

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

761032Orig1s000

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION ¹		
NDA # NA BLA # 761032	NDA Supplement # NA BLA Supplement # NA	If NDA, Efficacy Supplement Type: NA <i>(an action package is not required for SE8 or SE9 supplements)</i>
Proprietary Name: Siliq Established/Proper Name: brodalumab Dosage Form: injection		Applicant: Valeant Pharmaceuticals Luxembourg S.a r.l. Agent for Applicant (if applicable): NA
RPM: Strother D. Dixon		Division: Division of Dermatology and Dental Products
NDA Application Type: <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) Efficacy Supplement: <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) BLA Application Type: <input type="checkbox"/> 351(k) <input checked="" type="checkbox"/> 351(a) Efficacy Supplement: <input type="checkbox"/> 351(k) <input type="checkbox"/> 351(a)		<p style="margin: 0;"><u>For ALL 505(b)(2) applications, two months prior to EVERY action:</u></p> <ul style="list-style-type: none"> Review the information in the 505(b)(2) Assessment and submit the draft² to CDER OND IO for clearance. Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity) <p style="margin-left: 20px;"> <input type="checkbox"/> No changes <input type="checkbox"/> New patent/exclusivity <i>(notify CDER OND IO)</i> Date of check: </p> <p style="margin-left: 20px;"><i>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.</i></p>
❖ Actions		
<ul style="list-style-type: none"> Proposed action User Fee Goal Date is <u>February 16, 2017</u> 		<input checked="" type="checkbox"/> AP <input type="checkbox"/> TA <input type="checkbox"/> CR
<ul style="list-style-type: none"> Previous actions <i>(specify type and date for each action taken)</i> 		<input checked="" type="checkbox"/> 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 _____		<input checked="" type="checkbox"/> Received
❖ Application Characteristics ³		

¹ The **Application Information** Section is (only) a checklist. The **Contents of Action Package** Section (beginning on page 2) lists the documents to be included in the Action Package.

² For resubmissions, 505(b)(2) applications must be cleared before the action, but it is not necessary to resubmit the draft 505(b)(2) Assessment to CDER OND IO unless the Assessment has been substantively revised (e.g., new listed drug, patent certification revised).

³ Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA.

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

- | | |
|---|---|
| <input type="checkbox"/> Fast Track | <input type="checkbox"/> Rx-to-OTC full switch |
| <input type="checkbox"/> Rolling Review | <input type="checkbox"/> Rx-to-OTC partial switch |
| <input type="checkbox"/> Orphan drug designation | <input type="checkbox"/> Direct-to-OTC |
| <input type="checkbox"/> Breakthrough Therapy designation | |

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

NDAs: Subpart H

- Accelerated approval (21 CFR 314.510)
 Restricted distribution (21 CFR 314.520)

Subpart I

- Approval based on animal studies

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

BLAs: Subpart E

- Accelerated approval (21 CFR 601.41)
 Restricted distribution (21 CFR 601.42)

Subpart H

- Approval based on animal studies

- REMS: MedGuide
 Communication Plan
 ETASU
 MedGuide w/o REMS
 REMS not required

Comments:

❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 (approvals only)	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
❖ Public communications (approvals only)	
• Office of Executive Programs (OEP) liaison has been notified of action	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
• Indicate what types (if any) of information were issued	<input type="checkbox"/> None <input checked="" type="checkbox"/> FDA Press Release <input type="checkbox"/> FDA Talk Paper <input type="checkbox"/> CDER Q&As <input type="checkbox"/> 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	<input checked="" type="checkbox"/> No <input type="checkbox"/> 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.	<input type="checkbox"/> Verified <input type="checkbox"/> 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)	<input checked="" type="checkbox"/> Included
Documentation of consent/non-consent by officers/employees	<input checked="" type="checkbox"/> Included

Action Letters	
❖ Copies of all action letters (<i>including approval letter with final labeling</i>)	Approval 2/15/17
Labeling	
❖ Package Insert (<i>write submission/communication date at upper right of first page of PI</i>)	
• Most recent draft labeling (<i>if it is division-proposed labeling, it should be in track-changes format</i>)	<input checked="" type="checkbox"/> Included 2/9/17
• Original applicant-proposed labeling	<input checked="" type="checkbox"/> Included 11/16/15
❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling (<i>write submission/communication date at upper right of first page of each piece</i>)	<input checked="" type="checkbox"/> Medication Guide <input type="checkbox"/> Patient Package Insert <input checked="" type="checkbox"/> Instructions for Use <input type="checkbox"/> Device Labeling <input type="checkbox"/> None
• Most-recent draft labeling (<i>if it is division-proposed labeling, it should be in track-changes format</i>)	<input checked="" type="checkbox"/> Included 2/9/17
• Original applicant-proposed labeling	<input checked="" type="checkbox"/> Included 11/16/15
❖ Labels (full color carton and immediate-container labels) (<i>write submission/communication date on upper right of first page of each submission</i>)	
• Most-recent draft labeling	<input checked="" type="checkbox"/> Included 12/13/16
❖ Proprietary Name	Letter – 3/16/16 Review – 2/29/16
• Acceptability/non-acceptability letter(s) (<i>indicate date(s)</i>)	
• Review(s) (<i>indicate date(s)</i>)	
❖ Labeling reviews (<i>indicate dates of reviews</i>)	RPM: <input type="checkbox"/> None 1/12/16 DMEPA: <input type="checkbox"/> None 2/13/17 and 10/6/16 (see Clinical Other section) DMPP/PLT (DRISK): <input type="checkbox"/> None 11/17/16 (PLT) OPDP: <input type="checkbox"/> None 11/16/16 SEALD: <input checked="" type="checkbox"/> None CSS: <input checked="" type="checkbox"/> None Product Quality <input type="checkbox"/> None 12/16/16 Other: <input type="checkbox"/> None DPMH 8/12/16
Administrative / Regulatory Documents	
❖ RPM Filing Review ⁴ /Memo of Filing Meeting (<i>indicate date of each review</i>)	1/12/16
❖ All NDA 505(b)(2) Actions: Date each action cleared by 505(b)(2) Clearance Committee	<input checked="" type="checkbox"/> Not a (b)(2)
❖ NDAs/NDA supplements only: Exclusivity Summary (<i>signed by Division Director</i>)	<input type="checkbox"/> Completed (Do not include)
❖ Application Integrity Policy (AIP) Status and Related Documents http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	
• Applicant is on the AIP	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No

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

<ul style="list-style-type: none"> • This application is on the AIP <ul style="list-style-type: none"> ○ If yes, Center Director’s Exception for Review memo (<i>indicate date</i>) ○ If yes, OC clearance for approval (<i>indicate date of clearance communication</i>) 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> Not an AP action
<ul style="list-style-type: none"> ❖ Pediatrics (<i>approvals only</i>) <ul style="list-style-type: none"> • Date reviewed by PeRC <u>July 6, 2016</u> If PeRC review not necessary, explain: _____ 	
<ul style="list-style-type: none"> ❖ Breakthrough Therapy Designation 	<input checked="" type="checkbox"/> N/A
<ul style="list-style-type: none"> • Breakthrough Therapy Designation Letter(s) (granted, denied, an/or rescinded) 	
<ul style="list-style-type: none"> • CDER Medical Policy Council Breakthrough Therapy Designation Determination Review Template(s) (<i>include only the completed template(s) and not the meeting minutes</i>) 	
<ul style="list-style-type: none"> • CDER Medical Policy Council Brief – Evaluating a Breakthrough Therapy Designation for Rescission Template(s) (<i>include only the completed template(s) and not the meeting minutes</i>) (<i>completed CDER MPC templates can be found in DARRTS as clinical reviews or on the MPC SharePoint Site</i>) 	
<ul style="list-style-type: none"> ❖ Outgoing communications: letters, emails, and faxes considered important to include in the action package by the reviewing office/division (e.g., clinical SPA letters, RTF letter, Formal Dispute Resolution Request decisional letters, etc.) (<i>do not include OPDP letters regarding pre-launch promotional materials as these are non-disclosable; do not include Master File letters; do not include previous action letters, as these are located elsewhere in package</i>) 	<p>N=3</p>
<ul style="list-style-type: none"> ❖ 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) 	<p>Tcon dates: 1/23/17 10/5/16 9/21/16 8/31/16 8/22/16 8/15/16</p>
<ul style="list-style-type: none"> ❖ Minutes of Meetings 	
<ul style="list-style-type: none"> • If not the first review cycle, any end-of-review meeting (<i>indicate date of mtg</i>) 	<input checked="" type="checkbox"/> N/A or no mtg
<ul style="list-style-type: none"> • Pre-NDA/BLA meeting (<i>indicate date of mtg</i>) 	<input type="checkbox"/> No mtg 1/21/15 (CMC), 10/21/14, and 3/25/15
<ul style="list-style-type: none"> • EOP2 meeting (<i>indicate date of mtg</i>) 	<input checked="" type="checkbox"/> No mtg
<ul style="list-style-type: none"> • Mid-cycle Communication (<i>indicate date of mtg</i>) 	<input type="checkbox"/> N/A 4/20/16
<ul style="list-style-type: none"> • Late-cycle Meeting (<i>indicate date of mtg</i>) 	<input type="checkbox"/> N/A 6/28/16
<ul style="list-style-type: none"> • Other milestone meetings (e.g., EOP2a, CMC focused milestone meetings) (<i>indicate dates of mtgs</i>) 	<p>NA</p>

❖ Advisory Committee Meeting(s)	<input type="checkbox"/> No AC meeting
• Date(s) of Meeting(s)	7/19/16
Decisional and Summary Memos	
❖ Office Director Decisional Memo (<i>indicate date for each review</i>)	<input type="checkbox"/> None 2/8/17 and 12/28/16
Division Director Summary Review (<i>indicate date for each review</i>)	<input type="checkbox"/> None 2/6/17
Cross-Discipline Team Leader Review (<i>indicate date for each review</i>)	<input type="checkbox"/> None 9/16/16
PMR/PMC Development Templates (<i>indicate total number</i>)	<input type="checkbox"/> None n=7
Clinical	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> No separate review
• Clinical review(s) (<i>indicate date for each review</i>)	9/16/16
• Social scientist review(s) (if OTC drug) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here <input type="checkbox"/> and include a review/memo explaining why not (<i>indicate date of review/memo</i>)	p. 137 of 9/16/16 Clinical Review
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers (<i>indicate date of each review</i>) ⁵	<input type="checkbox"/> None
1. Division of Medication Error Prevention and Analysis	1. 2/13/17
2. Division of Epidemiology (ARIA)	2. 12/19/16
3. Division of Medication Error Prevention and Analysis	3. 10/6/16
4. Ethics	4. 8/10/16
5. Clinical Outcome Assessment	5. 7/12/16
6. Division of Cardiology and Renal	6. 6/30/16
7. Division of Epidemiology (Infection)	7. 6/27/16
8. Division of Epidemiology (MACE)	8. 6/8/16
9. Division of Psychiatry Products	9. 4/25/16
10. Division of Epidemiology (SIB)	10. 3/22/16
❖ Controlled Substance Staff review(s) and Scheduling Recommendation (<i>indicate date of each review</i>)	<input checked="" type="checkbox"/> N/A
❖ Risk Management	
• REMS Documents and REMS Supporting Document (<i>indicate date(s) of submission(s)</i>)	2/13/17
• REMS Memo(s) and letter(s) (<i>indicate date(s)</i>)	Memo – 2/14/17
• Risk management review(s) and recommendations (including those by OSE and CSS) (<i>indicate date of each review and indicate location/date if incorporated into another review</i>)	<input type="checkbox"/> None 2/15/17, 1/9/17, 1/4/17, 12/12/16
❖ OSI Clinical Inspection Review Summary(ies) (<i>include copies of OSI letters to investigators</i>)	<input type="checkbox"/> None requested Review: 8/24/16 Letters: 8/17/16, 8/16/16, 8/15/16

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

Clinical Microbiology		<input checked="" type="checkbox"/> None
❖ Clinical Microbiology Team Leader Review(s) (<i>indicate date for each review</i>)		<input type="checkbox"/> No separate review
Clinical Microbiology Review(s) (<i>indicate date for each review</i>)		<input type="checkbox"/> None
Biostatistics		<input type="checkbox"/> None
❖ Statistical Division Director Review(s) (<i>indicate date for each review</i>)		<input checked="" type="checkbox"/> No separate review
Statistical Team Leader Review(s) (<i>indicate date for each review</i>)		<input checked="" type="checkbox"/> No separate review
Statistical Review(s) (<i>indicate date for each review</i>)		<input type="checkbox"/> None DB7 - 7/6/16; 7/1/16
Clinical Pharmacology		<input type="checkbox"/> None
❖ Clinical Pharmacology Division Director Review(s) (<i>indicate date for each review</i>)		<input checked="" type="checkbox"/> No separate review
Clinical Pharmacology Team Leader Review(s) (<i>indicate date for each review</i>)		<input checked="" type="checkbox"/> No separate review
Clinical Pharmacology review(s) (<i>indicate date for each review</i>)		<input type="checkbox"/> None 7/5/16
❖ OSI Clinical Pharmacology Inspection Review Summary (<i>include copies of OSI letters</i>)		<input checked="" type="checkbox"/> None requested
Nonclinical		<input type="checkbox"/> None
❖ Pharmacology/Toxicology Discipline Reviews		
• ADP/T Review(s) (<i>indicate date for each review</i>)		<input type="checkbox"/> No separate review 5/9/16
• Supervisory Review(s) (<i>indicate date for each review</i>)		<input type="checkbox"/> No separate review 7/13/16
• Pharm/tox review(s), including referenced IND reviews (<i>indicate date for each review</i>)		<input type="checkbox"/> None 7/12/16
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer (<i>indicate date for each review</i>)		<input checked="" type="checkbox"/> None
❖ Statistical review(s) of carcinogenicity studies (<i>indicate date for each review</i>)		<input checked="" type="checkbox"/> No carc
❖ ECAC/CAC report/memo of meeting		<input checked="" type="checkbox"/> None Included in P/T review, page
❖ OSI Nonclinical Inspection Review Summary (<i>include copies of OSI letters</i>)		<input checked="" type="checkbox"/> None requested
Product Quality		<input type="checkbox"/> None
❖ Product Quality Discipline Reviews ⁶		
• Tertiary review (<i>indicate date for each review</i>)		<input checked="" type="checkbox"/> None
• Secondary review (e.g., Branch Chief) (<i>indicate date for each review</i>)		<input checked="" type="checkbox"/> None
• Integrated Quality Assessment (contains the Executive Summary and the primary reviews from each product quality review discipline) (<i>indicate date for each review</i>)		<input type="checkbox"/> None 11/14/16 Addendum; 7/1/16;
❖ Reviews by other disciplines/divisions/Centers requested by product quality review team (<i>indicate date of each review</i>)		<input type="checkbox"/> None CDRH GHDB - 6/28/16 CDRH Office of Compliance- 4/7/16

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

❖ Environmental Assessment (check one) (original and supplemental applications)	
<input checked="" type="checkbox"/> Categorical Exclusion (<i>indicate review date</i>)(<i>all original applications and all efficacy supplements that could increase the patient population</i>)	See page 8 of the 7/1/16 CMC review; Section IV of the Summary of Quality Assessments
<input type="checkbox"/> Review & FONSI (<i>indicate date of review</i>)	
<input type="checkbox"/> Review & Environmental Impact Statement (<i>indicate date of each review</i>)	
❖ Facilities Review/Inspection	
<input checked="" type="checkbox"/> Facilities inspections (indicate date of recommendation; within one week of taking an approval action, confirm that there is an acceptable recommendation before issuing approval letter) (<i>only original applications and efficacy supplements that require a manufacturing facility inspection(e.g., new strength, manufacturing process, or manufacturing site change)</i>)	<input checked="" type="checkbox"/> Acceptable 12/9/16 Re-evaluation date: <input type="checkbox"/> Withhold recommendation <input type="checkbox"/> Not applicable

Day of Approval Activities	
❖ For all 505(b)(2) applications: <ul style="list-style-type: none"> • Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity) 	<input type="checkbox"/> No changes NA <input type="checkbox"/> New patent/exclusivity (<i>Notify CDER OND IO</i>) NA
<ul style="list-style-type: none"> • Finalize 505(b)(2) assessment 	<input type="checkbox"/> Done NA
❖ For Breakthrough Therapy (BT) Designated drugs: <ul style="list-style-type: none"> • Notify the CDER BT Program Manager 	<input type="checkbox"/> Done NA (<i>Send email to CDER OND IO</i>)
❖ For products that need to be added to the flush list (generally opioids): Flush List <ul style="list-style-type: none"> • Notify the Division of Online Communications, Office of Communications 	<input type="checkbox"/> Done NA
❖ Send a courtesy copy of approval letter and all attachments to applicant by fax or secure email	<input checked="" type="checkbox"/> Done
❖ If an FDA communication will issue, notify Press Office of approval action after confirming that applicant received courtesy copy of approval letter	<input checked="" type="checkbox"/> Done
❖ Ensure that proprietary name, if any, and established name are listed in the <i>Application Product Names</i> section of DARRTS, and that the proprietary name is identified as the “preferred” name	<input checked="" type="checkbox"/> Done
❖ Ensure Pediatric Record is accurate	<input checked="" type="checkbox"/> Done
❖ Send approval email within one business day to CDER-APPROVALS	<input checked="" type="checkbox"/> Done

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

/s/

STROTHER D DIXON
02/17/2017

MEMORANDUM OF TELECONFERENCE

Teleconference Date: January 23, 2017

Application Number: BLA 761032

Product Name: brodalumab injection, 210 mg/1.5 ml

Applicant Name: Valeant Pharmaceuticals Luxembourg S.a.r.l. (VPL)

Subject: Risk Evaluation and Mitigation Strategy (REMS)

FDA Participants

Julie Beitz, MD, Director, Office of Drug Evaluation III

Kendall A. Marcus, MD, Director, Division of Dermatology and Dental Products (DDDP)

Tatiana Oussova, MD, MPH, Deputy Director for Safety, DDDP

David Kettl, MD, Clinical Team Leader, DDDP

Gary Chiang, MD, Clinical Reviewer, DDDP

Jamie Wilkins Parker, PharmD, Acting Deputy Director, Division of Risk Evaluation (DRISK)

Donella Fitzgerald, PharmD, Acting Team Leader, DRISK

Erin South, PharmD, RPh, Risk Management Analyst, DRISK

Yasmeen Abou-Sayed, PharmD, Risk Management Analyst, DRISK

Strother D. Dixon, Senior Regulatory Health Project Manager, DDDP

Applicant Participants

Binu Alexander, Sr. Director Clinical Operations

Susan Harris, Project Manager

Robert Israel, MD, Vice President Clinical and Medical Affairs

Jennifer Knicley, Senior Manager Regulatory Affairs

Karen M. Krstulich Executive Director Regulatory Affairs

Isabelle Lefebvre, Vice President Regulatory Affairs, Brand, Generic & Consumer Products

Radhakrishnan (RK) Pillai, PhD, Vice President Dermatology Development

Tage Ramakrishna, MD, Chief Medical Officer, President of Research & Development

Philip Sturno, Vice President Product Development

Sharon Tonetta, PhD, Head of Regulatory Affairs

Johnson Varughese, Vice President Clinical Operations

1.0 BACKGROUND:

The Agency provided comments and revisions to the BLA 761032 brodalumab REMS materials/proposal on December 13, 2016, and January 10, 2017. The applicant responded on January 17, 2017 with additional edits and noted that there were “version control issues”.

2.0 DISCUSSION:

The Agency informed the applicant that the current FDA-redlined version of the REMS materials/proposal had been carefully considered and reviewed by upper levels of CDER. The Agency encouraged the applicant to revise their REMS proposal to align with the FDA-redlined version; the only exceptions would be if further revisions were needed to align the REMS with the most current iteration of the labeling or if the applicant discovers an error in the REMS materials that requires revising.

3.0 ACTION ITEMS:

The Agency committed to providing the REMS materials/proposal by close of business January 23, 2017. The applicant was advised to submit their response by January 27, 2017.

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

/s/

STROTHER D DIXON
02/07/2017



BLA 761032

**REVIEW EXTENSION –
MAJOR AMENDMENT**

Valeant Pharmaceuticals Luxembourg S.a.r.l. (VPL)
c/o Valeant Pharmaceuticals North America LLC
Attention: Karen M. Krstulich
Executive Director Regulatory Affairs
400 Somerset Corporate Blvd.
Bridgewater, NJ 08807

Dear Ms. Krstulich:

Please refer to your Biologics License Application (BLA) dated and received November 16, 2015, submitted under section 351(a) of the Public Health Service Act for brodalumab injection, 210 mg/ml.

We received your October 18, 2016, major amendment to this application. Therefore, we are extending the goal date by three months to provide time for a full review of the submission. The extended user fee goal date is February 16, 2017.

In addition, we are establishing a new timeline for communicating labeling changes and/or postmarketing requirements/commitments in accordance with “PDUFA REAUTHORIZATION PERFORMANCE GOALS AND PROCEDURES – FISCAL YEARS 2013 THROUGH 2017.” If major deficiencies are not identified during our review, we plan to communicate proposed labeling and, if necessary, any postmarketing requirement/commitment requests by December 5, 2016.

If you have any questions, call Strother D. Dixon, Senior Regulatory Project Manager, at (301) 796-1015.

Sincerely,

{See appended electronic signature page}

Kendall A. Marcus, MD
Director
Division of Dermatology and Dental Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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

/s/

KENDALL A MARCUS
10/25/2016



BLA 761032

**REVIEW EXTENSION –
MAJOR AMENDMENT**

Valeant Pharmaceuticals Luxembourg S.a.r.l. (VPL)
c/o Valeant Pharmaceuticals North America LLC
Attention: Karen M. Krstulich
Executive Director Regulatory Affairs
400 Somerset Corporate Blvd.
Bridgewater, NJ 08807

Dear Ms. Krstulich:

Please refer to your Biologics License Application (BLA) dated and received November 16, 2015, submitted under section 351(a) of the Public Health Service Act for brodalumab injection, 210 mg/ml.

We received your October 18, 2016, major amendment to this application. Therefore, we are extending the goal date by three months to provide time for a full review of the submission. The extended user fee goal date is February 16, 2016.

In addition, we are establishing a new timeline for communicating labeling changes and/or postmarketing requirements/commitments in accordance with “PDUFA REAUTHORIZATION PERFORMANCE GOALS AND PROCEDURES – FISCAL YEARS 2013 THROUGH 2017.” If major deficiencies are not identified during our review, we plan to communicate proposed labeling and, if necessary, any postmarketing requirement/commitment requests by December 5, 2016.

If you have any questions, call Strother D. Dixon, Senior Regulatory Project Manager, at (301) 796-1015.

Sincerely,

{See appended electronic signature page}

Kendall A. Marcus, MD
Director
Division of Dermatology and Dental Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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

/s/

KENDALL A MARCUS
10/21/2016



BLA 761032

MEETING MINUTES

Valeant Pharmaceuticals Luxembourg S.a.r.l. (VPL)
c/o Valeant Pharmaceuticals North America LLC
Attention: Karen M. Krstulich
Executive Director Regulatory Affairs
400 Somerset Corporate Blvd.
Bridgewater, NJ 08807

Dear Ms. Krstulich:

Please refer to your Biologic License Application (BLA) submitted under section 351 of the Public Health Service Act for brodalumab injection, 210 mg/1.5 ml.

We also refer to the meeting between representatives of your firm and the FDA on October 5, 2016. The purpose of the meeting was to discuss the proposed Risk Evaluation and Mitigation Strategy (REMS).

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 Strother D. Dixon, Senior Regulatory Health Project Manager at (301) 796-1015.

Sincerely,

{See appended electronic signature page}

Kendall A. Marcus, MD
Director
Division of Dermatology and Dental Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Date and Time: October 5, 2016; 8:00 AM
Meeting Location: FDA, White Oak, Building 22

Application Number: BLA 761032
Product Name: brodalumab injection, 210 mg/1.5 ml
Proposed Indication: for the treatment of moderate to severe plaque psoriasis in adult patients who are candidates for systemic therapy or phototherapy
Applicant Name: Valeant Pharmaceuticals Luxembourg S.a.r.l. (VPL)

Meeting Chair: Kendall A. Marcus, MD
Meeting Recorder: Strother D. Dixon

FDA ATTENDEES

Julie Beitz, MD, Director, Office of Drug Evaluation III (ODE III)
Amy G. Egan, MD, MPH, Deputy Director, ODE III
Kendall A. Marcus, MD, Director, Division of Dermatology and Dental Products (DDDP)
Tatiana Oussova, MD, MPH, Deputy Director for Safety, DDDP
David Kettl, MD, Clinical Team Leader, DDDP
Gary Chiang, MD, Clinical Reviewer, DDDP
Claudia Manzo, PharmD, Director, Office of Medication Error Prevention and Risk Management
Cynthia LaCivita, PharmD, Director, Division of Risk Evaluation (DRISK)
Jamie Wilkins Parker, PharmD, Team Leader, DRISK
Erin South, PharmD, Risk Management Analyst, DRISK
Tri Bui-Nguyen, PhD, Safety Regulatory Project Manager, Office of Surveillance and Epidemiology (OSE)
Strother D. Dixon, Senior Regulatory Health Project Manager, DDDP

SPONSOR ATTENDEES

Mark Lebowhl, MD, Professor and Chairman, Kimberly and Eric J Waldman Department of Dermatology Icahn School of Medicine at Mount Sinai
Joseph C. Papa, Chairman of the Board and Chief Executive Officer
Tage Ramakrishna, MD, Chief Medical Officer, President of Research & Development
Sharon Tonetta, PhD, Vice President Regulatory Affairs

1. DISCUSSION

The decision to require an elements to assure safe use (ETASU) was very thoughtfully considered within the Agency and these discussions included multiple members of senior

management through the Center. Although the Agency has not definitively established a causal relationship between brodalumab and completed suicides we noted a threefold increase in completed suicides in the brodalumab program relative to other biologic development programs in psoriasis.

The Agency is interested in hearing alternative approaches to reduce undue burden on stakeholders, while maintaining safe use. The Agency proposed that the applicant look into electronic methods to document consent as a potential method of alleviating burden.

The applicant expressed concerns about the burden to prescribers if informed consent was obtained and filed in their offices. They believe the pharmacy could more efficiently obtain and file the consents thus reducing the burden on prescribers, with which the Agency disagreed. Dr. Lebwohl acknowledged that he had not seen or reviewed samples of the forms FDA would require in the REMS but would be happy to review if made available.

2. ACTION ITEMS

The applicant was informed that the Agency's review is stalled due to the applicant not having submitted revised labeling and a modified proposed REMS to include ETASU. The applicant intends to submit a response by October 12, 2016.

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

/s/

KENDALL A MARCUS
10/11/2016

MEMORANDUM OF TELECONFERENCE

Teleconference Date: September 21, 2016

Application Number: BLA 761032

Product Name: brodalumab injection, 210 mg/1.5 ml

Applicant Name: Valeant Pharmaceuticals Luxembourg S.a.r.l. (VPL)

Subject: The purpose of the teleconference was to discuss the Risk Evaluation Mitigation Strategy (REMS) elements necessary to ensure the benefits of brodalumab outweigh the risks. Reference is made to the August 31, 2016 teleconference between FDA and Valeant and the applicant's September 16, 2016 response (SDN 53/eCTD 52).

FDA Participants

Amy G. Egan, MD, MPH, Deputy Director, ODE III

Kendall A. Marcus, MD, Director, Division of Dermatology and Dental Products (DDDP)

Tatiana Oussova, MD, MPH, Deputy Director for Safety, DDDP

David Kettl, MD, Clinical Team Leader, DDDP

Gary Chiang, MD, Clinical Reviewer, DDDP

Cynthia LaCivita, PharmD, Director, Division of Risk Management (DRISK)

Jamie Wilkins Parker, PharmD, Team Leader, DRISK

Erin South, PharmD, Risk Management Analyst, DRISK

Anahita Takoli, MA, Senior Risk Management Analyst, DRISK

Louis R. Flowers III, PharmD, MS, CPH, Team Leader, Project Management Staff, Office of Surveillance and Epidemiology (OSE)

Tri Bui-Nguyen, PhD, Safety Regulatory Project Manager, OSE

CDR Dawn Williams, RN, BSN, USPHS, Safety Regulatory Health Project Manager, DDDP

Strother D. Dixon, Senior Regulatory Health Project Manager, DDDP

Applicant Participants

Binu Alexander, Sr. Director, Clinical Operations

Susan Harris, PhD, Project Manager

Robert Israel, MD, Vice President Clinical and Medical Affairs

Karen M. Krstulich Executive Director, Regulatory Affairs

Isabelle Lefebvre, Vice President, Regulatory Affairs

Peter Motta, MD, Vice President, Global Pharmacovigilance and Risk Management

Radhakrishnan (RK) Pillai, PhD, Vice President, Dermatology Development

Tage Ramakrishna, MD, Chief Medical Officer, President of Research & Development

Philip Sturno, Vice President Product Development

Sharon Tonetta, PhD, Vice President, Regulatory Affairs

Johnson Varughese, Vice President, Clinical Operations

1.0 BACKGROUND:

On August 22, 2016 the Agency held a teleconference with the applicant to discuss optimized product labeling and the proposed REMS. The applicant responded on August 26, 2016 (SDN 51/eCTD 50), “The Sponsor has reviewed the entire situation and conclude that the label and REMS that we [Sponsor] have submitted is reasonable and supported. The FDA has offered an opposing approach. Nonetheless, we would like to have a meeting to discuss a middle ground.”

On August 31, 2016, the Agency held a teleconference to provide its rationale for the requirements for optimized product labeling and a REMS with elements to assure safe use (ETASU).

The applicant responded on September 16, 2016 (SDN 53/eCTD 52). The response included proposed language for labeling “if an ETASU is not included.” The sponsor also stated in the response, “However, to address FDA’s concern, the Sponsor will consider adding an informed consent to the currently proposed REMS Communication Plan if a formal ETASU is not imposed.” The sponsor proposes to have the informed consent administered at the pharmacy.

2.0 DISCUSSION: The Agency clarified the requirements for a REMS with ETASU as outlined below:

- The REMS proposal you have described is a REMS with ETASU, it includes documentation of informed consent, a safe-use condition, whether it is administered by the prescriber or the pharmacy staff. Communication plans are directed at providers, not patients. (Refer to the Draft Guidance for Industry- Format and Content of Proposed Risk Evaluation and Mitigation Strategies (REMS), REMS Assessments, and Proposed REMS Modifications)
- A REMS with ETASU is the only way to ensure informed consent, and the FDA has determined that the ETASU is necessary..
- The FDA proposal contains the minimum elements necessary to ensure the benefits outweigh the risks of brodalumab. It is not complex.
- The FDA previously provided you with specific examples of REMS goals and REMS materials. Your proposed REMS should be revised to reflect our recommendations and be resubmitted.
- We request a timeline for your planned submission of the revised REMS proposal by 4:00 p.m., Friday, September, 23, 2016. In the interest of time, we request submission of your proposal as soon as possible.

3.0 ACTION ITEMS:

The applicant plans to submit a response after discussions with members of a patient advocacy group and physician advisory group. The Agency reminded the applicant of the urgency and the need for the applicant to submit a response as soon as possible due to the upcoming Prescription Drug User Fee Act (PDUFA) date.

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

/s/

STROTHER D DIXON
10/04/2016



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

BLA 761032

MEETING MINUTES

Valeant Pharmaceuticals North America LLC
Attn: Karen M. Krstulich
Executive Director, Regulatory Affairs
1301 Second Avenue, Suite 3700
Seattle, WA 98101

Dear Executive Director Krstulich:

Please refer to your Biologics License Application 761032 received November 16, 2015, submitted under section 351(a) of the Public Health Service Act for brodalumab.

Please refer to the meeting between representatives of your firm and the FDA on August 15, 2016.

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

If you have any questions please contact the Regulatory Business Project Manager, Andrew Shiber at 301-796-4798.

Sincerely,

{See appended electronic signature page}

Qing Zhou, Ph.D.
Team Leader
Division of Biotechnology Products Research and Review I
Office of Biotechnology Products
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research

Enclosure: Meeting Minutes

MEETING MINUTES

Meeting Type: C
Meeting Category: CMC Only
Meeting Date and Time: August 15, 2016 1:00 P.M. Eastern Daylight Savings Time
Format: Teleconference

Office of Biotechnology Products

Sarah Kennett, Ph.D. Review Chief
Qing Zhou, Ph.D. Team Leader
Willie Wilson, Ph.D. Product Quality

Office of Process and Facilities/Division of Microbiology Assessment

Patricia Hughes, Ph.D. Branch Chief

Office of Program and Regulatory Operations

Andrew Shiber, Pharm.D. Regulatory Business Project Manager

Valeant Pharmaceuticals, Inc.

Stephen Apone Senior Director, Analytical Services
Susan Harris Project Manager
Karen M. Krstulich Executive Director Regulatory Affairs
Venkata Nanduri Senior Manager, Regulatory CMC
E. Kwame Obeng, PhD Executive Director – Regulatory CMC
Philip Sturno Vice President Product Development

1.0 BACKGROUND

Purpose of meeting: This meeting was set up to ensure a complete response to the Agency information request from August 9, 2016.

1. A complete response to the Information request (dated 8/9/16) should be submitted without any delay by August 22, 2016.
2. The Agency would be open to have a teleconference with Valeant (this week), after preliminary responses to the information request are obtained, to further clarify our expectations for these comments. Please contact me with the proposed date and time to set up the teleconference.

2.0 DISCUSSION

Valeant responded to the questions that were submitted in a document sent before the meeting.

11 Pages 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/

QING ZHOU
09/16/2016

MEMORANDUM OF TELECONFERENCE

Teleconference Date: August 31, 2016

Application Number: BLA 761032

Product Name: brodalumab injection, 210 mg/1.5 ml

Applicant Name: Valeant Pharmaceuticals Luxembourg S.a.r.l. (VPL)

Subject: The purpose of the meeting was to discuss the applicant's August 26, 2016 (SDN 51/eCTD 50) response to the Agency's request for optimized product labeling and the proposed REMS.

FDA Participants

Julie Beitz, MD, Director, Office of Drug Evaluation III (ODE III)

Amy G. Egan, MD, MPH, Deputy Director, ODE III

Kendall A. Marcus, MD, Director, Division of Dermatology and Dental Products (DDDP)

Tatiana Oussova, MD, MPH, Deputy Director for Safety, DDDP

David Kettl, MD, Clinical Team Leader, DDDP

Gary Chiang, MD, Clinical Reviewer, DDDP

Cynthia LaCivita, PharmD, Director, Division of Risk Management (DRISK)

Doris Auth, PharmD, Team Leader, DRISK

Jamie Wilkins Parker, PharmD, Team Leader, DRISK

Jasminder Kumar, PharmD, RPh, Risk Management Analyst, DRISK

Erin South, PharmD, Risk Management Analyst, DRISK

Anahita Takoli, MA, Senior Risk Management Analyst, DRISK

Shivani Shah, Pharmacy Student, DRISK

Louis R. Flowers III, PharmD, MS, CPH, Team Leader, Project Management Staff, Office of Surveillance and Epidemiology (OSE)

Tri Bui-Nguyen, PhD, Safety Regulatory Project Manager, OSE

Barbara Gould, MBAHCM, Chief, Project Management Staff, DDDP

CDR Dawn Williams, RN, BSN, USPHS, Safety Regulatory Health Project Manager, DDDP

Strother D. Dixon, Senior Regulatory Health Project Manager, DDDP

Applicant Participants

Binu Alexander, Sr. Director, Clinical Operations

Susan Harris, PhD, Project Manager

Karen M. Krstulich Executive Director, Regulatory Affairs

Isabelle Lefebvre, Vice President, Regulatory Affairs

Peter Motta, MD, Vice President, Global Pharmacovigilance and Risk Management

Radhakrishnan (RK) Pillai, PhD, Vice President, Dermatology Development

Tage Ramakrishna, MD, Chief Medical Officer, President of Research & Development

Sharon Tonetta, PhD, Vice President, Regulatory Affairs

Johnson Varughese, Vice President, Clinical Operations

1.0 BACKGROUND:

In an Information Request dated July 27, 2016, the Agency requested the applicant propose “prescribing information with revisions that include a boxed warning for suicide, and suicidal ideation, and possible mitigation of these events.” The sponsor responded on August 10, 2016 (SDN 46/eCTD 45) that they “would like to engage with the Division in a discussion of the optimal labeling outcomes regarding the issue of suicidal ideation and behavior. There has been no causal association established between brodalumab and suicidal ideation and behavior. There are no currently labeled biologics for the treatment of psoriasis that are required to include a boxed warning for SIB.”

On August 22, 2016 the Agency held a teleconference with the applicant to discuss optimized product labeling and the proposed REMS. The applicant was provided with the Meeting Minutes on August 24, 2016. On August 26, 2016 (SDN 51/eCTD 50) the applicant responded, “The Sponsor has reviewed the entire situation and conclude that the label and REMS that we have submitted is reasonable and supported. The FDA has offered an opposing approach. Nonetheless, we would like to have a meeting to discuss a middle ground.”

2.0 DISCUSSION: The Agency provided its rationale for the requirements as outlined below:

2.1 Optimized Product Labeling

- 2.1.1 A Boxed Warning discussing the potential increased risk of suicidality with brodalumab.
- 2.1.2 A Limitation of Use that brodalumab should only be used in patients who have failed to respond, or lost response, to other biologic therapies.
- 2.1.3 A recommendation to discontinue therapy, or reassess the need to continue therapy, in patients who do not achieve an adequate response within 12 weeks.

2.2 The REMS with ETASU will include: Prescriber Certification, Pharmacy Certification, and Documentation of Safe Use conditions. The REMS appended materials should include:

- Siliq REMS Program Healthcare Provider Enrollment Form;
- Siliq REMS Program Patient Wallet Card;
- Siliq REMS Program Patient-Provider Agreement Form; and
- Siliq REMS Program Pharmacy Enrollment Form.

3.0 ACTION ITEMS:

The applicant plans to submit the revised labeling consistent with the Agency's requirements above, and will either submit a timeline for when they will provide the Agency with the various documents requested as part of the REMS with ETASU or a rationale as to why a REMS with ETASU should not be required with a proposal for how Informed Consent on the part of the patient can be assured.

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

/s/

STROTHER D DIXON
09/12/2016



BLA 761032

INFORMATION REQUEST

Valeant Pharmaceuticals Luxembourg S.a.r.l. (VPL)
c/o Valeant Pharmaceuticals North America LLC
Attention: Karen M. Krstulich
Executive Director Regulatory Affairs
400 Somerset Corporate Blvd.
Bridgewater, NJ 08807

Dear Ms. Krstulich:

Please refer to your Biologics License Application (BLA) dated and received November 16, 2015, submitted under section 351(a) of the Public Health Service Act for brodalumab injection, 210 mg/1.5 ml.

We are reviewing the Clinical section of your submission and have the following comments and information requests. We request a prompt written response by September 2, 2016 in order to continue our evaluation of your BLA.

Provide C-reactive protein (CRP) levels for the 6 completed suicides in the brodalumab program. Provide the absolute and percent change from baseline in CRP over time (Weeks 12, 24, and 48) for subjects who completed suicide. You can present the results graphically with an indication on the graph as to when the suicide event took place to correlate the CRP levels. Respond with the information in 48 hours for Agency review.

If you have any questions, please contact Strother D. Dixon, Senior Regulatory Project Manager, at (301) 796-1015.

Sincerely,

{See appended electronic signature page}

David Kettl, MD
Clinical Team Leader
Division of Dermatology and Dental Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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

/s/

DAVID L KETTL
08/31/2016



BLA 761032

MEETING MINUTES

Valeant Pharmaceuticals Luxembourg S.a.r.l. (VPL)
c/o Valeant Pharmaceuticals North America LLC
Attention: Karen M. Krstulich
Executive Director Regulatory Affairs
400 Somerset Corporate Blvd.
Bridgewater, NJ 08807

Dear Ms. Krstulich:

Please refer to your Biologic License Application (BLA) submitted under section 351 of the Public Health Service Act for brodalumab injection, 210 mg/1.5 ml.

We also refer to the teleconference between representatives of your firm and the FDA on August 22, 2016. The purpose of the meeting was to discuss product labeling and the proposed Risk Evaluation and Mitigation Strategy (REMS).

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

If you have any questions, call Strother D. Dixon, Senior Regulatory Health Project Manager at (301) 796-1015.

Sincerely,

{See appended electronic signature page}

Kendall A. Marcus, MD
Director
Division of Dermatology and Dental Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Date and Time: August 22, 2016; 12:00 PM
Meeting Location: Teleconference

Application Number: BLA 761032
Product Name: brodalumab injection, 210 mg/1.5 ml
Proposed Indication: for the treatment of moderate to severe plaque psoriasis in adult patients who are candidates for systemic therapy or phototherapy
Applicant Name: Valeant Pharmaceuticals Luxembourg S.a.r.l. (VPL)

Meeting Chair: Kendall A. Marcus, MD
Meeting Recorder: Strother D. Dixon

FDA ATTENDEES

Julie Beitz, MD, Director, ODE III
Amy G. Egan, MD, MPH, Deputy Director, ODE III
Kendall A. Marcus, MD, Director, DDDP
David Kettl, MD, Clinical Team Leader, DDDP
Gary Chiang, MD, Clinical Reviewer, DDDP
Cynthia LaCivita, PharmD, Director, DRISK
Jamie Wilkins Parker, PharmD, Team Leader, DRISK
Jasminder Kumar, PharmD, RPh, Risk Management Analyst, DRISK
Erin South, PharmD, Risk Management Analyst, DRISK
Anahita Takoli, MA, Senior Risk Management Analyst, DRISK
Shivani Shah, Pharmacy Student, DRISK
Darrell A. Jenkins, MS, Chief, Project Management Staff, OSE
Tri Bui-Nguyen, PhD, Safety Regulatory Project Manager, OSE
CDR Dawn Williams, RN, BSN, USPHS, Safety Regulatory Health Project Manager, DDDP
Strother D. Dixon, Senior Regulatory Health Project Manager, DDDP

SPONSOR ATTENDEES

Binu Alexander, Sr. Director Clinical Operations
Saberri Rana Ali, MD (Ophth.), MPH, Director, Risk Management, Global Pharmacovigilance and Risk Management
Susan Harris, PhD, Project Manager
Robert Israel, MD, Vice President Clinical and Medical Affairs
Karen M. Krstulich Executive Director Regulatory Affairs
Isabelle Lefebvre, Vice President Regulatory Affairs
Peter Motta, MD, Vice President Global Pharmacovigilance and Risk Management

Radhakrishnan (RK) Pillai, PhD, Vice President Dermatology Development
Tage Ramakrishna, MD, Chief Medical Officer, President of Research & Development
Philip Sturno, Vice President Product Development
Sharon Tonetta, PhD, Vice President Regulatory Affairs
Johnson Varughese, Vice President Clinical Operations

1. DISCUSSION

The purpose of the meeting was to discuss the following: product labeling and the proposed REMS. We are continuing to discuss internally what, if any, post marketing requirements will be necessary.

Subsequent to the July 19th Advisory Committee meeting, the Agency conducted internal meetings regarding options for the potential approval of the brodalumab application. These discussions included senior management from the Center for Drug Evaluation and Research (CDER), Office of New Drugs (OND), and Office of Surveillance and Epidemiology (OSE).

During these discussions regarding the risk-benefit assessment of brodalumab, FDA took into consideration the seriousness of the disease (moderate to severe psoriasis), the availability of alternative treatments with comparable efficacy profiles, and the presence of a potentially fatal risk (suicidal ideation and behavior [SIB]) observed in the clinical development program for brodalumab. The Agency has determined that, if this product is to be approved, it will require a REMS with Elements to Assure Safe Use (ETASU) in addition to optimized labeling, to mitigate the risk of suicidality observed with your product.

1.1. Optimized labeling will include:

- 1.1.1. A **Boxed Warning** discussing the potential increased risk of suicidality with brodalumab;
- 1.1.2. A **Limitation of Use** that brodalumab should only be used in patients who have failed to respond, or lost response, to other biologic therapies; and
- 1.1.3. A **recommendation to discontinue therapy**, or reassess the need to continue therapy, in patients who do not achieve an adequate response within 12 weeks.

1.2. The REMS with ETASU will include: Prescriber Certification, Pharmacy Certification, and Documentation of Safe Use conditions. The REMS appended materials should include:

- Siliq REMS Program Healthcare Provider Enrollment Form;
- Siliq REMS Program Patient Wallet Card;
- Siliq REMS Program Patient-Provider Agreement Form; and
- Siliq REMS Program Pharmacy Enrollment Form.

We are summarizing the elements to be included and referencing specific examples from other approved REMS Programs. Although we are providing examples of REMS materials, they are for the purpose of layout and format. Some content may not be applicable to your proposed REMS and should be revised to reflect only the elements and requirements we have discussed today.

- 1.2.1. **Prescriber certification:** Ensures that prescribers are educated on the potential risk of suicidal ideation and behavior (SIB) observed with brodalumab therapy, acknowledge understanding of the risk, and agree to counsel patients about this risk.
- Prescriber Certification should include: A 1- or 2-page document titled **“SILIQ REMS Program Healthcare Provider Enrollment Form”**
 - Refer to the “Addyi REMS Program Prescriber Enrollment Form” for reference:
http://www.accessdata.fda.gov/drugsatfda_docs/rems/Addyi_2016-05-10_Prescriber_Enrollment_Form.pdf
 - At this time, a Prescriber and Pharmacy Training Program (as referenced in the “Addyi REMS Program Prescriber Enrollment Form”) is not necessary.
 - Formatting of the “SILIQ REMS Program Healthcare Provider Enrollment Form” should include:
 - Instructions for stakeholders at the top of the document, as seen in the Lemtrada REMS Prescriber Enrollment Form:
http://www.accessdata.fda.gov/drugsatfda_docs/rems/Lemtrada_2016-04-05_Prescriber_Enrollment_Form.pdf
 - Check boxes next to each attestation in order to ensure each attestation is reviewed
 - For an example of check boxes, see the Entereg REMS Program Hospital Pharmacy Enrollment Form:
http://www.accessdata.fda.gov/drugsatfda_docs/rems/Entereg_2016-06-01_Pharmacy_Enrollment_Form.pdf
 - Healthcare Provider contact information at the end of the form, as seen with the “Addyi REMS Program Prescriber Enrollment Form”:
http://www.accessdata.fda.gov/drugsatfda_docs/rems/Addyi_2016-05-10_Prescriber_Enrollment_Form.pdf

- Healthcare Provider Certification should also include a “Patient Wallet Card”
 - We have reviewed your proposed Patient Wallet Card and request that you include the following elements:
 - Indication
 - Acknowledgement of risk seen with brodalumab therapy (regardless of whether or not patient has history of SIB)
 - Warning signs of suicide
 - Referral to the National Suicide Prevention Lifeline
 - It is the Agency’s preference that this information be included on wallet-size cardstock, similar to:
 - Soliris REMS Patient Safety Card:
http://www.accessdata.fda.gov/drugsatfda_docs/rems/Soliris_2016-07-12_Patient_Safety_Card.pdf;
 - Zinbryta REMS Patient Wallet Card:
http://www.accessdata.fda.gov/drugsatfda_docs/rems/Zinbryta_2016-05-27_Patient_Wallet_Card.pdf; or
 - iPledge REMS Patient ID Card (see p. 82 of the iPledge REMS Educational Kit for Female Patients Who Can Get Pregnant):
http://www.accessdata.fda.gov/drugsatfda_docs/rems/Isotretinoin_2016-07-08_Educational_Kit_For_Female_Patients_Who_Can_Get_Pregnant.pdf
- 1.2.2. **Pharmacy certification:** Ensures that brodalumab prescribers are certified and patients are enrolled in the SILIQ REMS Program.
- Pharmacy certification should include a 1-2 page document titled “**SILIQ REMS Program Pharmacy Enrollment Form**”
 - Refer to the Sabril REMS Program Pharmacy Enrollment Form as an example:
http://www.accessdata.fda.gov/drugsatfda_docs/rems/Sabril_2016-06-27_Pharmacy_Enrollment%20Form.pdf
- 1.2.3. **Documentation of Safe Use Conditions:** Ensures that patients are: counseled by their prescriber on the potential risk of SIB, understand the potential risk associated with brodalumab treatment, and are aware of the need to seek medical attention should they experience an emergence or worsening of suicidal thoughts or behavior.
- Documentation of Safe Use Conditions should include a “**SILIQ REMS Program Patient-Provider Agreement Form**”
 - Refer to the Addyi REMS Program Patient-Provider Agreement Form as an example:

http://www.accessdata.fda.gov/drugsatfda_docs/rems/Addyi_2016-05-10_Patient-Provider_Agreement.pdf

- 1.2.4. **REMS website:** Provides a resource for stakeholders, with the ability to access and print REMS materials.
 - Consider a “SILIQ REMS Program Website” similar to: Sabril’s:
<https://www.sabrilrems.com/>

We cannot begin working on the REMS until we have a substantially complete agreed upon label. Therefore, efforts should be turned to accomplishing that as quickly as possible.

2. ACTION ITEMS

The FDA requested that the applicant provide the following by 12:00 PM on August 25, 2016.

- 2.1. Labeling that includes language for a Boxed Warning, limitation of use, and duration of use.
- 2.2. A proposed timeline for an amended REMS submission, which includes the REMS Document, REMS Appended Materials (Healthcare Provider Enrollment Form, Patient Wallet Card, Patient-Provider Agreement Form, Pharmacy Enrollment Form, REMS Website screenshots), and REMS Supporting Document, all of which should reflect today’s discussion.

The applicant responded that they would respond by the end of the week.

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

/s/

KENDALL A MARCUS
08/24/2016



BLA 761032

DEFICIENCIES PRECLUDE DISCUSSION

Valeant Pharmaceuticals Luxembourg S.a.r.l. (VPL)
c/o Valeant Pharmaceuticals North America LLC
Attention: Karen M. Krstulich
Executive Director Regulatory Affairs
400 Somerset Corporate Blvd.
Bridgewater, NJ 08807

Dear Ms. Krstulich:

Please refer to your Biologics License Application (BLA) dated and received November 16, 2015, submitted under section 351(a) of the Public Health Service Act for brodalumab.

We also refer to our January 21, 2016, letter in which we notified you of our target date of July 20, 2016 for communicating labeling changes and/or postmarketing requirements/commitments in accordance with the "PDUFA Reauthorization Performance Goals And Procedures – Fiscal Years 2013 Through 2017."

As part of our ongoing review of your application, we have identified deficiencies that preclude discussion of labeling and postmarketing requirements/commitments at this time. Specifically, we have identified substantive review issues: a safety signal for suicidal ideation/behavior and an imbalance of major cardiovascular events (MACE) in subjects treated with brodalumab as compared to ustekinumab that require input from the Advisory Committee.

This notification does not reflect a final decision on the information under review.

If you have any questions, call Strother D. Dixon, Senior Regulatory Project Manager, at (301) 796-1015.

Sincerely,

{See appended electronic signature page}

Kendall A. Marcus, MD
Director
Division of Dermatology and Dental Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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

/s/

KENDALL A MARCUS
06/17/2016



BLA761032

MID-CYCLE COMMUNICATION

Valeant Pharmaceuticals Luxembourg S.a.r.l. (VPL)
Attention: Karen M. Krstulich
Executive Director Regulatory Affairs
1301 2nd Avenue
Seattle, WA 98101

Dear Ms. Krstulich:

Please refer to your Biologic License Application (BLA) submitted under section 351(a) of the Public Health Service Act for brodalumab.

We also refer to the teleconference between representatives of your firm and the FDA on April 20, 2016. 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 Strother D. Dixon, Senior Regulatory Project Manager at (301) 796-1015.

Sincerely,

{See appended electronic signature page}

David Kettl, MD
Clinical Team Leader
Division of Dermatology and Dental Products
Office of Drug Evaluation III
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: April 20, 2016; 2:30 PM EST

Application Number: 761032
Product Name: brodalumab
Proposed Indication: For the treatment of moderate to severe plaque psoriasis in adult patients who are candidates for systemic therapy or phototherapy
Applicant Name: Valeant Pharmaceuticals Luxembourg S.a.r.l., (VPL)

Meeting Chair: David Kettl, MD
Meeting Recorder: Strother D. Dixon

FDA ATTENDEES

Julie Beitz, MD, Director, ODE III
Amy G. Egan, MD, MPH, Deputy Director, ODE III
Maria R. Walsh, RN, MS, Associate Director for Regulatory Affairs, ODE III
Wes Ishihara, Regulatory Scientist, ODE III
Kendall A. Marcus, MD, Director, DDDP
David Kettl, MD, Clinical Team Leader, DDDP
Mohamed Alosch, PhD, Biostatistics Team Leader, DB III
Carin Kim, PhD, Biostatistics Reviewer, DB III
Yow-Ming Wang, PhD, Clinical Pharmacology Team Leader, DCP3
Jie Wang, PhD, Clinical Pharmacology Reviewer, DCP 3
Sarah Kennett, PhD, Review Chief, DMA
Jamie Wilkins Parker, PharmD, Risk Management Analyst, Acting Team Leader, DRISK
Jasminder Kumar, PharmD, RPh, Risk Management Analyst, DRISK
J. Paul Phillips, MS, Lead Regulatory Health Project Manager, DDDP
Strother D. Dixon, Senior Regulatory Health Project Manager, DDDP

EASTERN RESEARCH GROUP ATTENDEES

Peggha Khorrami, Independent Assessor, Eastern Research Group

APPLICANT ATTENDEES

Binu Alexander, Sr. Director Clinical Operations
Saber Rana Ali, MD (Ophth.), MPH, Director, Risk Management, Global Pharmacovigilance and Risk Management
Varsha Bhatt, PhD, Director, Dermatology Development
Robert Israel, MD Vice President Clinical and Medical Affairs
Karen Krstulich, Executive Director Regulatory Affairs

Isabelle Lefebvre, Vice President Regulatory Affairs
Ezra Lowe, Director, Clinical Pharmacology
Peter Motta, MD Vice President Global Pharmacovigilance and Risk Management
E. Kwame Obeng, PhD Executive Director – Regulatory CMC, Regulatory Affairs
Radhakrishnan Pillai, PhD Vice President Dermatology Development
Tage Ramakrishna, MD Chief Medical Officer, Head of Research & Development
Philip Sturno, Vice President Product Development
Sharon A. Tonetta, PhD Vice President Regulatory Affairs
Johnson Varughese, Vice President Clinical Operations

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

Product Quality:

Pending information request regarding post-licensure manufacturing sites and ability to avert any potential shortages of brodalumab after product launch.

Non Clinical: None

Clinical:

1. There appears to be a safety signal for your product for suicidal ideation/behavior. This continues to be a review issue.
2. Imbalance of cardiovascular deaths, myocardial infarctions, stroke, and overall major adverse cardiovascular events (MACE) compared to ustekinumab in the development program.

3.0 INFORMATION REQUESTS

Outstanding Information Requests

April 18, 2016 – Clinical

April 14, 2016 – Clinical and Product Quality

April 13, 2016 – Clinical, Clinical Pharmacology and Labeling

4.0 MAJOR SAFETY CONCERNS/RISK MANAGEMENT

At this time, review of the proposed brodalumab risk evaluation and mitigation strategy (REMS) is ongoing. We continue to determine the need for a REMS, and if needed, the specific REMS elements.

5.0 ADVISORY COMMITTEE MEETING

The focus of the Advisory Committee meeting on July 19, 2016 will concentrate on the adverse events observed in the development program, in particular SIB and MACE, and the risk benefit calculus for the application.

The sponsor inquired whether a change in the date of the Advisory Committee could be considered to enhance the availability of outside experts due to vacation conflicts. The Agency responded that they would discuss with the DACCM staff and provide a response within the next few weeks.

6.0 LATE-CYCLE MEETING /OTHER PROJECTED MILESTONES

The proposed date for the Late-Cycle Meeting is June 28, 2016.

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

/s/

DAVID L KETTL
04/26/2016



DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

BLA 761032

**PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE**

AstraZeneca UK Ltd
c/o AstraZeneca Pharmaceuticals LP
One MedImmune Way
Gaithersburg, MD 20878

ATTENTION: Mary Whealy
Senior Director, Regulatory Affairs

Dear Ms. Whealy:

Please refer to your Biologics License Application (BLA) dated and received November 16, 2015, submitted under section 351(a) of the Public Health Service Act for Brodalumab Injection, 210 mg/1.5 ml Pre-filled syringe.

We also refer to your correspondence, dated and received December 23, 2015, requesting review of your proposed proprietary name, Siliq.

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

If any of the proposed product characteristics as stated in your December 23, 2015, submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

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

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

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Janet Anderson, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-0675. For any other information regarding this application, contact Matthew White, Regulatory Project Manager in the Office of New Drugs, at (301) 796-4997.

Sincerely,

{See appended electronic signature page}

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

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

/s/

LOUIS R FLOWERS
03/16/2016

LUBNA A MERCHANT on behalf of TODD D BRIDGES
03/16/2016



BLA 761032

**FILING COMMUNICATION –
NO FILING REVIEW ISSUES IDENTIFIED**

AstraZeneca UK Ltd
c/o AstraZeneca Pharmaceuticals LP
Attention: Mary Whealy
Senior Director Regulatory Affairs
One MedImmune Way
Gaithersburg, MD 20878

Dear Ms. Whealy:

Please refer to your Biologics License Application (BLA) dated and received November 16, 2015, submitted under section 351(a) of the Public Health Service Act for brodalumab injection, 210 mg.

We also refer to your amendments dated December 15, 23 (3), 2015 and January 8, 2016.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 601.2(a), this application is considered filed 60 days after the date we received your application. The review classification for this application is **Standard**. Therefore, the user fee goal date is November 16, 2016. 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>).

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 July 20, 2016. In addition, the planned date for our internal mid-cycle review meeting is April 6, 2016.

We request that you submit the following information by February 4, 2016:

Center for Devices and Radiological Health/Division of Anesthesiology, General Hospital, Infection Control, and Dental Devices

You have provided data for the device constituent review of the 2.25 mL prefilled syringe with staked needle presentation.

1. Provide biocompatibility data for tissue communicating/limited contact for the needle component.
2. Provide biocompatibility data for skin contacting/limited for the glass syringe barrel, plunger rod, needle shield. The information may be available from the device component manufacturer.
3. If you intend to market an auto-injector, submit all relevant information. No information about an auto-injector was submitted with this application.

Division of Risk Evaluation

Your submitted Risk Evaluation and Mitigation Strategy (REMS) only includes a REMS document which refers to the following:

- Medication Guide
- Communication Plan (CP)
- Timetable for Submission of Assessments

You also indicate in your submission “specific elements to be included in the CP will be agreed upon with Agency during review.” However, a complete proposed REMS submission should include a REMS document, all appended materials to be included as part of the REMS (e.g., proposed communication and educational materials), and a REMS supporting document.

Therefore, provide the following, within 10 business days:

1. A complete REMS document, including specific elements in your proposed CP;
2. All appended materials referred to in your REMS document (e.g., proposed communication and education materials and forms, including REMS Letters for Healthcare Providers, REMS Letters for Professional Societies, and REMS Program Website screenshots, etc.); and
3. A REMS Supporting Document.

For further clarification on the format and contents of a proposed REMS, see guidance for industry *Format and Content of Proposed Risk Evaluation and Mitigation Strategies (REMS), REMS Assessments, and Proposed REMS Modifications* as well as a recently approved REMS found on the REMS@FDA website.

PRESCRIBING INFORMATION

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

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

At the end of labeling discussions, use the SRPI checklist to ensure that the PI conforms with format items in regulations and guidances.

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), Medication Guide, and Instructions for Use. Submit consumer-directed, professional-directed, and television advertisement materials separately and send each submission to:

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

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

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

Do not submit launch materials until you have received our proposed revisions to the package insert (PI), Medication Guide, and Instructions for Use, 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 request for a partial waiver of pediatric studies for this application. Once we have reviewed your request, we will notify you if the partial waiver request is denied.

We acknowledge receipt of your request for a partial deferral of pediatric studies for this application. Once we have reviewed your request, we will notify you if the partial deferral request is denied.

If you have any questions, call Matthew White, Senior Regulatory Project Manager, at (301) 796-4997.

Sincerely,

{See appended electronic signature page}

Kendall A. Marcus, MD
Director
Division of Dermatology and Dental Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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

/s/

KENDALL A MARCUS
01/21/2016



IND 104671

MEETING MINUTES

AstraZeneca UK Ltd
Attention: Mary E. Whealy
Global Regulatory Affairs Director, Regulatory Affairs
One MedImmune Way
Gaithersburg, MD 20878

Dear Ms. Whealy:

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

We also refer to the meeting between representatives of your firm and the FDA on October 21, 2015. The purpose of the meeting was to discuss the development plan for brodalumab.

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 Strother Dixon, Senior Regulatory Project Manager at (301) 796-1015.

Sincerely,

{See appended electronic signature page}

Kendall A. Marcus
Director
Division of Dermatology and Dental Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes
Sponsor Attachment



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type: B
Meeting Category: Pre-BLA

Meeting Date and Time: October 21, 2015 at 10:00 am
Meeting Location: FDA White Oak Campus

Application Number: IND 104671
Product Name: brodalumab
Proposed Indication: For the treatment of psoriasis
Sponsor: AstraZeneca UK Ltd

Meeting Chair: Kendall A. Marcus, MD
Meeting Recorder: Strother D. Dixon

FDA ATTENDEES

Julie Beitz, MD, Director, ODE III
Kendall A. Marcus, MD, Director, DDDP
Jill Lindstrom, MD, Deputy Director, DDDP
David Kettl, MD, Clinical Team Leader, DDDP
Gary Chiang, MD, Clinical Reviewer, DDDP
Barbara Hill, PhD, Pharmacology Supervisor, DDDP
Jie Wang, PhD, Clinical Pharmacology Reviewer, DCP 3
Qing Zhou, PhD, Product Quality Team Leader, OBP
Willie Wilson, PhD, Product Quality Reviewer, OBP
Zhihao Peter Qiu, PhD, Branch Chief, DIA
Sarah Kennett, PhD, Review Chief, DMA
Mohamed Alosch, PhD, Biostatistics Team Leader, DB III
Carin Kim, PhD, Biostatistics Reviewer, DB III
John Yap, PhD, Statistical Safety Reviewer, DB VII
Carlos Mena-Grillasca, RPh, Safety Evaluator, DMEPA
Jamie Wilkins Parker, PharmD, Risk Management Analyst, Acting Team Leader, DRISK
Jasminder Kumar, PharmD, Risk Management Analyst, DRISK
LCDR David Shih, MD, MS, FACPM, Deputy Director, DEPI
Andrew D. Mosholder, MD, MPH, Medical Officer, DEPI-I
LCDR Sukhminder K. Sandhu, PhD, MPH, MS, Epidemiology Team Leader, DEPI-I
Gabiella Anic PhD MPH, Epidemiologist, DEPI-I
Roy Blay, PhD, Reviewer, DGCAB
Sally Seymour, MD, Deputy Director for Safety, DPARP

Sarah Yim, MD, Supervisory Associate Director, DPARP
Maria R. Walsh, RN, MS, Associate Director for Regulatory Affairs, ODE III
LCDR Wes Ishihara, Regulatory Scientist, ODE III
Barbara Gould, MBAHCM, Chief, Project Management Staff, DDDP
Strother D. Dixon, Senior Regulatory Health Project Manager, DDDP

EASTERN RESEARCH GROUP ATTENDEES

Peggy Khorrama, Program Analyst

SPONSOR ATTENDEES

AstraZeneca

Joan Buenconsejo, PhD Biometrics Team Leader
Ruth Cordoba-Rodriguez, PhD Director, Regulatory CMC
David Chang, MD, MPH Vice President of Inflammation, Autoimmunity & Neuroscience
Global Medicines Development
Dhaval Desai, MD Director Clinical Development
Mark DeSiato Vice President Global Regulatory Respiratory, Inflammation and Autoimmune
Margaret Melville, MS Senior Director Global Products Global Medicines Development
Robert Miday, MD Senior Patient Safety Physician
Mayur Patel, PharmD Vice President Patient Safety Respiratory, Inflammation and Autoimmune
Mary Whealy Senior Director Regulatory Affairs
Zhengbin (Bing) Yao PhD Senior Vice President

Valeant

Binu Alexander, MD Senior Director Clinical Operations
Karen M. Krstulich Executive Director Regulatory Affairs
Radhakrishnan (RK) Pillai, PhD Vice President Dermatology Development
Peter Motta, MD Vice President Global Pharmacovigilance and Risk Management
Kwame Obeng, PhD Executive Director – Regulatory CMC, Regulatory Affairs
Tage Ramakrishna, MD Chief Medical Officer, Head of Research & Development
Philip Sturno Vice President Product Development
Sharon Tonetta, PhD Vice President Regulatory Affairs
Johnson Varughese Vice President Clinical Operations
Saber Rana Ali, MBBS, MD (Ophth.), MPH, Director, Risk Management, Global
Pharmacovigilance and Risk Management
Robert Israel, MD Vice President Clinical and Medical Affairs

Purpose of the Meeting:

To discuss the development plan for brodalumab

Regulatory Correspondence History

We have had the following meetings with you:

- May 13, 2015 – Safety
- March 25, 2015 – Pre-BLA
- January 21, 2015 – CMC Pre-BLA

- October 27, 2014 – Written Responses
- January 23, 2013 – Guidance
- March 9, 2011 – Guidance

We have sent the following correspondences:

- August 19, 2015 – Information Request
- May 14, 2015 – Proprietary Name Request Conditionally Acceptable
- April 21, 2015 – Advice
- January 15, 2015 – iPSP Written Response/Advice
- September 25, 2014 – iPSP Written Response/Advice
- May 7, 2014 – Advice/Information Request
- April 3, 2014 – Advice/Information Request
- March 17, 2014 – Advice/Information Request
- July 25, 2013 – Advice/Information Request
- July 24, 2013 – Advice/Information Request
- May 21, 2013 – Advice/Information Request
- June 6, 2012 – Advice/Information Request
- November 11, 2011 – Advice/Information Request
- July 12, 2011 – Advice/Information Request
- May 13, 2010 – Advice/Information Request
- April 9, 2010 – Advice/Information Request
- January 13, 2010 – Advice/Information Request
- September 2, 2009 – Advice/Information Request

Introductory Agency Comment:

This pre-BLA meeting is conducted due to a recent change in sponsor for this IND. You are specifically referred to the discipline specific Agency comments and advice from pre-BLA meetings conducted earlier this year:

- May 13, 2015 – Safety
- March 25, 2015 – Pre-BLA
- January 21, 2015 – CMC Pre-BLA

Chemistry, Manufacturing and Controls (CMC)

Question 3.1.1:

Does the FDA agree with the submission of a simple stability update within 30 days of BLA filing?

Response:

Yes, it is acceptable to provide a simple stability update within 30 days of BLA filing. Refer to the Agency's response to Question 1b during the Type B CMC pre-BLA meeting held on January 21, 2015 regarding the data and format that is appropriate for the simple stability update.

Question 3.1.2:

Does the FDA agree that this is sufficient for the BLA filing and review?

Response:

The information provided regarding the brodalumab drug product manufacturing schedule is acceptable.

The proposed brodalumab drug substance manufacturing schedule is not sufficient for BLA filing and review. The information provided in the meeting package indicates that brodalumab drug substance manufacturing activities will not occur during the BLA review period. A pre-licensure inspection should be conducted within the BLA review period while manufacturing activities for the product to be licensed are on-going. This allows for a meaningful evaluation of the GMP compliance, review of process validation data and adherence to commitments made in the BLA. These aspects cannot be fully assessed while another product is being manufactured for the purpose of an initial product licensure. Therefore, we request that you arrange for a rescheduling of the brodalumab drug substance manufacturing activities to coincide with the brodalumab BLA review period. Ideally, FDA would like to inspect after 2-5 months after BLA submission.

Meeting Discussion:

The sponsor provided a clarification of the proposal outlined in the briefing document which is appended to this document. The Agency reiterated that an FDA inspection within 5 months of BLA submission is still recommended. Inspections during manufacturing of related products would not satisfy Agency requirements.

Pharmacology/Toxicology

There were no Pharmacology/Toxicology questions submitted in the briefing package; however, we have the following comments for your consideration.

- Acanthosis, skin infections and histopathological changes of the skin were observed in three and six-month toxicity studies in monkeys exposed to brodalumab. It is recommended that the sponsor submit an explanation of these changes related to the mechanism of action of brodalumab and why these skin changes would not be a cause for concern in psoriasis patients.
- Treatment of psoriasis is a chronic indication; therefore, an evaluation of the carcinogenic potential of brodalumab for the psoriasis indication should be submitted to the IND before BLA submission. Refer to the ICH S6 guideline for possible alternatives for evaluating the carcinogenic potential of brodalumab.

Clinical Pharmacology

There were no Clinical Pharmacology questions submitted in the briefing package.

Clinical/Biostatistics

Question 3.2:

Does the Agency agree with AstraZeneca's proposed approach to address the recommendations made at the meetings of 13 May 2015?

Response:

Your proposal to include a comprehensive assessment of the potential risk of suicidal ideation and behavior (SIB) appears acceptable for review. The application should include a full risk assessment as well as adequate proposals for mitigation based on those known risks.

We have the following recommendations and requests for information to be included in the BLA submission:

- We acknowledge your commitment (on page 7 of your briefing document) to respond to our 6 questions from the May 13, 2015 meeting with Amgen. Regarding question #3 (deaths in brodalumab clinical trials), Amgen's preliminary response listed 29 deaths, including 6 suicides, but did not specify indication or treatment. Your briefing document (on page 11) gives a total of 18 deaths in psoriasis trials, 16 of them on brodalumab. In your submission, please enumerate all deaths in all brodalumab clinical trials, with information on cause of death, treatment received, and indication studied.
- On page 15 of the briefing document, you note that 2 suicides occurred during treatment (before the next scheduled dose), 2 occurred after the subject missed a dose, and 2 occurred beyond 2 missed doses. Given the length of treatment for most subjects, the fact that 4 of the 6 suicides followed missed doses suggests the timing was skewed towards the period after treatment interruption. All brodalumab subjects were discontinued from treatment earlier this year, which affords an opportunity to assess SIB in the period after stopping brodalumab treatment. Please include in the BLA an analysis of SIB after treatment discontinuation. The C-SSRS obtained at each subject's protocol termination visit should provide relevant data.
- In view of the importance of this safety issue, if you submit your analysis plan for the data on SIB, we can provide comments on it prospectively.

The BLA should include specific information on the ongoing trials that were terminated in May, 2015, and provide available information on the disposition and safety outcomes of subjects from those trials.

Question 3.3:

Does the Agency agree with the revised 120-day Safety Update plan?

Response:

Given the significance of the observed safety signals, and the need to plan for an Advisory Committee meeting within the PDUFA V Program timeline, the Agency recommends that your initial BLA submission contain all the relevant safety data for review (this should include all the

safety data in your other development plans). Complete safety data should be available in your comprehensive evaluation of the ISS (Integrated Safety Summary).

Meeting Discussion:

The sponsor provided a clarification of the exposures to be provided in the 120 day safety update, an outline of which is appended to this document. The sponsor anticipates an additional 1300 patient years of experience in the safety update.

The Agency reiterated concerns regarding the timing of the Advisory Committee meeting and allowing adequate time for Agency review.

The sponsor committed to submit the 120 day safety update as early as possible.

Upon further post-meeting discussion, the Agency concludes that the sponsor proposal is acceptable.

Administrative Comments

1. Comments shared today are based upon the contents of the briefing document, which is considered to be an informational aid to facilitate today's discussion. Review of information submitted to the IND or BLA might identify additional comments or information requests.
2. For applications submitted after February 2, 1999, the applicant is required either to certify to the absence of certain financial interests of clinical investigators or disclose those financial interests. For additional information, please refer to 21CFR 54 and 21CFR 314.50(k).
3. You should provide the Agency with SAS transport files in electronic form. The sponsor might refer to the Analysis Data model (ADaM) Examples in Commonly Used Statistical Analysis Methods for guidance:
http://www.cdisc.org/stuff/contentmgr/files/0/5aee16f59e8d6bd2083dbb5c1639f224/misc/adam_examples_final.pdf. The FDA prefers that the sponsor arrange a test submission, prior to actual submission. Please refer to the Submit a Sample eCTD or Standardized Data Sample to the FDA Website (<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm174459.htm>) for guidance on sending a test submission. You may request dataset(s) analysis for CDISC specifications compliance as part of the test submission. For additional information, contact the Electronic Submission Support Team at esub@fda.hhs.gov, or for standardized data submission questions, contact edata@fda.hhs.gov.

DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

As stated in our September 3, 2015 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>.

In addition, we note that chemistry and multidiscipline pre-submission meetings were held on January 21, and March 25, 2015. We refer you to the minutes of that meeting for any additional agreements that may have been reached.

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

For additional guidance on the timing, content, and submission of the PSP, including a PSP Template, please refer to the draft guidance for industry, *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans* at: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/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 [PLLR Requirements for Prescribing Information](#) websites including:

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

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

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).

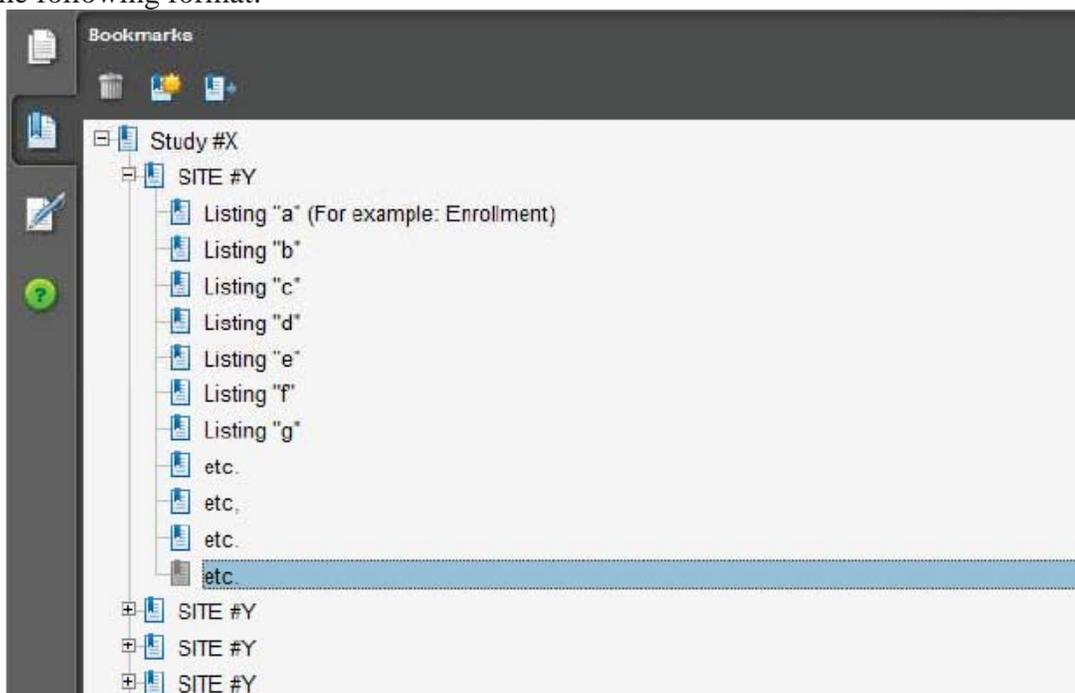
- I. Request for general study related information and comprehensive clinical investigator information (if items are provided elsewhere in submission, describe location or provide link to requested information).**

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.

I. 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

Sponsor Attachment

(b) (4)



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/

KENDALL A MARCUS
10/29/2015



IND 104671

MEETING MINUTES

Amgen Inc.
Attention: Audrey Mancini
Senior Manager, Regulatory Affairs
One Amgen Center Drive
Mail Stop: 17-2-C
Thousand Oaks, CA 91320-1799

Dear Ms. Mancini:

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

We also refer to the meeting between representatives of your firm and the FDA on March 25, 2015. The purpose of the meeting was to discuss the development plan for brodalumab.

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 Strother D. Dixon, Senior Regulatory Project Manager at (301) 796-1015.

Sincerely,

{See appended electronic signature page}

Kendall A. Marcus, MD
Director
Division of Dermatology and Dental Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes
Sponsor Attachment I



**FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH**

MEMORANDUM OF MEETING MINUTES

Meeting Type: Type B
Meeting Category: Pre-BLA

Meeting Date and Time: March 25, 2015, 10: 30 AM
Meeting Location: FDA White Oak, Building 21

Application Number: IND 104671
Product Name: brodalumab
Proposed Indication: For the treatment of psoriasis
Sponsor Name: Amgen, Inc.

Meeting Chair: Kendall A. Marcus, MD
Meeting Recorder: Strother D. Dixon

FDA ATTENDEES

Julie Beitz, MD, Director, ODE III
Amy G. Egan, MD, MPH, Deputy Director, ODE III
Kendall A. Marcus, MD, Director, DDDP
David Kettl, MD, Acting Deputy Director, DDDP
Tatiana Oussova, MD, MPH, Deputy Director for Safety, DDDP
Denise Cook, MD, Acting Clinical Team Leader, DDDP
Gary Chiang, MD, Clinical Reviewer, DDDP
Mohamed Alosch, PhD, Biostatistics Team Leader, DB III
Carin Kim, PhD, Biostatistics Reviewer, DB III
Yow-Ming Wang, PhD, Clinical Pharmacology Team Leader, DCP3
Jie Wang, PhD, Clinical Pharmacology Reviewer, DCP 3
Lisa Lin, Senior Regulatory Analyst, OBI
Jamie Wilkins Parker, PharmD, Risk Management Analyst, Acting Team Leader, DRISK
Gabriella Anic PhD MPH, Epidemiologist, DEPI I
Barbara Gould, MBAHCM, Chief, Project Management Staff, DDDP
Strother D. Dixon, Senior Regulatory Health Project Manager, DDDP

EASTERN RESEARCH GROUP ATTENDEES

Patrick Zhou, Independent Assessor

SPONSOR ATTENDEES

Gary Aras, PhD, Director, Biostatistics
Osa Eisele, MD, MPH, Medical Director, Global Safety

Christopher Endres, PhD, Principal Scientist, Clinical Pharmacology Modeling and Simulation

David J Harrison, PhD, Director, Global Health Economics

Paul Klekotka, MD, PhD, Medical Director, Global Development

Kathy Kross, MSc, Executive Director, Regulatory Affairs

Joanne Li, PhD, Senior Manager, Biostatistics

Ellen Lin, MS, Senior Manager, Global Statistical Programming

Audrey Mancini, BS, Senior Manager, Regulatory Affairs

Emmanuelle Magueur, PharmD, MSc, Director, Regulatory Affairs

Ajay Nirula, MD, PhD, Executive Medical Director, Global Development

John Sullivan, MD, Executive Medical Director, Global Safety

Mark Taisey, BS, Vice President, Global Regulatory

Sarah Tannehill-Gregg, DVM, PhD, Pathologist Director, Comparative Biology and Safety Sciences

Amy Xia, PhD, Executive Director, Biostatistics

Dhaval Desai, MD, Director, Clinical Development, AstraZeneca

Margaret Melville, MS, Senior Director, AstraZeneca

Purpose of the Meeting:

To discuss the development plan for brodalumab

Regulatory Correspondence History

We have had the following meetings with you:

- January 21, 2015 – CMC Pre-BLA
- October 27, 2014 – Written Responses
- January 23, 2013 – Guidance
- March 9, 2011 – Guidance

We have sent the following correspondences:

- January 15, 2015 – iPSP Written Response/Advice
- September 25, 2014 – iPSP Written Response/Advice
- May 7, 2014 – Advice/Information Request
- April 3, 2014 – Advice/Information Request
- March 17, 2014 – Advice/Information Request
- July 25, 2013 – Advice/Information Request
- July 24, 2013 – Advice/Information Request
- May 21, 2013 – Advice/Information Request
- June 6, 2012 – Advice/Information Request
- November 11, 2011 – Advice/Information Request
- July 12, 2011 – Advice/Information Request
- May 13, 2010 – Advice/Information Request
- April 9, 2010 – Advice/Information Request
- January 13, 2010 – Advice/Information Request
- September 2, 2009 – Advice/Information Request

Regulatory

Question 1:

Does the FDA agree with the proposed format and content of the eCTD table of contents for the BLA?

Response:

From a technical standpoint (not content related) yes, the proposed format for the planned BLA is acceptable. However, please see additional comments below:

- Until eCTD v2.3. is implemented, proprietary information should be placed in m1.2 section, with a clear leaf title
- For archival purposes, sponsor should submit a pdf file of any labeling document submitted in word. Also, leaf title of word documents should include "word", so reviewers could quickly identify the word version of the document.
- Form 1572s should be filed under the study tagging file (STF) of the specific study in m5 (not m1) and file tagged as "**list-description-investigator-site**".
- The tabular listing in module 5.2 and synopsis of individual studies in m2.7.6 should be provided in tabular format and linked to the referenced studies in m5.
- Study Tagging Files (STF) are required for submissions to the FDA when providing study information in modules 4 and 5 with the exception of module 4.3 Literature References, 5.2 Tabular Listing, 5.4 Literature References and 5.3.6 if the Periodic Report is a single PDF document. Each study should have an STF and all components regarding that study should be tagged and placed under the study's STF including case report forms (crfs). Case Report Forms need to be referenced under the appropriate study's STF, to which they belong, organized by site as per the specifications and tagged as "case report form". Please refer to The eCTD Backbone File Specification for Study Tagging Files 2.6.1 (PDF - 149KB) (6/3/2008).
<http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM163560.pdf>

Chemistry, Manufacturing and Controls (CMC)

There were no CMC questions submitted in the briefing package. A separate meeting to discuss CMC, manufacturing, and product quality microbiology issues was held on January 21, 2015.

Pharmacology/Toxicology

Question 5:

Does the Agency agree that the nonclinical studies constitute a complete package that supports the registration of brodalumab?

Response:

We agree that the conducted nonclinical studies support a BLA submission for brodalumab. The adequacy of the submitted nonclinical information will be determined during the BLA review.

Clinical Pharmacology

Question 11:

Does the Agency agree that the biopharmaceutics and clinical pharmacology studies constitute a complete package that supports the registration of brodalumab and its dosage forms?

Response:

Yes, based on the information provided in the briefing package, the biopharmaceutics and clinical pharmacology studies would constitute an adequate package for our review to determine whether or not the data would support the registration of brodalumab and its dosage forms.

We have the following Clinical Pharmacology comments regarding your BLA submission.

1. We acknowledge that you have planned to conduct population PK and exposure-response PK/PD analysis based on the pooled data from Phase 1, Phase 2 and Phase 3 trials to support your BLA submission. We have the following general recommendations regarding your population PK and exposure-response PK/PD analyses and datasets submission:
 - Submit NONMEM control streams of the base and final model for the population PK analysis.
 - Submit model codes or control streams and output listings for all major model building steps, e.g., base structural model, covariates models, final model, and validation model. These files should be submitted as ASCII text files with *.txt extension (e.g.: myfile_ctl.txt, myfile_out.txt).
 - Submit a model development decision tree and/or table which gives an overview of modeling steps.
 - In addition to the dose-exposure-response analysis for efficacy, conduct dose-exposure-response analysis for safety (e.g., adverse events of interests such as infections). The dose-exposure-response analyses for both efficacy and safety would help the selection of the dosing regimen that has the most favorable benefit-risk.
2. We acknowledge that you plan to include your analysis of the impact of immunogenicity by subjects' anti-drug antibodies (ADA) status on efficacy and safety in the Integrated Summary of Efficacy and Integrated Summary of Safety, respectively. Your briefing package did not provide detailed information regarding the evaluation of the impact of immunogenicity on PK of brodalumab. We have the following general recommendations regarding the assessment of the immunogenicity impact on PK:
 - For the evaluation of the ADA impact on PK, we recommend that you include between-subject comparison (i.e., between ADA positive subjects and ADA negative subjects) as well as within-subject comparison (i.e., before ADA positive and after ADA positive) of PK data.

- We encourage you to include subjects ADA status as a covariate in the population PK analysis on an exploratory basis to evaluate the impact of ADA on brodalumab PK. In the population PK analysis, further explore the necessity of treating the subject ADA status as a time-varying variable for ADA positive subjects.
- For the ADA positive subjects observed in Phase 3 trials, provide a summary table of study number, study subject ID, serum brodalumab concentrations at each PK time-point, sample ADA status at each immunogenicity assessment time-point, and the primary efficacy outcome.

Clinical/Biostatistics

Question 2:

Does the information outlined in the proposed PSI table of contents provide the relevant evidence needed for the Agency's evaluation of the PSI?

Response:

Yes, the proposed PSI table of contents is acceptable.

Question 3:

Is the organization shown in the table of contents a presentation that will assist the Agency in their review of the developmental history and measurement properties of the PSI? Are there any documents that are important for evaluation of the PSI dossier that are not currently included in the proposed appendices?

Response:

Yes, your PSI dossier proposal appears complete and sufficient for our review.

Question 4:

Does the Agency agree with Amgen's proposal for submission of the Financial Disclosure information?

Response:

In addition to the Financial Disclosure information you're providing, the Agency would recommend that you describe the number of investigators who are sponsor employees (including full time and part time), number of investigators with disclosable financial interest/arrangements (FDA 3455), if there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2 (a), (b), (c), and (f)), and provide details of the disclosable financial interests/arrangements. The sponsor is referred to guidance for industry *Financial Disclosure by Clinical Investigators*.

Question 6:

Does the Agency agree to the proposed principal concepts of the ISS and ISE packages detailed in the Integrated Statistical Analysis Plans (iSAPs), the Supplemental Statistical Analysis Plan (SSAP) for clinical meaningfulness of complete clearance of psoriasis, and the SSAP for impact of weight on efficacy and safety?

Response:

You submitted a supplement for your original SAP (SSAP) for ISE, and plan to carry out formal statistical testing; however, the SSAP specified that you do not plan to adjust for multiplicity. You stated that the primary goals of these integrated analyses are to allow for assessment of study results across the three Phase 3 studies and to enable analyses of interest for which individual studies are not powered. You also stated two additional goals of providing evidence for the clinical meaningfulness of achieving complete clearance of psoriasis (PASI 100) to support its relevance as a clinical endpoint, and evaluating the effect of body weight on the optimal dose.

It should be noted that the objective of the ISE is to support analyses findings of those obtained from the individual trials and not to establish a new efficacy claim based on pooling data from the individual trials for which you stated that they were not sufficiently powered for. Establishing an efficacy claim would be based on efficacy data from individual Phase 3 trials along with a replication of study findings. Refer to the guidance for industry *Integrated Summary of Effectiveness* (<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm079803.pdf>), the “integrated data analyses” refers to synthesizing the results of individual studies in an appropriate manner to collectively provide support for the claimed effectiveness of the study drug. Thus, in addition to pooled results, the ISE should include comprehensive in-depth analysis of the total efficacy results, and should discuss the extent to which the results of the relevant studies reinforce or do not reinforce each other. This may require additional discussion beyond individual study summaries and a pooled analysis. For additional information on the content of the ISE refer to guidance for industry *Integrated Summary of Effectiveness*.

Your proposed ISS analysis plan is acceptable. Refer to response to question 8.

Question 7:

Does the Agency agree that the proposed analyses in the SSAP for clinical meaningfulness of complete clearance of psoriasis will provide evidence to support the hypothesis that achieving complete skin clearance is clinically meaningful compared with a response without clearance?

Response:

The utility of your proposed integrated analyses of sPGA 0 vs. sPGA 1, PASI 100 vs. PASI 75 and <100, and alternatively, of composite clearance (defined as PASI 100 and sPGA 0) if concordance between sPGA 0 and PASI 100 is less than 90%, would depend on whether there is utility in making the clinical distinction between sPGA 0 and sPGA 1 or PASI 100 and PASI 75 and <100. The clinical meaningfulness of a measure needs to be based on clinical judgement, and not based on analyses of pooled data. Note that while the sPGA 0 or PASI 100 may be well defined, taking into account the continuous scale underlying the sPGA scale, the analyses of sPGA 0 vs. sPGA 1 would depend on the width of the sPGA 1 category (i.e., how widely sPGA 1 is defined) based on the underlying continuous scale.

Question 8:

In addition to the subgroups defined in the ISS and ISE, does the Agency require analyses of any other subgroups?

Response:

The Agency recommends the addition of analysis for depression/suicide ideation/suicide attempt/completed suicide in Specials subgroups analysis for all arms of your clinical trials in the ISS. This should include comparative rates in the general population, the psoriasis population, and relevant discussions on the observed rates in your clinical trials and whether the mechanism of action of your drug product predisposes the targeted population to higher rates of events. At this stage, there are no additional subgroup analyses required by the Agency for the ISE.

Question 9:

Does the Agency agree with Amgen's plan to provide the Columbia Classification Algorithm of Suicide Assessment (C-CASA) report in Module 5.3.5.3?

Response:

Yes.

Question 10:

Does the Agency agree with Amgen's proposal for the studies' planned analyses and proposed data cut-off dates for inclusion in the 120-day safety update?

Response:

Yes.

Question 12:

Does the Agency agree that the designs, statistical analyses, and results of the phase 3 Studies 20120102, 2012103, and 20120104 provide an adequate basis to support a BLA submission of brodalumab for the treatment of moderate to severe plaque psoriasis?

Response:

Yes.

Question 13:

Based on the proposed body of evidence that is indicative of PASI 100 clinical meaningfulness, will the Agency, upon review of the data submitted in the BLA, consider including this endpoint in the package insert?

Response:

Any primary or secondary endpoints appropriate for labeling will be determined during the review of the BLA. See above discussion for questions 6 and 7.

Question 14:

Does the Agency agree that the data from the ISE and the weight-based analyses are adequate to evaluate the proposed dosing recommendation of brodalumab 210 mg SC at weeks 0, 1, and 2, followed by 210 mg Q2W?

Response:

Your approach to evaluate the impact of body weight on the efficacy and safety of brodalumab in the integrated data from the Phase 3 studies by bodyweight subgroups appears to be reasonable.

We have the following recommendations for the body weight-based subgroup analysis of efficacy and safety:

- For efficacy analysis, you have planned to evaluate the PASI 75 response rate, PASI 100 response rate, and percent PASI improvement from baseline at Week 12. We recommend that you include sPGA success as an additional efficacy endpoint for the efficacy analysis.
- For safety analysis, you have planned to evaluate the incidence of treatment-emergent adverse events through Week 12. We recommend that you include infections as additional safety endpoints for the safety analysis.
- In addition to the 12-week induction phase efficacy/safety data, we recommend that you conduct similar bodyweight subgroup analyses for efficacy at Week 52 and safety through Week 52.

You may conduct analyses as you intend to evaluate the effect of body weight on the optimal dose. The utility of these analyses which are based on aggregate data would be a review issue. However, we do not anticipate that an efficacy claim can be established based on such analyses. See response to Question 6.

Question 15:

Does the Agency consider the size of the overall safety database and the duration of exposure at the time of the BLA submission sufficient to support approval of brodalumab for the proposed indication of treatment of moderate to severe plaque psoriasis?

Response:

The safety data base presented in your clinical program for brodalumab in the proposed treatment of moderate to severe plaque psoriasis appears sufficient for review.

Question 16:

Does the Agency concur with Amgen's approach to the proposed risk minimization and post-marketing safety strategy?

Response:

The Agency considers that depression and suicide ideation/suicide is a major safety concern identified in your development program. This safety signal will be a focused review issue for the brodalumab application. It is not clear that labeling will be sufficient to mitigate this risk, and additional risk mitigation strategies may be necessary to ensure that the benefits of the drug outweigh the risks of the drug. Additional discussion with the Agency is recommended to discuss this safety signal and risk mitigation prior to BLA submission.

Question 17:

The list of analysis data model (ADaM) data sets that will be included in the BLA data package is described in Section 4 of the Data Standardization Plan (DSP). Is this list acceptable to the Agency?

Response:

Your proposed list of ADaM datasets appears reasonable at this stage.

Question 18:

The list of studies for which SAS datasets and associated metadata will be included in the BLA is provided in Section 5 of the DSP. Is this list acceptable to the Agency?

Response:

Per your SN 272 Appendix 1 DSP, you mention a linear approach was employed in generating ADaM datasets from SDTM datasets from “raw” study data. While the content of your DSP is acceptable, also submit your raw study data in the appropriate folders, as per the latest Study Data Technical Conformance Guide, to allow the review team to verify traceability back to CRFs. The other datasets and metadata referenced is acceptable.

Question 19:

In the integrated ISS ADaM analysis dataset for adverse events (ADAE), Amgen will re-map adverse events from all studies to the most current Medical Dictionary for Regulatory Activities (MedDRA) version (including both character-coded terms and numeric codes, as well as secondary system organ class [SOC]), while also retaining the original coded terms in the older MedDRA version that was current at the time of study analysis. Is this acceptable to the Agency?

Response:

Your approach seems acceptable. In your define.xml, indicate which columns represent the original coded terms in the older MedDRA versions, to allow traceability from ISS to individual study datasets.

Question 20:

To support the ISE and ISS, Amgen will provide the integrated ADaM datasets as presented in [Section 7.1](#). Is this acceptable to the Agency?

Response:

Your approach seems acceptable for the ISE and ISS.

Question 21:

For the 3 phase 3 psoriasis studies (20120102, 20120103, and 20120104), Amgen collects investigator input in addition to the laboratory test results, when needed, to define CTCAE toxicity grades for uric acid (between increasing grade 1 and 3) and potassium (between decreasing grade 1 and 2). If the needed investigator input is missing due to data issues, the toxicity grade for the lab value is set to missing within the Study Data Tabulation Model (SDTM) laboratory (LB) domain and defaults to the higher grade (increasing grade 3 for uric acid or decreasing grade 2 for potassium) within the ADaM analysis dataset for laboratory tests (ADLB) dataset. This toxicity grade imputation is explained in the ADaM define.xml and flagged in the ADLB dataset. Analyses are done based on ADLB instead of LB. Is this setup acceptable to the Agency?

Response:

The setup you proposed for the laboratory data is acceptable.

Question 22:

Is the Basic Data Structure (BDS) that supports the key efficacy endpoints presented in the mock submission and clarified in Section 4 of the DSP acceptable to the Agency?

Does the Agency have any additional comments on the data structure that supports the key efficacy endpoints?

Response:

There are no additional comments on the data structure for the efficacy endpoints at this time.

Question 23:

Based on the mock submission, does the Agency have any further comments or suggestions concerning the data structures and metadata from the perspective of data reviewability and accessibility by the clinical and statistical reviewers of the planned BLA?

Response:

If the datasets exceed 1GB, you plan to split the datasets based on the Agency's study data specification guidance (FDA, 2012), and use numeric suffix starting from 01. Should you need to "split" any of the large datasets (i.e., 1GB and larger), it would be helpful to have the split datasets smaller in size (e.g. two 500 MB data are preferable than having a 900 MB and a 100 MB file).

Question 24:

Amgen proposes training, provided by a team of Amgen statisticians and programmers, consisting of a high-level overview of key dataset structures of the brodalumab BLA filing approximately 1 month after the submission for FDA reviewers who may need to access these datasets. Does the Agency agree with the proposal by Amgen and the timing or providing this training to FDA reviewers?

Response:

To enable navigation through your datasets, provide a written "Reviewer's Guide" document that includes sufficient details for definitions or descriptions of each variable, algorithms for derived variables (including source variables used), as well as all statistical programs for analyses.

Question 25:

Amgen plans to prospectively provide the bioresearch monitoring (BIMO) clinical site summary data set for the 3 phase 3 psoriasis studies (20120102, 20120103, 20120104) and to follow the specifications outlined in the FDA document "Specifications for Preparing and Submitting Summary Level Clinical Site Data for CDER's Inspection Planning", version 1.2 (FDA). In addition, Amgen plans to provide the site-specific individual subject data listings for the selected sites after FDA determines which site(s) will be selected for inspection. Is this acceptable to the Agency?

Response:

Yes. Submission of a summary level clinical site dataset as outlined in the FDA document “Specifications for Preparing and Submitting Summary Level Clinical Site Data for CDER’s Inspection Planning”, version 1.2 (FDA) is acceptable and it helps to facilitate the use of a risk-based approach for the timely identification of clinical investigator sites for on-site clinical inspection. Submit the site-specific individual subject data listings for all Phase 3 psoriasis studies (20120102, 20120103, 20120104) because they are essential both to plan and conduct clinical inspections efficiently.

Question 26:

Does the Agency agree with the proposed plan to provide electronic case report forms (eCRFs) from phase 2 and phase 3 psoriasis studies for all subjects who died on study or discontinued investigational product due to an adverse event?

Response:

Your proposal for eCRF submission is acceptable.

Question 27:

Is Amgen’s proposal for the submission of individual subject narratives (Section 7.3) acceptable to the Agency?

Response:

Yes.

Question 28:

Are there any other points the Agency feels are important to convey to Amgen with regard to the planned BLA?

Response:

We anticipate a separate discussion related to adverse events of depression and suicide which have been identified as the major safety concerns for your development program.

Question 29:

Based on the data presented, does the FDA intend to convene an Advisory Committee Meeting?

Response:

Yes.

Meeting Discussion:

The sponsor provided a slide set with clarifications and discussion points in advance of the meeting. These slides are appended to these meeting minutes.

The Agency noted that there were significant concerns regarding the suicide/suicide ideation and depression adverse events identified to date in the development program. This issue and whether

the risks can be mitigated will be the focus of discussion at a separate meeting with the sponsor on May 13, 2015.

There was general discussion regarding the content and format of the application. The Agency was in general agreement with the majority of the sponsor feedback contained in the sponsor submitted slides.

The Agency noted that for questions 6 and 7, justification for clinical meaningfulness should include context for the inclusion in labeling for additional PASI response endpoints.

Administrative Comments

1. Comments shared today are based upon the contents of the briefing document, which is considered to be an informational aid to facilitate today's discussion. Review of information submitted to the IND or BLA might identify additional comments or information requests.
2. For applications submitted after February 2, 1999, the applicant is required either to certify to the absence of certain financial interests of clinical investigators or disclose those financial interests. For additional information, please refer to 21CFR 54 and 21CFR 314.50(k).
3. You should provide the Agency with SAS transport files in electronic form. The sponsor might refer to the Analysis Data model (ADaM) Examples in Commonly Used Statistical Analysis Methods for guidance:
http://www.cdisc.org/stuff/contentmgr/files/0/5aee16f59e8d6bd2083dbb5c1639f224/misc/adam_examples_final.pdf. The FDA prefers that the sponsor arrange a test submission, prior to actual submission. Please refer to the Submit a Sample eCTD or Standardized Data Sample to the FDA Website (<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm174459.htm>) for guidance on sending a test submission. You may request dataset(s) analysis for CDISC specifications compliance as part of the test submission. For additional information, contact the Electronic Submission Support Team at esub@fda.hhs.gov, or for standardized data submission questions, contact edata@fda.hhs.gov.

DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

As stated in our February 11, 2015 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>.

In addition, we note that a chemistry pre-submission meeting was held on January 21, 2015. We refer you to the minutes of that meeting for any additional agreements that may have been reached.

PREA REQUIREMENTS

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

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

For additional guidance on the timing, content, and submission of the PSP, including a PSP Template, please refer to the draft guidance for industry, *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans* at: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/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](#). As you develop your proposed PI, we encourage you to review the labeling review resources on the [PLR Requirements for Prescribing Information](#) website including:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products
- Regulations and related guidance documents
- A sample tool illustrating the format for Highlights and Contents, and
- The Selected Requirements for Prescribing Information (SRPI) – a checklist of 42 important format items from labeling regulations and guidances.

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).

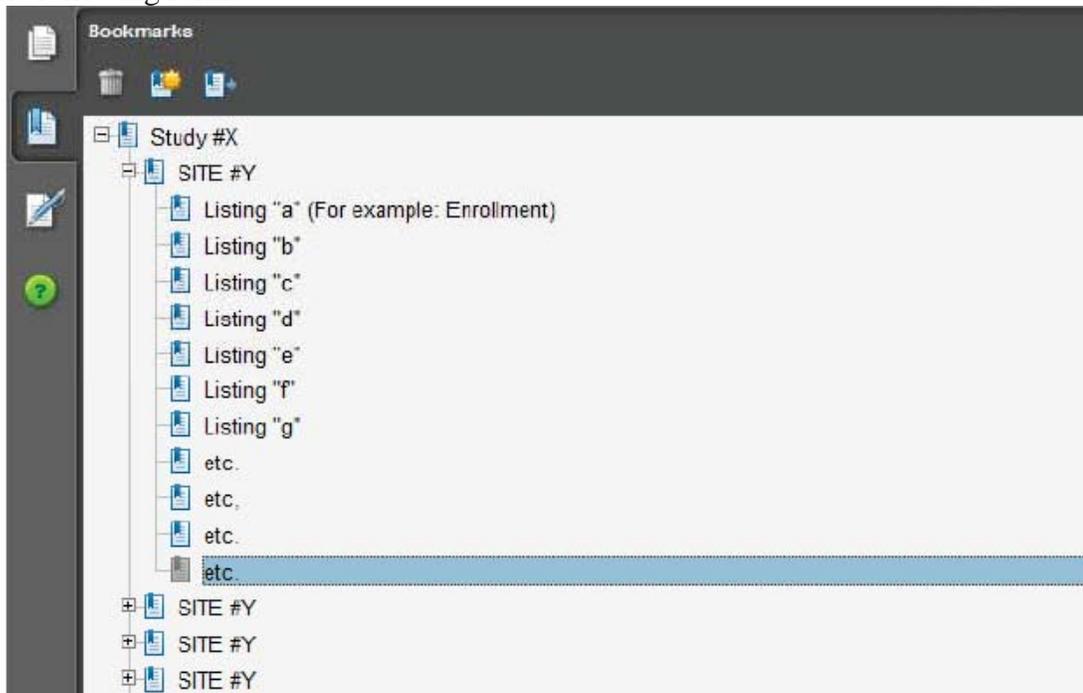
1. Please include the following information in a tabular format in the original NDA for each of the completed pivotal clinical trials:
 - a. Site number
 - b. Principal investigator

- 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.

1. 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

5 Page 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/

KENDALL A MARCUS
03/30/2015



IND 104671

MEETING MINUTES

Amgen, Inc.
Attention: Audrey Mancini
Senior Manager, Regulatory Affairs
One Amgen Center Drive
Mail Stop: 17-2-C
Thousand Oaks, CA 91320-1799

Dear Ms. Mancini:

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

We also refer to the meeting between representatives of your firm and the FDA on January 21, 2015. The purpose of the meeting was to discuss the development plan for brodalumab.

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 Strother D. Dixon, Regulatory Project Manager at (301) 796-1015.

Sincerely,

{See appended electronic signature page}

David Kettl, MD
Clinical Team Leader
Division of Dermatology and Dental Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes
Sponsor Attachment 1



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type: Type B
Meeting Category: CMC Pre-BLA

Meeting Date and Time: January 21, 2015, 8:30 AM
Meeting Location: FDA White Oak, Building 51

Application Number: IND 104671
Product Name: brodalumab
Proposed Indication: For the treatment of psoriasis
Sponsor Name: Amgen, Inc.

Meeting Chair: David Kettl, MD
Meeting Recorder: Strother D. Dixon

FDA ATTENDEES

David Kettl, MD, Clinical Team Leader, DDDP
Gary Chiang, MD, MPH, Clinical Reviewer, DDDP
Jie Wang, PhD, Clinical Pharmacology Reviewer, DCP 3
Sarah Kennett, PhD, Review Chief, DMA
Milos Dokmanovic, PhD, RAC, Product Quality Reviewer, DBRR I
Linan Ha, PhD, Team Leader, DBRR I
Patricia Hughes, PhD, Team Leader, OC/OMPQ/DGMPA/BMAB
Lana Shiu, MD, Captain, USPHS, Senior Medical Advisor, CDER/ODE/GHDB
Kendra Worthy, PharmD, Team Leader, DMEPA
Strother D. Dixon, Regulatory Health Project Manager, DDDP

SPONSOR ATTENDEES

Mike Abernathy, MS, RAC, Director, Regulatory Affairs, CMC
Katherine Chaloupka, ME, Senior Scientist, Process Development
Alice Cho, PhD, Senior Engineer, Device Technologies
Lori de los Reyes, MSN, JD, Senior Manager, Regulatory Affairs, Devices
Corinne Kikegawa, Product Quality Leader
Emmanuelle Magueur, PharmD, MSc, Director, Regulatory Affairs
Karen Manz, Global Operations Leader
Eric Meinke, Scientist, Analytical Sciences
Nolan Polson, PhD, Director, Product Quality
Lynn Quaranto, Senior Manager, Regulatory Affairs, CMC
Jesse Sullivan, PhD, Senior Scientist, Drug Product Process Engineering

Cathy Tamura, MS, Principal Engineer, Device Technologies
Audrey Mancini, Senior Manager, Regulatory Affairs

Purpose of the Meeting:

To discuss the development plan for brodalumab

Regulatory Correspondence History

We have had the following meetings with you:

- October 27, 2014 – Written Responses
- January 23, 2013 – Guidance
- March 9, 2011 – Guidance

We have sent the following correspondences:

- May 7, 2014 – Advice/Information Request
- April 3, 2014 – Advice/Information Request
- March 17, 2014 – Advice/Information Request
- July 25, 2013 – Advice/Information Request
- July 24, 2013 – Advice/Information Request
- May 21, 2013 – Advice/Information Request
- June 6, 2012 – Advice/Information Request
- November 11, 2011 – Advice/Information Request
- July 12, 2011 – Advice/Information Request
- May 13, 2010 – Advice/Information Request
- April 9, 2010 – Advice/Information Request
- January 13, 2010 – Advice/Information Request
- September 2, 2009 – Advice/Information Request

Meeting Discussion

The sponsor submitted slides with preliminary comments regarding the draft meeting communication which were referenced during the meeting, and are appended to the end of this document.

Chemistry, Manufacturing and Controls (CMC)

Question 1:

The drug product stability program includes primary, commercial (production) and supporting stability data as outlined in Table 2 and Table 3.

At the time of BLA filing, the following data is intended to be available:

- 48 months of primary stability data for the 0.5 mL, 0.75 mL, and 1.0 mL PFS presentations
- 12 months of primary stability data for the 1.5 mL PFS presentation

- 9 to 12 months of supporting stability data for the AI/pen with 0.75 mL PFS subassembly
- 12 months of accelerated aging data on the autoinjector components
- 3 months of commercial (production) stability data for the intended PFS and AI/pen with PFS subassembly commercial presentations

Additionally, analytical comparability of the 1.5 mL PFS to the 1.0 mL PFS with the same formulation and a similar stability profile was demonstrated and submitted to the Agency on 22 August 2014 (IND (b)(4)). Refer to Section 5.1 for additional details regarding the stability program.

Table 2. Pre-filled Syringe Drug Product Stability Program

Drug Substance Manufacturing Site	Drug product Fill Site	Stability Program	Fill Volume x Number of Lots	Latest Stability Timepoint Tested (in Months) ^a
(b)(4)	(b)(4)	Primary	0.5 mL x 3	48
		Primary	0.75 mL x 3	48
		Primary	1.0 mL x 3	48
		Primary	1.5 mL x 3	9 (1 lot at (b)(4))
		Primary		12 (2 lots at (b)(4))
		Commercial	0.75 mL x 3	3
		Commercial	1.0 mL x 3	3
		Commercial	1.5 mL x 3	3

a – Months of data planned for inclusion in original BLA

b – These manufacturing sites were inadvertently reversed in the meeting request

Table 3. Auto-Injector/Pen Drug Product Stability Program

Drug Substance Manufacturing Site	Drug product Fill Site	Stability Program	Fill Volume x Number of Lots	Latest Stability Timepoint Tested (in Months) ^a
(b)(4)	(b)(4)	Supporting	0.75 mL x 1	9 to 12
		Commercial	0.75 mL x 3	3
		Commercial	1.0 mL x 3	3

a – Months of data planned for inclusion in original BLA

Question 1a:

Based on 48 months of primary stability data for the 0.5 mL, 0.75 mL, and 1.0 mL PFS and 12 months of primary stability data for the 1.5 mL PFS, and comparability of the 1.5 mL PFS to the 1.0 mL PFS, Amgen is requesting a (b)(4) month expiry in the BLA for all commercial PFS presentations.

Does the Agency agree with the proposed (b)(4) month expiry for all PFS presentations based on the intended data for submission in the original BLA?

Response:

We note that you have not provided any information regarding the commercial product or its manufacturing process. Information to demonstrate that the clinical lots placed on primary stability protocol are fully representative of the commercial material will be required to support the proposed (b) (4) month expiry for all presentations. The information required should include, but not limited to, the following:

- a. Data to support the comparability between your clinical material manufactured at (b) (4) and the commercial material derived from (b) (4)
- b. Information to demonstrate that the clinical batches placed on primary stability protocol are formulated in the same formulation and packaged in the same container closure system as those proposed for your commercial material;
- c. Information to demonstrate that the manufacturing process used for primary clinical batches is representative of that used in the commercial process.

In addition, we note that a different container closure system is used for brodalumab drug product 1.5 mL presentation (2.25 mL syringe vs. 1 mL syringe for the 0.75 and 1.0 mL presentations). We also note that only 9-12 months primary stability data are available for the clinical 1.5 mL PFS presentation. Therefore, in addition to the information listed above, data to justify the use of stability data obtained from product lots stored in smaller containers (1mL syringe) for the determination of the shelf life of product lots stored in a larger container (2.25 mL syringe) should be provided. The adequacy of the justification will be a review issue.

Question 1b:

In the event that 48 months of primary stability data for the PFS presentations are not available for the initial BLA submission, does the Agency agree that updated 48 month stability data can be provided during the first 30 days of the review period without an extension of the review clock per PDUFA V guidelines?

Response:

Yes, it is acceptable to provide simple stability update during the first 30 days of the review period without an extension of the review clock. Simple stability updates refer to stability data and analyses performed under the same conditions, and for the same drug product batches in the same container closure system(s) as described in your stability protocol provided in the original submission. In addition, simple stability updates should use the same tabular presentation as in the original submission as well as the same mathematical or statistical analysis methods (if any) and should not contain any matrix or bracketing approaches which deviate from the stability protocol in the original BLA.

Question 1c:

In addition to the 3 months of commercial stability data and 9 to 12 months of supporting stability data for the AI/Pen with PFS subassembly, Amgen will have accelerated aging data to support a (b) (4) month expiry for the AI/Pen components to be included in the BLA at the time of submission. Stability data will continue to be available during the review period to support shelf-life extension.

Does the Agency agree with the proposed (b) (4) month expiry for the AI/Pen with PFS subassembly based on the accelerated aging data on the device components intended for submission in the original BLA?

Response:

Final determinations regarding expiry dating will be determined during the application review.

If Amgen is referring to pure device components accelerated aging (w/o biologic/drug filled into the device), then CDRH/ODE can consider this to be a device review issue. If this is indeed the case, CDRH/ODE can review the (b) (4) month accelerated aging test data for the device constituents at the time of the BLA submission.

Question 1d:

In the event that accelerated aging data on the device components to support a (b) (4) month expiry for the AI/Pen components becomes available during the first 30 days of the review period, does the Agency agree that this data could be provided, without an extension of the review clock per PDUFA V guidelines?

Response:

Yes, provided this update follows the pattern of a simple stability update as described in the response for Question 1b.

Question 2:

Amgen plans to verify and validate the sharps injury prevention feature of the auto-injector/pen in accordance with applicable sections of *ISO-23908, Sharps Injury protection – Requirements and test methods – Sharps protection features for single-use hypodermic needles, introducers for catheters and needles used for blood sampling.*

Please refer to Section 5.2 for additional details regarding Amgen’s planned approach for compliance with Sharp Injury prevention testing.

Does the agency agree with Amgen’s planned approach for compliance with Sharps Injury prevention testing?

Response:

If FDA Sharps Guidance for sharps injury prevention features requirements as outlined in *Section 5, Device Design, the testing required in Section 8, Bench Testing* as well as *Section 10, Simulated Clinical Use Testing* can all be justifiably met through compliance with ISO 23908 then it is acceptable to proceed. We recommend that the Sponsor should perform the sharp injury prevention feature testing as a separate test. It should be done prior to the human factors validation testing for the combination product to ensure that the feature itself is functional, has met all of the performance specifications, and there are no additional changes.

Meeting Discussion:

The sponsor inquired as to whether the sharps injury prevention testing could be conducted in parallel with human factors testing. They noted that the same sharps injury prevention features had been used for other products previously submitted to the Agency. The Agency concurred

that this would be acceptable provided that the sharps injury prevention feature is unchanged, and then the previous testing protocol/data of that feature can be leveraged if accompanied by an adequate supporting rationale and justification in the BLA submission.

Question 3:

Module 3 content of the BLA will be provided electronically in accordance with ICH M4Q, *Common Technical Document for the Registration of Pharmaceuticals for Human Use: Quality*. Module 3 will include a single drug substance section (3.2.S) for brodalumab. To facilitate clarity and enhance post-approval management, a separate drug product section (3.2.P) will be included for each commercial drug product presentation as appropriate. Information pertaining to the delivery device as it relates specifically to the combination product will be incorporated throughout each respective 3.2.P section. This information will include details of the delivery device as it relates to the design, manufacturing, risk management, verification/validation, post-approval complaint and adverse event reporting. Please refer to Section 5.3 and Section 9 for additional details regarding the content and format of Module 3 and the Device Reviewer's Guide.

Question 3a:

Does the Agency agree that the proposed Module 3 structure, content and format will facilitate a joint review by both CDER and CDRH?

Response:

Your proposed Module 3 structure and format appear to be adequate. The adequacy of Module 3 content will be determined after the application is submitted to the Agency. In addition, due to the multiple presentations associated with the brodalumab drug product, we recommend that you specify whether the information is related to all drug product presentations or specific to a particular presentation in each section.

We recommend the following when including and referencing device information in m3:

- a. You may reference files under 3.2.P.7 which are not currently listed as numerical items in ICH and FDA specifications and guidance.
- b. In 3.2.P.7 you could include a leaf titled something similar to the following, "Table of Contents for Drug-Device Autoinjector. This leaf/document, could provide reference links to the other files in module 3.2.P.7.
- c. The leaf titles of each device document should be clear, concise and indicative of the document's content.
- d. Do not use "node extensions" to create new elements in 3.2.p.7. Although this is described in the eCTD specification, and may be acceptable in some regions, it is not acceptable in submissions to FDA.

Additional Product Quality Microbiology Comments

All facilities should be registered with FDA at the time of the BLA submission and ready for inspection in accordance with 21 CFR 600.21 and 601.20(b)(2). The facility should be in operation and manufacturing the product during the inspection. A preliminary manufacturing

schedule for the drug substance and drug product should be provided in the Module 1 of the BLA to facilitate the planning of the pre-license inspections during the review cycle. Please include in the BLA submission a complete list of the manufacturing and testing sites with their corresponding FEI numbers.

The CMC Drug Substance section of the BLA (Section 3.2.S) should contain information and data summaries for microbial and endotoxin control. The provided information should include, but not be limited to the following:

- Bioburden and endotoxin levels at critical manufacturing steps should be monitored using qualified bioburden and endotoxin tests. The pre-established bioburden and endotoxin limits should be provided (3.2.S.2.4).
- Three successful consecutive product intermediate hold time validation runs at manufacturing scale. Bioburden and endotoxin levels before and after the maximum allowed hold time should be monitored and bioburden and endotoxin limits provided (3.2.S.2.5).
- Information and summary results data demonstrating microbial control (b) (4) (3.2.S.2.5).
- Bioburden and endotoxin data obtained during manufacture of at least three conformance lots (3.2.S.2.5).
- Information and summary results from the shipping validation studies for the drug substance (3.2.S.2.5).
- Drug substance bioburden and endotoxin release specifications (3.2.S.4). Please note that DS specification for bioburden is (b) (4)
- Summary report and results from bioburden and endotoxin test methods qualification performed for the drug substance (3.2.S.4).
- If the formulation contains polysorbate, the effect of hold time on endotoxin recovery should be assessed by spiking a known amount of endotoxin into undiluted drug substance and then testing for recoverable endotoxin over time. The studies should be conducted using containers of similar composition as those used for drug substance during hold. Effects of sampling containers on endotoxin recovery should also be evaluated (3.4.S.4).

The CMC Drug Product section of the BLA (Section 3.2.P) should contain validation data summaries to support the (b) (4) sterility assurance. For guidance on the type of data and information that should be submitted, refer to the 1994 “FDA Guidance for Industry, Submission Documentation for Sterilization Process Validation in Applications for Human and Veterinary Drug Products” at <http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm072171.pdf>

The following study protocols and validation data summaries should be included in Section 3.2.P.3.5:

- (b) (4) retention study (b) (4).
- Sterilization and depyrogenation of equipment and components that contact the sterile drug product. Provide summary data for the three most recent requalification studies and describe the equipment requalification program.
- In-process microbial controls and hold times. Three successful consecutive product intermediate hold time validation runs at manufacturing scale. Bioburden and endotoxin levels before and after the maximum allowed hold time should be monitored and bioburden and endotoxin limits provided.
- Pre-sterile filtration bioburden limits should be monitored and should be less than 10 CFU/100 mL.
- Isolator decontamination, if applicable.
- Three successful consecutive media fill runs, including summary environmental monitoring data obtained during the runs.
- A description of the routine environmental monitoring program.
- Shipping validation studies, including container closure integrity data for the pre-filled syringe and the PFS assembled with autoinjector device. Additionally for PFS, the difference in air pressures during air shipment may cause movement of the plunger which may breach the sterility of PFS. Include results to demonstrate that the PFS plunger movement during air transportation does not impact product sterility.

The following method validation information should be provided:

- Container closure integrity testing (3.2.P.2.5). System integrity (including maintenance of the microbial barrier) should be demonstrated initially and during stability. Container closure integrity methods validation should demonstrate that the assay is sensitive enough to detect breaches that could allow microbial ingress. We recommend that container closure integrity testing be performed in lieu of sterility testing for stability samples at the initial time point and every 12 months (annually) until expiry (3.2.P.8.2). BLA should also include provide information demonstrating that container closure integrity of the PFS is not breached during the assembly of the autoinjector device.
- Summary report and results for qualification of the bioburden, sterility and endotoxin test methods performed for in-process intermediates (if applicable) and the drug product, as appropriate.
- Summary report and results of the Rabbit Pyrogen Test conducted on three batches of drug product in accordance with 21 CFR 610.13(b).
- Formulations with certain excipient and polysorbate combinations have been reported to interfere with endotoxin recoverability in the USP LAL test methods over time. The effect of hold time on endotoxin recovery should be assessed by spiking a known amount of endotoxin into undiluted in-process samples (if applicable) and the drug product and

then testing for recoverable endotoxin over time. These studies should be conducted in the containers in which the product and samples are held prior to endotoxin testing.

Meeting Discussion:

There was discussion related to requirements for facility information and background required for facility inspections. Equipment qualifications, environmental monitoring, utility qualification/validation should be described at a high level in general terms in the application to facilitate facility inspections, as per regulations.

Question 3b:

Does the Agency agree that the proposed Device Reviewer's Guide structure, content and format will facilitate a joint review by both CDER and CDRH?

Response:

The Device Reviewer Guide appears to be acceptable.

For Device study reports, link the files into the Study Tagging File (STF) for each study. Leaf titles for this data should be named "DEVICE [study ID] [brief description of file being submitted]." In addition, a standalone "DEVICE" STF should be constructed and placed in Section 5.3.5.4 (Other Study reports and related information). The study ID for this STF should be "DEVICE." Files should be linked into this DEVICE STF using valid STF file tags from the FDA's "Comprehensive Table of Contents Headings and Hierarchy" technical specification, located at:

<http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM315023.pdf>

Question 3c:

Does the Agency agree that the proposed content of the CMC/device information, as outlined in the briefing document, is comprehensive and considered a complete application as underscored by PDUFA V?

Response:

The fileability and completeness of your BLA application will be determined after the application is submitted to the Agency. It is premature to make a determination based on the limited information provided in the current meeting package.

Clinical Comment

We recommend that your proposed prescribing information conform to the FDA published *Content and Format of Labeling for Human Prescription Drug and Biological Products; Requirements for Pregnancy and Lactation Labeling*, referred to as the "Pregnancy and Lactation Labeling Rule (PLLR or final rule).

Administrative Comments

1. Comments shared today are based upon the contents of the briefing document, which is considered to be an informational aid to facilitate today's discussion. Review of information submitted to the IND or BLA might identify additional comments or information requests.
2. For applications submitted after February 2, 1999, the applicant is required either to certify to the absence of certain financial interests of clinical investigators or disclose those financial interests. For additional information, please refer to 21CFR 54 and 21CFR 314.50(k).
3. We remind you of the Pediatric Research Equity Act of 2007 which requires all applications for a new active ingredient, new dosage form, new indication, new route of administration, or new dosing regimen to contain an assessment of the safety and effectiveness of the drug for the claimed indications in all relevant pediatric subpopulations unless this requirement is waived or deferred.
4. Please request a submission tracking number (STN) assignment prior to the submission of your BLA.
5. You should provide the Agency with SAS transport files in electronic form. The sponsor might refer to the Analysis Data model (ADaM) Examples in Commonly Used Statistical Analysis Methods for guidance:
http://www.cdisc.org/stuff/contentmgr/files/0/5aee16f59e8d6bd2083dbb5c1639f224/misc/adam_examples_final.pdf. The FDA prefers that the sponsor arrange a test submission, prior to actual submission. Please refer to the Submit a Sample eCTD or Standardized Data Sample to the FDA Website (<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm174459.htm>) for guidance on sending a test submission. You may request dataset(s) analysis for CDISC specifications compliance as part of the test submission. For additional information, contact the Electronic Submission Support Team at esub@fda.hhs.gov, or for standardized data submission questions, contact edata@fda.hhs.gov.

DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

As stated in our November 21, 2014 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 REQUIREMENTS

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

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

For additional guidance on the timing, content, and submission of the PSP, including a PSP Template, please refer to the draft guidance for industry, *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans* at: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/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](#). As you develop your proposed PI, we encourage you to review the labeling review resources on the [PLR Requirements for Prescribing Information](#) website including:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products
- Regulations and related guidance documents
- A sample tool illustrating the format for Highlights and Contents, and
- The Selected Requirements for Prescribing Information (SRPI) – a checklist of 42 important format items from labeling regulations and guidances.

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

7 Page 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/

DAVID L KETTL
01/26/2015

LATE-CYCLE COMMUNICATION
DOCUMENTS



BLA 761032

LATE-CYCLE MEETING MINUTES

Valeant Pharmaceuticals Luxembourg S.a.r.l. (VPL)
c/o Valeant Pharmaceuticals North America LLC
Attention: Karen M. Krstulich
Executive Director Regulatory Affairs
400 Somerset Corporate Blvd.
Bridgewater, NJ 08807

Dear Ms. Krstulich,

Please refer to your Biologic License Application (BLA) submitted under section 351 of the Public Health Service Act for brodalumab.

We also refer to the Late-Cycle Meeting (LCM) between representatives of your firm and the FDA on June 28, 2016.

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 Strother D. Dixon, Senior Regulatory Project Manager at (301) 796-1015.

Sincerely,

{See appended electronic signature page}

David Kettl, MD
Clinical Team Leader
Division of Dermatology and Dental Products
Office of Drug Evaluation III
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: June 28, 2016; 9:00 AM EST
Meeting Location: Teleconference

Application Number: BLA 761032
Product Name: brodalumab
Applicant Name: Valeant Pharmaceuticals Luxembourg S.a.r.l.

Meeting Chair: David Kettl, MD
Meeting Recorder: Strother D. Dixon

FDA ATTENDEES

Julie Beitz, MD, Director, ODE III
Amy G. Egan, MD, MPH, Deputy Director, ODE III
Kendall A. Marcus, MD, Director, DDDP
David Kettl, MD, Clinical Team Leader, DDDP
Gary Chiang, MD, Clinical Reviewer, DDDP
Claudia Manzo, PharmD, Director, Office of Medication Error Prevention and Risk Management
Jasminder Kumar, PharmD, RPh, Risk Management Analyst, DRISK
Strother D. Dixon, Senior Regulatory Health Project Manager, DDDP

EASTERN RESEARCH GROUP ATTENDEES

Peggh Khorrami, Independent Assessor

APPLICANT ATTENDEES

Binu Alexander, Sr. Director Clinical Operations
Robert Israel, MD Vice President Clinical and Medical Affairs
Karen M. Krstulich Executive Director Regulatory Affairs
Isabelle Lefebvre, Vice President Regulatory Affairs
John Metzger, Sr Manager, Regulatory CMC
Peter Motta, MD Vice President Global Pharmacovigilance and Risk Management
Radhakrishnan (RK) Pillai, PhD Vice President Dermatology Development
Tage Ramakrishna, MD Chief Medical Officer, President of Research & Development
Philip Sturno, Vice President Product Development
Sharon A. Tonetta, PhD Vice President Regulatory Affairs
Johnson Varughese, Vice President Clinical Operations

AstraZeneca:

Joan Buenconsejo, PhD Biometrics Team Leader
David Chang, MD, MPH Vice President of Inflammation, Autoimmunity & Neuroscience
Global Medicines Development

Dhaval Desai, MD Director Clinical Development
Margaret Melville, MS Senior Director Global Products Global Medicines Development
Robert Miday, MD Senior Patient Safety Physician

1.0 BACKGROUND

BLA 761032 was submitted on November 16, 2015 for brodalumab.

Proposed indication(s): For the treatment of moderate to severe plaque psoriasis in adult patients who are candidates for systemic therapy or phototherapy

PDUFA goal date: November 16, 2016

FDA issued a Background Package in preparation for this meeting on June 20, 2016.

2.0 DISCUSSION

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, Advisory Committee (AC) meeting plans (if scheduled), 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 or the AC meeting, if an AC is planned, 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 issues have been identified to date:
Clinical:

- a. There appears to be a safety signal for your product for suicidal ideation/behavior. This continues to be a review issue, and we anticipate it will be the primary focus of the upcoming Advisory Committee meeting on July 19, 2016.
- b. Imbalance of cardiovascular deaths, myocardial infarctions, stroke, and overall major adverse cardiovascular events (MACE) compared to ustekinumab in the development program.

ADVISORY COMMITTEE MEETING

Date of AC meeting: July 19, 2016

Date AC briefing package to be sent under separate cover by the Division of Advisory Committee and Consultant Management: June 28, 2016 for a June 29, 2016 delivery

Potential questions and discussion topics for AC Meeting are as follows:

The focus of the Advisory Committee meeting on July 19, 2016 will concentrate on the adverse events observed in the development program, in particular SIB and MACE, and the risk benefit calculus for the application.

We look forward to discussing our plans for the presentations of the data and issues for the upcoming AC meeting. Final questions for the Advisory Committee are expected to be posted two days prior to the meeting at this location:

<http://www.fda.gov/AdvisoryCommittees/Calendar/default.htm>

REMS OR OTHER RISK MANAGEMENT ACTIONS

At this time, review of the proposed brodalumab risk evaluation and mitigation strategy (REMS) is ongoing. We continue to assess the need for a REMS, and if needed, the specific REMS elements. Discussion of risk mitigation for the observed adverse events from the brodalumab development program, including a presentation of REMS options, is anticipated to be included in the Advisory Committee agenda for discussion by the panel.

LCM AGENDA

1. Introductory Comments

Welcome, Introductions, Ground rules, Objectives of the meeting

2. Discussion of Substantive Review Issues

Each issue will be introduced by FDA and followed by a discussion.

- a. There appears to be a safety signal for your product for suicidal ideation/behavior. This continues to be a review issue, and we anticipate it will be the primary focus of the upcoming Advisory Committee meeting on July 19, 2016.

- b. Imbalance of cardiovascular deaths, myocardial infarctions, stroke, and overall major adverse cardiovascular events (MACE) compared to ustekinumab in the development program.

3. Discussion of Upcoming Advisory Committee Meeting

4. REMS or Other Risk Management Actions

At this time, review of the proposed brodalumab risk evaluation and mitigation strategy (REMS) is ongoing. Based on the benefit-risk evaluation under consideration by the division, DRISK will complete a full evaluation of the need for a REMS for brodalumab, and if necessary, the specific REMS elements, after receiving input from the Advisory Committee regarding the efficacy and safety of brodalumab.

5. Postmarketing Requirements/Postmarketing Commitments

It has not yet been determined whether specific postmarketing requirements or postmarketing commitments will be necessary, and will be discussed at the Advisory Committee.

6. Major labeling issues

Description of the adverse event outcomes observed in the clinical trials, including the need for a Boxed Warning

Also refer to the Deficiencies Preclude Discussion letter sent on June 17, 2016.

7. Review Plans

At this time, the Agency anticipates that an action will be taken by the goal date of November 16, 2016.

8. Wrap-up and Action Items

The Agency will follow up with any additional informational needs with the Applicant following the Advisory Committee discussion.

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

/s/

DAVID L KETTL
07/08/2016