

BACKGROUND:

This meeting was held at the request of UCB, Inc. to discuss the status of its agreements reached with CBER in 2003 regarding the clinical development program for CIMZIA. UCB, Inc., believes that it had reached agreement with CBER's Office of Therapeutics Research and Review regarding its two pivotal clinical studies in patients with moderate to severe Crohn's disease. In particular, the sponsor believes that CBER agreed that if these studies met their endpoints then they would be adequate to support FDA approval of CIMZIA for the treatment of Crohn's disease. In the sponsor's view, language in CDER's Complete Response letter dated December 21, 2006, appears to imply that previous agreements with CBER were not honored.

MEETING OBJECTIVE:

Explore whether or not CDER has honored the sponsor's previous agreements with CBER, and if not, to reach an understanding as to why CDER has not.

DISCUSSION POINTS:

CDER acknowledged the purpose of the meeting as stated above, and indicated that the sponsor's current disagreement with their position regarding approvability of the CIMZIA BLA is more likely based on a difference in interpretation regarding the robustness of the results from Study 031.

UCB, Inc. provided a brief history of their development plan, discussions and agreements with CBER culminating in their submission of the CIMZIA (certolizumab pegol) BLA STN 125160/0 (See attached sponsor presentation for more detail). The major issues were outlined by the sponsor as follows:

- Cimzia was developed in accordance with an agreement reached with CBER in 2003
- Two Phase III pivotal clinical studies (031 & 032) were designed in response to CBER requirements
- CBER agreed that these two pivotal studies would be adequate to demonstrate efficacy of Cimzia for the treatment of Crohn's disease
- Both studies met their primary endpoints with statistical significance using pre-specified analyses

UCB, Inc. described the agreements they felt CDER was not honoring. They requested that the Division of Gastroenterology Products (DGP) review the Cimzia Complete Response (currently in house) in accordance with the agreements reached with CBER.

CDER stated that sponsors need to show that their drugs work for the indication they are seeking. Depending on the indication sought, clinical development plans may vary from product to product.

Again it was reiterated that CDER's original CR regarding efficacy was based upon an interpretation of the data reviewed by DGP. CDER referred to concerns about response classification and verification of CDAI scores in Study 031. In CDER's view, if the responder status of one or two particular patients were changed, the results of Study 031 would not be statistically significant. The sponsor stated that it had performed a re-analysis of this study and found that Study 031 met its endpoints.

CDER expressed its willingness to review the sponsor's current response to the Complete Response Letter in light of this discussion. In this review CDER will attempt to verify the sponsor's analyses of the studies, particularly those involving Study 031 working closely with UCB, Inc. If both studies were determined to demonstrate efficacy of Cimzia for the treatment of Crohn's disease by DGP, further discussions/negotiations would be needed to design an indication for which the clinical trials data was supportive.

CDER concluded the meeting stating that it believes it has honored the agreements UCB, Inc. reached with CBER in 2003.

ACTION ITEMS:

- CDER reviewers will continue their review of the data provided in the sponsor's April 30, 2007 response to the Complete Response Letter dated December 21, 2006.
- UCB Inc. will work closely with CDER's statistical and clinical reviewers to clarify data and analysis issues as they arise during review of the response to the Complete Response Letter.
- Review of the sponsor's SPA submitted on April 17, 2007 is ongoing.

ATTACHMENTS/HANDOUTS:

UCB Inc. May 30, 2007 slides

2 Page(s) Withheld

Trade Secret / Confidential

Draft Labeling

Deliberative Process



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

September 7, 2007.

The following information was requested to Ms. Deborah Hogerman, from Regulatory Affairs, UCB, Inc. in reference to their CIMZIA BLA 125160/0:

The group met yesterday and would like to obtain the PLR and Medication Guide as soon as possible. (Follow Remicade example for the Med Guide and the new directions for the PLR from FDA web site). We are meeting on Thursday next week again, so if you can have them by then it will be very advantageous to you and us. We are trying to finalize a new indication to propose to your firm and if agreeable we look for a most possible approval

A handwritten signature in cursive script, appearing to read "Marlene G. Swider".

Marlene G. Swider, MHSA
Regulatory Project Manager, DGP



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

July 15, 2007

The following information was requested to Ms. Deborah Hogerman, from Regulatory Affairs, UCB, Inc. in reference to their CIMZIA BLA 125160/0 on July 15, 2007:

Please justify and provide data to support the — limit of — . Justification should include manufacturing history and clinical experience. If you cannot provide adequate justification, please commit to revising and tightening the limit.

A handwritten signature in cursive script, appearing to read "Marlene G. Swider".

Marlene G. Swider, MHSA
Regulatory Project Manager, DGP



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

Our STN: BL 125160/0

APR 05 2007

UCB, Inc.
Ms. Deborah Hogerman
Director, Regulatory Affairs
1950 Lake Park Drive
Smyrna, Georgia 30080

Dear Ms. Hogerman:

Please refer to your biologics license application (BLA) submitted under the Public Health Service Act for CIMZIA.

We also refer to the Type A meeting held on March 8, 2007, between representatives of your firm and this agency. A copy of the official minutes of the meeting is attached for your information.

Please refer to <http://www.fda.gov/cder/biologics/default.htm> for information regarding therapeutic biological products, including the addresses for submissions.

If you have any questions, please contact me at (301) 796-2104.

Sincerely yours,

A handwritten signature in black ink, appearing to read "Marlène G. Swider".

Marlène G. Swider
Regulatory Project Manager
Division of Gastroenterology Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure: Meeting Summary

MEMORANDUM OF MEETING MINUTES

Meeting Type: Type A Meeting
Meeting Category: Protocol and Data Review and Discussion (previous to a CR Response)
Meeting Date and Time: March 8, 2007 10:30 A.M. – 11:30 A.M.
Meeting Location: WO Bldg. 22 Room 1415
Application Number: BLA STN 125160/0
Product Name: Certolizumab pegol
Received Briefing Package: February 21, 2007
Sponsor Name: UCB, Inc.
Meeting Requestor: FDA
Meeting Chair: Shewit Bezabeh, M.D., M.P.H.
Meeting Recorder: Marlène Swider, M.H.S.A.

FDA ATTENDEES:

OFFICE OF NEW DRUGS

Julie Beitz, M.D., Director Office of Drug Evaluation III
Brian Harvey, M.D., Ph.D., Director, Division of Gastroenterology Products (DGP)
Joyce Korvick, M.D., Deputy Director, Division of Gastroenterology Products
Shewit Bezabeh, M.D., Clinical Reviewer, DGP
John Hyde, Ph.D., M.D., Clinical Reviewer Team Leader, DGP
Christoffer Tornoe, Ph.D., Biometrics Expert
Tapash Ghosh, Ph.D., Biometrics Expert
Milton Fan, Ph.D., Statistician
Mike Welch, Ph.D., Statistics Team Leader
Marlene Swider, M.H.S.A., Regulatory Project Manager

THE REGIONAL NEONATAL CENTER ATTENDEES:

Patricia Fritz, M.S., Vice President, Global Regulatory Affairs
Deborah Hogerman, B.A., Director, US Regulatory Affairs
_____, Clinical consultant
_____, Clinical consultant
_____, Clinical consultant and Lead (Ad interm)
Thomas Senderovitz, M.D., Vice President, Global Clinical Pharmacology and Experimental
Medicine
_____, Pharmacometrics consultant
Armel Stockis, M.Sc., Ph.D., Head of Pharmacometrics, Clinical Pharmacology & Experimental
Medicine
David Mason, M.D., Vice President, RA/GI Therapeutic Area
Remy Von Frenckell, Ph.D., Head of Biostatistics

results for the induction study are marginally significant and remain sensitive to data assumptions. Given the observed p-values for a single study, the probability of a second study failing to achieve similar efficacy is high. Thus a second confirmatory induction study was recommended.

Sponsor questions and FDA response: (not discussed during the meeting)

1. The Complete Response Letter states “there is not substantial evidence to support use of certolizumab pegol for _____”

On 10 November 2006, UCB requested that the indication statement be amended to conform to the indication discussed at the pre-BLA meeting “reducing signs and symptoms and maintaining clinical response.” Our rationale for the proposed change was based on several considerations; firstly, the clinical trials were designed with FDA input and concurrence, as consistently documented in our mutual correspondence, to support such a claim. Secondly, we had interpreted _____

_____ in the label. In order to avoid any possible issue relating _____ we proposed to revert to the claim that had been the focus of our earlier discussions with the FDA about study design. Lastly, and consistent with these points, CDER concurred with UCB at the pre-BLA meeting that “the clinical studies planned for inclusion in the BLA appear to be adequate to support the submission of a BLA for your proposed indication”.

a. Importantly, our 10 November 2006 communication with the FDA also contained a detailed discussion of the regulatory history that led to the design of the phase III program which, with FDA full participation and concurrence, was intended – if successful – to support the _____

_____ This was entirely consistent with the reviewing Division’s view that Crohn’s disease must be treated as a chronic disease. Based on the regulatory history submitted on 10 November 2006 and reiterated within this document, does the Division concur that CBER agreed that the phase III studies were adequately designed to support an indication for the _____

FDA Response

The studies were designed to assess CIMZIA’s efficacy in Crohn’s Disease for inducing a response (study 031) and for maintaining the response (Study 032). The designs were adequate for those purposes.

b. Does the Division concur that UCB's clinical studies submitted in support of its BLA met all of the objectives agreed to by the Sponsor and CBER necessary for obtaining approval? If not, please provide a detailed explanation.

FDA Response

We do not concur. Please see the explanation in the Complete Response letter dated December 21, 2006. Please also refer to the Guidance Document *Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products* regarding evidence needed to support a claim. We did not conclude from your submission that substantial evidence had been presented to demonstrate an effect on producing a clinical response during active disease, because your submission provided only one clinical study whose statistical significance was sensitive to data assumptions, and that study could not provide substantial evidence on its own. We do not consider the results of your maintenance study as being able to contribute significantly toward substantial evidence of producing clinical response in acute disease. At the End-of-Phase-2 meeting in April 2003, the formal agreements reached regarding the development program for CIMZIA were relatively limited in scope, and did not include concurrence on the overall development program. There was no SPA agreement. Your application was evaluated applying the standards of substantial evidence and taking into consideration any formal agreements.

c. Did the Division consider the indication statement submitted on 10 November 2006 as appropriate for the product? If not, why not?

FDA Response

The indication statement submitted on November 10, 2006, "reducing signs and symptoms and maintaining clinical response" may imply that CIMZIA is effective in all phases of Crohn's Disease activity. Crohn's Disease is a chronic disease condition characterized by flares and quiescent disease activity. For a patient with chronic disease, treatment of an active flare is a crucial part of the disease management. The proposed indication does not provide a clear guide as the appropriate use of your product. "Reducing signs and symptoms" may imply an ability to produce clinical improvement during active disease; substantial evidence was not presented for that ability. If the indication is limited to maintenance of response, sufficient evidence was not presented to demonstrate the safety and efficacy for use of CIMZIA in conjunction with the agents that would be used to produce the response that CIMZIA would maintain. Although the proposed indication was changed, the development program does not provide the information needed to support adequate instructions for use.

d. Can the Division please comment as to whether it is the position of the Agency that all drugs being developed for the treatment of Crohn's disease must include, before initial approval can be obtained, studies to support induction and maintenance claims?

FDA Response

As Crohn's disease is a chronic disease, your proposed therapy needs to be evaluated for long-term safety, regardless its specific indication or role in the management of the disease.

The requirements for an application would usually depend on the effects of the therapy and the claims being sought. The clinical data presented in a submission would need to provide sufficient information so that one can provide adequate instructions for use during the different phases of the disease.

e. If so, how does the Division reconcile this position with the position of CBER regarding the labeling for signs and symptoms of Crohn's disease?

FDA Response

It is unclear whether you intend this question to apply to your product or other products approved for Crohn's Disease. The product labeling is only approved when the specific product has been approved for the US market. In addition, any FDA approved labeling for Crohn's Disease would be supported by the data that have been submitted to FDA for review, and is updated when new data become available.

2. Regarding comment 4 of the Complete Response Letter, although the treatment effect in study CDP870-031 was less than expected based on results of the phase II study, CDP870-005, the co-primary endpoints of clinical response at Week 6 and Weeks 6 and 26 in the CRP ≥ 10 mg/mL ITT population were statistically significant. These data are further supported by important secondary outcomes, including response in the overall population irrespective of CRP at baseline, response seen at Week 26, and consistency of clinical response at each study visit. The effectiveness of certolizumab pegol was also demonstrated in study CDP870-032 where subjects received open-label treatment followed by randomization of responders treated over 26 weeks. Lastly, the post-hoc analysis of study CDP870-005 gives further evidence of the efficacy of certolizumab pegol in the population of patients with CRP ≥ 10 mg/mL.

a. We find that the results of the primary analysis populations in studies CDP870-031 and CDP870-032 and the post-hoc analysis from CDP870-005 in high CRP patients support approval of certolizumab pego

_____ Does the
Division concur?

FDA Response

We do not concur. Please see responses to Question 1b. Note that results from the Phase 2 CDP870-005 study are considered exploratory and were not confirmed by a subsequent Phase 3 study.

b. Given the totality of data from the primary and key secondary outcomes from studies CDP870-031 and CDP870-032, the results of the study CDP870-005 and the initial indication for which the program was designed with and agreed to by CBER, why wouldn't the Division consider an alternative indication statement _____

FDA Response

Please see above response to 1c.

c. Based on the exposure response analyses presented in this document, does the Division concur that these data support the proposed dosing of 400mg at Week 0, 2, 4, and every 4 weeks thereafter?

FDA Response

We do not concur. The exposure-response is internally inconsistent across the trials and does not provide strong evidence for effectiveness. The trial data from US centers from the CDP870-031 and -032 do not support the exposure-response observed in the dose-finding trial. Further, interpreting 032 trial data is challenging as it has an open-label component and this seems to interfere with the scoring.

From a dose individualization point of view, which is a different issue from evidence for effectiveness, considerable variability in the exposure levels was observed for a fixed dose of 400 mg every 4 weeks in the confirmatory studies CDP870-031 and -32, with certolizumab pegol trough concentrations ranging between 0.5 and 80 mcg/mL. Therefore, we do not believe that you have fully explored the exposure-response relationship and suggest that you investigate higher dose frequency and/or amount in future clinical trials.

3. An Exposure-Response modeling project of the combined phase II and phase III data was commissioned by UCB with [redacted]. The report is included in the briefing package as Attachment 2.

a. Does the Division concur with the modeling approach and the findings of the Exposure-Response Modeling study?

b. Assuming concurrence with the findings, does the Division concur that no additional clinical data prior to approval are necessary to further define the exposure-response relationship?

FDA Response

The performed exposure-response modeling is very extensive and the conclusions seem to be similar to those from study report 40001559 in the original BLA submission.

Due to the different responses observed after open-label and double-blind treatment, and between Europe and US centers, we do not believe that a pooled meta-analysis of all the data is an appropriate method for analyzing the data.

Please see relevant excerpts from our technical pharmacometrics review for Cimzia to understand our exposure-response analysis (attached separately).

4. Regarding comment 4 of the Complete Response Letter, we understand from a teleconference with the statistical reviewers that the statement regarding the lack of statistical robustness of study CPP870-031 was based on a post-hoc analysis whereby the response status of some patients was changed resulting in the loss of statistical significance. In addition, we understood from this discussion that all of our pre-specified analyses were conducted by FDA statisticians and found to be in agreement with the data submitted to the BLA.

a. Given the unusual nature of the post-hoc analyses conducted by FDA, can the Division provide the model used to assign response to randomly selected patients?

FDA Response

The sensitivity analyses conducted by the statistical reviewer are standard reviewer practices which focus on a conservative imputation to data records that are missing and/or ambiguous. The rationale for the analyses is described below:

During the review process, the reviewer found that two placebo subjects had discrepancies in their status of complete response at Week 6.

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

Complied by this reviewer.

Where MRESP6 – Missing set to non-response

CLINRSP- Clinical response

NCLINRSP – Clinical response – no imputation

ORESP6 – Clinical response - observed data only

Your response to our information request provided the following explanations:

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

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

For subject 401, it was assumed that this subject completed the study, as *CLINRSP* and *NCLINRSP* which were created on 6 January 2006 were based on the observed CDAI score. Both *CLINRSP* and *NCLINRSP* were “Yes.” The *MRESP6* and *ORESP6* were created on 15 June 2006. Both *MRESP6* and *ORESP6* were “No.” For this subject, the classification of non-responder status was not clearly established.

Subject 525 had a complete response at Week 6 (*ORESP6*) but, the sponsor stated that this subject was withdrawn at Week 6. This subject had data at Week 6. The value for *MRESP6* for this subject should be “Yes”.

This reviewer also found that subject 401 had a discrepancy in status of complete response at Weeks 6 and 26.

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

Complied by this reviewer.

Where *MRESP626* – Missing set to non-response
CLIN626- Clinical response
NCLIN626 – Clinical response – no imputation
ORESP626 – Clinical response - observed data only

CLIN626 and *NCLIN626* which were created on 6 January 2006 were based on the observed CDAI score. The *MRESP626* and *ORESP626* were created on 15 June 2006. For this subject, the consideration of rescue therapy is unclear, so subject 401 was considered to be a responder at Weeks 6 and 26 based on values on *CLIN626* and *NCLIN626*.

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

This reviewer performed a “true” ITT analyses which included all randomized patients using the raw data set provided by you. It was found that some discrepancies existed between the raw data set and the study report regarding the number of subjects with clinical response at Week 6 and Week 6 and 26 in the stratum CRP \geq 10 mg/L at baseline for placebo. Your Table 14.2.2.7 gave numbers of 40 and 19 for week 6, and Weeks 6 and 26, respectively. However, from your raw data set, the numbers were 41 and 20 for Week 6 and Weeks 6 and 26, respectively.

In the reviewer’s analyses, patients with missing data were considered to be non-responders. Fisher’s exact test was performed by the reviewer. The results from that analysis are given below.

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

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

Compiled by this reviewer.

P-value was obtained by the Fisher’s exact test.

As seen from the table above, contrary to your analysis, treatment difference for clinical response at Weeks 6 and 26 in the CRP \geq 10 mg/L at baseline stratum does not achieve statistical significance.

As noted above, the reviewer found that two placebo subjects (401 and 525) had discrepancy in status of complete response. The analysis below assumes that both subjects 401 and 525 were assumed to be responders at Week 6 and subject 401 was assumed to be a responder at Weeks 6 and 26.

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

Week	CDP870 400mg (N=146)		placebo (N=156)		Difference	p-value
	n	(%)	n	(%)		
6	54	(37.0%)	42	(26.9%)	10.1%	0.0647

6 and 26	31	(21.2%)	20	(12.8%)	8.4%	0.0647
----------	----	---------	----	---------	------	--------

Compiled by this reviewer.

†If both subjects 401 and 525 were assumed to be responders at Week 6 and subject 401 was assumed to be a responder at Weeks 6 and 26.

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

As seen from table above, contrary to your finding, both treatment differences for clinical responses at Week 6 and at Weeks 6 and 26 in the CRP ≥ 10 mg/L at baseline stratum do not achieve statistical significance.

b. We submitted as part of the pre-BLA briefing package and in the BLA the results of several pre-specified sensitivity analyses. UCB considers the prospectively defined sensitivity analyses adequate to assess the effectiveness of the pivotal studies. Can the Division please comment?

FDA Response

For "best/worst" case analyses for Study 031, you assumed that 3 subjects (2 placebo and 1 CDP870) had missing data. But, from your data set, this reviewer found 24 CDP870 and 48 placebo subjects had missing data.

You stated "It has not been possible to reproduce the numbers mentioned in the question, 24 CDP870 and 48 placebo subjects. In order to understand the discrepancy, please indicate which data set and variables were used to generate these numbers."

The data set and variables used by the reviewer are shown below:

Data set = EFFCDAI (Jan 06, 2006)
Variables = CLINRSP
Visit = 6
Stratum = 1, 2, 3 and 4 (in order to select the CRP ≥ 10 mg/L Strata at Baseline subgroup)

The numbers of subjects with clinical response at Week 6 and in the CRP ≥ 10 mg /L baseline stratum. are thus 122 and 108 for CDP870 and placebo groups, respectively. Thus, 24 CDP870 and 48 placebo subjects were assumed to have missing data.

c. In addition, UCB has conducted further sensitivity analyses of the overall benefit of certolizumab pegol in the population with baseline CRP ≥ 10 mg/L in line with the Division's own analyses. Does the Division concur that the analyses of all randomized patients in study CDP870-031 shows a statistically significant difference between certolizumab pegol and placebo.

FDA Response

The sponsor's sensitivity analyses did not take into consideration the two placebo subjects who had discrepancies in status of complete responses at Week 6 and Weeks 6 and 26. As discussed in 4.a., statistical significance was not achieved when one placebo subject's status changed from "non-responder" to "responder."

5. In comment 5 of the Complete Response Letter, the Division states that patient 525 should have been included in the Week 6 results. Patient 525 was included in the results based on the pre-specified analyses. Would the Division please elaborate on why the pre-specified analysis of counting withdrawals as non-responders from the time of withdrawal onwards should not be applied to this patient?

FDA Response

The rationale for including Patient 525 was given in our response for Question 4a.

6. In response to comment 5 of the Complete Response Letter, which states that patient 525 should have been included in the Week 6 results, we have performed the analysis whereby patient 525 is included as a responder at Week 6. The difference in response rate changed from 26.0% to 26.6% and the p-value changed from 0.037 to 0.048 thus remaining statistically significant.

a. Given that the p-value remains <0.05 using this post-hoc analysis, will the Division please clarify the comment stating study CDP870-031 did not meet its primary objective?

FDA Response

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

For the secondary efficacy endpoints, both clinical remission at Week 6, and Weeks 6 and 26 in both the $CRP \geq 10$ mg/L at baseline stratum and the overall population failed to achieve statistical significance. Clinical responses at Week 6, and Weeks 6 and 26 in the

overall population achieved statistical significance for your ITT population, but they failed for the Per Protocol Population. Treatment differences on IBDQ were not statistically significant at Week 6, and Weeks 6 and 26 in both the CRP \geq 10 mg/L at baseline stratum and the overall population. The strength of evidence from Study CDP870-31 was not statistically persuasive.

b. At week 0, the CRP for subject 525 was 42.0 mg/L and was assigned to the CRP \geq 10 mg/L stratum. As described in this document, UCB has investigated the CRP values and has concluded that this subject was assigned to the correct stratum. Does the Division concur?

FDA Response

This information should be submitted as part of your response to our CR Letter dated December 21, 2006.

7. As requested in comment 7 of the Complete Response Letter, we have investigated possible explanations for the lack of effect of certolizumab pegol relative to placebo in the subgroup of United States (US) patients with regard to the apparent differences between the US and non-US sites in Study CDP870-032.

a. Does the Division concur with the analyses?

FDA Response

This information should be submitted as part of your response to our CR Letter dated December 21, 2006.

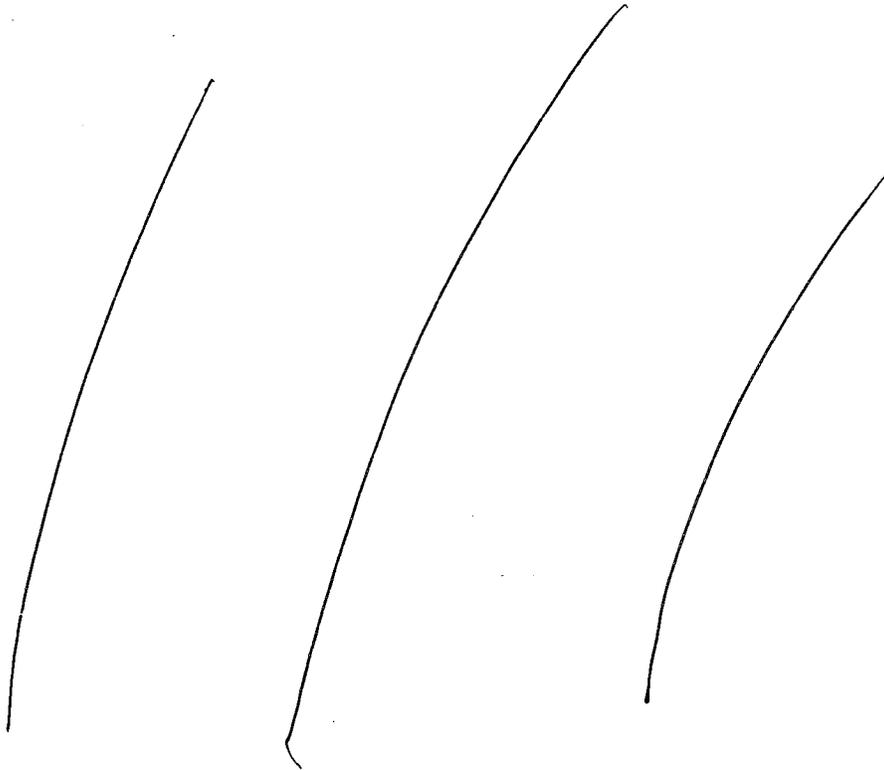
b. Based on the data presented in the briefing package, does the Division have additional suggestions for analyses.

FDA Response

Please see our answer to Question 3.

8. Specific to your comment “additional clinical data will be needed to address all of the clinical deficiencies”, and “could include additional studies of induction, possibly with dose ranging, or studies of maintenance therapy followed by induction with other approved products”, we would like to discuss approval of our application with the data already submitted for the proposed indication of

_____ We have
included _____
for review. _____



3.0 ISSUES REQUIRING FURTHER DISCUSSION

UCB, Inc., will be providing comments and requesting more guidance from the Biopharmaceutical Team.

4.0 ACTION ITEMS

UCB, Inc., will follow up with a response to the CR Letter sent to them back in December 21, 2006.

5.0 ATTACHMENTS AND HANDOUTS

UCB, Inc., Presentation

24 Page(s) Withheld

Trade Secret / Confidential

Draft Labeling

Deliberative Process

Swider, Marlene

From: Tornoe, Christoffer
Sent: Thursday, February 22, 2007 1:48 PM
To: Swider, Marlene
Subject: FW: Brief minutes from today's Cimzia t-con

Attachments: FW: BLA 125160: UCB proposal for answering Question 5 from the I RL

Hi Marlene

Below are the minutes from our tcon on September 20, 2006.

The second tcon with UCB on October 16 was cancelled since there was a misunderstanding whether we should have it or not. Since their response was adequate, we decided not to reschedule (see attached email).



FW: BLA 125160:
UCB proposal f...

Best

Chris

From: Tornoe, Christoffer
Sent: Wednesday, September 20, 2006 9:36 AM
To: Swider, Marlene
Cc: Gobburu, Jogarao V; Ghosh, Tapash
Subject: Brief minutes from today's Cimzia t-con

Dear Marlene

Here are the minutes from our 20 min t-con with the sponsor this morning about the Cimzia data.

The longitudinal efficacy and safety data format was further clarified with respect to the sponsor's question stated in CDP870-CD proposal for clarification RB 19-09-2006.doc.

It was decided that the sponsor will submit the longitudinal efficacy data for the phase II studies by Tuesday the 26th of September and the remaining efficacy and safety data will be provided during the week starting October 7th.

The data files for the PK modeling report CDP870-039 were shipped yesterday and should arrive at your desk by today.

The remaining data for PK modeling report 40001559 should be shipped within a short period of time.

Best

Christoffer

Christoffer W. Tornoe
Pharmacometrics, Office of Clinical Pharmacology, FDA
10903 New Hampshire Ave, Bld. 21 Rm 4514
Silver Spring, MD 20993-0002
Phone: (301) 796-2236
Email: christoffer.tornoe@fda.hhs.gov

MEMORANDUM OF TELECON

DATE: January 11, 2007

APPLICATION NUMBER: BLA 125160/0

Drug Name: CIMZIA (Certolizumab pegol)

PARTICIPANTS:

FDA

Milton Fan – Statistician

Michael Welch – Supervisory Statistician

John Hyde – Supervisory Medical Officer

Marlene Swider- Regulatory Project Manager

UCB

Deb Hogerman – Director, US Regulatory Affairs

Remy Von Frenckell – Vice President Biometry/ Outcomes

Alison Innes (AI) – Statistical Team Leader, Rheumatology/GI

Ralph Bloomfield – Principal Statistician

Dr. Welch stated that it is unusual to have a teleconference prior to a Type A meeting to discuss a Complete Response (CR) Letter and that we would attempt to clarify only statistical issues, and detailed discussions should take place at the meeting. Deb Hogerman stated that the purpose of this teleconference was to seek clarification on statistical statements in points #4 and #5 of the CR letter in preparation of the Type A meeting.

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

Ralph Bloomfield asked for definition of "statistically robust." Dr. Fan responded that there is no formal definition of "statistically robust." To see whether the results are robust or not, he noted that he performed some sensitivity analyses for "true" ITT analysis (including all randomized patients). Furthermore, he commented that changing the response status for only "a few patients" changed the outcome of the study from statistically significant ($p \leq 0.05$) to statistically non-significant ($p > 0.05$). Therefore, for Study CDP870-31, changing the response status of two to three subjects resulted in a non-significant p-value.

Ralph Bloomfield asked if they used the strict ITT definition as mentioned in point 4, rather than using their modified ITT population definition. Dr. Fan responded that in the placebo-controlled trial the true ITT population should be used. The true ITT analysis is more conservative for placebo-controlled study.

Regarding point #5: "We are also not able to concur with the conclusion that Study CDP870-031 was a positive study for its primary objective, because we believe there was inadequate justification for excluding patient 525 from Site 22025 from the Week 6 results. Further, that patient appeared to have his baseline CRP results entered incorrectly in the database."

Ralph Bloomfield asked for clarification for patient 525. Dr. Fan responded that this was more a clinical issue and should be addressed at the Type A meeting.

Teleconference ended.

H. Fan 1/31/07



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

Our STN: BL 125160/0

UCB, Inc.
Attention: Patricia Fritz
Vice President, Global Regulatory Affairs
1950 Lake Park Drive
Smyrna, Georgia 30080

Dear Ms. Fritz:

This letter is in regard to your biologics license application for Cimzia (certolizumab pegol) submitted under section 351 of the Public Health Service Act. Reference is also made to our October 12, 2006 letter, and your response dated November 10, 2006.

We have completed the review of your application, including all amendments received through December 7, 2006. Our review finds that the information and data submitted are inadequate for final approval action at this time based on the deficiencies outlined below.

Chemistry, Manufacturing, and Controls

1. In your submission dated December 5, 2006, you proposed to submit a report in February 2007 to support the establishment of in-process control at the step. The study report should contain data for levels for all batches manufactured to support your proposed in-process control. In addition, please provide an updated table for in-process controls to include for monitoring at
2. Your submission dated December 1, 2006, described an amended comparability protocol to support PEG2MAL40K scale up to ———. However, it appears from Table 1 in this submission that campaign → validation campaign) used PEG2MAL40K manufactured at the — scale. Since campaign → batches used the same process as your proposed commercial manufacturing process, there is no manufacturing change and thus no need for this comparability protocol. Therefore, please provide a statement for removal of the comparability protocol from the BLA. However, if there are differences between the manufacturing process used during the validation campaign and your proposed commercial manufacturing process, please highlight them in detail and submit a revised comparability protocol.

Clinical Pharmacology

3. Although the results of your phase 2 studies implied otherwise, analysis of your phase 3 studies (CDP870-031 and CDP870-032) suggests that there is not a significant exposure-

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

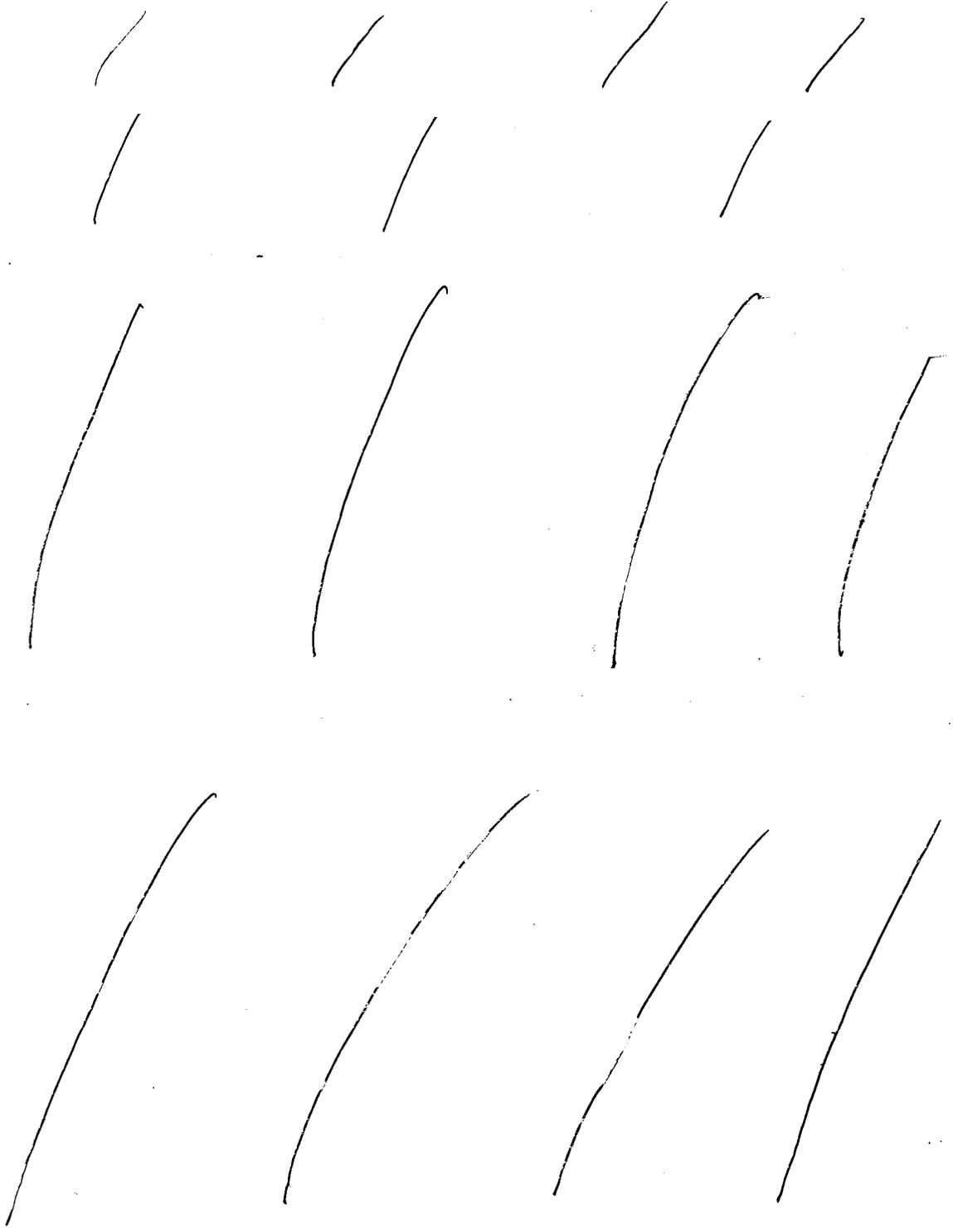
Clinical

Based upon our review of your BLA, there is not substantial evidence to support use of certolizumab pegol for inducing or maintaining clinical response in patients with moderately to severely active Crohn's disease. In particular, our concerns are:

4. Study CDP870-031 showed a small treatment effect that is not statistically robust when clinical response is assessed for the true intent-to-treat population (i.e., all patients randomized with a baseline CRP \geq 10 mg/L) and patients with missing information are counted as non-responders. We do not view the ability to maintain a response once it has been achieved, as shown in Study CDP870-032, as substantial evidence of an ability to accomplish the task of inducing a response by reducing symptoms in patients who have active disease.
5. We are also not able to concur with the conclusion that Study CDP870-031 was a positive study for its primary objective, because we believe there was inadequate justification for excluding patient 525 from Site 22025 from the Week 6 results. Further, that patient appeared to have his baseline CRP results entered incorrectly in the database.
6. Study CDP870-032 showed that certolizumab pegol could maintain response in patients who have been previously induced into clinical response. However, in the absence of a finding that certolizumab pegol is able to induce a clinical response, a confirmatory study would be necessary to support your proposed maintenance indication.
7. We are concerned by the observation that Study CDP870-032 showed no significant effect of certolizumab pegol relative to placebo in the subgroup of US patients. Please conduct additional analyses to investigate possible explanations for this observation such as differences in patient characteristics, concomitant therapy practices, lots used, or other factors, that might explain the apparent differences between US and non-US sites.

We conclude that additional clinical data will be needed to address all of the clinical deficiencies in your application. This could include additional studies of induction, possibly with further dose-ranging, or studies of maintenance therapy following induction with other approved agents. We recommend that you plan to meet with the Division of Gastroenterology Products to discuss

your options for ways to augment your product development program.



Please describe your plans to address the deficiencies identified in Items 3-9 above in sufficient detail to permit our evaluation of the adequacy of the proposals. We request that your response include:

- Protocols or detailed outlines describing all design features of the studies including sample size and justification, eligibility criteria with rationale, dosing regimens and duration, clinical assessments to be performed and their timing, and endpoints to be analyzed.
- Proposed schedule for conducting the studies, including all major milestones for the studies, e.g., submission of finalized protocols to the Division of Gastroenterology Products for review and comment, initiation and completion of patient accrual, completion of the studies, and submission of the final study reports, SAS datasets and applicable revised labeling to the Division.

Please be advised that submission of complete protocols for review and comment should be made to your IND and may be cross-referenced in your response to this letter.

We reserve comment on the proposed labeling until the application is otherwise acceptable.

You may request a meeting or teleconference with CDER to discuss the steps necessary for approval. Should you wish to have such a meeting, please submit your meeting request as described in the FDA Guidance for Industry: Formal Meetings With Sponsors and Applicants for PDUFA Products – February, 2000 (<http://www.fda.gov/cder/guidance/2125fnl.htm>).

Within 10 days after the date of this letter, you are requested to take one of the following actions: (1) amend the application [***file a new application***]; (2) notify us of your intent to file an amendment [***a new submission***]; (3) withdraw the application; or (4) request an opportunity for a hearing on the question of whether there are grounds for denying approval of the application. In the absence of any of the above responses, we may initiate action to deny the application.

Please note our review clock has been suspended with the issuance of this letter. Note also that any amendment should respond to all deficiencies listed and that a partial reply will not be considered for review nor will the review clock be reactivated until all deficiencies have been addressed.

Please refer to <http://www.fda.gov/cder/biologics/default.htm> for important information regarding therapeutic biological products, including the addresses for submissions.

If you have any questions, please contact the Regulatory Project Manager, Marlene Swider, at (301) 796-2104.

Sincerely,

Julie Beitz MD 12/21/06

Julie Beitz, M.D.
Director
Office of Drug Evaluation III
Center for Drug Evaluation and Research

MEMORANDUM

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

CLINICAL INSPECTION SUMMARY

DATE: November 20, 2006

TO: Marlene Swider, Regulatory Project Manager
Shewit Bezabeh, M.D., Clinical Reviewer
Division of Gastroenterology Products, HFD-180

THROUGH: Leslie K. Ball, M.D.
Branch Chief
Good Clinical Practice Branch 2, HFD-47
Division of Scientific Investigations

FROM: Dianne Tesch, Consumer Safety Officer

SUBJECT: Evaluation of Clinical Inspections

BLA: 125160/0

NME: Yes

APPLICANT: UCB Pharma

DRUG: certolizumab pegol (Cimzia)

THERAPEUTIC CLASSIFICATION: Priority

INDICATION: _____

CONSULTATION REQUEST DATE: May 15, 2006

DIVISION ACTION GOAL DATE: December 20, 2006

PDUFA DATE: December 30, 2006

I. BACKGROUND:

Crohn's disease is an inflammatory bowel disease (IBD), the general name for diseases that cause inflammation in the intestines. Crohn's disease affects males and females equally and seems to run in some families. Crohn's disease may also be called ileitis or enteritis.

Most people are first treated with drugs containing mesalamine, a substance that helps control inflammation. Sulfasalazine is the most commonly used of these drugs. Patients who do not benefit from it or who cannot tolerate it may be put on other mesalamine-containing drugs, generally known as 5-ASA agents, such as Asacol, Dipentum, or Pentasa. Some patients take corticosteroids to control inflammation.

These drugs are the most effective for active Crohn's disease, but they can cause serious side effects, including greater susceptibility to infection.

TNF is a naturally occurring cytokine that is involved in normal inflammatory and immune responses. Elevated levels of TNF play an important role in pathologic inflammation. Adalimumab binds specifically to TNF and neutralizes the biological function of TNF by blocking its interaction with the p55 and p75 cell surface TNF receptors.

There were four foreign sites chosen for the inspection. The sites were chosen because there was insufficient data from U.S. sites.

BLA 125160 Product Name - certolizumab
 Summary Report of Foreign Inspections

II. RESULTS (by protocol/site):

Name of CI and site #, if known	City, Country	Protocol #	Insp. Date	EIR Received Date	Final Classification
Jan Chojnacki, M.D. site 33012	Lodz, Poland	CDP870-031	August 14-16, 2006	October 16, 2006	VAI
Pieter Honiball, M.D. site 39006	Pretoria, South Africa	CDP870-031	July 24-28, 2006	October 17, 2006	VAI
Robert Petryka, M.D. site 33007	Warsaw, Poland	CDP870-032	July 31-August 4, 2006	October 30, 2006	VAI
Zbigniew Hebzda, M.D. site 33010	Krakow, Poland	CDP870-033	August 7-11, 2006	October 26, 2006	VAI

*If international site, please insert column for country.

Key to Classifications

NAI = No deviation from regulations. Data acceptable.

VAI-No Response Requested= Deviations(s) from regulations. Data acceptable.

VAI-Response Requested = Deviation(s) form regulations. See specific comments below for data acceptability

OAI = Significant deviations for regulations. Data unreliable.

A. Protocol # 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 Humanised anti-TNF PEG conjugate, CPD870 400 mg sc, (Dosed at Weeks 0, 2, 4 the 4-weekly to Week 24), in the Treatment of Patients with Active Crohn's Disease".

1. Jan Chojnacki, M.D., Lodz, Poland Site 33012

- a. Nine subjects were enrolled at the site. All nine records were audited for the inspection.
- b. There were no limitations to the inspection.
- c. One subject was admitted to the study who did not meet inclusion criteria due to incorrect calculation of the CDAI score. Three subjects had one instance each of inadequate source documentation for inclusion criteria, CDAI score, and past medical history.
- d. The instances of inadequate source documentation of various study parameters did not have an effect on data integrity. Subject 0428 did not meet inclusion criteria for CDAI score. This deficiency might have an effect on data integrity.

2. Pieter Honiball, M.D., Pretoria, South Africa Site 39006

- a. Fourteen subjects were enrolled at the site. Seven subjects completed the study. All records were reviewed for the inspection.
- b. There were no limitations to the inspection.
- c. Three subjects had chest x-rays prior to signing informed consent. Thirteen of fourteen subjects had incorrect information transcribed from source documents to case report forms. The incorrect information concerned the CDAI scores. The errors occurred as a result of a misunderstanding of when the reporting period began and ended. Following the inspection, the sponsor contacted the FDA inspector via letter and stated that all data from the site had been reviewed and corrected, and that "UCB will update the database and collaborate with the review division to update the Clinical Study Report and the BLA". This information was relayed to the medical officer for the application on November 3, 2006.
- d. There should be no problem with the corrected data being used in support of the application.

B. Protocol # 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 Humanised Anti-TNF Conjugate, CDP870 400 mg sc (Dosed 4-Weekly to 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"

1. Robert Petrycka, M.D., Warsaw, Poland Site 33007

- a. Fifteen subjects were enrolled at the site. Ten subjects completed the study. All fifteen records were reviewed for the inspection.
- b. There were no limitations to the inspection.
- c. The regulatory deficiencies were minor clerical errors that should not affect data integrity.
- d. The data from the site can be used in support of the application.

C. Protocol # CDP870-033 "A Phase III Multi-National, Multi-Centre, Open-Label, 52 Week Safety Study to Assess the Safety of Chronic Therapy with the Humanised anti-TNF PEG Conjugate CDP870 400 mg sc (Dosed 4-Weekly to Week 48) in the Treatment of Patients with Active Crohn's Disease Who Have Previously Completed Studies CDP870-031 or CDP870-032"

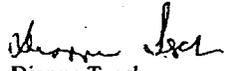
1. Zbigniew Hebzda, M.D., Krakow, Poland Site 33010

- a. Nine subjects were enrolled at the site. Eight subjects were ongoing at the time of the inspection. One subject withdrew due to lack of efficacy. All subject records were reviewed for the inspection.
- b. There were no limitations to the inspection.
- c. The most significant regulatory deficiency at this site was failure to report findings consistent with a urinary tract infection as an adverse event (AE), and failure to report hematuria as an adverse event. There were several instances of clerical errors which would not have had an effect on data integrity.
- d. The data from this site can be used in support of the application.

III. OVERALL ASSESSMENT OF FINDINGS AND GENERAL RECOMMENDATIONS

The studies at the sites appear to have been well conducted. With two exceptions, the regulatory deficiencies appear to have been minor and inadvertent. One subject was entered into the study who did not meet inclusion criteria. At one site the CDAI data was from the wrong reporting periods for 13 of 14 subjects. The sponsor corrected the information following the inspection and forwarded the correct information to the agency. The medical officer for this application was alerted to the problem

It is unlikely that any of the other regulatory deficiencies had an adverse effect on data integrity or reliability.


Dianne Tesch
Consumer Safety Officer

CONCURRENCE:

Supervisory comments

 11/29/00
Leslie K. Ball, M.D.
Branch Chief
Good Clinical Practice Branch II
Division of Scientific Investigations



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

Our STN: BL 125160/0

OCT 12 2006

UCB, Inc.
Ms. Deborah Hogerman
Director, Regulatory Affairs
1950 Lake Park Drive
Smyrna, Georgia 30080

Dear Ms. Hogerman:

This letter is in regard to your biologics license application submitted under Section 351 of the Public Health Service Act.

We have reviewed the Clinical, Product, and Biopharmaceutics sections of your application dated February 28, 2006, for Certolizumab pegol and have determined that the following information is necessary to take a complete action on your application:

CLINICAL

1. During the End of Phase 2 meeting of April 15, 2003, the imputation technique for handling missing data was discussed between the FDA and Celltech. On ~~September 22, 2003, Pfizer agreed to use the non-responder imputation technique for~~ missing data. Please submit primary efficacy results for Study 31 (PRECiSE 1) using the non-responder imputation for missing data, rather than using the last-observation-carried-forward technique.
2. During discussions held between the FDA and Celltech on April 15, 2003, two induction studies (originally designated as Studies 9 and 10) were being proposed as part of the clinical development program. However, data from only one induction study are submitted in the BLA. Are there any additional completed induction study results that are available for submission? If so, submit reports and analyses of those data.
3. Are there any Phase 2 clinical data or any other additional data to support the efficacy findings your induction study? If so, submit reports and analyses of those data.

CLINICAL PHARMACOLOGY

4. Considerable variability in the exposure levels is observed for a fixed dose of 400 mg. The trough certolizumab concentration range following a dose of 400 mg is between

0.5 and 80 mcg/mL. The probability of clinical response (defined as $\Delta\text{CDAI} < -100$) is clearly dependent upon the certolizumab concentration in Study 32 (PRECiSE 2). Patients having lower concentrations (e.g., less than 20 mcg/mL) exhibit lower response rates (see Figure 1, below). The relationship between the probability of response and the certolizumab concentration is not as clear for Study 31 as it is for Study 32, which might be due to the applied non-responder imputation technique. When exposure is highly variable and there is a strong 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. Is there evidence from clinical trials, other than Studies 31 and 32, supporting one fixed dose for all patients? Please provide your justification for selection of a fixed dose rather than an individualized dose.

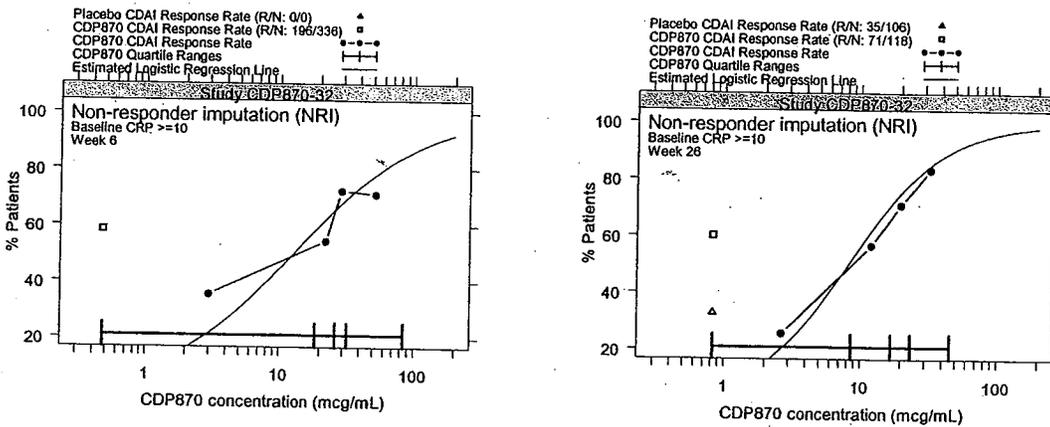


Figure 1 Probability of responding at Week 6 (left) and Week 26 (right) using non-responder imputation (NRI) for missing data with baseline CRP \geq 10 stratification for study CDP870-032.

5. Patients seem to be dropping out of Study 31 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, whereas only 5% of those patients with ΔCDAI score < -135 drop out of the study by Week 26. 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. You performed exposure-response modeling of the longitudinal CDAI data from Phase 2 data. Please produce graphs similar to Figure 1 above (and submit relevant data electronically) using the results of your modeling approach. Specifically, please use the *maximum Bayesian a posteriori* estimates to impute the CDAI scores at 6 and 26 weeks to determine responder status. Use observed data where data are available. If you have questions about this request, please forward them to Dr. Christoffer W. Tornoe, Pharmacometrics Reviewer, through Marlene Swider, Project Manager.

(R)

 1 Page(s) Withheld

Trade Secret / Confidential

Draft Labeling

Deliberative Process

It is requested that you promptly submit a complete response to the items enumerated above. Failure to respond in a timely manner or submission of a partial response may result in a determination that your application is not approvable. If your response to this information request is determined to constitute a major amendment, you will be notified of this decision in writing. Receipt of a major amendment during the last 90 days of the review period extends the review period by an additional 90 days.

Please refer to <http://www.fda.gov/cder/biologics/default.htm> for important information regarding therapeutic biological products, including the addresses for submissions.

Effective August 29, 2005, the new address for all submissions to this application is:

Food and Drug Administration
Center for Drug Evaluation and Research
Therapeutic Biological Products Document Room
5901-B Ammendale Road
Beltsville, MD 20705-1266

If you have any questions, please contact the Regulatory Project Manager, Marlène G. Swider, at (301) 796-2104.

Sincerely,

Brian Strongin, R.Ph., M.B.A.

Brian K. Strongin, R.Ph., M.B.A.
Chief, Project Management Staff
Office of Gastroenterology Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Swider, Marlene

From: Hogerman Deborah (ROC) [Deborah.Hogerman@ucb-group.com]
Sent: Wednesday, November 29, 2006 12:26 PM
To: Swider, Marlene
Cc: Fitzpatrick Stephen (SLH); Hooker Andy (SLH); Oliver Spencer (SLH)
Subject: BLA 125160: IRL response to question #6 (EDTA)
Attachments: BLA 125160 IRL response #6.doc

Hi Marlene

As we were reviewing our response to question #6 in preparation for today's telecon, we notice a publishing glitch that cut off our conclusion statement. As such, I have attached the response again so the reviewers can have a look.

Regards,
Deb

<<BLA 125160 IRL response #6.doc>>

Swider, Marlene

From: Hogerman Deborah (ROC) [Deborah.Hogerman@ucb-group.com]
Sent: Saturday, November 11, 2006 10:38 AM
To: Swider, Marlene
Subject: BLA 125160: Submission of Complete Response to Information Request Letter
Attachments: Cimzia 125160-15.pdf

Hi Marlene

Further to my email earlier this week, the complete response to the Information Request Letter received on 12 Oct was submitted yesterday (10 Nov). You will receive a desk copy by FedEx on Monday, 13 Nov. Copies have also been submitted to the document room. We have sent the submission as both paper and electronic. For your convenience, I've included a copy of the paper submission in this email. It does not contain the PK datasets, as those have been sent in electronic format.

I will call you on Monday to ensure that the package has arrived and to get an idea of when the review team will meet to discuss the responses.

Regards,
Deb

<<Cimzia 125160-15.pdf>>

To: Swider, Marlene

Subject: RE: BLA 125160: Requests for additional analyses for study 031

Hi Marlene

I had not received this but will forward to our stats group and determine when the requested information will be ready.

Regards,
Deb

-----Original Message-----

From: Swider, Marlene [mailto:marlene.swider@fda.hhs.gov]

Sent: Monday, November 06, 2006 10:21 AM

To: Hogerman Deborah (ROC)

Subject: RE: BLA 125160: Requests for additional analyses for study 031

Deborah,

Here are some responses to the study 031 received by me on October 10, 2006. I believe I may have conveyed this to you. If not, please let me know.

Marlene

From: Hogerman Deborah (ROC) [mailto:Deborah.Hogerman@ucb-group.com]

Sent: Tuesday, October 24, 2006 10:20 AM

To: Swider, Marlene

Subject: BLA 125160: Requests for additional analyses for study 031

Hi Marlene

We received from you a request for some additional analyses for study 031 on 9 September. We subsequently sent a proposal for how to comply with the request on 12 September (please see attached word file). I know you had not yet received any feedback on the proposal, but given the remaining time of the review clock, we decided to go ahead and perform the analyses as we proposed. The two attached pdf files contain the analyses.

I will also submit formally to the BLA but wanted the clinical reviewers to immediate access.

Please let me know if you have any questions.

Regards,
Deb

<<Response to request for information related to CDP870-031.doc>> <<CDP870-031 Background by response status.pdf>> <<CDP870-031 CDAI subtotals.pdf>>

Swider, Marlene

From: Hogerman Deborah (ROC) [Deborah.Hogerman@ucb-group.com]
Sent: Monday, November 06, 2006 2:58 PM
To: Swider, Marlene
Subject: BLA 125160: Submission as of 06 Nov 2006
Attachments: BLA 125160 Submissions as of 6 Nov 06.doc

Hi Marlene

Given where we are in the review cycle, I thought it would be useful to provide you with a table of submissions made to BLA 125160 as of today. You should have received full desk copies of most of these, as I know the lag time between the document room and the reviewers desk is quite long. Please let me know if you have not received any of the submissions listed in the attached table.

Regards,
Deb

<<BLA 125160 Submissions as of 6 Nov 06.doc>>

Swider, Marlene

From: Hogerman Deborah (ROC) [Deborah.Hogerman@ucb-group.com]
Sent: Tuesday, October 24, 2006 10:20 AM
To: Swider, Marlene
Subject: BLA 125160: Requests for additional analyses for study 031
Attachments: Response to request for information related to CDP870-031.doc; CDP870-031 Background by response status.pdf; CDP870-031 CDAI subtotals.pdf

Hi Marlene

We received from you a request for some additional analyses for study 031 on 9 September. We subsequently sent a proposal for how to comply with the request on 12 September (please see attached word file). I know you had not yet received any feedback on the proposal, but given the remaining time of the review clock, we decided to go ahead and perform the analyses as we proposed. The two attached pdf files contain the analyses.

I will also submit formally to the BLA but wanted the clinical reviewers to immediate access.

Please let me know if you have any questions.

Regards,
Deb

Response to request for information related to CDP870-031.doc>> <<CDP870-031 Background by response status.pdf>>
CDP870-031 CDAI subtotals.pdf>>

Swider, Marlene

From: Hogerman Deborah (ROC) [Deborah.Hogerman@ucb-group.com]
Sent: Friday, October 20, 2006 1:30 PM
To: Swider, Marlene
Subject: RE: BLA 125160: UCB proposal for answering Question 5 from the IRL

Thanks, Marlene. You have a great weekend as well. I'm planning to call you early next week to discuss the recent BLA submission regarding the clinical PAIs (for which you hopefully received a desk copy on either Monday or Tuesday of this week).

Regards,
Deb

-----Original Message-----

From: Swider, Marlene [mailto:marlene.swider@fda.hhs.gov]
Sent: Friday, October 20, 2006 9:45 AM
To: Hogerman Deborah (ROC)
Subject: FW: BLA 125160: UCB proposal for answering Question 5 from the IRL
Importance: High

FYI.

Have a great weekend.

From: Tornoe, Christoffer
Sent: Thursday, October 19, 2006 4:37 PM
To: Swider, Marlene
Subject: RE: BLA 125160: UCB proposal for answering Question 5 from the IRL

Hi Marlene

We have answered the questions from UCB regarding the longitudinal data analysis in the attached word document. There should therefore not be a need for a t-con.

Best

Chris

From: Swider, Marlene
Sent: Monday, October 16, 2006 11:57 AM
To: Tornoe, Christoffer
Subject: FW: BLA 125160: UCB proposal for answering Question 5 from the IRL
Importance: High

Christoffer,

Here is a proposal from UCB received last Friday. Please advise if scheduling another teleconference is needed.

I do not believe Deborah knew about the scheduled teleconference for this morning. Somehow, I was distracted by Shewit's last e-mails and was waiting from him to contact UCB and obviously I did not. (My apologies...)

Marlene

Swider, Marlene

From: Hogerman Deborah (ROC) [Deborah.Hogerman@ucb-group.com]
Sent: Friday, October 13, 2006 9:48 AM
To: Swider, Marlene
Subject: BLA 125160: UCB proposal for answering Question 5 from the IRL
Importance: High

Hi Marlene

Our modeling group has provided me with the following proposal to respond to question #5 of the Information Request Letter. Can you please forward to Chris Tornoe? If this meets with his approval and he has no questions, we can decide if a telecon is necessary. If not, we would still like to have a telecon.

Please let me know if Chris has any questions.

Regards,
Deb

Proposal for responding to Q5 of Cimzia IRL

UCB will perform a logistic regression on the probability of response versus plasma concentration at weeks 6 and 26 in study -031, using the same straightforward approach as indicated in Figure 1 of the Information Request Letter (ie, dataset summarized in four quartiles).

- Responder status is defined as $\Delta\text{CDAI} < -100$.
- pending further checking, it is assumed that all patients yielded efficacy/concentration data at week 6 (per protocol population); if not, the procedure outlined below for week 26 will also be followed
- The experimental observations will be used for all patients that were still in the study at week 26 (per protocol population)
- For patients that dropped out before week 26, the missing ΔCDAI data will be estimated using the longitudinal model with change over time (section 5.4, Table 9, of CSR)
- For the same patients that dropped out before week 26, the missing plasma concentration data will be carried forward (LOCF) from the last available 2-week post-dose plasma concentration. Indeed, there would be little added value and it would take more time to derive post hoc predicted concentrations from the population PK model (either Pharsight model or UCB model from study CD870-039). Neither of these pop-pk models is time-dependent.
- UCB assumes that the "maximum Bayesian a posteriori estimate" wording used in the FDA letter is synonymous to the more commonly used terminology of "Bayesian feedback method".

Swider, Marlene

From: Hogerman Deborah (ROC) [Deborah.Hogerman@ucb-group.com]
Sent: Thursday, October 12, 2006 1:23 PM
To: Swider, Marlene
Subject: RE: BLA 125160: Longitudinal datasets for studies 005 and 008

Hi Marlene

Thanks so much. Our PK team can be available at the convenience of Chris. Any day next week preferably in the morning (between 8am and 11am) as most of the UCB participants will be calling from Belgium or the UK. How about next Monday, Tuesday, or Wednesday?

Regards,
Deb

-----Original Message-----

From: Swider, Marlene [mailto:marlene.swider@fda.hhs.gov]
Sent: Thursday, October 12, 2006 12:44 PM
To: Hogerman Deborah (ROC)
Subject: RE: BLA 125160: Longitudinal datasets for studies 005 and 008

Hi Deb,

Here is the final IR Letter I am mailing to you today.

Please notice some additions and deletions. Also, when possible, provide me with three good times/dates for you to meet with us.

Marlene G. Swider, M.H.S.A.

Regulatory Health Project Manager

Division of Gastroenterology Products

Center for Drug Evaluation and Research

US Food and Drug Administration

10903 New Hampshire Ave, Silver Spring MD 20993-002

Office: (301) 796-2104

Swider, Marlene

From: Hogerman Deborah (ROC) [Deborah.Hogerman@ucb-group.com]
Sent: Friday, October 06, 2006 7:52 AM
To: Swider, Marlene; Tornoe, Christoffer
Subject: BLA 125160: pharmacometric analysis data set requests
Attachments: define.pdf; effpk.xpt; safe_aes.xpt; safe_inf.xpt

Dear Marlene and Chris

Attached are the longitudinal datasets for studies 005, 008, 031 and 032. Again, I apologize for the delay. I will submit this as a formal amendment to the BLA with a desk copy to Marlene. I wanted to get this to you today so that you could begin your work as soon as possible.

Please let me know if you have any questions.

Regards,
Deb

<<define.pdf>> <<effpk.xpt>> <<safe_aes.xpt>> <<safe_inf.xpt>>

Swider, Marlene

From: [redacted]
Sent: Thursday, October 05, 2006 4:40 PM
To: Swider, Marlene
Cc: Gill-Sangha, Gurpreet
Subject: RE: Request for more information on DMF — related to Cimzia BLA.

Dear Ms. Swider,

Once again I want to apologize for our phone issues. We spoke with Dr. Gill-Sangha regarding the clarification of the [redacted] impurity, the [redacted] impurity, and the testing performed for the [redacted]

Our technical group will be writing a description, including chemical structures and reaction flow, to show that the creation of the [redacted] impurity is a [redacted]. We will have this information to you by Monday, 10/9.

Many thanks for your assistance,

[Handwritten signature]

[Handwritten signature]

This message and any attachments are confidential and solely for the intended recipient. If you are not the intended recipient, disclosure, copying, use, or distribution of the information included in this message is prohibited -- please immediately and permanently delete this message.

From: [redacted]
Sent: Thursday, September 28, 2006 9:24 AM
To: 'Swider, Marlene'
Cc: Gill-Sangha, Gurpreet
Subject: RE: Request for more information on DMF —) related to Cimzia BLA.

Dear Ms. Swider,

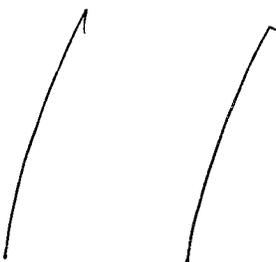
I would like to provide some clarification regarding the question you sent (below) via email. From the information submitted in DMF — it is noted that the [redacted] impurity is tested and controlled at the point of origin in the manufacturing process (i.e. [redacted]). The [redacted] impurity is tested by [redacted] and controlled to a specification of NMT [redacted]. The validation for [redacted] including the experiments related to the [redacted] impurity, is also included in the DMF. Additionally, the results for [redacted] are included in the Batch Analysis section.

Additional [redacted] impurity can not be created in the [redacted]

Further analysis for levels of [redacted] as it would exist in [redacted] is not completed.

Please let me know if I am misinterpreting the question, and what additional information may be needed. I will then follow up with a written response, as completed previously for the earlier inquiries.

Many thanks for your assistance —



This message and any attachments are confidential and solely for the intended recipient. If you are not the intended recipient, disclosure, copying, use, or distribution of the information included in this message is prohibited -- please immediately and permanently delete this message.

From: Swider, Marlene [mailto:marlene.swider@fda.hhs.gov]
Sent: Monday, September 25, 2006 2:14 PM
To: —
Cc: Gill-Sangha, Gurpreet
Subject: Request for more information on DMF — related to Cimzia BLA.
Importance: High

Dear —

Could you please address the request below?

— is to be controlled in PEG2MAL40K — to a level of NMT —, and is a part of the total impurity specifications at NMT —. However, no data is provided to support this impurity. Please provide data including chromatograms and validation to show that — is measurable by an analytical method as part of total impurity specification. Also, provide a summary data on levels of — obtained for PEG2MAL40K batches.

Thanks,

Marlene G. Swider, M.H.S.A.
Regulatory Health Project Manager
Division of Gastroenterology Products
Center for Drug Evaluation and Research
US Food and Drug Administration
10903 New Hampshire Ave, Silver Spring MD 20993-002
Office: (301) 796-2104

Swider, Marlene

From: Deborah.Hogerman@ucb-group.com
Sent: Thursday, September 28, 2006 11:11 AM
To: Swider, Marlene
Subject: BLA 125160: A questions for the Pharmcometrics reviewers
Importance: High

Hi Marlene

Can you please forward the following question to the Pharmacometric reviewers?

Thanks,
Deb

As stated before, the analysis referred to as No. 40001559 was commissioned by Celltech to — t prior to the Celltech-UCB merger, and the personnel involved at both Celltech and — have left the respective companies.

Following the request UCB received on August 30, we provided the final datasets, outputs and individual and diagnostic plots for the final models.

We were unable to retrieve the control streams and output listings for the intermediate model building steps, and the decision tree.

A great number of datasets were provided by Celltech to — t and all concentrations or individual exclusions were performed by hard-coding in S-Plus.

It would therefore be very cumbersome to reconstitute the datasets used for the analyses.

In light of the other request from the Pharmacometric Division to submit longitudinal PK, efficacy and safety data from studies CDP870-005, -008, -031 and -032 to perform an exposure-response modeling, and to ensure the most efficiency, we propose to also submit the data from studies 001, 002, 003 and 004 (used in the above mentioned exploratory PKPD analysis No. 40001559, further to studies 005 and 008) under the requested format. Does the FDA concur with this proposal?

Swider, Marlene

From: Deborah.Hogerman@ucb-group.com
Sent: Tuesday, September 26, 2006 11:00 AM
To: Swider, Marlene
Subject: BLA 125160 submissions this week (25-27 September)

Hi Marlene

I wanted to give you a heads up as to the planned submissions to the BLA this week. You will receive full desk copies of each submission.

We have 3 CMC submission related to the FDA Form 483 observations at _____ the drug substance contract manufacturer. In all cases, and because the 483 was issued to _____ they have submitted the responses and updated information to the Office of Compliance, Division of Product Manufacturing Quality. This information is being submitted to the BLA to ensure that the Division has all relevant documents related to the inspection at _____

- 1) _____ initial response to 483 observations and follow up information related to analytical methods comparability between _____ and UCB Rochester (submitted on 25 Sep)
- 2) Updated information related to the _____ parameters (submitted on 25 Sep)
- 3) Updated information related to _____ method validation (will be submitted on 27 Sep)

Pharmacometric requests:

- 1) Diagnostic plots or individually predicted and population predicted curves overlaid to the experimental data points for study number 40001559. These were not included in the 13 September submission as they were not yet available (will be submitted on 27 Sep)
- 2) Longitudinal datasets for Phase II studies, as discussed with Chris and Joe at our telecon last week (will be submitted on 27 Sep)

Last, we will submit this week the clinical investigator responses to the FDA 483 issued following the inspection at the 4 sites. This submission will also include UCB responses to some of the findings. I'll discuss this with you in more detail by phone.

Regards,
Deb

Swider, Marlene

From: Deborah.Hogerman@ucb-group.com
Sent: Thursday, September 21, 2006 7:53 AM
To: Swider, Marlene
Subject: BLA 125160 updates
Attachments: UCB response to Cimzia questions and data request_Biopharmacometrics.doc; Response to request for information related to CDP870-031.doc

Hi Marlene

Hope your doing well. Here's an update as to where we are:

1) We had a short but productive meeting with Chris and Joe yesterday. I had sent to you on Monday our responses to the clarification questions from pharmacometrics, but they had not received them. I told Chris I would follow up with you; I've reattached the document for you to send to them.

<<UCB response to Cimzia questions and data request_Biopharmacometrics.doc>>

We agreed with Chris and Joe that we would send the longitudinal datasets for the efficacy data from the Phase II studies by next Tuesday (26 Sep). I'll again send a desk copy to you. The remaining datasets will be submitted during the week of 2 Oct.

2) You should have received a desk copy yesterday (20 Sep) of the request data for study CDP870-039.

Have you received any feedback from the clinical stat reviewers on the clarifications for the datasets related to study CDP870-031 that we requested on 12 Sep (attached)?

<<Response to request for information related to CDP870-031.doc>>

4) Do you have any more information or a firm date for our meeting for the first week in October? I want to make sure all necessary staff are available.

I'll give you a call later today but wanted to also give a quick email update.

Regards,
Deb

Swider, Marlene

From: Deborah.Hogerman@ucb-group.com
Sent: Tuesday, September 19, 2006 4:40 PM
To: Swider, Marlene
Subject: Additional clarification for datasets requested by Biopharmacometrics
Attachments: CDP870-CD proposal for clarification RB 19-09-2006.doc

Hi Marlene

Thanks for sending the clarifications for the longitudinal datasets requested by the Biopharmacometric reviewers. Our stats/DM group is requesting some additional clarifications for the safety data. Can you please send the attached document to the Biopharmacometrics reviewers? It would be great if we can discuss this briefly at our telecon tomorrow.

Thanks so much,
Deb

<<CDP870-CD proposal for clarification RB 19-09-2006.doc>>

Swider, Marlene

From: Deborah.Hogerman@ucb-group.com
Sent: Monday, September 18, 2006 2:28 PM
To: Swider, Marlene
Subject: UCB responses to Biopharmacometric questions/requests
Attachments: UCB response to Cimzia questions and data request_Biopharmacometrics.doc

Hi Marlene

In preparation for our Biopharmacometrics telecon this Wednesday, I've attached a document with our responses to the requests outlined in your email dated 12 Sep 06.

<<UCB response to Cimzia questions and data request_Biopharmacometrics.doc>>

Also, we are in the process of compiling more of the requested data from **Study Number 40001559**. Can you please ask the Pharmacology reviewer(s) the following question:

UCB and — are working on locating the source files and will provide them as rapidly as possible. UCB enquires if the S-Plus data management script and the source data sets may be submitted to FDA, or whether UCB should insert the deleted data as flagged lines into the current final XPT file.

Thanks and regards,

b

Swider, Marlene

From: Deborah.Hogerman@ucb-group.com
Sent: Friday, September 15, 2006 12:19 PM
To: Swider, Marlene
Subject: BLA 125160 - today's update

Hi Marlene

Today's update as to the status of pending requests:

1) We submitted by email on 12 Sep a proposal to comply with the request for additional analyses for study 031. We will prepare and submit these data as soon as we receive feedback on the proposal.

2) Status of requests received on 12 Sep, which will be the basis for our discussion on 20 Sep:

*clarification of data discrepancies - we will submit our responses on 18 Sep for the reviewers to have before our meeting.

*request for submission of longitudinal data on PK, efficacy and safety - we submitted request for clarification on 13 Sep and will prepare and submit the data as soon as we receive feedback

*request for PK modeling data from study CDP87039 - these datasets have been compiled and will be submitted w/c 18 Sep.

3) We still owe some of the datasets for PK modelling report 40001559. We now have most of the data and will submit next week as well.

I'm out of the office for this afternoon, but I will call you on Monday. If you need to contact me, feel free to call my mobile.

Have a great weekend!

Regards,
Deb

1	031	400	15	2.0	10.1	1	0	0	1	0
2	032	400	10	12	5.6	1	1	1	0	0
2	032	400	30	4	5.6	1	1	0	0	1
3	005	X	50	7	15.0	0	1	0	1	0
4	008	X	20	8	7.0	1	0	1	0	0
...										

From: Deborah.Hogerman@ucb-group.com [mailto:Deborah.Hogerman@ucb-group.com]
Sent: Friday, September 15, 2006 12:19 PM
To: Swider, Marlene
Subject: BLA 125160 - today's update

Hi Marlene

Today's update as to the status of pending requests:

1) We submitted by email on 12 Sep a proposal to comply with the request for additional analyses for study 031. We will prepare and submit these data as soon as we receive feedback on the proposal.

2) Status of requests received on 12 Sep, which will be the basis for our discussion on 20 Sep:

*clarification of data discrepancies - we will submit our responses on 18 Sep for the reviewers to have before our meeting.

*request for submission of longitudinal data on PK, efficacy and safety - we submitted request for clarification on 13 Sep and will prepare and submit the data as soon as we receive feedback

*request for PK modeling data from study CDP87039 - these datasets have been compiled and will be submitted w/c 18 Sep.

3) We still owe some of the datasets for PK modelling report 40001559. We now have most of the data and will submit next week as well.

I'm out of the office for this afternoon, but I will call you on Monday. If you need to contact me, feel free to call my mobile.

Have a great weekend!

Regards,
 Deb

Swider, Marlene

From: Deborah.Hogerman@ucb-group.com
Sent: Tuesday, September 12, 2006 1:50 PM
To: Swider, Marlene
Subject: RE: Request for more information
Attachments: Response to request for information related to CDP870-031.doc

Hi Marlene

Please see the attached document relating to the request for information for CDP870-031. As I discussed, this is a proposal for complying with the request.

Thanks,
Deb

-----Original Message-----

From: Swider, Marlene [mailto:marlene.swider@fda.hhs.gov]
Sent: Monday, September 11, 2006 10:25 AM
To: Hogerman Deborah (ROC)
Subject: RE: Request for more information

Thanks. I look forward.

Marlene

From: Deborah.Hogerman@ucb-group.com [mailto:Deborah.Hogerman@ucb-group.com]
Sent: Monday, September 11, 2006 8:07 AM
To: Swider, Marlene
Subject: RE: Request for more information

Hi Marlene

I have just met with the clinical team regarding the questions below. I will get back to you by tomorrow morning at the latest with proposals for complying with these requests, as we want to be sure that we are appropriately interpreting each request.

Regards,
Deb

-----Original Message-----

From: Swider, Marlene [mailto:marlene.swider@fda.hhs.gov]
Sent: Friday, September 08, 2006 2:08 PM
To: Hogerman Deborah (ROC)
Subject: Request for more information

Deb,

The following information for Study CDP870-031 is being requested:

1. There is some discrepancy between the data set and the study report on the number of subjects with clinical response at Week 6 and Weeks 6 and 26 in the stratum CRP ≥ 10 mg /L at Baseline stratum for placebo group . Table 14.2.2.7 gave 40 and 19 for Week 6 and Weeks 6 and 26,

2/16/2007

respectively. But, from sponsor's data set, the numbers are 41 and 20, for Week 6 and Weeks 6 and 26, respectively. Please explain.

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

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

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

5. Also, please include the discrepancy noted between the number of patients that completed response as reported which was 660 and the number obtained from the raw data of 674?

As usual, your prompt response to these discrepancies would be greatly appreciated.

Have a wonderful weekend.

*Marlene G. Swider, M.H.S.A.
Regulatory Health Project Manager
Division of Gastroenterology Products
Center for Drug Evaluation and Research
US Food and Drug Administration
10903 New Hampshire Ave, Silver Spring MD 20993-002
Office: (301) 796-2104*

Swider, Marlene

From: Deborah.Hogerman@ucb-group.com
Sent: Monday, September 11, 2006 5:13 PM
To: Swider, Marlene
Cc: Tornoe, Christoffer; Ghosh, Tapash
Subject: RE: BLA 125160: Complete response submission

Hi Marlene

We will submit the requested information for study 4001548 on Tuesday, 12 September. We will submit some but not all information from study 40001559 on either Tuesday or Wednesday at the latest. The remaining information from study 1559 will be submitted as soon as possible. We are still working with the vendor _____ to obtain some of the outstanding information. However, we wanted to get you what we have as soon as possible.

I will follow up with you by telephone on 12 Sep to determine if official copies to the BLA and desk copies to you are the most efficient way to submit the information.

Regards,
Deb

-----Original Message-----

From: Swider, Marlene [mailto:marlene.swider@fda.hhs.gov]
Sent: Wednesday, August 30, 2006 9:51 AM
To: Hogerman Deborah (ROC)
Cc: Tornoe, Christoffer; Ghosh, Tapash
Subject: RE: BLA 125160: Complete response submission
Importance: High

Hi Deborah,

I hope you enjoyed your time away. I received the request below back in August 11, 2006 so my apologies to everyone for the lateness on this request. However, now that we are back I would appreciate if you can let me know **by today** when can we expect a response.

This request for information is for UCB CIMZIA BLA STN 125160/0 from the Pharmacometrics staff regarding pharmacology PK/PD data:

Please submit the following datasets to support the population analysis in Report Number 40001559 and 40001548:

All datasets used for model development and validation should be submitted as a SAS transport files (*.xpt). A description of each data item should be provided in a Define.pdf file. Any concentrations and/or subjects that have been **excluded from the analysis** should be flagged and maintained in the datasets.

Model codes or control streams and output listings should be provided for all major model building steps, e.g., base structural model, covariates models, final model, and validation model. These files should be submitted as ASCII text files with *.txt extension (e.g.: myfile_ctl.txt, myfile_out.txt).

A model development decision tree and/or table which gives an overview of modeling steps.

For the population analysis reports we request that you submit, in addition to the standard model diagnostic plots, individual plots for a representative number of subjects. Each individual plot should include observed

concentrations, the individual predication line and the population prediction line. In the report, tables should include model parameter names and units. For example, oral clearance should be presented as CL/F (L/h) and not as THETA(1). Also provide in the summary of the report a description of the clinical application of modeling results.

Thanks so much.

Marlene G. Swider, M.H.S.A.

Regulatory Health Project Manager

Division of Gastroenterology Products

Center for Drug Evaluation and Research

US Food and Drug Administration

10903 New Hampshire Ave, Silver Spring MD 20993-002

Office: (301) 796-2104

From: Deborah.Hogerman@ucb-group.com [mailto:Deborah.Hogerman@ucb-group.com]

Sent: Friday, July 28, 2006 9:35 AM

To: Swider, Marlene

Subject: RE: BLA 125160: Complete response submission

Hi Marlene

Attached are the responses for the requests outlined below. The reports are embedded in the word document. I will also submit formally with a cover letter to the BLA next week.

Also, I will be on vacation next week. However, if you need me for any reason, please feel free to call me on my mobile phone _____

Let me know if you have any questions on the attached.

Regards,
Deb

-----Original Message-----

From: Swider, Marlene [mailto:marlene.swider@fda.hhs.gov]

Sent: Wednesday, July 26, 2006 4:49 PM

To: Hogerman Deborah (ROC)

Subject: RE: BLA 125160: Complete response submission

Deborah -

Any word on my previous faxed request below:

- o Please submit for review a copy of a report referenced in the drug substance process validation narrative: R-2005-167 "Investigation of CDP-870"



Thanks,
Marlene Swider

From: Hogerman Deborah (ROC) [mailto:Deborah.Hogerman@ucb-group.com]
Sent: Tuesday, June 13, 2006 9:39 AM
To: Swider, Marlene
Subject: BLA 125160: Complete response submission

Hi Marlene

Just a heads-up; we are submitting this week the complete response to the requests in the BLA filing letter data 28 April 06. The submission will include the final report for the 52-week monkey study, the requested analysis datasets and SAS program. In addition to the formal submission copies, I have arranged for you to receive a desk copy.

Please let me know you have any questions.

Regards,
Deb

Swider, Marlene

From: Hogerman Deborah (ROC) [Deborah.Hogerman@ucb-group.com]
Sent: Friday, June 02, 2006 3:03 PM
To: Swider, Marlene
Subject: UCB (Pharmacia) pre-IND correspondence (IND 11,197)
Attachments: 04152003.pdf; 9999_22_May_2003.pdf; 9999_29_Jul_2003.pdf

Hi Marlene

I've attached the following:

- 1) Internal (Pharmacia; owner of the product at that time) minutes for the EOPII meeting with CBER dated April 15, 2003
- 2) Submission of revised clinical development plan following EOPII meeting dated May 22, 2003
- 3) Submission of final clinical development plan following review of May 22, 2003 submission, dated July 29, 2003. This submission was requested by Dr. Liang in order to document the agreements between CBER and Pharmacia. This represents the plan that was agreed by CBER just before the IND was submitted on July 30, 2003

Please let me know if you need anything else.

Regards,
Deb

-----Original Message-----

From: Swider, Marlene [mailto:marlene.swider@fda.hhs.gov]
Sent: Friday, June 02, 2006 1:33 PM
To: Hogerman Deborah (ROC)
Cc: Bezabeh, Shewit
Subject: RE: BLA 125160: Response to request for container/closure integrity testing

Thanks for your prompt response below.

Also, could you please provide me with copies of your minutes regarding agreement with FDA on how to conduct end of Phase 2 studies? (These most probably would be under minutes of End of Phase II meeting of April 15, 2003, Telephone contacts dated May 22, 2003 or July 29, 2003, for your IND 11197 and/or IND 9869).

I am trying to gather all history from our document room but would like to see what you have too.

Thanks much,

Marlene

From: Hogerman Deborah (ROC) [mailto:Deborah.Hogerman@ucb-group.com]
Sent: Friday, June 02, 2006 12:41 PM
To: Swider, Marlene
Subject: BLA 125160: Response to request for container/closure integrity testing

Hi Marlene

Attached are the responses from _____ to FDA's questions regarding container/closure testing. Although written by _____ UCB has reviewed and approved these responses as well. For any questions in the future, it's probably easiest to contact me and I'll facilitate the responses from either internally or our external contractors.

Please let me know if you have any questions on the responses. Also, should we file this as a formal submission to the BLA?

Thanks and regards,
Deb

<<_0602100151_001.pdf>>

Swider, Marlene

From: Deborah.Hogerman@ucb-group.com
Sent: Thursday, September 07, 2006 1:14 PM
To: Swider, Marlene
Subject: UCB (Pharmacia) pre-IND correspondence (IND 11,197) - documents
Attachments: 04152003.pdf, 9999_22_May_2003.pdf, 9999_29_Jul_2003.pdf

Hi Marlene,

The following documents should now be attached below:

- 1) Internal (Pharmacia; owner of the product at that time) minutes for the EOPII meeting with CBER dated April 15, 2003
- 2) Submission of revised clinical development plan following EOPII meeting dated May 22, 2003
- 3) Submission of final clinical development plan following review of May 22, 2003 submission, dated July 29, 2003. This submission was requested by Dr. Liang in order to document the agreements between CBER and Pharmacia. This represents the plan that was agreed by CBER just before the IND was submitted on July 30, 2003

Regards,
Nancy

Swider, Marlene

From: Deborah.Hogerman@ucb-group.com
Sent: Thursday, September 07, 2006 12:48 PM
To: Swider, Marlene
Subject: RE: UCB (Pharmacia) pre-IND correspondence (IND 11,197)

Hi Marlene,

As we discussed today, attached are the requested documents regarding agency interactions with Pharmacia. If there is anything else that you need please call me on my cell phone at _____, but I believe that this reflects the items requested.

Regards,
Deb

-----Original Message-----

From: Hogerman Deborah (ROC)
Sent: Friday, June 02, 2006 3:03 PM
To: 'Swider, Marlene'
Subject: UCB (Pharmacia) pre-IND correspondence (IND 11,197)

Hi Marlene

I've attached the following:

- 1) Internal (Pharmacia; owner of the product at that time) minutes for the EOPII meeting with CBER dated April 15, 2003
- 2) Submission of revised clinical development plan following EOPII meeting dated May 22, 2003
- 3) Submission of final clinical development plan following review of May 22, 2003 submission, dated July 29, 2003. This submission was requested by Dr. Liang in order to document the agreements between CBER and Pharmacia. This represents the plan that was agreed by CBER just before the IND was submitted on July 30, 2003

Please let me know if you need anything else.

Regards,
Deb

-----Original Message-----

From: Swider, Marlene [mailto:marlene.swider@fda.hhs.gov]
Sent: Friday, June 02, 2006 1:33 PM
To: Hogerman Deborah (ROC)
Cc: Bezabeh, Shewit
Subject: RE: BLA 125160: Response to request for container/closure integrity testing

Thanks for your prompt response below.

Also, could you please provide me with copies of your minutes regarding agreement with FDA on how to conduct end of Phase 2 studies? (These most probably would be under minutes of End of Phase II meeting of April 15, 2003, Telephone contacts dated May 22, 2003 or July 29, 2003, for your IND 11197 _____)

I am trying to gather all history from our document room but would like to see what you have too.

Thanks much,

Marlene

From: Hogerman Deborah (ROC) [mailto:Deborah.Hogerman@ucb-group.com]
Sent: Friday, June 02, 2006 12:41 PM
To: Swider, Marlene
Subject: BLA 125160: Response to request for container/closure integrity testing

Hi Marlene

Attached are the responses from _____ to FDA's questions regarding container/closure testing. Although written by _____ UCB has reviewed and approved these responses as well. For any questions in the future, it's probably easiest to contact me and I'll facilitate the responses from either internally or our external contractors.

Please let me know if you have any questions on the responses. Also, should we file this as a formal submission to the BLA?

Thanks and regards,
Deb

<<_0602100151_001.pdf>>

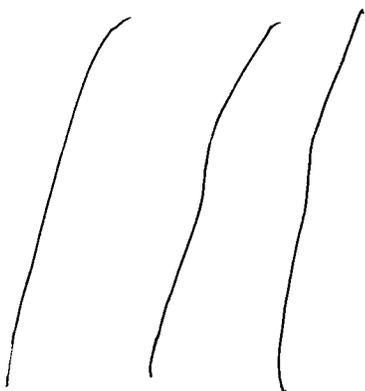
Swider, Marlene

From: _____
Sent: Wednesday, September 06, 2006 6:08 PM
To: Swider, Marlene
Cc: Gill-Sangha, Gurpreet
Subject: RE: Additional Questions for DMFs _____
Attachments: DMF — Response 090606.pdf

Dear Ms. Swider,

Please find attached the additional response from _____, regarding the Impurity question. This response, in duplicate, will be sent tomorrow to the FDA Document Room at the address you have provided. Please contact me if you have any questions regarding the attached information. I believe this covers the items we discussed in our teleconference, but if there is additional information you need please let me know. Thank you for your consideration.

Kind regards,



This message and any attachments are confidential and solely for the intended recipient. If you are not the intended recipient, disclosure, copying, use, or distribution of the information included in this message is prohibited -- please immediately and permanently delete this message.

From: _____
Sent: Friday, August 25, 2006 11:35 AM
To: 'Swider, Marlene'
Cc: Gill-Sangha, Gurpreet
Subject: RE: Additional Questions for DMFs _____

Dear Ms. Swider,

Please find attached the responses from _____ regarding the questions below. This response, in duplicate, has been sent today to the FDA Document Room at the address you have provided. Please contact me if you have any questions regarding the attached information. Thank you for your consideration.

Kind regards,



—
/ /

This message and any attachments are confidential and solely for the intended recipient. If you are not the intended recipient, disclosure, copying, use, or distribution of the information included in this message is prohibited -- please immediately and permanently delete this message.

From: —
Sent: Friday, August 04, 2006 4:28 PM
To: 'Swider, Marlene'
Subject: RE: Additional Questions for DMFs —

Marlene,

After discussions with my contributors, our estimated timeline for the response submission is August 25th. Please let me know if you have any questions regarding this information.

Thanks, —

/ / /

This message and any attachments are confidential and solely for the intended recipient. If you are not the intended recipient, disclosure, copying, use, or distribution of the information included in this message is prohibited -- please immediately and permanently delete this message.

From: Swider, Marlene [mailto:marlene.swider@fda.hhs.gov]
Sent: Wednesday, August 02, 2006 8:09 AM
To: —
Cc: Gill-Sangha, Gurpreet
Subject: Additional Questions for DMFs —

— Could you please add the following questions to my previous request below (July 26, 2006) and advise when you think responses can be available?

Thanks,

Marlene Swider

For DMF —



For DMF —



From: Swider, Marlene
Sent: Wednesday, July 26, 2006 4:56 PM
To: —
Subject: RE: DMF — Questions for UCB, Inc. BLA STN 125160/0

Please also provide information on the following:

1



/ Page(s) Withheld

 | Trade Secret / Confidential

 Draft Labeling

 Deliberative Process

Swider, Marlene

From: Deborah.Hogerman@ucb-group.com
Sent: Tuesday, September 05, 2006 4:47 PM
To: Swider, Marlene
Subject: Re: Information request for CIMZIA BLA 125160 Biopharmaceutical S tatistical Data

Hi Marlene

We received this request last Friday. I think I sent a follow up email and when we last spoke, indicated that information from our internal report would be sent next week. The other report was from an external vendor and we are seeking their assistance to comply with this request. Since this will also contain electronic data, it may be useful to work with _____ to make sure that we submit the correct format.

I'll let you know as soon as I have a firm date for submission of this information.

Regards,
Deb

----- Original Message -----

From: Swider, Marlene <marlene.swider@fda.hhs.gov>
To: Hogerman Deborah (ROC)
Cc: Ghosh, Tapash <tapash.ghosh@fda.hhs.gov>; Tornoe, Christoffer <Christoffer.Tornoe@fda.hhs.gov>
Sent: Tue Sep 05 16:29:57 2006
Subject: Information request for CIMZIA BLA 125160 Biopharmaceutical Statistical Data

b,

I believe I requested the information below sometime ago but have not heard from your staff yet. Can we have this information by the end of this week?

Please submit the following datasets to support the population analysis in Report Number 40001559 and 40001548:

* All datasets used for model development and validation should be submitted as a SAS transport files (*.xpt). A description of each data item should be provided in a Define.pdf file. Any concentrations and/or subjects that have been excluded from the analysis should be flagged and maintained in the datasets.

* Model codes or control streams and output listings should be provided for all major model building steps, e.g., base structural model, covariates models, final model, and validation model. These files should be submitted as ASCII text files with *.txt extension (e.g.: myfile_ctl.txt, myfile_out.txt).

* A model development decision tree and/or table which gives an overview of modeling steps.

For the population analysis reports we request that you submit, in addition to the standard model diagnostic plots, individual plots for a representative number of subjects. Each individual plot should include observed concentrations, the individual predication line and the population prediction line. In the report, tables should include model parameter names and units. For example, oral clearance should be presented as CL/F (L/h) and not as THETA(1). Also provide in the summary of the report a description of the clinical application of modeling results.

Thanks,

Marlene G. Swider, M.H.S.A.
Regulatory Health Project Manager
Division of Gastroenterology Products
Center for Drug Evaluation and Research
US Food and Drug Administration

2/16/2007

10903 New Hampshire Ave, Silver Spring MD 20993-002

Office: (301) 796-2104

Appears This Way
On Original

Swider, Marlene

From: _____
Sent: Monday, July 24, 2006 5:20 PM
To: Swider, Marlene
Cc: Gill-Sangha, Gurpreet
Subject: RE: DMF — Questions for UCB, Inc. BLA STN 125160/0

Dear Ms. Swider,

A CD desk copy of DMF — has been shipped by FedEx today to the address you have provided. The tracking number for this

Kind regards,

This message and any attachments are confidential and solely for the intended recipient. If you are not the intended recipient, disclosure, copying, use, or distribution of the information included in this message is prohibited -- please immediately and permanently delete this message.

From: Swider, Marlene [mailto:marlene.swider@fda.hhs.gov]
Sent: Monday, July 24, 2006 12:08 PM
To: _____
Cc: Gill-Sangha, Gurpreet
Subject: RE: DMF — Questions for UCB, Inc. BLA STN 125160/0

Please provide Dr. Gurpreet Gill-Sangha with a CD desk copy of the DMF — referred in your response today. This desk copy is needed to continue the review of your submission, so please submit **at your earliest** convenience.

Her address is: Att: Dr. Gurpreet Gill Sangha
8800 Rockville Pike
NIH (Room 3NN15)
Building 29B, HFD-123
Bethesda, Maryland 20892

Thanks again,

Marlene G. Swider, M.H.S.A.
Regulatory Health Project Manager

2/16/2007

*Division of Gastroenterology Products
Center for Drug Evaluation and Research
US Food and Drug Administration
9903 New Hampshire Ave, Silver Spring MD 20993-002
Office: (301) 796-2104*

From: _____

Sent: Monday, July 24, 2006 10:39 AM

To: Swider, Marlene

Cc: Gill-Sangha, Gurpreet

Subject: RE: DMF — Questions for UCB, Inc. BLA STN 125160/0

<< Message: Untitled Attachment >> << File: DMF — Response 072406.pdf >>

Swider, Marlene

From: Deborah.Hogerman@ucb-group.com
Sent: Monday, July 10, 2006 3:42 PM
To: Swider, Marlene
Subject: BLA 125160: — timepoint for effect — : on stability
Attachments: R-2006-107-02.pdf

Hi Marlene

Further to my email of July 5, attached is a copy of the summary report for the — timepoint from the study to assess the effect — on stability of CDP870. This will be formally submitted this week to the BLA, but I thought Kurt Brorson may like a copy before he goes to — next week.

Please let me know if you have any questions. Also, did you receive the desk copy of the complete response information from the 28 April filing letter?

Thanks and regards,
Deb

<<R-2006-107-02.pdf>>

Swider, Marlene

From: Deborah.Hogerman@ucb-group.com
Sent: Wednesday, July 05, 2006 8:06 AM
To: Swider, Marlene
Subject: BLA 125160: Submission since initial filing
Attachments: 20060526.pdf

Hi Marlene

I hope you had a nice holiday weekend. Further to our email exchange at the end of last week, I wanted to make sure that you have received all of the submission we have made since the initial BLA filing on 28 February:

1) On 26 May, we submitted an update of — elated information as part of our commitment made to the Agency at the pre-BLA meeting and in the initial BLA. In case you have not received it from the document room, a copy is attached. We still owe the — stability timepoint from the — spiked material, which will be officially submitted next week (I'll send you an email copy as well).

<<20060526.pdf>>

2) On 15 June, we submitted the complete response to the requests (52 week monkey study report, efficacy data files, and SAS program) in the filing letter dated 28 April 2006. We did send a desk copy to you at that time, but based on your email last Friday, you never received it. I arranged for another desk copy to be sent to you, which should have arrived on Monday 3 July. Can you please confirm receipt?

3) On 27 June, we submitted the 120 day safety update, for which you have confirmed receipt.

Apologies for all of the confusion with these submissions. I will make sure that you continue to receive desk copies and will follow up to confirm receipt.

Thanks and regards,
Deb

Swider, Marlene

From: Deborah.Hogerman@ucb-group.com
Sent: Thursday, June 29, 2006 8:46 AM
To: Swider, Marlene
Subject: BLA 125160: 120 day safety update

Hi Marlene

I hope you are well. We submitted the 120 day safety update to the BLA on 27 June. You may have already received it, but I wanted to give you a heads up just in case...

Regards,
Deb

Swider, Marlene

From: Hogerman Deborah (ROC) [Deborah.Hogerman@ucb-group.com]

Sent: Tuesday, June 13, 2006 9:39 AM

To: Swider, Marlene

Subject: BLA 125160: Complete response submission

Hi Marlene

Just a heads-up; we are submitting this week the complete response to the requests in the BLA filing letter data 28 April 06. The submission will include the final report for the 52-week monkey study, the requested analysis datasets and SAS program. In addition to the formal submission copies, I have arranged for you to receive a desk copy.

Please let me know you have any questions.

Regards,

Deb

Swider, Marlene

From: Hogerman Deborah (ROC) [Deborah.Hogerman@ucb-group.com]
Sent: Sunday, May 14, 2006 9:48 AM
To: Swider, Marlene
Subject: BLA 125160: April 28 2006 Request for additional information
Attachments: BLA 125160 Description of AD and SAS Program.doc; BLA 125160.Contents of AD.doc; BLA 125160 Filing Letter.pdf

Hi Marlene

We received the April 28 BLA filing letter with requests for additional information. Regarding points 2, 3, and 4, we want to ensure that we have interpreted the request correctly. Attached are two documents that describes our plan to comply with the requests. The first (titled "BLA 125160 Description of AD and SAS Programs") describes how the analysis datasets will be compiled and the endpoints to be included. The second document (titled "BLA 125160 Contents of AD") is the detailed specification of the analysis datasets to be provided.

Can you please share this with the statistician and/or data management and let me know if they concur? We plan to submit this information as a complete response to the file ASAP once FDA agrees with our approach. For your convenience, I have also included the April 28 letter from FDA.

I will call you on Monday to follow-up, but I thought that sending these documents would be useful.

Thanks and regards,
Deb Hogerman
UCB, Inc.

BLA 125160 Description of AD and SAS Programs
<<BLA 125160 Description of AD and SAS Program.doc>>

BLA 125160 Contents of AD
<<BLA 125160 Contents of AD.doc>>

BLA 125160 Filing Letter
<<BLA 125160 Filing Letter.pdf>>



Center for Drugs Evaluation and Research
Food and Drug Administration
Rockville, MD 20852

STN # 125160/0

Date: April 28, 2006
From: Brian E. Harvey, M.D., Ph.D. Division Director
Subject: Designation of Review Schedule for BLA review
Sponsor: UCB, Inc.
Product: Certolizumab pegol, CIMZIA™

Clinical Indication:

Standard (10 month)
 Priority (6 month)

Signature/Date

Brian E. Harvey 4/28/06



Our STN: BL 125160/0

APR 28 2006

UBC, Inc.
Attention: Ms. Deborah Hogerman
Director, Regulatory Affairs
755 Jefferson Road
Rochester, New York 14623

Dear Ms. Hogerman:

This letter is in regard to your biologics license application (BLA) STN BL 125160/0 submitted under section 351 of the Public Health Service Act.

We have completed an initial review of your application dated February 28, 2006 for Certolizumab pegol to determine its acceptability for filing. Under 21 CFR 601.2(a) we have filed your application today. The user fee goal date is December 30, 2006. This acknowledgment of filing does not mean that we have issued a license nor does it represent any evaluation of the adequacy of the data submitted.

During the process of reviewing your application, we determined that the following information is necessary to take a complete action:

1. Please provide the final results for the "52-week study with recovery period in monkeys to examine the effects of CDP870 on hematological and morphological parameters following repeat subcutaneous dosing, "(Study #506771).
2. Please provide summary efficacy file for co-primary efficacy endpoints. This file needs to include patient ID, investigator, stratum, treatment group, race, gender, age, outcomes from primary efficacy endpoints, completion status, the reason for withdrawal, and compliance. One patient per record.
3. Please provide summary efficacy file for secondary efficacy endpoints. This file should include patient ID, investigator, stratum, treatment group, race, gender, age, outcomes from primary efficacy and secondary efficacy endpoints, completion status, the reason for withdrawal, and compliance. One patient per record.
4. Please provide SAS programs for analysis of co-primary efficacy endpoints and secondary efficacy endpoints. So, the results reported in clinical reports could be duplicated.

It is requested that you promptly submit a complete response to the items enumerated above. Failure to respond in a timely manner or submission of a partial response may result in a determination that your supplement is not approvable. Review of your supplement is continuing.

We are providing the above comments to give you preliminary notice of potential review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our complete review. Issues may be added, deleted, expanded upon, or modified as we review the application. If you respond to these issues during this review cycle, we may not consider your response before we take an action on your application. Following a review of the application, we shall advise you in writing of any action we have taken and request additional information if needed.

If you have not already done so, we request that you submit the *content of labeling* [21 CFR 601.14(b)] in Structured Product Labeling (SPL) format as described at the following website: <http://www.fda.gov/oc/datacouncil/spl.html>.

Please refer to <http://www.fda.gov/cder/biologics/default.htm> for important information regarding therapeutic biological products, including the addresses for submissions.

Effective August 29, 2005, the new address for all submissions to this application is:

Food and Drug Administration
Center for Drug Evaluation and Research
Therapeutic Biological Products Document Room
5901-B Ammendale Road
Beltsville, MD 20705-1266

If you have any questions, please contact the Regulatory Project Manager, Marlène G. Swider, at (301) 796-2104.

Sincerely,

*Melissa Hancock Furness
for Brian K. Strongin 04/28/06*

Brian K. Strongin, R.Ph., M.B.A.
Chief, Project Management Staff
Office of Gastroenterology Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Regulatory Filing Review Memo for BLAs and Supplements

The filing review should seek to identify all omissions of clearly necessary information such as information required under the statute or regulations or omissions or inadequacies so severe that a meaningful review cannot be accomplished. CBER may refuse to file (RTF) an application or supplement as provided by 21 CFR 601.2, and 21 CFR 314.101, including those reasons consistent with the published RTF policy (<http://www.fda.gov/cber/regsopp/8404.htm>). An RTF decision may also be appropriate if the agency cannot complete review of the application without significant delay while major repair or augmentation of data is being done. To be a basis for RTF, the omissions or inadequacies should be obvious, at least once identified, and not a matter of interpretation or judgement about the meaning of data submitted. Decisions based on judgments of the scientific or medical merits of the application would not generally serve as bases for RTF unless the underlying deficiencies were identified and clearly communicated to the applicant prior to submitting a license application, e.g., during the review of the IND or during pre-BLA communications. The attached worksheets, which are intended to facilitate the filing review, are largely based upon the published RTF policy and guidance documents on the ICH Common Technical Document (CTD) (see <http://www.fda.gov/cber/ich/ichguid.htm>).

Where an application contains more than one indication for use, it may be complete and potentially approvable for one indication, but inadequate for one or more additional indications. The agency may accept for filing those parts of the application that are complete for a particular indication, but refuse to file those parts of the application that are obviously incomplete for other indications.

CBER management may, for particularly critical biological products, elect not to use the RTF procedure, even where it can be invoked, if it believes that initiating the full review at the earliest possible time will better advance the public health.

STN: 125160/0 Product: Certolizumab pegol Applicant: UCB, Inc.

Final Review Designation (circle one): Standard Priority

Submission Format (circle all that apply): Paper Electronic Combination

Submission organization (circle one): Traditional CTD

Filing Meeting: Date 4/21/06 Committee Recommendation (circle one): File RTF

RPM: [Signature] / 4/27/06
(signature/date)

Attachments:

Discipline worksheets (identify the number of lists attached for each part and fill-in the name of the reviewer responsible for each attached list):

Part A – RPM

Part B – Product/CMC/Facility Reviewer(s): K. Bronson G. Schul J. Barletta

Part C – Non-Clinical Pharmacology/Toxicology Reviewer(s): S. Chakder

Part D – Clinical (including Pharmacology, Efficacy, Safety, and Statistical)

Reviewers S. Af-Fayumi S. Bezaheh Milton Fan

Memo of Filing Meeting