CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

205437Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

EXCLUSIVITY SUMMARY

NDA # 205437 SUPPL # HFD # 570

Trade Name Otezla

Generic Name Apremilast

Applicant Name Celgene Corporation

Approval Date, If Known March 21, 2014

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES ☒ NO ☐

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3,SE4, SE5, SE6, SE7, SE8

505(b)(1)

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES ☒ NO ☐

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES ☒ NO ☐

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

3 years

e) Has pediatric exclusivity been granted for this Active Moiety?

YES ☐ NO ☒

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES ☐ NO ☒

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES ☐ NO ☒

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES ☐ NO ☒

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.)
IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a)

is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES ☐ NO ☐

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES ☐ NO ☐

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES ☐ NO ☐

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES ☐ NO ☐

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES ☐ NO ☐

If yes, explain:

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Investigation #1:
Investigation #2:

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1	YES ☐	NO ☐
Investigation #2	YES ☐	NO ☐

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1	YES ☐	NO ☐
Investigation #2	YES ☐	NO ☐

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

Investigation #1:
Investigation #2:

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1:
Investigation #2:

!

IND # YES ☐ ! NO ☐
! Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that

the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES ☐ NO ☐

If yes, explain:

==========

Name of person completing form: Michelle Jordan Garner
Title: Senior Regulatory Management Officer
Date: 2/28/14

Name of Office/Division Director signing form: Badrul A. Chowdhury
Title: Director, DPARP

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05; removed hidden data 8/22/12

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

/s/

MICHELLE Y JORDAN GARNER
03/11/2014

BADRUL A CHOWDHURY
03/11/2014

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION[1]

NDA # 205437 BLA #	NDA Supplement # BLA Supplement #	If NDA, Efficacy Supplement Type: *(an action package is not required for SE8 or SE9 supplements)*
Proprietary Name: Otezla Established/Proper Name: apremilast Dosage Form: tablet		Applicant: Celgene Corporation Agent for Applicant (if applicable):
RPM: Michelle Jordan Garner		Division: DPARP

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 3/21/14	☒ 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, (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. For example, if the application is a pending BLA supplement, then a new *RMS-BLA Product Information Sheet for TBP* must be completed.

Review priority: ☒ Standard ☐ Priority
Chemical classification (new NDAs only): Type 1
(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

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: Ensure *RMS-BLA Product Information Sheet for TBP* and *RMS-BLA Facility Information Sheet for TBP* have been completed and forwarded to OPI/OBI/DRM (Vicky Carter)	☐ Yes, dates
❖ 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 ☐ No
• 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.

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

Version: 2/7/2014

Action Letters	
❖ Copies of all action letters *(including approval letter with final labeling)*	Action(s) and date(s) AP/3/21/14
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
• 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
• 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
❖ Proprietary Name • Acceptability/non-acceptability letter(s) *(indicate date(s))* • Review(s) *(indicate date(s)*	6/21/13 1/30/14; 6/20/13
❖ Labeling reviews *(indicate dates of reviews)*	RPM: ☐ None 8/2/13 DMEPA: ☐ None 3/5/14, 12/18/13; 9/11/13 DMPP/PLT (DRISK): ☒ None OPDP: ☐ None 11/25/13 SEALD: ☒ None CSS: ☒ None Other: ☐ None MHT-12/6/13
Administrative / Regulatory Documents	
❖ Administrative Reviews *(e.g., RPM Filing Review[4]/Memo of Filing Meeting) (indicate date of each review)* ❖ All NDA (b)(2) Actions: Date each action cleared by (b)(2) Clearance Committee	RPM – 2/28/14 (completed 5/1/13) ☒ Not a (b)(2)
❖ NDAs only: Exclusivity Summary *(signed by Division Director)*	☒ Included
❖ Application Integrity Policy (AIP) Status and Related Documents http://www fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	
• Applicant is on the AIP	☐ Yes ☒ No

[4] Filing reviews for scientific disciplines should be filed with the respective discipline.

• 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
❖ Pediatrics *(approvals only)* • Date reviewed by PeRC 11/20/13 If PeRC review not necessary, explain: _____	
❖ Outgoing communications: letters, emails, and faxes considered important to include in the action package by the reviewing office/division (e.g., clinical SPA letters) *(do not include previous action letters, as these are located elsewhere in package)*	Lblg Fax: 3/20/14; Lblg Fax: 3/19/14; Lblg Fax: 3/10/14; Lblg Fax: 2/19/14; Clin IR: 1/15/14; Lblg Fax: 11/27/13; LCM Bkgd Pkge: 11/25/13; CMC IR: 11/13/13; 11/8/13; Methods Valid. Rec'd ltr: 10/23/13 Addt'l Rqst Methods Valid Mat.: 10/17/13; Methods Valid Rec'd ltr: 10/10/13 Rqst Methods Valid Mat: 10/7/13; CRO Inspec. NAI ltr:10/4/13; CMC IR: 9/24/13; Stats IR: 7/30/13; Pharmacometrics. IR: 7/25/13; Stats IR: 7/3/13; 74-day Comments email: 6/21/13; 6/20/13; Filing Communication: 6/3/13; Proprietary Name IR: 5/28/13; Name Review IR: 5/28/13; Fdbk email to Stats IR: 4/11/13; Stats IR: 4/8/13; Ack Ltr: 4/1/13
❖ 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)*	☐ No mtg 12/19/12
• EOP2 meeting *(indicate date of mtg)*	☐ No mtg 3/25/10
• Mid-cycle Communication *(indicate date of mtg)*	☐ N/A 8/20/13
• Late-cycle Meeting *(indicate date of mtg)*	☐ N/A 12/6/13
• Other milestone meetings (e.g., EOP2a, CMC pilots) *(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 3/21/14
Division Director Summary Review *(indicate date for each review)*	☐ None 2/7/14
Cross-Discipline Team Leader Review *(indicate date for each review)*	☐ None 2/6/14
PMR/PMC Development Templates *(indicate total number)*	☐ None 2(PMR; PMC)
Clinical	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) *(indicate date for each review)*	☐ No separate review 2/6/14
• Clinical review(s) *(indicate date for each review)*	Primary: 1/23/14;11/20/13; Filing: Clinical – 4/30/13
• 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)*	2/6/14
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers *(indicate date of each review)*	☐ None 1/21/14
❖ 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)*	1/3/14 ☒ None
❖ OSI Clinical Inspection Review Summary(ies) *(include copies of OSI letters to investigators)*	☐ None requested 1/22/14; Inspec. NAI ltr: 9/5/13; Inspec. VAI ltr: 9/5/13;
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)*	☐ None Primary: 11/25/13; Filing- 5/15/13

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)*	☐ None Primary: 11/20/13; Filing: 4/28/13
❖ OSI Clinical Pharmacology Inspection Review Summary *(include copies of OSI letters)*	☒ None requested
Nonclinical ☐ None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) *(indicate date for each review)*	☐ No separate review 3/13/14
• Supervisory Review(s) *(indicate date for each review)*	☐ No separate review 11/27/13
• Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	☐ None Primary: 11/21; 11/20/13; Filing 5/21/13
❖ 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 11/15/13
❖ ECAC/CAC report/memo of meeting	☐ None 7/10/13 Included in P/T review, page
❖ OSI Nonclinical Inspection Review Summary *(include copies of OSI letters)*	☒ None requested
Product Quality ☐ None	
❖ Product Quality Discipline Reviews	
• ONDQA/OBP Division Director Review(s) *(indicate date for each review)*	☐ No separate review 3/10/14
• Branch Chief/Team Leader Review(s) *(indicate date for each review)*	☒ No separate review
• Product quality review(s) including ONDQA biopharmaceutics reviews *(indicate date for each review)*	☐ None Primary: CMC-3/5/14; 1/14/14; 11/20/13 ; Filing: CMC-4/30/13; Biopharm-Primary: 11/21/13; Biopharm-Filing: 5/9/13
❖ Microbiology Reviews ☒ NDAs: Microbiology reviews (sterility & pyrogenicity) (OPS/NDMS) *(indicate date of each review)* ☐ BLAs: Sterility assurance, microbiology, facilities reviews (OMPQ/MAPCB/BMT) *(indicate date of each review)*	☐ Not needed 11/25/13
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer *(indicate date of each review)*	☒ None
❖ 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)*	CMC 1/14/14; pg 189
☐ Review & FONSI *(indicate date of review)*	
☐ Review & Environmental Impact Statement *(indicate date of each review)*	

❖ Facilities Review/Inspection	
☒ NDAs: Facilities inspections (include EER printout or EER Summary Report only; do NOT include EER Detailed Report; date completed must be within **2 years** of action date) *(only original NDAs and supplements that include a new facility or a change that affects the manufacturing sites[5])*	Date completed: 2/27/14 ☒ Acceptable ☐ Withhold recommendation ☐ Not applicable
☐ BLAs: TB-EER (date of most recent TB-EER must be within **30 days** of action date) *(original and supplemental BLAs)*	Date completed: ☐ Acceptable ☐ Withhold recommendation
❖ NDAs: Methods Validation *(check box only, do not include documents)*	☒ Completed (12/2/13) ☐ Requested ☐ Not yet requested ☐ Not needed (per review)

[5] i.e., a new facility or a change in the facility, or a change in the manufacturing process in a way that impacts the Quality Management Systems of the facility.

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
❖ 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

---

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

/s/

MICHELLE Y JORDAN GARNER
03/21/2014

We are currently reviewing your pending NDA 205437. Submit revised labeling incorporating changes shown below, and in the attached marked up PI. Additional labeling changes may be forthcoming.

A. [redacted] Sample Starter Blister Pack Label

1. The starter blister pack contains 10 mg, 20 mg, and 30 mg tablets. However, only the [redacted] strength presentation is highlighted on the principal display panel (PDP) and side panel. To clarify the contents of the starter pack, delete the [redacted] strength presentation from the PDP and side panel. Revise the statement [redacted] under the "STARTER PACK" and "SAMPLE-NOT FOR SALE" statements with the following:

   This pack contains the following for titration over 5 days up to the prescribed dose of 30 mg:

   Four-10 mg tablets

   Four-20 mg tablets

   Nineteen-30 mg tablets

   27 TABLETS

B. [redacted] Sample Carton Labeling

1. The starter blister pack contains 10 mg, 20 mg, and 30 mg tablets. However, only the [redacted] strength presentation is highlighted on the principal display panel (PDP) and side panel. To clarify the contents of the starter pack, delete the [redacted] strength presentation from the PDP and side panel. Revise the statement [redacted] under the "STARTER PACK" statement with the following:

   Each pack contains the following for titration over 5 days up to the prescribed dose of 30 mg:

   Four-10 mg tablets

   Four-20 mg tablets

   Nineteen-30 mg tablets

   Five starter packs each containing 27 TABLETS

C. [redacted] Sample Starter Blister Pack Labels and Sample Carton Labeling

1. See Comments A1 and B1

D. The Selected Requirements of Prescribing Information (SRPI) is a checklist of 42 important format prescribing information (PI) items, based on labeling regulations [21 CFR 201.56(d) and 201.57] and guidances. Use this document as a guide to ensure your label is in the correct format. The SRPI is located at the following web page, under "Additional Label Resources":

http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/ucm084159.htm

Submit your response to me via email at michelle.jordan@fda.hhs.gov on or before 4:00p.m Thursday March 13, 2014. Your response will subsequently need to be submitted officially to the NDA.

If you have any questions, please contact me at 301-796-4786.

Drafted by: MichelleJG 3/10/14
Concurrence by: SandyB 3/10/14

Finalized: MichelleJG 3/10/14

13 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

---

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

/s/

MICHELLE Y JORDAN GARNER
03/10/2014

We are currently reviewing your pending NDA 205437. Submit revised labeling incorporating changes shown in the attached marked up PI. Additional labeling changes may be forthcoming. If necessary we will schedule a tcon to accommodate discussion, for questions you may have.

However, if you are in agreement with these changes, submit your response to me via email at michelle.jordan@fda.hhs.gov on or before 4:00p.m Wednesday, February 26, 2014. Your response will subsequently need to be submitted officially to the NDA.

If you have any questions, please contact me at 301-796-4786.

Drafted by: MichelleJG 2/19/14
Concurrence by: SandyB 2/19/14

Finalized: MichelleJG 2/19/14

12 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

---

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

/s/

MICHELLE Y JORDAN GARNER
02/19/2014

Your NDA205437, submitted March 21, 2013, is currently under review, and we have the following request for information:

For the assessment of common Adverse Events (AEs) for labeling, we request the following additional analyses:

1. For the common AEs, provide analyses of the data for patients "as initially randomized" and "as treated," as defined in the ISS, for each of the following time periods:
    a. Titration period (Days 1 to 5)
    b. Full apremilast dose (Day 6 to Week 16)

    Note: For the "as treated" population, patients who escaped at Week 16 or transitioned at Week 24 to apremilast should be counted in the denominator in both groups based on their actual on-treatment time. The numerator count will depend on the timing of the event.

    Clarify what attribution windows you are proposing to use for the safety analyses. For patients on placebo, it makes sense that attribution stops immediately upon escape, change in therapy, or discontinuation from study. However, for patients on apremilast, the attribution window should remain consistent with what you have used in your safety database, i.e. 28 days after the last apremilast dose.

2. Provide a listing of all identified and potential cases of depression, <u>including</u> suicidal ideations, suicidal attempts, completed suicides and self-injury, identified by both SMQ term search and C-CASA search, for each apremilast dose and placebo, and <u>for each studied indication</u>, using the following format:

Study-Subject ID	**Age/ Gender**	**AE term**	**Total apremilast exposure, days**	**Concomitant medications**	**Relevant history**	**Comments**

3. Currently, the analyses of psychiatric events are presented separately for depression, and suicide and self-injury. Provide analysis to combine all cases of depression, suicidal ideations, suicidal attempts, completed suicides, and self-injury, identified by both SMQ term search and C-CASA search, <u>in the PsA program only</u>, in a format consistent with the analyses in ISS, section 5.5.2.5, Tables 137, 138 (placebo-controlled period) and Tables 139, 140 (apremilast-exposure period). For the apremilast-exposure period, also include the description and estimated exposure-adjusted incidence rates (EAIR) for placebo group as well.

Submit your responses to me via email at michelle.jordan@fda.hhs.gov by **4:00p.m., January 30, 2014.** Your responses will subsequently need to be submitted officially to the NDA. If you have any questions, please contact Michelle Jordan Garner, Senior Regulatory Project Manager, at 301-796-4786.

Drafted by: MichelleJG1/14/14

Concurrence by: SandyB 1/15/14
Finalized by: MichelleJG1/15/14

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

/s/

MICHELLE Y JORDAN GARNER
01/15/2014

PeRC PREA Subcommittee Meeting Minutes
November 20, 2013

PeRC Members Attending:
Lynne Yao
Rosemary Addy
Hari Cheryl Sachs
George Greeley
Jane Inglese
Wiley Chambers
Tom Smith
Karen Davis-Bruno
Colleen LoCicero
Gregory Reaman
Daiva Shetty
Shrikant Pagay
Ruthanna Davi
Kevin Krudys
Lily Mulugeta
Maura O'Leary
Robert Nelson
Dianne Murphy
William J. Rodriguez

Agenda

(b) (4)

NDA 205437 Otezla (apremilast) Full Waiver

(b) (4)

(b) (4)

Otezla (apremilast) Full Waiver

- NDA 205437 seeks marketing approval for Otezla (apremilast) for the treatment of adult patients with active psoriatic arthritis.
- The application has a PDUFA goal date of March 21, 2014.
- The application triggers PREA as directed to a new active ingredient.

- *PeRC Recommendations:*
  - The PeRC agreed with a full waiver because studies are impossible or highly impractical. Full waivers have been previously granted for this indication.

(b) (4)

[redacted]

1 Page has been Withheld in Full as b4 (CCI/TS) immediately following this page

---

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

/s/

JANE E INGLESE
12/02/2013

We are currently reviewing your pending NDA 205437. Submit revised labeling incorporating changes shown in the attached marked up PI. In addition, change the product name from TRADENAME to Otezla throughout the PI. Additional labeling changes may be forthcoming.

Submit your response to me via email at michelle.jordan@fda.hhs.gov on or by COB (4:00p.m.) Tuesday December 3, 2013. Your response will subsequently need to be submitted officially to the NDA.

If you have any questions, please contact me at 301-796-4786.

Drafted by: MichelleJG 11/27/13
Concurrence by: SandyB 11/27/13

Finalized: MichelleJG 11/27/13

10 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

---

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

/s/

MICHELLE Y JORDAN GARNER
11/27/2013

Liu, Youbang

From: Liu, Youbang
Sent: Tuesday, November 12, 2013 10:06 PM
To: clbarnes@celgene.com
Cc: Lucy Chen (lchen@celgene.com)
Subject: Information Request for NDA 205437 (Microbiology)

NDA 205437

Celgene Corporation
Attention: Casilda Luck-Barnes, PharmD
Associate Director, Regulatory Affairs
33 Technology Drive
Warren, NJ 07059

Dear Dr. Luck-Barnes:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Apremilast Tablet.

We are reviewing the CMC section of your submission and have the following comments and information requests. We request a prompt written response (preferably by November 20, 2013) in order to continue our evaluation of your NDA.

Microbiology Information Request:

1. We acknowledge the microbial limits specification and referenced test methods, however, results of methods suitability testing were not included. Please provide verification of the methods suitability for the finished drug product; study summaries may be provided.
2. Drug product microbial limits acceptance criteria were listed as "Complies with USP <1111> and Ph. Eur 5.1.4 requirements" in Table1, Specifications for Apremilast Drug Product (3.2.P.5.1, specification.pdf). Although both documents contain recommendations for microbial limits acceptance criteria, the drug product specification should be modified to include numerical limits for Total Aerobic Microbial Count and Total Yeasts and Molds Count, and also indicate testing for absence of specified microorganisms.
3. You propose to (b) (4) If a drug product release specification includes tests and acceptance criteria for a given attribute, then the test must be performed on every batch. However, microbial limits testing may be omitted from the product release specification provided adequate upstream microbiological controls are established and documented. If you wish to omit the microbial limits specification, more information on your process is needed. Address the following points.
    a) Identify and justify critical control points in the manufacturing process that could affect microbial load of the drug product.
    b) Describe microbiological monitoring and acceptance criteria for the critical control points that you have identified. Verify the suitability of your testing methods for your drug

product. Conformance to the acceptance criteria established for each critical control point should be documented in the batch record in accordance with 21 CFR 211.188.

c) Describe activities taken when microbiological acceptance criteria are not met at control points.

d) In addition to these points, you should minimally perform microbial limits testing at the initial stability testing time point. Provide an updated stability schedule to reflect this testing.

If you choose to omit microbial limits testing for release, then remove the microbial limits tests and acceptance criteria from the drug product release specification. Alternatively, you may retain a microbial limits specification for product release, but testing must be performed on every lot of drug product produced.

Please submit a revised drug product release specification for whichever microbial limits testing alternative that you select.

4. Please submit your response to this Information Request to both NDAs 205437 and (b) (4)

Please provide the appropriate information as an amendment to the submission. In addition, a copy of your response submitted by e-mail (youbang.liu@fda.hhs.gov) will expedite the review of your request. In your cover letter refer to the date on which this information was requested.

Please acknowledge the receipt of this email and provide the response timely.

Youbang Liu, Ph.D.
Regulatory Project Manager
Division III, ONDQA/OPS/CDER/FDA
10903 New Hampshire Avenue
Building 21, Room 2525
Silver Spring, MD 20993
Phone: (301) 796-1926

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

/s/

YOUBANG LIU
11/13/2013

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 205437 **INFORMATION REQUEST**

Celgene Corporation
Attention: Casilda Luck-Barnes, PharmD
Associate Director, Regulatory Affairs
33 Technology Drive
Warren, NJ 07059

Dear Dr. Luck-Barnes:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Apremilast Tablet.

We are reviewing the CMC section of your submission and have the following comments and information requests. We request a prompt written response (preferably by November 20, 2013) in order to continue our evaluation of your NDA.

Drug Substance:

1. Your specification for appearance of the drug substance is (b) (4) You have stated that the appearance of the drug substance to date is (b) (4) However, to keep the current specification for appearance, a quantitative test for color is needed. See ICH Q6A.

2. For (b) (4) related impurities, assay of final drug substance, chiral purity and residual solvents, you have provided the name of the column or equivalent to determine the assay of each substance listed above. Provide an explanation and data to support what an equivalent column will be or remove the term equivalent when describing an assay in your application.

Drug Product:

1. Provide an updated list of the manufacturing sites for the drug product, which includes the stability testing site(s) for Celgene International Sarl.

2. In your last response Table 3: Process Parameters in DoE Studies and Commercial Manufacturing under the process parameter (b) (4) you have a DoE study range of (b) (4) and the (b) (4)

(b) (4) which is outside your DoE study range. Provide data to support the (b) (4) after (b) (4) at the (b) (4)

3. Provide the in-process test results for tablet weight and tablet hardness for each of the registration batches.

4. For the analytical test methods in the drug product section for the analysis of assay, related impurities and content uniformity, you use (b) (4)

5. Provide an identification test for the HDPE bottles, (b) (4) cap and innerseal/liner of your container closure systems.

6. Regarding your analytical procedure for (b) (4)

   a. Where is the analysis done? (at-line or off-line in a QA laboratory)
   b. Approach to collect (b) (4)
   c. In your (b) (4)
   d. It is noted that all (b) (4) Provide justification for the number of factors used. The justification can be in the form of (b) (4)
   e. Your calibration data sets are not adequate. It is understood that considering development timelines (b) (4)
   f. The general requirement for external validation is that it is performed on independent data, preferably from full scale production batches. Calibration and validation data (b) (4) are not considered independent. Indicate if external validation was performed on data that is independent from the calibration data.
   g. In general calibration models associated with (b) (4) require maintenance and adjustment over the product lifecycle and that these adjustments are assessed and implemented through internal change control procedures within the site quality system. Hence, to assure that product of consistent quality is delivered with such model modifications; provide a high level summary of your plan for maintenance of the (b) (4) (b) (4) over the lifecycle of the product. This should include (but may not be limited to): management of outliers, triggers for model update, maintenance and update of (b) (4) criteria for their recalibration, and level of re-validation following update.

Additionally, it is the agency's expectation that details regarding model maintenance would be maintained on site within your internal quality system.

h. To demonstrate the verification of the [redacted] (b) (4) at commercial scale, provide available data from commercial scale batches comparing [redacted] (b) (4) [redacted] The scope of data should be sufficient to make reliable statistics based determination of results equivalency.

7. Your proposal to finalize the dissolution method and acceptance criterion as a post marketing commitment is acceptable. However, your proposed interim dissolution acceptance criterion of Q= [redacted] (b) (4) at [redacted] (b) (4) minutes is not acceptable. As discussed during our 28 October 2013 teleconference, FDA recommends a final sampling time point where Q= [redacted] (b) (4) occurs. Based on the data you have provided, we recommend an interim dissolution acceptance criterion of Q = [redacted] (b) (4) at 30 minutes. Provide a revised drug product specification table with the recommended changes.

If you have any questions, contact Youbang Liu, Regulatory Project Manager, at (301) 796-1926.

Sincerely,

{See appended electronic signature page}

Prasad Peri, Ph.D.
Branch Chief, Branch VIII
Division of New Drug Quality Assessment III
Office of New Drug Quality Assessment
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/

YOUBANG LIU
11/08/2013

PRASAD PERI
11/08/2013

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 205437

METHODS VALIDATION
MATERIALS RECEIVED

Celgene Corporation
Attention: Casilda Luck-Barnes, PharmD
Associate Director, Regulatory Affairs
33 Technology Drive
Warren NJ, 07059
FAX: (908) 860-7515

Dear Casilda Luck-Barnes:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Apremilast Film-coated tablet, 10, 20 and 30 mg and to our October 17, 2013, letter requesting sample materials for methods validation testing.

We acknowledge receipt on October 22, 2013, of the sample materials and documentation that you sent to the Division of Pharmaceutical Analysis (DPA) in St. Louis.

If you have questions, you may contact me by telephone (314-539-3815), FAX (314-539-2113), or email (Michael.Trehy@fda.hhs.gov).

Sincerely,

{See appended electronic signature page}

Michael L. Trehy
MVP Coordinator
Division of Pharmaceutical Analysis
Office of Testing and Research
Office of Pharmaceutical Science
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/

MICHAEL L TREHY
10/23/2013

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 205437

REQUEST FOR METHODS VALIDATION MATERIALS

Celgene Corporation
Attention: Casilda Luck-Barnes, PharmD
Associate Director, Regulatory Affairs
33 Technology Drive
Warren, NJ 07059
FAX: (908) 860-7515

Dear Casilda Luck-Barnes:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Apremilast Film-coated tablets, 10, 20 and 30 mg.

We will be performing methods validation studies on Apremilast Film-coated tablets, 10, 20 and 30 mg, as described in NDA 205437.

In order to perform the necessary testing, we request the additional following sample materials and equipments:

Method, current version

Alternate Content Uniformity Determination by Near IR Spectroscopy

Samples and Reference Standards

(b) (4)

[redacted]

Please include the MSDSs and the Certificates of Analysis for the sample and reference materials.

Forward these materials via express or overnight mail to:

Food and Drug Administration
Division of Pharmaceutical Analysis
Attn: Sample Custodian
645 S Newstead
St. Louis, MO 63110

Please notify me upon receipt of this FAX. You may contact me by telephone (314-539-3815), FAX (314-539-2113), or email (michael.trehy@fda.hhs.gov).

Sincerely,

{See appended electronic signature page}

Michael L. Trehy, Ph.D.
MVP coordinator
Division of Pharmaceutical Analysis
Office of Testing and Research
Office of Pharmaceutical Science
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/

MICHAEL L TREHY
10/17/2013

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 205437

METHODS VALIDATION
MATERIALS RECEIVED

Celgene Corporation
Attention: Casilda Luck-Barnes, PharmD
Associate Director, Regulatory Affairs
33 Technology Drive
Warren NJ, 07059
FAX: (908) 860-7515

Dear Casilda Luck-Barnes:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Apremilast Film-coated tablet, 10, 20 and 30 mg and to our October 7, 2013, letter requesting sample materials for methods validation testing.

We acknowledge receipt on October 10, 2013, of the sample materials and documentation that you sent to the Division of Pharmaceutical Analysis (DPA) in St. Louis.

If you have questions, you may contact me by telephone (314-539-3815), FAX (314-539-2113), or email (Michael.Trehy@fda.hhs.gov).

Sincerely,

{See appended electronic signature page}

Michael L. Trehy
MVP Coordinator
Division of Pharmaceutical Analysis
Office of Testing and Research
Office of Pharmaceutical Science
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/

MICHAEL L TREHY
10/10/2013

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 205437

REQUEST FOR METHODS VALIDATION MATERIALS

Celgene Corporation
Attention: Casilda Luck-Barnes, PharmD
Associate Director, Regulatory Affairs
33 Technology Drive
Warren, NJ 07059
FAX: (908) 860-7515

Dear Casilda Luck-Barnes:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Apremilast Film-coated tablets, 10, 20 and 30 mg.

We will be performing methods validation studies on Apremilast Film-coated tablets, 10, 20 and 30 mg, as described in NDA 205437.

In order to perform the necessary testing, we request the following sample materials and equipments:

Method, current version

Assay, Related Impurities, Identification, and Content Uniformity Determination
Alternate Content Uniformity Determination by Near IR Spectroscopy

Samples and Reference Standards

2 x 200 mg of apremilast drug reference standard
150 Apremilast Film-coated tablets, 10 mg
150 Apremilast Film-coated tablets, 20 mg
150 Apremilast Film-coated tablets, 30 mg
(b) (4)

Equipment

(b) (4)

Please include the MSDSs and the Certificates of Analysis for the sample and reference materials.

Forward these materials via express or overnight mail to:

Food and Drug Administration
Division of Pharmaceutical Analysis
Attn: Sample Custodian
645 S Newstead
St. Louis, MO 63110

Please notify me upon receipt of this FAX. You may contact me by telephone (314-539-3815), FAX (314-539-2113), or email (michael.trehy@fda.hhs.gov).

Sincerely,

{See appended electronic signature page}

Michael L. Trehy, Ph.D.
MVP coordinator
Division of Pharmaceutical Analysis
Office of Testing and Research
Office of Pharmaceutical Science
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/

MICHAEL L TREHY
10/07/2013

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 205437 **INFORMATION REQUEST**

Celgene Corporation
Attention: Casilda Luck-Barnes, PharmD
Associate Director, Regulatory Affairs
33 Technology Drive
Warren, NJ 07059

Dear Dr. Luck-Barnes:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Apremilast Tablet.

We are reviewing the CMC section of your submission and have the following comments and information requests. We request a prompt written response (preferably by October 9, 2013) in order to continue our evaluation of your NDA.

Drug Substance:

1. In the drug substance process development section S.2.6, for some of the parameters you list wide "Study Range" values in the following tables:

    a. Table 7. "Summary of Characterization Studies Which Demonstrated No Impact on (b) (4)

    b. Table 15. "Summary of Characterization Studies Which Demonstrated No Impact for (b) (4)

    c. Table 18. Summary of (b) (4) Parameters and Ranges Studied Which Demonstrated No Impact on the Quality of Apremilast"

    d. Table 20. "Summary of (b) (4) Parameters and ranges Studied Which Demonstrated No Impact on the Quality of Apremilast."

    Provide available data to support the proposed ranges. Clarify if only the extremes of the ranges were studied or if there were other studies conducted between the ranges. Additionally, comment on your approach to scale up the process parameter ranges from lab/pilot to commercial scale.

In addition, a complete description of the commercial scale drug substance and drug product manufacturing processes is required to fully evaluate the adequacy of your commercial scale control strategy and should include all process parameters. Therefore, include a master batch record and/or a detailed manufacturing process description in section S.2.2 (drug substance) of the application. The Agency recognizes that changes to non-critical process parameters can usually be managed under the firm's quality system without the need for regulatory review and approval prior to implementation. However, notification of all changes including changes to process parameters should be provided in accordance with 21CFR 314.70.

2. In your application, you state "Any potential future changes in supply of (b) (4) will be qualified as appropriate and managed by Celgene's Quality System." Provide details how you would approach this qualification. Confirm whether or not a similar approach applies to the (b) (4) and if so, provide the details of the qualification scheme.

3. According to your specification for the appearance (visual examination) of Apremilast is (b) (4) For the batch analysis, you state the actual color but for stability you put conforms to specification. As per ICH Q6A, if the color changes on stability, a quantitative procedure is recommended. (e.g., APHA color method)

4. Provide details of your analytical method and validation data for the (b) (4)

Drug Product:

1. You proposed two methods for Content Uniformity, (b) (4) Clarify which is the primary regulatory method and the alternate method. Describe the criteria for use of the secondary test method, in case the drug product fails the test of the primary method, to ensure the quality of the drug product.

2. In your application, you state that each facility will use different equipment. Provide side by side comparison of manufacturing process at drug product facility (Celgene International, (b) (4) that includes batch size, ranges/set points for process parameters, equipment type and size.. Also include in this table proposed design space ranges for each of the parameters.

3. Provide available data to show how the process parameter ranges (b) (4) were scaled from development to commercial scale.

4. You have provided data to show that (b) (4) . However, compendial acceptance criteria are proposed for these

excipients that does not include (b) (4) Revise the acceptance criteria for (b) (4) to include limits for (b) (4)

If you have any questions, contact Youbang Liu, Regulatory Project Manager, at (301) 796-1926.

Sincerely,

{See appended electronic signature page}

Prasad Peri, Ph.D.
Branch Chief, Branch VIII
Division of New Drug Quality Assessment III
Office of New Drug Quality Assessment
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/

PRASAD PERI
09/24/2013

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 205437

MID-CYCLE COMMUNICATION

Celgene Corporation
33 Technology Drive
Warren, NJ 07059

Attention: Casilda Luck-Barnes, PharmD
Associate Director, Regulatory Affairs

Dear Dr. Luck-Barnes:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for apremilast.

We also refer to the teleconference between representatives of your firm and the FDA on August 20, 2013. The purpose of the teleconference was to provide you an update on the status of the review of your application.

A record of the teleconference is enclosed for your information.

If you have any questions, call me at (301) 796-4786.

Sincerely,

{See appended electronic signature page}

Michelle Jordan Garner, MS, OTR/L
Senior Regulatory Management Officer
Division of Pulmonary, Allergy, and Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure:
Mid-Cycle Communication

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MID-CYCLE COMMUNICATION

Meeting Date and Time: August 20, 2013; 3:30 P.M.

Application Number: NDA 205437
Product Name: Otezla (apremilast)
Indication: Psoriatic Arthritis (PsA)
Applicant Name: Celgene Corporation

Meeting Chair: Sarah Yim, MD
Meeting Recorder: Michelle Jordan Garner, MS, OTR/L

FDA ATTENDEES

Division of Pulmonary, Allergy, and Rheumatology Products
Badrul A. Chowdhury, MD, Ph.D., Division Director
Sarah Yim, MD, Supervisory Associate Director
Janet Maynard, MD, (Acting) Clinical Team Leader
Keith Hull, M.D., Clinical Reviewer,
Marice Wood, Ph.D., Pharmacology/Toxicology Supervisor
Steve Leshin, Ph.D., Pharmacology/Toxicology Reviewer

Division of Clinical Pharmacology 2
Satjit Brar, Ph.D., Clinical Pharmacology Team Leader
Sheetal Agarwal, Ph.D., Division of Clinical Pharmacology 2, Office of Clinical Pharmacology

Division of Biometrics II
Joan Buenconsejo, Ph.D., Biostatistics Team Leader

APPLICANT ATTENDEES

Judith Abrams, MD, FRCPC, Executive Director, Clinical Research and Development
Jay Backstrom, MD, MPH, Senior Vice President, Global Regulatory Affairs & Pharmacovigilance
Lucy Chen, Director, Global Regulatory CMC
Gary Cline, Ph.D., Senior Director, Biostatistics and Programming
Marla Hochfeld, MD, Executive Director, Clinical Research
Angela Hu, EdM, MS, Director, Biostatistics and Programming
Kara Hodes-Wechsler, R.Ph, Executive Director, Regulatory Affairs
Casilda Luck-Barnes, PharmD, Associate Director, Regulatory Affairs
Philippe Martin, MS, MBA, Executive Director, Global Project Leadership
Maria Palmisano, MD, Vice President, Clinical Pharmacology

Maria Paris, MD, Senior Director, Lead Global Product Safety & Drug Safety/Risk Management
Matthew Hoffman, Ph.D., Director, DMPK
Julia Hui, Ph.D., Senior Director, Toxicology
Peter Schafer, Ph.D., Director, Senior Principal Investigator, Translational Development
Kamal Shah, MD, Head, Pharmacovigilance I & I, Early Development & CCT Global Drug Safety & Risk Management
Dorothy Waddleton, Senior Director, Regulatory Affairs
Xiaojiang Zhan, Ph.D., Principal Statistician

1.0 INTRODUCTION

We are providing these comments to you before we complete our review of the 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.

2.0 SIGNIFICANT ISSUES

No significant issues have been identified to date.

3.0 INFORMATION REQUESTS

There are no information requests at this time.

4.0 MAJOR SAFETY CONCERNS/RISK MANAGEMENT

There are no major safety concerns identified at this time and there is currently no need for a REMS.

5.0 ADVISORY COMMITTEE MEETING

There are no plans at this time for an AC meeting.

6.0 LATE-CYCLE MEETING/OTHER PROJECTED MILESTONES

a. LCM – December 6, 2013

    i. Agency Briefing Package due to applicant – November 25, 2013

b. Other Projected Milestones

    i. Post-Marketing Labeling negotiations begin November 27, 2013

    ii. PDUFA goal date: March 21, 2014

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

/s/

MICHELLE Y JORDAN GARNER
09/19/2013

Your NDA 205437, submitted March 21, 2013, is currently under review, and we have the following request for information:

> Provide dates of all database locks for studies cc10004psa0002, cc10004psa0003 and cc10004psa0004.

Submit your response to me via email at michelle.jordan@fda.hhs.gov by COB Thursday August 6, 2013. Your responses will subsequently need to be submitted officially to the NDA. If you have any questions, please contact Michelle Jordan Garner, Senior Regulatory Project Manager, at 301-796-4786.

Drafted by: BobA7/23/13; MichelleJG7/30/13

Concurrence by: MJordanGarner (for SBarnes) 7/30/13

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

/s/

MICHELLE Y JORDAN GARNER
07/30/2013

Your NDA205437, submitted March 21, 2013, is currently under review, and we have the following request for information:

1. In section 12.3 in the package insert under 'Race and Ethnicity', you state that "Population pharmacokinetic analysis showed that apremilast exposure is similar among Hispanic Caucasians, non-Hispanic Caucasians, and African Americans". Provide data evidence to support this claim.

2. Provide PK datasets including a list of studies used, definition of variables etc., supporting Figure 8 in summary-clin-pharm.pdf, 'Simulated Steady-state Apremilast Concentration versus Time in PsA Patients with or without Severe Renal Impairment'.

Submit your responses to me via email at michelle.jordan@fda.hhs.gov by **noon, July 31, 2013.** Your responses will subsequently need to be submitted officially to the NDA. If you have any questions, please contact Michelle Jordan Garner, Senior Regulatory Project Manager, at 301-796-4786.

Drafted by: LZhang7/24/13; MichelleJG7/24/13

Concurrence by: SandyB 7/25/13
Finalized by: MichelleJG7/24/13

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

/s/

MICHELLE Y JORDAN GARNER
07/25/2013

Executive CAC
Date of Meeting: July 2, 2013

Committee: David Jacobson-Kram, Ph.D., OND IO, Chair
Abby Jacobs, Ph.D., OND IO, Member
Paul Brown, Ph.D., OND IO, Member
Alex Jordan, Ph.D., DRUP, Alternate Member
Presenting: Marcie Wood, Ph.D., DPARP, Team Leader
L. Steven Leshin, D.V.M., Ph.D., DPARP, Presenting Reviewer

Also attending: Barbara Hill, Ph.D., DDDP
Lynnda Reid, Ph.D., DRUP

Author of Draft: L. Steven Leshin, D.V.M., Ph.D., DPARP

The following information reflects a brief summary of the Committee discussion and its recommendations.

NDA 205437
Drug Name Apremilast (Otezla, CC-10004)
Sponsor Celgene Corp.

Background:

Two-year mouse and rat carcinogenicity studies with CC-10004 were conducted by (b) (4) The sponsor received ECAC concurrence for doses used with mice and rats (see Meeting Minutes dated September 26, 2006).

CC-10004 was negative in the bacterial reverse mutation and human peripheral blood lymphocyte chromosomal aberration assays and in the in vivo micronucleus assay in mice.

Mouse Carcinogenicity Study:

Crl:CD-1 (ICR) Mice (n=70/sex/dose) were dosed once daily by gavage with CC-10004 at doses of 0 (vehicle:1.0% sodium carboxymethylcellulose in deionized water), 100, 300, and 1000 mg/kg/day. Due to morbidity and deaths in the latter part of the study, dosing of the high dose males was terminated and dosing of the high dose females was reduced to 500 mg/kg/day during week 73 (month 18). The dose of the 300 mg/kg/day group was also lowered to 200 mg/kg/day at this time and maintained through weeks 98 and 96 in males and females, respectively. Dosing was then stopped and the remaining

animals were maintained until the scheduled necropsy (study weeks 103 and 102 in males and females, respectively).

There were no definitive CP-10004-related malignancies in either male or female rats. For combined osteomas and osteosarcomas in females, there was a statistically significant trend of increasing incidence with dose ($p = 0.0128$). However these tumors were only present in the high dose group and pairwise comparison with the control group was not significant due to the low incidences in the control and high dose groups (0 and 3, respectively; $p= 0.0918$).

Rat Carcinogenicity Study:

CC-10004 was administered once daily by gavage to Crl:CD(SD) rats (n=70/sex/dose) at 0 (vehicle, 1.0% methocellulose), 2, 10 or 20 mg/kg/day in males and at 0 (vehicle, 1.0% methocellulose), 0.3, 1, or 3 mg/kg/day in females. In study week 66 (16.5 months), dosing of the 20 mg/kg/day males was stopped and the mid group dose of 10 mg/kg/day was reduced to 6 mg/kg/day due to animal morbidity and deaths. All dose groups were terminated between study week 91 and 104.

There were no malignancies related to CC-10004 treatment in either male or female rats. In female rats, there was a significant trend ($p=0.046$) for a dose-related increase in the incidence of ovarian Sertoli cell tumors. However with the low incidences of only 1 at the mid dose and 2 at the high dose of 70 animals per dose group, the pairwise comparison with control incidences of 0 were not significant.

Executive CAC Recommendations and Conclusions:

Mouse:

- The Committee concurred that the study was adequate, noting prior Exec CAC concurrence with the protocol.

- The Committee concurred that there were no drug-related neoplasms.

Rat:

- The Committee concurred that the study was adequate, noting prior Exec CAC concurrence with the protocol.

- The Committee concurred that there were no drug-related neoplasms.

David Jacobson-Kram, Ph.D.
Chair, Executive CAC

cc:\
/Division File, DPARP
/Team leader, MWood
/Reviewer, LSLeshin
/CSO/PM, DPARP
/ASeifried, OND IO

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

/s/

ADELE S SEIFRIED
07/10/2013

DAVID JACOBSON KRAM
07/10/2013

Your NDA 205437, submitted March 21, 2013, is currently under review, and we have the following request for information:

Provide a reference in the literature for the CMH weighting scheme used by program 'primaryendpointresponsetable.txt' you submitted April 16, 2013, to calculate stratum adjusted point estimates and associated confidence intervals for differences in binomial proportions in studies cc10004psa0002, cc10004psa0003 and cc10004psa0004.

Submit your response to me via email at michelle.jordan@fda.hhs.gov by COB Thursday July 18, 2013. Your responses will subsequently need to be submitted officially to the NDA. If you have any questions, please contact Michelle Jordan Garner, Senior Regulatory Project Manager, at 301-796-4786.

Drafted by: BobA7/3/13; MichelleJG7/3/13

Concurrence by: SandyB 7/3/13
Finalized by: MichelleJG7/3/13

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

/s/

MICHELLE Y JORDAN GARNER
07/03/2013

From:	Jordan, Michelle
To:	Casilda Luck-Barnes
Cc:	Jordan, Michelle
Subject:	RE: NDA 205437
Date:	Thursday, June 13, 2013 4:39:59 PM

Hi Casilda,

Your proposed responses appear appropriate. However, an additional comment in responding to #1 (CMC information) is as follows:

Provide a copy of the QA signed off analytical procedure and validation report for the dissolution test method, as opposed to (b) (4)

Let me know if you have any additional questions.

Michelle JGarner

Michelle Jordan Garner, MS, OTR/L
CDR, U.S. Public Health Service
Sr. Regulatory Management Officer
Food and Drug Administration
Center for Drug Evaluation and Research/ODEII
Division of Pulmonary, Allergy, and Rheumatology Products
10903 New Hampshire Ave., Bldg 22, Room 3200
Silver Spring, MD 20993
☎ 301-796-4786
🖷 301-796-9728
✉ michelle.jordan@fda.hhs.gov

From: Casilda Luck-Barnes [mailto:clbarnes@celgene.com]
Sent: Friday, June 07, 2013 4:35 PM
To: Jordan, Michelle
Subject: RE: NDA 205437

Hi Michelle

I hope your well. My Team has two clarifying questions to ask the Division as it relates to requested information in the Day 74 communication as follows:

#1 FDA Question 14: Provide a methods validation package in accordance with the FDA's "Guideline for Submitting Samples and Analytical Data for Methods Validation."

Celgene Comment: Celgene will be submitting the following information in the package based on the FDA guidance cited above. Can the Division confirm that the following information will address your question:

1. A tabular listing of all samples to be submitted
    a. One batch for drug substance

b. One batch of each strength (10 mg, 20 mg and 30 mg) for drug product
c. Reference standard

2. Certificates of analysis for each sample submitted
3. Reference standard qualification tests and results
4. [redacted] (b) (4)

Celgene plans to only cross reference respective NDA sections for the following information in our response:

1. A listing of all proposed regulatory specifications (drug substance and drug product)
2. Physical description of the material, including its color and physical constants
3. Appropriate chemical attributes, such as structural formula, empirical formula, and molecular weight
4. Quantitative composition of drug product
5. Method validation data (drug substance and drug product)
6. [redacted] (b) (4)

#2: In the comments sent to the Sponsor related to submitted labeling, Celgene will be resubmitting proposed labeling (WORD version) that addresses the issues identified. Celgene wanted to confirm that your requested changes to the WORD version of proposed labeling do not also require resubmission of the submitted SPL or annotated label to show similar change at this time.

If you could get back to us by the 11th of June that would be helpful.

Regards

Casilda Luck-Barnes, PharmD
Associate Director, Regulatory Affairs
Celgene Corporation
33 Technology Drive
Warren, NJ 07059
Tel (732) 652-6506
Fax (908) 860-7515
clbarnes@celgene.com

CLB

From: Jordan, Michelle [mailto:Michelle.Jordan@fda.hhs.gov]
Sent: Monday, June 03, 2013 4:01 PM
To: Casilda Luck-Barnes
Subject: RE: NDA 205437

Hi Casilda,

See attached.

Michelle JGarner

Michelle Jordan Garner, MS, OTR/L
CDR, U.S. Public Health Service
Sr. Regulatory Management Officer
Food and Drug Administration
Center for Drug Evaluation and Research/ODEII
Division of Pulmonary, Allergy, and Rheumatology Products
10903 New Hampshire Ave., Bldg 22, Room 3200
Silver Spring, MD 20993
☎ 301-796-4786
🖷 301-796-9728
✉ michelle.jordan@fda.hhs.gov

From: Casilda Luck-Barnes [mailto:clbarnes@celgene.com]
Sent: Monday, June 03, 2013 3:59 PM
To: Jordan, Michelle
Subject: RE: NDA 205437

Hi Michelle

I wanted to check to see when we might receive the Day 74 letter from FDA. Let me know if there is anything I can assist with. Regards

Regards

Casilda Luck-Barnes, PharmD
Associate Director, Regulatory Affairs
Celgene Corporation
33 Technology Drive
Warren, NJ 07059
Tel (732) 652-6506
Fax (908) 860-7515
clbarnes@celgene.com

CLB

From: Jordan, Michelle [mailto:Michelle.Jordan@fda.hhs.gov]
Sent: Thursday, April 11, 2013 10:17 AM
To: Casilda Luck-Barnes
Subject: RE: Stats IR - NDA 205437

Hi Casilda,

The following is the feedback from our stats review team:

You stated that study PSA-001 data were originally in legacy format and were then converted to SDTM format for submission. We appreciate that you converted your legacy datasets to CDISC-formatted datasets for this submission. However, in order to properly review study PSA-001, we need the actual datasets you used to generate the results in the study report. Therefore, please clarify which data format was used to generate the results in the study report and whether the analysis datasets you submitted are of the same format. If the results were generated using the legacy datasets, submit the analysis datasets (in legacy format) you used, as well as the data definition file that contains information on how variables were derived. Also, include the programs and macros used to analyze the primary and secondary efficacy endpoints.

As I stated in a previous email, we do not need an orientation meeting with Celgene at this time.

Michelle JGarner

Michelle Jordan Garner, MS, OTR/L
CDR, U.S. Public Health Service
Sr. Regulatory Management Officer
Food and Drug Administration
Center for Drug Evaluation and Research/ODEII
Division of Pulmonary, Allergy, and Rheumatology Products
10903 New Hampshire Ave., Bldg 22, Room 3200
Silver Spring, MD 20993
☎ 301-796-4786
🖷 301-796-9728
✉ michelle.jordan@fda.hhs.gov

From: Casilda Luck-Barnes [mailto:clbarnes@celgene.com]
Sent: Thursday, April 11, 2013 8:55 AM
To: Jordan, Michelle
Cc: Casilda Luck-Barnes
Subject: RE: Stats IR - NDA 205437

Hi Michelle

Any feedback on the concern indicated with PsA-001 and they still need to be submitted. Also do you anticipate the need for an orientation meeting with Celgene.

Casilda

From: Casilda Luck-Barnes
Sent: Monday, April 08, 2013 9:55 AM
To: 'Jordan, Michelle'
Subject: RE: Stats IR - NDA 205437

Dear Michelle

I hope you had a good weekend. We are fine with fulfilling your request for PSA-002, PSA-003, PSA-004. Concerning PSA-001 is it possible to confirm with FDA that PSA-001 is needed? Being the study was a paper based phase 2 legacy study, SDTM was converted later for submission only. The macros/programs were support legacy dataset and not SDTM.

Let me know

Casilda

From: Jordan, Michelle [mailto:Michelle.Jordan@fda.hhs.gov]
Sent: Monday, April 08, 2013 8:57 AM
To: Casilda Luck-Barnes
Subject: Stats IR - NDA 205437

Hi Casilda,

See attached statistical information request. Let me know if you have any questions/concerns.

Michelle JGarner

Michelle Jordan Garner, MS, OTR/L
CDR, U.S. Public Health Service
Sr. Regulatory Management Officer
Food and Drug Administration
Center for Drug Evaluation and Research/ODEII
Division of Pulmonary, Allergy, and Rheumatology Products
10903 New Hampshire Ave., Bldg 22, Room 3200
Silver Spring, MD 20993
☎ 301-796-4786
🖷 301-796-9728
✉ michelle.jordan@fda.hhs.gov

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

/s/

MICHELLE Y JORDAN GARNER
06/21/2013

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

NDA 205437

PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE

Celgene Corporation
33 Technology Drive
Warren, NJ 07059

ATTENTION: Casilda Luck-Barnes, PharmD
Associate Director, Regulatory Affairs

Dear Dr. Luck-Barnes:

Please refer to your New Drug Application (NDA) dated March 20, 2013, received March 21, 2013, submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act for Apremilast Tablets, 10 mg, 20 mg, and 30 mg.

We also refer to:

- your March 27, 2013, correspondence, received March 27, 2013, requesting review of your proposed proprietary name, Otezla
- your April 9, 2013, correspondence, received April 9, 2013, clarifying the location of the proposed professional labeling and proposed container labels and labeling

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

The proposed proprietary name, Otezla, will be re-reviewed 90 days prior to the approval of the NDA. If we find the name unacceptable following the re-review, we will notify you.

If **any** of the proposed product characteristics as stated in your March 27, 2013, submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Nichelle Rashid, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-3904. For any other information regarding this application contact the Office of New Drugs (OND) Regulatory Project Manager, Michelle Jordan-Garner, at (301) 796-4786.

Sincerely,

{See appended electronic signature page}

Carol Holquist, 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/

CAROL A HOLQUIST
06/21/2013

From: Jordan, Michelle
To: Casilda Luck-Barnes
Cc: Jordan, Michelle
Subject: RE: NDA 205437
Date: Thursday, June 20, 2013 6:11:03 PM

Hi Casilda,

For the registration stability studies, you may forgo the additional dissolution testing. We may, however, request additional data from the ongoing stability studies at the commercial sites based on your response information to the No Filing Issues Identified letter; which is pending at this time.

Michelle JGarner

Michelle Jordan Garner, MS, OTR/L
CDR, U.S. Public Health Service
Sr. Regulatory Management Officer
Food and Drug Administration
Center for Drug Evaluation and Research/ODEII
Division of Pulmonary, Allergy, and Rheumatology Products
10903 New Hampshire Ave., Bldg 22, Room 3200
Silver Spring, MD 20993
☎ 301-796-4786
🖷 301-796-9728
✉ michelle.jordan@fda.hhs.gov

From: Jordan, Michelle
Sent: Tuesday, June 18, 2013 2:55 PM
To: 'Casilda Luck-Barnes'
Cc: Jordan, Michelle (Michelle.Jordan@fda.hhs.gov)
Subject: RE: NDA 205437

Hi Casilda,

In response to:

1) You only need to re-submit the Word version of the PI/IFU(Instructions for Use). Unless content changes have been made, you should not have to re-submit an annotated label
2) Submission of requested information by June 28th is acceptable
3) I will forward to the CMC team and will have to get back to you with their reply.

In the future, it would be most helpful if these types of 'clarification' emails could be conveyed as comprehensive as possible; so that we may answer all of your inquiries.

Michelle JGarner

Michelle Jordan Garner, MS, OTR/L
CDR, U.S. Public Health Service
Sr. Regulatory Management Officer
Food and Drug Administration

Center for Drug Evaluation and Research/ODEII
Division of Pulmonary, Allergy, and Rheumatology Products
10903 New Hampshire Ave., Bldg 22, Room 3200
Silver Spring, MD 20993
☎301-796-4786
🖷301-796-9728
✉michelle.jordan@fda.hhs.gov

From: Casilda Luck-Barnes [mailto:clbarnes@celgene.com]
Sent: Tuesday, June 18, 2013 11:13 AM
To: Jordan, Michelle
Subject: RE: NDA 205437

Hi Michelle

I have the following questions related to the Labeling and CMC questions posed in the Day 74 letter:

1. In the comments sent to the Sponsor related to submitted labeling, Celgene will be resubmitting proposed labeling (WORD version) that addresses the issues identified. Celgene wanted to confirm that your requested changes to the WORD version of proposed labeling do not also require resubmission of the submitted SPL or annotated label to show similar changes at this time.

2. Is it acceptable for the Agency to received CMC requested information by June 28th 2013. The requested Labeling modification in the Day 74 letter will be submitted on June 24th.

3. We seek clarification on Question 19 as follows:

Question 19: FDA recommends adding dissolution sampling at 10 and 20 minutes to the ongoing stability studies and including the complete dissolution data in your next stability update.

Regards

Casilda Luck-Barnes, PharmD
Associate Director, Regulatory Affairs
Celgene Corporation

33 Technology Drive
Warren, NJ 07059
Tel (732) 652-6506
Fax (908) 860-7515
clbarnes@celgene.com

CLB

From: Jordan, Michelle [mailto:Michelle.Jordan@fda.hhs.gov]
Sent: Thursday, June 13, 2013 4:40 PM
To: Casilda Luck-Barnes
Cc: Jordan, Michelle
Subject: RE: NDA 205437

Hi Casilda,

Your proposed responses appear appropriate. However, an additional comment in responding to #1 (CMC information) is as follows:

Provide a copy of the QA signed off analytical procedure and validation report for the dissolution test method, as opposed to (b) (4) **n" and cross references to** (b) (4)

Let me know if you have any additional questions.

Michelle JGarner
Michelle Jordan Garner, MS, OTR/L
CDR, U.S. Public Health Service
Sr. Regulatory Management Officer
Food and Drug Administration
Center for Drug Evaluation and Research/ODEII
Division of Pulmonary, Allergy, and Rheumatology Products
10903 New Hampshire Ave., Bldg 22, Room 3200
Silver Spring, MD 20993
☎ 301-796-4786
🖷 301-796-9728
✉ michelle.jordan@fda.hhs.gov

From: Casilda Luck-Barnes [mailto:clbarnes@celgene.com]
Sent: Friday, June 07, 2013 4:35 PM
To: Jordan, Michelle
Subject: RE: NDA 205437

Hi Michelle

I hope your well. My Team has two clarifying questions to ask the Division as it relates to

requested information in the Day 74 communication as follows:

#1 FDA Question 14: Provide a methods validation package in accordance with the FDA's "Guideline for Submitting Samples and Analytical Data for Methods Validation."

Celgene Comment: Celgene will be submitting the following information in the package based on the FDA guidance cited above. Can the Division confirm that the following information will address your question:

1. A tabular listing of all samples to be submitted
    a. One batch for drug substance
    b. One batch of each strength (10 mg, 20 mg and 30 mg) for drug product
    c. Reference standard
2. Certificates of analysis for each sample submitted
3. Reference standard qualification tests and results
4. [redacted] (b) (4)

Celgene plans to only cross reference respective NDA sections for the following information in our response:

1. A listing of all proposed regulatory specifications (drug substance and drug product)
2. Physical description of the material, including its color and physical constants
3. Appropriate chemical attributes, such as structural formula, empirical formula, and molecular weight
4. Quantitative composition of drug product
5. Method validation data (drug substance and drug product)
6. [redacted] (b) (4)

#2: In the comments sent to the Sponsor related to submitted labeling, Celgene will be resubmitting proposed labeling (WORD version) that addresses the issues identified. Celgene wanted to confirm that your requested changes to the WORD version of proposed labeling do not also require resubmission of the submitted SPL or annotated label to show similar change at this time.

If you could get back to us by the 11th of June that would be helpful.

Regards

Casilda Luck-Barnes, PharmD
Associate Director, Regulatory Affairs
Celgene Corporation
33 Technology Drive
Warren, NJ 07059
Tel (732) 652-6506
Fax (908) 860-7515

clbarnes@celgene.com

CLB

From: Jordan, Michelle [mailto:Michelle.Jordan@fda.hhs.gov]
Sent: Monday, June 03, 2013 4:01 PM
To: Casilda Luck-Barnes
Subject: RE: NDA 205437

Hi Casilda,

See attached.

Michelle JGarner

Michelle Jordan Garner, MS, OTR/L
CDR, U.S. Public Health Service
Sr. Regulatory Management Officer
Food and Drug Administration
Center for Drug Evaluation and Research/ODEII
Division of Pulmonary, Allergy, and Rheumatology Products
10903 New Hampshire Ave., Bldg 22, Room 3200
Silver Spring, MD 20993
☎ 301-796-4786
🖷 301-796-9728
✉ michelle.jordan@fda.hhs.gov

From: Casilda Luck-Barnes [mailto:clbarnes@celgene.com]
Sent: Monday, June 03, 2013 3:59 PM
To: Jordan, Michelle
Subject: RE: NDA 205437

Hi Michelle

I wanted to check to see when we might receive the Day 74 letter from FDA. Let me know if there is anything I can assist with. Regards

Regards

Casilda Luck-Barnes, PharmD
Associate Director, Regulatory Affairs
Celgene Corporation
33 Technology Drive
Warren, NJ 07059
Tel (732) 652-6506
Fax (908) 860-7515

clbarnes@celgene.com

CLB

From: Jordan, Michelle [mailto:Michelle.Jordan@fda.hhs.gov]
Sent: Thursday, April 11, 2013 10:17 AM
To: Casilda Luck-Barnes
Subject: RE: Stats IR - NDA 205437

Hi Casilda,

The following is the feedback from our stats review team:

You stated that study PSA-001 data were originally in legacy format and were then converted to SDTM format for submission. We appreciate that you converted your legacy datasets to CDISC-formatted datasets for this submission. However, in order to properly review study PSA-001, we need the actual datasets you used to generate the results in the study report. Therefore, please clarify which data format was used to generate the results in the study report and whether the analysis datasets you submitted are of the same format. If the results were generated using the legacy datasets, submit the analysis datasets (in legacy format) you used, as well as the data definition file that contains information on how variables were derived. Also, include the programs and macros used to analyze the primary and secondary efficacy endpoints.

As I stated in a previous email, we do not need an orientation meeting with Celgene at this time.

Michelle JGarner

Michelle Jordan Garner, MS, OTR/L
CDR, U.S. Public Health Service
Sr. Regulatory Management Officer
Food and Drug Administration
Center for Drug Evaluation and Research/ODEII
Division of Pulmonary, Allergy, and Rheumatology Products
10903 New Hampshire Ave., Bldg 22, Room 3200
Silver Spring, MD 20993
☎ 301-796-4786
🖷 301-796-9728
✉ michelle.jordan@fda.hhs.gov

From: Casilda Luck-Barnes [mailto:clbarnes@celgene.com]
Sent: Thursday, April 11, 2013 8:55 AM
To: Jordan, Michelle
Cc: Casilda Luck-Barnes
Subject: RE: Stats IR - NDA 205437

Hi Michelle

Any feedback on the concern indicated with PsA-001 and they still need to be submitted. Also do you anticipate the need for an orientation meeting with Celgene.

Casilda

From: Casilda Luck-Barnes
Sent: Monday, April 08, 2013 9:55 AM
To: 'Jordan, Michelle'
Subject: RE: Stats IR - NDA 205437

Dear Michelle

I hope you had a good weekend. We are fine with fulfilling your request for PSA-002, PSA-003, PSA-004. Concerning PSA-001 is it possible to confirm with FDA that PSA-001 is needed? Being the study was a paper based phase 2 legacy study, SDTM was converted later for submission only. The macros/programs were support legacy dataset and not SDTM.

Let me know

Casilda

From: Jordan, Michelle [mailto:Michelle.Jordan@fda.hhs.gov]
Sent: Monday, April 08, 2013 8:57 AM
To: Casilda Luck-Barnes
Subject: Stats IR - NDA 205437

Hi Casilda,

See attached statistical information request. Let me know if you have any questions/concerns.

Michelle JGarner

Michelle Jordan Garner, MS, OTR/L
CDR, U.S. Public Health Service
Sr. Regulatory Management Officer
Food and Drug Administration
Center for Drug Evaluation and Research/ODEII
Division of Pulmonary, Allergy, and Rheumatology Products
10903 New Hampshire Ave., Bldg 22, Room 3200
Silver Spring, MD 20993
☎ 301-796-4786
🖷 301-796-9728
✉ michelle.jordan@fda.hhs.gov

****
THIS ELECTRONIC MAIL MESSAGE AND ANY ATTACHMENT IS
CONFIDENTIAL AND MAY CONTAIN LEGALLY PRIVILEGED
INFORMATION INTENDED ONLY FOR THE USE OF THE INDIVIDUAL
OR INDIVIDUALS NAMED ABOVE.
If the reader is not the intended recipient, or the
employee or agent responsible to deliver it to the
intended recipient, you are hereby notified that any
dissemination, distribution or copying of this
communication is strictly prohibited. If you have
received this communication in error, please reply to the
sender to notify us of the error and delete the original
message. Thank You.
****

****
THIS ELECTRONIC MAIL MESSAGE AND ANY ATTACHMENT IS
CONFIDENTIAL AND MAY CONTAIN LEGALLY PRIVILEGED
INFORMATION INTENDED ONLY FOR THE USE OF THE INDIVIDUAL
OR INDIVIDUALS NAMED ABOVE.
If the reader is not the intended recipient, or the
employee or agent responsible to deliver it to the
intended recipient, you are hereby notified that any
dissemination, distribution or copying of this
communication is strictly prohibited. If you have
received this communication in error, please reply to the
sender to notify us of the error and delete the original
message. Thank You.
****

****
THIS ELECTRONIC MAIL MESSAGE AND ANY ATTACHMENT IS
CONFIDENTIAL AND MAY CONTAIN LEGALLY PRIVILEGED
INFORMATION INTENDED ONLY FOR THE USE OF THE INDIVIDUAL
OR INDIVIDUALS NAMED ABOVE.
If the reader is not the intended recipient, or the
employee or agent responsible to deliver it to the
intended recipient, you are hereby notified that any
dissemination, distribution or copying of this
communication is strictly prohibited. If you have
received this communication in error, please reply to the
sender to notify us of the error and delete the original
message. Thank You.
****

****
THIS ELECTRONIC MAIL MESSAGE AND ANY ATTACHMENT IS
CONFIDENTIAL AND MAY CONTAIN LEGALLY PRIVILEGED
INFORMATION INTENDED ONLY FOR THE USE OF THE INDIVIDUAL
OR INDIVIDUALS NAMED ABOVE.
If the reader is not the intended recipient, or the
employee or agent responsible to deliver it to the
intended recipient, you are hereby notified that any
dissemination, distribution or copying of this
communication is strictly prohibited. If you have
received this communication in error, please reply to the
sender to notify us of the error and delete the original

message. Thank You.
****

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

/s/

MICHELLE Y JORDAN GARNER
06/20/2013

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 205437

FILING COMMUNICATION

Celgene Corporation
33 Technology Drive
Warren, NJ 07059

Attention: Casilda Luck-Barnes, PharmD
Associate Director, Regulatory Affairs

Dear Dr. Luck-Barnes:

Please refer to your New Drug Application (NDA) dated March 20, 2013, received March 21, 2013, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act, for apremilast tablets, 30 mg.

We also refer to your amendment dated April 16, 2013.

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 314.101(a), this application is considered filed 60 days after the date we received your application. The review classification for this application is Standard. This application is also subject to the provisions of "the Program" under the Prescription Drug User Fee Act (PDUFA) V (refer to http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm272170.htm. Therefore, the user fee goal date is March 21, 2014.

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 November 27, 2013. In addition, the planned date for our internal mid-cycle review meeting is August 12, 2013. We are currently planning to hold an advisory committee meeting to discuss this application.

At this time, we are notifying you that, we have not identified any potential review issues. Please note that our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review.

We request that you submit the following information:

1. Add a detailed description of the drug substance manufacturing process in section 3.2.S.2.2.

2. Provide in section 3.2.S.2.3 more details for the methods for starting materials, and summary validation data as a minimum. Specifications for many reagents and solvents only consist of appearance and identity attributes. This is insufficient. If you rely on certificates of analysis (CoAs) in order to assure the quality of these materials, provide them, and provide details of test methods to periodically validate the accuracy of the CoAs.

3. Provide more detailed information pertaining to the methods used in section 3.2.S.2.4 and at least summary validation data.

4. You have only provided a short method summary for each analytical procedure in the controls for the drug substance (3.2.S.4.2). Provide detailed analytical methods sufficient to allow their accurate reproduction by FDA laboratories.

5. Develop and implement, at least, a qualitative specification and method for (b) (4) for the drug substance. Alternatively, demonstrate that your (b) (4) as an identification test for (b) (4), relative to the other potential (b) (4)

6. Provide the profiles of residual solvents in the drug substance across the different manufacturing processes used in drug substance development.

7. Provide the excipient specifications, even if they are compendial, along with certificates of analysis (CoAs) for the excipients. Your specifications should indicate what specifications are applied on receipt of the excipients, and what specifications are used to periodically validate the data on the certificates of analysis. This latter comment also applies to the (b) (4) film coating materials.

8. Include a detailed manufacturing description for the proposed commercial process in Section 3.2.P.3.3, including the packaging and labeling processes. Alternatively, Section 3.2.P.3.3. may cross reference detailed information (e.g. specific batch records) provided in Section 3.2.R.

9. Provide a master batch record (or an executed batch record) for each strength product for each commercial site, or alternatively provide comparably detailed descriptions for each site. Provide a list of any substantive differences between the sites, for

manufacturing and control processes for pilot [redacted] (b) (4) and commercial batches.

10. Provide in Section 3.2.P.7 of your NDA, illustrations of each container closure system proposed, and provide dimensional information.

11. Justify the lack of a drug product specification for [redacted] (b) (4). Include an appropriate "related impurities" specification for any unspecified degradation product (NMT [redacted] (b) (4) Specify individual impurities which may be present at levels greater than [redacted] (b) (4) in the specification (at least by relative retention time, for example).

12. Provide complete descriptions of all of the analytical procedures for the drug product so that they may be reviewed, and reproduced in an FDA laboratory. Provide the details of the compendial microbial limits method as performed for this NDA.

13. Provide updated long term and accelerated stability data for the three proposed commercial drug product manufacturing sites, as soon as it is available. If these data are provided too late in the review cycle, they may or may not be able to be reviewed, depending on our available resources.

14. Provide a methods validation package in accordance with the FDA's "Guideline for Submitting Samples and Analytical Data for Methods Validation."

15. Revise the container label so that it indicates where the lot number and expiry date will be printed.

16. Provide the complete dissolution method development report for review. The report should include the following:

    a. The complete drug substance pH solubility profile.

    b. A detailed description of the testing done to select the proposed dissolution method as optimal for your product [redacted] (b) (4). We note that a [redacted] (b) (4) is proposed and data supporting the selected type and concentration should be provided. In general, the least amount of [redacted] (b) (4) should be used. For each variable tested, clearly specify the testing conditions. Complete dissolution data (individual values, mean, RSD, and profiles) should be provided for all variables tested. Also, the sampling time points should be sufficient to characterize the complete dissolution profile, which means sampling at early time points (i.e., 5, 10, 15 and 20 minutes) in the event of rapid product dissolution. The data in the NDA do not include complete dissolution profile information.

c. Testing conducted to demonstrate the discriminating capability of the selected dissolution test. Your proposed assessment of [redacted] is inadequate. The optimal dissolution method should be able to distinguish between [redacted] drug substance [redacted] owing to the significant effect of drug substance [redacted] on bioavailability, as observed in Study CC-10004-BA-001, and the designation of drug substance [redacted] distribution as a critical quality attribute. Further, a dissolution method that achieves [redacted] dissolution in [redacted] for a poorly soluble drug substance is generally not sufficiently robust to detect meaningful manufacturing changes.

d. The complete dissolution method validation report.

17. Provide the complete dissolution data (individual values, mean, RSD, and profiles) for all Design of Experiments (DOE) studies supporting the proposed commercial manufacturing process and site changes that used dissolution as a response factor and the results of similarity f2 testing, using a clinical batch as a reference, where appropriate.

18. FDA understands that the proposed dissolution method (USP 2, 75 rpm, 0.3% SLS pH 6.8 sodium phosphate buffer) was not used for testing any clinical supplies or the primary registration stability lots. Please confirm.

19. FDA recommends adding dissolution sampling at 10 and 20 minutes to the ongoing stability studies and including the complete dissolution data in your next stability update.

During our preliminary review of your submitted labeling, we have identified the following labeling format issues:

1. The section headings and subheadings in the TOC must match the headings and subheadings in the FPI. Therefore list, "7.1 Potent CYP3A4 Inducers" under DRUG INTERACTIONS.

2. FDA-approved patient labeling must not be included as a subsection under Section 17 (Patient Counseling Information). All patient labeling must appear at the end of the PI upon approval. Therefore remove, [redacted] and put at the end of the PI. In addition, any FDA-approved patient labeling, include the type of patient labeling, and use the following statement at the beginning of Section 17: "See FDA-approved patient labeling (Instructions for Use)"

We request that you resubmit labeling that addresses these issues by June 24, 2013. The resubmitted labeling will be used for further labeling discussions.

Please respond only to the above requests for information. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

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), and patient PI. Submit consumer-directed, professional-directed, and television advertisement materials separately and send each submission to:

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

Do not submit launch materials until you have received our proposed revisions to the package insert (PI), and patient PI, 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.

We acknowledge receipt of your requests for a partial waiver, and a partial deferral, of pediatric studies for this application. Once we have reviewed your request, we will notify you if these requests are denied.

If you have any questions, call Michelle Jordan Garner, Regulatory Project Manager, at (301) 796-4786.

Sincerely,

{See appended electronic signature page}

Badrul A. Chowdhury, MD, PhD
Director,
Division of Pulmonary, Allergy, and Rheumatology Products
Office of Drug Evaluation II
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/

BADRUL A CHOWDHURY
06/03/2013

Rashid, Nichelle E

From: Rashid, Nichelle E
Sent: Friday, May 10, 2013 1:51 PM
To: Casilda Luck-Barnes (clbarnes@celgene.com)
Cc: Rashid, Nichelle E; Bradley, Sean
Subject: Information Request for Proprietary Name Review/ NDA 205437/ Apremilast

Good Afternoon Ms. Luck-Barnes,

Your Request for Proprietary Name Review for NDA 205437 submitted on March 27, 2013 is currently under review. We have the following request for information:

Your proprietary name submission for the proposed proprietary name, Otezla (Apremilast) indicated that the dosage and frequency for the psoriatic arthritis indication is 20 mg and/or 30 mg twice daily. However, the Prescribing Information indicated that the recommended dose for the psoriatic arthritis indication is 30 mg twice daily, but the following initial titration is required:

Day 1	Day 2		Day 3		Day 4		Day 5		Day 6 & thereafter	
AM	AM	PM	AM	PM	AM	PM	AM	PM	AM	PM
10 mg	10 mg	10 mg	10 mg	20 mg	20 mg	20 mg	20 mg	30 mg	30 mg	30 mg

Please clarify the dosage and frequency for the psoriatic arthritis indication for the proposed name, Otezla (apremilast) and specify what strengths are intended to be marketed.

In order to facilitate the review of your proprietary name, please provide the requested information no later than noon Wednesday, May 15, 2013. If you have any questions, please contact me via email or at (410) 796-3904.

Thanks,

Nichelle E. Rashid
Senior Safety Regulatory Project Manager
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research
Food and Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002
Tel: (301) 796-3904
Fax: (301) 796-9725
nichelle.rashid@fda.hhs.gov

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

/s/

NICHELLE E RASHID
05/28/2013

Rashid, Nichelle E

From: Rashid, Nichelle E
Sent: Friday, April 05, 2013 11:31 AM
To: Casilda Luck-Barnes (clbarnes@celgene.com)
Cc: Rashid, Nichelle E; Anderson, Janet; Bradley, Sean
Subject: Request for PN Review/ NDA 205437/ Otezla

Follow Up Flag: Follow up
Flag Status: Flagged

Categories: Proprietary Name

Good Morning Ms. Luck-Barnes,

As a follow-up to our teleconference conversation, DMEPA requests that you submit an amendment to the PN Request review to indicate the location of the label and labeling in the original submission of the NDA.

Please ensure that you submit this information in the NDA as an "Amendment to the PN Request for Review" on the cover letter. Please reference the date and SDN of the PN request for review.

Please revise the original cover letter by including the paragraphs as listed in your previous email below with the current location of the label and labeling. The second paragraph clarifies how the 10 mg strength will be available for use.
We do not need you to resubmit label and labeling with the proposed proprietary name, Otezla, at this time.

If you have any questions, please do not hesitate to contact me.

Thanks,

Nichelle E. Rashid
Safety Regulatory Project Manager
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research
Food and Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002
Tel: (301) 796-3904
Fax: (301) 796-9725
nichelle.rashid@fda.hhs.gov

From: Thomas, Teena
Sent: Thursday, April 04, 2013 7:26 AM
To: Rashid, Nichelle E
Subject: FW: NDA 205437 Otezla Apremilast

FYI

From: Casilda Luck-Barnes [mailto:clbarnes@celgene.com]
Sent: Monday, April 01, 2013 10:42 AM
To: Thomas, Teena

Cc: Brennan, Colleen; Jenkins, Darrell
Subject: RE: NDA 205437 Otezla Apremilast

Dear Dr. Thomas

In follow up to my email I wanted to clarify that we did submit proposed labeling with our application NDA 205437 on March 21, 2013. The proposed professional labeling can be found in the e-CTD Module 1, Section 14.1.2 and 14.1.3. Further proposed container labels and labeling for apremilast were submitted as well. The proposed container labels and labeling can be found in the e-CTD Module 1, Section 14.1.1 but without the proposed name Otezla. Please confirm if providing the location in the NDA for where you can find these items is acceptable in meeting your needs or would you like to see the proposed container labels and labeling with Otezla provided in place of Trade Name.

Please note in our professional labeling under How Supplied as well as noted in our proposed container labels and labeling it is the Sponsors intent that the 10mg strength will not be commercially available as a dose to be prescribed as a dose by a physician. The 10mg strength tablet will only be available as part of a titration starter package which will include 10mg, 20mg and 30mg tablets. A physician has to write for Trade Name starter package not the individual 10mg strength. The Sponsor wishes that this is kept under consideration when comparing apremilast based on product characteristics to other products as a doctor will not be able to write a 10mg strength.

If you have any questions please let me know and I look for your confirmation on if what has been provided is acceptable or if you need me to revise container labeling to include Otezla.

Regards

Casilda Luck-Barnes, PharmD
Associate Director, Regulatory Affairs
Celgene Corporation
33 Technology Drive
Warren, NJ 07059
Tel (732) 652-6506
Fax (908) 860-7515
clbarnes@celgene.com

CLB

From: Casilda Luck-Barnes
Sent: Friday, March 29, 2013 5:12 PM
To: 'Thomas, Teena'
Cc: Brennan, Colleen; Jenkins, Darrell
Subject: RE: NDA 205437 Otezla Apremilast

Dear Dr. Thomas

It is my understanding that you would like a copy of the carton and container labeling that has Otezla on it per your request below. As part of the NDA submission we submitted carton and container labeling that presented "Trade Name" in place of the proposed brand name Otezla. In response to your question I will add the proposed name Otezla to the carton and container labeling and resubmit it to the NDA. I will send an electronic version of this to you by Tuesday. Please confirm that you do not need proposed physician package insert with Otezla on it as well.

Regards

Casilda Luck-Barnes, PharmD
Associate Director, Regulatory Affairs
Celgene Corporation
33 Technology Drive
Warren, NJ 07059
Tel (732) 652-6506
Fax (908) 860-7515
clbarnes@celgene.com

CLB

From: Thomas, Teena [mailto:Teena.Thomas@fda.hhs.gov]
Sent: Friday, March 29, 2013 9:59 AM
To: Casilda Luck-Barnes
Cc: Brennan, Colleen; Jenkins, Darrell; Thomas, Teena
Subject: NDA 205437 Otezla Apremilast

Hi Ms. Barnes,

We have received a proprietary name request for NDA 205437 Otezla from you. We noticed you haven't submitted the labels and labeling with the proposed name. The proprietary name review for an NDA submission requires the review of all labels and labeling. Due to the time constraints of the review process, please respond within 7 business days from receipt of this request.

I am the OSE project manager covering for Nichelle Rashid and please contact Nichelle for any future reference.

Thank you,

Teena

Teena Thomas, Pharm.D,CGP
Safety Regulatory Project Manager
FDA, CDER
Office of Surveillance and Epidemiology
Bldg.22, Room 3461
10903 New Hampshire Ave.
Silver Spring, Maryland 20993-0002

Tel: 301.796.0549
E-mail : teena.thomas@fda.hhs.gov

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

/s/

NICHELLE E RASHID
05/28/2013

NDA 205437:
Apremilast for the treatment of Psoriatic Arthritis

Filing Meeting

Clinical Team

April 24, 2013

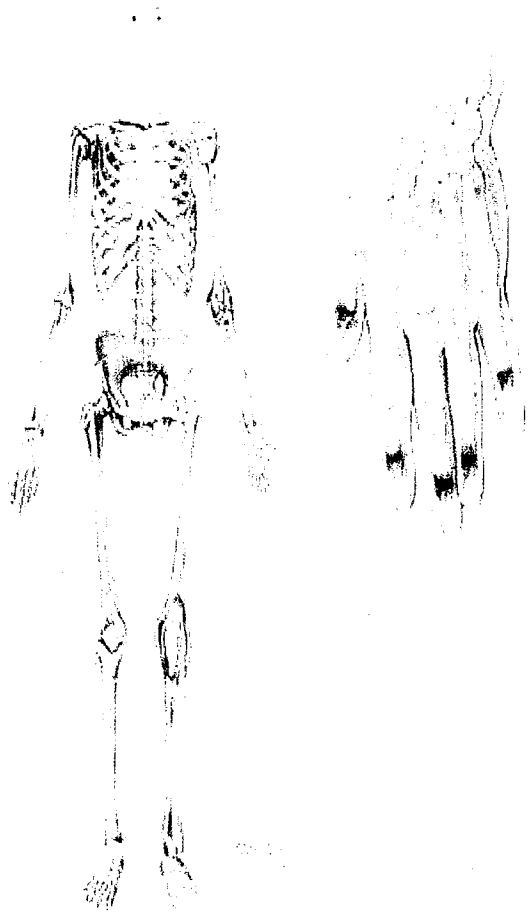
Summary

- Apremilast is a PDE4-inhibitor
- Proposed Indication:
  - Treatment of Adult Patients with Psoriatic Arthritis
  - Proposing the single Apremilast 30 mg BID dose for approval
- Fileable
  - Well-conducted studies
  - Information clearly presented
- Consults
  - DSI
  - QT/QTc Study Group

Disease Background

Psoriatic Arthritis = Rheumatoid Arthritis (+)

- 10-40% of patients with psoriasis develop Psoriatic Arthritis (PsA)
- Seronegative (RF-)
- Joint involvement similar to RA with some additions
  - Distal interphalangeal (DIP) joints
  - Axial skeleton
- Radiographic Findings
  - Erosions
    - "pencil in cup" deformation
  - New bone formation



Psoriatic Arthritis-Current Available Therapies

- Traditional DMARDs
  - NSAIDS, SSZ, MTX

- Biologics: TNFi

Biologics in PsA: ACR20 @ Week 24

Product	Placebo	Drug
Etanercept	15%	57%
Adalimumab	15%	57%
Infliximab	16%	51%
Golimumab	12%	52%

Regulatory Background

Key Regulatory Interactions

- **March 2010-EOP2 Meeting**
  - Agreement reached on Study Designs and Endpoints
- **June 2012-Written Correspondence**
  - Agreement reached on changing Primary Endpoints from Week 24 to Week 16
- **December 2012-pre NDA Meeting**
  - Agreement reached on submission data and additional safety data analyses

Apremilast Development Program Overview

Clinical Studies

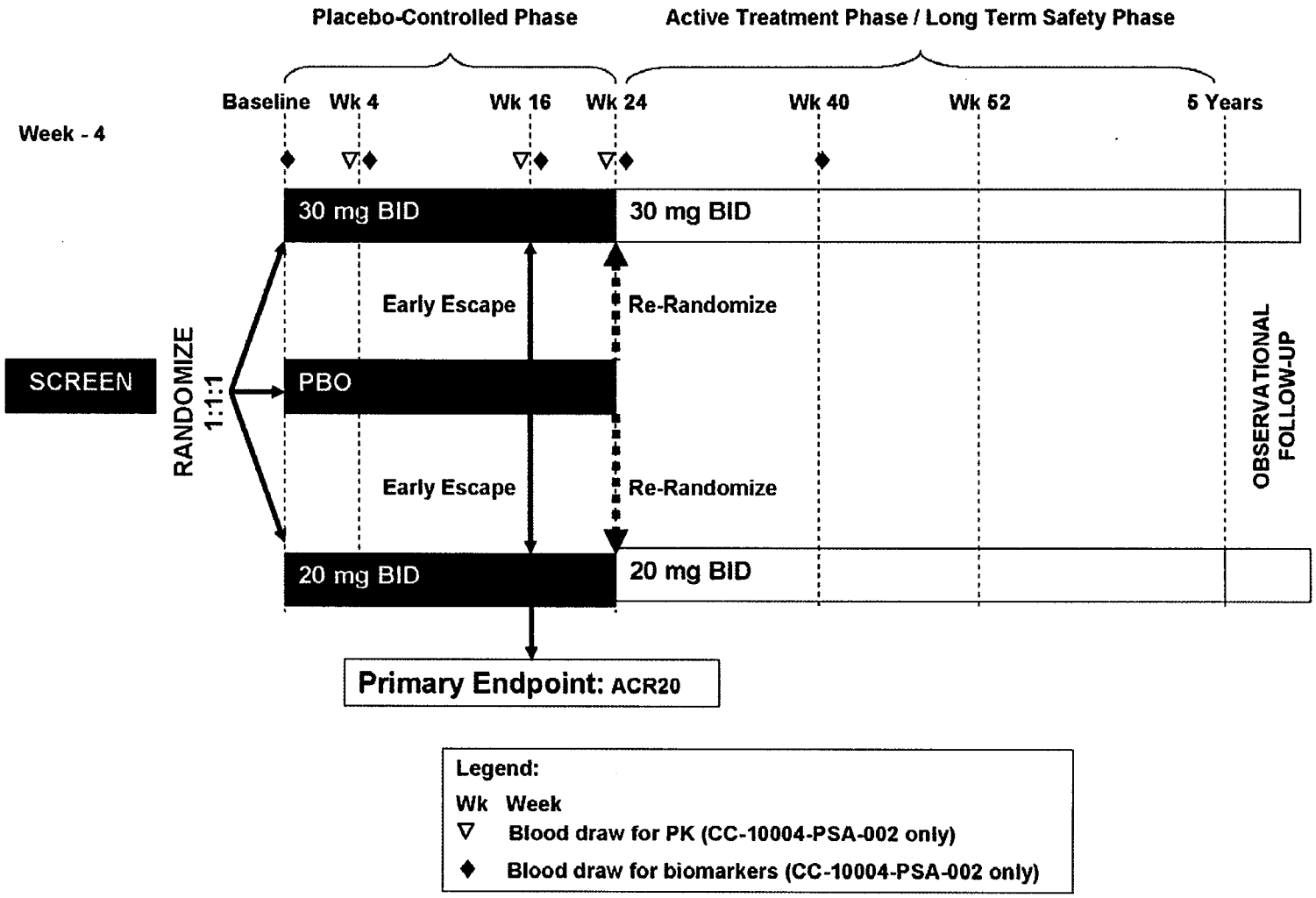
Study #	Patients N (Dropout %)	Study Design	Apremilast Dosing	Primary Endpoint
Phase 2				
PSA-001	204 (19%)	R, DB, PC, PG	APR 40 mg QD APR 20 mg BID	ACR 20 @ Day 85
Phase 3				
PSA-002	504 (12%)	R, DB, PC, PG	APR 20 mg BID APR 30 mg BID	ACR 20 @ Week 16
PSA-003	488 (11%)	R, DB, PC, PG	APR 20 mg BID APR 30 mg BID	ACR 20 @ Week 16
PSA-004	505 (13%)	R, DB, PC, PG	APR 20 mg BID APR 30 mg BID	ACR 20 @ Week 16
PSA-005	528 (n/a) R, DB, PC, PG	APR 20 mg BID	APR 30 mg BID	ACR 20 @ Week 16
	DMARD-naïve, APR monotherapy Study---ONGOING			

Apremilast-Dose Selection

- Study PSA-001
  - APR 20 mg BID
    - ACR20 and ACR50 significant compared to PBO
  - APR 40 mg QD
    - ACR20, but not ACR50, significant compared to PBO
- PK analysis
  - BID dosing much better tolerated than QD dosing
    - Fewer GI-associated AEs

Efficacy

Phase 3 Study Design



Phase 3 Study Results

- A total of ~1500 patients randomized across the studies
- Baseline demographics and disease characteristics similar between treatment groups and representative of US population
- ~93% completion rate through Week 16
  - AEs, LOE, Withdrawal by subject

Phase 3 Efficacy Results-Primary Endpoint

Table 2: Proportion of Subjects Achieving ACR 20 at Week 16 (FAS Population; NRI)

Study	Placebo	APR 20 BID		APR 30 BID	
	n/N (%)[a]	n/N (%)[a]	P-value[b]	n/N (%)[a]	P-value[b]
CC-10004-PSA-002	32/168 (19.0)	51/168 (30.4)	0.0166	64/168 (38.1)	0.0001
CC-10004-PSA-003	30/159 (18.9)	61/163 (37.4)	0.0002	52/162 (32.1)	0.0060
CC-10004-PSA-004	31/169 (18.3)	48/169 (28.4)	0.0295	68/167 (40.7)	< 0.0001

- Weak Dose-Response Effect
  - APR 20 BID: ~13% Treatment Effect Size
  - APR 30 BID: ~18% Treatment Effect Size
- Efficacy much lower than that seen with TNF-inhibitors
  - >40% Treatment Effect Size

Phase 3 Study Results: Secondary Endpoints

Endpoint Study	n[a]/N (%) of Subjects Placebo	APR 20 BID	APR 30 BID
ACR 20 Response			
PSA-002	22/168 (13.1)	59/168 (35.1)	73/168 (43.5)
PSA-003	25/159 (15.7)	69/163 (42.3)	60/162 (37.0)
PSA-004	26/169 (15.4)	62/169 (36.7)	63/167 (37.7)
ACR 50 Response			
PSA-002	7/168 (4.2)	26/168 (15.5)	35/168 (20.8)
PSA-003	14/159 (8.8)	26/163 (16.0)	25/162 (15.4)
PSA-004	13/169 (7.7)	28/169 (16.6)	33/167 (19.8)
ACR 70 Response			
PSA-002	1/168 (0.6)	9/168 (5.4)	19/168 (11.3)
PSA-003	5/159 (3.1)	9/163 (5.5)	5/162 (3.1)
PSA-004	6/169 (3.6)	9/169 (5.3)	9/167 (5.4)

Safety

Extent of Drug Exposure

Table 14: PsA Phase 3 Data Pool: Extent of Apremilast Exposure During the Apremilast-exposure Period (Apremilast Subjects as Treated Population)

Exposure Category[a]	APR 10 BID (N=720) n (%)	APR 30 BID (N=721) n (%)	APR Total (N=1441) n (%)
≥ 1 Day	720 (100.0)	721 (100.0)	1441 (100.0)
≥ 4 Weeks	693 (96.3)	686 (95.1)	1379 (95.7)
≥ 12 Weeks	630 (87.5)	625 (86.7)	1255 (87.1)
≥ 24 Weeks	516 (71.7)	527 (73.1)	1043 (72.4)
≥ 36 Weeks	332 (46.1)	340 (47.2)	672 (46.6)
≥ 48 Weeks	176 (24.4)	183 (25.4)	359 (24.9)
≥ 60 Weeks	92 (12.8)	84 (11.7)	176 (12.2)
≥ 72 Weeks	35 (4.9)	35 (4.9)	70 (4.9)

Safety Profile: PBO-Treatment Phase

- Deaths
  - 6 deaths total (3 APR vs. 3 PBO)
- SAEs
  - PBO-4%
  - APR 20-3%
  - APR30-4%
- AEs leading to Early Withdrawal
  - PBO-(1%)
  - APR 20-(3%)
  - APR 30-(5%)
- No apparent difference in rates/types of infections or events of special interest
- Most common AEs related to GI (d/n/v, HA)
  - Most reported as mild in severity

Safety Profile: PBO-Treatment Phase

- QT/QTc Study
  - No apparent QT prolongation
  - Consult for formal review
- No apparent cases of vasculitis in PsA study

Summary

Summary

- Submission is Fileable
- Apremilast appears mildly efficacious with acceptable safety

Mid-Cycle Deliverables

- Efficacy Analyses of Primary and Major Secondary Endpoints

- Safety Analyses of Deaths, SAEs, AEs, Events of Special Interest

Filing Checklist

NDA [illegible]
Ligand Corporation

Apremilast
Treatment of Psoriatic Arthritis

CLINICAL FILING CHECKLIST FOR A NEW NDA/BLA

	Yes	No	NA	Comment
FORM/ORGANIZATION/CONTENTS				
1. On its face, is the clinical section of the application organized in a manner to allow substantive review to begin?	X			
2. Is the clinical section of the application indexed (table of contents) and paginated in a manner to allow substantive review to begin?	X			
3. For submissions in electronic format, is it possible to navigate the application in order to allow a substantive review to begin (i.e., are the hyperlinks clickable)?	X			
4. Are all documents submitted in English or are English translations provided when necessary?	X			
5. On its face, is the clinical section of the application legible so that substantive review can begin?	X			
LABELING				
6. Has the applicant submitted draft labeling in structured format compliant with 21 CFR 201.56 and 201.57, current division and Office policies, and the changes for the drug/biologic package?	X			
SUMMARIES				
7. Has the applicant submitted all the required Integrated Summaries (i.e., Module 2 summaries)?	X			
8. Has the applicant submitted the integrated summary of safety (ISS)?	X			
9. Has the applicant submitted the integrated summary of efficacy (ISE)?	X			
10. Has the applicant submitted a benefit-risk assessment for the product?	X			
DATA				
11. If needed, has the sponsor made an appropriate attempt to determine the current therapeutic landscape for this product (i.e., a current publication that describes the current therapies)?	X			
EFFICACY				
12. On its face, do there appear to be adequate and well-controlled studies submitted in the application?	X			
13. Do all primary efficacy studies appear to be adequate and well-controlled studies (based on review of the protocol for the method agreed to previously with the applicant in the FDA response to the application for approvability of this product based on proposed draft labeling)?	X			
SAFETY				
14. Has the applicant presented the safety data in a manner consistent with Clinical guidelines and in a manner appropriate for the filing type?	X			
15. Has the applicant submitted adequate information to assess the risk of drug dependence, potential of the product for misuse, abuse, or diversion, if needed?	X			
16. Has the applicant presented a safety assessment based on all available clinical information regarding this product?	X			

[illegible]

BEST AVAILABLE COPY

NDA 20[illegible]
Ligand Corporation

Apremilast
Treatment of Psoriatic Arthritis

BEST AVAILABLE COPY

CLINICAL FILING CHECKLIST FOR A NEW NDA/BLA

	Yes	No	N/A	Comment
FORMAT/ORGANIZATION/ACCESSIBILITY				
1. On its face, is the clinical section of the application organized in a manner to allow substantive review to begin?	X			
2. Is the clinical section of the application indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?	X			
3. Are the data sets in a format that is compatible with our review tools and is it possible to navigate the application in order to allow a substantive review to begin (i.e., are the Study Data Standardization Plan requirements met)?	X			
4. Are all Case Report Tabulations in English or with English translations provided when necessary?	X			
5. Can we begin the substantive review of the application (i.e., is the application sufficiently complete to permit a substantive review to begin)?	X			
LABELING				
6. Has the applicant submitted draft labeling in structured format compliant with 21 CFR 201.56[illegible] and 201.57, content proposal and Carton/container labels, and the Medication Guide or Patient Package Insert?	X			
SUMMARIES				
7. Has the applicant submitted all the required Integrated Summaries (i.e., Module 2 summaries)?	X			
8. Has the applicant submitted the integrated summary of safety (ISS)?	X			
9. Has the applicant submitted the integrated summary of effectiveness (ISE)?	X			
10. Has the applicant submitted a benefit-risk assessment for the product?	X			
PDUFA				
11. If needed, has the sponsor submitted an appropriate request to determine the user fee category and schedule for this application (i.e., a complete clinical data package)?	X			
EFFICACY				
12. On its face, do there appear to be adequate numbers of adequate and well-controlled studies in the application?	X			
13. Do all pivotal efficacy studies appear to be adequate and well-controlled studies (based on review of the protocol, the statistical approach previously agreed to by the applicant in the SPA letter, and/or appropriateness of this product based on previously approved labeling)?	X			
SAFETY				
14. Has the applicant presented the safety data in a manner consistent with the Common Data Standards Issues Document (i.e., is the safety presentation organized in the Division's preferred format)?	X			
15. Has the applicant submitted adequate information to assess the risk of clinically significant potential drug-drug interactions of the product (i.e., CYP interaction, P-gp studies)?	X			
16. Has the applicant provided adequate safety assessment based on all available knowledge regarding this product?	X			

[1] http://www.accessdata.fda.gov/scripts/cder/ndabla/index.cfm

---

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

/s/

KEITH M HULL
04/30/2013

NIKOLAY P NIKOLOV
04/30/2013

From: Jordan, Michelle
To: "Casilda Luck-Barnes"
Subject: RE: Stats IR - NDA 205437
Date: Thursday, April 11, 2013 10:17:00 AM

Hi Casilda,

The following is the feedback from our stats review team:

You stated that study PSA-001 data were originally in legacy format and were then converted to SDTM format for submission. We appreciate that you converted your legacy datasets to CDISC-formatted datasets for this submission. However, in order to properly review study PSA-001, we need the actual datasets you used to generate the results in the study report. Therefore, please clarify which data format was used to generate the results in the study report and whether the analysis datasets you submitted are of the same format. If the results were generated using the legacy datasets, submit the analysis datasets (in legacy format) you used, as well as the data definition file that contains information on how variables were derived. Also, include the programs and macros used to analyze the primary and secondary efficacy endpoints.

As I stated in a previous email, we do not need an orientation meeting with Celgene at this time.

Michelle JGarner

Michelle Jordan Garner, MS, OTR/L
CDR, U.S. Public Health Service
Sr. Regulatory Management Officer
Food and Drug Administration
Center for Drug Evaluation and Research/ODEII
Division of Pulmonary, Allergy, and Rheumatology Products
10903 New Hampshire Ave., Bldg 22, Room 3200
Silver Spring, MD 20993
☎ 301-796-4786
🖷 301-796-9728
✉ michelle.jordan@fda.hhs.gov

From: Casilda Luck-Barnes [mailto:clbarnes@celgene.com]
Sent: Thursday, April 11, 2013 8:55 AM
To: Jordan, Michelle
Cc: Casilda Luck-Barnes
Subject: RE: Stats IR - NDA 205437

Hi Michelle

Any feedback on the concern indicated with PsA-001 and they still need to be submitted. Also do you anticipate the need for an orientation meeting with Celgene.

Casilda

From: Casilda Luck-Barnes
Sent: Monday, April 08, 2013 9:55 AM
To: 'Jordan, Michelle'
Subject: RE: Stats IR - NDA 205437

Dear Michelle

I hope you had a good weekend. We are fine with fulfilling your request for PSA-002, PSA-003, PSA-004. Concerning PSA-001 is it possible to confirm with FDA that PSA-001 is needed? Being the study was a paper based phase 2 legacy study, SDTM was converted later for submission only. The macros/programs were support legacy dataset and not SDTM.

Let me know

Casilda

From: Jordan, Michelle [mailto:Michelle.Jordan@fda.hhs.gov]
Sent: Monday, April 08, 2013 8:57 AM
To: Casilda Luck-Barnes
Subject: Stats IR - NDA 205437

Hi Casilda,

See attached statistical information request. Let me know if you have any questions/concerns.

Michelle JGarner

Michelle Jordan Garner, MS, OTR/L
CDR, U.S. Public Health Service
Sr. Regulatory Management Officer
Food and Drug Administration
Center for Drug Evaluation and Research/ODEII
Division of Pulmonary, Allergy, and Rheumatology Products
10903 New Hampshire Ave., Bldg 22, Room 3200
Silver Spring, MD 20993
☎ 301-796-4786
🖷 301-796-9728
✉ michelle.jordan@fda.hhs.gov

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

/s/

MICHELLE Y JORDAN GARNER
04/11/2013

Your NDA205437, submitted March 21, 2013, is currently under review, and we have the following request for information:

> Provide the programs and macros you used to analyze the primary and secondary efficacy endpoints for studies cc10004psa0001, cc10004psa0002, cc10004psa0003 and cc10004psa0004.

Submit your responses to me via email at michelle.jordan@fda.hhs.gov by COB Friday, April 17, 2013. Your responses will subsequently need to be submitted officially to the NDA. If you have any questions, please contact Michelle Jordan Garner, Senior Regulatory Project Manager, at 301-796-4786.

Drafted by: BobA4/5/13; MichelleJG4/5/13

Concurrence by: SandyB 4/5/13
Finalized by: MichelleJG4/8/13

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

/s/

MICHELLE Y JORDAN GARNER
04/08/2013

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 205437

NDA ACKNOWLEDGMENT

Celgene Corporation
33 Technology Drive
Warren, NJ 07059

Attention: Casilda Luck-Barnes, PharmD
Associate Director, Regulatory Affairs

Dear Dr. Luck-Barnes:

We have received your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for the following:

Name of Drug Product: apremilast, tablets 30 mg

Date of Application: March 21, 2013

Date of Receipt: March 21, 2013

Our Reference Number: NDA 205437

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 May 20, 2013, in accordance with 21 CFR 314.101(a).

If you have not already done so, promptly submit the content of labeling [21 CFR 314.50(l)(1)(i)] 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 under 21 CFR 314.101(d)(3). 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 NDA 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 Pulmonary, Allergy, and Rheumatology Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size. Non-standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission. For additional information, please see http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/DrugMasterFilesDMFs/ucm073080.htm.

Secure email between CDER and applicants is useful for informal communications when confidential information may be included in the message (for example, trade secrets or patient information). If you have not already established secure email with the FDA and would like to set it up, send an email request to SecureEmail@fda.hhs.gov. Please note that secure email may not be used for formal regulatory submissions to applications.
If you have any questions, call me, at (301) 796-4786.

Sincerely,

{See appended electronic signature page}

Michelle Jordan Garner, MS, OTR/L
Senior Regulatory Management Officer
Division of Pulmonary, Allergy, and Rheumatology Products
Office of Drug Evaluation II
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/

MICHELLE Y JORDAN GARNER
04/01/2013

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 101761

MEETING MINUTES

Celgene Corporation
86 Morris Avenue
Summit, NJ 07901

Attention: Casilda Luck-Barnes, PharmD
Associate Director, Regulatory Affairs

Dear Dr. Luck-Barnes:

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

We also refer to the meeting between representatives of your firm and the FDA on December 19, 2012. The purpose of the meeting was to discuss the submission of an NDA for apremilast in the treatment of PsA. .

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 at (301) 796-4786.

Sincerely,

{See appended electronic signature page}

Michelle Jordan Garner, MS, OTR/L
Senior Regulatory Management Officer
Division of Pulmonary, Allergy, and Rheumatology Products
Office of Drug Evaluation II
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:	Type B
Meeting Category:	Pre-NDA
Meeting Date and Time:	December 19, 2012
Meeting Location:	White Oak Building 22, Conference Room: 1309
Application Number:	IND 101761
Product Name:	Apremilast
Indication:	Psoriatic Arthritis
Sponsor/Applicant Name:	Celgene
Meeting Chair:	Badrul A. Chowdhury, MD, PhD
Meeting Recorder:	Michelle Jordan Garner, MS, OTR/L

FDA ATTENDEES

Division of Pulmonary, Allergy, and Rheumatology Products
Badrul A. Chowdhury, MD, Ph.D., Division Director
Sarah Yim, MD, Associate Director
Susan Limb, M.D., Clinical Team Leader
Rosemarie Neuner, M.D., Clinical Reviewer
Michelle Jordan Garner, MS, OTR/L, Senior Regulatory Management Officer
Division of Clinical Pharmacology 2
Suresh Doddapaneni, Director
Arun Agrawal, PhD, Clinical Pharmacology Reviewer
Division of Biometrics II
Joan Buenconsejo, Ph.D., Biostatistics Team Leader
Robert Abugov, Ph.D., Biostatistics Reviewer

SPONSOR ATTENDEES

Judith Abrams, MD, FRCPC, Exec Direc, Clinical Research and Development; Kamal Shah, MD, Exec Direc, Global Drug Safety and Risk Management; Gary Cline, Ph.D., Sr Direc, Biostatistics and Programming; Angela Hu, EdM, MS, Direc, Biostatistics and Programming; Dorothy Waddleton, Sr Direc, Global Regulatory Affairs; Casilda Luck-Barnes, PharmD, Assoc Direc, Regulatory Affairs; Kara Hodes-Weschler, R.Ph, Exec Direc, Reg Affairs; Shih-Yi Kim, PharmD, Mgr, Reg Affairs; Christopher Griffett, VP, Reg Affairs; Peter Schafer, Ph.D., Direc, Sr P.I., Translational; Dev;
Philippe Martin, MS, MBA, Exec Direc, Global Project Leadership

1.0 BACKGROUND

Celgene submitted a Type B meeting request, dated August 27, 2012, to discuss the submission of an NDA for apremilast in the treatment of PsA. The focus and discussion of the meeting was based on questions 3, 4, and 10; which Celgene provided responses to (see below). Celgene stated that they plan to submit their NDA sometime in March 2013. Celgene's questions – along with their responses to FDA's preliminary comments - are in *italics* font; FDA's preliminary responses are in **bold** font; and discussion is in normal font.

2.0 DISCUSSION

NONCLINICAL

Question 1:

Celgene believes the nonclinical studies constitute a complete package that supports the registration of apremilast. Does the Agency agree?

FDA Response:

Yes, we agree.

Discussion:

No discussion.

CLINICAL PHARMACOLOGY

Question 2:

Celgene believes the clinical pharmacology studies constitute a complete package that supports the registration of apremilast. Does the Agency agree?

FDA Response:

In general, the types of clinical pharmacology studies comprising the proposed package seem appropriate for filing the NDA. However, adequacy of data is a review issue. It appears that different formulations may have been used during product development. Confirm that the to-be-marketed formulation is the clinically tested formulation and if not an adequate BA/BE bridge exists between the two. In addition, provide information specifying what formulations were used in the different studies and the BA/BE bridge between those formulations. Since hepatic and renal impairment studies were not

conducted in all categories of impairment, address the labeling language in the categories of impairment not studied. Justify that the highest dose (50 mg bid) studied in the TQT study is indeed the supratherapeutic dose.

Discussion:

No discussion.

CLINICAL

Question 3:

Does the Agency agree that the design, analysis, and results of the phase 3 program in PsA (CC-10004-PSA-002, CC-10004-PSA-003, CC-10004-PSA-004) provide substantial evidence of efficacy to support NDA submission of apremilast 30 mg BID for the treatment of active psoriatic arthritis?

FDA Response:

In principle, there appears to be adequate efficacy data to support the filing of an NDA for apremilast as a treatment for psoriatic arthritis (PsA) based on our review of the summarized information from the three randomized, controlled, pivotal Phase 3 studies (CC-10004-PSA-002, CC-10004-PSA-003, CC-10004-PSA-004) contained in your meeting package. However, we have concerns regarding the clinical relevance of the observed treatment benefit. The concerns are amplified by the questionable demonstration of a dose response for the 20 mg bid versus the 30 mg bid dosing regimen of apremilast in view of the summarized results from studies CC-10004-PSA-002 and CC-10004-PSA-003. The adequacy of the data to support the efficacy of apremilast will be a review issue.

Celgene Response:

There remains an unmet medical need for novel agents for the treatment of psoriatic arthritis (PsA). Any single disease modifying anti-rheumatic drugs (DMARDs) currently used in patients with psoriatic arthritis fails to achieve a meaningful clinical response in at least 30% of the psoriatic arthritis patient population. Ultimately, most patients fail to maintain a clinical response to a given anti-psoriatic DMARD over time. Apremilast would be the first PDE4 inhibitor approved for the treatment of patients with active psoriatic arthritis. The ability to offer patients with a novel mechanism of action in the treatment armamentarium would be of benefit to this patient population.

Apremilast across three Phase III pivotal studies demonstrated a statistically significant response in the reduction of the signs and symptoms of PsA at Week 16, the primary endpoint,

for both the 20 and 30 mg bid dose group compared to placebo. The studies were sized to demonstrate an approximate 20% treatment difference when comparisons are made between any active treatment group and placebo. This is considered a clinically meaningful treatment effect (Felson,1995). Notably, the patient population accrued to our Phase III program had failed or had an inadequate response to one or more small molecule or biologic DMARDs (Table 9 of Briefing Book). Additionally, baseline concomitant DMARDs were utilized by more than 65% of our study population (Table 10 of Briefing Book). A robust and consistent improvement in ACR20 response rates at Week 16 durable through Week 24 were observed in this setting where patients had previously failed to demonstrate adequate disease control, including in patients who continued concomitant DMARDs. In summary, we therefore consider these data highly clinically relevant and indicative of a meaningful treatment benefit.

Two active dose groups (20mg BID, 30mg BID) were carried throughout our Phase III program in PsA to ensure that an optimal treatment regimen was identified for this patient population. As referenced above, statistically significant and clinically meaningful responses compared to placebo were observed for the primary endpoint, ACR20 response rate at Week 16, for both active dose groups. In two out of the three studies there were numerically higher response rates observed in the 30 mg BID versus 20mg BID for the primary endpoint. Across all 3 studies, there were numerically higher response rates observed for 30 mg BID versus 20 mg BID in the majority of the secondary endpoints. Furthermore, more secondary endpoints achieved statistical significance in the 30mg BID arm than in the 20mg BID arm across all three studies (Appendix A).

Discussion:

Celgene asked if the dose response for the 20 mg bid versus the 30 mg bid dosing regimen of apremilast provides adequate efficacy data to support an indication of PsA. FDA stated that it is premature to determine if the data from studies CC-10004-PSA-002 and CC-10004-PSA-003 would support a PsA indication, and reiterated that the adequacy would be a review issue based on the information provided in the NDA submission.

Question 4:

Does the Agency agree that the study design (including the endpoint of HAQ-DI) and analyses from the individual pivotal phase 3 studies in PsA (CC-10004-PSA-002, CC-10004-PSA-003, CC-10004-PSA-004) and supportive pre-specified pooled efficacy analyses provides sufficient information to support a therapeutic claim for improvement of physical function in the Clinical Studies section of the package insert?

FDA Response:

We have concerns regarding the adequacy of the data you are planning to submit in support of an improvement of physical function claim for apremilast. We acknowledge that the results for the HAQ-DI assessments were statistically significant, but the mean results

do not meet the minimally clinically important difference (MCID) of -0.30 for which there is regulatory precedent. We question the clinical meaningfulness of the treatment difference reported for apremilast. This information may be pertinent for labeling purposes. In addition, while you may include pooled efficacy analyses in the NDA as secondary support, we typically do not rely on such analyses as the basis for regulatory decision-making or labeling claims.

Celgene Response:

We recognize the registrational precedent for the use of a mean decrease from baseline in HAQ DI score of greater than or equal to 0.30 units as the minimally clinically important difference (MCID) for this measure (95% CI: 0.24 to 0.35). Although there has been a wealth of literature to define the MCID for HAQ-DI in Rheumatoid Arthritis dating from 1993 (Wells, 1993; Redelmeier, 1993), the derivation of MCID for HAQ-DI in patients with psoriatic arthritis (PsA) is more recent and relied upon a single estimate from a study by Mease first published in abstract form in 2004 (Mease, 2004a). With the publication by Kwok (Kwok, 2010) there is now a second estimate of the MCID for HAQ-DI in patients with PsA. This second HAQ-DI MCID value has been established to be 0.131 units (95% CI: 0.0436 to 0.219).

The Kwok study compared to the Mease study (Mease, 2011) appears to have produced a more relevant benchmark for the MCID for HAQ-DI based upon the differences in the methodology and demographics of the two study populations employed in the derivation of these estimates. In both studies approximately 200 patients were followed for six to eight months and overall health status anchors were employed. Of note, however, was the use within the Mease study of a single agent (biologic DMARD) in an interventional trial setting where there was a paucity of data within the "minimally important/satisfactory" response category. The MCID estimate for the Mease study relied upon a total of 11 of 388 responses reporting a "minimally important" response necessitating the use of a linear model to determine MCID. The Kwok study population, by contrast, was exposed to an array of small-molecule and biologic DMARDs in an outpatient setting where 35 of the 249 patients enrolled in this observational study reported a response of "better," defined as the MCID. The MCID for HAQ-DI in PsA patients exposed to a novel small-molecule DMARD may therefore be better estimated by the value derived from the more recently published Kwok study.

For the purposes of our submission, we have employed both estimates of MCID for HAQ-DI in patients with PsA, the methodologically more relevant Kwok estimate and the Mease estimate. As outlined in Table 15 of the Briefing Book for the apremilast Type B, Pre-NDA Meeting, across our three pivotal studies, the mean change in HAQ-DI from baseline at Week 16 for 30mg BID (Week 24) were -0.244 (-0.258), -0.193 (-0.206), and -0.192 (-0.192) for Studies PSA-002, PSA 003, and PSA-004, respectively. In each study, not only were these changes statistically significant compared to those observed in the placebo cohort, but each of these changes exceeded the estimated MCID for HAQ-DI of -0.13 provided by the Kwok study and approximated or exceeded the lower bounds of the confidence interval surrounding the Mease study estimate. The analysis of the proportion of subjects achieving both the 0.13 and 0.30

MCID estimates at Weeks 16 and 24 (Table 16 of the Briefing Book) were supportive of the conclusions for the key secondary endpoint, mean change from baseline in HAQ-DI at Week 16.

In addition to HAQ-DI, the SF-26v2 physical functioning domain scores were aligned with the statistically significant and clinically meaningful results obtained for the improvement in physical function in patients administered apremilast in our phase 3 program. The mean change from baseline and the proportion of patients achieving an MCID ≥ 2.5-point improvement (Revicki,2008) can be found in Appendix A.

Discussion:

Celgene asked for clarification regarding interpretation of HAQ-DI results. FDA responded that their preliminary response outlines their preliminary concerns with the HAQ-DI data. The clinical relevance of the results will be a review issue.

Question 5:

Does the Agency agree with the proposed Integrated Summary of Efficacy (ISE) /Summary of Clinical Efficacy (SCE) Statistical Analysis Plan?

FDA Response:

Your proposed SAP for the ISE and SCE in which pooled analyses of endpoints from the three pivotal Phase 3 studies (CC-10004-PSA-002, CC-10004-PSA-003, CC-10004-PSA-004) will be conducted at both the Week 16 and Week 24 time points and will employ the same methodology as used in the individual study SAPs to handle early escapes at Week 16 as well as missing data at Week 16 and Week 24 as pre-specified in the individual study SAPs is acceptable. The rationale you provide for conducting these pooled analyses is to generate more precise estimates of the treatment effect of apremilast in select subgroups in which the sample size is inadequate to reliably estimate the drug's treatment effect. However, for regulatory decision-making the primary analyses to be relied upon will be from the individual studies. (b) (4) (b) (4) **See the response to Question 4.**

Discussion:

No discussion.

SAFETY QUESTIONS

Question 6:

Does the Agency agree that the safety profile from the three Phase 3 studies in PSA (CC- 10004-PSA-002, CC-10004-PSA-003, CC-10004-PSA-004) demonstrates an acceptable safety profile in this patient population?

FDA Response:

Based on our review of the safety data summarized in the meeting package, we concur in principle that apremilast's safety profile appears to be generally acceptable for NDA filing. However, determination of the drug's overall safety will be a review issue.

Discussion:

No discussion.

Question 7:

Does the Agency agree that the extent and duration of subject exposure and the overall safety profile presented in this briefing document support registration of apremilast 30 mg BID in the proposed indication?

FDA Response:

According to the exposure projections in your meeting package, you estimate that the safety database for apremilast at the time you submit your NDA will include 1,444 subjects who have been exposed to any dose for any duration of apremilast. This will include a total of 721 subjects with PsA, out of which 527 subjects received 30 mg bid of apremilast for at least 24 weeks while the remaining 183 subjects received 30 mg bid for at least 48 weeks. Based on these exposure projections, we concur that there are a sufficient number of subjects who have been exposed to apremilast to support NDA submission. However, additional safety data may be required if safety signals are identified over the course of the NDA review. Refer to our response to Q.10 below for addition clarification.

Discussion:

No discussion.

Question 8:

Celgene is proposing to provide the following for unblinded patients in the planned NDA submission for apremilast:

- *Case Report Forms (CRFs) for deaths (for placebo and apremilast treated subjects) Case Report Forms (CRFs) for all serious adverse events and all discontinuations due to*

Adverse Events (AEs) for pivotal and supportive studies (for apremilast treated subjects only)

- *Prose narratives for deaths (for placebo and apremilast treated subjects)*
- *Prose narratives for serious adverse events (for apremilast treated subjects only)*
- *Brief narratives with modified patient profiles for discontinuations due to AEs (for apremilast treated subjects only)*

For the ongoing blinded studies (PSOR-008, PSOR-009, PSA-005), Celgene is proposing to provide only prose narratives for subjects who died and those who had expedited safety reports.

FDA Response:

Overall, we concur with your proposed plan for submission of CRFs and prose narratives for all placebo and apremilast treated patients who died and all apremilast treated patients who withdrew from the studies due to an AE as described above. However, additional information may be required if safety signals are identified over the course of the NDA review.

Discussion:

No discussion.

Question 9:

Does the Agency agree with Celgene's proposed plan for blinded independent adjudication?

FDA Response:

You are proposing to utilize blinded, independent, experts to review and retrospectively adjudicate cases of MACE, possible MACE, malignancies, and infections (e.g., serious and opportunistic including tuberculosis) observed in the clinical trial database for all Phase 2 and 3 trials for the apremilast clinical program. You have already conducted a retrospective evaluation of suicidality using the Columbia Classification Algorithm of Suicide Assessment (C-CASA) of the clinical trial database for all Phase 2 and 3 completed and ongoing studies in PsA, plaque psoriasis and rheumatoid arthritis. In principle we concur that your proposed plans for the adjudication and analysis of MACE, malignancies and infections, and your retrospective evaluation of suicidality using the C-CASA appears to be adequate. We may have additional data requests regarding these analyses over the course of the NDA review.

Discussion:

No discussion.

Question 10:

Does the Agency agree with Celgene's proposed Statistical Analysis Plan For the Integrated Summary of Safety?

FDA Response:

You propose to submit safety analyses with comparisons of percent occurrence or exposure adjusted event rate between apremilast doses and placebo during the placebo controlled period and between apremilast doses regardless of time of exposure.

In addition to your proposed analyses, because all three protocols included provisions for patients taking placebo to receive treatment with apremilast at Month 4 by patient response (based on uncontrolled disease activity) or at Month 6 by design, you should provide comparisons which account for the timing of adverse events by including placebo patients who advanced to apremilast. In addition, for major events of interest, you should apply modeling approaches to analyze the pooled data (including adjusting for study) instead of relying on crude rates described by time point of measurement.

Celgene Response:

Celgene does not plan to apply modeling for major events of interest as there are too few subjects who reported major event of interest.

Provide two sets of safety analyses between placebo and Apremilast during months 0 to 4 of treatment based on the following patient populations:

1. **patients' original randomized treatment arms (i.e., as randomized)**
2. **patients' original randomized treatment arms PLUS placebo patients who transitioned to apremilast by design or by escape (i.e., as treated)**

Celgene Response:

1. *Celgene agrees to provide these tables for patients as originally randomized. A sample of the Table is provide below*

Table 1: TEAE by SOC /PT – Placebo controlled period (0-4 months)

System Organ Class[1)]	*Number (%) of Subjects*

		Apremilast		
	PBO n (%)	*APR 20 BID n(%)*	*APR 30 BID n(%)*	*APR Total n (%)*

2. *As the majority of the adverse events occur within 8 weeks, Celgene will provide the following table to demonstrate the AE profile during the 8 weeks of initial exposure to apremilast regardless of when apremilast was initiated (at Week 0, Week 16, Week 24):*

Provide two sets of safety analyses between apremilast 20 BID and apremilast 30 BID during months 0 to 4 of treatment, months 0 to 6 of treatment, and months 0 to 12 of treatment based on the following patient populations:

Celgene Response:

1. *We will provide these tables. An example of these tables is provided above (Table 1)*
2. *Celgene proposes to provide three tables 20 mg BID, 30mgBID, and combined for apremilast subjects as treated in the following format.*

	Apremilast xx mg BID (N=) Apremilast-exposure Period							
Preferred Term[1)]	*< 4 Wks n (%)*	*4 - < 12 Wks n (%)*	*12 - < 24 Wks n (%)*	*24 - < 36 Wks n (%)*	*36 - < 48 Wks n (%)*	*48 - < 60 Wks n (%)*	*60 - < 72 Wks n (%)*	*≥ 72 Wks n (%)*

Table 2: New TEAEs Reported By Exposure Interval

In addition, we will provide a single table of 0 to 12+ months of exposure for 20mg BID, 30mg BID, and combined including all subjects exposed to apremilast.

1. **patients' original randomized treatment arms (i.e., as randomized)**

Celgene Response:

Celgene agrees to provide these tables for patients as originally randomized. A sample of the Table is provide below

Table 1: ***TEAE by SOC /PT – Placebo controlled period (0-4 months)***

	Number (%) of Subjects			
		Apremilast		
System Organ Class[1)]	***PBO n (%)***	***APR 20 BID n(%)***	***APR 30 BID n(%)***	***APR Total n (%)***

2. patients' original randomized treatment arms PLUS placebo patients who transitioned to apremilast by design or by escape (i.e., as treated)

Celgene Response:

1. *As the majority of the adverse events occur within 8 weeks, Celgene will provide the following table to demonstrate the AE profile during the 8 weeks of initial exposure to apremilast regardless of when apremilast was initiated (at Week 0, Week 16, Week 24):*

Table 2: Subject Incidence of TEAEs for first 8 wks of exposure

TEAE	*Randomized at week 0*		*Treated at week 16*		*Treated at week 24*	
	20 mg BID	*30 mg BID*	*20 mg BID*	*30 mg BID*	*20 mg BID*	*30 mg BID*
	n (%)	*n (%)*	*n (%)*	*n (%)*	*n (%)*	*n (%)*

As an example, suppose a patient who was initially treated with placebo but who advanced to apremilast 20 BID at month 4 experienced an adverse event at month 5. In the "as treated" population, you should report the event in the 0 - 4 month apremilast 20 BID group since this patient had been receiving apremilast for a month. Some sample tables are provided below.

0 to ≤4 Month Period	**Placebo**	**Apremilast**		
		20 mg*	**30 mg***	**Combined**
Total no. patients				
Total no. events				

No. of patients with ≥1 event				
Patient-year exposure				
Incidence in no./pts with at least one event/pt-year (95% CI)				

***Includes randomized patients and patients who escaped/transitioned and are within the first 4 months of treatment with this regimen**

0 to ≤6 Month Period	**Apremilast**	
	20 mg*	**30 mg***
Total no. patients		
Total no. events		
No. of patients with ≥1 event		
Patient-year exposure		
Incidence in no./pts with at least one event/pt-year (95% CI)		

***Includes randomized patients and patients who escaped/transitioned and within the first 6 months of treatment with this regimen**
****Includes all placebo patients (whether they stayed on placebo or escaped)**

0 to ≤12 Month Period	**Apremilast**	
	20 mg*	**30 mg***
Total no. patients		
Total no. events		
No. of patients with ≥1 event		
Patient-year exposure		
Incidence in no./pts with at least one event/pt-year (95% CI)		

***Includes randomized patients and patients who escaped/transitioned and within the first 6 months of treatment with this regimen**
****Includes all placebo patients (whether they stayed on placebo or escaped)**

Discussion:

Celgene expressed that they did not intend to apply modeling for major events of interest, due to the low number of subjects who reported a major event of interest. FDA responded that this is

reasonable. FDA indicated that they will be looking at the overall risk-benefit and may ask for additional safety analysis, if deemed necessary, during review of the NDA submission.

FDA agreed with Celgene's general proposal for the safety table. FDA reiterated their request for safety tables with cut-offs of 0-4, 0-6, and 0-12 months regardless of when the subjects started apremilast. Celgene can provide information beyond 12 months but FDA wants tables with these cut-offs included in the submission. Because the Phase 3 studies used essentially a cross-over type design, FDA recommends including tables for patients that reflect a transition/switch between groups. FDA also clarified that these types of tables are also requested for laboratory values. Celgene indicated the original plan was not to provide the total number of events but events by subject. FDA suggested that Celgene include tables looking at the number of events. FDA also suggested that Celgene refer to the approval package of a recently FDA approved drug that confronted similar issues in the safety analysis and contains safety tables with a specific format, requested by FDA.

Celgene asked if, under PDUFA V, it was possible to submit these additional tables no later than 30 days after the original submission of the NDA. FDA indicated that these tables must be included as part of the initial submission of the original NDA.

Question 11:

Does the Agency agree with Celgene's proposed plan for the 120-Day Safety Update?

FDA Response:

According to your meeting package, you are proposing to submit a high-level summary of unblinded SAEs, deaths, discontinuation due to AEs from the Phase 3 plaque psoriasis studies (CC-10004-PSOR-008 and CC-10004-PSOR-009), unblinded data from the ongoing Phase 3 study (CC-10004-PsA-005) in DMARD naïve psoriatic arthritis patients and any other information that may have an impact on the safety assessment of apremilast as a treatment for PsA. We agree in principle with your proposed plan for the 120-Day Safety Update for this application.

Discussion:

No discussion.

Question 12:

Based on the safety profile of apremilast presented, Celgene does not believe a Risk Evaluation and Mitigation Strategy (REMS) is needed to ensure benefits exceed risks and therefore is not planning on submitting a REMS as part of the NDA. Does the Agency agree?

FDA Response:

It is unlikely that a REMS will be required for the safe use of apremilast as a treatment of PsA based on our review of the summarized information contained in your meeting package. However, the final determination for a REMS depends on the overall risk benefit assessment of your application and will be decided after your application has been reviewed.

Discussion:

No discussion.

REGULATORY QUESTIONS

Question 13: (Pediatric Research Equity Act Waiver Request-Psoriatic Arthritis)

Does the Agency agree with Celgene's proposal to request a waiver for all pediatric groups at the time of NDA submission for adults with active PsA?

FDA Response:

A new drug application for apremilast as a treatment for adults with PsA will trigger PREA. We consider polyarticular juvenile inflammatory arthritis (JIA) as the juvenile equivalent of PsA. If approved, apremilast potentially could be used to treat polyarticular JIA. Therefore, we do not agree with your proposed rationale for requesting a waiver for conducting a study in children for all age groups. We recommend instead that you include in the NDA submission a pediatric plan in children with polyarticular JIA in order to satisfy PREA.

Discussion:

No discussion.

Question 14: (Waiver/Deferral Request (b) (4)

(b) (4)

FDA Response:

It is premature at this time to discuss this issue in view of our written responses to your questions regarding your [redacted] (b) (4) for apremilast. (Refer to Agency letter dated December 4, 2012.)

Discussion:

No discussion.

Question 15: (Data Integrity Review and Inspection Proposal)

Does the Agency agree with the approach Celgene is taking in providing summary level clinical site data for FDA data integrity review and inspection for the three PsA pivotal studies (CC-10004-PSA-002, CC-10004-PSA-003, CC-10004-PSA-004) and the BD study (CC-10004-BCT-001)?

a. *Further, does the Agency agree with Celgene's placement of this information as one dataset for all the PsA pivotal trials and one dataset for the BD pivotal trial in Module 5.3.5.4 of the NDA submission?*

FDA Response:

Yes, we agree. The FDA may also request additional subject data listings, as deemed necessary.

Discussion:

No discussion.

Question 16: (SAS Datasets)

Celgene requests guidance on the acceptable size of individual SAS datasets for inclusion in the eCTD. Celgene plans to split SAS transport datasets that are larger than 1GB, and will provide both split and non-split datasets for submission. Is this acceptable?

FDA Response:

We agree with your proposal to split datasets larger than 1GB.

Discussion:

No discussion.

Question 17: (Priority Review)

Acknowledging that review designation is not made until FDA filing of the application, would the Agency consider that the proposed NDA in PsA would likely qualify for priority review?

FDA Response:

In view of the fact that there are a number of products licensed in this country as treatments for adults with PsA, it is highly unlikely that your proposed NDA for apremilast would qualify for priority review based on our review of the summarized safety and efficacy data contained in your meeting package. However, if you are still interested in applying for a priority review, you must include a request and a reasonable rationale for consideration of granting this status at the time you file your application.

Discussion:

No discussion.

Question 18: (b) (4)

(b) (4)

(b) (4)

FDA Response:

(b) (4)

Discussion:

No discussion.

Additional Comment:

The ongoing, 5-year, open-label extension study in PsA patients who participated in the Phase 3 studies CC-10004-PSA-002, CC-10004-PSA-003, CC-10004-PSA-004 is not required for regulatory decision-making. Ensure that the patients who decided to continue receiving treatment with apremilast are adequately monitored for disease progression and have the option of exiting this study in the event that their underlying PsA requires additional therapy.

Discussion:

No discussion.

3.0 OTHER IMPORTANT INFORMATION

DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

As stated in our September 17, 2012 communication granting this meeting, if, at the time of submission, the application that is the subject of this meeting is for a new molecular entity or an original biologic, the application will be subject to "the Program" under PDUFA V. Therefore, at this meeting be prepared to discuss and reach agreement with FDA on the content of a complete application, including preliminary discussions on the need for risk evaluation and mitigation strategies (REMS) or other risk management actions. You and FDA may also reach agreement on submission of a limited number of minor application components to be submitted not later than 30 days after the submission of the original application. These submissions must be of a type that would not be expected to materially impact the ability of the review team to begin its review. All major components of the application are expected to be included in the original application and are not subject to agreement for late submission.

Discussions and agreements will be summarized at the conclusion of the meeting and reflected in FDA's meeting minutes. If you decide to cancel this meeting and do not have agreement with FDA on the content of a complete application or late submission of any minor application components, your application is expected to be complete at the time of original submission.

In addition, we remind you that the application is expected to include a comprehensive and readily located list of all clinical sites and manufacturing facilities.

Finally, in accordance with the PDUFA V agreement, FDA has contracted with an independent contractor, Eastern Research Group, Inc. (ERG), to conduct an assessment of the Program. ERG will be in attendance at this meeting as silent observers to evaluate the meeting and will not participate in the discussion. Please note that ERG has signed a non-disclosure agreement.

Information on PDUFA V and the Program is available at
http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm272170.htm

PREA PEDIATRIC STUDY PLAN

The Food and Drug Administration Safety and Innovation Act of 2012 changes the timeline for submission of a PREA Pediatric Study Plan and includes a timeline for the implementation of these changes. You should review this law and assess if your application will be affected by these changes. If you have any questions, please email the Pediatric Team at Pedsdrugs@fda.hhs.gov.

PRESCRIBING INFORMATION

Proposed prescribing information (PI) submitted with your application must conform to the content and format regulations found at 21 CFR 201.56 and 201.57.

Summary of the Final Rule on the Requirements for Prescribing Information for Drug and Biological Products, labeling guidances, sample tool illustrating Highlights and Table of Contents, an educational module concerning prescription drug labeling, and fictitious prototypes of prescribing information are available at:
http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/ucm084159.htm . We encourage you to review the information at this website and use it as you draft prescribing information for your application.

MANUFACTURING FACILITIES

To facilitate our inspectional process, the Office of Manufacturing and Product Quality in CDER's Office of Compliance requests 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.				

4.0 ISSUES REQUIRING FURTHER DISCUSSION

No issues requiring further discussion.

5.0 ACTION ITEMS

No action items.

6.0 ATTACHMENTS AND HANDOUTS

No attachments or handouts.

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

/s/

MICHELLE Y JORDAN GARNER
01/18/2013

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

IND 101761

MEETING MINUTES

Celgene Corporation
106 Allen Road
Basking Ridge, NJ 07920

Attention: Dorothy Waddleton
Director, Regulatory Affairs

Dear Ms. Waddleton:

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

We also refer to the teleconference between representatives of your firm and the FDA on March 25, 2010. The purpose of the End-of-Phase 2 meeting was to discuss your Phase 3 clinical development program for active psoriatic arthritis.

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

If you have any questions, call Ramani Sista, Regulatory Project Manager, in the Division of Pulmonary, Allergy, and Rheumatology Products, at (301) 796-1236.

Sincerely,

{See appended electronic signature page}

Matthew W. Sullivan
Regulatory Project Manager
Division of Anesthesia and Analgesia Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure

INDUSTRY MEETING

MEETING DATE:	March 25, 2010
TIME:	10:00AM-11:00AM
LOCATION:	Changed from Face-to-Face to Teleconference
APPLICATION:	IND 101761
PRODUCT:	Apremilast
INDICATIONS:	Treatment of active psoriatic arthritis (b) (4)
SPONSOR:	Celgene Corporation
TYPE OF MEETING:	Type B/ EOP2
MEETING CHAIR:	Rigoberto Roca, M.D., Deputy Division Director, Division of Anesthesia and Analgesia Products (DAAP)
MEETING RECORDER:	Sara Stradley, M.S., Chief Project Management Staff for Matthew Sullivan, M.S., Regulatory Project Manager, Division of Anesthesia and Analgesia Products (DAAP)

FDA Attendees	Title
Rigoberto Roca, M.D.	Deputy Division Director, DAAP
Kathy Coyle, M.D.	Clinical Reviewer, Division of Pulmonary, Allergy, and Rheumatology Products (DPARP)
Yongman Kim, Ph.D.	Statistical Reviewer, DAAP
Suresh Doddapaneni, Ph.D.	Clinical Pharmacology Team Leader, DAAP
Zhihong Li, Ph.D.	Clinical Pharmacology Reviewer, DAAP
Olen Stephens, Ph.D.	CMC Reviewer, Office of New Drugs Quality Assessment (ONDQA)
Alan Schroeder, Ph.D.	Pharmaceutical Assessment Lead, ONDQA
Carlic Huynh, Ph.D.	Non-clinical Reviewer, DAAP
Sara Stradley, M.S.	Chief, Project Management Staff, DAAP
Sponsor Attendees	**Title**
Rick Couch	Senior Director, Global Regulatory CMC
William Leong	Senior Director, Process Chemistry
Angela Hu	Associate Director, Biostatistics and Statistical Programming
Julia Hui, PhD	Director, Toxicology
Kevin Klopfer	Associate Director, Manufacturing Operations
Wolf Ulrich-Nickel Ph.D.	Global Project Leader
Peter Schafer Ph.D.	Director, Translational Development
Kamal Shah M.D.	Head of Trials Safety Surveillance
Victor Sloan, M.D.	VP, Clinical Research, Rheumatology
Dorothy Waddleton	Director, Regulatory Affairs
Kara Hodes-Wechsler	Senior Director, Regulatory Affairs
Anfan Wu, Ph.D.	Senior Director, Exploratory Clinical Pharmacology

Background:
On March 22, 2010, (prior to the March 25 meeting) the Agency forwarded to the firm the Agency's comments and responses to the questions posed by the Sponsor in their February 19, 2010, meeting package.

The firm responded on March 23, 2010 and indicated they would like to discuss Questions 5, 14, 16 and Additional CMC Comments. The face-to-face meeting was changed to a teleconference.

Presented below are the Agency's comments and responses to questions in the background meeting package. The Sponsor's questions are listed in *italics*, with Agency responses and comments in **bold**. The firm's replies follow the response to which they pertain are in normal text, and discussion that took place at the meeting is captured in normal text following the question to which it pertains.

Nonclinical Questions

Question 1. *Does the Agency agree that the nonclinical studies completed to date are sufficient to support the conduct of the proposed phase 3 studies in PsA?*

FDA Response:
Yes, we agree that the studies previously submitted are adequate to initiate Phase 3 studies.

Discussion:
There was no discussion beyond the Division's initial written response.

Question 2. *Does the Agency agree that the completed and proposed nonclinical studies are sufficient to support registration of apremilast for the treatment of active PsA?*

FDA Response:
Based upon the information provided, the completed and proposed nonclinical studies appear to support filing the NDA application. However, final determination of their adequacy to support registration can only be provided upon review of the final study reports during the NDA review.

Discussion:
There was no discussion beyond the Division's initial written response.

Question 3. *Does the Agency agree with Celgene's assessment that a nonclinical phototoxicity study is not warranted?*

FDA Response:
We concur that nonclinical phototoxicity studies are not necessary for this drug product.

Discussion:
There was no discussion beyond the Division's initial written response.

Clinical Questions

Question 4. *Does the Agency agree that the completed and planned clinical pharmacology studies are sufficient to support registration of apremilast for the treatment of active PsA?*

FDA Response:
The clinical pharmacology studies that are completed and proposed appear to support filing of the NDA application. However, final determination of their adequacy to support registration can only be provided upon review of the final study reports during the NDA review. We note that the information provided in your meeting package does not appear to provide information on the specific formulations used in each study. As a reminder, if the commercial formulation is significantly different from the formulations(s) used during development, bridging data may be needed if the data obtained with the formulations used during development are intended to be used in support of product approval and labeling language.

Additionally, we want you to be aware that the Agency is currently revising the guidance on renal impairment studies, and a renal impairment study may be required in the future for drugs eliminated primarily by metabolic pathways as well. Even if a drug is primarily metabolized or secreted in bile, renal impairment can inhibit some pathways of hepatic and gut drug metabolism and transport, so that a pharmacokinetic (PK) study in renal impairment would be required for most drugs intended for chronic use.

Discussion:
There was no discussion beyond the Division's initial written response.

Question 5. *Does the Agency agree that the proposed phase 3 studies in PsA (CC-10004-PSA-002, CC-10004-PSA-003 and CC-10004-PSA-004) will provide sufficient data to support registration of apremilast for the treatment of active PsA?*

FDA Response:
For the NDA submission for the treatment of active PsA, you propose to include 24-week efficacy data from three Phase 3 studies in PsA: CC-10004-PSA-002, CC-10004-PSA-003, and CC-10004-PSA-004. These 3 proposed studies have similar

designs and will target patients with active PsA. Each of the proposed Phase 3 studies will be multicenter, international, randomized, double-blind, placebo-controlled, parallel group efficacy and safety studies of two doses of apremilast (20 mg and 30 mg BID). Approximately 495 subjects (165 per dose group) will be randomized in each study. The core study period will be 24 weeks, however blinding will be maintained during the first 6 months of the long-term extension (Week 24 through Week 52) to obtain blinded efficacy data, including ACR responses and HAQ-DI, up to 1 year. At the end of 24 weeks, placebo subjects will be re-randomized 1:1 in blinded fashion to apremilast 20 mg or 30 mg dose groups. Placebo-treated subjects whose total SJC and TJC have not improved by at least 20% at Week 16 will be re-randomized to apremilast and considered treatment failures. Subjects initially randomized to apremilast will remain in their assigned dose groups through the end of the active treatment period (total treatment duration of up to 5 years for continued safety evaluation).

As described in your meeting package, the proposed Phase 3 studies are adequate and actually exceed minimum requirements to support an NDA filing, as the Agency ordinarily requires a minimum of two adequate and well-controlled trials. Furthermore, a controlled period of 12 weeks duration would be adequate to support the primary evaluation of efficacy for this chronic treatment and indication, with longer-duration open-label data to provide evidence of safety. However, if you wish to continue with the Phase 3 program as currently proposed, this would be acceptable as well.

Celgene's March 23, 2010, response:
In your response you state that a controlled period of 12-weeks duration would be adequate to support the primary evaluation of efficacy for this chronic treatment and indication, with longer duration open-label data to provide evidence of safety. Can you clarify that an evaluation of the primary endpoint of ACR 20 and the major secondary endpoint of HAQ-DI at 12 weeks with longer duration open-label data to provide evidence of safety would support an indication of "treatment in active psoriatic arthritis."

Discussion:
The Division stated that an evaluation of the primary endpoint of ACR 20 and the major secondary endpoint of HAQ-DI at 12 weeks with longer duration open-label data may provide evidence of safety that would support an indication of "treatment in active psoriatic arthritis."

Question 6. *Does the Agency agree that the primary and secondary endpoints, ACR-20 and HAQ-DI at 24 weeks in the phase 3 studies, support registration of apremilast for the treatment of active PsA?*

FDA Response:
Your proposed primary endpoint, the proportion of ACR20 responders at Week 24, is acceptable. Secondary endpoints of change from baseline in HAQ-DI score and

proportion of ACR50 responders are also acceptable. Of note, specific outcome measures related to psoriatic skin disease should be consistent with Division of Dermatology and Dental Products (DDDP) expectations for the psoriasis indication.

Discussion:
There was no discussion beyond the Division's initial written response.

Question 7. *Does the Agency agree that the proposed patient populations in the phase 3 studies (PSA-002, PSA-003 and PSA-004) support registration of apremilast for the treatment of active PsA?*

FDA Response:
The proposed Phase 3 studies target patients with active PsA, defined as patients who meet criteria described by the Classification of Psoriatic Arthritis (CASPAR) study group, who have at least 3 swollen and at least 3 tender joints, who have had PsA for at least 6 months, and who do not have only axial involvement. Study PSA-004 is intended to enroll patients with at least one ≥2 cm qualifying psoriasis lesion. Patients will be on stable background DMARD therapy for at least 4 weeks prior to screening and throughout the study.

The patient populations targeted for the Phase 3 studies appear to be appropriate. We recommend you collect data in the clinical trials that will allow for subgroup analyses based on PsA subtypes and geographic region.

Discussion:
There was no discussion beyond the Division's initial written response.

Question 8. *Does the Agency agree with the proposed analysis plans for the primary and secondary endpoints ACR-20 and HAQ-DI at 24 weeks in the phase 3 PsA studies (CC-10004-PSA-002, CC-10004-PSA-003, and CC-10004-PSA-004)?*

FDA Response:
The Cochran-Mantel-Haenszel test will be used to analyze the ACR-20. The analysis of the HAQ-DI will employ an analysis of covariance model. You will use the Hochberg procedure to control the type I error for testing multiple doses, and you will use a sequential strategy to control the type I error for testing multiple endpoints. Dropouts will be treated as treatment failures.

The proposed analyses appear to be acceptable.

Discussion:
There was no discussion beyond the Division's initial written response.

Question 9. *The study design of each of the phase 3 trials includes 3 arms, placebo, 20 mg BID and 30 mg BID. Does the Agency agree with the doses chosen for the phase 3 studies?*

FDA Response:
Yes, we agree with the proposed doses. Your proposal to study 20 mg BID and 30 mg BID dose regimens of apremilast in the Phase 3 program is based on results from your Phase 2 studies CC-10004-PSA-001 (204 subjects with PsA) and CC-10004-PSOR-005 (352 subjects with plaque psoriasis). In PSA-001, a total daily dose of 40 mg (40 mg daily or 20 mg BID) was compared to placebo. After 12 weeks of treatment, both regimens had statistically significant ACR20 response rates. Although a statistically significant greater number of subjects on 20 mg BID achieved ACR50, the response rate was of marginal clinical significance.

In Study PSOR-005, a clear dose response was demonstrated in subjects with moderate-to-severe psoriasis (doses studied were 10 mg, 20 mg, and 30 mg BID). Thus, we agree that studying a higher dose (30 mg BID) in PsA would be helpful to determine whether additional efficacy in PsA could be achieved. Furthermore, the safety and tolerability of 20 mg BID and 30 mg BID appear to be acceptable, based on the information in the briefing document; therefore, study of these two dose regimens in the Phase 3 studies would be acceptable.

Discussion:
There was no discussion beyond the Division's initial written response.

Question 10. *Does the Agency agree that the proposed safety database will be sufficient to support registration of apremilast for the treatment of active PsA?*

FDA Response:
Your safety database at time of NDA submission is estimated to include 4043 subjects (1821 PsA) who have received any dose/duration of apremilast, 1841 subjects (695 PsA) who will have received 30 mg BID for 6 months, and 1335 subjects (620 PsA) who will have received 30 mg BID for one year. The proposed database exceeds the minimum requirement for drugs being developed for chronic use in non-life-threatening conditions (ICH E1) and are acceptable. However, additional safety data may be required if new safety signals are observed that require further characterization.

Discussion:
There was no discussion beyond the Division's initial written response.

Question 11. *Does the Agency agree with Celgene's plan to have a separate unblinded internal team to prepare data for the NDA filing at the 24 week primary endpoint while the study teams remain blinded while monitoring ongoing clinical trials through week 52?*

FDA Response:
Your plan is acceptable.

Discussion:
There was no discussion beyond the Division's initial written response.

Question 12. Does the agency agree with the proposed safety monitoring in the phase 3 program?

FDA Response:
The types and frequency of safety assessments described in the Phase 3 protocol synopsis (Appendix 7.1 of the meeting package) are acceptable.

Discussion:
There was no discussion beyond the Division's initial written response.

Question 13. Does the Agency agree with Celgene's proposal to discontinue screening for latent TB in our phase 3 studies?

FDA Response:
Based on its mechanism of action (PDE4 inhibition), apremilast would not be expected to increase susceptibility to TB reactivation; however, Phase 2 studies to date have included tuberculin screening and exclusion of subjects with positive tests for latent TB. Currently, there have been no reports of opportunistic or mycobacterial infections in the development program. Your proposal to discontinue tuberculin screening yet retain chest radiography and brief review of systems to evaluate the presence of active TB at study entry is acceptable. However, occurrence of opportunistic or mycobacterial infections during the Phase 3 trials would necessitate re-evaluation of the proposed TB screening.

Discussion:
There was no discussion beyond the Division's initial written response.

Question 14. Does the Agency agree with the proposed contraception and pregnancy monitoring in phase 3?

FDA Response:
Contingent upon results of an ongoing embryo-fetal developmental study in the cynomolgus monkey, you propose the following contraceptive measures in study subjects:

1. **Females of child-bearing potential who engage in activity in which conception is possible will require at least one form of medically approved birth control while on study drug, and for at least 1 month following last study dose drug.**

2. **Pregnancy testing will be performed at screening, baseline, end of treatment phase and observational follow up visit.**
3. **Male subjects (including those who have had a vasectomy) who engage in activity in which conception is possible will be required to use barrier contraception (latex condoms) while on study medication and for at least 28 days after taking the last dose of study medication.**

Your pregnancy testing plan is acceptable. However, for both male and female subjects, double barrier contraception should be required.

Celgene's March 23, 2010, response:
In your response you stated that Celgene's proposed pregnancy testing was acceptable. However, for both male and female subjects double barrier contraception should be required. Is your proposal meant to replace the one form of medically approved birth control proposed by Celgene? Can you please outline the requirements for double barrier contraception?

Discussion:
The double barrier is required due to possible drug interactions and lack of Segment II data. The Sponsor should include two forms of contraception. The double barrier method is quite common (i.e., condom with either diaphragm/spermicide or sponge/spermicide). The Sponsor clarified that their in vitro studies did not show any significant drug- drug interactions. The Division stated that a highly effective method (i.e., hormonal) and one additional method (i.e., condom) would be acceptable as well. The Sponsor stated that they have audited draft reports from the Segment II study and will submit both the high-dose and low-dose once the reports have been finalized, and will request comment from the Division. In the meantime, the Sponsor will submit a revised protocol to include double barrier contraception.

Question 15. *Does the Agency agree with the Celgene's proposal to request a waiver for all pediatric groups at the time of NDA submission for the adult PsA indication?*

FDA Response:
Your proposal to request a waiver for all pediatric age groups due to the rarity of PsA in pediatric age groups is reasonable. However, the decision to grant a waiver request will be made upon review of the request submitted in the NDA for the adult PsA indication. You will need to provide written justification for the waiver and evidence to support the request. This evidence should include the referenced article by Paller and any other available information on the prevalence of juvenile PsA.

Discussion:
There was no discussion beyond the Division's initial written response.

Chemistry, Manufacturing and Controls Questions

Question 16. *Does the Agency agree with Celgene's plans to use the following starting materials for the manufacture of the apremilast API based on the characterization plans provided?*

- (b) (4)
-

FDA Response:
No, we do not agree with your proposed starting materials for the drug substance. Among the reasons that make the proposed starting materials inappropriate are the following:

1. **The major impurities in the proposed starting materials are not identified.**
2. **You have not demonstrated that the impurities in the proposed starting materials do not carry over to the drug substance by challenging the manufacturing process with an impure lot of the starting material.**
3. **You do not appear to have well-characterized reference standards (i.e., in-house testing).**
4. **The current specifications on the materials lack an orthogonal method for identification, residue on ignition, residual solvents, or specified impurities testing.**
5. **It is not apparent that either of the proposed starting materials is readily available on the commercial market.**

We believe that (b) (4) are more appropriate starting materials for the drug substance.

Celgene's March 23, 2010, response:
FDA did not agree with the designation of the (b) (4) (b) (4) as starting materials because of lack of characterization (impurities in the starting materials, fate of the starting materials impurities, reference standard, and appropriate specifications) and commercial availability of starting materials. Celgene is currently generating the appropriate characterization data for the (b) (4) (b) (4) as well as identifying viable manufacturers for commercial supplies of the starting materials manufactured for Celgene. To date, Celgene has identified several potential manufacturers of the (b) (4) starting material. In addition, we've used three different manufacturers for the (b) (4) starting materials. In addition, Celgene will be evaluating (b) (4) manufactured by a different synthetic route for its appropriateness in the apremilast synthesis. Celgene would like FDA agreement that (b) (4) could

be designated starting materials if Celgene provides the appropriate characterization, knowledge on the fate of impurities, establish reference standards, and develop appropriate specifications. Celgene could submit this information and have further discussion about the appropriateness of these compounds as starting materials in 1Q2011, if the FDA so desires.

Discussion:
The Division expressed concern about the proposed starting materials in that they are [redacted] (b) (4) The Division stated that the Sponsor can submit their information and it will be reviewed as resources permit. The Sponsor should provide a justification to support their starting material to their IND or at the time of NDA submission.

Additional CMC Comments:

1. **We encourage you to submit your proposed stability protocol for future NDA stability batches prior to the initiation of stability programs. Your proposal should include intended drug substance and drug product specifications.**
2. **At the time of the NDA submission, include a well-documented Pharmaceutical Development Report as per ICH-Q8 guideline and highlight how critical quality attributes and critical process parameters are identified and controlled.**
3. **It is expected that at least 12 months of real time data and 6 months of accelerated data be included in the NDA. Alternatively, submit an appropriate amount of satisfactory stability data to cover the proposed expiry dating.**
4. **At the time of the NDA submission, provide a list of all manufacturing and testing facilities and their complete addresses in alphabetical order, and a statement about their cGMP status. For all sites, provide a name contact and address with telephone number and facsimile number at the site. Clearly specify the responsibilities (e.g., manufacturer, packager, release tester, stability tester etc.) of each facility, the site CFN numbers and which sites are intended to be primary or alternate sites. Note that facilities with unacceptable cGMP compliance may risk approvability of the NDA.**
5. **Ensure that all of the above facilities are ready for inspection by the day the application is submitted, and include a statement confirming this in the NDA cover letter.**
6. **Provide summary stability data on a parameter-by-parameter basis (instead of only on a batch to batch basis), and in addition, provide graphical plots of critical parameters and trending parameters. The graphical plots should indicate the proposed acceptance criteria, and they should include both mean and individual data points.**
7. **You are reminded that registration batches must be within 1/10 the intended commercial scale.**

8. **The drug substance specifications should include microbial testing and testing for** (b) (4)

Celgene's March 23, 2010, response:
FDA has encouraged us to submit our proposed stability protocols for future NDA stability batches prior to the initiation of stability programs. We are currently planning on performing both our drug substance and drug product NDA stability program as per ICH Q1A(R2). For the drug substance we are planning on placing (b) (4) (b) (4) from at least one commercial site at long term and accelerated stability conditions. We intend to have at least 12-months long term and 6-months accelerated data at the time of NDA submission. For the drug product we are planning on placing (b) (4) (b) (4) of each strength from at least one commercial/clinical GMP site at long term and accelerated stability conditions. We intend to have at least 12-months long term and 6-months accelerated data at the time of NDA submission. Based on this information, does the FDA want to see the stability protocol prior to the initiation of the stability program?

Discussion:
Prior to commenting on your stability program, a full stability protocol, including the complete list of the attributes, should be submitted for review.

The Division clarified that comment #4 (above) is a standard request from the Office of Compliance.

The Sponsor summarized their understanding of the meeting as follows (includes action items):

1. The evaluation of the primary endpoint of ACR 20 and the major secondary endpoint of HAQ-DI at 12 weeks with longer duration open-label data may provide evidence of safety that would support an indication of "treatment in active psoriatic arthritis."

2. The Sponsor will revise their protocol to include two forms of birth control. The final Segment II reports, including the results from high and low doses, will be submitted for comment.

3. The choice of starting material will be a review issue. The Sponsor can submit their rationale prior to NDA submission or as part of their NDA. (b) (4) (b) (4) is of concern to the Division.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
IND-101761	GI-1	CELGENE CORP	CC-10004 (Apremilast)

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

/s/

MATTHEW W SULLIVAN
04/13/2010

LATE-CYCLE COMMUNICATION DOCUMENTS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 205437

LATE-CYCLE MEETING MINUTES

Celgene Corporation
33 Technology Drive
Warren, NJ 07059

Attention: Casilda Luck-Barnes, PharmD
Associate Director, Regulatory Affairs

Dear Dr. Luck-Barnes:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Otezla (apremilast), 10, 20, 30 mg tablet.

We also refer to the Late-Cycle Meeting (LCM) between representatives of your firm and the FDA on December 6, 2013.

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

If you have any questions, call Michelle Jordan Garner, Regulatory Project Manager at (301) 796-4786.

Sincerely,

{See appended electronic signature page}

Nikolay Nikolov, MD
Clinical Team Leader
Division of Pulmonary, Allergy, and Rheumatology
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure:
Late Cycle Meeting Minutes

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF LATE-CYCLE MEETING MINUTES

Meeting Date and Time: December 6, 2013; 1:00 PM
Meeting Location: Teleconference

Application Number: NDA 205437
Product Name: Otezla (apremilast)
Indication: Treatment of adult patients with active psoriatic arthritis
Applicant Name: Celgene Corporation

Meeting Chair: Nikolay Nikolov (CDTL)
Meeting Recorder: Michelle Jordan Garner

FDA ATTENDEES

Office of Drug Evaluation II
Mary Parks, MD, Deputy Director
Division of Pulmonary, Allergy, and Rheumatology Products
Badrul A. Chowdhury, MD, PhD, Director
Sally Seymour, MD, Deputy Director for Safety
Sarah Yim, MD, Supervisory Associate Director
Nikolay Nikolov, MD, Clinical Team Leader
Keith Hull, MD, Clinical Reviewer
Marcie Wood, PhD, Pharmacology Toxicology Supervisor
Lawrence Leshin, PhD, Pharmacology Toxicology Reviewer
Michelle Jordan Garner, MS, OTR/L, Senior Regulatory Management Officer
Office of New Drug Quality Assessment
Eric Duffy, PhD, Product Quality Supervisor
Ciby Abraham, PhD, Product Quality Reviewer
Minerva Hughes, PhD, Biopharmaceutics Reviewer
Division of Biometrics II
Joan Buenconsejo, PhD, Biostatistics Team Leader
Division of Clinical Pharmacology 2
Satjit Brar, PhD, Clinical Pharmacology Team Leader
Sheetal Agarwal, PhD, Clinical Pharmacology Reviewer
Li Zhang, PhD, Pharmacometrics Reviewer
Office of Compliance/Office of Manufacturing & Product Quality
Linda Ng, Ph.D., Senior Policy Advisor
Pediatric and Maternal Health Staff
Jeanine Best, Maternal Health Team Leader
Carrie Ceresa, Maternal Health Regulatory Reviewer
Office of Pharmaceutical Science
Neal Sweeney, PhD, Microbiology Reviewer

Office of Surveillance and Epidemiology
Nichelle Rashid, Senior Regulatory Project Manager
Ling-Yu Wu, Safety Evaluator Team Leader
Teresa McMillan, Safety Evaluator
Margie Goulding, Safety Evaluator Team Leader
Jie Li, Safety

EASTERN RESEARCH GROUP ATTENDEES
So Hyun Kim, Independent Assessor

APPLICANT ATTENDEES
Casilda Luck-Barnes, PharmD, Associate Director, Regulatory Affairs
Judith Abrams, MD, FRCPC Executive Director, Clinical Research & Development
Julia Hui, Ph.D., Senior Director, Toxicology
Peter Schafer, Ph.D., Senior Principal Investigator, Translational Development
Maria Palmisano, MD Vice President, Clinical Pharmacology
Kamal Shah, MD Executive Director, Head, Pharmacovigilance I&I, Early Development & CCT Global Drug Safety & Risk Management
Philippe Martin, MS, MBA Executive Director, Global Project Leadership
Lucy Chen, MS, Director, Global Regulatory CMC
Dorothy Waddleton, BS Senior Director, Regulatory Affairs
Gary Cline, Ph.D. Senior Director, Biostatistics & Programming
Angela Hu, EdM, MS Director, Biostatistics & Programming
Matthew Hoffman, Ph.D. Director, DMPK
Maria Paris, MD Senior Director, Lead Global Product Safety & Drug Safety/Risk Management
Marla Hochfeld, MD Executive Director, Clinical Research
Rick Couch, MS Executive Director, Global Regulatory CMC
Michael Morrissey, BSc Corporate Vice President, International Technical Operations
Paul D'Angio, RPh, MSJ Senior Vice President, Global Technical Operations
Thomas Guebeli, Ph.D. Executive Director, Quality Assurance Operations
Randall Stevens, MD Vice President, of Immunology and Inflammatory
Jay Backstrom, MD, MPH Senior Vice President, Global Regulatory Affairs and Pharmacovigilance

1.0 BACKGROUND

NDA 205437 was submitted on March 20, 2013 for Otezla (apremilast).

Proposed indication: Psoriatic arthritis

PDUFA goal date: March 21, 2014

FDA issued a Background Package in preparation for this meeting on November 25, 2013.

2.0 DISCUSSION

1. *Introductory Comments*

   Discussion

   Introductions of FDA and Celgene Corporation participants were made. The Cross-Discipline Team Leader (CDTL), Dr. Nikolov, started the meeting by stating that the purpose of the meeting was to share information and to discuss any review issues that the Agency has identified to date, and the objectives for the remainder of the review. Further, Dr. Nikolov stated that the application reviews have not been completed and therefore, the meeting will not address the final regulatory decision for the application. Dr. Nikolov also clarified that discussion of an Advisory Committee meeting was not included on the LCM agenda because the Agency has determined that based on the ongoing reviews of the application, there were no issues that would warrant discussion at an Advisory Committee meeting. Another item not included on the LCM meeting agenda was "Major Labeling Issues," because labeling was discussed with the applicant in a separate labeling meeting on December 4, 2013.

2. *Discussion of Substantive Review Issues*

   All facilities must be found in compliance with CGMP as evaluated by the Office of Compliance. However, we note that your Celgene International, Boudry, CHE facility is listed as performing stability studies and as communicated through an IR dated November 08, 2013, the inspection of that facility uncovered that there were no in-house stability chambers. This raises concerns about the compliance with CGMP and needs to be addressed under the current NDA. Note that the overall evaluation, including all facilities, is ongoing and additional information may be required.

   Discussion:

   FDA sought clarification regarding Celgene's Boudry facility and the fact that at the time of FDA inspection, the stability chambers were not ready. The sponsor explained that IO/OQ is currently on-going for the chambers. FDA reiterated that at the time of NDA submission, all facilities listed in the NDA should be ready to perform the function(s) that has been designated in the NDA. FDA recommended that Celgene remove the Boudry facility to conduct stability testing. This function at this site can be added post-approval. In addition,

another site needs to be designated for stability testing. It is recommended that Celgene select a facility that has already been submitted in the NDA.

3. *Information Requests*

Outstanding

- *Two CMC Information Requests were issued recently (CMC dated November 8, 2013, and Microbiology related dated November 13, 2013). Responses were received November 21, 2013. Review of these responses are ongoing.*

New

- *No new information requests are anticipated at this time.*

Discussion:

The responses to the CMC information requests (IR) have been found to be acceptable, and there are no new IRs at this time.

4. *Postmarketing Requirements (PMR)/Postmarketing Commitments (PMC)*

- *Biopharmaceutics PMC:*

  As agreed to in the November 4, 2013 amendment, submit the final dissolution method development and validation report and proposed final dissolution acceptance criterion for your drug product within 6 months of the action letter date.

  Discussion:

  Celgene requested to submit the final dissolution acceptance criteria in September 2014, in order to generate six months of stability data from the Boudry facility. FDA stated that the six month time frame, from the action letter date, was intended to include the requested September completion date. FDA will review the PMC timeline language and modify as appropriate for clarity.

- *Pregnancy registry PMR:*

  The FDA plans on requiring a post-marketing, prospective, observational, pregnancy exposure registry study to follow apremilast-exposed female subjects who become pregnant to accrue additional data to assess whether apremilast exposure in humans could negatively impact pregnancy outcomes in comparison to an internal control group. The primary concerns are based on:

  - *Animal data suggesting that apremilast:*
    - *Increases the incidence of embryo-fetal deaths in mice and abortions in monkeys in a dose-dependent manner,*

- *Teratogenic effect of apremilast could not be adequately assessed in monkeys due to high incidence of pregnancy loss and limited examination of the lost fetuses, and*
- *Limited pre-marketing embryo-fetal apremilast exposure data in humans.*

A prospective, observational pregnancy exposure registry study conducted in the United States that compares the pregnancy and fetal outcomes of women exposed to a drug during pregnancy to an unexposed control population is the ideal method of collecting pregnancy exposure data. However, the Agency recognizes that this method of pregnancy data collection is not suitable or feasible for all drug products. An acceptable alternative approach for collecting apremilast pregnancy exposure data is to collaborate with an existing disease-based pregnancy registry. Any pregnancy exposure registry contact information must appear in apremilast pregnancy labeling.

Discussion:

(b) (4)

FDA requested that Celgene provide a submission, with their agreement, to conduct the pregnancy registry PMR. The response should include proposed milestones for final protocol submission, study completion date, and final study report submission as well as general information on the proposed study design.

5. *REMS or Other Risk Management Actions*

- *None anticipated at this time*

Discussion:

Although no issue requiring a REMS has been identified at this time, Celgene was reminded that FDA's review of their NDA is ongoing.

6. *Review Plans*

- *Review of responses to outstanding information requests*
- *Completion of consults and tertiary reviews*
- *Completion of inspections*
- *Labeling discussions (as needed)*

Discussion:

Celgene inquired if FDA had any feedback regarding the artwork on the packaging, submitted. FDA stated that at the present time, there are no comments to convey; however, the amended carton and container label is under review.

7. Wrap-up and Action Items

This application has not yet been fully reviewed by the signatory authority, division director, and Cross-Discipline Team Leader (CDTL) and therefore, this meeting did not address the final regulatory decision for the application.

Discussion:

The CDTL summarized that there is a general agreement between FDA and Celgene, on the Biopharmaceutics PMC and Pregnancy Registry PMR; Celgene will provide a response in writing regarding the pregnancy registry; and labeling discussions will continue between Celgene and the Division.

Celgene will amend the NDA to assign another drug product stability testing site and will withdraw Celgene Sarl International (Celgene International Sarl, FEI: 3006323509) for stability testing. The stability testing function can be added post-approval through a supplement when the stability chambers are ready.

Post-Meeting Addendum:

Following the LCM, Celgene has proposed to keep Celgene International Sarl, FEI: 3006323509 for testing of stability samples and store the stability samples in (b) (4) The PAI inspection is scheduled for February 3, 2013. This proposal is currently under review.

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

/s/

NIKOLAY P NIKOLOV
12/19/2013

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 205437

LATE CYCLE MEETING
BACKGROUND PACKAGE

Celgene Corporation
33 Technology Drive
Warren, NJ 07059

Attention: Casilda Luck-Barnes, PharmD
Associate Director, Regulatory Affairs

Dear Dr. Luck-Barnes:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Otezla (apremilast), 10, 20, 30 mg tablet.

We also refer to the Late-Cycle Meeting (LCM) scheduled for December 6, 2013.

Attached is our background package, including our agenda, for this meeting.

If you have any questions, call Michelle Jordan Garner, Regulatory Project Manager, at (301) 796-4786.

Sincerely,

{See appended electronic signature page}

Badrul A. Chowdhury, MD, PhD
Director,
Division of Pulmonary, Allergy, and Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

ENCLOSURE:
Late-Cycle Meeting Background Package

LATE-CYCLE MEETING BACKGROUND PACKAGE

Meeting Date and Time: December 6, 2013; 1:00 PM
Meeting Location: Teleconference

Application Number: NDA 205437
Product Name: Otezla (apremilast)
Indication: Treatment of adult patients with active psoriatic arthritis
Sponsor/Applicant Name: Celgene Corporation

INTRODUCTION

The purpose of a Late-Cycle Meeting (LCM) is to share information and to discuss any substantive review issues that we have identified to date, and our objectives for the remainder of the review. The application has not yet been fully reviewed by the signatory authority, division director, and Cross-Discipline Team Leader (CDTL) and therefore, the meeting will not address the final regulatory decision for the application. We are sharing this material to promote a collaborative and successful discussion at the meeting.

During the meeting, we may discuss additional information that may be needed to address the identified issues and whether it would be expected to trigger an extension of the PDUFA goal date if the review team should decide, upon receipt of the information, to review it during the current review cycle. If you submit any new information in response to the issues identified in this background package prior to this LCM, we may not be prepared to discuss that new information at this meeting.

BRIEF MEMORANDUM OF SUBSTANTIVE REVIEW ISSUES IDENTIFIED TO DATE

1. Discipline Review Letters

No Discipline Review letters have been issued to date.

2. Substantive Review Issues

The following substantive review issue has been identified to date:

Celgene International, Boudry, CHE facility is listed as performing stability studies. However, the inspection of that facility uncovered that there were (b) (4) raising concerns about the compliance with current good manufacturing practice (CGMP).

ADVISORY COMMITTEE MEETING

An Advisory Committee meeting is not planned.

REMS OR OTHER RISK MANAGEMENT ACTIONS

No issues related to risk management have been identified to date.

LCM AGENDA

1. Introductory Comments – 15 minutes

   Welcome, Introductions, Ground rules, Objectives of the meeting

2. Discussion of Substantive Review Issues – 20 minutes

   All facilities must be found in compliance with CGMP as evaluated by the Office of Compliance. However, we note that your Celgene International, Boudry, CHE facility is listed as performing stability studies and as communicated through an IR dated November 08, 2013, the inspection of that facility uncovered that there were (b) (4) This raises concerns about the compliance with CGMP and needs to be addressed under the current NDA. Note that the overall evaluation, including all facilities, is ongoing and additional information may be required.

3. Information Requests – 20 minutes

   Outstanding

   - Two CMC Information Requests were issued recently (CMC dated November 8, 2013, and Microbiology related dated November 13, 2013). Responses were received November 21, 2013. Review of these responses are ongoing.

   New

   - No new information requests are anticipated at this time.

4. Postmarketing Requirements/Postmarketing Commitments – 20 minutes

   - Biopharmaceutics PMC:

     As agreed to in the November 4, 2013 amendment, submit the final dissolution method development and validation report and proposed final dissolution acceptance criterion for your drug product within 6 months of the action letter date.

- Pregnancy registry PMR:

  The FDA plans on requiring a post-marketing, prospective, observational, pregnancy exposure registry study to follow apremilast-exposed female subjects who become pregnant to accrue additional data to assess whether apremilast exposure in humans could negatively impact pregnancy outcomes in comparison to an internal control group. The primary concerns are based on:

  - Animal data suggesting that apremilast:
    - Increases the incidence of embryo-fetal deaths in mice and abortions in monkeys in a dose-dependent manner,
  - Teratogenic effect of apremilast could not be adequately assessed in monkeys due to high incidence of pregnancy loss and limited examination of the lost fetuses, and
  - Limited pre-marketing embryo-fetal apremilast exposure data in humans.

  A prospective, observational pregnancy exposure registry study conducted in the United States that compares the pregnancy and fetal outcomes of women exposed to a drug during pregnancy to an unexposed control population is the ideal method of collecting pregnancy exposure data. However, the Agency recognizes that this method of pregnancy data collection is not suitable or feasible for all drug products. An acceptable alternative approach for collecting apremilast pregnancy exposure data is to collaborate with an existing disease-based pregnancy registry. Any pregnancy exposure registry contact information must appear in apremilast pregnancy labeling.

5. REMS or Other Risk Management Actions
   - None anticipated at this time

6. Review Plans – 5 minutes
   - Review of responses to outstanding information requests
   - Completion of consults and tertiary reviews
   - Completion of inspections
   - Labeling discussions (as needed)

7. Wrap-up and Action Items – 5 minutes

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

/s/

BADRUL A CHOWDHURY
11/25/2013