CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761044Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION[1]

NDA # BLA # 761044	NDA Supplement # BLA Supplement #	If NDA, Efficacy Supplement Type: *(an action package is not required for SE8 or SE9 supplements)*
Proprietary Name: STELARA Established/Proper Name: Ustekinumab Dosage Form: 5 mg/mL solution for IV infusion		Applicant: Janssen Biotech Agent for Applicant (if applicable):
RPM: Lawrence Allan		Division: DGIEP

NDA Application Type: ☐ 505(b)(1) ☐ 505(b)(2)
Efficacy Supplement: ☐ 505(b)(1) ☐ 505(b)(2)

BLA Application Type: ☐ 351(k) ☒ 351(a)
Efficacy Supplement: ☐ 351(k) ☐ 351(a)

For ALL 505(b)(2) applications, two months prior to EVERY action:

- **Review the information in the 505(b)(2) Assessment and submit the draft[2] to CDER OND IO for clearance.**
- **Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity)**

☐ No changes
☐ New patent/exclusivity *(notify CDER OND IO)*
Date of check:

Note: If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.

❖ Actions	
• Proposed action • User Fee Goal Date is 25 Sep 2016	☒ AP ☐ TA ☐ CR
• Previous actions *(specify type and date for each action taken)*	☒ None
❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain _____	☐ Received
❖ Application Characteristics[3]	

[1] The **Application Information** Section is (only) a checklist. The **Contents of Action Package** Section (beginning on page 2) lists the documents to be included in the Action Package.
[2] For resubmissions, 505(b)(2) applications must be cleared before the action, but it is not necessary to resubmit the draft 505(b)(2) Assessment to CDER OND IO unless the Assessment has been substantively revised (e.g., new listed drug, patent certification revised).
[3] Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA.

Reference ID: 3990257

Review priority: ☒ Standard ☐ Priority
Chemical classification (new NDAs only):
(confirm chemical classification at time of approval)

☐ Fast Track
☐ Rolling Review
☐ Orphan drug designation
☐ Breakthrough Therapy designation
☐ Rx-to-OTC full switch
☐ Rx-to-OTC partial switch
☐ Direct-to-OTC

(NOTE: Set the submission property in DARRTS and notify the CDER Breakthrough Therapy Program Manager; Refer to the "RPM BT Checklist for Considerations after Designation Granted" for other required actions: CST SharePoint)

NDAs: Subpart H
☐ Accelerated approval (21 CFR 314.510)
☐ Restricted distribution (21 CFR 314.520)
Subpart I
☐ Approval based on animal studies

BLAs: Subpart E
☐ Accelerated approval (21 CFR 601.41)
☐ Restricted distribution (21 CFR 601.42)
Subpart H
☐ Approval based on animal studies

☐ Submitted in response to a PMR
☐ Submitted in response to a PMC
☐ Submitted in response to a Pediatric Written Request

REMS: ☐ MedGuide
☐ Communication Plan
☐ ETASU
☐ MedGuide w/o REMS
☒ REMS not required

Comments:

❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 *(approvals only)*	☐ Yes ☒ No
❖ Public communications *(approvals only)*	
• Office of Executive Programs (OEP) liaison has been notified of action	☒ Yes 24 Aug 2016
• Indicate what types (if any) of information were issued	☒ None ☐ FDA Press Release ☐ FDA Talk Paper ☐ CDER Q&As ☐ Other
❖ Exclusivity	
• Is approval of this application blocked by any type of exclusivity (orphan, 5-year NCE, 3-year, pediatric exclusivity)? • If so, specify the type	☒ No ☐ Yes
❖ Patent Information (NDAs only)	
• Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought.	☐ Verified ☐ Not applicable because drug is an old antibiotic. ☒ N/A

CONTENTS OF ACTION PACKAGE

Officer/Employee List

❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list *(approvals only)*	☒ Included
Documentation of consent/non-consent by officers/employees	☐ Included

Action Letters	
❖ Copies of all action letters *(including approval letter with final labeling)*	Action(s) and date(s): Approval on 23 Sep 2016
Labeling	
❖ Package Insert *(write submission/communication date at upper right of first page of PI)*	
• Most recent draft labeling *(if it is division-proposed labeling, it should be in track-changes format)*	☐ Included 9/22/2016
• Original applicant-proposed labeling	☒ Included
❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling *(write submission/communication date at upper right of first page of each piece)*	☒ Medication Guide ☐ Patient Package Insert ☒ Instructions for Use ☐ Device Labeling ☐ None
• Most-recent draft labeling *(if it is division-proposed labeling, it should be in track-changes format)*	☐ Included 9/22/2016
• Original applicant-proposed labeling	☒ Included
❖ Labels (**full color** carton and immediate-container labels) *(write submission/communication date on upper right of first page of each submission)*	
• Most-recent draft labeling	☐ Included 9/16/2014; 9/14/2016
❖ Proprietary Name • Acceptability/non-acceptability letter(s) *(indicate date(s))* • Review(s) *(indicate date(s)*	 11 Mar 2016 10 Mar 2016
❖ Labeling reviews *(indicate dates of reviews)*	RPM: ☒ None DMEPA: ☒ 18 Jul 2016 DMPP/PLT: ☒ 9 Aug 2016 OPDP: ☒ 9 Aug 2016 SEALD: ☒ None CSS: ☒ None Product Quality ☒ 22 Sep 2016 Other: ☒ None
Administrative / Regulatory Documents	
❖ RPM Filing Review[4]/Memo of Filing Meeting *(indicate date of each review)* ❖ All NDA 505(b)(2) Actions: Date each action cleared by 505(b)(2) Clearance Committee	3 Dec 2015 ☒ Not a (b)(2)
❖ NDAs/NDA supplements only: Exclusivity Summary *(signed by Division Director)*	☐ Completed
❖ Application Integrity Policy (AIP) Status and Related Documents http://www fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default htm	
• Applicant is on the AIP	☐ Yes ☒ No
• This application is on the AIP ○ If yes, Center Director's Exception for Review memo *(indicate date)* ○ If yes, OC clearance for approval *(indicate date of clearance communication)*	☐ Yes ☐ No ☐ Not an AP action

[4] Filing reviews for scientific disciplines are NOT required to be included in the action package.

❖ Pediatrics *(approvals only)* • Date reviewed by PeRC 24 Aug 2016 If PeRC review not necessary, explain: This product has orphan designation; PREA does not apply.	
❖ Breakthrough Therapy Designation	☒ N/A
• Breakthrough Therapy Designation Letter(s) (granted, denied, an/or rescinded)	
• CDER Medical Policy Council Breakthrough Therapy Designation Determination Review Template(s) *(include only the completed template(s) and not the meeting minutes)*	
• CDER Medical Policy Council Brief – Evaluating a Breakthrough Therapy Designation for Rescission Template(s) *(include only the completed template(s) and not the meeting minutes)* *(completed CDER MPC templates can be found in DARRTS as clinical reviews or on the MPC SharePoint Site)*	
❖ Outgoing communications: letters, emails, and faxes considered important to include in the action package by the reviewing office/division (e.g., clinical SPA letters, RTF letter, Formal Dispute Resolution Request decisional letters, etc.) *(do not include OPDP letters regarding pre-launch promotional materials as these are non-disclosable; do not include Master File letters; do not include previous action letters, as these are located elsewhere in package)*	• Discipline review letter – 21 Jul 2016 • ODD status granted – 18 May 2016
❖ Internal documents: memoranda, telecons, emails, and other documents considered important to include in the action package by the reviewing office/division (e.g., Regulatory Briefing minutes, Medical Policy Council meeting minutes)	
❖ Minutes of Meetings	
• If not the first review cycle, any end-of-review meeting *(indicate date of mtg)*	☐ N/A or no mtg
• Pre-NDA/BLA meeting *(indicate date of mtg)*	☒ 12 May 2015
• EOP2 meeting *(indicate date of mtg)*	☒ 19 Jul 2007
• Mid-cycle Communication *(indicate date of mtg)*	☐ N/A
• Late-cycle Meeting *(indicate date of mtg)*	☐ N/A
• Other milestone meetings (e.g., EOP2a, CMC focused milestone meetings) *(indicate dates of mtgs)*	
❖ Advisory Committee Meeting(s)	☒ No AC meeting
• Date(s) of Meeting(s)	
Decisional and Summary Memos	
❖ Office Director Decisional Memo *(indicate date for each review)*	☒ None
Division Director Summary Review *(indicate date for each review)*	☐ 9/23/2016
Cross-Discipline Team Leader Review *(indicate date for each review)*	☐ 9/23/2016
PMR/PMC Development Templates *(indicate total number)*	☐ Four (4) 9/23/2016
Clinical	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) *(indicate date for each review)*	☒ No separate review
• Clinical review(s) *(indicate date for each review)*	7 Sep 2016

• Social scientist review(s) (if OTC drug) *(indicate date for each review)*	☒ None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here ☐ and include a review/memo explaining why not *(indicate date of review/memo)*	Refer to pgs. 82 – 83 and Appendix 12.2 in the Clinical review (30 Aug 2016)
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers *(indicate date of each review)*[5]	☒ None
❖ Controlled Substance Staff review(s) and Scheduling Recommendation *(indicate date of each review)*	☒ N/A
❖ Risk Management • REMS Documents and REMS Supporting Document *(indicate date(s) of submission(s))* • REMS Memo(s) and letter(s) *(indicate date(s))* • Risk management review(s) and recommendations (including those by OSE and CSS) *(indicate date of each review and indicate location/date if incorporated into another review)*	☒ 29 Jul 2016
❖ OSI Clinical Inspection Review Summary(ies) *(include copies of OSI letters to investigators)*	☒ 28 Jul 2016 ☒ 21 Jul 2016 ☒ 21 Jul 2016 ☒ 11 Jul 2016 ☒ 07 Jul 2016 ☒ 27 Jun 2016 ☒ 20 Jun 2016 ☒ 16 Jun 2016
Clinical Microbiology ☒ None	
❖ Clinical Microbiology Team Leader Review(s) *(indicate date for each review)*	☐ No separate review
Clinical Microbiology Review(s) *(indicate date for each review)*	☐ None
Biostatistics ☐ None	
❖ Statistical Division Director Review(s) *(indicate date for each review)*	☒ No separate review
Statistical Team Leader Review(s) *(indicate date for each review)*	☒ No separate review
Statistical Review(s) *(indicate date for each review)*	☒ 31 Aug 2016
Clinical Pharmacology ☐ None	
❖ Clinical Pharmacology Division Director Review(s) *(indicate date for each review)*	☒ No separate review
Clinical Pharmacology Team Leader Review(s) *(indicate date for each review)*	☒ No separate review
Clinical Pharmacology review(s) *(indicate date for each review)*	☒ 9 Aug 2016 ☒ 24 Aug 2016 addendum
❖ OSI Clinical Pharmacology Inspection Review Summary *(include copies of OSI letters)*	☒ None requested

[5] For Part 3 combination products, all reviews from the reviewing Center(s) should be entered into the official archive (for further instructions, see "Section 508 Compliant Documents: Process for Regulatory Project Managers" located in the CST electronic repository).

Nonclinical ☐ None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) *(indicate date for each review)*	☒ No separate review
• Supervisory Review(s) *(indicate date for each review)*	☒ No separate review
• Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	☒ 19 Jul 2016
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer *(indicate date for each review)*	☒ None
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	☒ No carc
❖ ECAC/CAC report/memo of meeting	☒ None
❖ OSI Nonclinical Inspection Review Summary *(include copies of OSI letters)*	☒ None requested
Product Quality ☐ None	
❖ Product Quality Discipline Reviews[6]	
• Tertiary review (*indicate date for each review*)	☐ None
• Secondary review (e.g., Branch Chief) *(indicate date for each review)*	☐ None
• Integrated Quality Assessment (contains the Executive Summary and the primary reviews from each product quality review discipline) *(indicate date for each review)*	☒ 18 Aug 2016
❖ Reviews by other disciplines/divisions/Centers requested by product quality review team *(indicate date of each review)*	☒ 1 Sep 2016
❖ Environmental Assessment (check one) (original and supplemental applications)	
☒ Categorical Exclusion *(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)*	Previous claim for exclusion made under BLA 125261 (refer to pg. 6)
☐ Review & FONSI *(indicate date of review)*	
☐ Review & Environmental Impact Statement *(indicate date of each review)*	
❖ Facilities Review/Inspection	
☒ Facilities inspections (indicate date of recommendation; within one week of taking an approval action, confirm that there is an acceptable recommendation) *(only original applications and efficacy supplements that require a manufacturing facility inspection(e.g., new strength, manufacturing process, or manufacturing site change)*	☒ Acceptable Re-evaluation date: ☐ Withhold recommendation ☐ Not applicable

[6] Do not include Master File (MF) reviews or communications to MF holders. However, these documents should be made available upon signatory request.

Day of Approval Activities	
❖ For all 505(b)(2) applications: • Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity)	☐ No changes ☐ New patent/exclusivity *(Notify CDER OND IO)*
• Finalize 505(b)(2) assessment	☐ Done
❖ For Breakthrough Therapy (BT) Designated drugs: • Notify the CDER BT Program Manager	☐ Done *(Send email to CDER OND IO)*
❖ For products that need to be added to the flush list (generally opioids): Flush List • Notify the Division of Online Communications, Office of Communications	☐ Done
❖ Send a courtesy copy of approval letter and all attachments to applicant by fax or secure email	☒ Done
❖ If an FDA communication will issue, notify Press Office of approval action after confirming that applicant received courtesy copy of approval letter	☐ Done
❖ Ensure that proprietary name, if any, and established name are listed in the *Application Product Names* section of DARRTS, and that the proprietary name is identified as the "preferred" name	☒ Done
❖ Ensure Pediatric Record is accurate	☐ Done
❖ Send approval email within one business day to CDER-APPROVALS	☒ Done

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This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

KELLY D RICHARDS
09/23/2016

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

BLA 761044

DISCIPLINE REVIEW LETTER

Janssen Biotech
Attention: Joseph Lallier
Associate Director, Global Regulatory Affairs
Welsh & McKean Roads; PO Box 776
Spring House, PA 19477

Dear Joseph Lallier:

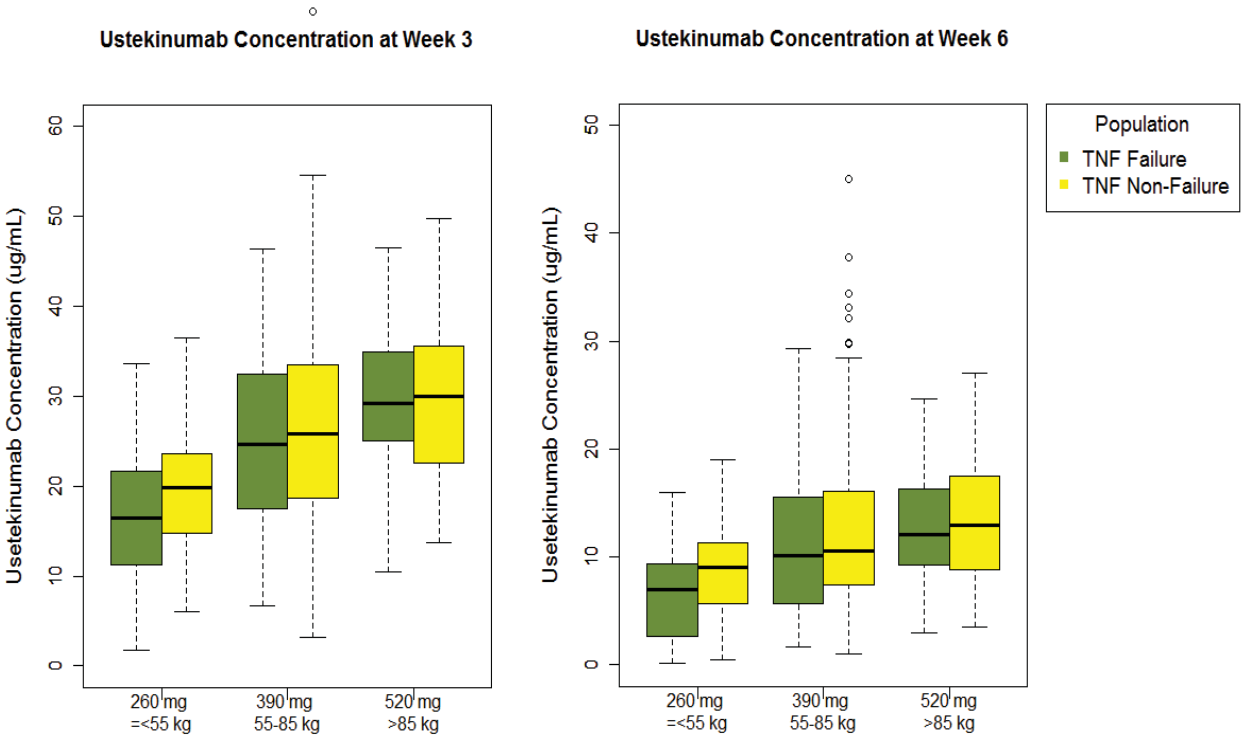
Please refer to your Biologics License Application (BLA) dated November 25, 2015, received November 25, 2015, submitted under section 351(a) of the Public Health Service Act for STELARA (Ustekinumab), 5 mg/mL solution for intravenous administration.

Our review of the clinical and clinical pharmacology section(s) of your submission is complete, and we have identified the following deficiencies:

Based on our ongoing review of the clinical and clinical pharmacology sections of your submission, we have identified the following deficiencies. Our areas of concern are outlined below and we have several information requests.

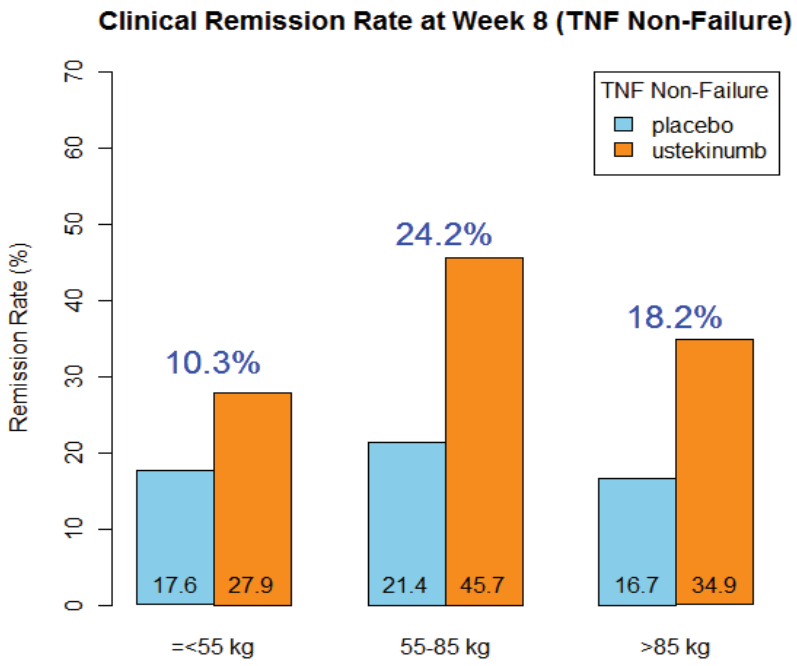
1) For the proposed body weight-tiered dosing regimen in the induction phase, patients in the lower body weight (BW) group (≤ 55 kg) appear to have lower exposures compared to patients with BW > 55 kg (see Figure 1 below).

Figure 1: Effect of weight-tiered induction dosing regimen on Week 3 and Week 6 ustekinumab concentrations



It is possible that lower exposures in ≤ 55 kg weight group may have resulted in lower clinical remission rates at week 8 in study 3002 (see Figure 2 below). Note that the numbers in blue are the placebo corrected clinical remission rate at week 8.

Figure 2: Placebo corrected clinical remission at week 8 in study 3002.



Furthermore, the clinical remission rate in patients ≤ 55 kg in the 6 mg/kg treatment arm is similar to the clinical remission rate in the 130 mg treatment arm (11%). This is important to consider since efficacy with130 mg treatment arm was generally lower than the 6 mg/kg treatment arm. In addition, the finding of lower remission rate at week 8 in the ≤ 55 kg group compared to other weight groups is also consistent with your pre-specified subgroup analysis conducted for clinical remission at week 8 for the study 3002. Your pre-specified subgroup analysis indicated a trend of lower efficacy in lower body weight patients among all patients who received 6 mg/kg.

We are concerned about this finding because clinical remission at week 8 is considered a clinically relevant endpoint; however, we acknowledge that the effect of lower exposures on clinical response at week 6 in study 3002 is not evident. Furthermore, the impact of lower exposures on efficacy in the study 3001 patient population is not evident.
To further clarify the body weight effect on efficacy (i.e., whether lower efficacy in the induction phase patients ≤ 55 kg is related to the lower exposure), we have the following requests for additional analyses of the data from the 130 mg treatment arm for both Studies 3001 and 3002:

a) Provide the descriptive statistics and box plot of distribution of concentrations at week 0 (1 hour post administration), week 3, week 6, and week 8 by various body weight groups (≤ 55 kg, >55 to ≤85 kg, and > 85 kg).

b) Provide subgroup analyses for both primary and secondary efficacy end points by body weight groups (≤ 55 kg, >55 to ≤85 kg, and > 85 kg).

c) After induction, patients who were not in clinical response received either a 90 mg subcutaneous (SC) dose or 130 mg intravenous (IV) dose of ustekinumab for further evalaution of clinical response. Eight weeks later, 50.5% of the patients achieved clinical response. Provide a descriptive statistics of clinical response by body weight strata (≤ 55 kg, >55 to ≤85 kg, and > 85 kg) for these patients. In addition, for these 50.5% patients who continued to receive maintenance dosing every 8 weeks, summarize their efficacy in the maintenance phase at week 44 by the body weight strata (≤ 55 kg, >55 to ≤85 kg, and > 85 kg).

d) To help better understand the response of the patients across the three different weight groups (i.e., ≤ 55 kg, >55 – ≤85 kg, and >85 kg) during induction and maintenance, complete Table 1 and Table 2 below. In addition, please provide distribution of exposures in responders by body weight groups as described in Table 3 below.

Table 1. Summary of efficacy data for patients with different body weights who failed TNF antagonists

Dose group (mg)	Body weight (kg)	No. of subjects randomized for induction (N)	No. of W6 responders during induction (N)	No. of subject randomized for maintenance (N)		No. of W48 remitters by randomization (N)		No. of W48 remitters without dose adjustment (N)		No. of W48 remitters without dose adjustment (N)
				q8w	q12w	q8w	q12w	q8w → q8w	q12w → q12w	q12w → q8w
130	≤55	xx	yy	x	y	x1	y1	x2	y2	y1 – y2
130	>55 – ≤85									
130	>85									
260	≤55									
390	>55 – ≤85									
520	>85									

Table 2. Summary of efficacy data for patients with different body weights who failed conventional therapy

Dose group (mg)	Body weight (kg)	No. of subjects randomized for induction (N)	No. of W6 responders during induction (N)	No. of subject randomized for maintenance (N)		No. of W48 remitters by randomization (N)		No. of W48 remitters without dose adjustment (N)		No. of W48 remitters without dose adjustment (N)
				q8w	q12w	q8w	q12w	q8w → q8w	q12w → q12w	q12w → q8w
130	≤55	xx	yy	x	y	x1	y1	x2	y2	y1 – y2
130	>55 – ≤85									
130	>85									
260	≤55									
390	>55 – ≤85									
520	>85									

Table 3. Summary of exposure data for week 6 responders from the study 3001 and 3002 who entered study 3003

Dose group (mg)	Body weight (kg)	No. of W6 responders during induction (N)	Study 3001				Study 3002			
			Concentration (ug/mL)				Concentration (ug/mL)			
			Week 0 (1 h post administration)	Week 3	Week 6	Week 8	Week 0 (1 h post administration)	Week 3	Week 6	Week 8
130	≤55									
130	>55 – ≤85									
130	>85									
260	≤55									
390	>55 – ≤85									
520	>85									

2) In addition, we have concerns regarding the ustekinumab 90 mg every 12 weeks subcuteneous (SC) maintenance dose regimen. It appears that the maintenance dose regimen of 90 mg SC every 12 weeks offers inferior clinical benefit as compared to 90 mg SC every 8 weeks regimen for the following reasons:

   a. Statistical significance was not achieved in the every 12 week dose arm on the clinically important endpoint of sustaining clinical remission, defined by the proportion of patients who maintained clinical remission from Week 0 of the maintenance study (i.e., end of induction) through week 44 of maintenance.

   b. The proportion of patients discontinuing the study for adverse events in the every 12 week dose arm was double the proportion in the every 8 week dose arm. We note that most of the reported adverse events were related to the underlying Crohn's disaease, which further supports concerns of inferior clinical benefit.

(b) (4)

We are providing these comments to you before completing our review of your entire application to give you preliminary notice of issues that we have identified. In conformance with the prescription drug user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and subject to change as we finalize our review of your application. In addition, we may identify other information that must be provided before we can approve this application. If you respond to these issues during this review cycle, depending on the timing of your response, and in conformance with the user fee reauthorization agreements, we may or may not be able to consider your response before we take an action on your application during this review cycle.

If you have any questions, contact Lawrence Allan, Regulatory Project Manager, at (240) 402 – 2786.

Sincerely,

{See appended electronic signature page}

Joyce Korvick, M.D., M.P.H.
Deputy Director for Safety
Division of Gastroenterology and Inborn Errors Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

JOYCE A KORVICK
07/21/2016

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Office of Orphan Products Development
Food and Drug Administration
10903 New Hampshire Avenue
WO32- 5295
Silver Spring, MD 20993

MAY 1 8 2016

Janssen Research & Development, LLC
1400 McKean Road
PO Box 776
Spring House, PA 19477

Attention: Joseph Lallier, MS, MBA
Associate Director, North American Regulatory Liaison
Global Regulatory Affairs, Immunology

Re: Designation request # 16-5209
Dated: February 9, 2016
Received: February 10, 2016

Dear Mr. Lallier:

This letter responds to your request for orphan-drug designation of ustekinumab for "treatment of pediatric Crohn's disease."

Pursuant to section 526 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 360bb), your orphan-drug designation request of ustekinumab is granted for *treatment of pediatric Crohn's disease (0 through 16 years of age).* Please be advised that it is the active moiety or principal molecular structural features of the drug[1] and not the formulation of the drug that is designated.

If your drug receives marketing approval for an indication broader than what is designated, it may not be entitled to exclusive marketing rights under section 527 (21 U.S.C. 360cc). Therefore, prior to submission of your marketing application, we request that you compare the drug's orphan designation with the proposed marketing indication and submit additional information to amend the orphan-drug designation if warranted. 21 CFR 316.26.

[1] The term "drug" in this letter includes drug and biological products.

If the same drug is approved for the same orphan indication before you obtain marketing approval of your drug, you will have to demonstrate that your drug is clinically superior to the already approved same drug in order to obtain orphan-drug exclusivity. Failure to demonstrate clinical superiority over the already approved same drug will result in your drug not receiving orphan-drug exclusivity. 21 CFR 316.34(c).

You must submit to the Office of Orphan Products Development a brief progress report of drug development within 14 months after this date and annually thereafter until marketing approval. 21 CFR 316.30.

Please notify this Office within 30 days of submitting a marketing application for the drug's designated use. Once your marketing application is approved, please contact Florence Moore, M.S., Ph.D., at 301-796-9226 or alternatively at 301-796-8660 to assess eligibility for orphan-drug exclusivity.

If you have questions regarding the development of your designated product, please feel free to contact Kui Xu, MD, PhD, at 301-796-8464 or alternatively at 301-796-8660. Congratulations on obtaining your orphan-drug designation.

Sincerely,

Hey H. Stanford III for Gayatri R. Rao

Gayatri R. Rao, MD, JD
Director
Office of Orphan Products Development

cc:

OOPD/File # 16-5209
OOPD/CHRON

History:
Jdb5/17/16
KXu
DESIGNATION GRANTED

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

BLA 761044

PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE

Janssen Biotech, Inc.
Welsh & McKean Roads, P.O. Box 776
Spring House, PA 19477

ATTENTION: Joseph Lallier, MS, MBA,
Associate Director, Global Regulatory Affairs, Immunology

Dear Mr. Lallier:

Please refer to your Biologics License Application (BLA) dated and received November 25, 2015, submitted under section 351(a) of the Public Health Service Act for Ustekinumab, 130 mg/26 mL (5 mg/mL).

We also refer to your correspondence, dated and received December 16, 2015, requesting review of your proposed proprietary name, Stelara.

We have completed our review of the proposed proprietary name, Stelara and have concluded that it is conditionally acceptable.

If any of the proposed product characteristics as stated in your December 16, 2015, submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you require information on submitting requests for proprietary name review or PDUFA performance goals associated with proprietary name reviews, we refer you to the following:

- Guidance for Industry Contents of a Complete Submission for the Evaluation of Proprietary Names (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075068.pdf)
- PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2013 through 2017, (http://www.fda.gov/downloads/ForIndustry/UserFees/PrescriptionDrugUserFee/UCM270412.pdf)

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Aleksander Winiarski, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at 301-796-5295. For any other information regarding this application, contact Lawrence Allan, Regulatory Project Manager in the Office of New Drugs, at 240-402-2786.

Sincerely,

{See appended electronic signature page}

Todd Bridges, RPh
Director
Division of Medication Error Prevention and Analysis
Office of Medication Error Prevention and Risk Management
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

TODD D BRIDGES
03/11/2016

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

BLA 761044

FILING COMMUNICATION –
NO FILING REVIEW ISSUES IDENTIFIED

Janssen Biotech
Attention: Joseph Lallier
Associate Director, Global Regulatory Affairs
Welsh & McKean Roads, PO Box 776
Spring House, PA 19477

Dear Joseph Lallier:

Please refer to your Biologics License Application (BLA) dated November 25, 2015, received November 25, 2015, submitted under section 351(a) of the Public Health Service Act for STELARA (Ustekinumab), 130 mg/26mL solution for IV administration.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 601.2(a), this application is considered filed 60 days after the date we received your application. The review classification for this application is **Standard**. Therefore, the user fee goal date is September 23, 2016.

We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, mid-cycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing commitment requests by August 25, 2016.

We are not currently planning to hold an advisory committee meeting to discuss this application.

PRESCRIBING INFORMATION

Your proposed prescribing information (PI) must conform to the content and format regulations found at 21 CFR 201.56(a) and (d) and 201.57. As you develop your proposed PI, we encourage you to review the labeling review resources on the *PLR Requirements for Prescribing Information* and *PLLR Requirements for Prescribing Information* websites including:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products
- The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information in the PI on pregnancy, lactation, and females and males of reproductive potential
- Regulations and related guidance documents
- A sample tool illustrating the format for Highlights and Contents
- The Selected Requirements for Prescribing Information (SRPI) − a checklist of important format items from labeling regulations and guidances and
- FDA's established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

PROMOTIONAL MATERIAL

You may request advisory comments on proposed introductory advertising and promotional labeling. Please submit, in triplicate, a detailed cover letter requesting advisory comments (list each proposed promotional piece in the cover letter along with the material type and material identification code, if applicable), the proposed promotional materials in draft or mock-up form with annotated references, and the proposed package insert (PI), Medication Guide, and patient PI (as applicable). Submit consumer-directed, professional-directed, and television advertisement materials separately and send each submission to:

OPDP Regulatory Project Manager
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion (OPDP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

Alternatively, you may submit a request for advisory comments electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft Guidance for Industry (available at:

http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM443702.pdf).

Do not submit launch materials until you have received our proposed revisions to the package insert (PI), Medication Guide, and patient PI (as applicable), and you believe the labeling is close to the final version.

For more information regarding OPDP submissions, please see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm. If you have any questions, call OPDP at 301-796-1200.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

If you have any questions, call Lawrence Allan, Regulatory Project Manager, at (240) 402 – 2786.

Sincerely,

{See appended electronic signature page}

Andrew E. Mulberg, MD, FAAP, CPI
Deputy Director
Division of Gastroenterology and Inborn Errors Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ANDREW E MULBERG
02/05/2016

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

BLA 761044

BLA ACKNOWLEDGMENT

Janssen Biotech
Attention: Joseph Lallier
Associate Director, Global Regulatory Affairs
Welsh & McKean Roads; PO Box 776
Spring House, PA 19477

Dear Joseph Lallier:

We have received your Biologics License Application (BLA) submitted under section 351(a) of the Public Health Service Act (PHS Act) for the following:

Name of Biological Product: STELARA (Ustekinumab), 5 mg/mL solution for intravenous administration

Date of Application: November 25, 2015

Date of Receipt: November 25, 2015

Our Reference Number: BLA 761044

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on January 24, 2016, in accordance with 21 CFR 601.2(a).

If you have not already done so, promptly submit the content of labeling [21 CFR 601.14(b) in structured product labeling (SPL) format as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action. The content of labeling must conform to the content and format requirements of revised 21 CFR 201.56-57.

You are also responsible for complying with the applicable provisions of sections 402(i) and 402(j) of the Public Health Service Act (PHS Act) [42 USC §§ 282 (i) and (j)], which was amended by Title VIII of the Food and Drug Administration Amendments Act of 2007 (FDAAA) (Public Law No, 110-85, 121 Stat. 904).

The BLA number provided above should be cited at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Gastroenterology and Inborn Errors Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

If you have any questions, call Lawrence Allan, Regulatory Project Manager, at (240) 402 – 2786.

Sincerely,

{See appended electronic signature page}

Kevin Bugin, MS, RAC
Chief, Project Management Staff (Acting)
Division of Gastroenterology and Inborn Errors Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

KEVIN B BUGIN
12/07/2015

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 011632

MEETING MINUTES

Janssen Research and Development, LLC
Attention: Donna Kipphorn
Associate Director, Global Regulatory Affairs, Immunology
Welsh and McKean Roads
PO Box 776
Spring House, Pennsylvania 19477

Dear Ms. Kipphorn:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for STELARA (ustekinumab).

We also refer to the meeting between representatives of your firm and the FDA on May 12, 2015. The purpose of the meeting was to discuss the proposed analyses to support the safety and efficacy of STELARA in the treatment of adults with Crohn's disease in preparation of Janssen's submitting a supplemental Biologics License Application in late 2015. Based on the statement of purpose, objectives, and proposed agenda, we consider the meeting a type B meeting.

A copy of the official minutes of the meeting is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me, Regulatory Project Manager at 240-402-4275.

Sincerely,

{See appended electronic signature page}

Jennifer Sarchet RN, BSN, MSHA
LCDR, U.S. Public Health Service Corps
Regulatory Project Manager
Division of Gastroenterology and Inborn Errors Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type:	B
Meeting Category:	Pre-sBLA
Meeting Date and Time:	**May 12, 2015 9:00 AM– 10:00 AM ET**
Meeting Location:	Teleconference
Application Number:	011632
Product Name:	STELARA
Indication:	Treatment of Crohn's disease
Sponsor/Applicant Name:	Janssen Research and Development, LLC
Meeting Chair:	Andrew E. Mulberg, M.D., F.A.A.P., C.P.I., Deputy Director, Division of Gastroenterology and Inborn Errors Products
Meeting Recorder:	Jennifer Sarchet, RN, BSN, MSHA, Regulatory Project Manager

FDA ATTENDEES
Andrew E. Mulberg, M.D., Deputy Director, Division of Gastroenterology and Inborn Errors Products (DGIEP)
Joette Meyer, Pharm. D., Associate Director of Labeling, DGIEP
Jessica Lee, M.D., M.M.Sc., Medical Officer, DGIEP
Preeti Venkataraman, M.D., Medical Officer, DGIEP
Sushanta Chakder, Ph.D., Supervisory Pharmacologist, DGIEP
Tamal Chakraborti, Ph.D., Pharmacology Reviewer, DGIEP
Jennifer Sarchet, RN, BSN, MSHA, Regulatory Project Manager, DGIEP
Yeh-Fong Chen, Ph.D., Statistical Team Leader, Division of Biometrics III
Shahla Farr, M.S., Biostatical Reviewer, Division of Biometrics III
Yow-Ming Wang, Ph.D., Clinical Pharmacology Team Leader, Division of Clinical Pharmacology 3
Christine Hon, Ph.D., Clinical Pharmacology Reviewer, Division of Clinical Pharmacology 3
Nitin Mehrotra, Ph.D., Pharmacometrics Reviewer, Division of Pharmacometrics
Susan Leibenhaut, M.D., Medical Office, Division of Good Clinical Practice Compliance

SPONSOR ATTENDEES
Long-Long Gao, PhD, Sr. Manager, Clinical Biostatistics
Jewel Johanns, PhD, Director, Clinical Biostatistics
Judy Wenrich, PhD, Clinical Biostatistics Head, Immunology
Grace Lang, PhD, Clinical Biostatistics
Chris Gasink, MD, Senior Director, Immunology

Philippe Szapary, MD, Vice President, Immunology
Newman Yeilding, MD, Head of Immunology Development
Elyssa Ott, MPH, Immunology
Donna Kipphorn, Associate Director, Regulatory Affairs
Kim Shields, Senior Director, Global Regulatory Affairs, Immunology
Karen Weiss, MD, Vice President Global Regulatory Affairs, Immunology
Joseph Adedokun, RPh, MS, Associate Scientific Director, Clinical Pharmacology
Michael Xu, PhD, Senior Scientific Director and Fellow, Clinical Pharmacology

1.0 BACKGROUND

On February 23, 2015 Janssen Research and Development, LLC submitted a type B Pre-sBLA meeting request for STELAREA (ustekinumab) approved for the treatment of adults with moderate to severe plaque psoriasis who are candidates for phototherapy or systemic therapy and for the treatment of adults with active psoriatic arthritis. The purpose of the meeting is to discuss the proposed analyses to support the safety and efficacy of STELARA in the treatment of adults with Crohn's disease in preparation of Janssen submitting a supplemental Biologic License Application in December 2015.

FDA sent Preliminary Comments to Janssen on May 5, 2015.

2.0 DISCUSSION

Question 1: **Given positive results from the two Phase 3 induction studies and anticipating positive results from the maintenance study, does the Division agree that the clinical development program will support the proposed indication statements?**

FDA Response to Question 1: The wording of the indication statements ultimately will be a review issue; however, the design of the clinical program in general appears to be sufficient to allow for review of the data intended to support these proposed indications. Please note that the FDA favors general indications statements that describe what the drug is indicated for (e.g., "treatment, prevention, etc. of a disease or condition) along with other information necessary to describe the appropriate use (e.g., the population to be treated). As such, the design of your clinical program, in general, appears to be sufficient to support indications for [redacted] (b) (4) moderately to severely active Crohn's disease in patients who have failed or were intolerant of immunomodulators and/or corticosteroids and/or TNF-inhibitors. A description of the studies conducted to support these indications would be included in Section 14 (Clinical Studies) of the label, [redacted] (b) (4)

We do not agree with your efficacy endpoint definition of mucosal healing as stated in Section 6.1.1 of the endoscopic substudy SAP. We agree that there is currently no universally accepted, validated histological scoring system; however as Crohn's disease is a transmural disease, a determination of mucosal healing may not be limited to the visual appearance of the mucosa alone. In addition, we note that you define mucosal healing in the endoscopic substudy as the proportion of subjects achieving a lack of ulcerations (i.e., healing) at Week

44 in the subset of subjects who volunteer to be evaluated, have evaluable ileo colonoscopies and who have ulcerations at baseline (Week 0 of induction). It is not clear if this analysis represents a subgroup analyses or, as you propose, a separate and dedicated substudy; this will likely need further discussion with you. (b) (4) [redacted]

[redacted] (b) (4) [redacted] We recommend additional supportive analyses of the proportion of patients that discontinue corticosteroids during the study and can remain off steroids through week 44 (for a period of at least 30, 90, etc. days).

We recommend that you perform stratified randomization for the subset of subjects who volunteer to be evaluated, have evaluable ileo-colonoscopies and who have ulcerations at baseline (Week 0 of induction), to ensure meaningful comparison between the drug and Placebo. To control the overall Type 1 error rate, you can either perform a sequential test by testing the overall population first and then the subset, or split alpha level for these two tests. You should propose another procedure for controlling multiplicity due to multiple doses.

Discussion:

The FDA confirmed that the approach to writing Indications and Usage statements is evolving for all therapeutic areas, not just for Crohn's disease or other GI indications. The preference is to grant general indication statements that describe the disease and population being treated and not to focus on the specific endpoints studied. It was acknowledged that this approach is recommended for future drug approvals and may not be consistent with the approach taken in the past for applications for Crohn's disease (e.g., vedolizumab).

The following items were discussed regarding the proposed endoscopic substudy:

1) ***The sponsor clarified that*** [redacted] (b) (4) ***all ulcers present at baseline would have to be healed/resolved in all segments.***

2) ***The sponsor clarified that*** [redacted] (b) (4) [redacted] ***patients would need to be off corticosteroid treatment for a specified amount of time and in remission.***

3) ***The FDA recommended that endoscopic substudy data from the two induction trials (CNTO1275CRD3001 and CNTO1275CRD3002) be analyzed separately first, before any statistical inference is made for the pooled data from both studies. The FDA was open to reviewing more detailed justification for pooling the endoscopic substudy data. The FDA recommended the sponsor submit their Statistical Analysis Plan (SAP) as soon as possible, and prior to the BLA submission.***

Question 2: **Does the Division agree with the proposal for analysis and presentation of efficacy data in the Summary of Clinical Efficacy?**

FDA Response to Question 2: FDA encourages you to present within the SCE a summary of the efficacy of Stelara for CD using various prespecified responder definitions and analyses using abdominal pain, stool frequency (from CDAI) and the SES-CD. Justification of the responder definitions used (and the numerical cutoffs) is of particular interest to DGIEP; correlation to legacy definitions of response/remission using the CDAI is of lesser importance.

Discussion:

The sponsor plans to present the following analyses of response and remission based on abdominal pain and stool frequency for the phase 3 induction trials:

- ***The proportions of subjects with a ≥ 50 point decrease from baseline in the combined abdominal pain and stool frequency score***
- ***The proportions of subjects with a combined abdominal pain and stool frequency score < 75 points***
- ***The proportions of subjects with both an abdominal pain mean daily score ≤ 1 and a stool frequency mean daily score ≤ 3***

The sponsor stated that above cut points were derived from the analyses they performed in preparation for the GREAT 3 workshop held on March 30, 2015. FDA stated that whether the proposed analyses are adequate to support labeling claims will depend on the strength of evidence provided, as well as the interpretability and clinical meaningfulness of the data.

The sponsor inquired whether the FDA recommends any specific analyses regarding the SES-CD. FDA did not recommend specific analyses; however, the sponsor should conduct appropriate analyses to inform a responder definition that reflects a clinically meaningful improvement.

Question 3: **Does the Division agree with the analyses described in the revised SAP for the Phase 3 maintenance study (CNTO1275CRD3003) submitted on 16 March 2015 (Serial No. 0318)?**

FDA Response to Question 3: To control the overall type I error rate, we suggest you consider a Parallel Gatekeeping method which is more powerful
(ref., http://www.ncbi.nlm.nih.gov/pubmed/15568191 Chen X., Luo X., Capizzi T.)

Discussion: ***No discussion occurred.***

Question 4: **Does the Division agree with the plans for analysis of the endoscopic substudy data?**

FDA Response to Question 4: Regarding the endoscopic substudy endpoints and definitions, please refer to the Response to Question 1.

Whether or not pooling the endoscopic substudy data to assess endoscopic endpoints, as you have proposed, results in valid and interpretable results will be a review issue.

Discussion: ***Refer to Discussion following the response to Question 1.***

Question 5: **Does the Division agree that a separate Integrated Summary of Efficacy (ISE) is not required for the BLA?**

FDA Response to Question 5: We agree.

Discussion: ***No discussion occurred.***

Question 6: **Does the Division agree that the proposed safety analyses and data presentations for the SCS are adequate to allow the Division to assess the safety of ustekinumab in the treatment of Crohn's disease?**

FDA Response to Question 6: Your plan appears to be reasonable.

Discussion: ***No discussion occurred.***

Question 7: **Does the Division accept the sponsor's proposal to provide a comprehensive safety analysis in the Summary of Clinical Safety in Module 2.7.4 with supportive documentation and additional integrated analyses in the Integrated Summary of Safety, Module 5.3.5.3?**

FDA Response to Question 7: Your proposed plan appears reasonable.

Discussion: ***No discussion occurred.***

Question 8: **Does the Division agree with the proposed plan and data cutoff for the 4-month safety update?**

FDA Response to Question 8: Yes, we agree.

Discussion: ***No discussion occurred.***

Question 9: **Does the Division agree with the proposed analyses for the Summary of Clinical Pharmacology?**

FDA Response to Question 9: The overall analysis plan that you proposed appears reasonable for the Summary of Clinical Pharmacology. However, we have the following recommendations:

1. The assessment of the impact of immunogenicity on safety should not be limited to injection site reactions and should include hypersensitivity reactions including anaphylaxis.

2. Based on the information provided in the briefing package, you intend to only use phase 3 data to perform population PK analysis and develop exposure-response models for efficacy and safety. We have the following recommendations for the population PK and the exposure-response analysis.

   a) You should utilize all available data, including phase 2 PK data, for the population PK analysis.

   b) You should combine data from phase 2 and phase 3 trials to develop the exposure- response models such that information on wide range of doses can be included. For example, since the patient population of phase 2b and the 3001 trial is the same, data from these two trials could be combined to develop exposure-response models of efficacy and safety. The exposure-response models for efficacy and safety should be utilized to support the proposed dosing recommendations.

   c) For general expectations on submitting pharmacometric data and models, please refer to the following website: http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm180482.htm.

Discussion:

The sponsor provided clarification that the assay for determination of ustekinumab concentration has changed; the old assay was used in the phase 2a study and the new assay was used in the phase 2b and phase 3 studies. Additionally, the immunogenicity assay has also changed; the old assay was used in the phase 2a and 2b studies whereas the new assay was used in the phase 3 study. The sponsor believes that the phase 3 study has data from 850 patients, which they consider to be sufficient for the population PK analysis. Given the changes in assays, the FDA agreed with not including the data from the phase 2a study in the population PK modeling analysis; however, the FDA recommended that the sponsor consider including the data from phase 2b study in the population PK modeling analysis. The sponsor further clarified that the structural model for the population PK analysis is well-informed by the data in the phase 2a study, and the pharmacokinetic sampling schedules were similar in the phase 2b and phase 3 studies.

With respect to the evaluation of immunogenicity impact on pharmacokinetics of ustekinumab in the phase 3 program, the FDA recommended using both model-based approach (e.g., covariate analysis in population PK modeling) and non-model-based approach. Examples of non-model based approach may include descriptive analysis comparing trough concentrations in ADA-positive vs. ADA-negative subgroups at selected time points, comparing trough concentrations before and after the formation of ADA in individual ADA-positive subjects, and evaluating quantitative relationship between ADA titer

data and the trough concentration data. The sponsor indicated that they plan to conduct additional analyses beyond the covariate analysis in the population PK modeling.

Based on the FDA's recommendation, the sponsor agreed to pool data from the phase2b study along with relevant phase 3 study for the exposure-response analysis. The FDA asked the sponsor to explore various exposure metrics in building the exposure-response model before selecting exposure metrics for the final analysis and provide justification for the choice of exposure metrics in the BLA submission.

The Sponsor stated that no cases of anaphylaxis or delayed hypersensitivity to ustekinumab have been reported in completed clinical studies. However, should such cases of hypersensitivity occur, the sponsor agreed that it would be important to note and report. FDA referred the sponsor to the Guidance for Industry: Immunogenicity Assessment for Therapeutic Protein Products, available at http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm338856.pdf

Question 10: **Does the Division concur with the rationale to submit an original BLA for Crohn's disease and our proposal for the user fees?**

FDA Response to Question 10: We have no objection to the submission of a new BLA for the treatment of Crohn's disease, along with the payment of the appropriate user fee (anticipated to be the fee for a new application that requires review of clinical data for approval), so long as the application follows the bundling guidance requirements (Guidance for Industry – *Submitting Separate Marketing Applications and Clinical Data for Purposes of Assessing User Fees* available at www.fda.gov/pdufa under the menu selection - Guidances and MAPPs (PDUFA)). The anticipated performance goal of ten months from the filing date will be determined by the review division and is based on the determination that the application will receive a standard review priority.

Discussion: ***No discussion occurred.***

Question 11: **Does the Division agree with the proposed plan for providing narratives and CRFs?**

FDA Response to Question 11: Yes, however please create hyperlinks between the narratives and the clinical study report to the case report forms for all subjects.

Discussion: ***No discussion occurred.***

Question 12: **Does the Division agree with the proposed plan for submission of datasets?**

FDA Response to Question 12: Yes, the proposal is acceptable. Please specify the standards version you plan to use. The Agency prefers Sponsor to submit datasets based on the *Study Data TechnicalConformanceGuide* listed on *StudyDataStandardsResources* website.

Discussion: ***No discussion occurred.***

Question 13: **Does the Division agree with the proposed list of covered studies for the submission of financial disclosure information?**

FDA Response to Question 13: Yes we agree.

Discussion: ***No discussion occurred.***

Question 14: **Does the Division agree that the proposed content (TOC) and cross referencing plan is acceptable?**

FDA Response to Question 14: Yes we agree.

Discussion: ***No discussion occurred.***

3.0 PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Please be advised that under the Food and Drug Administration Safety and Innovation Act (FDASIA), you must submit an Initial Pediatric Study Plan (iPSP) within 60 days of an End of Phase (EOP2) meeting. In the absence of an End-of-Phase 2 meeting, refer to the draft guidance below. The PSP must contain an outline of the pediatric study or studies that you plan to conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation, and any previously negotiated pediatric plans with other regulatory authorities. The PSP should be submitted in PDF and Word format. Failure to include an agreed iPSP with a marketing application could result in a refuse to file action.

For additional guidance on the timing, content, and submission of the PSP, including a PSP Template, please refer to the draft guidance for industry, *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans* at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/U CM360507.pdf. In addition, you may contact the Division of Pediatric and Maternal Health at 301-796-2200 or email pdit@fda.hhs.gov. For further guidance on pediatric product development, please refer to:

http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm.

4.0 PRESCRIBING INFORMATION

In your application, you must submit proposed prescribing information (PI) that conforms to the content and format regulations found at 21 CFR 201.56(a) and (d) and 201.57 including the Pregnancy and Lactation Labeling Rule (PLLR) (for applications submitted on or after June 30,
2015). As you develop your proposed PI, we encourage you to review the labeling review resources on the *PLR Requirements for Prescribing Information* and *PLLR Requirements for PrescribingInformation* websites including:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products
- The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information related to pregnancy, lactation, and females and males of reproductive potential in the PI for human drug and biological products
- Regulations and related guidance documents
- A sample tool illustrating the format for Highlights and Contents, and
- The Selected Requirements for Prescribing Information (SRPI) − a checklist of 42 important format items from labeling regulations and guidances.
- FDA's established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

Prior to submission of your proposed PI, use the SRPI checklist to ensure conformance with the format items in regulations and guidances.

5.0 DATA STANDARDS FOR STUDIES

CDER strongly encourages IND sponsors to consider the implementation and use of data standards for the submission of applications for investigational new drugs and product registration. Such implementation should occur as early as possible in the product development lifecycle, so that data standards are accounted for in the design, conduct, and analysis of clinical and nonclinical studies. CDER has produced a web page that provides specifications for sponsors regarding implementation and submission of clinical and nonclinical study data in a standardized format. This web page will be updated regularly to reflect CDER's growing experience in order to meet the needs of its reviewers. The web page may be found at:
http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm

6.0 LABORATORY TEST UNITS FOR CLINICAL TRIALS

CDER strongly encourages IND sponsors to identify the laboratory test units that will be reported in clinical trials that support applications for investigational new drugs and product registration. Although Système International (SI) units may be the standard reporting mechanism globally, dual reporting of a reasonable subset of laboratory

tests in U.S. conventional units and SI units might be necessary to minimize conversion needs during review. Identification of units to be used for laboratory tests in clinical trials and solicitation of input from the review divisions should occur as early as possible in the development process. For more information, please see CDER/CBER Position on Use of SI Units for Lab Tests (http://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/default.htm).

7.0 MANUFACTURING FACILITIES

To facilitate our inspectional process, we request that you clearly identify *in a single location*, either on the Form FDA 356h, or an attachment to the form, all manufacturing facilities associated with your application. Include the full corporate name of the facility and address where the manufacturing function is performed, with the FEI number, and specific manufacturing responsibilities for each facility.

Also provide the name and title of an onsite contact person, including their phone number, fax number, and email address. Provide a brief description of the manufacturing operation conducted at each facility, including the type of testing and DMF number (if applicable). Each facility should be ready for GMP inspection at the time of submission.

Consider using a table similar to the one below as an attachment to Form FDA 356h. Indicate under Establishment Information on page 1 of Form FDA 356h that the information is provided in the attachment titled, "Product name, NDA/BLA 012345, Establishment Information for Form 356h."

Site Name	Site Address	Federal Establishment Indicator (FEI) or Registration Number (CFN)	Drug Master File Number (if applicable)	Manufacturing Step(s) or Type of Testing [Establishment function]
1.				
2.				

Corresponding names and titles of onsite contact:

Site Name	Site Address	Onsite Contact (Person, Title)	Phone and Fax number	Email address
1.				
2.				

The Office of Scientific Investigations (OSI) requests that the following items be provided to facilitate development of clinical investigator and sponsor/monitor/CRO inspection assignments,

and the background packages that are sent with those assignments to the FDA field investigators who conduct those inspections (Item I and II). This information is requested for all major trials used to support safety and efficacy in the application (i.e. Phase 3 pivotal trials CNTO1275CRD3001, 3002 and 3003). Please note that if the requested items are provided elsewhere in submission in the format described, the Applicant can describe location or provide a link to the requested information.

The dataset that is requested in Item III below is for use in a clinical site selection model that is being piloted in CDER. Electronic submission of the site level dataset is voluntary and is intended to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process.

This request also provides instructions for where OSI requested items should be placed within an eCTD submission (Attachment 1, Technical Instructions: Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format).

I. Request for general study related information and comprehensive clinical investigator information (if items are provided elsewhere in submission, describe location or provide link to requested information).

1. Please include the following information in a tabular format in the original NDA for each of the completed pivotal clinical trials:
   a. Site number
   b. Principal investigator
   c. Site Location: Address (e.g. Street, City, State, Country) and contact information (i.e., phone, fax, email)
   d. Location of Principal Investigator: Address (e.g. Street, City, State, and Country) and contact information (i.e., phone, fax, email). If the Applicant is aware of changes to a clinical investigator's site address or contact information since the time of the clinical investigator's participation in the study, we request that this updated information also be provided.

2. Please include the following information in a tabular format, *by site*, in the original NDA for each of the completed pivotal clinical trials:
   a. Number of subjects screened at each site
   b. Number of subjects randomized at each site
   c. Number of subjects treated who prematurely discontinued for each site by site

3. Please include the following information in a tabular format in the NDA for each of the completed pivotal clinical trials:
   a. Location at which sponsor trial documentation is maintained (e.g., , monitoring plans and reports, training records, data management plans, drug accountability records, IND safety reports, or other sponsor records as described ICH E6, Section 8). This is the actual physical site(s) where documents are maintained and would be available for inspection

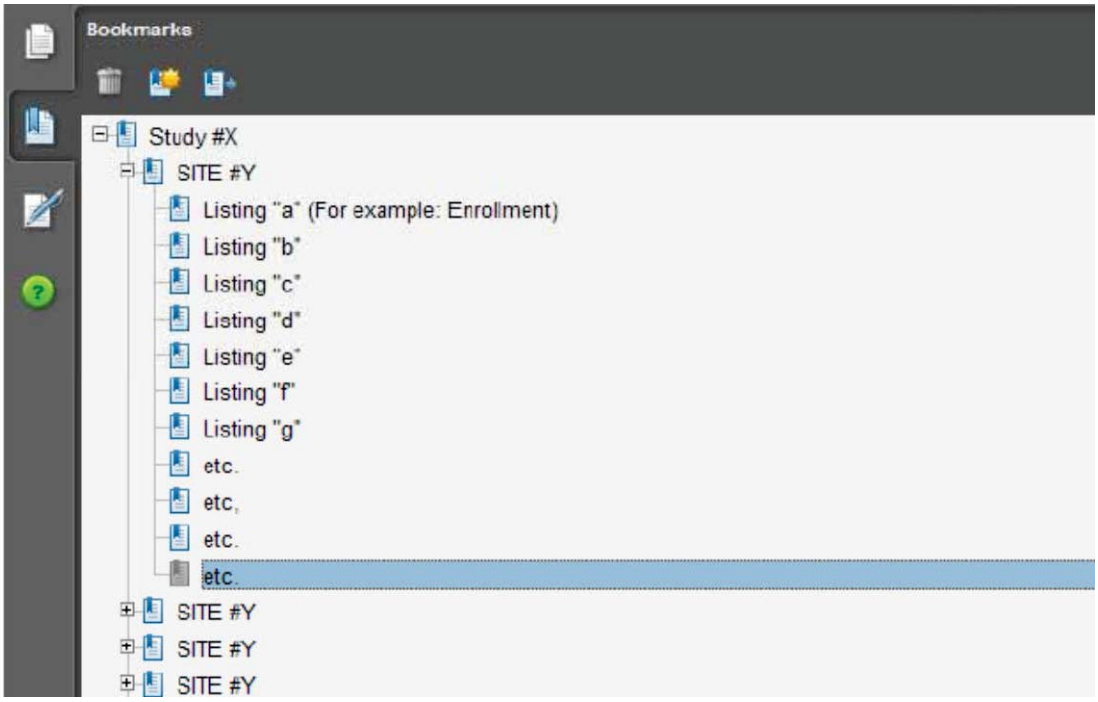
b. Name, address and contact information of all Contract Research Organization (CROs) used in the conduct of the clinical trials and brief statement of trial related functions transferred to them. If this information has been submitted in eCTD format previously (e.g. as an addendum to a Form FDA 1571, you may identify the location(s) and/or provide link(s) to information previously provided.
c. The location at which trial documentation and records generated by the CROs with respect to their roles and responsibilities in conduct of respective studies is maintained. As above, this is the actual physical site where documents would be available for inspection.

4. For each pivotal trial, provide a sample annotated Case Report Form (or identify the location and/or provide a link if provided elsewhere in the submission).
5. For each pivotal trial provide original protocol and all amendments ((or identify the location and/or provide a link if provided elsewhere in the submission).

II. Request for Subject Level Data Listings by Site

1. For each pivotal trial: Site-specific individual subject data listings (hereafter referred to as "line listings"). For each site, provide line listings for:
   a. Listing for each subject consented/enrolled; for subjects who were not randomized to treatment and/or treated with study therapy, include reason not randomized and/or treated
   b. Subject listing for treatment assignment (randomization)
   c. Listing of subjects that discontinued from study treatment and subjects that discontinued from the study completely (i.e., withdrew consent) with date and reason discontinued
   d. Listing of per protocol subjects/ non-per protocol subjects and reason not per protocol
   e. By subject listing of eligibility determination (i.e., inclusion and exclusion criteria)
   f. By subject listing, of AEs, SAEs, deaths and dates
   g. By subject listing of protocol violations and/or deviations reported in the NDA, including a description of the deviation/violation
   h. By subject listing of the primary and secondary endpoint efficacy parameters or events. For derived or calculated endpoints, provide the raw data listings used to generate the derived/calculated endpoint.
   i. By subject listing of concomitant medications (as appropriate to the pivotal clinical trials)
   j. By subject listing, of testing (e.g., laboratory, ECG) performed for safety monitoring

2. We request that one PDF file be created for each pivotal Phase 2 and Phase 3 study using the following format:



III. Request for Site Level Dataset:

OSI is piloting a risk based model for site selection. Voluntary electronic submission of site level datasets is intended to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process. If you wish to voluntarily provide a dataset, please refer to the draft "Guidance for Industry Providing Submissions in Electronic Format – Summary Level Clinical Site Data for CDER's Inspection Planning" (available at the following link http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/UCM332468.pdf) for the structure and format of this data set.

Attachment 1

Technical Instructions:
Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format

A. Data submitted for OSI review belongs in Module 5 of the eCTD. For items I and II in the chart below, the files should be linked into the Study Tagging File (STF) for each study. Leaf titles for this data should be named "BIMO [list study ID, followed by brief description of file being submitted]." In addition, a BIMO STF should be constructed and placed in Module 5.3.5.4, Other Study reports and related information. The study ID for this STF should be "bimo." Files for items I, II and III below should be linked into this BIMO STF, using file tags indicated below. The item III site-level dataset filename should be "clinsite.xpt."

DSI Pre-NDA Request Item[1]	STF File Tag	Used For	Allowable File Formats
I	data-listing-dataset	Data listings, by study	.pdf
I	annotated-crf	Sample annotated case report form, by study	.pdf
II	data-listing-dataset	Data listings, by study (Line listings, by site)	.pdf
III	data-listing-dataset	Site-level datasets, across studies	.xpt
III	data-listing-data-definition	Define file	.pdf

B. In addition, within the directory structure, the item III site-level dataset should be placed in the M5 folder as follows:

C. It is recommended, but not required, that a Reviewer's Guide in PDF format be included. If this Guide is included, it should be included in the BIMO STF. The leaf title should be "BIMO Reviewer Guide." The guide should contain a description of the BIMO elements being submitted with hyperlinks to those elements in Module 5.

[1] Please see the OSI Pre-NDA/BLA Request document for a full description of requested data files

References:

eCTD Backbone Specification for Study Tagging Files v. 2.6.1
(http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM163560.pdf)

FDA eCTD web page
(http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm153574.htm)

For general help with eCTD submissions: ESUB@fda.hhs.gov

8.0 ISSUES REQUIRING FURTHER DISCUSSION

None.

9.0 ACTION ITEMS

None.

10.0 ATTACHMENTS AND HANDOUTS

APPEARS THIS WAY ON ORIGINAL

Stelara Crohn's Disease Responses

We would like to thank the Agency for getting their comments to us in a timely manner. We have had an opportunity to review the Agency's feedback and we wish to discuss questions 1, 2, 4 & 9. The Agency's comments are in **bold** followed by the Sponsor comments/ questions. The order for discussion is presented below.

a. Indication Statement:

Q1 Agency Comment: The wording of the indication statements ultimately will be a review issue; however, the design of the clinical program in general appears to be sufficient to allow for review of the data intended to support these proposed indications. Please note that the FDA favors general indications statements that describe what the drug is indicated for (e.g., "treatment, prevention, etc. of a disease or condition) along with other information necessary to describe the appropriate use (e.g., the population to be treated). As such, the design of your clinical program, in general, appears to be sufficient to support indications for (b) (4) **moderately to severely active Crohn's disease in patients who have failed or were intolerant of immunomodulators and/or corticosteroids and/or TNF-inhibitors. A description of the studies conducted to support these indications would be included in Section 14 (Clinical Studies) of the label,** (b) (4)

Sponsor Response: We understand that this will ultimately be a review issue. As described in the briefing document (5.1), each component of the indication is very important to prescribers. The sponsor is interested in maintaining the indication statement as provided below.

(b) (4)

(b) (4)

In addition, at the GREAT workshops, it appeared that these concepts continued to be very relevant to both patients and prescribers. Given the importance of these concepts, it is important to keep them in the highlights section of the label rather than limited to the clinical studies section of the label, which is not routinely used by patients or prescribers.

It appears that the Agency's thinking is evolving and the Division is proposing the following general format of the indication statement.

Reference ID: 3778009

(b) (4)

The sponsor would like to discuss the Agency's current thinking regarding the construct of indication statements for Crohn's disease.

b. Endoscopic sub-study and mucosal healing

We appreciate the feedback and realize this will be a review issue but would appreciate clarification on the following points.

Q1 and Q4 Agency Comment: It is not clear if this analysis represents a subgroup analyses or, as you propose, a separate and dedicated substudy; this will likely need further discussion with you.

(Q4) Whether or not pooling the endoscopic substudy data to assess endoscopic endpoints, as you have proposed, results in valid and interpretable results will be a review issue.

Sponsor Response: A total of 327 subjects consented to participate in the endoscopic substudy across the CNTO1275CRD3001 and CNTO1275CRD3002 induction studies, of which approximately 290 had evaluable ileocolonoscopies at baseline (approximately 120 and 170 subjects in each of the studies, respectively. Given the issues in quantifying endoscopic disease, the Sponsor consulted with external experts (b) (4) to create a separate substudy with a specific pre-specified analysis plan with relevant endpoints and a testing procedure independent of the main study which is focused on signs and symptoms of the disease. Since there is no strong rationale that endoscopic outcomes, importance, or meaningfulness are different in the populations in CNTO1275CRD3001 vs. CNTO1275CRD3002, the planned analyses will be presented by pooling the 2 trials. A sensitivity analyses will be performed looking at the 2 trials individually. With this pooling it is simply as if this Phase 3 program was one single large induction study (with ~1400 subjects), rather than being split into 2 studies (of ~700 subjects each), a reasonable design alternative.

Combination of Q1 and Q4: Q1 Agency Comments:
To control the overall Type 1 error rate, you can either perform a sequential test by testing the overall population first and then the subset, or split alpha level for these two tests.

You should propose another procedure for controlling multiplicity due to multiple doses/ Q4 Whether or not pooling the endoscopic substudy data to assess endoscopic endpoints, as you have proposed, results in valid and interpretable results will be a review issue.

Sponsor Response: Could the agency clarify what they consider to be the "overall population?" In addition, could the agency clarify the need for testing the overall population in addition to the

Reference ID: 3778009

targeted population of subjects with ulcerations at baseline (if this was the subset you were referring to)?

Since the Sponsor is primarily looking for evidence of a drug effect on mucosal healing and to increase power of any statistical comparisons, the Sponsor proposed to pool the ustekinumab dose groups in induction and maintenance and to compare them to placebo as the primary analysis. The Sponsor will also summarize the endoscopic endpoint results by dose group to look for positive trends within each dose. As an example, we recognize that if the overall results are driven by a dose regimen higher than the recommended labeled dose, this would be an issue.

c. SCE

Q2 Comment: FDA encourages you to present within the SCE a summary of the efficacy of Stelara for CD using various prespecified responder definitions and analyses using abdominal pain, stool frequency (from CDAI) and the SES-CD. Justification of the responder definitions used (and the numerical cutoffs) is of particular interest to DGIEP; correlation to legacy definitions of response/remission using the CDAI is of lesser importance.

Sponsor response: The Sponsor plans to present analyses of response and remission based on abdominal pain and stool frequency for the Phase 3 induction studies, as described in section 4.2.1 of the briefing book. The specific analyses that are planned were detailed in the SAP for the CNTO1275CRD3002 study (Section 5.4.1, with the rationale provided in Attachment 2). These analyses are:

- The proportions of subjects with a ≥ 50 point decrease from baseline in the combined abdominal pain and stool frequency score
- The proportions of subjects with a combined abdominal pain and stool frequency score < 75 points
- The proportions of subjects with both an abdominal pain mean daily score ≤ 1 and a stool frequency mean daily score ≤ 3

Could the Agency indicate what SES-CD or other analyses the Agency believes is important to support the Agency's review?

Question 9 Agency comment 2a: Based on the information provided in the briefing package, you intend to only use phase 3 data to perform population PK analysis and develop exposure-response models for efficacy and safety. We have the following recommendations for the population PK and the exposure response analysis.
a) You should utilize all available data, including phase 2 PK data, for the population PK analysis

Sponsor Response: The Sponsor's rationale for the use of only Phase 3 data for the integrated population PK analysis is provided below:

- Serum ustekinumab data from the Phase 2a study (C0379T07) were analyzed using a PK assay different from that used in the Phase 2b and Phase 3 studies. In addition, although

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there was no subject positive for antibodies to ustekinumab in C0379T07, the immunogenicity assay which was used for that study is different from the assay being employed for the current Phase 3 studies

- The immunogenicity data from the Phase 2b study (C0743T26) were obtained using a different assay from that being employed for the current Phase 3 studies
- Pharmacokinetic data from the three Phase 3 studies (CNTO1275CRD3001, CNTO1275CRD3002, and CNTO1275CRD3003) is sufficiently large (~850 subjects) to develop a robust population PK model for ustekinumab in subjects with Crohn's disease

In summary, the Sponsor is of the opinion that PK data from the Phase 2a study (C0379T07) may not be appropriate for inclusion in the integrated population PK analysis given the differences in assay methodology. While PK assay differences may not be an issue for the Phase 2b study (C0743T26), the use of a different immunogenicity assay in Phase 3 may be a concern during the development of a covariate model. Finally, the number of subjects with PK data from the Phase 3 studies is sufficiently large for the development of a population PK model of ustekinumab in Crohn's disease. Please let us know if this appropriately justifies our proposed approach.

Question 9 Agency comment 2b: You should combine data from phase 2 and phase 3 trials to develop the exposure response models such that information on wide range of doses can be included. For example, since the patient population of phase 2b and the 3001 trial is the same, data from these two trials could be combined to develop exposure-response models of efficacy and safety. The exposure-response models for efficacy and safety should be utilized to support the proposed dosing recommendations.

Sponsor Response 2b: Based on the Agency's recommendation, the Sponsor plans to include data from the Phase 2b study (C0743T26) along with the PK and efficacy data from the Phase 3 studies (not the small number of subjects from C0379T07) in the exposure-response analyses as appropriate.

Reference ID: 3778009

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

JENNIFER S SARCHET
06/11/2015

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

IND 11,632

Centocor, Inc.
Attention: Susan Popma, OD
Associate Director, Worldwide Regulatory Affairs
200 Great Valley Parkway
Malvern, Pennsylvania 19355-1307

Dear Dr. Pompa:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for CNTO 1275 (Anti-IL 12/23p40).

We also refer to the meeting held on July 19, 2007, between representatives of your firm and this agency. A copy of the official minutes of the meeting is attached for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

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

Sincerely,

{See appended electronic signature page}

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

Enclosure - Meeting Minutes

MEMORANDUM OF MEETING MINUTES

MEETING DATE: July 19, 2007
TIME: 10 – 11:00 A.M.
LOCATION: WO Room 1315 Bldg. 22
APPLICATION: IND 11,632
DRUG NAME: CNTO 1275 (Anti-IL12/23p40)
TYPE OF MEETING: Type B (End of Phase 2)

MEETING CHAIR: John Hyde, PhD, MD

MEETING RECORDER: Marlene G. Swider, MHSA

FDA ATTENDEES: (Title and Office/Division)

Joyce Korvick, MD, MPH, Deputy Director, Division of Gastroenterology Products (DGP)
Anil Rajpal, MD, Clinical Reviewer, DGP
John Hyde, PhD, MD, Clinical Team Leader, DGP
Milton Fan, PhD, Statistician
Marlene Swider, MHSA, Regulatory Project Manager
Matthew Scherer, MBA, Regulatory Project Manager

EXTERNAL CONSTITUENT ATTENDEES:

Centocor, Inc. Representatives:

Mohan Bala, PhD; Senior Director, Health Economics
Marion Blank, PhD; Senior Director, Immunology Clinical Research and Development
Adedigbo Fasanmade, PhD; Director, Clinical Pharmacology and Experimental Medicine
Christopher Gasink, MD; Associate Director, Immunology Clinical Research and Development
Kevin Horgan, MD; Vice President, Immunology Clinical Research and Development
Jewel Johanns, PhD; Assistant Director, Biostatistics
Stella Jones, PhD; Vice President, Regulatory Affairs
Jiandong Lu, PhD; Associate Director, Biostatistics
Susan Popma, OD; Associate Director, Regulatory Affairs
Barbara Rake; Associate Director, Regulatory Affairs
Kim Shields-Tuttle; Director, Regulatory Affairs

BACKGROUND:

Centocor, Inc., is requesting a Type B Meeting (End-of-Phase II) to discuss the clinical development plan, including the designs of the planned Phase 3 studies, that is intended to support a marketing application for CNTO 1275 in the treatment of moderate to severely active Crohn's disease.

MEETING OBJECTIVES:

Obtain FDA guidance in order to finalize studies before starting Phase 3.

DISCUSSION POINTS:

Sponsor questions and FDA responses:

4.1 Patient Population In Proposed Studies

The target population for all studies will be patients with moderately to severely active Crohn's disease of at least 6 weeks' duration with a Crohn's Disease Activity Index (CDAI) of ≥ 220 and ≤ 450 at baseline (Week 0). Subjects must have received REMICADE and/or HUMIRA (or another commercially available TNF antagonist, should another one be approved for Crohn's disease) at an approved label dose for CD and not responded initially, responded initially but then lost response, and/or have been intolerant to this TNF antagonist. Thus, Centocor is targeting patients who have no other medical options available to them. Because of this, Centocor will also pursue Fast Track designation for the development program.

1. Does the Agency agree that this is a distinct population for labeling purposes? Does the FDA agree with the proposed documentation (outlined in Section 3.2.3) to define the target patient population [redacted] (b) (4)

   - Centocor would like to enroll patients who have received an approved dose of a commercially approved TNF antagonist in a clinical trial. Is this acceptable to the Agency?

<u>FDA Response:</u>

Both the criteria [redacted] (b) (4) **need to be tailored to each specific agent and should specify the dose and duration that must be tried to be considered an adequate trial. The selected population may be acceptable for enrollment in each of the Phase 3 studies. In other respects the study should be as broadly inclusive as possible.** [redacted] (b) (4) **require collecting data that provide adequate documentation to support that characterization of the patient population.**

Your proposed washout period [redacted] (b) (4) **is acceptable for those TNF antagonist therapies that are currently approved.**

Your rationale for pursuing the proposed target population rather than a broader population at this stage in your development program is not entirely clear, and such an indication may be unnecessarily restrictive. Although your Phase 2 study data appeared to suggest a higher treatment effect in subjects with prior anti-TNF use, that was a post-hoc analysis. We suggest that you consider studying a broader population such as subjects who have failed conventional therapies. One of your induction studies, or pre-specified subsets of your induction studies, could be used to target the population with an inadequate response to anti-TNF agents. Data from an additional Phase 2 study may be helpful if there are uncertainties about the appropriate target population for Phase 3 studies.

Discussion:

The Division stated that past history with a vague report of failure of TNF antagonist therapies would not be adequate documentation of failure. Centocor stated that the documentation of failure of TNF antagonist therapies that they intended to submit is similar to that used for the adalimumab GAIN trial.

Centocor noted that lower doses of adalimumab are approved for induction in Europe than in the U.S., and asked if failure of those lower doses can be used in the definition of failure of adalimumab for those patients that are enrolled in the clinical trials in Europe. The Division stated that the dose of adalimumab should be documented, and added that the Division would have to review Centocor's proposal. The Division invited Centocor to propose a definition of an inadequate clinical response to a therapeutic trial of prior TNF antagonists for the Division's review and comment.

Centocor stated that it would be very difficult to enroll patients who had failed more than one TNF antagonist in view of practice patterns and particularly in view of European reimbursement restrictions. Centocor asked if (b) (4) could be the basis of an indication. The Division responded that the labeling would reflect the studies actually done; how that is characterized in the indication statement would be a review issue.

FDA clarified that the recommendation that the study be "broadly inclusive" referred to medical criteria other than those relating to Crohn's disease, i.e., that there should be as few restrictions as possible regarding renal function, hepatic function, etc.

4.2 Adequacy of Clinical Program for Registration

The study designs outlined in the proposed clinical development plan are intended to support both an IV induction claim and an SC maintenance claim for CNTO 1275.

2. Does the FDA agree with the clinical development plan to achieve the proposed indication (as written in Section 3.1) in patients with moderately to severely active Crohn's disease (b) (4)

FDA Response:

The proposed population of moderately to severely active Crohn's disease defined by CDAI between 220 and 450 inclusive appears to be acceptable. The proposed selection criteria for use of TNF antagonist therapies is acceptable for the purpose of enrollment; (b) (4) With regard to the time point for measurement of clinical response, we suggest that you consider studying clinical response at Week 4 as a secondary endpoint because the results of your Phase 2 study appeared to show the same treatment effect at Week 4 and at Week 6. Your plans for analysis of endpoints to be included in labeling should be statistically rigorous. It is premature to discuss the specific wording of the indication statement. Such discussions will occur after results of the appropriate studies have been reviewed, and it is determined that the studies have each met the primary endpoint and other relevant endpoints.

- Does the Agency agree that Part 2 of Protocol [redacted] (b) (4) and [redacted] (b) (4) provide independent substantiation of efficacy of CNTO 1275 to support the indication for [redacted] (b) (4) adult patients with moderately to severely active Crohn's disease [redacted] (b) (4)

FDA Response:

Substantial evidence of efficacy usually requires at least two adequate and well-controlled studies. Part 2 of each of the proposed studies might be determined to be adequate and well-controlled studies. Critical features of that determination are the adequacy of the study design and the conduct of each of the studies to demonstrate evidence of effectiveness. (See the guidance document "*Providing Evidence of Clinical Effectiveness in Human Drugs and Biologic Products*" for a broader discussion of this issue.)

Although it is premature to discuss specific wording of the indication statement, the primary endpoint proposed is clinical response at Week 6, [redacted] (b) (4) In your Protocol for each study, please pre-specify whether the major secondary endpoints are rank-ordered, and propose an analysis plan for assessing the hierarchy of secondary endpoints. Your plans for analysis of endpoints to be included in labeling should control for experiment-wide Type 1 error.

For the portion of the proposed indication statement relating to [redacted] (b) (4) see the Response to Question 1.

For the portion of the proposed indication statement relating to [redacted] (b) (4) see the Response to the question below.

- [redacted] (b) (4)

  i. Will the primary endpoint of clinical response at week 6 in the two induction trials be adequate to support an indication [redacted] (b) (4)

  ii. Will the primary endpoint of [redacted] (b) (4) in the maintenance trial be adequate to support an indication [redacted] (b) (4) [redacted] (b) (4)

FDA Response:

The primary endpoint of clinical response at Week 6 in each of your proposed induction trials would be adequate to support an indication [redacted] (b) (4) However, actual wording of the indication would be based on clinical trial results and would be discussed after a determination that the primary endpoint and other key endpoints were met. The maintenance study endpoint is also adequate.

Discussion:

The Division added that it will be important to have a precise definition of "maintenance of response" if that will be the primary endpoint. Specifically, would it be defined in terms of maintaining a change from pre-induction baseline, or in terms of a change from status at entry into the maintenance trial?

- [redacted] (b) (4)

  i. Will the major secondary endpoint of clinical remission at week [redacted] (b) (4) in the two induction trials be adequate [redacted] (b) (4)

  ii. Will the major secondary endpoint of [redacted] (b) (4) [redacted] in the maintenance trial be adequate to support an indication [redacted] (b) (4) [redacted]

FDA Response:

The major secondary endpoint of clinical remission at Week [redacted] (b) (4) and of [redacted] (b) (4) [redacted] in the induction trials and in the maintenance trial, respectively, appear to be reasonable secondary endpoints. In your Protocol for each of the studies, please pre-specify whether the major secondary endpoints are rank-ordered, and propose an analysis plan for assessing the hierarchy of secondary endpoints. Your plans for analysis of endpoints to be included in labeling should control for experiment-wide Type 1 error.

- [redacted] (b) (4) Does the FDA agree that the major secondary endpoint of clinical remission and not receiving corticosteroids at week [redacted] (b) (4) in the maintenance trial will be adequate to support an indication [redacted] (b) (4)

FDA Response:

The major secondary endpoint of clinical remission and not receiving corticosteroids at Week [redacted] (b) (4) in the maintenance trial appears to be a reasonable secondary endpoint for your proposed maintenance study. A claim [redacted] (b) (4) based on results from the maintenance study may meet the standards for evidence from a single study set out in the guidance on clinical evidence of effectiveness; otherwise, an additional study would be needed.

In your Protocol for that study, please pre-specify whether the major secondary endpoints are rank-ordered, and propose an analysis plan for assessing the hierarchy of secondary endpoints. Your plans for analysis of endpoints to be included in labeling should control for experiment-wide Type 1 error.

3. Does the Agency agree that subjects induced into clinical response following CNTO 1275 therapy, regardless of the dose they received in the induction studies, would be an acceptable

population for the primary and major secondary efficacy analyses in the maintenance study, (b) (4) ?

FDA Response:

Responders to induction therapy with CNTO 1275 at the same dose or a lower dose than the induction dose that is approved might be an acceptable population for the primary and major secondary efficacy analyses in the maintenance study. However, responders to induction therapy with CNTO 1275 at a dose higher than the induction dose that is approved could bias the estimate of the effect of maintenance therapy. These patients would only be an acceptable population for the primary and major secondary efficacy analyses in the maintenance study if there is pharmacokinetic or other data that are clinically meaningful. Also, the data need to demonstrate that the effect of the higher induction dose would not have any carryover effect into the maintenance phase. If this cannot be convincingly demonstrated, then the analyses of efficacy for the maintenance study should only include subjects receiving the same or lower induction doses than the approved induction dose.

Discussion:

Centocor stated that from a pharmacokinetic basis, they believe that levels of the higher dose will be reduced to approximately the same levels as the lower dose at approximately 20 to 30 weeks. Centocor further stated that they believe that there is a low probability that there will be a clinical carry-over effect, but stated that they cannot exclude that possibility. Centocor added that if there is a carry-over effect, it should not invalidate the finding of a treatment difference because carry-over would affect both the placebo and active treatment groups; in fact it may bias against the test agent because the placebo patients would be less likely to flare in the presence of a carry-over effect. Centocor stated that they will plan to perform sensitivity analyses that may help to elucidate the carry-over effect.

The Division reminded Centocor that there are two issues, demonstration of efficacy in maintenance, and having information for the purpose of labeling that will inform the practitioner what to expect when the product is used as directed; thus, one of Centocor's goals should be having results that are as clear as possible about the estimated clinical effects of the approved dose. The Division recommended that Centocor look at early and late maintenance separately as part of the sensitivity analyses that they plan to conduct. Centocor summarized that the analysis will be done in the overall population, and that additional analyses to help determine the contribution of the carry-over effect will also be done.

4. Does the FDA agree that an initial submission comprised of the two induction trials would be sufficient to support an indication (b) (4)

FDA Response:

We strongly recommend that you submit a BLA that is comprised of complete results of the two induction studies and the maintenance study. Because Crohn's disease is a chronic condition, an understanding of the role of CNTO 1275 in the chronic care of patients would be important for writing adequate instruction for use. The final determination of the

adequacy of the application will be determined at the time of BLA filing, and the specific wording of the indication would depend on results of the clinical trials (see Response to Question 2 also).

5. Given the unmet medical need in Crohn's disease patients who have failed or are intolerant to TNF antagonist therapies, does the FDA agree that the CNTO 1275 development plan qualifies for fast track designation?

FDA Response:

A decision on fast track designation of the CNTO 1275 development plan would be made upon submission of a fast track designation request.

Fast track designation includes a determination of the following: (1) if the aspect of the condition anticipated to be benefited is serious or life-threatening; (2) if the drug shows potential (given its stage of development) to treat this serious aspect of the condition; (3) if the drug shows potential (given its stage of development) to address unmet medical needs; (4) if the drug development plan is designed to determine whether the drug will affect a serious aspect of the condition; (5) if the drug development plan is designed to address unmet medical needs; (6) if there is any accepted/approved treatment for the same serious or life-threatening aspect of the condition being studied.

We agree that there may be an unmet medical need in Crohn's disease patients who have failed or are intolerant to TNF antagonist therapies. A stronger argument might be made for patients who have failed all available TNF antagonist therapies rather than only one. The CNTO 1275 development plan should be designed so that it can clearly demonstrate clinical benefit of CNTO 1275, so that it addresses a serious aspect of the disease, addressing so the unmet medical need.

If there are other accepted/approved treatments for CD patients who have failed or are intolerant to TNF antagonist therapies, then the following should be described: (1) improved effect(s) of CNTO 1275 on the serious outcome that represents an improvement over existing therapy; (2) ability of CNTO 1275 to provide benefits in patients who are unable to tolerate or are unresponsive to the alternative therapy; (3) ability of CNTO 1275 to provide benefit(s) similar to those of alternatives while avoiding serious toxicity; (4) ability of CNTO 1275 to provide benefit(s) similar to those of alternatives but with improvement in some factor such as compliance or convenience leading to a favorable effect on the serious outcome.

See the guidance document *Guidance for Industry: Fast Track Drug Development Programs – Designation, Development, and Application Review* for a broader discussion of this issue.

Discussion:

Centocor stated that the clinical practice of cycling patients among agents in the anti-TNF class is limited at present. Therefore, Centocor reiterated that it will be difficult, particularly in Europe, to study patients that have been treated with more than one prior anti-TNF agent.

4.3 Dose and Dosing Schedule

6. Does the Agency agree that the proposed dosing strategy for the 3 studies is appropriate to support the desired indication?

FDA Response:

The rationale for the proposed doses for the induction studies appear to be reasonably supported by the results of the Phase 2 study in CD. However, the rationale for the proposed doses in the maintenance study is not well supported by Phase 2 data: the rationale that the proposed doses will be efficacious appears to be based on the assumption that higher doses are required to demonstrate efficacy for CD than in psoriasis, and the rationale that the proposed doses are safe is based on a comparison between concentrations expected from pharmacokinetic modeling and concentrations found in a completed MS study.

We recommend that you consider a smaller Phase 2 maintenance study using a range of doses and dosing regimens to help estimate the optimal maintenance dose and regimen for use in the Phase 3 maintenance study (b) (4).

Discussion:

Centocor stated that they recognize that the selection of doses for the maintenance study is somewhat speculative, but emphasized that they feel they have sufficient data to justify the doses selected. Centocor stated they do not plan to conduct a Phase 2 study of maintenance.

4.4 Statistical Considerations for all 3 trials

A description of the statistical plan for the primary and major secondary endpoints for the induction and maintenance trials is provided in Attachment 2 and Attachment 3, respectively.

7. For the 2 induction trials (b) (4), an adaptive randomization procedure, with investigative site and initial response to TNF antagonist therapy (yes or no) as the stratification variables, will be used to allocate subjects to a treatment regimen. The primary endpoint of clinical response at Week 6 will be analyzed using the Cochran Mantel Haenszel chi-square test, stratified by initial response to TNF antagonist therapy (yes or no).

For the maintenance trial (b) (4), an adaptive randomization procedure with investigative site, baseline body weight, and a 4-level cross-classification of clinical remission status at baseline (yes or no) and baseline corticosteroid use (yes or no) as the stratification variables will be used to allocate subjects to a treatment regimen. The primary endpoint of maintenance of clinical response through Week 48 will be analyzed using the Cochran-Mantel-Haenszel (CMH) chi-square test stratified by clinical remission status at Week 0 (yes or no) and baseline body weight.

Does the Agency agree with the choice of stratification variables used in the randomization and in the analyses of the three trials?

FDA Response:

From a clinical and statistical point of view, the choice of stratification variables for each of the proposed three trials appears reasonable. However, regarding randomization, we recommend a permuted block design.

Additional FDA Statistical Comments:

We recommend you submit the complete study protocols and statistical analysis plans for review and comment. However, based on your study synopses, we have the following preliminary statistical comments:

1. For patient allocation to treatment group, you are proposing an adaptive randomization. Please clarify if you are planning to use the minimization method proposed by Pocock and Simon (1975). Minimization, even with a probabilistic component, raises questions about the resulting analyses using tests that rely on standard asymptotic methods and random assignment. If minimization is used, re-randomization tests of hypotheses should be planned to confirm any inferences made. We recommend you use permuted blocks for the randomization method for all Phase 3 studies.

2. In Part 1 of your proposed Phase 3 study designs the primary endpoint is the change from baseline in the CDAI score at Week 6. This differs from the clinical response at Week 6, which will be used as the primary efficacy endpoint in Part 2, dosing-confirmation. Please comment how the dose regimen(s) to be selected in Part 1 from the change from baseline in the CDAI score will be the optimum dose regimen(s) for clinical response. It is recommended the same endpoint, i.e., clinical response at Week 6 (the primary efficacy endpoint), be used for both Part 1 and Part 2 for a useful and consistent dose adaptation/dose confirmation.

3. Those patients enrolled and randomized before the dose selection decision is made in Part 2 will not be included for primary efficacy analysis in Part 2. The efficacy data from those patients enrolled and randomized before dose selection made in Part 2 will not be utilized for efficacy. Please comment on the efficiency of this design with respect to number of patients enrolled.

4. The time saved with this Phase 3 "seamless" study design may be minimal if there is a large time gap between the end of Part 1 and dose selection. If that is the case, we suggest that you perform traditional Phase 2 and Phase 3 studies.

Discussion:

Regarding Comment 1, Centocor confirmed that they will use the Pocock method and that they will provide a sensitivity analysis.

In response to Comment 2, Centocor acknowledged that the Phase 2 endpoint will differ from the Phase 3 endpoint, but they will look at the change in CDAI as a dichotomous endpoint as well.

There was extensive discussion regarding Comments 3 and 4. FDA suggested the sponsor conduct separate Phase 2 and Phase 3 studies in order to be more efficient and employ

separate randomizations. Specifically, FDA said a single randomization should be the basis for the primary analysis of Part 2. Centocor stated that the statistical plan and analysis was intended to follow the same procedures being proposed for CNTO 148 (Golimumab) under IND 100,181. From the discussion, it appeared that some of the lack of agreement between Centocor and FDA may have been due to different understandings about the intended details of the statistical plan. Centocor agreed to provide a full Statistical Analysis Plan (SAP) for the FDA to consider, and a follow-up discussion can be held after the Agency has reviewed the details of the SAP.

4.5 Hospitalizations and IBDQ

8. In the maintenance study, we will be assessing time to first hospitalization through 48 weeks after first study agent administration as a major secondary endpoint. Statistical analysis methods will be pre-defined in the Statistical Analysis Plan.

   If a significantly beneficial effect is seen in time to first hospitalization with CNTO 1275, compared with placebo, (b) (4)

FDA Response:

Time to first hospitalization could be considered a reasonable secondary endpoint for your proposed maintenance study. However, there are no Phase 2 data that provide information on this endpoint. Concerns include loss to follow-up and proper identification of CD-related, versus other-cause, hospitalizations.

In your protocol, please include plans to ensure that follow-up is as complete as possible and explain how incomplete follow-up will be handled in the analysis. You may wish to consider using exclusion criteria (e.g., potential move, plans that may interfere with study participation) to try to enhance the likelihood of obtaining complete follow-up. Also, in your protocol, please discuss procedures to properly identify CD-related hospitalizations and pre-specify whether the major secondary endpoints are rank-ordered by proposing an analysis plan for assessing the hierarchy of secondary endpoints. Your plans for analysis of endpoints to be included in labeling should control for experiment-wide Type 1 error.

9. If the change from baseline to week 6 in the IBDQ is significantly greater with CNTO 1275 than with placebo, (b) (4)

FDA Response:

No. The IBDQ is not an adequate patient-reported outcome (PRO) instrument (b) (4) The Agency's (b) (4) Team has evaluated the IBDQ and has concluded that it does not have adequate content validity as an instrument to measure patient-reported outcomes. Some particular deficiencies of the IBDQ include: (1) it has questions that combine two or more issues in a single question; (2) it requires patients to recall and average their symptoms over a two week period; (3) it requires patients to compare their present state to a previous non-quantified time period; and (4) it has not been translated or culturally

adapted from (b) (4) into acceptable versions for use in international clinical trials. (b) (4)

4.6 Safety Database

Centocor intends to file an sBLA for Crohn's disease on the program described in Section 3.2. At the time of the 48 week submission, it is estimated that approximately 1423 Crohn's disease subjects will have been treated with CNTO 1275, including 884 for at least 6 months and 419 for approximately 1 year. When considering the greatest possible exposure to CNTO 1275 in the Crohn's disease development program, the number of subjects that will have been exposed to both the highest induction dose (9 mg/kg) in (b) (4) and the highest maintenance dose regimen (90 mg q8 weeks) in (b) (4) is estimated to be 215. A large safety database will be available from studies of CNTO 1275 in other indications at the time of the sBLA submission for Crohn's disease including at least 1800 psoriasis subjects who will have been exposed to CNTO 1275 for at least a year.

10. Does the Agency agree that the proposed safety database is adequate to support registration in CD?

<u>FDA Response</u>:

If your target population for Phase 3 studies will be patients that previously failed or lost response to anti-TNF therapies, then it may be necessary to obtain additional safety data in a broader CD population (i.e., patients that are not failures or inadequate responders to anti-TNF therapies) in which it may be used off-label. Otherwise, the proposed safety database appears reasonable, barring any new safety concerns that may be identified, as it appears to be generally consistent with the ICH E1A Guidance regarding numbers of patients exposed for the various durations. It will be important to include all exposed patients regardless of indication in your application. If special concerns in CD patients are identified in the course of the CD studies, additional safety data may be needed. To help clarify some questions that have arisen in your psoriasis studies regarding cardiovascular risk, you should be sure to obtain a baseline ECG on all patients in your proposed studies.

<u>Discussion</u>:

In response to the Division's comment that additional safety data may be necessary in a broader CD population in which the study agent may be used off-label, Centocor stated that they believe that there is very little off-label use of biologics, so they believe that safety data in a broader CD population should not be necessary. FDA clarified that such additional safety data were not being requested at present, but that Centocor should be aware of the possibility that the safety data requirements could change depending on what is learned about the product and its potential uses.

With regard to the Division's recommendation to obtain baseline ECG data on all patients in the proposed studies, Centocor stated that the cardiovascular co-morbidity in the psoriasis population may not be present in the CD population. FDA strongly recommended that Centocor consider obtaining the baseline ECG information at this stage in their drug

development program, because such information may prove useful pending the resolution of the concerns that have been raised in the psoriasis studies, and it might help avoid a need for doing additional investigations to address the issue later if the concerns are not resolved.

4.7 Pediatric Population

Centocor intends to investigate the safety and efficacy of CNTO 1275 in the pediatric Crohn's disease population. However, Centocor proposes to defer initiation of any pediatric trials until the safety and efficacy of CNTO 1275 has been established in the adult population.

11. Does the Agency agree with the timing of the proposed pediatric plan?

FDA Response:

Deferring the initiation of CNTO 1275 studies in pediatric trials until the safety and efficacy of CNTO 1275 have been established in the adult population is appropriate. Once there is an adequate basis for extending the development of CNTO 1275 to the pediatric CD population, you should pursue those investigations with due diligence.

DECISIONS (AGREEMENTS) REACHED:

(b) (4)

UNRESOLVED ISSUES OR ISSUES REQUIRING FURTHER DISCUSSION:

Centocor will be providing a submission with more information regarding their Statistical Analysis Plan, to be followed by additional discussions with FDA.

ACTION ITEMS:

Centocor will be requesting a teleconference to further discuss their statistical plan.

ATTACHMENTS/HANDOUTS:

None

Linked Applications	Sponsor Name	Drug Name
IND 11632	CENTOCOR INC	Human Monoclonal Antibody (CNTO 1275) to Interleukin 12p40

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/s/

MARLENE SWIDER
08/16/2007