV)[b]	34.8	40.7
Inter-subject variability in BAS (%CV)[b]	69.9	9.16
Residual variability in concentration (%CV)[b]	25.0	6.35

(a) Precision was calculated as the s.e. divided by the parameter estimate × 100.
(b) The %CV for both inter-subject and residual variability is an approximation taken as the square root of the variance × 100. CLAB is the clearance of AB+ subjects

As seen from the 95% confidence intervals, CL, Vc, F, ka, D1 and Baseline were estimated with a good precision (CV $\leq$ 12.2%). For k23 and k32 the precision of the estimation was moderate (CV of 24 and 19.3%, respectively). The precision of the estimation for the covariates effect ranged from 2.41 to 35.6% CV.

The inter-subject variabilities for ka and D1 were very large and estimated with poor precision. For D1, especially, the parameter was estimated only in healthy volunteers receiving the drug by SC route (n=60). It was however kept in the model because withdrawing it in the final model led to a very bad estimation of k23, k32, its variability as well as the variability of ka.

With the BASE 1 model, the inter-subject variability in Vc, CL and inter-occasion variability of CL were 21.6%, 35.1% and 22.0% respectively (**Table 11**). It was reduced for Vc to 16.9% while for CL the inter-subject variability remained similar at 38.3% and the inter-occasion variability decreased to 16.4% when all the statistically significant covariates were incorporated in the model. The inter-subject variability in F decreased from 25.4 to 15.6% between the BASE 1 and FINAL model. This decrease was due to introducing the weight covariate on both CL and Vc.

A difference in Vc between phase III and other studies was observed irrespective of the laboratory where the assay was performed. This difference is the same as that observed when the assays were performed in one laboratory or the other. Therefore a specific causal relationship to this difference could not be assigned.

Discussion

The main objective of this retrospective analysis was to characterize the CDP870 pharmacokinetics and identify significant covariates in Crohn's disease patients. However, healthy volunteers and rheumatoid arthritis subjects were added in the dataset in order to provide information allowing a proper assessment of some of the pharmacokinetic parameters.

A large number of covariates were tested on clearance, volume of distribution, bioavailability and absorption rate constant. During the univariate analysis, the effects of age, gender, creatinine clearance, white blood cells count and concomitant drug treatment such as steroids, aminosalicylic acid and analogs or anti-infectives were found not significant on all the pharmacokinetic parameters tested, meaning they do not affect CDP870 pharmacokinetics. Therefore, although this analysis did not reveal any impact of liver dysfunction on CDP870 pharmacokinetics, the low number of subjects and the mild severity of the liver dysfunction were not sufficient to draw any definitive conclusion.

After the multiple regression analysis, a statistically significant association was observed between the presence of antibodies against the drug, repeated administration of the drug, body weight, ethnicity, monocyte count, health status and the clearance of CDP870. The antibody positive subjects had a typical clearance approximately 4-fold higher than antibody negative subjects. The clearance of the drug was found 35% higher after repeated administration as compared to single administration in antibody negative subjects. Due to the interference of CDP870 itself with the anti-certolizumab antibody assay an underestimation of the antibody concentration is likely to occur in a number of samples. Some of the subjects could therefore be falsely antibody negative. This might be an explanation for the higher clearance after repeated administration in this population. Caucasians had a typical clearance about 15% higher than non Caucasians. Although the

effect of monocyte count was statistically significant, the clearance was only slightly changed when taking into account the range of this variable in the dataset (-2.4% to +4.3% around the mean value).

When all the statistically significant covariates were used for simulating typical concentration time profiles at steady state in Crohn's disease patients, in reference with a 70 kg subject, only the presence of antibodies led to a change higher than 30% in Cmax, Ctrough and/or AUCτ. The main patient-dependent covariate, after antibodies, was the weight which influenced mainly Cmax which increased by 1.77 fold from 150 to 40 kg. When weight was changed from 70 to 40 kg and from 70 to 150 kg Cmax increases by 27% and decreases by 28% respectively.

Sponsor's Population PK Modeling Conclusions
Finally, the overall conclusions are the following:

- At steady state, in comparison with a 70 kg subject, only the presence of antibodies had a more than 30% effect on Cmax, Ctrough and/or AUCτ. Therefore dose adjustment is recommended for antibody positive patients.

- Repeated administration, weight, monocyte count, immunosuppressant intake and ethnicity had a statistically significant impact on the pharmacokinetics of CDP870 in Crohn's disease patients. However, dose adjustment is not warranted.

- Age, gender, creatinine clearance, white blood cells count and concomitant drug treatment such as steroids, amino-salicylic acid and analogs or anti-infectives did not impact the pharmacokinetics of CDP870.

- No definitive conclusion can be drawn for the effect of liver dysfunction on the pharmacokinetics of the drug because the limited number of patients with liver function abnormalities included in these studies was small.

- A difference in the estimated volume of distribution was observed between Phase III and Phase II studies in Crohn's disease patients which could not be explained by a specific covariate. This difference did not lead to a clinically relevant difference in drug exposure (maximum change of 17% for Cmax).

- Given the safety profile of the drug there were no other patient dependent covariates requiring any dose adjustment of the drug for safety reasons.

5.2.8 Reviewer's Population PK modeling Comments

- *Sponsor's population PK analysis was performed using the first-order (FO) method in NONMEM and not the first-order conditional estimation (FOCE) method which generally gives more reliable parameter estimates. However, the major findings are unlikely to change if the FOCE method had been used.*

- *The covariate modeling strategy is purely driven by statistical methods and does not take into account the mechanistic understanding of the system or visual inspection.*

5.2.9 Reviewer's Population PK Modeling

The following figures illustrate the identified relationship between PK parameters and covariates (see **Figure 27** and **Figure 28**). Only body weight and the presence of anti-CDP870 seems to influence the clearance of CDP870 and hence the steady-state CDP870 concentration. Body weight and the use of immunosuppressant also seem to influence the volume of distribution.

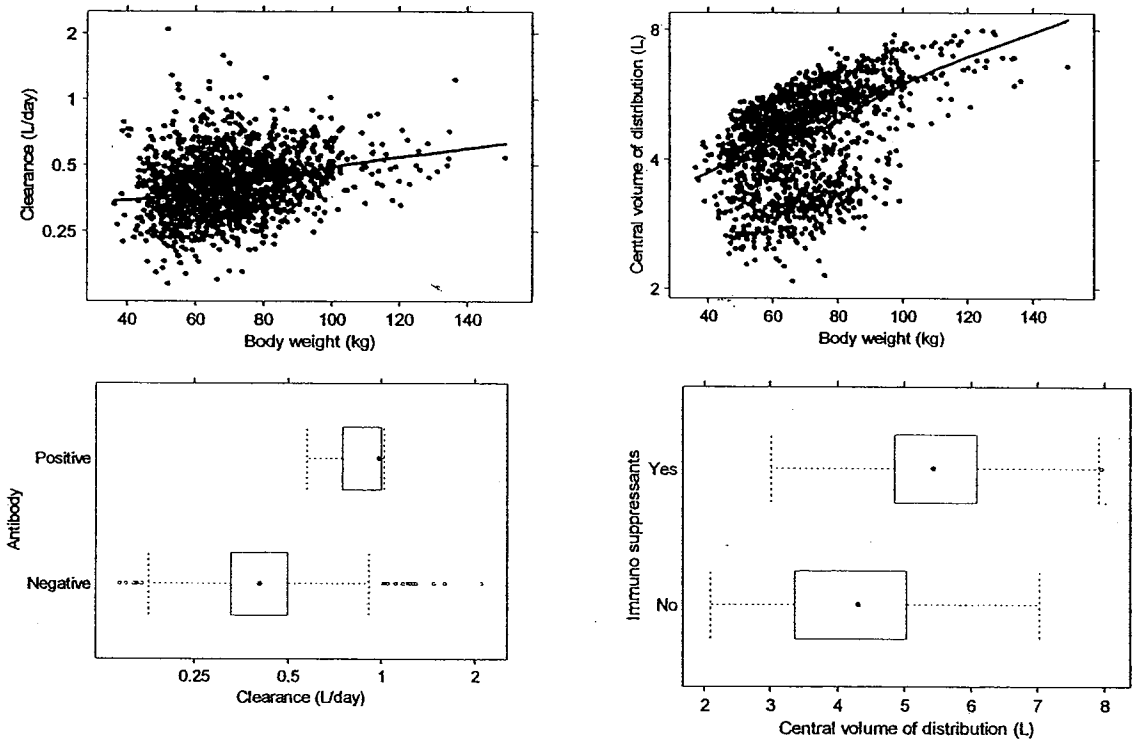


Figure 27 Covariates identified from the covariate modeling which can be confirmed by visual inspection.

Monocyte count, ethnicity, sex, formulation, creatinine clearance, and age could not be identified to be clinical significant based on visual inspection of PK parameter-covariate relationships.

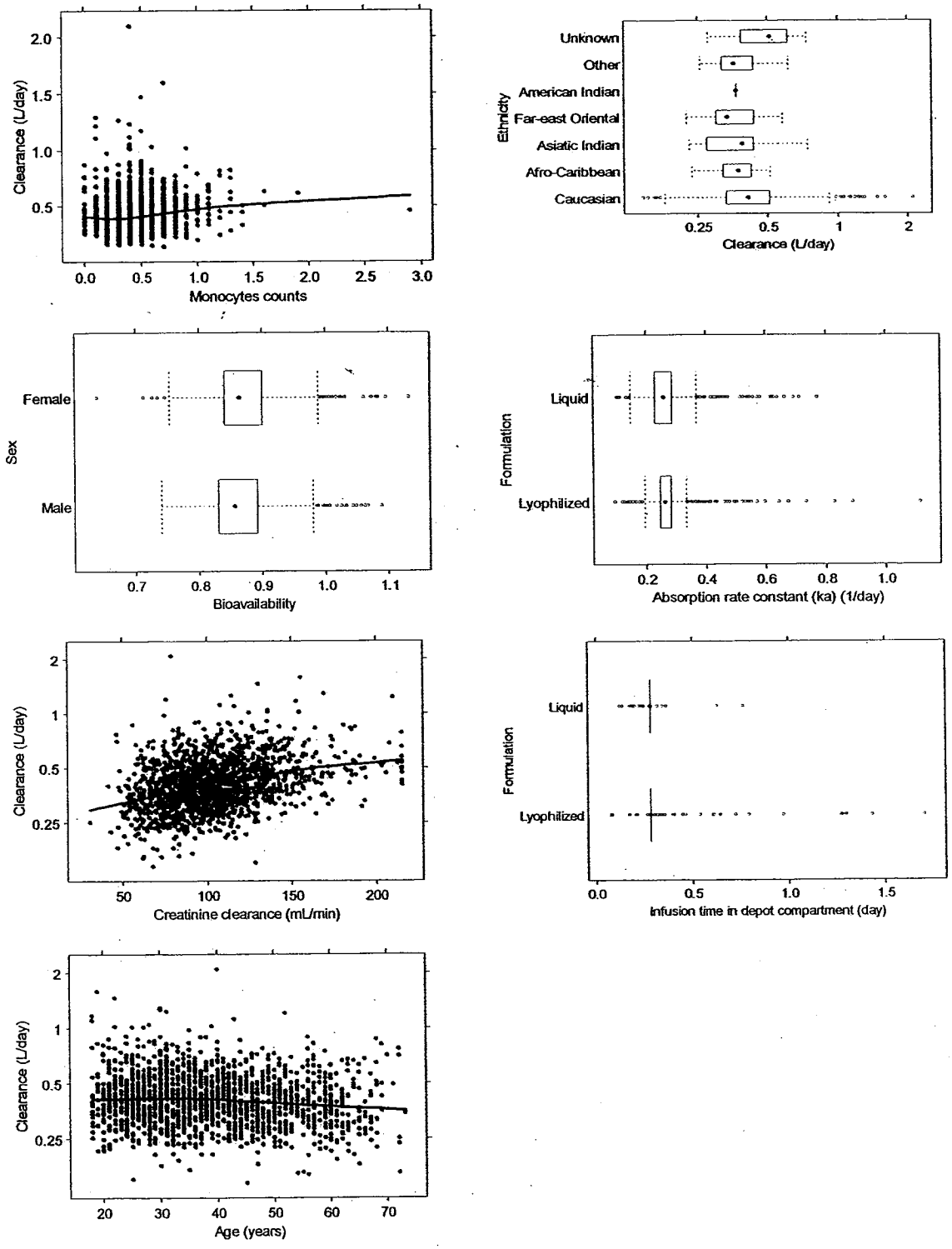


Figure 28 Covariates that do not significantly influence the pharmacokinetics of CDP870.

5.2.10 Pharmacometric Review Conclusions

The overall conclusions for the Pharmacometric review are:

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

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

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

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

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

- *The sponsor should perform clinical trial simulations before the next trial to explore the impact of different analyses techniques on various drug effect sizes and dropout rates. To learn the titration value, increase dose for non-responders. Please discuss with Office of Clinical Pharmacology/Pharmacometrics group.*

7 Page(s) Withheld

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_____ Draft Labeling

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Exposure-Response Plots

Exposure-Response CDP870-005 at week 6

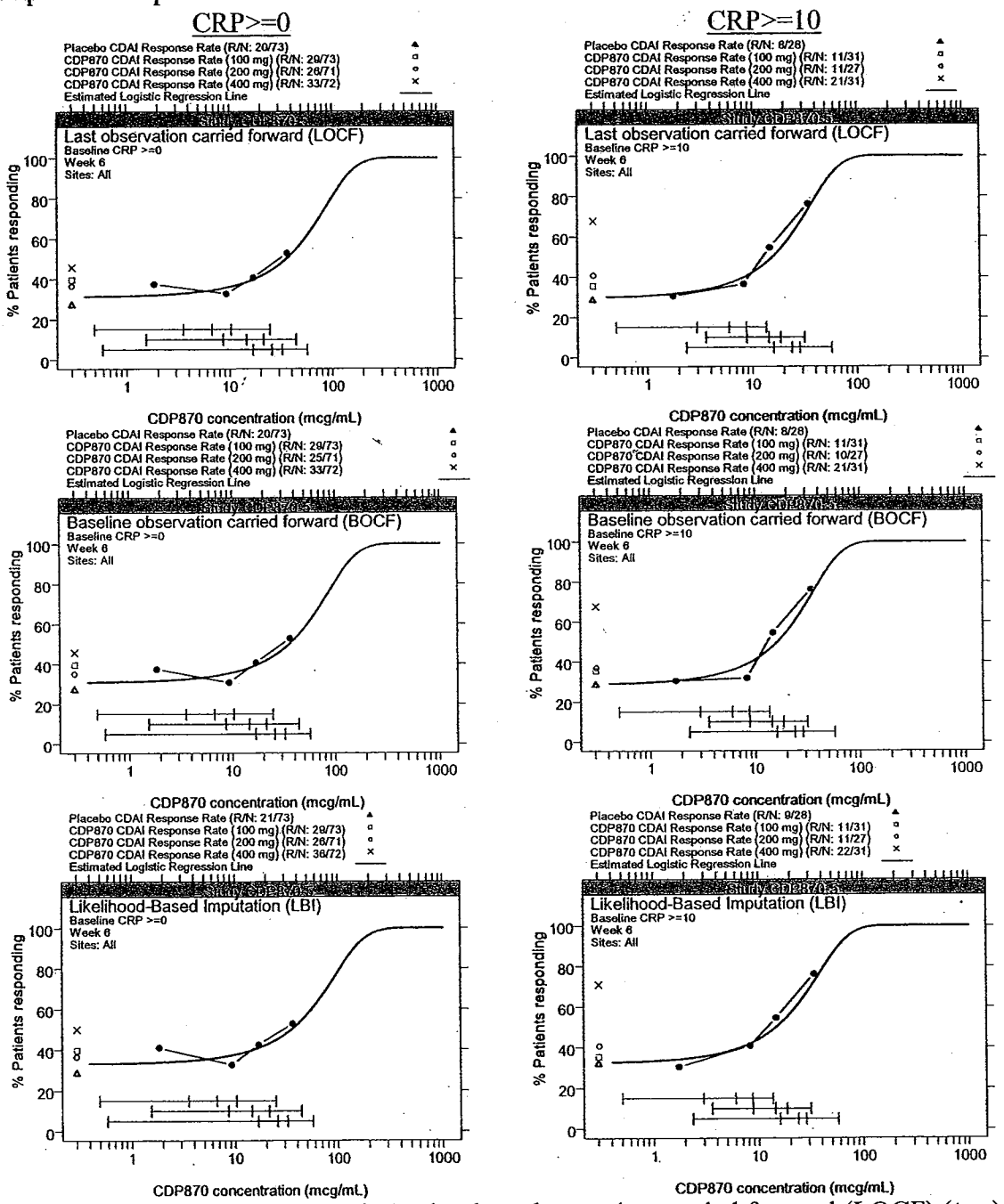

Figure 30 Response rate at week 6 using last observation carried forward (LOCF) (**top**), non-responder imputation (NRI) for missing data (**middle**), and modeling approach (**bottom**) for baseline CRP≥0 (left) and baseline CRP≥10 (right) for study CDP870-005.

Exposure-Response CDP870-008 at week 4

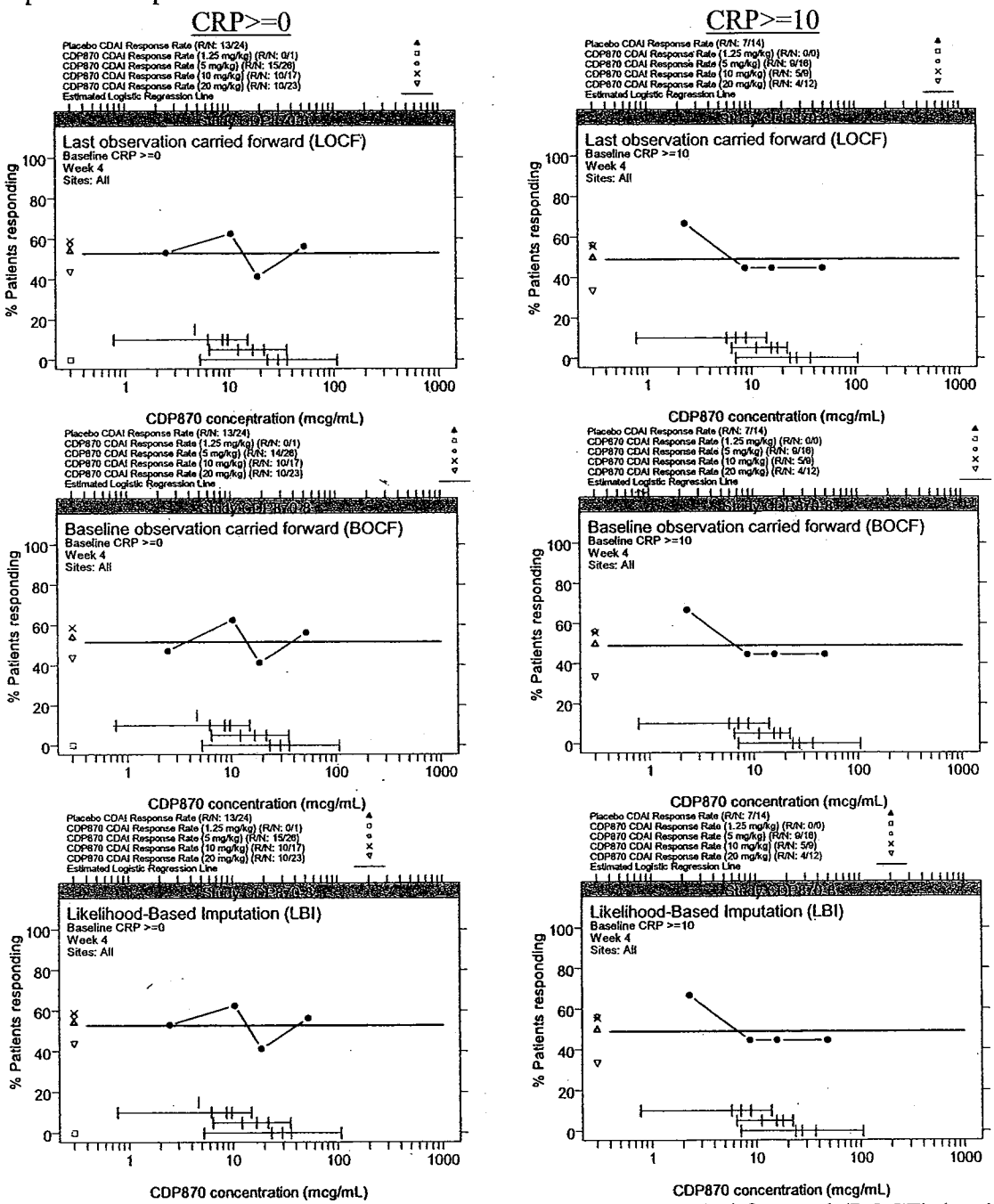

Figure 31 Response rate at week 4 using last observation carried forward (LOCF) (**top**), non-responder imputation (NRI) for missing data (**middle**), and modeling approach (**bottom**) for baseline CRP≥0 (left) and baseline CRP≥10 (right) for study CDP870-008.

Exposure-Response CDP870-031 at week 6

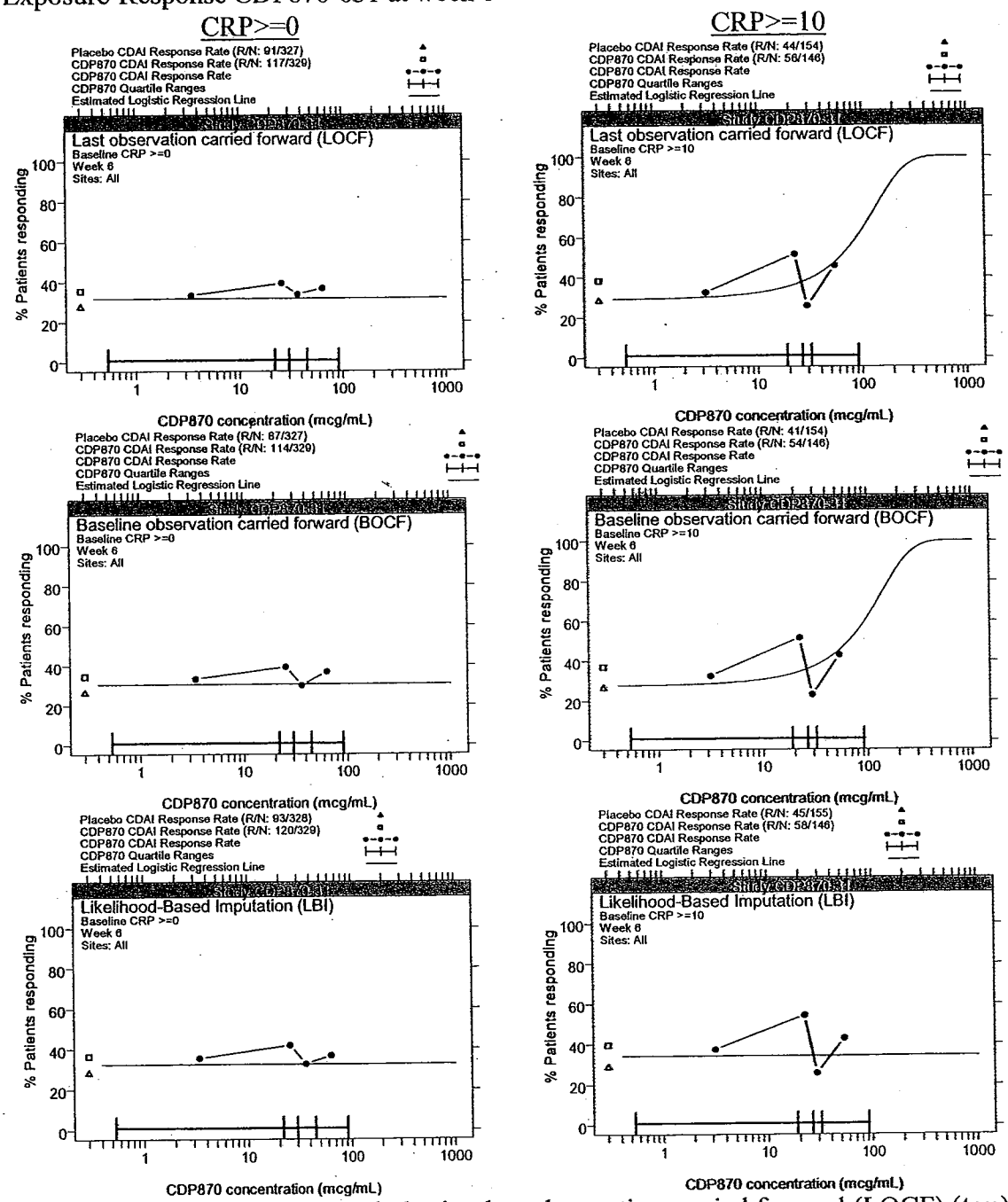

Figure 32 Response rate at week 6 using last observation carried forward (LOCF) (**top**), baseline observation carried forward (BOCF) (**middle**), and likelihood-based imputation (LBI) (**bottom**) method for missing data for baseline CRP≥0 (left) and baseline CRP≥10 (right) for study CDP870-032.

Exposure-Response CDP870-031 at week 26

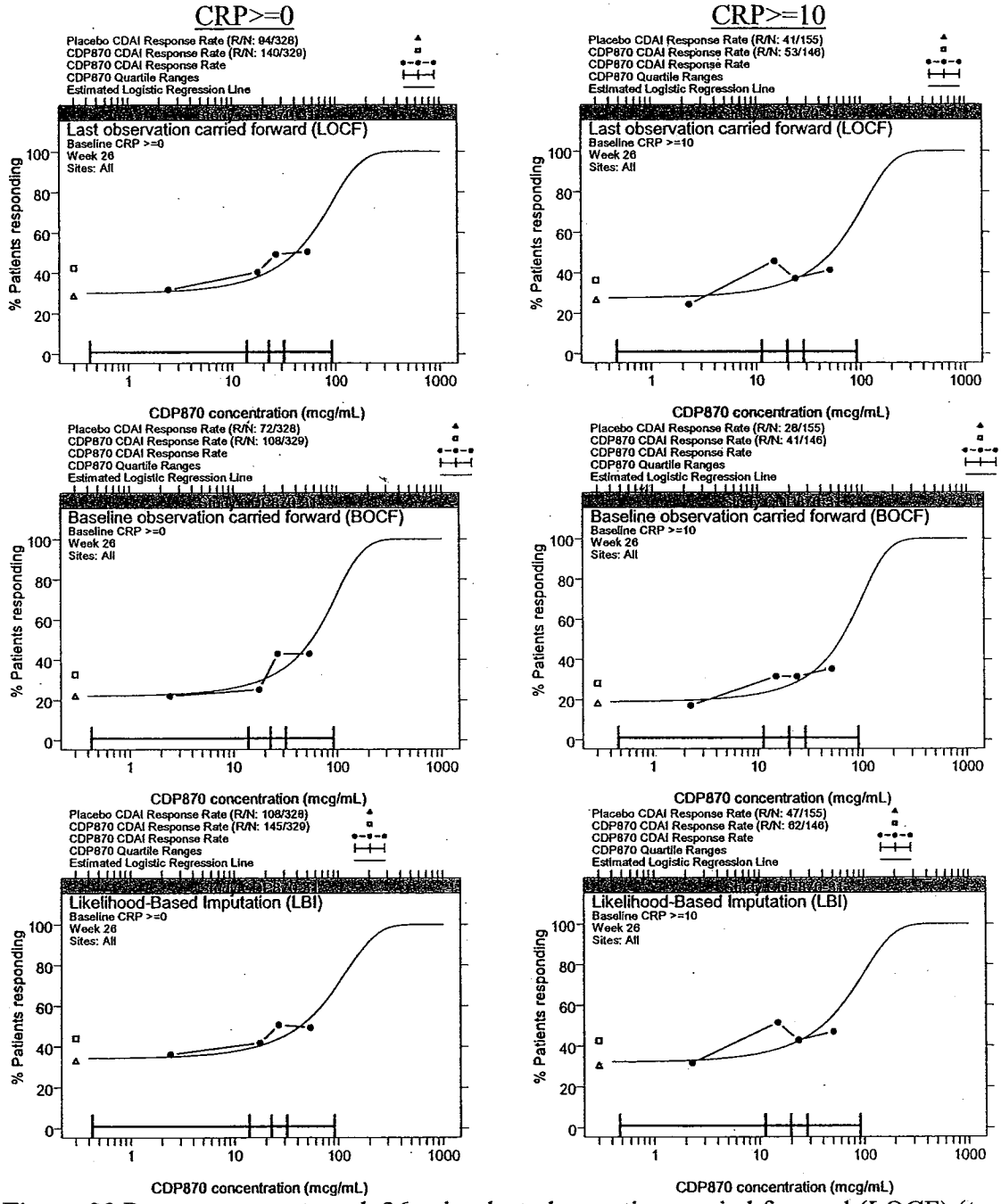

Figure 33 Response rate at week 26 using last observation carried forward (LOCF) (**top**), baseline observation carried forward (BOCF) (**middle**), and likelihood-based imputation (LBI) (**bottom**) method for missing data for baseline CRP≥0 (left) and baseline CRP≥10 (right) for study CDP870-032.

Exposure-Response CDP870-032 at week 6

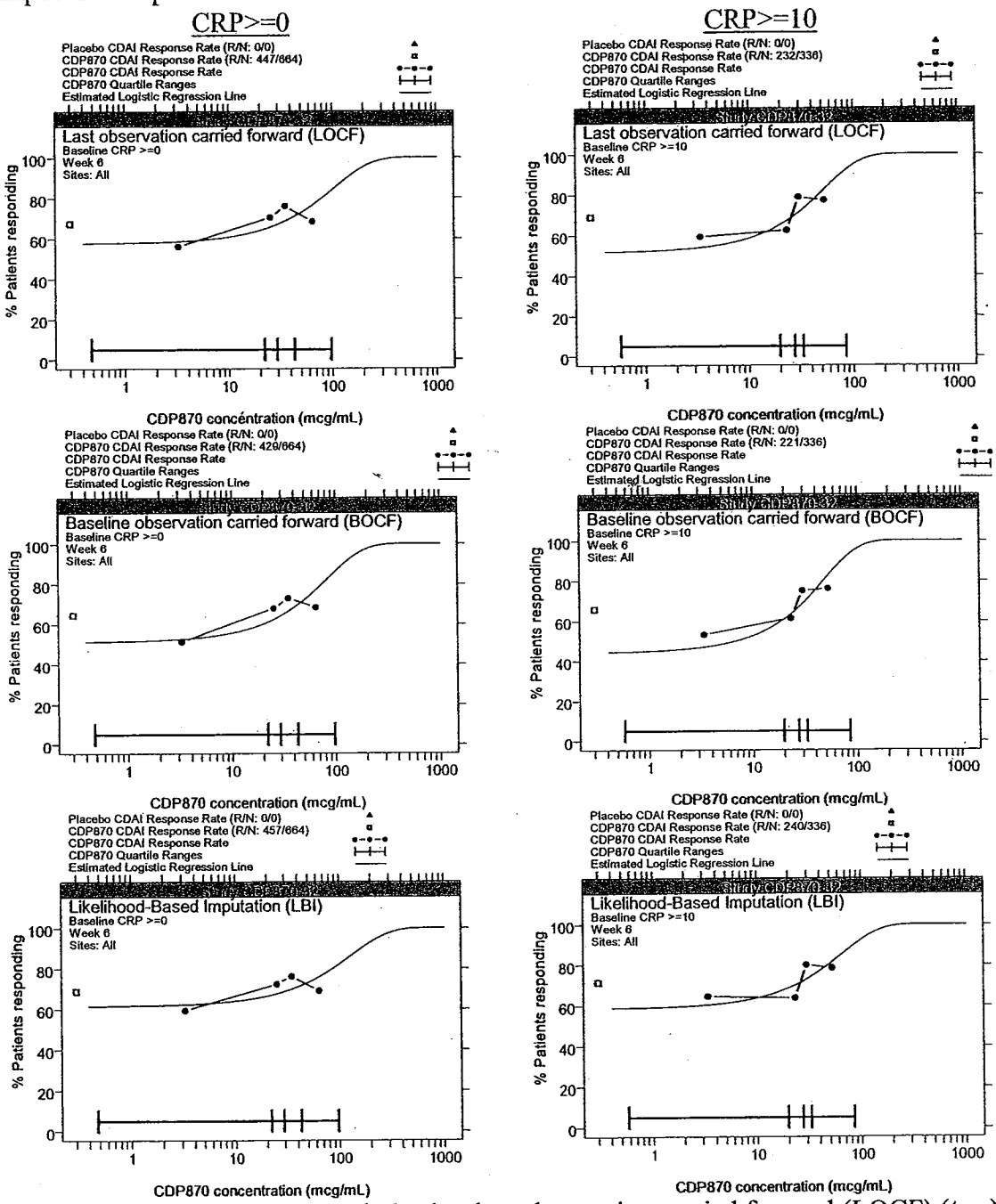

Figure 34 Response rate at week 6 using last observation carried forward (LOCF) (**top**), baseline observation carried forward (BOCF) (**middle**), and likelihood-based imputation (LBI) (**bottom**) method for missing data for baseline CRP≥0 (left) and baseline CRP≥10 (right) for study CDP870-032.

Exposure-Response CDP870-032 at week 26

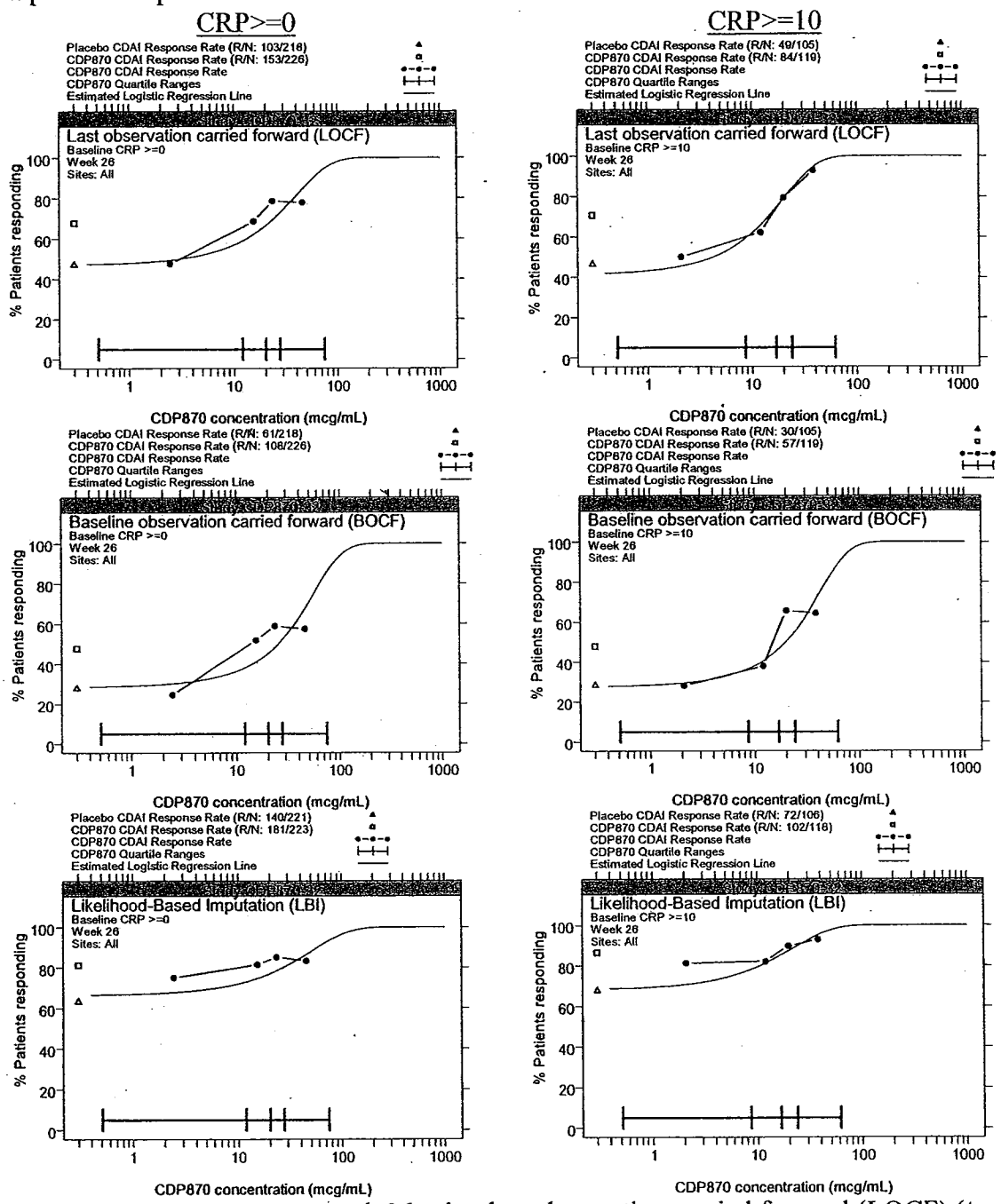

Figure 35 Response rate at week 26 using last observation carried forward (LOCF) (**top**), baseline observation carried forward (BOCF) (**middle**), and likelihood-based imputation (LBI) (**bottom**) method for missing data for baseline CRP≥0 (left) and baseline CRP≥10 (right) for study CDP870-032.

Exposure-Response CDP870-031 at week 6 US/non-US Sites

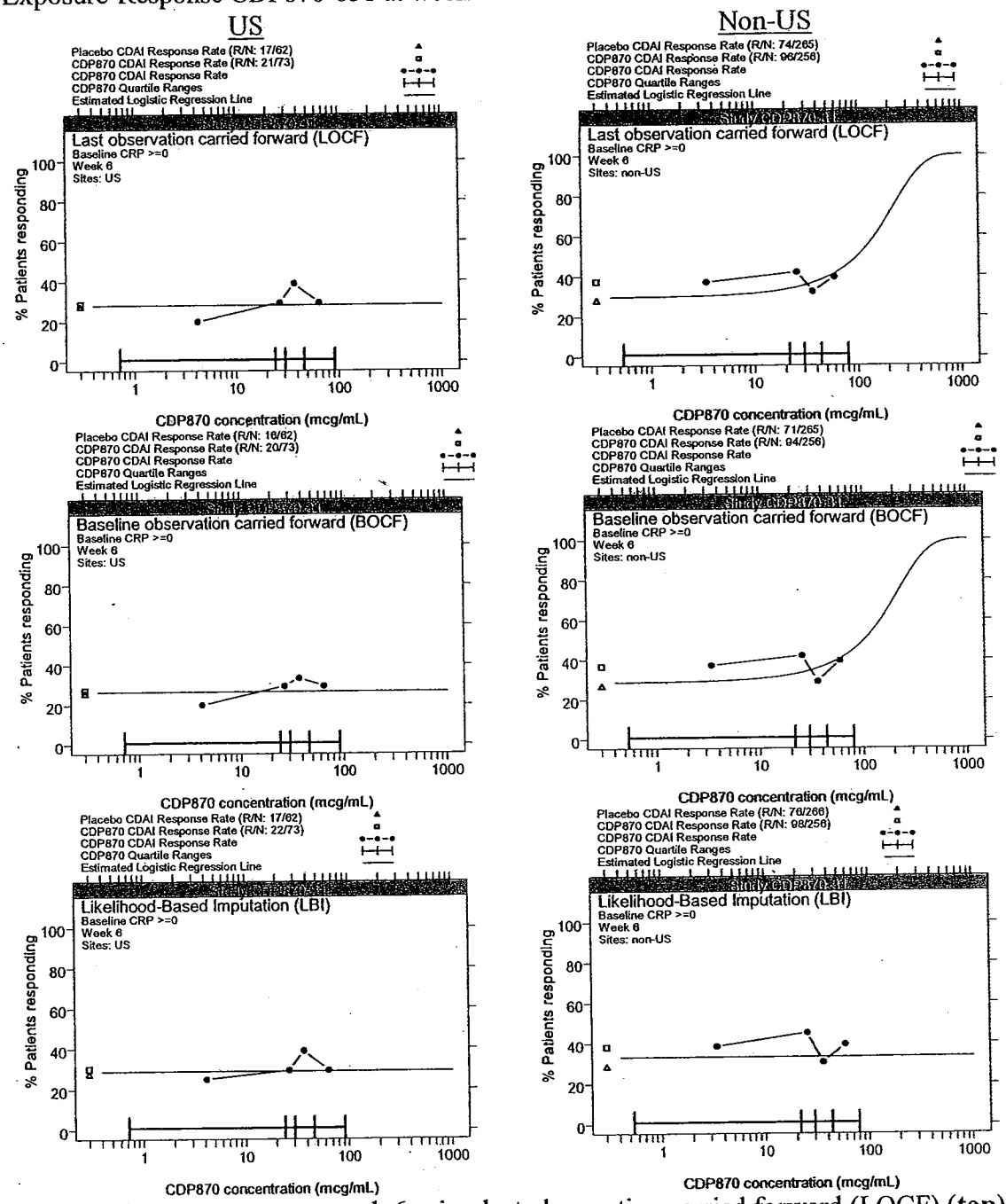

Figure 36 Response rate at week 6 using last observation carried forward (LOCF) (**top**), baseline observation carried forward (BOCF) (**middle**), and likelihood-based imputation (LBI) (**bottom**) method for missing data for US (**left**) and non-US (**right**) sites for study CDP870-032.

Exposure-Response CDP870-031 at week 26 US/non-US Sites

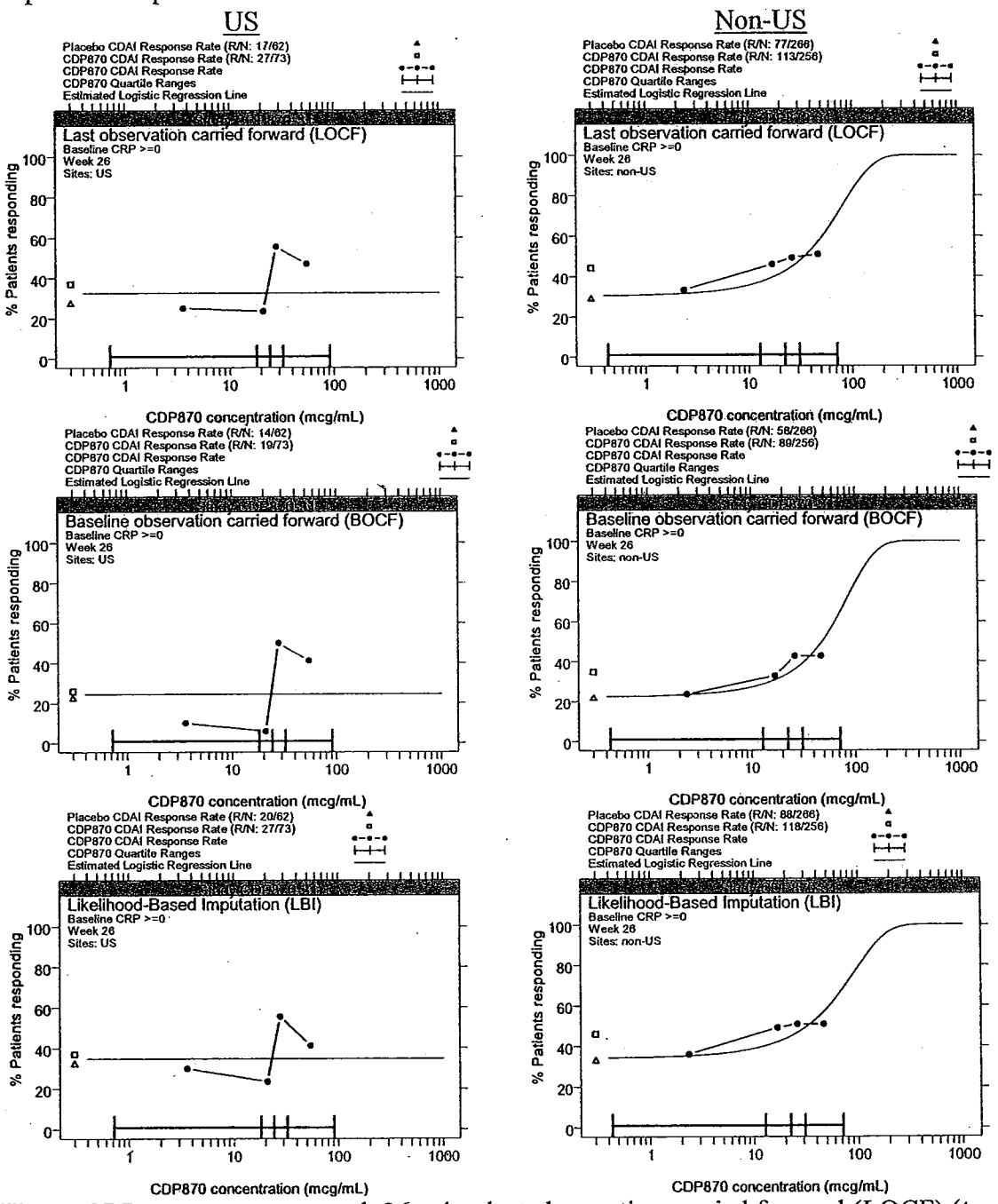

Figure 37 Response rate at week 26 using last observation carried forward (LOCF) (**top**), baseline observation carried forward (BOCF) (**middle**), and likelihood-based imputation (LBI) (**bottom**) method for missing data for US (left) and non-US (right) sites for study CDP870-032.

Exposure-Response CDP870-032 at week 6 US/non-US Sites

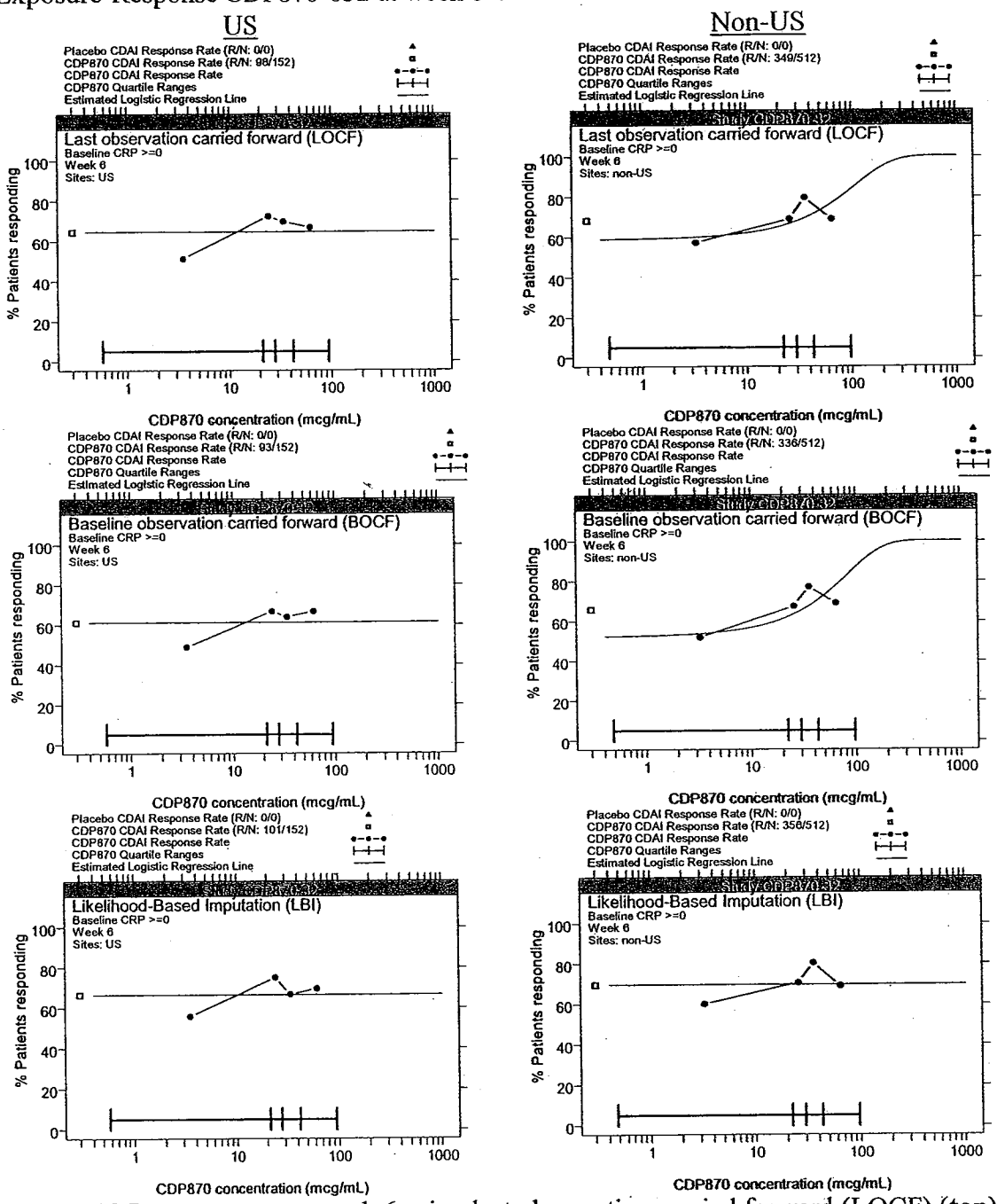

Figure 38 Response rate at week 6 using last observation carried forward (LOCF) **(top)**, baseline observation carried forward (BOCF) **(middle)**, and likelihood-based imputation (LBI) **(bottom)** method for missing data for US (left) and non-US (right) sites for study CDP870-032.

Exposure-Response CDP870-032 at week 26 US/non-US Sites

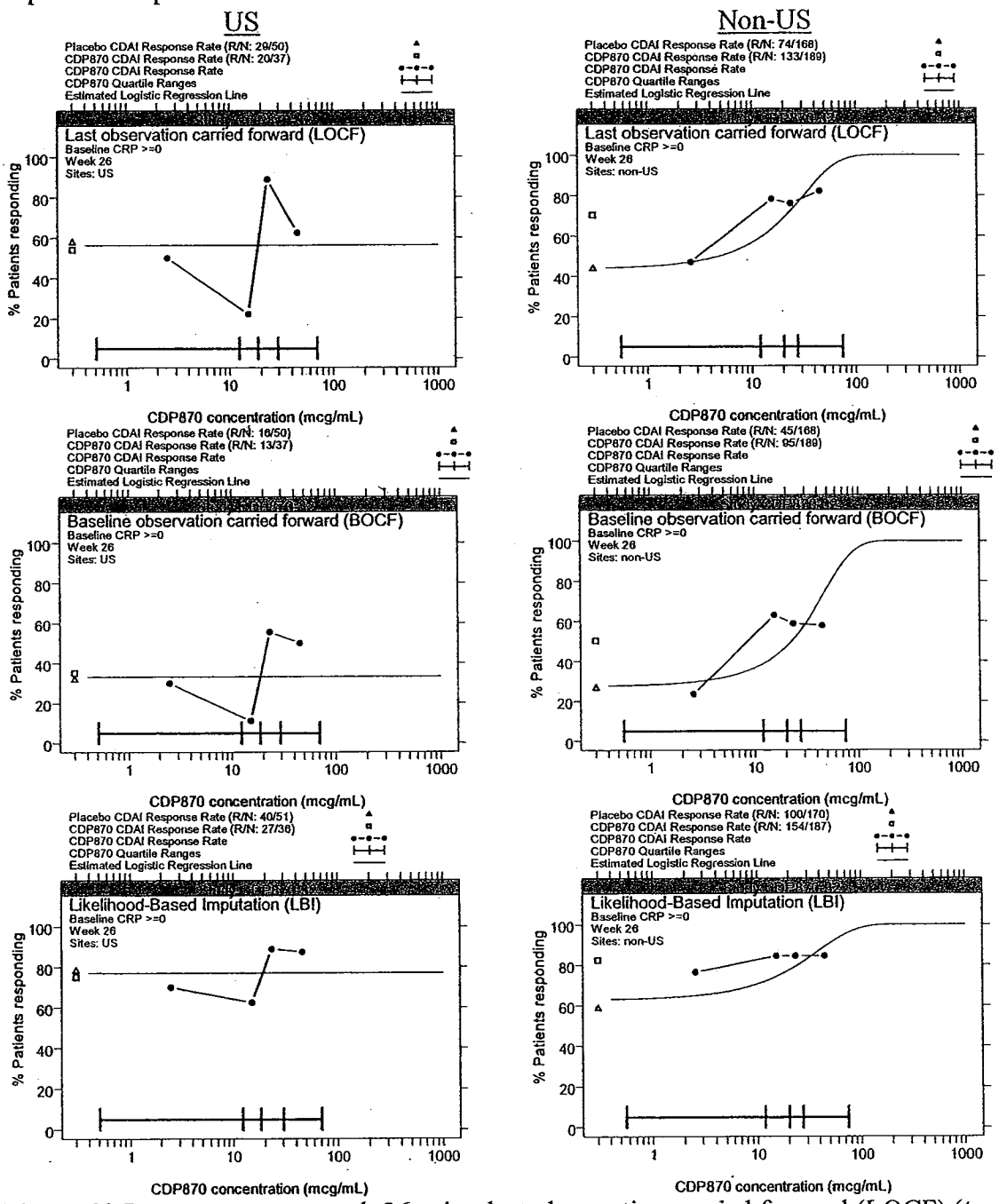

Figure 39 Response rate at week 26 using last observation carried forward (LOCF) (**top**), baseline observation carried forward (BOCF) (**middle**), and likelihood-based imputation (LBI) (**bottom**) method for missing data for US (left) and non-US (right) sites for study CDP870-032.

6 Appendices

6.1 Proposed Package Insert

6.2 Cover Sheet and OCPB Filing/Review Form

Appendix

6.1 Proposed Package Insert

26 Page(s) Withheld

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__✓__ Draft Labeling

_____ Deliberative Process

Appendix

6.2 Cover Sheet and OCPB Filing/Review Form

Office of Clinical Pharmacology and Biopharmaceutics
New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
STN Number	**103772/5089**	**Proposed Brand Name**	**Remicade**
OCP Division	**3**	**Generic Name**	**Infliximab**
Medical Division	**Gastroenterology**	**Drug Class**	**Immunosuppressant**
OCPB Reviewer	**Suliman Al-Fayoumi**	**Indication(s)**	
OCPB Team Leader	**Dennis Bashaw**	**Dosage Form**	**Lyophilized powder**
		Dosing Regimen	**5 mg/kg at 0, 2, and 6 weeks followed by a maintenance regimen of 5 mg/kg every 8 weeks thereafter.**
Date of Submission	**12/19/05**	**Route of Administration**	**I.V.**
Estimated Due Date of OCPB Review	**8/19/06**	**Sponsor**	**Centocor**
PDUFA Due Date	**10/19/06**	**Priority Classification**	**Standard**
Estimated Division Due Date	**9/19/06**		

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies	X			
HPK Summary	X			
Labeling	X			
Reference Bioanalytical and Analytical Methods	X			
I. Clinical Pharmacology				
Mass balance:	X	1	1	
Isozyme characterization:	X	1	1	
Blood/plasma ratio:	X	1	1	
Plasma protein binding:	X	1	1	
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:	X	1	1	
multiple dose:				
Patients-				
single dose:	X	1	1	
multiple dose:	X	2	2	
Dose proportionality -				
fasting / non-fasting single dose:	X	1	1	
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:	X	1	1	
In-vivo effects of primary drug:				
In-vitro:	X	2	2	
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
PD:				
Phase 2:	X	2	2	
Phase 3:	X	1	1	
PK/PD:				
Phase 1 and/or 2, proof of concept:	X	1	1	
Phase 3 clinical trial:				

Population Analyses –				
Data rich:	X	1	1	
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability:				
Relative bioavailability -				
solution as reference:	X	1	1	
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies:	X	3	3	
Dissolution:	X	2	2	
(IVIVC):				
Bio-waiver request based on BCS				
BCS class	X	1	1	
III. Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies	X	9	9	

Filability and QBR comments		
	"X" if yes	Comments
Application filable ?	X	
Comments sent to firm ?	**Not needed at this time**	
QBR questions (key issues to be considered)	• **Is there a need for a PK study in hepatic impairment?**	
Other comments or information not included above		
Primary reviewer Signature and Date		
Secondary reviewer Signature and Date		