

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

761061Orig1s000

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION ¹		
BLA # 761061	BLA Supplement # N/A	If NDA, Efficacy Supplement Type: N/A <i>(an action package is not required for SE8 or SE9 supplements)</i>
Proprietary Name: TREMFYA Established/Proper Name: Guselkumab Dosage Form: Injection		Applicant: Janssen Biotech, Inc. Agent for Applicant (if applicable): N/A
RPM: Matthew White		Division: DDDP
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><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><input type="checkbox"/> No changes <input type="checkbox"/> New patent/exclusivity <i>(notify CDER OND IO)</i> Date of check:</p> <p><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>July 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 _____		N/A
❖ 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 (<i>approvals only</i>)	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
❖ Public communications (<i>approvals only</i>)	
<ul style="list-style-type: none"> Office of Executive Programs (OEP) liaison has been notified of action 	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
<ul style="list-style-type: none"> Indicate what types (if any) of information were issued 	<input type="checkbox"/> None <input type="checkbox"/> FDA Press Release <input type="checkbox"/> FDA Talk Paper <input type="checkbox"/> CDER Q&As <input checked="" type="checkbox"/> Other: tweet, DDI listserv announcement
❖ Exclusivity	
<ul style="list-style-type: none"> 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)	
<ul style="list-style-type: none"> Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought. 	N/A
CONTENTS OF ACTION PACKAGE	
Officer/Employee List	
❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list (<i>approvals only</i>)	<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	Approval: 7/13/2017
Labeling	
❖ Package Insert	
• Most recent draft labeling	<input checked="" type="checkbox"/> Included
• Original applicant-proposed labeling	<input checked="" type="checkbox"/> Included
❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling	<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	<input checked="" type="checkbox"/> Included
• Original applicant-proposed labeling	<input checked="" type="checkbox"/> Included
❖ Labels (full color carton and immediate-container labels)	
• Most-recent draft labeling	<input checked="" type="checkbox"/> Included
❖ Proprietary Name	Letters 4/26/17: Proprietary name granted 2/9/17: Proprietary name denied Reviews 4/19/17: Proprietary name review 4/6/17: Proprietary name review 2/8/17: Proprietary name review
• 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: 12/2/16 DMEPA: 5/15/17 DMPP/PLT (DRISK): 4/21/17 OPDP: 4/21/17 SEALD: <input checked="" type="checkbox"/> None CSS: <input checked="" type="checkbox"/> None Product Quality: 5/31/17 Other: <input checked="" type="checkbox"/> None
Administrative / Regulatory Documents	
❖ RPM Filing Review ⁴ /Memo of Filing Meeting All NDA 505(b)(2) Actions: Date each action cleared by 505(b)(2) Clearance Committee	01/12/17 <input checked="" type="checkbox"/> Not a (b)(2)
❖ NDAs/NDA supplements only: Exclusivity Summary	N/A
❖ 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 If yes, OC clearance for approval 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> Not an AP action
❖ Pediatrics (<i>approvals only</i>) <ul style="list-style-type: none"> Date reviewed by PeRC <u>3/15/17</u> If PeRC review not necessary, explain: <u>N/A</u> 	
❖ Breakthrough Therapy Designation	N/A
<ul style="list-style-type: none"> Breakthrough Therapy Designation Letter(s) (granted, denied, an/or rescinded) 	N/A
<ul style="list-style-type: none"> CDER Medical Policy Council Breakthrough Therapy Designation Determination Review Template(s) 	N/A
<ul style="list-style-type: none"> CDER Medical Policy Council Brief – Evaluating a Breakthrough Therapy Designation for Rescission Template(s) 	N/A
❖ 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.)	1/13/17: Filing Communication 5/3/17: Late-Cycle Meeting Background Package
❖ 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)	N/A
❖ Minutes of Meetings	
<ul style="list-style-type: none"> If not the first review cycle, any end-of-review meeting 	<input checked="" type="checkbox"/> N/A
<ul style="list-style-type: none"> Pre-NDA/BLA meeting 	4/6/16
<ul style="list-style-type: none"> EOP2 meeting 	4/9/2014
<ul style="list-style-type: none"> Mid-cycle Communication 	3/8/17
<ul style="list-style-type: none"> Late-cycle Meeting 	5/16/17
<ul style="list-style-type: none"> Other milestone meetings (e.g., EOP2a, CMC focused milestone meetings) 	10/19/16: Guidance 1/27/16: Guidance 6/26/13: Guidance 11/16/11: Guidance
❖ Advisory Committee Meeting(s)	<input checked="" type="checkbox"/> No AC meeting
<ul style="list-style-type: none"> Date(s) of Meeting(s) 	N/A
Decisional and Summary Memos	
❖ Office Director Decisional Memo/Multi-disciplinary review	7/13/17
Division Director Summary Review	See Multi-disciplinary review
Cross-Discipline Team Leader Review	6/19/17 – Review completion memo - see multi-disciplinary review for full review
PMR/PMC Development Templates	6 templates - 6/23/17
Clinical	
❖ Clinical Reviews	
<ul style="list-style-type: none"> Clinical Team Leader Review(s) 	See Multi-disciplinary review
<ul style="list-style-type: none"> Clinical review(s) 	6/19/17 – Review completion memo - see unireview for full

	review
<ul style="list-style-type: none"> Social scientist review(s) (if OTC drug) (<i>indicate date for each review</i>) 	<input checked="" type="checkbox"/> None
<ul style="list-style-type: 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 	See Multi-disciplinary review
<ul style="list-style-type: none"> ❖ Clinical reviews from immunology and other clinical areas/divisions/Centers⁵ 	Cardiology: 4/17/17 COA: 4/8/17 DPMH: 4/12/17 QT-IRT: 2/10/17 DPP: 4/10/17
<ul style="list-style-type: none"> ❖ Controlled Substance Staff review(s) and Scheduling Recommendation 	<input checked="" type="checkbox"/> N/A
<ul style="list-style-type: none"> ❖ Risk Management <ul style="list-style-type: none"> REMS Documents and REMS Supporting Document REMS Memo(s) and letter(s) Risk management review(s) and recommendations (including those by OSE and CSS) 	4/14/17: Aria Sufficiency memo 6/28/17: Risk management review
<ul style="list-style-type: none"> ❖ OSI Clinical Inspection Review Summary(ies) 	6/1/17: Clinical inspection summary 6/5/17: Letter - Bhutani
Clinical Microbiology <input checked="" type="checkbox"/> None	
<ul style="list-style-type: none"> ❖ Clinical Microbiology Team Leader Review(s) 	<input type="checkbox"/> No separate review
<ul style="list-style-type: none"> Clinical Microbiology Review(s) 	<input type="checkbox"/> None
Biostatistics <input type="checkbox"/> None	
<ul style="list-style-type: none"> ❖ Statistical Division Director Review(s) 	<input checked="" type="checkbox"/> No separate review
<ul style="list-style-type: none"> Statistical Team Leader Review(s) 	<input checked="" type="checkbox"/> No separate review
<ul style="list-style-type: none"> Statistical Review(s) 	7/14/17 – Review completion memo - see multi-disciplinary review for full review
Clinical Pharmacology <input type="checkbox"/> None	
<ul style="list-style-type: none"> ❖ Clinical Pharmacology Division Director Review(s) 	<input checked="" type="checkbox"/> No separate review
<ul style="list-style-type: none"> Clinical Pharmacology Team Leader Review(s) 	<input checked="" type="checkbox"/> No separate review
<ul style="list-style-type: none"> Clinical Pharmacology review(s) 	4/17/17: Review completion memo - see multi-disciplinary for full review
<ul style="list-style-type: none"> ❖ OSI Clinical Pharmacology Inspection Review Summary 	<input checked="" type="checkbox"/> None requested

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

Nonclinical <input type="checkbox"/> None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s)	<input checked="" type="checkbox"/> No separate review
• Supervisory Review(s)	<input checked="" type="checkbox"/> No separate review
• Pharm/tox review(s), including referenced IND reviews	4/11/17: Review completion memo - see unireview for full review
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer	<input checked="" type="checkbox"/> None
❖ Statistical review(s) of carcinogenicity studies	<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	<input checked="" type="checkbox"/> None requested
Product Quality <input type="checkbox"/> None	
❖ Product Quality Discipline Reviews ⁶	
• Tertiary review	<input checked="" type="checkbox"/> None
• Secondary review (e.g., Branch Chief)	<input checked="" type="checkbox"/> None
• Integrated Quality Assessment (contains the Executive Summary and the primary reviews from each product quality review discipline)	Executive Summary: 4/15/17 DS/DP: 4/14/17 OPQ Micro – DP: 5/5/17 OPQ Micro – DS: 5/1/17 Facilities: 3/14/17
❖ Reviews by other disciplines/divisions/Centers requested by product quality review team	CDRH-GHDB: 3/22/17
❖ Environmental Assessment (check one) (original and supplemental applications)	
<input checked="" type="checkbox"/> Categorical Exclusion	4/14/17
<input type="checkbox"/> Review & FONSI	N/A
<input type="checkbox"/> Review & Environmental Impact Statement	N/A
❖ 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) (only original applications and efficacy supplements that require a manufacturing facility inspection(e.g., new strength, manufacturing process, or manufacturing site change)	<input checked="" type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation <input type="checkbox"/> Not applicable

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

Day of Approval Activities	
❖ For all 505(b)(2) applications: <ul style="list-style-type: none"> • Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity) 	N/A
<ul style="list-style-type: none"> • Finalize 505(b)(2) assessment 	N/A
❖ For Breakthrough Therapy (BT) Designated drugs: <ul style="list-style-type: none"> • Notify the CDER BT Program Manager 	N/A
❖ 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 	N/A
❖ 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	NA - BLA
❖ Send approval email within one business day to CDER-APPROVALS	<input checked="" type="checkbox"/> Done
❖ Take Action Package (if in paper) down to Document Room for scanning within two business days	

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/s/

MATTHEW E WHITE
07/17/2017



BLA 761061

**PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE**

Janssen Biotech, Inc.
920, Route 202 South
Raritan, NJ 08869

ATTENTION: Manomi Tennakoon, PhD
Associate Director, Global Regulatory Affairs, Immunology

Dear Dr. Tennakoon:

Please refer to your Biologics License Application (BLA) dated and received November 16, 2016, submitted under section 351(a) of the Public Health Service Act for Guselkumab, 100 mg/mL.

We also refer to your correspondence, dated and received April 7, 2017, requesting review of your proposed proprietary name, Tremfya.

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

If any of the proposed product characteristics as stated in your April 7, 2017, submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review. Additionally, if your application receives a complete response, a new request for name review for your proposed name should be submitted when you respond to the application deficiencies.

If you require information on submitting requests for proprietary name review or BsUFA 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>)
- Biosimilar Biological Product Authorization Performance Goals and Procedures Fiscal Years 2013 through 2017,
(<http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/TherapeuticBiologicApplications/Biosimilars/UCM281991.pdf>)

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Tri Bui Nguyen, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (240) 402-3726. For any other information regarding this application, contact Mathew E. 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

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/s/

DANIELLE M HARRIS on behalf of TODD D BRIDGES
04/26/2017



BLA 761061

MID-CYCLE COMMUNICATION

Janssen Biotech, Inc.
Attention: Manomi Tennakoon, PhD
Associate Director, Global Regulatory Affairs, Immunology
920, Route 202 South
Raritan, NJ 08869

Dear Dr. Tennakoon:

Please refer to your Biologic License Application (BLA) submitted under section 351(a) of the Public Health Service Act for guselkumab injection, 100 mg/mL.

We also refer to the teleconference between representatives of your firm and the FDA on March 8, 2017. 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 Matthew White, Senior Regulatory Project Manager at (301) 796-4997.

Sincerely,

{See appended electronic signature page}

Gordana Diglisic, 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: March 8, 2017 at 10:00 a.m.

Application Number: BLA 761061

Product Name: Guselkumab injection, 100 mg/mL

Indication: The treatment of adult patients with moderate-to-severe plaque psoriasis who are candidates for systemic therapy or phototherapy

Applicant Name: Janssen Biotech, Inc.

Meeting Chair: Gordana Diglisic, MD

Meeting Recorder: Matthew White

FDA ATTENDEES

Julie Beitz, MD, Director, Office of Drug Evaluation III (ODE III)
Kendall A. Marcus, MD, Acting Deputy Director, ODE III
Jill Lindstrom, MD, FAAD, Acting Director, Division of Dermatology and Dental Products (DDDP)
Gordana Diglisic, MD, Clinical Team Leader, DDDP
Melinda McCord, MD, Clinical Reviewer, DDDP
Kevin Clark, MD, Clinical Reviewer, DDDP
Laura Zendel, PharmD, BCPS, Risk Management Analyst, Division of Risk Management
Carlos Mena-Grillasca, RPh, Safety Evaluator, Division of Medication Error Prevention & Analysis
Tri Bui-Nguyen, PhD, Safety Regulatory Project Manager, Office of Surveillance and Epidemiology, OSE
Matthew White, Senior Regulatory Project Manager, DDDP

APPLICANT ATTENDEES

Herren Edra, RAC, Manager, North America Regulatory Affairs
Shu Li, PhD, Director, Quantitative Sciences
Heidi Needleman, PhD, Senior Director, Compound Development Team Leader
Liza O'Dowd, MD, Vice President, Global Regulatory Affairs
Susan Popma, OD, Director, Global Regulatory Leader
Bruce Randazzo, MD, PhD, Senior Director, Clinical Development
Philippe Szapary, MD, MSCE, Vice President, Clinical Development
Manomi Tennakoon, PhD, Associate Director, Global Regulatory Affairs, Immunology
Steven Wan, PhD, Director, Global Regulatory Affairs, CMC
Yasmine Wasfi, MD, PhD, Senior Director, Clinical Development
Newman Yeilding, MD, Head Immunology Development

Michael Song, MD, Director, Clinical Development
Yaung-Kaung Shen, PhD, Senior Manager, Clinical Biostatistics
John Krayner, MS, Associate Scientific Director, Biologics Toxicology
Steve Fakharzadeh, MD, PhD, Senior Director, Global Medical Affairs Leader
Lisa Tarantino, Associate Director, Regulatory Project Management
Jonathan Uy, MD, Dermatology Strategic Lead, US Medical Affairs
Honghui Zhou, PhD, Senior Director and Janssen Fellow, Global Clinical Pharmacology
Immunology Group Leader
Mark Teeters, PhD, Associate Director, API Large Molecule
Jeannie Rojas, PhD, Director, CMC Team Leader
Michael Henry, Associate Director, CMC Analytical Development Scientific Integrator

1.0 INTRODUCTION

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

2.0 SIGNIFICANT ISSUES

- No significant review issues have been identified to date.

3.0 INFORMATION REQUESTS

- Information request sent February 21, 2017
- Information requests sent March 1 and 3, 2017

Meeting Discussion:

The Agency acknowledged receipt of the response to the information request sent February 21, 2017 and stated that additional information requests may be forthcoming.

4.0 MAJOR SAFETY CONCERNS/RISK MANAGEMENT

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

5.0 ADVISORY COMMITTEE MEETING

There are no plans at this time for an Advisory Committee meeting.

6.0 LATE-CYCLE MEETING /OTHER PROJECTED MILESTONES

- If major deficiencies are not identified during the review, we plan to communicate proposed labeling by April 28, 2017.

- The proposed date for the Late-Cycle Meeting is May 16, 2017.
- The user fee goal date is July 16, 2017.

Meeting Discussion:

The Applicant requested Agency comment regarding their general approach to postmarketing commitments (PMCs) and postmarketing requirements (PMRs). The Agency deferred PMC/PMR discussion to the late-cycle meeting.

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/s/

GORDANA DIGLISIC
04/03/2017



BLA 761061

**PROPRIETARY NAME REQUEST
UNACCEPTABLE**

Janssen Biotech, Inc.
920, Route 202 South
Raritan, NJ 08869

ATTENTION: Manomi Tennakoon, Ph.D.
Associate Director, Global Regulatory Affairs, Immunology

Dear Dr. Tennakoon:

Please refer to your Biologics License Application (BLA) dated and received November 16, 2016, submitted under section 351(a) of the Public Health Service Act for Guselkumab 100 mg/mL.

We also refer to your correspondence, dated and received November 21, 2016, requesting review of your proposed proprietary name, Tremfya.

We have completed our review of this proposed proprietary name and have concluded that this name is unacceptable for the following reasons:

The proposed proprietary name, Tremfya, is vulnerable to medication errors due to confusion with another product that is also under review. Therefore, the ultimate acceptability of your proposed proprietary name, Tremfya, is dependent upon which underlying application is approved first. If another product is approved prior to your product, with a name that would be confused with your proposed name of Tremfya, you will be requested to submit another name.

We note that you have not proposed an alternate proprietary name for review. If you intend to have a proprietary name for this product, we recommend that you submit a new request for a proposed proprietary name review.

If you require additional information on developing proprietary names for drugs, proposing alternative proprietary names for consideration, or requesting reconsideration of our decision, we refer you to the following:

- Draft Guidance for Industry Best Practices in Developing Proprietary Names for Drugs, (<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM398997.pdf>)
- 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 Tri M. Bui Nguyen, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (240) 402-3726. 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

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/s/

DANIELLE M HARRIS on behalf of TODD D BRIDGES
02/09/2017



BLA 761061

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

Janssen Biotech, Inc.
Attention: Manomi Tennakoon, PhD
Associate Director, Global Regulatory Affairs, Immunology
920, Route 202 South
Raritan, NJ 08869

Dear Dr. Tennakoon:

Please refer to your Biologics License Application (BLA) dated and received November 16, 2016, submitted under section 351(a) of the Public Health Service Act for guselkumab injection, 100 mg/mL.

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 **Priority**. Therefore, the user fee goal date is July 16, 2017. 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 requirement/commitment requests by April 28, 2017. In addition, the planned date for our internal mid-cycle review meeting is February 16, 2017. We are not currently planning to hold an advisory committee meeting to discuss this application.

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

We request that you submit the following information or provide the location in your BLA submission:

Clinical

1. Provide your rationale/discussion regarding the acceptability of your foreign data. The acceptance of the foreign clinical data depends on its ability to be extrapolated to the US population. Refer to the ICH guidance for industry *E5 Ethnic factors in the Acceptability of Foreign Clinical Data*, September 2006.
2. Identify the investigational sites where the US-licensed Humira was used as a comparator.

General Hospital Devices

3. Submit a Letter of Authorization (LOA) for [REDACTED] (b) (4).
4. Submit essential performance specifications.
5. Submit design verification and validation testing of the combination product (submitted for the needlestick feature, but not overall such as dose accuracy, breakloose/glide force, etc.).
6. Submit design and lot release specifications for the device (not available in module in 3.2.P.5.1).
7. Submit risk analysis for final device constituent of combination product.
8. Submit biocompatibility testing.
9. Submit shipping studies.

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) and Medication Guide. 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) and Medication Guide, 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
01/13/2017



IND 105004

MEETING MINUTES

Janssen Research & Development, LLC.
Attention: Pansy Minnick, MBA
Associate Director, Global Regulatory Affairs, Immunology
Welsh & McKean Roads
P.O. Box 776
Spring House, PA 19477

Dear Ms. Minnick:

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

We also refer to the teleconference between representatives of your firm and the FDA on October 19, 2016. The purpose of the meeting was to discuss the development program for guselkumab.

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 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

Enclosure:
Meeting Minutes



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type: C
Meeting Category: Guidance

Meeting Date and Time: October 19, 2016 at 11:30 a.m.
Meeting Location: Teleconference

Application Number: IND 105004
Product Name: Guselkumab
Proposed Indication: For the treatment of adult patients (18 years and older) with moderate to severe plaque psoriasis who are candidates for phototherapy or systemic therapy

Sponsor Name: Janssen Research & Development, LLC.

Meeting Chair: Kendall A. Marcus, MD
Meeting Recorder: Matthew White

FDA ATTENDEES

Kendall A. Marcus, MD, Director, Division of Dermatology and Dental Products (DDDP)
Leah Christl, PhD, Associate Director for Therapeutic Biologics, OND Therapeutic Biologics and Biosimilars Staff (TBBS)
Snezana Trajkovic, MD, Clinical Team Leader, DDDP
Melinda McCord, MD, Clinical Reviewer, DDDP
Mohamed Alosh, PhD, Biostatistics Team Leader, Division of Biometrics III (DB III)
Matthew Guerra, PhD, Biostatistics Reviewer, DB III
Barbara Hill, PhD, Pharmacology Supervisor, DDDP
Yow-Ming Wang, PhD, Clinical Pharmacology Team Leader, Division of Clinical Pharmacology 3 (DCP 3)
Christine Hon, PharmD, Clinical Pharmacology Reviewer, DCP 3
Matthew E. White, Senior Regulatory Health Project Manager, DDDP

SPONSOR ATTENDEES

Norman Bohidar, PhD, Senior Director, Quantitative Sciences
Herren Edra, RAC, Manager, North America Regulatory Affairs
Susan Flavin, PhD, Director, Clinical Development
Ming-Chun Hsu, PhD, Associate Director, Quantitative Sciences
Amy Krutsick, MS, Lead Associate, Global Regulatory Affairs
Shu Li, PhD, Director, Quantitative Sciences
Pansy Minnick, MBA, Director, Global Regulatory Leader

Heidi Needleman, PhD, Senior Director, Compound Development Team Leader
Liza O'Dowd, MD, Vice President, Global Regulatory Affairs
Susan Popma, OD, Director, Global Regulatory Leader
Bruce Randazzo, MD, PhD, Senior Director, Clinical Development
Philippe Szapary, MD, MSCE, Vice President, Clinical Development
Manomi Tennakoon, PhD, Associate Director, Global Regulatory Affairs, Immunology
Steven Wan, PhD, Director, Global Regulatory Affairs, CMC
Yasmine Wasfi, MD, PhD, Senior Director, Clinical Development
Newman Yeilding, M.D., Head Immunology Development

1.0 BACKGROUND

Purpose of the Teleconference:

The purpose of this meeting is to discuss the development program for guselkumab, an anti-IL-23 monoclonal antibody (mAb), for the treatment of adults with moderate to severe plaque psoriasis.

Regulatory Correspondence History:

We have had the following meetings/teleconferences with you:

- 4/27/2016: Type B (Pre-BLA) meeting
- 1/27/2016: Type C (Guidance) meeting
- 4/9/2014: Type B (End-of-Phase 2) meeting
- 6/26/2013: Type C (Guidance) meeting
- 11/16/2011: Type C (Guidance) meeting

We have sent the following correspondences:

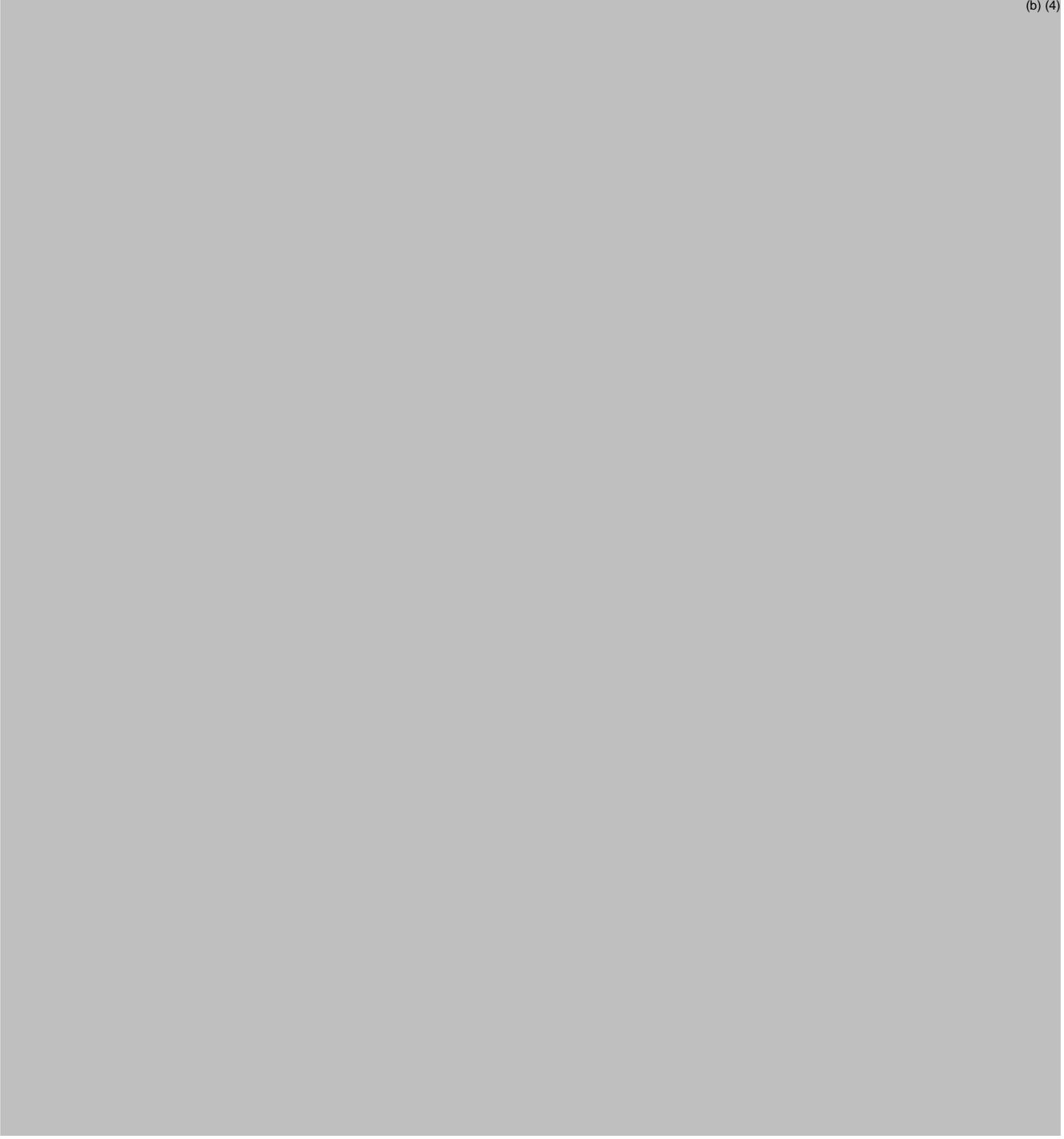
- 9/23/2016: Advice letter
- 9/6/2016: Information request letter
- 2/22/2016: Advice letter
- 2/2/2016: Information request letter
- 4/27/2015: Advice letter
- 3/21/2015: Advice letter
- 11/21/2014: Initial pediatric study plan (iPSP) – agreement letter
- 10/15/2014: Advice/information request letter
- 8/12/2014: iPSP written response letter
- 8/12/2014: Inadequate study request letter
- 7/7/2014: Advice letter
- 5/30/2014: Advice letter
- 3/5/2014: Information request letter
- 10/7/2013: Advice letter
- 9/5/2013: Information request letter
- 7/3/2013: Advice letter
- 6/8/2013: Information request
- 11/30/2011: Advice/information request letter

- 8/18/2011: Information request letter
- 6/3/2011: Written responses to questions submitted in a 3/11/11 briefing document
- 7/1/2009: Advice/information request letter
- 5/12/2009: Advice/information request letter

2.0 DISCUSSION

2.1. Chemical, Pharmaceutical, and Biological Development

(b) (4)



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3.0 ADDITIONAL COMMENTS

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>.

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/s/

KENDALL A MARCUS
11/18/2016



IND 105004

MEETING MINUTES

Janssen Research & Development, LLC.
Attention: Pansy Minnick, MBA
Associate Director, Global Regulatory Affairs, Immunology
Welsh & McKean Roads
P.O. Box 776
Spring House, PA 19477

Dear Ms. Minnick:

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

We also refer to the teleconference between representatives of your firm and the FDA on April 6, 2016. The purpose of the meeting was to discuss the development program for guselkumab.

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 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

Enclosure:
Meeting Minutes



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: April 6, 2016 at 9:00 a.m.
Meeting Location: Teleconference

Application Number: IND 105004
Product Name: Guselkumab

Proposed Indication: For the treatment of adult patients (18 years and older) with moderate to severe plaque psoriasis who are candidates for phototherapy or systemic therapy

Sponsor Name: Janssen Research & Development, LLC.

Meeting Chair: Kendall A. Marcus, MD
Meeting Recorder: Matthew White

FDA ATTENDEES

Julie Beitz, MD, Director, Office of Drug Evaluation III (ODE III)
Kendall A. Marcus, MD, Director, Division of Dermatology and Dental Products (DDDP)
Snezana Trajkovic, MD, Clinical Team Leader, DDDP
Melinda McCord, MD, Clinical Reviewer, DDDP
Barbara Hill, PhD, Pharmacology Supervisor, DDDP
Mohamed Alesh, PhD, Biostatistics Team Leader, Division of Biometrics III (DB III)
Matthew Guerra, PhD, Biostatistics Reviewer, DB III
Yow-Ming Wang, PhD, Clinical Pharmacology Team Leader, Division of Clinical Pharmacology 3 (DCP 3)
Jie Wang, PhD, Clinical Pharmacology Reviewer, DCP 3
Qing Zhou, PhD, Product Quality Team Leader, Division of Biotechnology Research and Review 1 (DBRR1)
Deborah Schmiel, PhD, Product Quality Reviewer, DBRR1
Wen Jin Wu, MD, PhD, Senior Investigator, DBRR1
Jessica Weintraub, PharmD, Safety Evaluator, Division of Pharmacovigilance I (DPV I)
Jasminder Kumar, PharmD, RPh, Risk Management Analyst, Division of Risk Management (DRISK)
Kira Leishear, PhD, MS, Epidemiologist, Division of Epidemiology (DEPI) I
Carolyn Cochenour, BBME, Biomedical Engineer, CDRH, General Hospital Devices Branch
Roy Blay, PhD, Reviewer, Division of Good Clinical Practice Compliance (DGPCPC)

Yasmin Choudhry, MD, Reviewer, Clinical Outcome Assessment (COA) Staff
Matthew E. White, Senior Regulatory Health Project Manager, DDDP

EASTERN RESEARCH GROUP ATTENDEES

Pegah Khorrami, Independent Assessor

SPONSOR ATTENDEES

Norm Bohidar, PhD, Clinical Biostatistics Head
Herren Edra, RAC, Manager, North America Regulatory Affairs
Chun-Yuan Guo, MD, PhD, Director, Global Medical Safety
Chenglong Han, PhD, Director, Patient Reported Outcomes
Isaac Hatzell, Associate Director, Data Delivery and Analysis
Shu Li, PhD, Director, Clinical Biostatistics
Gail Miller, Associate Director, Global Regulatory Affairs CMC
Pansy Minnick, Associate Director, North America Regulatory Leader
Heidi Needleman, PhD, Senior Director, Compound Development Team Leader
Liza O'Dowd, MD, Vice President, Global Regulatory Affairs
Susan Popma, OD, Director, Global Regulatory Leader
Bruce Randazzo, MD, PhD, Senior Director, Clinical Development
Yaung-Kaung Shen, PhD, Associate Director, Clinical Biostatistics
Michael Song, MD, Director, Clinical Development
Philippe Szapary, MD, MSCE, Vice President, Clinical Development
Steven Wan, PhD, Director, Global Regulatory Affairs, CMC
Yasmine Wasfi, MD, PhD, Senior Director, Clinical Development
Yaowei Zhu, PhD, Associate Director, Biologics Clinical Pharmacology

Purpose of the Meeting:

The purpose of this meeting is to discuss the development program for guselkumab, an anti-IL-23 monoclonal antibody (mAb), for the treatment of adults with moderate to severe plaque psoriasis. Guselkumab is a biological product-device combination product for delivery in a prefilled glass syringe with a passive needle guard.

Regulatory Correspondence History

We have had the following meetings/teleconferences with you:

- 1/27/2016: Type C (guidance) meeting
- 4/9/2014: Type B (End-of-Phase 2) meeting
- 6/26/2013: Type C (guidance) meeting
- 11/16/2011: Type C (guidance) meeting

We have sent the following correspondences:

- 2/22/2016: Advice letter
- 2/2/2016: Information request letter
- 4/27/2015: Advice letter
- 3/21/2015: Advice letter
- 11/21/2014: Initial pediatric study plan (iPSP) – agreement letter

- 10/15/2014: Advice/information request letter
- 8/12/2014: iPSP written response letter
- 8/12/2014: Inadequate study request letter
- 7/7/2014: Advice letter
- 5/30/2014: Advice letter
- 3/5/2014: Information request letter
- 10/7/2013: Advice letter
- 9/5/2013: Information request letter
- 7/3/2013: Advice letter
- 6/8/2013: Information request
- 11/30/2011: Advice/information request letter
- 8/18/2011: Information request letter
- 6/3/2011: Written responses to questions submitted in a 3/11/11 briefing document
- 7/1/2009: Advice/information request letter
- 5/12/2009: Advice/information request letter

Operational:

Question 15:

Does the Agency agree with the proposed list of covered studies for submission of financial disclosure information?

Response:

Your proposal to provide financial disclosure information for covered studies CNTO1959PSO3001, CNTO1959PSO3002, CNTO1959PSO3003 and CNTO1959PSO2001 appears reasonable.

Question 16:

Does the Agency agree with the proposed dossier content (TOC) for the guselkumab BLA?

Response:

Yes. The overall Table of Contents (TOC) appears reasonable.

To support the approval of a new molecular entity, the Agency requires a comprehensive assessment of the benefits and risks of your drug product. The information needed to complete this analysis is described in the guidance for industry *Structured Approach to Benefit-Risk Assessment in Drug Regulatory Decision-Making Draft PDUFA V Implementation Plan* which is available at

<http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm326192.htm>.

Your application may include the following information:

1. Analysis of the condition which includes
 - Clinical manifestations (frequency and severity) and potential for progression
 - Prevalence in the general population and subpopulations

- Proportion of patients who experience mild, moderate or severe disease
 - Severity across subpopulations (e.g., pediatric subgroups versus adult subgroups)
 - Impact on daily living in all populations and subpopulations
 - Uncertainties in the understanding of the condition
 - Subpopulations of particular concern
2. Current treatment options
- Standard of care: list of approved therapies, drugs used off-label, nonprescription drugs, medical and surgical procedures, and non-drug therapies
 - Efficacy information and safety/tolerability issues associated with each these therapies
 - Uncertainties in the understanding of the risks and benefits of the treatment options
 - Adequacy of current therapies to meet the medical needs of the affected population and subpopulations (e.g., patients with refractory disease, etc.)
3. Benefit
- Trial design(s) and effect size
 - Limitations of the data
 - Clinical relevance of endpoints
 - Durability of benefit
 - Variation of benefit across subpopulations
 - Any exclusions in the studied population that would limit use in the general population
 - The number needed to treat (NNT) to achieve the treatment response/prevent bad outcome (e.g., likelihood of benefit)
 - Uncertainties in the evidence or about the product
4. Risk
- Ability of the safety database to reflect expected use in the patient population
 - The most important safety concern
 - Important aspects of the safety concern (e.g., range of severity, dose relationship, prevention/mitigation, reversibility, etc.)
 - Risks associated with suboptimal management of the disease
 - Uncertainties regarding risk
5. Conclusions
- This information may be tabulated in the following framework:

Figure 1: FDA Benefit-Risk Framework

Decision Factor	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition		
Current Treatment Options		
Benefit		
Risk		
Risk Management		
Benefit-Risk Summary Assessment		

Also, refer to pharmacology/toxicology comments.

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

- Documents leaf titles should be clear and indicative of the content (e.g., FDA-Form-3454-CNTO1959PS02001).
- Please note that Study Tagging Files (STF) files are required for submissions to the Agency 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. There should be a single m4 and m5 section. Each study should have an STF and all components regarding that study should be properly file tagged and placed under the study's STF, including case report forms (CRFs).
- Regarding use of the m5-3-7 heading element, the Agency does not use module 5.3.7 Case Report Forms (CRFs). Instead, CRFs needs to be referenced in the appropriate study's STF to which they belong, organized by site as per the specifications and tagged as "case report form".
- The tabular listing in module 5.2 and synopsis of individual studies in m2.7.6 (tabular format), should be linked to the referenced studies in m5.
- For additional recommendations on the location of information related to the device constituent part refer to page 1, 13-15, and 17 of the recent eCTD Technical Conformance Guide: Technical Specifications Document: The guidance for industry *Providing Regulatory Submissions in Electronic Format —Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications* is available at <http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM465411.pdf>.

Question 17:

Does the Agency agree with the proposed plan for providing narratives and CRFs?

Response:

Response:

Your proposed plan for providing narratives and CRFs appears reasonable. The same plan is appropriate for the 120-Day safety update.

The CRFs for each trial should be placed in a CRF folder under the applicable trial with a file tag of "case-report-forms."

1. Also provide electronic links for the following:
 - a) all serious AEs
 - b) all severe AEs
 - c) all patients discontinued regardless of reason
 - d) all deaths
2. CRF should be referenced under the trial in which it belongs and tagged as
 - a) "casereportforms" in that trial's stf.xml file.
3. CRFs that are not submitted should be readily available upon request.

Meeting Discussion:

The sponsor proposed not to submit narratives for severe AEs. For discontinued subjects, the sponsor proposed to submit narratives only for patients discontinued due to AEs. The Agency agreed.

Question 18:

Does the Agency agree with the proposed plan for submission of datasets?

Response:

Your proposal to submit Analysis Data Model (ADaM IG v 1.0) and SDTM (SDTM IG v 3.1.3) formatted datasets for Trials CNTO1959PSO3001, CNTO1959PSO3002 and CNTO1959PSO3003 is acceptable. In addition, your proposal to submit ADaM formatted analysis datasets containing the pooled data from the studies that form the basis for the summaries of clinical safety, efficacy, and pharmacology is acceptable. Submit the NONMEN datasets as txt or SAS xpt transport files.

For the analysis datasets, we have the following general comments:

1. Each analysis dataset should include the treatment assignments, baseline assessments, and key demographic variables. The analysis datasets should include all variables needed for conducting all primary, secondary, and sensitivity analyses included in the study report. For endpoints that include imputations, both observed and imputed variables should be included and clearly identified. If any subjects were enrolled in more than one

study, include a unique subject ID that permits subjects to be tracked across multiple studies.

2. The analysis dataset documentation (Define.xml) should include sufficient detail, such as definitions or descriptions of each variable in the dataset, algorithms for derived variables (including source variable used), and descriptions for the code used in factor variables. For ease of viewing by the reviewer and printing, submit corresponding Define.pdf files in addition to the Define.xml files.

In addition to the electronic datasets, submit study protocols including the statistical analysis plan, all protocol amendments (with dates), generated treatment assignment lists, and the actual treatment allocations (along with the date of enrollment).

See the clinical pharmacology comments in the response to Question 10.

Chemistry, Manufacturing and Controls (CMC)

Question 12:

Based on the inspection status of the manufacturing sites, can a Pre-Approval Inspection waiver be granted for guselkumab drug substance and drug product?

Response:

We do not agree that the Pre-Approval Inspection waivers can be granted based on the information in the briefing package. Please note that per 21 CFR 601.20(d), "A biologics license shall be issued or a biologics license application approved only after inspection of the establishment(s) listed in the biologics license application and upon determination that the establishment(s) complies with standards established in the biologics application and the requirements prescribed in applicable regulations." Although mechanisms exist for waiving inspections, when appropriate, the items covered in a Pre-Approval Inspection for a specific BLA would not have been covered by the previous inspections listed in your briefing package.

Question 13:

Does the Agency agree with the plan to submit the 6 month Prefilled Syringe stability report during the first 30 days of the review?

Response:

It would be acceptable to submit a simple stability update, as described in the meeting package, for the 6 month drug product Prefilled Syringe stability data for the process validation batches within 30 days of the initial BLA submission.

Question 14:

Does the Agency agree with the plan to submit [REDACTED] during the first 30 days of the review?

(b) (4)

Response:

We do not agree. (b) (4)

Additional Comments:

1. The (b) (4) Passive needle guard is a 510(k) cleared device. Due to its presentation as a combination product, include the requirements for the (b) (4) Passive needle guard in your design specification documents. Also include the lot release criteria related to the safe and effective use of the sharps injury prevention feature for use with your drug product and container closure system. In your BLA submission you will need to provide information demonstrating acceptable performance and safety for use of the PFS (b) (4)
2. As a combination product under 21 CFR Part 3, guselkumab with the prefilled syringe (b) (4) Passive needle guard is subject to 21 CFR Part 4 “Current Good Manufacturing Practice Requirements for Combination Products” accessible at <https://www.federalregister.gov/articles/2013/01/22/2013-01068/current-good-manufacturing-practice-requirements-for-combination-products>.
3. The CMC Drug Substance section of the BLA (Section 3.2.S) should contain the following product quality microbiology information:
 - a. Bioburden and endotoxin levels at critical manufacturing steps should be monitored using qualified bioburden and endotoxin tests. Bioburden samples should be collected (b) (4). Pre-determined bioburden and endotoxin limits should be provided (3.2.S.2.4).
 - b. Microbial data from three successful product intermediate hold time validation runs at manufacturing scale should be provided. 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). Bioburden samples should be collected (b) (4).
 - c. Data demonstrating microbial control (b) (4) (3.2.S.2.5).
 - d. Bioburden and endotoxin data obtained during manufacture of the three process qualification batches (3.2.S.2.5).
 - e. Summary of shipping validation studies and data (3.2.S.2.5).
 - f. Drug substance bioburden and endotoxin release specifications (3.2.S.4). (b) (4)

endotoxin over time. The studies should be conducted using containers of similar composition as those used for drug product during hold.

8. Inspection Readiness: 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). Please include in the BLA submission a complete list of manufacturing and testing sites with their corresponding FEI numbers. An updated manufacturing schedule for the (b) (4) drug substance and drug product fill finish sites should be included in Module 1 of the BLA.

Pharmacology/Toxicology

No nonclinical questions were included in the meeting package. However, we have the following nonclinical comment.

Provide an updated comprehensive carcinogenicity risk assessment for your biologic product when you submit the nonclinical data for your BLA. A summary of the comprehensive carcinogenicity risk assessment for your biologic product should be included in Module 2. A detailed comprehensive carcinogenicity risk assessment for your biologic product, with copies of full supporting literature reports, should be included in Module 4. Appropriate information about the carcinogenicity risk assessment for your biologic product should be incorporated into Section 13.1 of the label for your biologic product.

Clinical Pharmacology/Biopharmaceutics

Question 9:

Does the Agency agree that the proposed PK analyses and immunogenicity assessments are adequate for the Summary of Clinical Pharmacology (Module 2.7.2)?

Response:

Yes, based on the information provided in the briefing package, your overall plan for pharmacokinetic (PK) analyses and immunogenicity assessments appears to be reasonable to constitute Summary of Clinical Pharmacology for our review of the BLA.

We have the following general recommendations regarding the immunogenicity assessments:

1. For the evaluation of the anti-drug antibodies (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.
2. We encourage you to include subject's ADA status as a covariate in the population PK analysis on an exploratory basis to evaluate the impact of ADA on guselkumab 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.

3. For the ADA positive subjects observed in Phase 3 trials, provide a summary table of study number, study subject ID, serum guselkumab concentrations at each PK time-point, sample ADA status at each immunogenicity assessment time-point, and the primary efficacy outcome.

In addition to the overall ADA and neutralizing antibodies incidences across the Phase 3 trials, report the immunogenicity incidences in subjects who have continuously received the proposed dosing regimen in both the initial 16-Week treatment period and the maintenance dosing period up to Week 48.

Question 10:

Does the Agency consider the proposed population PK and PK/PD modeling analyses adequate to support the dose rationale and product labeling?

Response:

We acknowledge that you have planned to conduct population PK and exposure-response PK/PD analyses based on the pooled data from Phase 2 study (CNTO1959PSO2001) and two Phase 3 studies (CNTO1959PSO3001 and CNTO1959PSO3002) to support your BLA submission. Your overall plan for PK and PK/PD analyses appears to be reasonable at this time; however, whether such analyses would be adequate to support the dose rationale and product labeling will be a review issue as your Phase 3 trials are still ongoing.

In Section 5.4.2 “Association of Efficacy with Pharmacokinetics” of your briefing package, you proposed exploratory exposure-response analyses between Investigator Global Assessment (IGA) and Psoriasis Area and Severity Index (PASI) responses and serum guselkumab concentrations at Week 28. We recommend that you additionally conduct exposure-response analyses for the co-primary endpoints at Week 16 and for other key efficacy endpoints during the maintenance dosing period. In addition to the exposure-response analysis for efficacy, conduct exposure-response analysis for safety (e.g., adverse events of interest such as infections). Submit these analyses of exposure-response relationships for both the efficacy and safety results in the BLA to support your dose rationale, with consideration of the benefit/risk for the entire indicated patient population proposed in the product labeling.

We have the following general recommendations regarding your population PK and exposure-response PK/PD datasets to be included in the BLA submission:

1. Submit NONMEM control streams of the base and final model for the population PK analysis.
2. Provide the output tables for final model runs for population PK and PK/PD models.
3. 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).

4. Submit a model development decision tree and/or tables which give an overview of modeling steps.
5. Include a USUBJID (unique subject ID) column to all the population PK and PK/PD datasets so that we can relate these datasets to other clinical analysis datasets.

Question 11a:

Does the Agency agree that if the final clinical study report for the Phase 1 drug-drug interaction study CNTO1959PSO1003 cannot be completed at the time of the BLA submission, it can be submitted as a postmarketing commitment after approval of the BLA?

Response:

Yes, we agree that the final clinical study report (CSR) for the Phase 1 drug-drug interaction (DDI) study CNTO1959PSO1003 can be submitted as a postmarketing commitment if your BLA is approved.

Question 11b:

If the Sponsor is able to complete a final CSR for Study CNTO1959PSO1003 in time for the 4-month safety update, would FDA be able to accept the data at that time without considering it as a major BLA amendment?

Response:

Yes, if the final CSR for Study CNTO1959PSO1003 is submitted in the 4-month safety update, we would not consider it as a major BLA amendment.

When you submit the CSR for Study CNTO1959PSO1003, also provide the following:

1. An update to Section 7 and Section 12.3 of your proposed product labeling;
2. A brief summary of study findings and rationale for your proposed labeling changes;
3. All the datasets related to the study results and DDI analysis; and
4. Bioanalytical method validation reports for the small molecule drug(s) used in the DDI study.

Clinical/Biostatistics

Question 1a:

Does the Agency agree with the Sponsor's proposal to focus Module 2.7.3 on a summary and comparison of efficacy from the individual Phase 3 psoriasis studies as described in Section 5.4?

Response:

Your proposal to focus Module 2.7.3 on a summary and comparison of efficacy from the individual Phase 3 trials appears to be acceptable.

Question 1b:

Does the Agency agree with the Sponsor's plan to pool data from Phase 3 studies CNTO1959PSO3001 and CNTO1959PSO3002 for evaluation of efficacy in subpopulations?

Response:

You are encouraged to present results of the subgroup analyses for each trial individually as well as for the pooled data. In addition, you may consider combining the estimates from the individual trials inversely weighted by their variances.

Findings from subgroup analyses are important for investigating consistency of treatment effect across subgroups; consequently, they are useful for the interpretation of clinical trial findings. For establishing an efficacy claim based on findings from a subgroup analysis, the hypothesis and the analysis need to be prespecified in the protocol and the statistical testing need to control for the Type I error rate.

Meeting Discussion:

The Sponsor asked for clarification regarding their understanding that all commercial Humira[®] (adalimumab) is identical regardless of site of manufacture. The Agency clarified that US-licensed Humira[®] and EU-approved adalimumab are not necessarily considered identical and that a scientific bridge is needed.

In the absence of a scientific bridge, the sponsor inquired whether they could use data for the US-licensed Humira[®] for subjects enrolled in the US and Canada to support comparison against guselkumab. The Agency noted that this may be acceptable, provided that the analysis is done for each study separately and that there are sufficient numbers of subjects.

Post-meeting Addendum:

Specific to your development program, we agree it may be reasonable to use US-licensed Humira[®] at certain study sites and EU-approved adalimumab at other study sites for the active comparator arm of your superiority clinical trials if you can establish an adequate scientific bridge to justify the relevance of data obtained with EU-approved adalimumab. If you seek to use data from clinical studies comparing guselkumab to EU-approved adalimumab, to support a claim of superiority of guselkumab to US-licensed Humira[®], you should provide adequate data or information to scientifically justify the relevance of this comparative data and establish an acceptable scientific bridge to US-licensed Humira[®]. With respect to your development program, the type of bridging data that may be needed to provide adequate scientific justification for this approach would include data from direct, comparative analytical studies (e.g., structural and functional data) of US-licensed Humira[®] and EU-approved adalimumab, and is likely to also include bridging clinical PK study data. The comparisons should meet the pre-specified acceptance criteria for analytical and PK similarity. You may submit publicly available information regarding EU-approved adalimumab to justify the extent of comparative data needed to establish a bridge to US-licensed Humira[®]. The complexity of the product, particularly with respect to higher order structure, post-translational modifications (e.g., glycosylation) and the degree of heterogeneity associated with the product may impact the considerations for the scientific justification regarding the extent of bridging data. You should address any other factors

that may affect the extent of bridging data to support such an approach. The adequacy of this scientific justification and bridge would be a review issue.

Please note, however, that the use of both US-licensed Humira® and EU-approved adalimumab as active comparators in a clinical trial may have labeling implications should the data generated using both products be necessary to support approval. As a general matter, US-licensed Humira® and a non-US-licensed adalimumab product are considered distinct products.

Question 1c:

Does the Agency agree that the proposed analysis plans and table and figure formats for presenting efficacy analyses of subpopulations using pooled data are adequate?

Response:

See response to Question 1b.

Question 2:

Does the Agency accept the Sponsor's proposal that the need to provide a comprehensive efficacy analysis of the guselkumab data can be met within Module 2.7.3 without the need for a separate Integrated Summary of Efficacy in Module 5.3.5.3?

Response:

Your proposal appears to be reasonable, provided that the Summary of Clinical Efficacy (Module 2.7.3) contains a complete presentation of the efficacy of guselkumab for the treatment of plaque psoriasis. For additional information on the content of the Integrated Summary of Effectiveness (ISE), refer to guidance for industry *Integrated Summary of Effectiveness* (<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM079803.pdf>).

Question 3a:

Has the Agency determined that the SF-36 is a relevant and valid instrument to measure general health status in psoriasis? If not, can the Agency provide advice as to what type of information would be necessary to support this determination?

Response:

We consider the SF-36 used in the Phase 3 trials as exploratory, as it was not included in the testing hierarchy. Exploratory endpoints are generally inadequate to support labeling claims due to their exploratory status.

If a claim of superiority in a particular patient-reported outcome (PRO) concept is sought, we suggest that sponsors:

1. Pre-specify the PRO hypothesis and test it within the statistical hierarchy of hypothesis testing in the clinical trial;
2. Control overall type I error rate for hypothesis-based testing on primary and all secondary endpoints;

3. Prospectively define the statistical analysis methods, especially procedures for handling missing values; and
4. Provide justification in advance for the endpoint definition, including what constitutes meaningful change, for FDA review and comment.

Question 3b:

Does the Agency agree that the proposed analysis plans will be adequate (b) (4)

Response:

No, we do not agree. See response to Question 3a.

Question 4:

Does the Agency agree with the strategy for an integrated analysis of safety, including pooling of safety data from studies CNTO1959PSO3001 and CNTO1959PSO3002 to serve as the primary dataset?

Response:

To characterize the safety profile of guselkumab, you plan to summarize adverse events from three different pools of the data (described below).

1. The Placebo-controlled Period through Week 16:
Safety data from CNTO1959PSO3001 and CNTO1959PSO3002 will be summarized in three columns:
 - Placebo
 - Guselkumab 100 mg
 - Adalimumab
2. Common Active Comparator-Controlled Period:
Safety data through Week 28 from CNTO1959PSO3001 and CNTO1959PSO3002 studies will be summarized in two columns:
 - Guselkumab 100 mg
 - Adalimumab
3. Through the End of the Reporting Period:
Safety data through Week 48 for CNTO1959PSO3001 and CNTO1959PSO3002 studies will be summarized using three columns:
 - **Placebo:** Safety data during the placebo period from subjects randomized to and treated with placebo
 - **Guselkumab 100 mg:** Safety data in all subjects treated with guselkumab 100 mg, that includes:
 - a) Placebo → guselkumab 100 mg: Safety data after crossover to guselkumab 100 mg from placebo through Week 48.

- b) Guselkumab 100 mg: Safety data from Week 0 through Week 48 for subjects initially randomized to and treated with guselkumab.
- c) Adalimumab → guselkumab 100 mg: Safety data after switch to guselkumab 100 mg from adalimumab through Week 48 (CNTO1959PSO3002).
 - **Adalimumab**: Safety data for adalimumab subjects who are initially randomized to and received adalimumab only or received treatment with adalimumab prior to receiving treatment with guselkumab from Week 0 through Week 48.

We have the following comments:

- For the “Placebo-controlled Period through Week 16” pool, provide raw incidence rates (at $\geq 1\%$) by treatment group. For the “Common Active Comparator-Controlled Period” pool and “Through the End of the Reporting Period” pool, provide raw incidence rates (at $\geq 1\%$) as well as the exposure-adjusted rates (in patient-years) by treatment group.
- For the “Common Active Comparator-Controlled Period” include placebo comparator group.
- For the “Through the End of the Reporting Period”, in Guselkumab 100mg group, **exclude** subjects treated with adalimumab and switched to guselkumab (adalimumab → guselkumab 100 mg; study CNTO1959PSO3002).
- For the major adverse cardiac events (MACE) we agree with your strategy to pool studies CNTO1959PSO3001, CNTO1959PSO3002 and CNTO1959PSO2001. We request that you present exposure adjusted MACE events for the following treatment groups:
 - Placebo
 - Guselkumab 100mg every 8 weeks
 - Guselkumab at doses lower than 100mg
 - Guselkumab 200mg every 12 weeks.

Question 5:

Does the Agency agree with the proposed plan for safety analyses during withdrawal and retreatment in study CNTO1959PSO3002?

Response:

You define rebound as an event of new erythrodermic or pustular psoriasis, or PASI of $\geq 125\%$ of the baseline PASI that occurs within 3 months of guselkumab withdrawal at Week 28. The 3 month cutoff for evaluation of rebound will not allow for capture of rebound events in subjects who may experience guselkumab response lasting more than 3 months. All events of new erythrodermic or pustular psoriasis or PASI of $\geq 125\%$ of the baseline PASI, at any time after the guselkumab withdrawal at Week 28, should be included.

You plan to assess safety (adverse event (AE), serious adverse event (SAE), discontinued due to AE, infection, and injection site reactions) for subjects who are withdrawn from guselkumab at Week 28 and subsequently retreated upon loss of response. Safety data from these subjects

should be compared to safety data from subjects treated with placebo (Week 0 through Week 16) and from subjects who were on continuous guselkumab treatment (Week 0 through Week 48), using exposure-adjusted rates.

Question 6:

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

Response:

The integrated summary of safety (ISS) is a detailed integrated analysis of all relevant data from clinical study reports and is required by the regulations to be located in Module 5. If you believe Section 2.7.4 (Summary of Clinical Safety) would be sufficiently detailed to serve as the summary portion of the ISS, then you may place the summary portion of your integrated assessment in Module 2 and place the appendices of tables, figures, and datasets in Section 5.3.5.3. In this case, a description of the contents of each section should be included in both Module 2 and Module 5 {21 CFR 314.50(d)(5)(v) and 21 CFR 314.50(d)(5)(vi)(a)}.

For additional information about the location of ISS and ISE in the CTD, refer to guidance for industry *Integrated Summaries of Effectiveness and Safety: Location Within the Common Technical Document* at the FDA website.

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM136174.pdf>

Question 7:

Does the Agency agree with the proposed plan and data cutoff for the 4-month safety update?

Response:

Under section 505(i) of the act, the applicant should update the BLA application with new safety information learned about the drug that may reasonably affect the statement of contraindications, warnings, precautions, and adverse reactions in the draft labeling.

To support filing of your BLA submission, you state that you intend to submit safety data through Week 48 for Trial CNTO1959PSO3001 and Trial CNTO1959PSO3002 and through Week 40 for Trial CNTO1959PSO3003. However, you do not provide the date of the database lock. For the 120 day safety update, you propose a cut-off date of October 31, 2016 for all completed and ongoing trials. Without the date of the database lock it is difficult to assess how much additional data that you intend to provide in the 120-day safety update from the ongoing trials. We recommend you choose a cut-off date at least 3 months or longer after the cut-off date for the safety data included in your BLA submission.

Question 8:

Does the Agency agree with the proposal to provide the clinical study reports for studies CNTO1959PSO3003 (60-week CSR), CNTO1959PSO3004 (32-week CSR), or CNTO1959PSO3005 (52-week CSR) to the IND as routine clinical amendments when they become available?

Response:

Study reports for studies CNTO1959PSO3004, CNTO1959PSO3005 and CNTO1959PSO3003 can be submitted to the IND. If study reports become available during the review cycle, they can be included in the 120-day safety update report and submitted to the NDA.

Additional Comments:

1. At the time of BLA submission, submit the coding dictionary used for mapping investigator verbatim terms to preferred terms or identify where this will be located in the proposed submission. The “coding dictionary” consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).
2. Include the full text version of any referenced articles.
3. Provide your rationale/discussion regarding the acceptability of your foreign data. The acceptance of the foreign clinical data depends on its ability to be extrapolated to the US population. Refer to the ICH guidance for industry, *E5 Ethnic factors in the Acceptability of Foreign Clinical Data*, September 2006.
4. You proposed to allow concomitant short-term use of corticosteroids for other indications during the Phase 3 trials where there was no adequate alternative. Provide a discussion of the impact of corticosteroids on the efficacy and safety of your product in this subset of subjects.
5. You should include the following in your pooled analysis (Trial CNTO1959PSO3001 and Trial CNTO1959PSO3002):
 - a. Line listings for all abnormal safety findings (e.g., adverse events, vital signs, etc.);
 - b. Shift tables for all laboratory values. Provide the normal range of values for all parameters, the threshold for concern for a clinically significant change and your justification for why this threshold is appropriate; and
 - c. Shift tables for all vital signs. Provide the normal range of values for all parameters.

In addition, provide baseline demographic data for the pooled safety dataset (CNTO1959PSO3001 and CNTO1959PSO3002).

6. Provide an analysis of ECG data (CNTO1959PSO3001 and CNTO1959PSO3002) and submit electronic links to the following information:

- a. Copies of the study report(s) for any clinical assessments of the effect of product administration on the QT interval that have been performed
- b. Electronic copy of the study report
- c. Electronic copy of the clinical protocol
- d. Electronic copy of the Investigator's Brochure
- e. Annotated CRF
- f. A data definition file which describes the contents of the electronic data sets
- g. Electronic data sets as SAS.xpt transport files (in CDISC SDTM format – if possible) and all the SAS codes used for the primary statistical and exposure-response analyses
- h. Please make sure that the ECG raw data set includes at least the following: subject ID, treatment, period, ECG date, ECG time (up to second), nominal day, nominal time, replicate number, heart rate, intervals QT, RR, PR, QRS and QTc (any corrected QT as points in your report, e.g. QTcB, QTcF, QTcI, etc., if there is a specifically calculated adjusting/slope factor, please also include the adjusting/slope factor for QTcI, QTcN, etc.), Lead, and ECG ID (link to waveform files if applicable)
- i. Dataset whose QT/QTc values are the average of the above replicates at each nominal time point
- j. Narrative summaries and case report forms for any
 - i. Deaths
 - ii. Serious adverse events
 - iii. Episodes of ventricular tachycardia or fibrillation
 - iv. Episodes of syncope
 - v. Episodes of seizure
 - vi. Adverse events resulting in the subject discontinuing from the study
- k. ECG waveforms to the ECG warehouse (www.ecgwarehouse.com)
- l. A completed Highlights of Clinical Pharmacology Table

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

- The content of a complete application was discussed.

All applications are expected to include a comprehensive and readily located list of all clinical sites and manufacturing facilities included or referenced in the application.

- A preliminary discussion on the need for a REMS was held and it was concluded that at this time, the Office of New Drugs and the Office of Surveillance and Epidemiology have insufficient information to conclusively determine whether a risk evaluation and mitigation strategy (REMS) will be necessary to ensure that the benefits of the drug outweigh the risks. However, based on the information currently available, we do not believe that a REMS will be necessary. We will make a final determination for the need for a REMS during the review of your application.
- Major components of the application are expected to be submitted with the original application and are not subject to agreement for late submission. We agreed that the following minor application components may be submitted within 30 calendar days after the submission of the original application:
 - A simple stability update, as described in the meeting package, for the 6 month drug product Prefilled Syringe stability data for the process validation batches.

Prominently identify the submission containing your late component with the following wording in bold capital letters at the top of the first page of the submission:

BLA NUMBER: LATE COMPONENT - QUALITY

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 [Pregnancy and Lactation Labeling Final Rule](#) websites, which include:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products
- The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information related to pregnancy, lactation, and females and males of reproductive potential
- Regulations and related guidance documents
- A sample tool illustrating the format for Highlights and Contents, and

- The Selected Requirements for Prescribing Information (SRPI) – a checklist of important format items from labeling regulations and guidances.
- FDA’s established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

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

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

SUBMISSION FORMAT REQUIREMENTS

The Electronic Common Technical Document (eCTD) is CDER and CBER’s standard format for electronic regulatory submissions. Beginning **May 5, 2017**, the following submission types: **NDA, ANDA, BLA and Master Files** must be submitted in eCTD format. **Commercial IND** submissions must be submitted in eCTD format beginning **May 5, 2018**. Submissions that do not adhere to the requirements stated in the eCTD Guidance will be subject to rejection. For more information please visit: <http://www.fda.gov/ectd>.

MANUFACTURING FACILITIES

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

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

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

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

Corresponding names and titles of onsite contact:

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

Office of Scientific Investigations (OSI) Requests

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

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

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

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

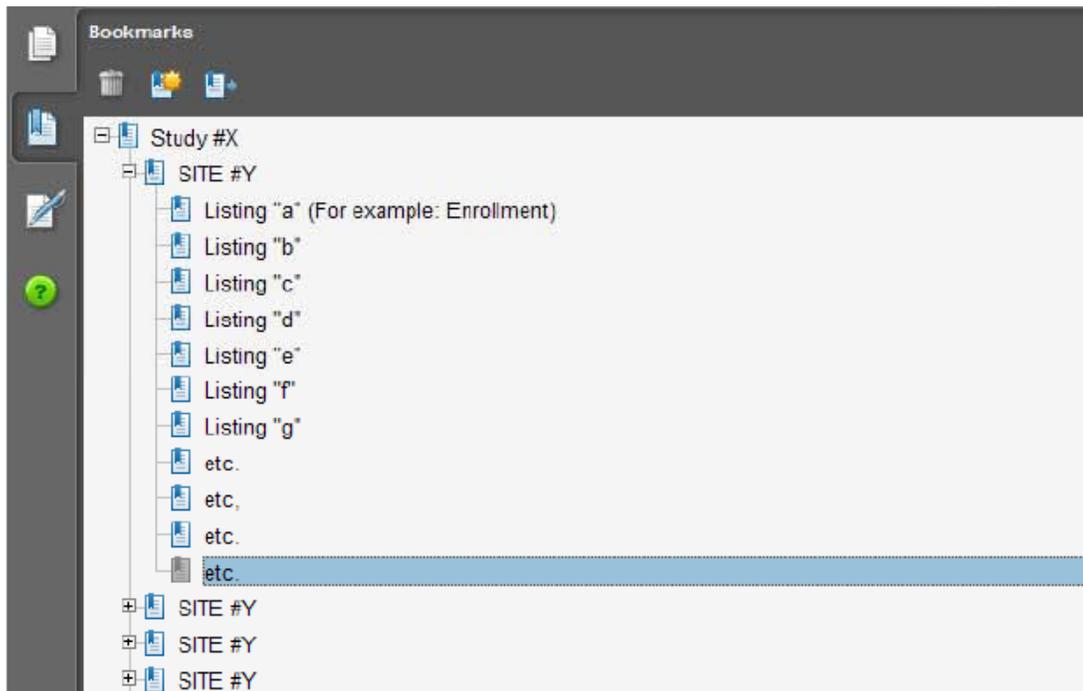
1. Please include the following information in a tabular format in the original NDA for each of the completed pivotal clinical trials:

- a. Site number
 - b. Principal investigator
 - c. Site Location: Address (e.g., Street, City, State, Country) and contact information (i.e., phone, fax, email)
 - d. Location of Principal Investigator: Address (e.g., Street, City, State, and Country) and contact information (i.e., phone, fax, email). If the Applicant is aware of changes to a clinical investigator's site address or contact information since the time of the clinical investigator's participation in the study, we request that this updated information also be provided.
2. Please include the following information in a tabular format, *by site*, in the original NDA for each of the completed pivotal clinical trials:
- a. Number of subjects screened at each site
 - b. Number of subjects randomized at each site
 - c. Number of subjects treated who prematurely discontinued for each site by site
3. Please include the following information in a tabular format in the NDA for each of the completed pivotal clinical trials:
- a. Location at which sponsor trial documentation is maintained (e.g., , monitoring plans and reports, training records, data management plans, drug accountability records, IND safety reports, or other sponsor records as described ICH E6, Section 8). This is the actual physical site(s) where documents are maintained and would be available for inspection
 - b. Name, address and contact information of all Contract Research Organization (CROs) used in the conduct of the clinical trials and brief statement of trial related functions transferred to them. If this information has been submitted in eCTD format previously (e.g., as an addendum to a Form FDA 1571, you may identify the location(s) and/or provide link(s) to information previously provided.
 - c. The location at which trial documentation and records generated by the CROs with respect to their roles and responsibilities in conduct of respective studies is maintained. As above, this is the actual physical site where documents would be available for inspection.
4. For each pivotal trial, provide a sample annotated Case Report Form (or identify the location and/or provide a link if provided elsewhere in the submission).
5. For each pivotal trial provide original protocol and all amendments ((or identify the location and/or provide a link if provided elsewhere in the submission).

II. Request for Subject Level Data Listings by Site

1. For each pivotal trial: Site-specific individual subject data listings (hereafter referred to as "line listings"). For each site, provide line listings for:

- a. Listing for each subject consented/enrolled; for subjects who were not randomized to treatment and/or treated with study therapy, include reason not randomized and/or treated
 - b. Subject listing for treatment assignment (randomization)
 - c. Listing of subjects that discontinued from study treatment and subjects that discontinued from the study completely (i.e., withdrew consent) with date and reason discontinued
 - d. Listing of per protocol subjects/ non-per protocol subjects and reason not per protocol
 - e. By subject listing of eligibility determination (i.e., inclusion and exclusion criteria)
 - f. By subject listing, of AEs, SAEs, deaths and dates
 - g. By subject listing of protocol violations and/or deviations reported in the NDA, including a description of the deviation/violation
 - h. By subject listing of the primary and secondary endpoint efficacy parameters or events. For derived or calculated endpoints, provide the raw data listings used to generate the derived/calculated endpoint.
 - i. By subject listing of concomitant medications (as appropriate to the pivotal clinical trials)
 - j. By subject listing, of testing (e.g., laboratory, ECG) performed for safety monitoring
2. We request that one PDF file be created for each pivotal Phase 2 and Phase 3 study using the following format:



III. Request for Site Level Dataset:

OSI is piloting a risk based model for site selection. Voluntary electronic submission of site level datasets is intended to facilitate the timely selection of appropriate clinical sites for FDA

inspection as part of the application and/or supplement review process. If you wish to voluntarily provide a dataset, please refer to the draft Guidance for Industry Providing Submissions in Electronic Format – Summary Level Clinical Site Data for CDER’s Inspection Planning” (available at the following link <http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/UCM332468.pdf>) for the structure and format of this data set.

Attachment 1

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

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

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

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



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

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

References:

eCTD Backbone Specification for Study Tagging Files v. 2.6.1

(<http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM163560.pdf>)

FDA eCTD web page

(<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm153574.htm>)

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

Attachment 2

Pre-NDA General Advice for Planned Marketing Applications

NDA and BLA applications must comply with all applicable statutes and regulations (e.g. 21 CFR 314, 21 CFR Part 201, and 21 CFR Parts 600 and 601). In addition, FDA has published many guidance documents (available at www.fda.gov/RegulatoryInformation/Guidances/default.htm) that contain important information necessary for preparing a complete, quality application.

Based on our experience with marketing applications, the following tables focus on specific areas of an application and are intended to help you plan and prepare for submitting a quality application. These comments do not include all issues you need to consider in preparing an application, but highlight areas where we have seen problems and/or issues that can delay our timely review of applications. These are general comments; if you believe some are inapplicable to your planned application we encourage you to provide justification and discuss it with us.

The **Study Data Standards Common Issues Document** can be found at: <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm> The purpose of the document is to highlight important aspects of CDISC and STDM datasets that should be addressed by the Sponsor/Applicant regarding submission of CDISC data in support of an application for registration.

NDA/BLA content and format
CLINICAL
1) Original versions of all protocols, statistical analysis plans, Data Safety Monitoring Board (DSMB) and adjudication committee charters, and all amendments.
2) Minutes of all DSMB and efficacy endpoint review/adjudication committee meetings.
3) Investigator instructions that may have been produced in addition to the protocol and investigator brochure
4) All randomization lists and, if used, IVRS datasets (in SAS transport format)
5) All datasets used to track adjudications (in SAS transport format), if any
6) A Reviewers Guide to the data submission that includes, but is not limited to the following: a) description of files and documentation b) description of selected analysis datasets c) key variables of interest, including efficacy and safety variables d) SAS codes for sub-setting and combining datasets e) coding dictionary used f) methods of handling missing data

<ul style="list-style-type: none">g) list of variable contained in every dataseth) listing of raw data definitionsi) analysis data definitionsj) annotated CRF (the annotated CRF should contain links connecting to the document that defines the variable name and lists the data sets that contain the specific item)k) documentation of programs
7) Clinical study report(s) for all trials (should follow the ICH E3 Structure and Content of Clinical Study Reports guidance (http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm073113.pdf)).
8) <u>Pediatric Studies:</u> All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is exempt (i.e. orphan designation), waived or deferred. We request that you submit a pediatric plan that describes development of your product to provide important information on the safe and effective use of in the pediatric population where it may be used. If the product will not be used in pediatric populations your application must include a specific waiver request with the NDA submission, including supporting data. A request for deferral, must include a pediatric plan, certification of the grounds for deferring the assessments, and evidence that the studies are being conducted or will be conducted with due diligence and at the earliest possible time.
9) A statement that the manufacturing facilities are ready for inspection upon FDA receipt of the application
10) A chronology of prior substantive communications with FDA and copies of official meeting/telecom minutes.
11) <u>References:</u> There should be active links from lists of references to the referenced article.
Studies, Data And Analyses
12) Provide a table listing all of the manufacturing facilities (e.g. drug product, drug substance, packaging, control/testing), including name of facility, full address including street, city, state, country, FEI number for facility (if previously registered with FDA), full name and title, telephone, fax number and email for on-site contact person, the manufacturing responsibility and function for each facility, and DMF number (if applicable).
13) Provide a table with the following columns for each of the completed Phase 3 clinical trials: <ul style="list-style-type: none">a) Site numberb) Principle investigatorc) Location: City State, Countryd) Number of subjects screenede) Number of subjects randomizedf) Number of subjects treated who prematurely discontinued (or other characteristic of

<p>interest that might be helpful in choosing sites for inspection)</p> <p>g) Number of protocol violations (Major, minor, including definition)</p>
<p>14) Provide an assessment of safety as per the Guidance for Industry: Premarketing Risk Assessment (www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072002.pdf).</p>
<p>15) Provide detailed information, including a narrative (data listings are not an acceptable substitute for a narrative), for all patients who died while on study or who terminated study drug or participation in the study prematurely including those categorized as other, lost to follow up, physician decision, or subject decision. Narrative summaries should contain the following components:</p> <ul style="list-style-type: none">a) subject age and genderb) signs and symptoms related to the adverse event being discussedc) an assessment of the relationship of exposure duration to the development of the adverse eventd) pertinent medical historye) concomitant medications with start dates relative to the adverse eventf) pertinent physical exam findingsg) pertinent test results (for example: lab data, ECG data, biopsy data)h) discussion of the diagnosis as supported by available clinical datai) a list of the differential diagnoses, for events without a definitive diagnosisj) treatment providedk) re-challenge and de-challenge results (if performed)l) outcomes and follow-up informationm) an informed discussion of the case, allowing a better understanding of what the subject experienced.
<p>16) Provide complete case report forms (CRFs) for all patients with serious adverse events, in addition to deaths and discontinuations due to adverse events. You should be prepared to supply any additional CRFs with a rapid turnaround upon request.</p> <p>17) Provide reports for any autopsies conducted on study.</p>
<p>18) For patients listed as discontinued due to “investigator decision,” “sponsor request,” “withdrew consent,” or “other,” the verbatim reason for discontinuation (as written in the CRF) should be reviewed to ensure that patients did not dropout because of drug-related reasons (lack of efficacy or adverse effects). If discrepancies are found between listed and verbatim reasons for dropout, the appropriate reason for discontinuation should be listed and patient disposition should be re-tabulated. In addition, the verbatim description from the CRF should be included as a variable in the adverse event data set.</p>
<p>19) Regulations require that the safety and effectiveness data be presented for subgroups including “by gender, age, and racial subgroups”. Therefore, as you are gathering your data and compiling your application, we request that you include this data and pertinent analysis</p>
<p>20) The clinical information contained in the NDA/BLA will be reviewed utilizing the CDER</p>

Clinical Review Template. Details of the template may be found in the Manual of Policies and Procedures (MAPP) 6010.3

(www.fda.gov/downloads/AboutFDA/ReportsManualsForms/StaffPoliciesandProcedures/ucm080121.pdf). To facilitate the review, we request you provide analyses and discussion, where applicable, that will address the items in the template, including:

- a) Other Relevant Background Information – important regulatory actions in other countries or important information contained in foreign labeling.
- b) Exposure-Response Relationships – important exposure-response assessments.
- c) Less common adverse events (between 0.1% and 1%).
- d) Laboratory Analyses focused on measures of central tendency. Also provide the normal ranges for the laboratory values.
- e) Laboratory Analyses focused on outliers or shifts from normal to abnormal. Also provide the criteria used to identify outliers.
- f) Marked outliers and dropouts for laboratory abnormalities.
- g) Analysis of vital signs focused on measures of central tendencies.
- h) Analysis of vital signs focused on outliers or shifts from normal to abnormal.
- i) Marked outliers for vital signs and dropouts for vital sign abnormalities.
- j) A comprehensive listing of patients with potentially clinically significant laboratory or vital sign abnormalities should be provided. Also, a listing should be provided of patients reporting adverse events involving abnormalities of laboratory values or vital signs, either in the “investigations” SOC or in a SOC pertaining to the specific abnormality. For example, all AEs coded as “hyperglycemia” (SOC metabolic) and “low blood glucose” (SOC investigations) should be tabulated. Analyses of laboratory values should include assessments of changes from baseline to worst value, not simply the last value.
- k) Overview of ECG testing in the development program, including a brief review of the nonclinical results.
- l) Standard analyses and explorations of ECG data.
- m) Overdose experience.
- n) Analysis and summary of the reasons and patterns of discontinuation of the study drug. Identify for each patient the toxicities that result in study discontinuation or dose reduction.
- o) Explorations for:
 - i) Possible factors associated with a higher likelihood of early study termination; include demographic variables, study site, region, and treatment assignment.
 - ii) Dose dependency for adverse findings, which should be supported by summary tables of the incidence of adverse events based on the cumulative dose and the average dose administered.
 - iii) Time dependency for adverse finding, which should be supported by analyses summarizing the length of time subjects experience adverse events and whether recovery occurs during treatment.
 - iv) Drug-demographic interactions
 - v) Drug-disease interactions
- p) Drug-drug interactions

- i) Dosing considerations for important drug-drug interactions.
- ii) Special dosing considerations for patients with renal insufficiency, patients with hepatic insufficiency, pregnant patients, and patients who are nursing.

Financial Disclosure Information

21) Marketing applications must include certain information concerning the compensation to, and financial interests of, any clinical investigator conducting clinical studies, including those at foreign sites, covered by the regulation. This requires that investigators provide information to the sponsor during the course of the study and after completion. See Guidance for Industry - Financial Disclosure by Clinical Investigators (<http://www.fda.gov/downloads/regulatoryinformation/guidances/ucm341008.pdf>).

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/s/

JULIE G BEITZ

04/07/2016

Signing for Kendall Marcus, MD



IND 105004

MEETING MINUTES

Janssen Research & Development, LLC.
Attention: Donna Kipphorn
Associate Director, Global Regulatory Affairs, Immunology
Welsh & McKean Roads
P.O. Box 776
Spring House, PA 19477

Dear Ms. Kipphorn:

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

We also refer to the teleconference between representatives of your firm and the FDA on January 27, 2016. The purpose of the teleconference was to discuss the development program for guselkumab.

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 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

Enclosure:
Meeting Minutes



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type: C
Meeting Category: Guidance

Meeting Date and Time: January 27, 2016 at 8:30 a.m.
Meeting Location: Teleconference

Application Number: IND 105004
Product Name: Guselkumab

Proposed Indication: For the treatment of adults patients with moderate to severe plaque psoriasis who are candidates for phototherapy or systemic therapy
Sponsor Name: Janssen Research & Development, LLC.

Meeting Chair: Kendall A. Marcus, MD
Meeting Recorder: Matthew White

FDA ATTENDEES

Kendall A. Marcus, MD, Director, Division of Dermatology and Dental Products (DDDP)
Snezana Trajkovic, MD, Clinical Team Leader, DDDP
Melinda McCord, MD, Clinical Reviewer, DDDP
Mohamed Alosch, PhD, Biostatistics Team Leader, Division of Biometrics III (DB III)
Matthew Guerra, PhD, Biostatistics Reviewer, DB III
Yow-Ming Wang, PhD, Clinical Pharmacology Team Leader, Division of Clinical Pharmacology 3 (DCP 3)
Jie Wang, PhD, Clinical Pharmacology Reviewer, DCP 3
Qing Zhou, PhD, Product Quality Team Leader, Division of Biotechnology Research and Review 1 (DBRR1)
Deborah Schmiel, PhD, Product Quality Reviewer, DBRR1
Mishale Mistry, PharmD, MPH, Team Leader, Division of Medication Error Prevention & Analysis (DMEPA)
Carlos Mena-Grillasca, RPh, Safety Evaluator, DMEPA
Carolyn Cochenour, BBME, Biomedical Engineer, CDRH, General Hospital Devices Branch
Matthew E. White, Senior Regulatory Health Project Manager, DDDP

SPONSOR ATTENDEES

Herren Edra, RAC, Manager, North American Regulatory Affairs
Heather Guerin, PhD, Manager, Regulatory Affairs, CMC, Devices
Ming-Chun Hsu, PhD, Senior Manager, Clinical Biostatistics

Donna Kipphorn, Associate Director, North American Regulatory Liaison
Peter Krulevitch, PhD, Director, Device Development
Shu Li, PhD, Director, Clinical Biostatistics
Douglass Mead, MSBME, Senior Director, Regulatory Affairs, CMC, Devices
Gail Miller, Associate Director, Global Regulatory Affairs, CMC
Susan Popma, OD, Director, Global Regulatory Leader
Philippe Szapary, MD, Vice President, Clinical Development, Immunology
Yasmine Wasfi, MD, PhD, Senior Director, Clinical Development, Immunology
Zhenhua (Mike) Xu, PhD, Senior Director, Biologics Clinical Pharmacology
Mingqi (Mitch) Zhao, PhD, Principal Engineer, Device Development
Yaowei Zhu, PhD, Associate Scientific Director, Biologics Clinical Pharmacology

Purpose of the Teleconference:

To discuss the development program for guselkumab, an anti-IL-23 monoclonal antibody (mAb), for the treatment of adults with moderate to severe plaque psoriasis

Regulatory Correspondence History

We have had the following meeting(s)/teleconference(s) with you:

- 4/9/2014: Type B (End-of-Phase 2) meeting
- 6/26/2013: Type C (guidance) meeting
- 11/16/2011: Type C (guidance) meeting

We have sent the following correspondences:

- 4/27/2015: Advice letter
- 3/21/2015: Advice letter
- 11/21/2014: Initial pediatric study plan (iPSP) – agreement letter
- 10/15/2014: Advice/information request letter
- 8/12/2014: iPSP written response letter
- 8/12/2014: Inadequate study request letter
- 7/7/2014: Advice letter
- 5/30/2014: Advice letter
- 3/5/2014: Information request letter
- 10/7/2013: Advice letter
- 9/5/2013: Information request letter
- 7/3/2013: Advice letter
- 6/8/2013: Information request
- 11/30/2011: Advice/information request letter
- 8/18/2011: Information request letter
- 6/3/2011: Written responses to questions submitted in a 3/11/11 briefing document
- 7/1/2009: Advice/information request letter
- 5/12/2009: Advice/information request letter

Chemistry, Manufacturing and Controls (CMC)/Device

(b) (4)



Meeting Discussion:

The Sponsor's proposal (attached) appears reasonable pending final review of the data.

Clinical

(b) (4)



Meeting Discussion:

Further information is needed to evaluate the Sponsor's proposal appended to the meeting minutes. The Agency will send a detailed information request to the Sponsor and will provide comments following review of the submitted information.

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 might identify additional comments or information requests.
2. You are encouraged to request a Pre-BLA Meeting at the appropriate time.

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.

If you have questions related to requirements under PREA, 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>.

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/s/

KENDALL A MARCUS
01/27/2016



IND 105004

MEETING MINUTES

Janssen Research & Development, LLC.
Attention: Donna Kipphorn
Associate Director, Global Regulatory Affairs, Immunology
Welsh & McKean Roads
P.O. Box 776
Spring House, PA 19477

Dear Ms. Kipphorn:

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

We also refer to the meeting between representatives of your firm and the FDA on April 9, 2014. The purpose of the meeting was to discuss the development program for guselkumab, an anti-IL-23 monoclonal antibody (mAb), for the treatment of adults with moderate to severe plaque psoriasis.

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 Matthew White, Regulatory Project Manager at (301) 796-4997.

Sincerely,

{See appended electronic signature page}

Tatiana Oussova, MD, MPH
Deputy Director for Safety
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 Type: Type B
Meeting Category: End-of-Phase 2

Meeting Date and Time: April 9, 2014; 10:00 am
Meeting Location: White Oak Building 22, Room 1415

Application Number: IND 105004
Product Name: guselkumab
Proposed Indication: For the treatment of adults with moderate to severe plaque psoriasis

Sponsor Name: Janssen Research & Development, LLC.

Meeting Chair: Tatiana Oussova, MD, MPH
Meeting Recorder: Matthew White

FDA ATTENDEES

Julie Beitz, MD, Director, ODE III
Amy G. Egan, MD, MPH, Acting Deputy Director, ODE III
Tatiana Oussova, MD, MPH, Deputy Director for Safety, DDDP
Gordana Diglisic, MD, Clinical Team Leader, DDDP
Melinda McCord, MD, Clinical Reviewer, DDDP
Barbara Hill, PhD, Pharmacology Supervisor, DDDP
Jiaqin Yao, PhD, Pharmacology Reviewer, DDDP
Mohamed Alish, PhD, Biostatistics Team Leader, DB III
Matthew Guerra, PhD, Biostatistics Reviewer, DB III
Jie Wang, PhD, Clinical Pharmacology Reviewer, DCP 3
Lin Zhou, PhD, Clinical Pharmacology Reviewer, DCP 3
Jeff Florian, PhD, Pharmacometrics Reviewer, OCP/DPM
Michele Dougherty, PhD, Product Quality Team Leader, DMA
Ram Sihag, PhD, Product Quality Reviewer, OBP/DMA
Elektra Papadopoulos, MD, Medical Officer, SEALD
Yasmin Choudhry, MD, Medical Officer, SEALD
Haihao Sun, MD, PhD, Medical Officer, SEALD
LCDR Keith Marin, MS, MBA, OCN, USPHS, Regulatory Research Officer, CDRH ODE
Lt. Quynh Nhu Nguyen, USPHS, Biomedical Engineer/Combination Products Human Factors Specialist, CDRH ODE
Jennifer Kelly, PhD, Interdisciplinary Scientist, CDRH OC
Barbara Gould, MBAHCM, Chief, Project Management Staff, DDDP
Matthew E. White, Regulatory Health Project Manager, DDDP

SPONSOR ATTENDEES

Herren Edra, RAC, Manager, North American Regulatory Affairs
Chuanpu Hu, PhD, Scientific Director, Model Based Drug Development
Donna Kipphorn, Associate Director, North American Regulatory Leader
Dennis Kraichely, PhD, Associate Director, Pharmaceutical Development
John Krayner, MS, Associate Scientific Director, Biologics Toxicology
Shu Li, PhD, Director, Clinical Biostatistics
Kelly McQuarrie, BSN, Associate Director, Patient Reported Outcomes
Douglas Mead, MSBME, Director, Global Regulatory Affairs, CMC
Heidi Needleman, PhD, Senior Director, Compound Development Team Leader
Susan Popma, OD, Director, Global Regulatory Leader
Yaung-Kaung Shen, PhD, Senior Manager, Clinical Biostatistics
Michael Song, MD, Director, Clinical Development
Kevin Wanczyk, Associate Director, Global Regulatory Affairs, CMC
Yasmine Wasfi, MD, PhD, Director, Clinical Development
Karen D. Weiss, MD, MPH, Vice President, Global Regulatory Affairs
Zhenhua Xu, PhD, Director and Fellow, Biologics Clinical Pharmacology
Newman Yeilding, MD, Vice President, Clinical Development
Yaowei Zhu, PhD, Associate Scientific Director, Pharmacokinetics

Purpose of the Meeting:

To discuss the development program for guselkumab, an anti-IL-23 monoclonal antibody (mAb), for the treatment of adults with moderate to severe plaque psoriasis

Regulatory Correspondence History

We have had the following meeting(s)/teleconference(s) with you:

- 6/26/13: Type C (guidance) meeting
- 11/16/11: Type C (guidance) meeting

We have sent the following correspondences:

- 10/7/13: Advice letter
- 9/5/13: Information request letter
- 7/3/13: Advice letter
- 6/8/13: Information request
- 11/30/11: Advice/information request letter
- 8/18/11: Information request letter
- 6/3/11: Written responses to questions submitted in a 3/11/11 briefing document
- 7/1/09: Advice/information request letter
- 5/12/09: Advice/information request letter

Chemistry, Manufacturing and Controls (CMC)

Question 1:

Does the Agency agree that the comparability data provided have demonstrated appropriate biochemical and biophysical comparability between the Phase 2 (lyophilized formulation) and Phase 3 (liquid in pre-filled syringe) clinical materials?

Response:

The data provided to date appear acceptable to support comparability of the Phase 2 lyophilized formulation and the Phase 3 liquid pre-filled syringe (PFS) formulation. FDA notes the potency of Phase 2 material is assessed by an ELISA binding assay and potency of Phase 3 material is assessed by a bioassay. As communicated previously, implementation of the bioassay as a new potency assay should be supported by data demonstrating that the bioassay is an appropriate replacement for the previous assay with respect to the information each assay provides, including information related to the assays' stability-indicating properties. FDA recommends that the binding assay is retained on the specification until data are available that demonstrate the binding assay provides no additional information on guselkumab product quality than the bioassay. FDA notes that the potency of material manufactured by different processes cannot be compared using different assay methods until data are submitted to the IND or in the licensing application demonstrating that the assays perform equivalently. FDA also recommends that the stability indicating properties of the bioassay be thoroughly characterized.

Data from additional stability timepoints for the Phase 3 drug substance (DS) and drug product (DP) batches currently being assessed to support comparability should be collected to characterize the stability profile of the Phase 3 material. Data from Phase 3 batches can be assessed against historical data from the Phase 2 DS and DP to support comparability. Please see additional comments in the FDA response to question 3 regarding stability studies for Phase 3 DS and DP.

Question 2:

Does the Agency agree with the proposed process validation plan for the validation batches?

Response:

The proposed process validation plans described in the meeting package appear to be acceptable. Final concurrence on the process validation strategy to support licensure of guselkumab will be dependent on all of the data provided in a licensing application. We have the following additional comments:

1.

2.

(b) (4)

3.

[Redacted]

(b) (4)

4. Regarding drug substance [Redacted] studies:

(b) (4)

[Redacted]

(b) (4)

5.

6.

7.

8. With regard to the drug product, shipping validation studies should be conducted and summary results provided in the BLA.

9. The Rabbit Pyrogen Test should be performed on three batches of drug product in accordance with 21 CFR 610.13(b) and summary data submitted to the BLA.

10. Certain formulations with polysorbate are known to interfere with endotoxin recovery over time in the LAL tests. The effect of hold time on endotoxin recovery should be assessed by spiking a known amount of endotoxin into undiluted drug product and then testing for recoverable endotoxin over time. The studies should be conducted using containers of similar composition as those used for drug product during hold. Effects of sampling containers on endotoxin recovery should also be evaluated.
11. 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.

Question 3:

Does the Agency agree with the proposed stability plans to support the Phase 3 clinical material and validation batches?

Response:

The proposed stability plan for guselkumab drug product appears to identify appropriate accelerated and stressed storage conditions. The impact of conditions such as, but not limited to, exposure to variations in pH or exposure to light should also be assessed as part of the stability program for guselkumab drug product. See ICH guidance on the full range of stability studies that should be performed for licensure (ICH Q5C, Q1AR2 and Q1B).

Regarding the proposed drug substance stability plan:

1. Sufficient information is not provided (b) (4)
Data supporting that (b) (4)
should be provided in the licensing application.
2. The stability program for drug substance should take into consideration recommendations found in ICH Q5C and ICH Q1A and include conditions that promote product degradation to identify stability indicating assays and the predominant degradation pathways for guselkumab drug substance.

Question 4:

Does the Agency agree that the proposed plan for design verification and validation tests, assembly process validation, and functional stability tests for the (b) (4) Passive Delivery System (PFS) (b) (4) will be sufficient to support ap oval (u) (4) with guselkumab?

Response:

Your proposed plan appears reasonable.

In addition, include the following design verification and validation tests and functional stability tests in the BLA submission:

1.  (b) (4)
2. For the pre-filled syringe: provide a 510(k) number for the syringe or a declaration of conformity to the relevant ISO standard {e.g., glass (11040) or plastic syringes (7886)}.
3. For the staked needle: provide a declaration of conformity to the ISO standard for staked needles (9626).
4.  (b) (4)
5. For the needle stick protection device: provide the 510(k) number or provide performance data according to the FDA guidance for industry *Medical Devices with Sharps Injury Prevention Features*.
6. For the  PFS: conduct performance/functional testing at the end of expected shelf life {e.g., testing of activation force, dose accuracy or ability to extrude complete dose , breakloose force and glide force (for the PFS)}.

Pharmacology/Toxicology

Question 5:

Does the Agency agree that the completed nonclinical toxicology program is sufficient to support registration of guselkumab for a psoriasis indication?

Response:

It appears that the nonclinical toxicology program is sufficient to support registration of guselkumab for a psoriasis indication, in principle. However, in the male fertility and early

embryonic development toxicology study in guinea pigs, five untreated sows in the 100 mg/kg dose group had 100% early resorbed litters. As a result, the average number of early resorptions per litter and the percentage of post-implantation loss were increased in the 100 mg/kg dose group, as compared to controls. It appears that sperm motility, sperm count, and/or sperm density in the 5 males treated with 100 mg/kg guselkumab and mated with the 5 sows with 100% early resorbed litters were less than those in all groups. Provide the historical control ranges for these parameters in male guinea pigs and provide a more detailed rationale to support that these effects are not treatment related.

Question 6:

Does the Agency agree with the Sponsor's position that additional in vitro or in vivo studies to assess the potential carcinogenicity of guselkumab are not necessary?

Response:

Yes, we agree that additional in vitro or in vivo studies to assess the potential carcinogenicity of guselkumab are not necessary. The Executive Carcinogenicity Assessment Committee provided concurrence with this assessment on February 18, 2014. The carcinogenic potential of guselkumab will be further reviewed under the BLA.

Question 7:

- a. Does the Agency agree that the PK comparability of the 2 formulations of guselkumab (lyophilized formulation and liquid formulation) has been adequately demonstrated?
- b. (b) (4)
[Redacted]

Response:

We do not agree that PK comparability of the 2 formulations of guselkumab (lyophilized formulation and liquid formulation) has been adequately demonstrated. The results of your PK comparability study (CNT01959NAP1001) as summarized in the briefing package showed that the exposure of guselkumab appeared to be comparable between the lyophilized formulation and the liquid formulation supplied as PFS^{(b) (4)} following a single 100 mg subcutaneous injection in healthy subjects; (b) (4)
[Redacted]



We have the following additional comments:

1.  (b) (4)
2. 
3. Regarding the liquid Guselkumab in a PFS with  (b) (4) Passive Delivery System (PFS  (b) (4) presentation, clarify if you plan to submit a human factors study (HFS) protocol for review. You indicated that you have completed a PFS  (b) (4) HFS in 2012 as a platform device that included normal and hand impaired patients and a high and low viscosity PFS. If you intend to use these data to support the use of  (b) (4)  Passive Delivery System (PFS  (b) (4) with liquid guselkumab then provide the following:

- a. Provide a description of any modifications to the device and in particular to the user interface, to accommodate its use with liquid guselkumab, and indicate whether the changes have been validated.
- b. Provide a use-related risk analysis. This analysis should include all use-related risks with particular emphasis on any differences in use or in risks associated with use errors that are specific to the new drug (such as the risk of overdose or underdose, how the drug is handled, or how dose is determined by the user).
- c. Provide a rationale for why you believe that additional human factors testing is not needed for the use of the device with the proposed drug.

Meeting Discussion:

The sponsor stated that their justification was provided to the IND. The Agency will review the submission and provide a response.

Post Meeting Addendum:

We have the following comments regarding your Summative Human Factor Protocol.

A. Study Design

1. Your Human Factors Protocol does not address: (a) evaluation of the back of the arm as an injection site by a healthcare provider or caregiver, (b) injection experience versus injection naïve users, and (c) the literacy level of the study participants.

Your current study design includes two study arms: Group 1 – 15: patients with Rheumatoid Arthritis and/or Psoriatic Arthritis to represent worst case scenario in terms of patient handling/ergonomics and Group 2 – 15: patients with Psoriasis, Ulcerative Colitis, and/or Crohn’s Disease. These study participants will perform a self injection in either the thigh or the abdomen. Therefore, we recommend that you add a third arm to your study (n=15 participants) that include healthcare providers and/or caregivers that will perform the simulated injection on the back of the arm. This scenario will evaluate the safe and effective use of the pre-filled syringe (b) (4) injection device when used by another person attempting to inject on the arm of a patient.

In addition, you should recruit participants that are injection naïve as well as injection experienced for each of the three arms of the study.

Finally, you should ensure that the literacy levels for the chosen demographics are representative of the current United States Literacy Level. Justify your approach in the summary report.

2. We note that you plan to evaluate some tasks by means of reading comprehension and/or knowledge probe. However, while this is appropriate for tasks such as “wash hands”, “identify allowable injection sites”, and “device disposal”, we find that it is unacceptable for tasks such as “inspect fluid in window” and “clean injection site” as these are easily

assessed by observation during the HF session. Revise the Human Factors protocol to include assessment of the inspection of fluid and cleaning injection site by direct observation during the study session.

B. Appendix C – Session Introduction/Overview (page 36)

1. We note that your script for the Study Introduction to the participant includes the following sentence, (b) (4)
(b) (4) This statement may bias the participants (b) (4). To better represent the real world scenario in which a patient would pick up a prescription from the pharmacy and use the product at home with or without help (either from another person or by referencing the materials provided with the product), you should only provide the study participant with the box containing the pre-filled syringe-facilitated injection device and the IFU and ask the patient to perform the injection as they would do at home. Therefore, we request that you delete the statement (b) (4)
(b) (4)

C. Appendix E – Validation Test Protocol

1. Supervised Injection (page 37)
 - a. To address comment A.2. above, under observations add “Failure to inspect fluid in window” and “Failure to clean injection site”.
2. Session 2 Protocol, Section 2, Unaided Injection (page 41)
 - a. Add “back of arm” as an allowable injection site.
 - b. Delete the phrase (b) (4) so that the statement reads “When you are ready, go ahead and administer the injection in the same manner as you would if this was your very first time doing your injection at home.” The phrase (b) (4) may bias the participants (b) (4).
 - c. To address comment A.2. above, under observations add “Failure to inspect fluid in window” and “Failure to clean injection site”.

D. Appendix F – Enrollment Form (page 44)

1. We note that participants that (b) (4) will not be enrolled in the study. However, this is not representative of the real life scenario where a patient is not expected to (b) (4) as a condition to being prescribed a drug. By excluding study participants that (b) (4) the results of the study would not be representative or all type of users and will bias the study towards favorable results. We request that you do not include (b) (4) criterion to the training session and to not exclude study participants that (b) (4) the training.

E. Appendix G – Failure and High-Risk Error Debrief Log (page 45)

1. Add “back of arm” as an allowable injection site.
2. To address comment A.2. above, under Task Failure add “Failure to inspect fluid in window” and “Failure to clean injection site”.

Question 9:

Does the Agency agree that in vivo drug interaction studies designed specifically to address the effect of guselkumab on other drugs (i.e., therapeutic protein-drug interaction studies) are not required to support the submission and registration of guselkumab?

Response:

No, we do not agree. You should conduct in vivo studies in the target patient population to evaluate the disease-drug-drug interaction (Disease-DDI) potential between guselkumab and other CYP substrates. We prefer that the results from such disease-DDI studies are submitted in the original BLA package.

Our recommendation is based on the current understanding that elevated cytokines associated with inflammatory disease conditions can suppress some CYP enzymes which could be normalized upon improvement of the inflammatory disease conditions due to reduction of proinflammatory cytokines following treatment with therapeutic proteins. Psoriasis is a chronic inflammatory disease condition that involves altered expression of a broad spectrum of proinflammatory cytokines and the treatment of psoriasis with biological products can reduce proinflammatory cytokine levels.

We recommend a step-wise approach. For instance, one can conduct a study to first define the impact of psoriasis disease condition on the exposure of CYP substrate drugs (i.e., the disease-drug interaction). Such study may involve evaluating the exposures of CYP substrate drugs in healthy subjects and in subjects with psoriasis. In the event that the disease-drug interaction is deemed clinically meaningful, the impact of guselkumab treatment on observed disease-drug interaction as measured by the exposure of CYP substrate drugs can be further evaluated in a subsequent study to evaluate the Disease-DDI. We are open to further discussion regarding the clinical study design to evaluate the psoriasis disease-DDI for your product.

Refer to the following guidance for more information:

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM292362.pdf>

Question 10:

Does the Agency agree that the current assay for antibodies to guselkumab is adequate for assessing the immunogenicity of guselkumab in Phase 3 studies to support the submission and registration of guselkumab?

Response:

Adequate information is not provided to assess the appropriateness of the anti-drug antibody (ADA) assay for assessing immunogenicity in the Phase 3 clinical program. To reach

concurrence on the appropriateness of the ADA assay to support phase 3 clinical development and licensure, submit the full validation report and method SOP to the IND.

No information is provided regarding an assay capable of detecting neutralizing anti-drug antibodies. FDA recommends that a neutralizing assay that is capable of sensitively detecting neutralizing antibodies in the presence of levels of guselkumab expected to be present in patient samples be developed and appropriately validated.

Clinical/Biostatistics

Introductory Clinical/Biostatistics Comments:

You proposed to conduct the following 3 Phase 3 clinical trials conducted in subjects with moderate to severe plaque-type psoriasis:

1. **Trial CNTO1959PSO3001:** multicenter, randomized, double-blind, active comparator (adalimumab)-controlled study in 400 subjects. Trial consists of two periods: Blinded Treatment Period (Week 0 to Week 52) and Open Label Treatment Period (Week 52 to Week 156)

Primary Objectives:

- To compare the efficacy of guselkumab to adalimumab
- To assess the safety and tolerability of guselkumab

Primary Endpoint:

- The proportion of subjects who achieve an IGA score of 0 (clear) or 1 (minimal) at Week 28

2. **Trial CNTO1959PSO3002:** multicenter, randomized, double-blind, placebo and active comparator-controlled (adalimumab) study in 1000 subjects. Trial consists of Active Comparator Controlled Period (Week 0 to Week 28), Randomized Withdrawal Period (Week 32 to Week 52) and Open Label Treatment Period (Week 52 to Week 156)

Primary Objectives

- To evaluate the efficacy and safety of guselkumab

Secondary objectives:

- To compare the efficacy of guselkumab to adalimumab
- To evaluate the maintenance of response to guselkumab in subjects continuing on a 100 mg q8w regimen compared with the maintenance of response in subjects that have active treatment withdrawn

Primary Endpoint:

- The proportion of subjects who achieve an IGA score of 0 (clear) or 1 (minimal) at Week 16 between the guselkumab treatment group and the placebo treatment group

Major Secondary Endpoints:

- The proportion of subjects who achieve a PASI 75 response at Week 16 between the guselkumab treatment group and placebo treatment group
- The proportion of subjects who achieve an IGA score of 0 (clear) or 1 (minimal) at Week 28 between the guselkumab treatment group and adalimumab treatment group

3. **Trial CNTO1959PSO3003:** multicenter, randomized, double-blind study evaluating the efficacy and safety of guselkumab vs. ustekinumab (STELARA[®]) in the treatment of 800 subjects who have had an incomplete response ((b) (4)) at Week 16) to treatment with ustekinumab

Primary Objectives:

- To compare the efficacy of switching to guselkumab to that of continuing on ustekinumab in subjects who have an incomplete response to ustekinumab ((b) (4)) at Week 16
- To assess the safety of guselkumab

Primary Endpoint:

- The proportions of subjects who achieve an IGA score of 0 at Week 40 among randomized subjects with an incomplete response to ustekinumab ((b) (4)) at Week 16

It should be noted that the proposed Phase 3 trials have different designs, different timepoints for efficacy evaluation and different endpoints. Regarding trial CNTO1959PSO3001, the absence of a placebo arm may impact the efficacy assessment. By including a placebo arm in the trial, you would enable a more objective assessment of efficacy and consequently a more meaningful interpretation. Two placebo-controlled clinical trials are recommended.

In trial CNTO1959PSO3001 and CNTO1959PSO3002, you intend to evaluate superiority of guselkumab over adalimumab at Week 28. However, the efficacy evaluation for the approved product (adalimumab) was conducted at Week 16. For a claim against an active comparator, the comparison should be made for the same timepoint for which the comparator was approved; therefore, an efficacy claim against adalimumab should be done at Week 16 using the same endpoint (IGA of “clear” or “almost clear” and PASI 75). In trial CNTO1959PSO3002, the definition of “response” for the re-randomization at Week 32 and the definition of “loss of response” are based on PASI 90, while success is based on IGA. The Agency recommends that the definitions of response, relapse, and rebound be based on IGA and PASI 75 so that the same endpoints are used throughout the various periods of the trial.

Regarding trial CNTO1959PSO3003, you should evaluate subjects who are non-responders (e.g., subjects who fail to achieve IGA of “clear” or “almost clear” and PASI 75) to ustekinumab at the same timepoint for which the comparator was approved.

In addition, there is a lack of specificity in the statistical methodology. In trial CNTO1959PSO3001, testing for superiority will be conducted first and, if not significant, then

testing for non-inferiority will be conducted; however, it should be noted that such an approach does not control the Type I error rate. In trial CNTO1959PSO3003, the interim analysis is based on a subset of subjects without specifying the number of subjects or providing sufficient detail on the implementation of the proposed approach. For all primary endpoints, missing data will be imputed as nonresponders/failures. However, the appropriateness of such an approach is dependent on the amount of missing data in each treatment arm. The method for handling missing data for the secondary endpoints is not indicated.

(b) (4)

Question 12:

Does the Agency agree with the dose rationale and the proposed dose and regimen selected for study in Phase 3 of 100 mg every 8 weeks?

Response:

The proposed dosing regimen of 100 mg every 8 weeks (q8w) is reasonable for evaluation in Phase 3 based on the results from trial CNTO1959PSO2001 and the provided pharmacokinetic/pharmacodynamics (PK/PD) analyses.

However, the provided information does not exclude that a lower dose (50 mg q8w) could attain similar efficacy results, nor does it exclude that increases in more stringent endpoints (PASI 100

or PGA 0) could be achieved with higher dosing. Finally, the available safety data is not sufficient to conclude whether there are any dose- or exposure-related toxicities associated with guselkumab treatment. As such, inclusion of the 50 mg q8w dosing regimen in your Phase 3 trials may be beneficial. We recommend additional simulations as justifications for selecting 100 mg q8w as the only regimen to study in Phase 3.

We acknowledge that the current exposure-response PASI and PGA modeling analyses may provide additional information regarding the predicted responses rates of alternate dosing regimens; however, it is difficult to discern differences between a 50 mg q8w, 100 mg q8w, and 200 mg q8w regimen based upon the analyses currently included in the briefing package. To assist the review team in assessing differences between these three regimens you may provide additional simulations as part of dosing justification when the Phase 3 protocols are submitted for review.

Provide additional simulations using the developed PK/PD model for endpoints of PGA 0/1, PGA 0, PASI 75, and PASI 100, at treatment weeks 8, 16, 24, and 32 for the dosing regimens listed above. These simulations should include the predicted median (90% PI) response rate for each of these endpoints at the listed time points. In addition, we request a similar analysis be provided for patients with body weight >90 kg and body weight ≤90 kg to assist the review team in interpreting whether response rates would be consistent across a range of body weights.

Question 13:

- a. Does the Agency agree that the proposed study designs for studies CNTO1959PSO3001 and CNTO1959PSO3002 are adequate to potentially demonstrate superiority of guselkumab over adalimumab?
- b. In the event these studies demonstrate superiority of guselkumab over adalimumab, the Sponsor intends to describe the results, including a superiority claim, in the Clinical Trials section of the USPI; does the Agency agree?

Response:

See the responses to the previous questions regarding various trial design deficiencies.

Comparative efficacy information for systemic psoriasis products could be a useful addition to product labeling.

Replication of findings would be required; therefore, both trials should use the same endpoint and the comparison should be made for the same timepoint for which the comparator (adalimumab) was approved (i.e., Week 16).

Furthermore, trials utilizing comparator products should use the U.S. approved product.

The final content of labeling will be determined by review of the data submitted in your BLA.

Meeting Discussion:

The Agency made a distinction between a comparative efficacy claim against an approved product and comparative information during maintenance. For establishing a comparative

efficacy claim, the same endpoints as well as timepoints should be used as for the approved product. For describing maintenance of response, the trial should pre-specify criteria for loss of response using the same endpoints as for defining success and pre-specify a targeted response by a certain timepoint(s). Maintenance information can be pre-specified as secondary endpoints.

Question 14:

The Sponsor intends to seek labeling indicating that guselkumab should be used as continuous maintenance therapy (i.e., 100 mg q8w). As such, the Sponsor has designed the CNTO1959PSO3002 study to evaluate maintenance of response, safety of retreatment, and duration of response after cessation of therapy.

- a. Does the Agency agree that the proposed evaluation of maintenance of response in the randomized withdrawal design, including 1) criteria for withdrawal and 2) endpoints for the evaluation of maintenance of response, are adequate to potentially demonstrate that continuous maintenance therapy is superior to withdrawal of therapy?
- b. Does the Agency agree that the proposed evaluation of withdrawal and retreatment will adequately address safety questions, e.g., rebound psoriasis, the appearance of variant forms of psoriasis upon withdrawal, and the occurrence of hypersensitivity reactions with retreatment?
- c. Does the Agency agree that the proposed evaluation of withdrawal and retreatment will adequately evaluate duration of response after cessation of therapy and recapture of response after retreatment?

Response:

Refer to the Clinical/Statistical Introductory Comments.

Response to a and c:

In Trial CNTO1959PSO3002 at Week 32, non-responders, defined as subjects who do not achieve a PASI 90, will continue on guselkumab and responders will be re-randomized to continued treatment with guselkumab or withdrawal of treatment. Upon loss of response, defined as a loss of 50% of the improvement in PASI achieved at Week 32, subjects will be retreated with guselkumab. However, success at Week 16 is based on IGA.

The Agency recommends that the definitions of response, relapse, and rebound be based on IGA and PASI 75 so that the same endpoints are used throughout the various periods of the trial. It may be more useful to estimate the proportion or compare response to a pre-specified fixed threshold on IGA. In addition, due to possible subject dropout and the inherent branching of the treatment arms in your trial design, it might be difficult to produce reliable estimates for endpoints related to this period of the trial.

Response to b:

If you intend to address the appearance of variant forms of psoriasis upon withdrawal, and the occurrence of hypersensitivity reactions with retreatment, you should include in the protocol the specific assessments that you intend to conduct in your evaluation.

Meeting Discussion:

See the meeting discussion below Question 13. In particular, the Agency recommended that the same endpoints be used consistently throughout the trial.

Following establishing efficacy based on the co-primary endpoints (IGA and PASI 75), success on PASI 90 can be a key secondary endpoint.

The sponsor should provide justification that the difference between PASI 75 and PASI 90 is clinically meaningful.

Question 15:

The Sponsor intends to seek labeling indicating that guselkumab is effective in subjects with an incomplete response to ustekinumab (STELARA), supported by data from the proposed CNTO1959PSO3003 study, if positive. Does the Agency agree that this proposed study design, including the definition of the population of ustekinumab incomplete responders [REDACTED] (b) (4) is adequate for the assessment of guselkumab efficacy in this population and inclusion of the results in the Clinical Trials section of the USPI if the data support this?

Response:

For your proposed comparative labeling claim, data from 2 adequate and well-controlled trials are recommended. A more clinically meaningful comparison may be to evaluate whether guselkumab is effective in subjects who are non-responders to ustekinumab (fail to achieve IGA of “clear” or “almost clear” and PASI 75). Since the primary efficacy endpoint for ustekinumab approval was Week 12, then treatment effect should be assessed at that time point for reassignment of non-responders to guselkumab.

Address how you will analyze the data with regard to the potential synergistic effect of the two products in subjects who will receive guselkumab at Week 16. In addition, provide your rationale for proposing the timepoint for primary efficacy assessment at Week 40.

Refer to the Clinical/Statistical Introductory Comments regarding the interim analysis.

Meeting Discussion:

The Agency stated that the definition of non-responders as well as the enrollment criteria needs to be the same for guselkumab and ustekinumab.

Question 16:

Does the Agency agree that the proposed static 5 point IGA is appropriate to assess psoriasis severity and the efficacy of guselkumab in the Phase 3 program?

Response:

Your proposed 5-point “Investigator’s Global Assessment (IGA)” scale is calculated from a number of variables that are not used routinely in clinical settings and not easily translated into labeling.

As previously communicated, we prefer a global assessment scale with a limited number of categories which are clinically meaningful, clearly defined, mutually exclusive, and non-comparative. The category descriptors should incorporate the relevant aspects of the disease, which for psoriasis includes erythema, scaling and plaque elevation. The scale should be static and objective. The “Clear” category should represent true absence of disease (Advice Letter dated 11/30/2011).

Question 17:

Does the Agency agree that symptom score data from the Psoriasis Symptom and Sign Diary (PSSD), evaluated as a secondary endpoint is sufficient to support inclusion of the data in the Clinical Trials section of the USPI if positive?

Response:

As previously communicated, the Agency notes that information and advice about the ability of the instrument to measure psoriasis symptoms does not necessarily imply that those particular patient-reported outcomes are appropriate for eventual product labeling.

As recommended by the Agency (Guidance Meeting conducted June 26, 2013) , you modified the Psoriasis Symptom and Sign Diary (PSSD) to include separate sub-scales for psoriasis symptoms (itching, pain, stinging, burning and skin tightness) and psoriasis signs (skin dryness, cracking, scaling, shedding or flaking, redness and bleeding) for the validation study. Some items such as burning, stinging, pain may represent essentially the same concept. It is not clear how you distinguish the concept of pain from the closely related concepts of stinging and burning. We recommend that you provide the rationale for including “pain/burning/ stinging” and “skin tightness” as symptoms and provide a description of the percentage of subjects who spontaneously mentioned “pain/burning/ stinging” and “skin tightness” in the qualitative research. Present data which indicates that subjects understood the item on skin tightness as intended. Our review of a previous submission indicated that subjects participating in the qualitative research understood this item variably. Provide qualitative data to support your conclusion that subjects with moderate to severe psoriasis can distinguish the closely related concepts of pain, burning and stinging.

Some patients with psoriasis may have pruritus. The subpopulation with symptom of pruritus should be defined in the inclusion criteria with this symptom severity measured on an acceptable, validated scale. You should propose a success criteria based on the severity of symptoms which takes into account assessment of symptom severity during the course of the trial. The responder definition should be specified *a priori* using data from previously conducted clinical trials or observational studies. Additionally, to include the results for a particular subgroup analysis in labeling, you should pre-specify the subgroup(s) you plan to investigate, have a sufficient number of subjects in the subgroup(s), and should have replication of the findings from two well-controlled trials. You should also consider stratification to ensure balance across the treatment arms for subgroup size.

If symptoms vary from day to day, you may want to consider using a daily diary (rather than a longer recall period) to minimize recall effect and to avoid requiring patients to mentally average

symptoms across a long period of time. This is not a regulatory requirement, but may improve the ability of the instrument to detect treatment effect on pruritus.

Meeting Discussion:

The sponsor stated that pruritus [REDACTED] (b) (4) will be used as an inclusion criterion for a subpopulation of patients with pruritus. The Agency noted that for describing treatment benefit for this symptom, subjects should have a minimum symptom severity at baseline along with protocol specified criteria defining treatment success for this symptom.

Question 18:

[REDACTED] (b) (4)

Question 19:

The Sponsor intends to describe the primary endpoints, major secondary endpoints and relevant other secondary endpoints (e.g., (b) (4)

(b) (4) in the product labeling if data supports. Does the Agency agree with the planned primary and major secondary endpoints and the analysis approaches, including the multiplicity adjustment for the primary and major secondary endpoints for the three Phase 3 studies with guselkumab?

Response:

To establish the safety and efficacy of your product in subjects with moderate to severe psoriasis, 2 adequate placebo-controlled trials are recommended. See the response to Question 13.

The Agency prefers that you use co-primary endpoints based on a static IGA scale (where success is defined as “clear” or “almost clear” with a 2 grades reduction from baseline) and PASI 75.

See the Clinical/Statistical Introductory Comments and responses to Questions 14 and 16.

In addition, the Agency has the following comments:

- Your proposal to analyze binary endpoints using a Cochran-Mantel-Haenszel (CMH) test stratified by the variables used to stratify the randomization appears reasonable. For continuous endpoints, you plan to analyze these endpoints using an analysis of variance

(ANOVA) model based on “appropriate rank scores” with the variables used to stratify the randomization as factors. You did not provide your justification as to why rank data should be used instead of unranked data. It should be noted that unless there is extreme departure for the assumptions required for ANOVA, the preference is for analysis and interpretation of the original data.

- You propose many major and other secondary endpoints. Secondary endpoints intended for labeling should be limited in number, clinically meaningful, and adjusted for multiplicity. Your proposed sequential testing procedure for testing the primary and major secondary endpoints does control the Type I error rate for the endpoints included in the sequence. It should be noted that the results from endpoints not included in the multiplicity strategy will be considered exploratory.
- The Agency is interested in evaluating the center-to-center variability to assess the consistency in your efficacy findings. Therefore, the Agency recommends that randomization be stratified by center and the analysis should account for such stratification. In addition, the trial should be designed to have a reasonable number of subjects per treatment arm per center (e.g., 8 subjects). Efficacy results by weight can be obtained from subgroup analysis.

Meeting Discussion:

The Agency reiterated the comment that trial CNTO1959PSO3001 should include a placebo arm to facilitate interpretation of study findings. In addition, the Agency reiterated the comment regarding randomization stratified by center to investigate center to center variability in assessment of response.

Question 20:

Does the Agency agree with [REDACTED] (b) (4)

Response:

No. [REDACTED] (b) (4)

Question 21:

Does the Agency agree that the proposed safety database is adequate to support initial registration of guselkumab for the treatment of moderate to severe plaque-type psoriasis?

Response:

See the response to Question 19.

Your proposal appears reasonable. The number of subjects needed to demonstrate safety may be substantially higher than the number of subjects needed to demonstrate efficacy and as such will greatly depend on the safety data collected from previous trials and any safety signal detected.

Refer to the guideline for industry *The Extent of Population Exposure to Assess Clinical Safety: for Drugs Intended for Long term Treatment of Non-Life-Threatening Conditions*.

Additional Comments

1. You proposed to dose subjects over 52 weeks (trial CNTO1959PSO3001 and CNTO1959PSO3002). Withholding of therapy from subjects who are not responders for this extended period of time is unethical. You should propose a plan on how you will address this issue.

Meeting Discussion:

The sponsor will propose stopping criteria and the Agency will review and comment.

2. You propose to stratify enrollment by baseline weight in all 3 Phase 3 trials {e.g. trial CNTO1959PSO3001 and Trial CNTO1959PSO3002 (e.g. ≤ 90 kg, > 90 kg) and trial CNTO1959PSO3003 (e.g. ≤ 100 kg, > 100 kg)}. Clarify your rationale for not selecting the same stratification criteria (e.g. ≤ 100 kg, > 100 kg) for all trials.
3. You propose to exclude subjects with previous exposure to guselkumab and adalimumab in trial CNTO1959PSO3001 and trial CNTO1959PSO3002; you propose to exclude subjects with previous exposure to guselkumab and ustekinumab in trial CNTO1959PSO3003. Discuss your approach to the analysis of data from subjects previously exposed to biologic products.
4. Because you propose to include FDA approved biologic products as comparators in your Phase 3 trials, we remind you to document in your Phase 3 protocols that you are using US-licensed products.
5. You propose to allow concomitant short-term use of corticosteroids for other indications during the trials and hydrocortisone 2.5% after Week 16 on the face and groin in Trial CNTO1959PSO3002. The use of oral corticosteroids or any class of topical steroid products should not be allowed during the trials because it may confound the assessment of treatment effect.
6. Provide your rationale for requiring 2 highly effective methods of birth control for female subjects of child-bearing-potential and males who are sexually active with females of child-bearing-potential.
7. Your safety evaluation should include an analysis of pre-specified adverse events of special interest (e.g., malignancy, infection, hypersensitivity, cardiovascular disease, autoimmune disease, depression, etc.) to fully characterize the risks and benefits of your product in the proposed target population.

8. We recommend periodic cardiac safety monitoring in clinical trials (e.g., ECGs baseline, steady state and end of treatment) to capture any important cardiovascular effects. If there is evidence of a proarrhythmic signal (e.g., QT prolongation on routine ECG or ventricular arrhythmia) from exposure to your drug product during your trials, then a TQT or additional data may be requested.

Your cardiovascular assessment should include documentation and adjudication of thrombotic events, cerebrovascular events and Major Adverse Cardiovascular Events (MACE). Major adverse cardiovascular events include non-fatal myocardial infarction (MI), non-fatal stroke, and cardiovascular death. Extended MACE includes the following events: non-fatal MI, non-fatal stroke, cardiovascular death, unstable angina documented by a hospitalization or emergency department visit, and coronary revascularization (percutaneous coronary intervention (PCI) or coronary artery bypass graft surgery (CABG)).

Other cardiovascular events include unstable angina documented by a hospitalization, coronary revascularization, transient ischemic attack, venous and peripheral arterial vascular thrombotic events, congestive heart failure, cardiac arrhythmia – no evidence of ischemia, and other serious non-MACE cardiovascular events such as syncope of a cardiovascular origin and severe/accelerated hypertension leading to hospitalization.

- a. To capture all possible MACE and thrombotic events, examine all preferred terms (PT) and Standardized MedDRA Queries (SMQs) under:
 - Ischemic Heart Disease SMQ /Myocardial Infarction SMQ/ Other Ischemic Heart Disease SMQ)
 - Cardiac Arrhythmias SMQ
 - Cardiac Failure SMQ
 - Embolic and Thrombotic Events SMQ (including Embolic and Thrombotic Events, Vessel Type Unspecified and Mixed Arterial and Venous SMQ)
 - Shock SMQ
 - Torsade de pointes/QT prolongation SMQ
 - Cerebrovascular Disorders SMQ
 - Central Nervous System Haemorrhages and Cerebrovascular Accidents SMQ
 - Vasculitis SMQ
 - Cardiomyopathy SMQ
 - Hemodynamic Edema, effusions, and fluid overload SMQ
 - Hypertension SMQ
 - Pulmonary Hypertension SMQ
 - Renovascular Disorders SMQ

- b. Review all of the following SOCs for possible cardiac events, thrombotic and MACE, since cardiac events may be found in several SOCs:
 - Vascular Disorders
 - Cardiac Disorders
 - Nervous System Disorders
 - Respiratory, Thoracic, and Mediastinal Disorders
 - General Disorders and Administration Site Conditions
 - Injury, Poisoning, and Procedural Complications
 - Investigations
 - Musculoskeletal and Connective Tissue Disorders
 - Surgical and Medical Procedures
- c. Have all possible cardiovascular events (rather than only MACE) reviewed by a DMC with expertise in cardiovascular adverse events.
- d. Have all TIAs reviewed by the DMC (rather than only those resulting in hospitalization).
- e. Evaluate possible thrombotic events alone and MACE alone during the uncontrolled period of the global psoriasis studies.

Refer to Appendix 1 for definitions of MACE events and other cardiovascular events.

9. Since pharmacogenomics analyses were proposed in this protocol, the following are recommended:
 - All the steps involved in sample collection, storage, RNA/DNA isolation, RNA/DNA storage should take sample integrity and quality into consideration. Poor quality RNA/DNA, impure, and/or contaminated RNA/DNA can lead to suboptimal results and will not perform well in downstream applications. We understand that it is not always possible to draw definitive conclusions from the downstream application studies. In such cases, we encourage the Sponsor to submit these studies to the FDA as a Voluntary Genomic Data Submission (VGDS). Please see the FDA genomics website at www.fda.gov/cder/genomics for information.

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 might identify additional comments or information requests.
2. Please refer to the Guidance for Industry: Special Protocol Assessment and submit final protocol(s) to the IND for FDA review as a **REQUEST FOR SPECIAL PROTOCOL**

ASSESSMENT (SPA). Please clearly identify this submission as an SPA in bolded block letters at the top of your cover letter. Also, the cover letter should clearly state the type of protocol being submitted (i.e., clinical or carcinogenicity) and include a reference to this End-of-Phase 2 meeting. Ten desk copies (or alternatively, an electronic copy) of this SPA should be submitted directly to the project manager.

3. 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).
4. In your clinical development program, you will need to address the clinical evaluation of the potential for QT/QTc interval prolongation (see ICH E14). Please plan to address this issue early in development.
5. You are encouraged to request a Pre-BLA Meeting at the appropriate time.

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. 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 Pediatric and Maternal Health Staff 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 of 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, 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. We encourage you to use the SRPI checklist as a quality assurance tool before you submit your proposed PI.

DATA STANDARDS FOR STUDIES

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

LABORATORY TEST UNITS FOR CLINICAL TRIALS

CDER strongly encourages IND sponsors to identify the laboratory test units that will be reported in clinical trials that support applications for investigational new drugs and product registration. Although Système International (SI) units may be the standard reporting mechanism globally, dual reporting of a reasonable subset of laboratory tests in U.S. conventional units and SI units might be necessary to minimize conversion needs during review. Identification of units to be used for laboratory tests in clinical trials and solicitation of input from the review divisions should occur as early as possible in the development process. For more information, please see [CDER/CBER Position on Use of SI Units for Lab Tests](#).

ABUSE POTENTIAL ASSESSMENT

Drugs that affect the central nervous system, are chemically or pharmacologically similar to other drugs with known abuse potential, or produce psychoactive effects such as mood or cognitive changes (e.g., euphoria, hallucinations) need to be evaluated for their abuse potential and a proposal for scheduling will be required at the time of the NDA submission [21 CFR 314.50(d)(5)(vii)]. For information on the abuse potential evaluation and information required at the time of your NDA submission, see the draft guidance for industry, “Guidance for Industry Assessment of Abuse Potential of Drugs”, available at:

IND 105004
Meeting Minutes
Type B (End-of-Phase 2)

Office of Drug Evaluation III
Division of Dermatology and Dental Products

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM198650.pdf>.

Appendix 1

Major Adverse Cardiovascular Events (MACE) Events – Definitions

Non-Fatal Myocardial Infarction:

The presence of 2 of the 3 following criteria: a) chest pain, b) any abnormal value of cardiac biomarkers (MB fraction of creatinine phosphokinase and/or troponin), c) myocardial injury current or the development of Q waves in 2 contiguous leads of the electrocardiogram.

Non-Fatal Stroke:

Ischemic or hemorrhagic stroke defined as an acute, focal neurologic event that persisted for > 24 hours. Confirmation by imaging studies (magnetic resonance imaging or computerized tomography of the brain) will be sought in all cases, but will not be required for adjudication of the event.

Cardiovascular death:

Including sudden/unexplained death, or other cardiac death (arrhythmia or congestive heart failure)

Other Cardiovascular Events (includes serious ischemic, heart failure, and arrhythmia categories that do not meet the MACE criteria) – Definitions

Unstable Angina:

Documented by a hospitalization or emergency department visit, not meeting the acute MI definition above, and characterized by ischemic discomfort at rest for at least 10 minutes. Corroboration with cardiac testing and/or imaging typically is required.

Coronary Revascularization:

Defined as percutaneous coronary intervention (PCI) or coronary artery bypass graft surgery

Transient Ischemic Attack:

Documented by a hospitalization or emergency department visit, not meeting the stroke definition above, and characterized by focal, transient (< 24 hours) neurological signs and symptoms

Venous and Peripheral Arterial Vascular Thrombotic Events:

Defined as evidence of deep venous thrombosis of the lower extremities or pelvis, pulmonary embolism, peripheral arterial embolism and/or occlusion, peripheral artery revascularization, including carotid endarterectomy.

Congestive Heart Failure:

Defined as hospitalization due to dyspnea, shortness of breath, and/or edema accompanied by auscultator findings of pulmonary vascular congestion. Treatment of the heart failure with conventional parenteral therapy is required. Radiographic and/or echocardiographic documentation is typically required

Cardiac Arrhythmia, no evidence of ischemia:

Defined as atrial arrhythmias (atrial fibrillation, supraventricular tachycardias), ventricular arrhythmias (ventricular tachycardia (inclusive of torsades de pointe) or ventricular fibrillation), and high grade atrioventricular block (2nd degree Mobitz II or 3rd degree)

Other Serious Non-MACE Cardiovascular Events:

Include syncope of a cardiovascular origin and severe/accelerated hypertension leading to hospitalization

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/s/

TATIANA OUSSOVA
04/15/2014



IND 105004

MEETING MINUTES

Janssen Research & Development, LLC.
Attention: Herren Edra
Manager, Global Regulatory Affairs, Immunology
3210 Merryfield Row
San Diego, CA 92121

Dear Mr. Edra:

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

We also refer to the teleconference between representatives of your firm and the FDA on June 26, 1976. The purpose of the meeting was to discuss the development program for (guselkumab).

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 Matthew White, Regulatory Project Manager at (301) 796-4997.

Sincerely,

{See appended electronic signature page}

Susan J. Walker, MD, FAAD
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 Type: Type C
Meeting Category: Guidance

Meeting Date and Time: June 26, 2013 at 9:00 a.m.
Meeting Location: Teleconference

Application Number: IND 105004
Product Name: (guselkumab) (b) (4) sterile
(b) (4) Solution (PFS) for subcutaneous administration

Indication: Treatment of moderate to severe plaque psoriasis in adult patients
Sponsor Name: Janssen Research & Development, LLC.

Meeting Chair: Susan J. Walker, MD, FAAD
Meeting Recorder: Matthew White

FDA ATTENDEES

Susan J. Walker, MD, FAAD, Director, DDDP
Tatiana Oussova, MD, MPH, Deputy Director for Safety, DDDP
Gordana Diglisic, MD, Clinical Team Leader, DDDP
Melinda McCord, MD, Clinical Reviewer, DDDP
Jessica Voqui, PharmD, Endpoints Reviewer, SEALD
Mohamed Alosch, PhD, Biostatistics Team Leader, DB III
Yuqing Tang, PhD, Biostatistician, DB III
Jie Wang, PhD, Clinical Pharmacology Reviewer, DCP 3
Ram Sihag, PhD, Product Quality Reviewer, DMA
Matthew E. White, Regulatory Health Project Manager, DDDP

SPONSOR ATTENDEES

Bruce Randazzo, MD, Senior Director, Clinical Research
Chenglong Han, PhD, Director, Patient Reported Outcomes
Karen D. Weiss, MD, MPH, Vice President, Regulatory Affairs
Herren Edra, Manager, Regulatory Affairs
Kimberly Shields-Tuttle, Senior Director, Regulatory Affairs
Susan Popma, OD, Director, Regulatory Affairs
Yasmine Wasfi, MD, Director Clinical Research
Shu Li, PhD, Director, Biostatistician

Purpose of the Meeting:

To discuss the development program for (guselkumab)

We have had the following meeting(s)/teleconference(s) with you:

- 11/16/11: Type C (Guidance) Meeting

We have sent the following correspondences:

- 11/30/11: Advice/Information Request Letter
- 8/18/11: Information Request Letter
- 6/3/11: Written responses to questions submitted in a 3/11/11 briefing document
- 7/1/09: Advice/Information Request letter
- 5/12/09: Advice/Information Request letter

Introductory Comments

You are developing CNTO 1959 (a fully humanized monoclonal antibody (mAb) directed against the p19 subunit of IL-23) for the treatment of patients with moderate to severe plaque psoriasis. The efficacy evaluation will be based on the Physician's Global Assessment (PGA) and Psoriasis Area and Severity Index (PASI).

You propose to develop a Psoriasis Symptoms Diary (PSD) to assess the severity of the symptoms of moderate to severe plaque psoriasis as a secondary endpoint. The Agency notes that information and advice about the ability of the instrument to measure psoriasis symptoms does not necessarily imply that those particular patient-reported outcomes are appropriate for eventual product labeling. In order for an endpoint to be considered for labeling, the set of secondary endpoints should be limited in number, clinically relevant, and the statistical analysis plan needs to include a framework for addressing multiplicity among secondary endpoint analyses.

Before the Agency can reach agreement on the adequacy of the PSD patient-reported outcome (PRO) measure for its use as secondary endpoint in Phase 3 studies, it is necessary to agree upon the specific concept of interest to be measured and the clinical trial context in which the measure will be used.

Concept of interest to be measured by the PRO measure:

The concept of interest targeted for measurement is unclear. In your description of the meeting purpose, you stated that you seek the following claim using the PSD: [REDACTED] (b) (4)

[REDACTED] However, in Question 1 to the Agency it appears that you intend for the PSD to assess the underlying concept of "severity of plaque psoriasis".

As a path forward, we recommend that you measure patient-reported symptoms relevant to plaque psoriasis (e.g., itch). Symptoms should be measured separately from observable signs, which are best assessed by the clinicians with expertise in the rating of severity of plaque psoriasis. Therefore, we view the observable signs as reported by the patient as exploratory [REDACTED] (b) (4). While you propose 11 items in [REDACTED].

your instrument, some of these items may represent the same concept. It is not clear how you distinguished the concept of pain from the closely related concepts of stinging and burning. In addition, plaque color can vary considerably across skin types and also during the day depending on when the patient bathes or showers and applies topical treatments. It is unclear whether patients can reliably report on this concept. Lastly, bleeding is not a sign of psoriasis but the result of trauma to a psoriatic plaque.

Context of use for the PRO measure:

Your briefing package contains an inadequate description of the use to which the measure will be put in the clinical trial design and analysis. You should propose appropriate measures for the patient-reported outcome along with a relevant response scale to measure the severity of the symptoms. You will need to propose an approach to investigate the validity and reliability of these instruments. For assessing the utility of the PRO, you should propose measurement on the above scale over the course of the trial.

Clinical

Question 1:

Does the Agency agree that the items and the wording of each item in the PSD are appropriate for assessing the underlying concept of severity of plaque psoriasis?

Response:

No. See Introductory Comments.

Question 2:

Does the Agency agree that an 11-point NRS response option with anchors of “Absent” and “Worst Imaginable” is appropriate to assess the severity of plaque psoriasis-related symptoms?

Response:

We agree in principle that an 11-point NRS response option as proposed is appropriate.

Question 3:

Does the Agency agree that it is appropriate to calculate two separate scores (symptom severity and symptom frequency scores) to assess psoriasis severity based on data collected from the PSD?

Response:

No. See Introductory Comments.

Question 4:

Does the Agency agree that the instructions for the completion of the severity of symptom assessment in the PSD are appropriate?

Response:

Yes. We agree the instructions are acceptable if supported by the evidence obtained from cognitive interviews.

Question 5:

Does the Agency agree that the definition of a responder can be defined using data from the guselkumab Phase 3 program through pre-defined criteria and analysis and that the response data from the Phase 3 studies can then be used to support labeling claims?

Response:

You should propose a success criteria based on the severity of symptoms which takes into account assessment of symptom severity during the course of the trial. Your success criteria should be based on a clinically meaningful difference. Once an agreement with the Agency on the success criteria is reached and the measurement scales are well defined, then you should propose an analysis method for your PRO data. If the PRO endpoint is to be considered for labeling along with other secondary endpoints, then a multiplicity adjustment should be considered to control Type 1 error rate. The responder definition should be specified *a priori* using data from previously conducted clinical trials or observational studies. We consider both anchor-based and distribution-based methods in the development of a responder definition.

Question 6:

Does the Agency agree that the 24-hour or 7-day recall versions of the Psoriasis Symptoms Diary will be adequate for use in the Phase 3 studies (b) (4)?

Response:

No. See the response to Question 3 and Introductory Comments.

Meeting Discussion:

The Agency stated that we are not agreeing with either instrument at this point as a measure to assess psoriasis severity. The Agency acknowledged the importance of symptoms frequency measurement during the course of the trial. However, your proposed approach for assessing frequency of symptoms is based on a binary assessment; i.e., whether the patient has the symptom or not during the last 7 days, which is less informative than the severity of symptoms which you have proposed to evaluate during the 24 hours. This is in addition to the issue of recall of the 7 day period compared to the 24 hour period. It is generally recommended that a 24 hour recall period is more informative for a symptom assessment. Another issue which will need to be considered is how to analyze repeated measurement about the frequency of symptoms during the course of the trial along with the severity of symptoms you are measuring on a daily basis.

You are encouraged to continue discussion with the Agency regarding your instrument development.

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 the information submitted to the IND might identify additional comments or information requests.
2. You are encouraged to request and attend an End-of-Phase 2 meeting at the appropriate time to obtain regulatory agreements for clinical endpoints and study design for Phase 3 trials. Comments on Phase 1 and 2 trials do not necessarily constitute commitments that can be extrapolated to Phase 3 trials.
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.

PREA REQUIREMENTS

Be advised that under the Food and Drug Administration Safety and Innovation Act (FDASIA), you must submit a Pediatric Study Plan (PSP) within 60 days of an End-of-Phase 2 (EOP2) meeting held on or after November 6, 2012. If an EOP2 meeting occurred prior to November 6, 2012 or an EOP2 meeting will not occur, then:

- if your marketing application is expected to be submitted prior to January 5, 2014, you may either submit a PSP 210 days prior to submitting your application or you may submit a pediatric plan with your application as was required under the Food and Drug Administration Amendments Act (FDAAA).
- if your marketing application is expected to be submitted on or after January 5, 2014, the PSP should be submitted as early as possible and at a time agreed upon by you and FDA. We strongly encourage you to submit a PSP prior to the initiation of Phase 3 studies. In any case, the PSP must be submitted no later than 210 days prior to the submission of your application.

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. For additional guidance on submission of the PSP, including a PSP Template, refer to:

<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm>. In addition, you may contact the Pediatric and Maternal Health Staff at 301-796-2200 or email pdit@fda.hhs.gov.

DATA STANDARDS FOR STUDIES

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

<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm>.

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/s/

TATIANA OUSSOVA

07/22/2013

Signing for Dr. Susan Walker



IND 105004

MEETING MINUTES

Janssen Biotech, Inc.
Attention: Barbara Rake
Director, Global Regulatory Affairs, Immunology
200 Great Valley Parkway
Malvern, PA 19355

Dear Ms. Rake:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for CNTO 1959, a Human Monoclonal Antibody Against Interleukin 23.

We also refer to the teleconference between representatives of your firm and the FDA on November 16, 2011. The purpose of the meeting was to discuss the proposed clinical development plan intended to support CNTO 1959 registration [REDACTED] (b) (4)

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 Matthew White, Regulatory Project Manager, at (301) 796-4997.

Sincerely,

{See appended electronic signature page}

Susan J. Walker, M.D., F.A.A.D.
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 Type: Type C
Meeting Category: Guidance

Meeting Date and Time: November 16, 2011, 9:00 AM
Meeting Location: Teleconference

Application Number: IND 105004
Product Name: CNTO 1959, a Human Monoclonal Antibody Against Interleukin 23
Proposed Indication: Treatment of moderate to severe psoriasis
Sponsor/Applicant Name: Janssen Biotech, Inc.

Meeting Chair: Susan Walker, M.D., F.A.A.D.
Meeting Recorder: Matthew White

FDA ATTENDEES

Susan J. Walker, M.D., F.A.A.D., Director, DDDP
Gordana Diglicic, M.D., Clinical Team Leader, DDDP
Melinda McCord, M.D., Clinical Reviewer, DDDP
Yow-Ming Wang, Ph.D., Clinical Pharmacology Team Leader, DCP3
Jie Wang, Ph.D., Clinical Pharmacology Reviewer, DCP3
Ruth Cordoba-Rodriquez, Ph.D., Product Quality Team Leader, DMA
Ram Sihag, Ph.D., Product Quality Reviewer, DMA
Matthew White, Regulatory Health Project Manager, DDDP

SPONSOR ATTENDEES

Cindy Guzzo, Vice President, Immunology
Stella Jones, PhD, Vice President, Immunology
John Krayner, Assistant Director, Toxicology
Peter Krulevitch, PhD, Research Fellow, Drug Delivery & Device Development
Shu Li, MS, Director, Biostatistics
Douglas Mead, MSBME, Director, Global Regulatory Affairs, CMC, Devices
Barbara Rake, Director, Global Regulatory Affairs, Immunology
Kim Shields, Senior Director, Global Regulatory Leader, Immunology
Philippe Szapary, MD, Senior Director Clinical Research
Steven Wan, PhD, Associate Director, Global Regulatory Affairs, CMC
Yasmine Wasfi, MD, PhD, Director, Clinical Research
Zhenhua (Michael) Xu, PhD, Director, Pharmacokinetics
Yanli Zhuang, PhD, Principal Research Scientist, Pharmacokinetics

Purpose of the Meeting:

The purpose of this meeting is to discuss the proposed clinical development plan intended to support CNTO 1959 registration [REDACTED] (b) (4).

Regulatory Correspondence History

We have had the following meetings with you:

- 06/03/2011 Written responses to questions submitted in a briefing package (dated 03/11/2011)

We have sent the following correspondences:

- 05/12/2009 Advice/IR Letter
- 07/01/2009 Advice/IR Letter
- 08/18/2011 Advice/IR Letter

Questions 1 and 2:

Assuming successful completion of the registration program for CNTO 1959, JBI intends to request marketing approval [REDACTED] (b) (4) for SC injection:

- PFS [REDACTED] (b) (4) PFS with a device to prevent needle sticks following use [REDACTED] (b) (4)

[REDACTED] (b) (4)

Assuming positive data from the proposed program, does the FDA agree that the development strategy as proposed supports the approval [REDACTED] (b) (4)

[REDACTED] (b) (4)

Response:

Chemistry, Manufacturing and Controls (CMC)

The information provided in the meeting package is insufficient to determine if the development strategy supports the proposed commercial PFS [REDACTED] (b) (4) CNTO 1959 drug product [REDACTED] (b) (4). Quality data presented for the effect of injection force and velocity on CNTO 1959 protein integrity (attachment 3, table 2) are not sufficient to address appropriate support for approval [REDACTED] (b) (4). See the following comments for recommendations on your development strategy:

1. We note that for the Phase 3 program, CNTO 1959 will be formulated as a solution into PFS- [REDACTED] (b) (4). Prior to conducting the proposed study, confirm that the drug

substance and drug product quality profiles that support product safety are unchanged or submit data assessing the comparability of Phase 3 material to material used previously in the clinical trials. This should include an assessment of the impact of manufacturing changes on product quality (including stability), safety and efficacy. Please refer to ICH Q5E for guidance on comparability exercises.

2. As drug development proceeds, consider the following specific concerns regarding the PFS-
[REDACTED] (b) (4)
 - a. An analysis of the immunogenicity of the PFS [REDACTED] (b) (4) drug product (DP) will be required. This includes an assessment of the percent of patients who develop anti-product antibody responses as well as the percent that develop neutralizing responses. Qualified immunogenicity assays for the detection of binding and neutralizing antibodies to CNTO 1959 should be developed. A detailed description of the assays including specificity and sensitivity information should be submitted to the IND. Also, provide data to demonstrate that your assay for immunogenicity of CNTO 1959 can detect antibody against the product in the presence of relevant CNTO 1959 concentrations. Until assays have been developed and validated, patients samples collected from clinical studies should be banked under appropriate storage conditions.
 - b. Pre-filled syringe (PFS) formats have the potential to introduce impurities such as [REDACTED] (b) (4) that are not normally present in a vial format and which can affect product stability and immunogenicity. Potential leachables should be identified and data on the level of these impurities in the PFS drug product reported. The impact of leachables on product quality can be assessed using spiking studies with new impurities found in the PFS drug product.
 - c. For licensure, [REDACTED] (b) (4) studies should be performed to evaluate the effect of [REDACTED] (b) (4) on drug product quality and stability. These studies should include, but not be limited to, a concentration of [REDACTED] (b) (4) that is at least an order of magnitude greater than the highest amount detected in the PFS drug product lots.
 - d. To support licensure of the PFS formats, information on the concentration of [REDACTED] (b) (4) drug product should include information from drug product lots produced from more than one syringe lot. Data to support drug product quality and stability in the presence of [REDACTED] (b) (4) should come from PFS lots which contain a 'worst case scenario' of [REDACTED] (b) (4) leachate. A robust characterization on the consistency of [REDACTED] (b) (4) application to syringe lots should also be carried out.
 - e. Visible and/or sub-visible particle formation can represent a significant degradation pathway for monoclonal antibody products and impact product quality and safety. It is recommended that testing for visible and sub-visible particle be incorporated into the accelerated/stressed stability program to determine whether particulate formation is a component of the product's degradation pathway. This information can then be used to develop and support the testing interval used for particulate testing at the recommended

storage temperature. It is recommended that testing for subvisible particulates be performed at least on an annual basis in the drug product stability program.

- f. Recent information suggests that subvisible particles can be shed from a (b) (4) -contact surfaces which may then nucleate protein aggregation and/or particulate formation. It is recommended that in addition to USP <788> particulate testing, smaller sub-visible particles (e.g. between 2 and 10 µm in size) be characterized at release and at regular intervals in the drug product stability program including under accelerated and/or stressed conditions. While your product should comply with compendial limits for particles greater in size than 10 micron and 25 micron during development, it is not necessary to establish acceptance criteria at this time for smaller sub-visible particles. Data from these characterization studies can be used to develop and provide support in your license application for an overall control strategy for particulate matter.

Clinical Pharmacology

We acknowledge that your completed Phase 1 trial and ongoing Phase 2 trial are conducted with lyophilized formulation (b) (4). You should assess comparative pharmacokinetics (PK) between the Phase 2 formulation (b) (4) to facilitate extrapolation of optimal dose from the Phase 2 trial to Phase 3 pivotal trials.

(b) (4)

We also want to remind you that human PK data after the administration using the to-be-marketed formulation/presentation is required to support the marketing approval and labeling of your product.

Meeting Discussion:

(b) (4)

Center for Devices and Radiological Health (CDRH)

Your overall development strategy is not adequate. CDRH recommends additional performance testing which you have not proposed in the pre-meeting package. See the following comments:

1. Provide a letter of authorization so that CDRH may review the DMF for the (b) (4) syringe with 27gauge (b) (4) stake-in needle that will be the primary container closure for your drug. This information is needed to assure that the primary drug delivery device is safe and effective for its intended use.
2. Clarify if the users of CNTO 1959 will, on average, have a similar level of manual dexterity impairment as did users in the (b) (4) human factors validation study. If the user population for CTNO 1959 will have different levels of impairment, a new human factors usability study may be required for the PF (b) (4) presentation.
3. Provide a rationale for the performance tests that you chose; describe the test methods in detail and acceptance criteria. (b) (4)
4. Submit biocompatibility testing data according to ISO 10993-1 1997, Biological Evaluation of Medical devices- Part 1: Evaluation and Testing.
5. (b) (4)

Clinical

The objective of this meeting is to discuss the proposed clinical development strategy intended to support the registration (b) (4). Our current recommendation is that the pivotal Phase 3 trials be conducted with the intended commercial product presentation (b) (4).

You have completed a single dose Phase 1 trial and your Phase 2 program is still ongoing. You have not completed dose-ranging trial(s) to assess the safety and efficacy of your proposed dosing regimen for CNTO 1959 in psoriasis patients. Therefore, we are unable to provide comments on the proposed design of Phase 3 trials given the limited experience presented to date. You should request and attend an End-of-Phase 2 meeting when your Phase 2 program is reasonably complete and study results are available for review.

Meeting Discussion:

(b) (4)

(b) (4)
(b) (4)
The Agency reiterated the recommendation that the pivotal Phase 3 trials be conducted with the intended commercial product presentation (b) (4)

Administrative Comments

PRESCRIBING INFORMATION

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

Summary of the Final Rule on the Requirements for Prescribing Information for Drug and Biological Products, labeling guidances, sample tool illustrating Highlights and Table of Contents, an educational module concerning prescription drug labeling, and fictitious prototypes of prescribing information are available at:

<http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/ucm084159.htm>. We encourage you to review the information at this website and use it as you draft prescribing information for your application.

DATA STANDARDS FOR STUDIES

CDER strongly encourages IND sponsors to consider the implementation and use of data standards for the submission of applications for product registration. Such implementation should occur as early as possible in the product development lifecycle, so that data standards are accounted for in the design, conduct, and analysis of studies. CDER has produced a web page that provides specifications for sponsors regarding implementation and submission of study data in a standardized format. This web page will be updated regularly to reflect CDER's growing experience in order to meet the needs of its reviewers. The web page may be found at the following link:

<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm>

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/s/

SUSAN J WALKER
11/22/2011

LATE-CYCLE COMMUNICATION
DOCUMENTS



BLA 761061

LATE-CYCLE MEETING MINUTES

Janssen Biotech, Inc.
Attention: Manomi Tennakoon, PhD
Associate Director, Global Regulatory Affairs, Immunology
920, Route 202 South
Raritan, NJ 08869

Dear Dr. Tennakoon:

Please refer to your Biologic License Application (BLA) submitted under section 351 of the Public Health Service Act for guselkumab injection, 100 mg/mL.

We also refer to the Late-Cycle Meeting (LCM) between representatives of your firm and the FDA on May 16, 2017.

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 Matthew White, Senior Regulatory Project Manager at (301) 796-4997.

Sincerely,

{See appended electronic signature page}

Gordana Diglisic, 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
Applicant LCM discussion points (received via email on May 12, 2017)



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF LATE-CYCLE MEETING MINUTES

Meeting Date and Time: May 16, 2017 at 1:00 p.m. EST

Meeting Location: Teleconference

Application Number: BLA 761061

Product Name: Guselkumab injection, 100 mg/mL

Applicant Name: Janssen Biotech, Inc.

Meeting Chair: Gordana Diglisic, MD

Meeting Recorder: Matthew White

FDA ATTENDEES

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

Kendall A. Marcus, MD, Acting Deputy Director, ODE III

Tatiana Oussova, MD, MPH, Acting Deputy Director, Deputy Director for Safety, Division of Dermatology and Dental Products (DDDP)

Nancy Xu, MD, Acting Associate Director for Labeling, DDDP

Gordana Diglisic, MD, Clinical Team Leader, DDDP

Kevin Clark, MD, Clinical Reviewer, DDDP

Melinda McCord, MD, Clinical Reviewer, DDDP

Leah Christl, PhD, Associate Director for Therapeutic Biologics, Therapeutic Biologics and Biosimilars Staff (TBBS)

Sukhminder Sandhu, PhD, MPH, MS, Acting Deputy Director, Division of Epidemiology I (DEPI I)

Joel L. Weissfeld, MD, MPH, Epidemiologist, DEPI I

Mohamed Alosch, PhD, Biostatistics Team Leader, Division of Biometrics III (DB III)

Matthew Guerra, PhD, Biostatistics Reviewer, DB III

Yow-Ming Wang, PhD, Clinical Pharmacology Team Leader, Division of Clinical Pharmacology 3 (DCP 3)

Anand Balakrishnan, PhD, Clinical Pharmacology Reviewer, DCP 3

Sarah Kennett, PhD, Review Chief, Division of Biotechnology Research and Review 1 (DBRR1)

Willie Wilson, PhD, Product Quality Reviewer, DBRR1

Tamara Johnson, MD, Team Leader, Division of Pediatric and Maternal Health (DPMH)

Leyla Sahin, MD, Medical Officer, DPMH

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

Matthew E. White, Senior Regulatory Health Project Manager, DDDP

APPLICANT ATTENDEES

Chenglong Han, PhD Director, Patient Reported Outcomes

Herren Edra, RAC, Manager, North America Regulatory Affairs

Shu Li, PhD, Director, Quantitative Sciences

Heidi Needleman, PhD, Senior Director, Compound Development Team Leader
Liza O'Dowd, MD, Vice President, Global Regulatory Affairs
Susan Popma, OD, Director, Global Regulatory Leader
Bruce Randazzo, MD, PhD, Senior Director, Clinical Development
Philippe Szapary, MD, MSCE, Vice President, Clinical Development
Manomi Tennakoon, PhD, Associate Director, Global Regulatory Affairs, Immunology
Yasmine Wasfi, MD, PhD, Senior Director, Clinical Development
Newman Yeilding, M.D., Head Immunology Development
Michael Song, MD, Director, Clinical Development
John Kraye, MS, Associate Scientific Director, Biologics Toxicology
Andy Greenspan, MD, Vice President, Medical Affairs Immunology
Steven Fakhrazadeh, MD, PhD, Senior Director, Global Medical Affairs Leader
Rada Dubashinsky, Senior Manager, Product Quality Management, PQM
Yaowei Zhu, PhD, Associate Scientific Director, Biologics Clinical Pharmacology
Jeannie Rojas, PhD, Director, CMC Team Leader
Steven Wan, PhD, Director, Global Regulatory Affairs, CMC
Gail Miller, Associate Director, Global CMC Regulatory Affairs
Michael Kapcsos, Associate Director, BRQC Regulatory Compliance Inspection Management
Yiting Wang, Director of Epidemiology
Paul Stang, PhD, Vice President, Global R&D Epidemiology
Bhaskar Srivastava, Director, Medical Affairs, Dermatology

1.0 BACKGROUND

BLA 761061 was submitted on November 16, 2016, for guselkumab injection, 100 mg/mL.

Proposed indication: The treatment of adult patients with moderate-to-severe plaque psoriasis who are candidates for systemic therapy or phototherapy

PDUFA goal date: July 16, 2017

FDA issued a Background Package in preparation for this meeting on May 3, 2017.

2.0 DISCUSSION

1. Introductory Comments – RPM/CDTL

Welcome, Introductions, Ground rules, Objectives of the meeting

2. Discussion of Substantive Review Issues – RPM

No substantive review issues have been identified to date.

3. REMS or Other Risk Management Actions – RPM

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

4. Postmarketing Requirements/Postmarketing Commitments – RPM/Clinical

Postmarketing Requirements Under 505(o):

- a. A prospective, registry based observational exposure cohort study that compares the maternal, fetal, and infant outcomes of women exposed to guselkumab during pregnancy to an unexposed control population. The registry will detect and record major and minor congenital malformations, spontaneous abortions, stillbirths, elective terminations, small for gestational age, and any other adverse pregnancy outcomes. These outcomes will be assessed throughout pregnancy. Infant outcomes, including neonatal deaths, infections in the first 6 months of life, and effects on postnatal growth and development, will be assessed through at least the first year of life.

And

An additional study that uses a different study design (for example a retrospective cohort study using claims or electronic medical record data or a case control study) to assess major congenital malformations, spontaneous abortions, stillbirths, small for gestational age, neonatal deaths, and infant infections in women exposed to guselkumab during pregnancy compared to an unexposed control population.

- b. Conduct (b) (4) observational study to assess the long-term safety of guselkumab compared to other therapies used in the treatment of adults with moderate-to-severe plaque psoriasis who are candidates for systemic therapy or phototherapy in the course of actual clinical care. The study's primary outcome is long-term malignancy. Secondary outcomes include, but are not limited to, serious infections, tuberculosis, opportunistic infections, hypersensitivity reactions, autoimmune disease, neurologic or demyelinating disease, cardiovascular, gastrointestinal and hematologic adverse events.

Describe and justify the choice of appropriate comparator population(s) and estimated background rate(s) relative to guselkumab-exposed patients; clearly define the primary comparator population for the primary objective. Design the study around a testable hypothesis to assess, with sufficient sample size and power, a clinically meaningful increase in malignancy risk above the comparator background rate(s), with a pre-specified statistical analysis method. Specify concise case definitions and validation algorithms for both primary and secondary outcomes. For the guselkumab-exposed and comparator(s) cohorts, clearly define the study drug initiation period and any exclusion and inclusion criteria. Enroll patients over an initial (b) (4) year period and follow for a minimum of 8 years from the time of enrollment.

Meeting Discussion:

(b) (4)

The FDA agreed with the Applicant's proposal to strike (b) (4) from the first sentence of the proposed PMR language.

Required Pediatric Assessments: Pediatric Research Equity Act (PREA) (21 U.S.C. 355c)

- c. Conduct a Pharmacokinetics (PK), Safety and Efficacy Study in pediatric subjects 6 years to <18 years of age with moderate to severe plaque psoriasis (with a duration of exposure to guselkumab of at least one year).

We are waiving the pediatric study requirement for ages 0 to less than 6 years because necessary studies are impossible or highly impracticable. This is because:

- The prevalence of psoriasis in the 0 to less than 6 years age group is low (with the highest prevalence published of 0.3%) and the proportion of children with a severe condition in need of a systemic treatment is 4%, giving a final prevalence of the condition to be about 1 per 10,000 in this age group.

(b) (4)

We are deferring submission of your pediatric studies for ages 6 years to less than 18 years for this application because this product is ready for approval for use in adults and the pediatric studies have not been completed.

Postmarketing Commitments:

- d. Perform a leachable study to evaluate the drug product container closure system through the end of shelf-life when stored under the recommended conditions. Testing will be performed at regular intervals and will include appropriate methods to detect, identify, and quantify organic non-volatile (e.g., HPLC-UV-MS), volatile (e.g., headspace GC-MS) and semi-volatile (e.g., GC-MS) species and metals (e.g., ICP-MS). Study results will be updated annually in the BLA Annual Report. The complete data and risk evaluation for potential impact of leachables on product safety and quality will be submitted to the BLA.

- e. Provide additional data comparing the (b) (4) (b) (4) . Include the (b) (4) in the (b) (4) revalidation program if the new information indicates that the (b) (4) .

5. Major labeling issues – Clinical/Biostatistics

(b) (4)

(b) (4)

Meeting Discussion:

(b) (4)

The Agency stated that the final clinical study report for drug-drug interaction study CNTO1959PSO1003, submitted to the BLA on March 16, 2017, is under review and that additional edits to the corresponding sections of the package insert may be forthcoming.

6. Review Plans – RPM

- Labeling discussions
- PMC/PMR discussions
- Manufacturing and clinical site inspection recommendations
- Take action on BLA application

7. Wrap-up and Action Items – RPM

- Wrap-up: (see above review plans summary)

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

In FDA's late cycle pre-meeting background package, the FDA outlines a PMR for a long-term (b) (4) observational study for guselkumab in psoriasis patients (PMR, 4b, FDA pre-meeting background package dated May 3, 2017). Janssen is considering the use of (b) (4) to meet the requirement for an assessment of the long-term safety of guselkumab and would like to discuss the acceptability of this approach at the FDA late-cycle meeting.



(b) (4)

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/s/

GORDANA DIGLISIC
05/19/2017



BLA 761061

**LATE CYCLE MEETING
BACKGROUND PACKAGE**

Janssen Biotech, Inc.
Attention: Manomi Tennakoon, PhD
Associate Director, Global Regulatory Affairs, Immunology
920, Route 202 South
Raritan, NJ 08869

Dear Dr. Tennakoon:

Please refer to your Biologic License Application (BLA) submitted under the Public Health Service Act for guselkumab injection, 100 mg/mL.

We also refer to the Late-Cycle Meeting (LCM) scheduled for May 16, 2017. Attached is our background package, including our agenda, for this meeting.

Please email me a list of your attendees at Matthew.White@fda.hhs.gov, at least one week prior to the meeting.

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

Sincerely,

{See appended electronic signature page}

Jill Lindstrom, MD, FAAD
Acting Director
Division of Dermatology and Dental Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

ENCLOSURE:
Late-Cycle Meeting Background Package

LATE-CYCLE MEETING BACKGROUND PACKAGE

Meeting Date and Time: May 16, 2017 at 1:00 p.m. EST
Meeting Location: White Oak Building 22/Room 1201

Application Number: BLA 761061
Product Name: Guselkumab injection, 100 mg/mL
Proposed Indication: The treatment of adult patients with moderate-to-severe plaque psoriasis who are candidates for systemic therapy or phototherapy
Applicant Name: Janssen Biotech, Inc.

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

No substantive review issues have been identified to date.

ADVISORY COMMITTEE MEETING

An Advisory Committee meeting is not planned.

REMS OR OTHER RISK MANAGEMENT ACTIONS

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

LCM AGENDA

1. Introductory Comments – RPM/CDTL

Welcome, Introductions, Ground rules, Objectives of the meeting

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No substantive review issues have been identified to date.

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- b. Conduct ^{(b) (4)} observational study to assess the long-term safety of guselkumab compared to other therapies used in the treatment of adults with moderate-to-severe plaque psoriasis who are candidates for systemic therapy or phototherapy in the course of actual clinical care. The study's primary outcome is long-term malignancy. Secondary outcomes include, but are not limited to, serious infections, tuberculosis, opportunistic infections, hypersensitivity reactions, autoimmune disease, neurologic or demyelinating disease, cardiovascular, gastrointestinal and hematologic adverse events.

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(b) (4)

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- d. Perform a leachable study to evaluate the drug product container closure system through the end of shelf-life when stored under the recommended conditions. Testing will be performed at regular intervals and will include appropriate methods to detect, identify, and quantify organic non-volatile (e.g., HPLC-UV-MS), volatile (e.g., headspace GC-MS) and semi-volatile (e.g., GC-MS) species and metals (e.g., ICP-MS). Study results will be updated annually in the BLA Annual Report. The complete data and risk evaluation for potential impact of leachables on product safety and quality will be submitted to the BLA.

- e. Provide additional data comparing the (b) (4) (b) (4) . Include the (b) (4) in the (b) (4) revalidation program if the new information indicates that the (b) (4) .

5. Major labeling issues – Clinical/Biostatistics



6. Review Plans – RPM

- Labeling discussions
- PMC/PMR discussions
- Manufacturing and clinical site inspection recommendations
- Take action on BLA application

7. Wrap-up and Action Items – RPM

- Wrap-up: (see above review plans summary)
- Action items: TBD

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/s/

JILL A LINDSTROM
05/03/2017