CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

210745Orig1s000
210745Orig2s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

IND 121919

MEETING PRELIMINARY COMMENTS

Amgen Inc.
One Amgen Center Drive
Mail Stop: 30E-3-B
Thousand Oaks, CA 91320-1799

Attention: Dohan Weeraratne, MS
Manager, Regulatory Affairs

Dear Mr. Weeraratne:[1]

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 your correspondence, dated and received April 12, 2023, requesting a meeting to discuss the planned NDA submission for the extended-release tablet formulation of apremilast.

Our preliminary responses to your meeting questions are enclosed.

You should provide, to the Regulatory Project Manager, a hardcopy or electronic version of any materials (i.e., slides or handouts) to be presented and/or discussed at the meeting.

In accordance with FDA policy, you should not make audio or visual recordings of the discussion at this meeting. Consistent with 21 CFR 10.65(e), the official record of this meeting will be the FDA-generated minutes.

[1] We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

If you have any questions, call me at (240) 402-0139.

Sincerely,

{See appended electronic signature page}

Saharat Patanavanich, PharmD, BCACP
Regulatory Project Manager
Rheumatology and Transplant Medicine
Division of Regulatory Operations -
Immunology and Inflammation
Office of Regulatory Operations
Center for Drug Evaluation and Research

ENCLOSURE:
Preliminary Meeting Comments

U.S. FOOD & DRUG ADMINISTRATION

PRELIMINARY MEETING COMMENTS

Meeting Type: B
Meeting Category: Pre-NDA

Meeting Date and Time: June 7, 2023, at 1:00 to 2:00 PM ET
Meeting Location: Virtual/Videoconference

Application Number: IND 121919
Product Name: Apremilast
Indication: Psoriatic arthritis, plaque psoriasis, Behcet's disease

Sponsor Name: Amgen Inc.
Regulatory Pathway: 505(b)(1) of the Federal Food, Drug, and Cosmetic Act

Introduction:
This material consists of our preliminary responses to your questions and any additional comments in preparation for the discussion at the meeting scheduled for June 7, 2023, between Amgen, Inc., and the Division of Rheumatology and Transplant Medicine. We are sharing this material to promote a collaborative and successful discussion at the meeting. The meeting minutes will reflect agreements, important issues, and any action items discussed during the meeting and may not be identical to these preliminary comments following substantive discussion at the meeting. If you determine that discussion is needed for only some of the original questions, you have the option of reducing the agenda. Contact the Regulatory Project Manager (RPM) if there are any major changes to your development plan, the purpose of the meeting, or the questions based on our preliminary responses, as we may not be prepared to discuss or reach agreement on such changes at the meeting.

1.0 BACKGROUND

On April 12, 2023, Amgen requested a Pre-NDA meeting to discuss the planned NDA submission for the extended-release tablet formulation of apremilast. The meeting request was granted on April 17, 2023.

Amgen's questions from April 28, 2023, meeting package, are noted below in *italics*, followed by FDA responses in normal font.

2.0 DISCUSSION

2.1. Clinical Pharmacology

Question 1: *Does the FDA agree that the results of Amgen's pivotal relative BA study (Study 20200369) support registration of the apremilast XR formulation for the indications in which Otezla is approved?*

FDA Response to Question 1:
The results from your pivotal relative BA study (Study 20200369) to support the filing of apremilast XR formulation appears reasonable. The adequacy of the submitted data and results will be a review issue.

Question 2: *Does the FDA agree that the food effect results of Study 20200369 support that the apremilast XR formulation can be administered without regard to meals?*

FDA Response to Question 2:
The results from your food effects study (Study 20200369) to support the filing of apremilast XR formulation appears reasonable. The adequacy of the submitted data and results will be a review issue.

2.2. Clinical and Regulatory

Question 3: *Does the FDA agree with the proposed content and structure of the NDA application?*

FDA Response to Question 3:
We agree. See FDA Additional Clinical Comment.

Question 4: *Does the FDA agree with Amgen's proposal for the case report forms (CRFs) and narratives to be included in the NDA submission?*

FDA Response to Question 4:
We agree.

Question 5: *Does the Agency agree with the content and timing of the submissions to be made after the NDA is submitted?*

FDA Response to Question 5:
Your proposed content and timing of the submission of drug product stability data appears reasonable.

FDA Additional Clinical Comment:
We acknowledge that the PREA requirements for PsA have, in the past, been waived with the justification that studies in juvenile PsA have been impossible or highly

impracticable because there are too few children with the disease/condition to study. However, our thinking on the default waiver for PsA has evolved.

We note that the justification supporting the default waiver has been based on the assumption that adequate and well-controlled studies were needed to address PREA requirements for PsA, which would have made such studies impracticable, even though there are pediatric patients with PsA. However, based on developing and better understanding of the high degree of similarity of the disease between adults and pediatric patients with PsA, as well as considerations of pharmacokinetic (PK)-matching and extrapolation of efficacy from adults to pediatric patients, we consider that such studies are now possible.

Respectively, we have reconsidered the approach to PREA requirements for PsA and recommend that these requirements are addressed via PK study in pediatric PsA patients to support the extrapolation of efficacy from the adult PsA indication. Assessment of safety from the PK study could be supplemented by safety information from other relevant pediatric indications.

Please also refer to the PREA Requirements section below for additional information. Since you have previous Agreed iPSPs for PsA and PsO (BD was granted orphan indication and exempt from PREA requirements) and if the submission of the NDA for the apremilast XR dosage form will be submitted this calendar year, we recommend that you submit the Agreed iPSPs that you have with the NDA **and** also include a pediatric plan that addresses PREA for PsA (format the pediatric plan like an Amended iPSP). We will assess the updated pediatric plan with review of the NDA, as the formal iPSP (as well as an Amended iPSP) process does not continue after the marketing application has been submitted. If the NDA will be submitted after this calendar year, submit an Amended iPSP to the IND.

3.0 ADDITIONAL INFORMATION

PREA REQUIREMENTS

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

Please be advised that under the Food and Drug Administration Safety and Innovation Act (FDASIA), you must submit an Initial Pediatric Study Plan (iPSP) within 60 days of an End-of-Phase-2 (EOP2) meeting. In the absence of an EOP2 meeting, refer to the draft guidance below. The iPSP must contain an outline of the pediatric study or studies that you plan to conduct (including, to the extent practicable study objectives and

design, age groups, relevant endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation, and any previously negotiated pediatric plans with other regulatory authorities. The iPSP should be submitted in PDF and Word format. Failure to include an Agreed iPSP with a marketing application could result in a refuse to file action.

For additional guidance on the timing, content, and submission of the iPSP, including an iPSP Template, please refer to the draft guidance for industry *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans*.[2] In addition, you may contact the Division of Pediatric and Maternal Health at 301-796-2200 or email Pedsdrugs@fda.hhs.gov. For further guidance on pediatric product development, please refer to FDA.gov.[3]

PRESCRIBING INFORMATION

In your application, you must submit proposed prescribing information (PI) that conforms to the content and format regulations found at 21 CFR 201.56(a) and (d) and 201.57 including the Pregnancy and Lactation Labeling Rule (PLLR) (for applications submitted on or after June 30, 2015). As you develop your proposed PI, we encourage you to review the labeling review resources on the PLR Requirements for Prescribing Information[4] and Pregnancy and Lactation Labeling Final Rule[5] websites, which include:

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

Pursuant to the PLLR, you should include the following information with your application to support the changes in the Pregnancy, Lactation, and Females and Males of Reproductive Potential subsections of labeling. The application should include a review

[2] When final, this guidance will represent the FDA's current thinking on this topic. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.
[3] https://www.fda.gov/drugs/development-resources/pediatric-and-maternal-health-product-development
[4] https://www.fda.gov/drugs/laws-acts-and-rules/plr-requirements-prescribing-information
[5] https://www.fda.gov/drugs/labeling/pregnancy-and-lactation-labeling-drugs-final-rule

and summary of the available published literature regarding the drug's use in pregnant and lactating women and the effects of the drug on male and female fertility (include search parameters and a copy of each reference publication), a cumulative review and summary of relevant cases reported in your pharmacovigilance database (from the time of product development to present), a summary of drug utilization rates amongst females of reproductive potential (e.g., aged 15 to 44 years) calculated cumulatively since initial approval, and an interim report of an ongoing pregnancy registry or a final report on a closed pregnancy registry. If you believe the information is not applicable, provide justification. Otherwise, this information should be located in Module 1. Refer to the draft guidance for industry *Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products – Content and Format*.

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

DISCUSSION OF SAFETY ANALYSIS STRATEGY FOR THE ISS

After initiation of all trials planned for the phase 3 program, you should consider requesting a Type C meeting to gain agreement on the safety analysis strategy for the Integrated Summary of Safety (ISS) and related data requirements. Topics of discussion at this meeting would include pooling strategy (i.e., specific studies to be pooled and analytic methodology intended to manage between-study design differences, if applicable), specific queries including use of specific standardized MedDRA queries (SMQs), and other important analyses intended to support safety. The meeting should be held after you have drafted an analytic plan for the ISS, and prior to programming work for pooled or other safety analyses planned for inclusion in the ISS. This meeting, if held, would precede the Pre-NDA meeting. Note that this meeting is optional; the issues can instead be addressed at the pre-NDA meeting.

To optimize the output of this meeting, submit the following documents for review as part of the briefing package:

- Description of all trials to be included in the ISS. Please provide a tabular listing of clinical trials including appropriate details.
- ISS statistical analysis plan, including proposed pooling strategy, rationale for inclusion or exclusion of trials from the pooled population(s), and planned analytic strategies to manage differences in trial designs (e.g., in length, randomization ratio imbalances, study populations, etc.).
- For a phase 3 program that includes trial(s) with multiple periods (e.g., double-blind randomized period, long-term extension period, etc.), submit planned criteria for analyses across the program for determination of start / end of trial period (i.e., method of assignment of study events to a specific study period).
- Prioritized list of previously observed and anticipated safety issues to be evaluated, and planned analytic strategy including any SMQs, modifications to

specific SMQs, or sponsor-created groupings of Preferred Terms. A rationale supporting any proposed modifications to an SMQ or sponsor-created groupings should be provided.

When requesting this meeting, clearly mark your submission "**DISCUSS SAFETY ANALYSIS STRATEGY FOR THE ISS**" in large font, bolded type at the beginning of the cover letter for the Type C meeting request.

MANUFACTURING FACILITIES

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

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

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

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

Corresponding names and titles of onsite contact:

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

To facilitate our facility assessment and inspectional process for your marketing application, we refer you to the instructional supplement for filling out Form FDA 356h[6] and the guidance for industry, *Identification of Manufacturing Establishments in Applications Submitted to CBER and CDER Questions and Answers*[7]. Submit all related manufacturing and testing facilities in eCTD Module 3, including those proposed for commercial production and those used for product and manufacturing process development.

OFFICE OF SCIENTIFIC INVESTIGATIONS (OSI) REQUESTS

The Office of Scientific Investigations (OSI) requests that the items described in the draft guidance for industry, *Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions,* and the associated conformance guide, *Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications,* be provided to facilitate development of clinical investigator and sponsor/monitor/CRO inspection assignments, and the background packages that are sent with those assignments to the FDA ORA investigators who conduct those inspections. This information is requested for all major trials used to support safety and efficacy in the application (i.e., phase 2/3 pivotal trials). Please note that if the requested items are provided elsewhere in submission in the format described, the Applicant can describe location or provide a link to the requested information.

Please refer to the draft guidance for industry *Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions* (February 2018) and the associated *Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications*.[8]

[6] https://www.fda.gov/media/84223/download
[7] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/identification-manufacturing-establishments-applications-submitted-cber-and-cder-questions-and
[8] https://www.fda.gov/media/85061/download

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

SAHARAT PATANAVANICH
06/02/2023 03:16:21 PM

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 121919

MEETING PRELIMINARY COMMENTS

Celgene Corporation
Attention: Thomas Dowling, Ph. D.
Associate Director, Global Regulatory CMC
86 Morris Avenue
Summit, NJ 07901

Dear Dr. Dowling:

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

We also refer to your June 2, 2017, correspondence requesting a type C meeting to discuss the results of the drug-alcohol interaction studies performed on the (b) (4) tablets and reach an agreement that the results demonstrate no alcohol induced dose dumping occurs and no further studies are required.

Our preliminary responses to your meeting questions are enclosed.

You should provide, to the Regulatory Business Process manager, a hardcopy or electronic version of any materials (i.e., slides or handouts) to be presented and/or discussed at the meeting.

In accordance with 21 CFR 10.65(e) and FDA policy, you may not electronically record the discussion at this meeting. The official record of this meeting will be the FDA-generated minutes.

If you have any questions, call me at (240) 402-2691.

Sincerely,

{See appended electronic signature page}

Florence Aisida, Pharm. D, BCPS
Regulatory Business Process Manager
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research

ENCLOSURE:
Preliminary Meeting Comments

PRELIMINARY MEETING COMMENTS

Meeting Type: Type C
Meeting Category: Pre-NDA

Meeting Date and Time: July 12, 2017, 9:00 am-10:00 am

Application Number: IND 121919
Product Name: Otezla® (apremilast).
Indication: Treatment of adult patients with active psoriatic arthritis (PsA) and moderate to severe plaque psoriasis who are candidates for phototherapy or systemic therapy**.**
Sponsor/Applicant Name: Celgene Corporation

This material consists of our preliminary responses to your questions and any additional comments in preparation for the discussion at the meeting scheduled for July 12, 2017, 9:00 am-10:00 am between Celgene Corporation and the Division of Pulmonary, Allergy and Rheumatology Products. We are sharing this material to promote a collaborative and successful discussion at the meeting. The meeting minutes will reflect agreements, important issues, and any action items discussed during the meeting and may not be identical to these preliminary comments following substantive discussion at the meeting. However, if these answers and comments are clear to you and you determine that further discussion is not required, you have the option of cancelling the meeting (contact the regulatory project manager (RPM)). If you choose to cancel the meeting, this document will represent the official record of the meeting. If you determine that discussion is needed for only some of the original questions, you have the option of reducing the agenda and/or changing the format of the meeting (e.g., from face to face to teleconference). It is important to remember that some meetings, particularly milestone meetings, can be valuable even if the pre-meeting communications are considered sufficient to answer the questions. Contact the RPM if there are any major changes to your development plan, the purpose of the meeting, or the questions based on our preliminary responses, as we may not be prepared to discuss or reach agreement on such changes at the meeting.

1.0 BACKGROUND

The purpose of the meeting is to discuss the results of the drug-alcohol interaction studies performed on the (b) (4) tablets and reach an agreement that the results demonstrate no alcohol induced dose dumping occurs and no further studies are required.

2.0 DISCUSSION

Question 1: Does the Agency agree that the results from the in vitro dissolution testing for drug-alcohol interaction study demonstrate that no alcohol induced dose dumping occurs and no further studies are required?

FDA Response to Question 1: *There is a significant increase in apremilast dissolution in 40% alcohol compared to the control as evidenced by the f2 similarity metrics being less than 50, which suggests the potential for dose dumping. However upon consultation with the clinical pharmacology team, no further alcohol-interaction studies are needed.*

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

/s/

BAMIDELE F AISIDA
07/10/2017

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 121919

MEETING PRELIMINARY COMMENTS

Celgene Corporation
86 Morris Avenue
Summit, NJ 07901

Attention: Dennis Everton, RPh
Sr. Manager, Regulatory Affairs

Dear Mr. Everton:
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 your March 1, 2017, correspondence, received March 1, 2017, requesting a meeting to obtain feedback on a proposed NDA submission for a once daily formulation of Otezla (apremilast).

Our preliminary responses to your meeting questions are enclosed.

You should provide, to the Regulatory Project Manager, a hardcopy or electronic version of any materials (i.e., slides or handouts) to be presented and/or discussed at the meeting.

In accordance with 21 CFR 10.65(e) and FDA policy, you may not electronically record the discussion at this meeting. The official record of this meeting will be the FDA-generated minutes.

If you have any questions, call at (240) 402-2605.

Sincerely,

{See appended electronic signature page}

LeAnn Brodhead, PharmD, MPH
Regulatory Project Manager
Division of Pulmonary, Allergy, and Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

ENCLOSURE:

Preliminary Meeting Comments

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PRELIMINARY MEETING COMMENTS

Meeting Type:	Type B
Meeting Category:	Pre-NDA
Meeting Date and Time:	May 19, 2017, 1:00 P.M. – 2:00 P.M.
Meeting Location:	10903 New Hampshire Avenue White Oak Building 22, Conference Room: 1313 Silver Spring, Maryland 20903
Application Number:	IND 121919
Product Name:	Otezla (Apremilast)
Indication:	Treatment of patients with active psoriatic arthritis.
Sponsor Name:	Celgene Corporation

FDA ATTENDEES (tentative)

Badrul A. Chowdhury, MD, PhD, Division Director, Division of Pulmonary, Allergy, and Rheumatology Products (DPARP)
Nikolay Nikolov, MD, Clinical Team Leader, DPARP
Keith Hull, MD, PhD, Clinical Reviewer, DPARP
Anshu Marathe, PhD, Clinical Pharmacology Team Leader, Division of Clinical Pharmacology II
Sang Chung, PhD, Clinical Pharmacology reviewer, Division of Clinical Pharmacology II
Carol Galvis, PhD, Pharmacology/Toxicology Acting Team Leader, DPARP
Steve Leshin, PhD, Pharmacology/Toxicology Reviewer, DPARP
Julia Pinto, PhD, Branch Chief, Office of Product Quality (OPQ), Branch IV
Xiaobin Shen, PhD, CMC Reviewer, Division of New Drug Products Branch IV, ONDP, OPQ
Gregory Levin, PhD, Biostatistics Team Leader, Division of Biometrics II, Office of Biostatistics (OB)
Yongman Kim, PhD, Biostatistics Reviewer, Division of Biometrics II, OB

SPONSOR ATTENDEES

Ralph Ceres, MBA	Executive Director, Project Leadership
Thomas Dowling, PhD	Associate Director, Global Regulatory CMC
Dennis Everton, RPh	Associate Director, Regulatory Affairs
Khaled Bannout, MD	Senior Director, Lead Product Safety Physician
Matthew Lamb, PharmD, RPh	Vice President, Regulatory Affairs
Yong Liu, PhD	Senior Principal Scientist, Translational Development -Clinical Pharmacology

Christine Manyak, PhD	Executive Director, Project Leadership
Darshan Parikh, RPh, PhD	Associate Director, Technical Support-Drug Product
Francisco Ramirez-Valle, MD, PhD	Director, Translational Development – Clinical Pharmacology
Julia Hui, PhD	Executive Director, Nonclinical Development Administration
Keith Usiskin, MD	Executive Director, Clinical Research & Development

Introduction:

This material consists of our preliminary responses to your questions and any additional comments in preparation for the discussion at the meeting scheduled for May 19, 2017, 1:00 P.M. at FDA White Oak Building 22, Conference Room 1313 between Celgene Corporation and the Division of Pulmonary, Allergy, and Rheumatology Products. We are sharing this material to promote a collaborative and successful discussion at the meeting. The meeting minutes will reflect agreements, important issues, and any action items discussed during the meeting and may not be identical to these preliminary comments following substantive discussion at the meeting. If you determine that discussion is needed for only some of the original questions, you have the option of reducing the agenda and/or changing the format of the meeting (e.g., from face to face to teleconference). Contact the Regulatory Project Manager (RPM) if there are any major changes to your development plan, the purpose of the meeting, or the questions based on our preliminary responses, as we may not be prepared to discuss or reach agreement on such changes at the meeting.

1.0 BACKGROUND

Celgene Corporation submitted a meeting request to the Division of Pulmonary, Allergy, and Rheumatology Products to discuss clinical pharmacokinetic data generated from the bioavailability study CP-035 and determine if the data is suitable to support the registration of an extended release 75 mg QD formulation of apremilast in the indications for which the Otezla 30 mg twice daily immediate release formulation is approved. The meeting was granted on March 15, 2017.

Celgene's questions from the briefing document dated April 12, 2017, are provided below in *italics* followed by FDA responses in normal font.

2.1. CLINICAL

Question 1:

Apremilast is the active moiety for both OTEZLA® and APRE XL. The pivotal BA study (CP-035) has demonstrated that APRE XL dosed once daily provides equivalent PK exposure (AUC0-t, AUC0-∞, and/or AUC0-24 and Cmax) to OTEZLA® (30 mg BID IR) following multiple and single dose administration under the standard meal and fasting conditions respectively. Does the Agency agree that the pivotal study supports registration of APRE XL for the indications in which OTEZLA® is approved?

FDA Response:
The registration of APRE XL for the PsA and psoriasis indications based on equivalent pharmacokinetic exposure (AUC and C_{max}) to the approved 30 mg BID formulation (OTEZLA®) seems reasonable. In the NDA, submit a PK/PD analysis linking the systemic exposure of APRE XL to efficacy using data from the previous studies in NDA 205437. Specifically, identify the most relevant PK parameter (e.g. AUC, Cmax, Ctrough and/or tmax) for efficacy in order to appropriately bridge the IR efficacy information to the XL formulation. Your justification on the impact of difference in concentration-time profile following APRE XL compared to those of OTEZLA on safety and efficacy of apremilast in both PsA and psoriasis indications will be a review issue.

Further, in the NDA, address the following issues. We refer you to Agency Written Response document dated November 23, 2015:

a. We note that the nominal doses between the 75 mg QD for APRE XL and 30 mg BID for OTEZLA are not the same. Provide rationale and data/studies supporting the selection of 75 mg for APRE XL as equivalent systemic exposure indicates different bioavailability between the two formulations.

b. Provide evaluation of the differences in the local gastrointestinal (GI) exposure of APRE XL relative to OTEZLA with respect to local GI toxicity.

c. Provide development plans and labeling for the initial titration schedule in terms of the dosage and administration.

We remind you that your NDA should be complete upon initial submission.

Question 2:
The pivotal BA study (CP-035) has demonstrated that APRE XL dosed once daily provides equivalent PK exposure (AUC0-t, AUC0-∞, and/or AUC0-24 and Cmax) to OTEZLA® (30 mg BID IR) following multiple and single dose administration under the standard meal and fasting conditions respectively. CP-035 has also demonstrated that Cmax, AUC0-t and AUC0-∞ were comparable when APRE XL was administered with either the high fat or standard meal condition, indicating that a high fat meal does not meaningfully affect the absorption and PK of APRE XL. These data indicate that, just as with the OTEZLA® 30 mg BID IR reference formulation, APRE XL can be administered without regard to meals. Does the Agency agree?

FDA Response:
Yes, we agree. The adequacy of your data to support labeling for administration regardless of meals will be a review issue.

Question 3:
For the NDA submission, Celgene intends to cross-reference the existing apremilast NDA for PsA (205437) submitted on 21 Mar 2013 to the Division of Pulmonary, Allergy, and Rheumatology Products. The existing NDA 205437 will be cross-referenced for the integrated summary of safety (ISS) and the integrated summary of efficacy (ISE). Sections 2.2, 2.3, 2.5, 2.7.1, and 2.7.6 of Module

2 will be updated and submitted in the NDA. Module 3 will be updated with drug product information related to the APRE XL formulation. Module 5 will be updated to include the pilot BA study CP-034 and the pivotal BA study CP-035 full clinical study reports.
Does the Agency agree with Celgene's proposal?

FDA Response:
This proposal is reasonable.

Question 4:
No death or other serious adverse event (SAE) was reported in studies CP-034 and CP-035 supporting this NDA. Celgene is proposing to provide the following for subjects who discontinued due to adverse events (AEs) in the planned NDA submission for the APRE XL formulation:

- *Case Report Forms (CRFs) for the pilot study CP-034 and the pivotal study CP-035*
- *Subject narratives*

Does the Agency agree with Celgene's proposal?

FDA Response:
This proposal is reasonable.

Question 5:
As the pilot study CP-034 and the pivotal study CP-035 have been completed and full clinical study reports will be included in the NDA, no additional safety data for the APRE XL formulation are expected during the NDA review period. As such, Celgene does not plan to submit a 4-month safety update during the NDA review period (as described in 21 CFR 314.50 (d)(5)(vi)(b)). Does the Agency agree?

FDA Response:
While your proposal is reasonable, it is expected that a 4-month safety update is submitted to the NDA. However, in that submission you can provide your rationale for why you are not including additional safety data for the APRE XL formulation.

Question 6:
Celgene plans to submit an original NDA for APRE XL to the Division of Pulmonary, Allergy and Rheumatology Products to support approval of the QD formulation for inclusion in approved labeling for the following indications:

- *the treatment of adult patients with active psoriatic arthritis.*
- *the treatment of patients with moderate to severe plaque psoriasis who are candidates for phototherapy or systemic therapy.*

The pivotal study supporting this application (CP-035), is a comparative BA study. For the purposes of assessing user fees, the NDA will not contain clinical data as defined in FDA Guidance for Industry: Submitting Separate Marketing Applications and Clinical Data for Purposes of Assessing User Fees (FDA Dec 2004). Therefore, one half of a full user fee will be assessed.
Does the agency agree with the submission plan and assessment of user fees?

FDA Response:
This approach sounds reasonable, however, please contact the User Fee Waiver Office directly to gain their perspective on your proposal and how this may impact the user fee.

3.0 OTHER IMPORTANT MEETING INFORMATION

PREA REQUIREMENTS

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

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

For additional guidance on the timing, content, and submission of the iPSP, including an iPSP Template, please refer to the draft guidance for industry, *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans* at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM360507.pdf. In addition, you may contact the Division of Pediatric and Maternal Health at 301-796-2200 or email pdit@fda.hhs.gov. For further guidance on pediatric product development, please refer to: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm.

PRESCRIBING INFORMATION

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

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

The application should include a review and summary of the available published literature regarding drug use in pregnant and lactating women, a review and summary of reports from your pharmacovigilance database, and an interim or final report of an ongoing or closed pregnancy registry (if applicable), which should be located in Module 1. Refer to the draft guidance for industry – *Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products – Content and Format* (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM425398.pdf).

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

MANUFACTURING FACILITIES

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

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

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

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

Corresponding names and titles of onsite contact:

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

Office of Scientific Investigations (OSI) Requests

The Office of Scientific Investigations (OSI) requests that the following items be provided to facilitate development of clinical investigator and sponsor/monitor/CRO inspection assignments, and the background packages that are sent with those assignments to the FDA field investigators who conduct those inspections (Item I and II). This information is requested for all major trials used to support safety and efficacy in the application (i.e., phase 2/3 pivotal trials). Please note that if the requested items are provided elsewhere in submission in the format described, the Applicant can describe location or provide a link to the requested information.

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

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

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

1. Please include the following information in a tabular format in the original NDA for each of the completed pivotal clinical trials:
   a. Site number

b. Principal investigator
c. Site Location: Address (e.g., Street, City, State, Country) and contact information (i.e., phone, fax, email)
d. Location of Principal Investigator: Address (e.g., Street, City, State, and Country) and contact information (i.e., phone, fax, email). If the Applicant is aware of changes to a clinical investigator's site address or contact information since the time of the clinical investigator's participation in the study, we request that this updated information also be provided.

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

3. Please include the following information in a tabular format in the NDA for each of the completed pivotal clinical trials:
   a. Location at which sponsor trial documentation is maintained (e.g., , monitoring plans and reports, training records, data management plans, drug accountability records, IND safety reports, or other sponsor records as described ICH E6, Section 8). This is the actual physical site(s) where documents are maintained and would be available for inspection
   b. Name, address and contact information of all Contract Research Organization (CROs) used in the conduct of the clinical trials and brief statement of trial related functions transferred to them. If this information has been submitted in eCTD format previously (e.g., as an addendum to a Form FDA 1571, you may identify the location(s) and/or provide link(s) to information previously provided.
   c. The location at which trial documentation and records generated by the CROs with respect to their roles and responsibilities in conduct of respective studies is maintained. As above, this is the actual physical site where documents would be available for inspection.

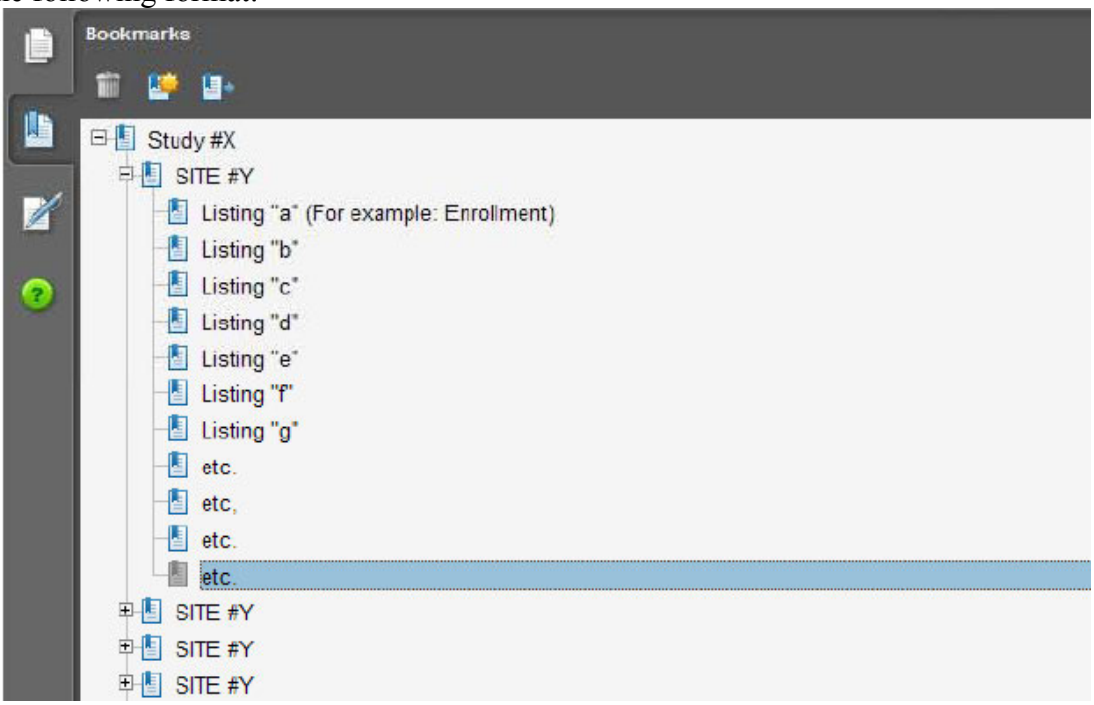
4. For each pivotal trial, provide a sample annotated Case Report Form (or identify the location and/or provide a link if provided elsewhere in the submission).
5. For each pivotal trial provide original protocol and all amendments ((or identify the location and/or provide a link if provided elsewhere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

II. Request for Subject Level Data Listings by Site

1. For each pivotal trial: Site-specific individual subject data listings (hereafter referred to as "line listings"). For each site, provide line listings for:
   a. Listing for each subject consented/enrolled; for subjects who were not randomized to treatment and/or treated with study therapy, include reason not randomized and/or treated
   b. Subject listing for treatment assignment (randomization)

c. Listing of subjects that discontinued from study treatment and subjects that discontinued from the study completely (i.e., withdrew consent) with date and reason discontinued
d. Listing of per protocol subjects/ non-per protocol subjects and reason not per protocol
e. By subject listing of eligibility determination (i.e., inclusion and exclusion criteria)
f. By subject listing, of AEs, SAEs, deaths and dates
g. By subject listing of protocol violations and/or deviations reported in the NDA, including a description of the deviation/violation
h. By subject listing of the primary and secondary endpoint efficacy parameters or events. For derived or calculated endpoints, provide the raw data listings used to generate the derived/calculated endpoint.
i. By subject listing of concomitant medications (as appropriate to the pivotal clinical trials)
j. By subject listing, of testing (e.g., laboratory, ECG) performed for safety monitoring

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



III. Request for Site Level Dataset:

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

http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/UCM332468.pdf) for the structure and format of this data set.

Attachment 1

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

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

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

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

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

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

References:

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

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

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

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

/s/

LEANN D BRODHEAD
05/17/2017