

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

761067Orig1s000

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION ¹		
NDA # BLA # 761067	NDA Supplement # BLA Supplement #	If NDA, Efficacy Supplement Type: <i>(an action package is not required for SE8 or SE9 supplements)</i>
Proprietary Name: Ilumya Established/Proper Name: tildrakizumab Dosage Form: injection		Applicant: Merck Sharp & Dohme Corporation Agent for Applicant (if applicable):
RPM: Dawn Williams		Division: Division of Dermatology and Dental Products
NDA Application Type: ☐ 505(b)(1) ☐ 505(b)(2) Efficacy Supplement: ☐ 505(b)(1) ☐ 505(b)(2) BLA Application Type: ☒ 351(k) ☐ 351(a) Efficacy Supplement: ☐ 351(k) ☐ 351(a)		<u>For ALL 505(b)(2) applications, two months prior to EVERY action:</u> - 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) ☐ No changes ☐ New patent/exclusivity <i>(notify CDER OND IO)</i> Date of check: <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>
❖ Actions		
- Proposed action - User Fee Goal Date is <u>March 23, 2018</u>		☒ AP ☐ TA ☐ CR
Previous actions <i>(specify type and date for each action taken)</i>		☐ None
❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain _____		☐ Received
❖ Application Characteristics ³		

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

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

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

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

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

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

NDAs: Subpart H

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

Subpart I

- ☐ Approval based on animal studies

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

BLAs: Subpart E

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

Subpart H

- ☐ Approval based on animal studies

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

Comments:

❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 (approvals only)	☐ Yes ☒ No
❖ Public communications (approvals only)	
• Office of Executive Programs (OEP) liaison has been notified of action	☒ Yes ☐ No
• Indicate what types (if any) of information were issued	☒ None ☐ FDA Press Release ☐ FDA Talk Paper ☐ CDER Q&As ☐ Other
❖ Exclusivity	
• Is approval of this application blocked by any type of exclusivity (orphan, 5-year NCE, 3-year, pediatric exclusivity)? • If so, specify the type	☒ No ☐ Yes
❖ Patent Information (NDAs only)	
• Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought.	☐ Verified ☐ Not applicable because drug is an old antibiotic.
CONTENTS OF ACTION PACKAGE	
Officer/Employee List	
❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list (approvals only) (link)	☒ Included
Documentation of consent/non-consent by officers/employees (link)	☒ Included

Action Letters	
❖ Copies of all action letters (including approval letter with final labeling)	March 20, 2018 Approval
Labeling	
❖ Package Insert (write submission/communication date at upper right of first page of PI)	
Most recent draft labeling (if it is division-proposed labeling, it should be in track-changes format)	☒ Included
Original applicant-proposed labeling	☒ Included
❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling (write submission/communication date at upper right of first page of each piece)	☒ Medication Guide ☐ Patient Package Insert ☐ Instructions for Use ☐ Device Labeling ☐ None
Most-recent draft labeling (if it is division-proposed labeling, it should be in track-changes format)	☒ Included
Original applicant-proposed labeling	☒ Included
❖ Labels (full color carton and immediate-container labels) (write submission/communication date on upper right of first page of each submission)	
Most-recent draft labeling	☒ Included
❖ Proprietary Name - Acceptability/non-acceptability letter(s) (indicate date(s)) - Review(s) (indicate date(s))	General Advice letter February 7, 2018; Acceptable letter June 28, 2017; February 5, 2018 Nonproprietary Name Suffix review; June 28, 2017 Proprietary Name review
❖ Labeling reviews (indicate dates of reviews)	RPM: ☒ None DMEPA: ☐ None November 22, 2017 DMPP/PLT (DRISK): ☐ None December 22, 2017 OPDP: ☐ None December 21, 2017 SEALD: ☒ None CSS: ☒ None Product Quality ☒ None Other: ☐ None
Administrative / Regulatory Documents	
❖ RPM Filing Review ⁴ /Memo of Filing Meeting (indicate date of each review)	May 26, 2017
❖ All NDA 505(b)(2) Actions: Date each action cleared by 505(b)(2) Clearance Committee	☒ Not a (b)(2)
❖ NDAs/NDA supplements only: Exclusivity Summary (signed by Division Director)	☐ Completed (Do not include)

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

❖ Application Integrity Policy (AIP) Status and Related Documents http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	
• Applicant is on the AIP	☐ Yes ☒ No
• This application is on the AIP ○ If yes, Center Director's Exception for Review memo (<i>indicate date</i>) ○ If yes, OC clearance for approval (<i>indicate date of clearance communication</i>)	☐ Yes ☒ No ☐ Not an AP action
❖ Pediatrics (<i>approvals only</i>) • Date reviewed by PeRC <u>December 20, 2017</u> If PeRC review not necessary, explain: _____	
❖ Breakthrough Therapy Designation	☒ N/A
• Breakthrough Therapy Designation Letter(s) (granted, denied, an/or rescinded)	
• CDER Medical Policy Council Breakthrough Therapy Designation Determination Review Template(s) (<i>include only the completed template(s) and not the meeting minutes</i>)	
• CDER Medical Policy Council Brief – Evaluating a Breakthrough Therapy Designation for Rescission Template(s) (<i>include only the completed template(s) and not the meeting minutes</i>) (<i>completed CDER MPC templates can be found in DARRTS as clinical reviews or on the MPC SharePoint Site</i>)	
❖ Outgoing communications: letters, emails, and faxes considered important to include in the action package by the reviewing office/division (e.g., clinical SPA letters, RTF letter, Formal Dispute Resolution Request decisional letters, etc.) (<i>do not include OPDP letters regarding pre-launch promotional materials as these are non-disclosable; do not include Master File letters; do not include previous action letters, as these are located elsewhere in package</i>)	June 2, 2017 Filing Communication- No Filing Issues Identified; June 9, 2016 Agreed Initial Pediatric Study Plan- Agreement; July 18, 2012 Special Protocol- Agreement (3)
❖ 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	
• If not the first review cycle, any end-of-review meeting (<i>indicate date of mtg</i>)	☐ N/A or no mtg
• Pre-NDA/BLA or BPD Type 4 meeting (<i>indicate date of mtg</i>)	☐ No mtg August 31, 2016
• EOP2 meeting (<i>indicate date of mtg</i>)	☐ No mtg April 11, 2012
• Mid-cycle Communication (<i>indicate date of mtg</i>)	☐ N/A September 13, 2017
• Late-cycle Meeting (<i>indicate date of mtg</i>)	☐ N/A December 6, 2017
• Other milestone meetings (e.g., EOP2a, BPD Type 3, CMC focused milestone meetings) (<i>indicate dates of mtgs</i>)	April 15, 2008 Pre-IND

❖ Advisory Committee Meeting(s)	☒ No AC meeting
• Date(s) of Meeting(s)	
Decisional and Summary Memos	
❖ Office Director Decisional Memo (<i>indicate date for each review</i>)	☐ None Unireview March 13, 2018
Division Director Summary Review (<i>indicate date for each review</i>)	☒ None
Cross-Discipline Team Leader Review (<i>indicate date for each review</i>)	☐ None March 19, 2018, and Contained in Unireview March 13, 2018
PMR/PMC Development Templates (<i>indicate total number</i>)	☐ None 4
Clinical	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) (<i>indicate date for each review</i>)	☒ No separate review
• Clinical review(s) (<i>indicate date for each review</i>)	Contained in Unireview March 13, 2018; March 12, 2018; May 17, 2017
• Social scientist review(s) (if OTC drug) (<i>indicate date for each review</i>)	☒ None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here ☐ and include a review/memo explaining why not (<i>indicate date of review/memo</i>)	Contained in March 13, 2018 Unireview, pages 163-165
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers (<i>indicate date of each review</i>) ⁵	☐ None December 21, 2017 DPMH; October 19, 2017 DPP; October 1, 2017 DCRP; September 29, 2017 QT/IRT; September 26, 2017 DPARP
❖ Controlled Substance Staff review(s) and Scheduling Recommendation (<i>indicate date of each review</i>)	☒ N/A
❖ Risk Management	
• REMS Documents and REMS Supporting Document (<i>indicate date(s) of submission(s)</i>)	☐ None
• REMS Memo(s) and letter(s) (<i>indicate date(s)</i>)	March 20, 2018 Sentinel ARIA Sufficiency for Pregnancy Concerns;
• Risk management review(s) and recommendations (including those by OSE and CSS) (<i>indicate date of each review and indicate location/date if incorporated into another review</i>)	March 19, 2018 Sentinel ARIA Sufficiency; March 7, 2018 DRISK REMS Review
❖ OSI Clinical Inspection Review Summary(ies) (<i>include copies of OSI letters to investigators</i>)	☐ None requested OSI Summary February 7, 2018; NAI letter January 5, 2018; NAI letter January 5, 2018;

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).

	NAI letter January 5, 2018
Clinical Microbiology	☒ None
❖ Clinical Microbiology Team Leader Review(s) (indicate date for each review)	☐ No separate review
Clinical Microbiology Review(s) (indicate date for each review)	☐ None
Biostatistics	☐ None
❖ Statistical Division Director Review(s) (indicate date for each review)	☒ No separate review
Statistical Team Leader Review(s) (indicate date for each review)	☒ No separate review
Statistical Review(s) (indicate date for each review)	☐ None March 21, 2018; Contained in Unireview March 13, 2018; May 17, 2017 Filing Review
Clinical Pharmacology	☐ None
❖ Clinical Pharmacology Division Director Review(s) (indicate date for each review)	☒ No separate review
Clinical Pharmacology Team Leader Review(s) (indicate date for each review)	☒ No separate review
Clinical Pharmacology review(s) (indicate date for each review)	☐ None Contained in Unireview March 13, 2018; December 21, 2017; May 11, 2017 Filing Review
❖ OSI Clinical Pharmacology Inspection Review Summary (include copies of OSI letters)	☒ None requested
Nonclinical	☐ None
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) (indicate date for each review)	☒ No separate review
• Supervisory Review(s) (indicate date for each review)	☒ No separate review
• Pharm/tox review(s), including referenced IND reviews (indicate date for each review)	☐ None Contained in Unireview March 13, 2018; December 13, 2017; May 11, 2017 Filing Review
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer (indicate date for each review)	☒ None
❖ Statistical review(s) of carcinogenicity studies (indicate date for each review)	☒ No carc
❖ ECAC/CAC report/memo of meeting	☐ None March 21, 2012 Included in P/T review, page
❖ OSI Nonclinical Inspection Review Summary (include copies of OSI letters)	☒ None requested

Product Quality ☐ None	
❖ Product Quality Discipline Reviews ⁶	
• Tertiary review (<i>indicate date for each review</i>)	☒ None
• Secondary review (e.g., Branch Chief) (<i>indicate date for each review</i>)	☒ None
• Integrated Quality Assessment (contains the Executive Summary and the primary reviews from each product quality review discipline) (<i>indicate date for each review</i>)	☐ None Contained in Unireview March 13, 2018; November 10, 2017
❖ Reviews by other disciplines/divisions/Centers requested by product quality review team (<i>indicate date of each review</i>)	☒ None
❖ Environmental Assessment (check one) (original and supplemental applications)	
☐ Categorical Exclusion (<i>indicate review date</i>)(<i>all original applications and all efficacy supplements that could increase the patient population</i>)	
☐ Review & FONSI (<i>indicate date of review</i>)	
☐ Review & Environmental Impact Statement (<i>indicate date of each review</i>)	
❖ Facilities Review/Inspection	
☐ Facilities inspections (<i>indicate date of recommendation; within one week of taking an approval action, confirm that there is an acceptable recommendation before issuing approval letter</i>) (<i>only original applications and efficacy supplements that require a manufacturing facility inspection(e.g., new strength, manufacturing process, or manufacturing site change)</i>)	☒ Acceptable ☐ Withhold recommendation ☐ Not applicable

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

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

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/s/

DAWN WILLIAMS
03/22/2018



BLA 761067

GENERAL ADVICE

Merck Sharp & Dohme Corp.
Attention: Nadine Margaretten, Ph.D.
Director, Global Regulatory Affairs
126 E. Lincoln Avenue
P.O. Box 2000, RY34-B1126
Rahway, NJ 07065

Dear Dr. Margaretten:

Please refer to your Biologics License Application (BLA) submitted under section 351(a) of the Public Health Service Act for MK-3222.

We also refer to your October 18, 2017, submission, containing your request for review of the proposed suffixes for the nonproprietary name of your proposed product.

We have reviewed the referenced material and have the following comments:

We find the nonproprietary name, tildrakizumab-asmn, conditionally acceptable for your proposed product. Should your 351(a) BLA be approved during this review cycle, tildrakizumab-asmn will be the proper name designated in the license and you should revise your proposed labels and labeling accordingly. However, please be advised that if your application receives a complete response, the acceptability of your proposed suffix will be re-evaluated when you respond to the deficiencies. If we find your proposal unacceptable upon our re-evaluation, we would inform you of our finding.

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 Dawn Williams, Regulatory Project Manager in the Office of New Drugs, at (301) 796-5376.

Sincerely,

{See appended electronic signature page}

Lubna Merchant, M.S., Pharm.D.
Acting Deputy Director
Office of Medication Error Prevention and Risk Management
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

LUBNA A MERCHANT
02/07/2018

**PeRC Meeting Minutes
December 20, 2017**

PeRC Members Attending:

Lynne Yao
Meshawn Payne
Rosemary Addy
Jacqueline Yancy
Gerri Bauer
Raquel Tapia
James Travis
Dionna Greene
Donna Snyder
Victor Baum
Gil Burkhart
Kevin Krudys
Kristiana Brugger
Greg Reamann
Mark Rothmann
Wiley Chambers
Thomas Smith
George Greeley
Adrienne Hornatko Munoz
Maura O'Leary
Hari Cheryl Sachs

Agenda

9:00	NON-RESPONSIVE				
9:50					
10:10					
10:30					
10:50					
11:00					
11:10					
11:20	BLA 761067	Ilumya (tildrakizumab) Partial Waiver/Deferral	DDDP	Dawn Williams	For the treatment of adults with moderate-to-severe plaque psoriasis who are candidates for systemic therapy or phototherapy
11:30	NON-RESPONSIVE				
11:45					

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NON-RESPONSIVE

- Proposed Indication: For the treatment of adults with moderate-to-severe plaque psoriasis who are candidates for systemic therapy or phototherapy
- This product triggers PREA as a new indication, new dosing regimen, new route of administration and new dosage form. This application has a PDUFA goal date of March 23, 2018.
- The sponsor plans to request a waiver in pediatrics under 6 years as studies are impossible or highly impracticable due to the low prevalence of moderate to severe psoriasis in this population.
- The sponsor plans to request a deferral for pediatrics 6 to 17 years.
- The PeRC noted that the sponsor had previously obtained an Agreed iPSP and the plan for studies is well conceived.
- The PeRC agreed to the final study submission date for the deferred studies for this product.
- *PeRC Recommendations*
 - The PeRC agreed with the plan for partial waiver of pediatrics less than 6 years because studies are impossible or highly impractical and deferral of pediatric studies for the 6 to less than 17 years old. The PeRC also agreed with the general plan as outlined in the agreed iPSP.

NON-RESPONSIVE

5 Pages have been Withheld in Full as Non-Responsive

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/s/

JACQUILINE A YANCY
01/17/2018



BLA 761067

MID-CYCLE COMMUNICATION

Merck Sharp & Dohme Corp.
Attention: Nadine Margaretten, PhD
Director, Global Regulatory Affairs
126 E Lincoln Avenue
PO Box 2000, RY34-B1126
Rahway, NJ 07065

Dear Dr. Margaretten:

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

We also refer to the teleconference between representatives of your firm and the FDA on September 13, 2017. The purpose of the teleconference was to provide you with 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, please contact Dawn Williams, Regulatory Project Manager, at (301) 796-5376.

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: September 13, 12:00 PM ET

Application Number: BLA 761067
Product Name: tildrakizumab
Proposed Indication: The treatment of adults with moderate-to-severe plaque psoriasis who are candidates for systemic therapy or phototherapy
Applicant Name: Merck Sharp & Dohme Corp.

Meeting Chair: Gordana Diglisic, MD
Meeting Recorder: Strother D. Dixon

FDA ATTENDEES

Hylton V. Joffe, MD, MMSc, Acting Deputy Director, Office of Drug Evaluation III
Jill Lindstrom, MD, Deputy Director, Division of Dermatology and Dental Products (DDDP)
Gordana Diglisic, MD, Clinical Team Leader, DDDP
Kevin Clark, MD, Clinical Reviewer, 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
Jie Wang, PhD, Clinical Pharmacology Reviewer, Division of Clinical Pharmacology 3
Juhong Liu, PhD, Review Chief, Division of Biotechnology Review and Research II (DBRR II)
Arulvathani Arudchandran, PhD, Microbiologist, DBRR II
Strother D. Dixon, Senior Regulatory Health Project Manager, DDDP

APPLICANT ATTENDEES

Merck Participants:

Stuart Green, MD, Vice President, Clinical Research
Carmen La Rosa, MD, Sr. Principal Scientist, Clinical Research
(b) (4) Contractor, Quantitative Pharmacology & Pharmacometrics
Nadine Margaretten, PhD, Director, Global Regulatory Affairs
Heather Eurenus, BChE, Director, Regulatory Affairs CMC
Sauzanne Khalilieh, PharmD, Sr. Principal Scientist, Translational Pharmacology
Marian Iwamoto, MD, PhD, Scientific AVP, Translational Pharmacology
Amy Cheng, BA, Associate Principal Scientist, Clinical Operations
Diana Montgomery PhD, Principal Scientist, Pharmacokinetics
Scott Korn- MD, VP of Regulatory Affairs
Raymond Evers, PhD, Director of Pharmacokinetics
Larissa Wenning, PhD, Sr. Principal Scientist, Quantitative Sciences
Qing Li, PhD, Associate Principal Scientist, Clinical Biostatistics

Amarjot Kaur, PhD, Executive Director, Clinical Biostatistics
Kathryn Krantz, MD, FACOG, Senior Principal Scientist, Clinical Safety and Risk Management
Dena Ramey B.A. Senior Principal Scientist, Pharmacoepidemiology

Sun Pharma Participants:

Jeffrey Yuan, PhD, Associate Vice President, Clinical Regulatory Affairs, Sun Pharmaceutical Industries Inc.

Patrick Burnett, MD, PhD, Associate Vice President, Clinical Development, Sun Pharmaceutical Industries Inc.

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.

1.0 SIGNIFICANT ISSUES

1.1 Nonclinical

No significant issues have been identified to date.

1.2 Clinical Pharmacology

The overall dose-/exposure-response relationship for efficacy does not support your proposed dosage regimen that (b) (4)

1.3 Chemistry, Manufacturing and Controls/Clinical/Biostatistics

Your approach establishing a scientific bridge between US-licensed Enbrel and EU-approved etanercept is inadequate. A scientific bridge consisting of chemical, physical, and bioactivity comparisons with side-by-side analysis between the lots of US-licensed Enbrel and EU-approved etanercept used in the pivotal Phase 3

(b) (4)

(4)

Meeting Discussion:

The applicant inquired whether they could provide data from expired product lots to establish the scientific bridge. The Agency responded that data from expired product lots cannot be used to establish the scientific bridge.

2.0 INFORMATION REQUESTS

2.1 Chemistry, Manufacturing and Controls

None at this time.

2.2 Nonclinical

None at this time.

2.3 Clinical Pharmacology

None at this time.

2.4 Clinical/Biostatistics

None at this time.

3.0 MAJOR SAFETY CONCERNS/RISK MANAGEMENT

There are no major safety concerns at this time and there are currently no plans for a Risk Evaluation and Mitigation Strategy (REMS).

4.0 ADVISORY COMMITTEE MEETING

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

5.0 LATE-CYCLE MEETING /OTHER PROJECTED MILESTONES

The Late-Cycle Meeting will occur on or before December 14, 2017.

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/s/

GORDANA DIGLISIC
09/27/2017



BLA 761067

**PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE**

Merck Sharp & Dohme Corp.
126 E. Lincoln Avenue
P.O. Box 2000, RY34-B1126
Rahway, NJ 07065

ATTENTION: Nadine Margaretten, Ph.D.
Director, Global Regulatory Affairs

Dear Dr. Margaretten:

Please refer to your Biologics License Application (BLA) dated and received March 23, 2017, submitted under section 351(a) of the Public Health Service Act for Tildrakizumab, 100 mg/mL.

We also refer to your correspondence, dated and received April 10, 2017, requesting a review of your proposed proprietary name, Ilumya.

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

If any of the proposed product characteristics as stated in your April 10, 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 PDUFA performance goals associated with proprietary name reviews, we refer you to the following:

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

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact 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 Dawn Williams, Regulatory Project Manager, in the Office of New Drugs at (301) 796-5376.

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
06/28/2017



BLA 761067

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

Merck Sharp & Dohme Corp.
Attention: Nadine Margaretten, PhD
Director, Global Regulatory Affairs
126 E Lincoln Avenue
PO Box 2000, RY34-B1126
Rahway, NJ 07065

Dear Dr. Margaretten:

Please refer to your Biologics License Application (BLA) dated and received March 23, 2017, submitted under section 351(a) of the Public Health Service Act for tildrakizumab for injection.

We also refer to your amendment dated April 24, 2017.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 601.2(a), this application is considered filed 60 days after the date we received your application. The review classification for this application is Standard. Therefore, the user fee goal date is March 23, 2018. This application is also subject to the provisions of “the Program” under the Prescription Drug User Fee Act (PDUFA) V (refer to <http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm272170.htm>).

We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, mid-cycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing commitment requests by November 30, 2017. This date conforms to the 21st Century Review timeline for your application. If our review continues on an expedited timeline, we may communicate revised dates for labeling and postmarketing requirement/commitment requests. In addition, the planned date for our internal mid-cycle review meeting is August 23, 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:

1. Address the acceptability of your foreign data, or identify the location of this information in the application. 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 Feign Clinical Data, September 2006*.
2. Submit information to BLA 761067 to establish an adequate scientific bridge between the EU-approved etanercept (used in Trial P011) and US-licensed Enbrel.

To support approval of a claim

(b) (4)

(b) (4)

(b) (4)

You may submit information, including publicly available information, regarding US-licensed Enbrel and EU-approved etanercept to justify the extent of the data (comparative analytical data and potentially comparative PK/PD data) needed to establish a bridge between the EU-approved etanercept comparator and US-licensed Enbrel. For example, in support of an adequate scientific bridge between EU-approved etanercept and US-licensed Enbrel, you may submit detailed data and information to allow FDA to assess whether US-licensed Enbrel and EU-approved etanercept are manufactured at the same drug substance and drug product sites using the same processes (e.g., the drug substance and drug product manufacturing processes used for the manufacture of EU-approved etanercept are performed according to the manufacturing process and controls described in the BLA approved for US-licensed Enbrel), the same release criteria (e.g., specifications and Quality Unit batch release requirement), and the same cell bank. Such data and information could help support and justify the extent of data needed to establish a scientific bridge between US-licensed Enbrel and EU-approved etanercept, but may not be sufficient to establish a scientific bridge in the absence of data from a comparative study or studies of US-licensed Enbrel and EU-approved etanercept.

3. Provide, or identify the location in the application of, the coding dictionary.
4. Your proposed product labeling specifies that your product should only be administered by a health care provider. Similar products for the treatment of moderate to severe plaque psoriasis which are administered via subcutaneous injection are labeled for self-administration. Clarify your rationale for labeling your product for administration by a healthcare provider.

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, 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 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 patient PI. 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 patient PI, and you believe the labeling is close to the final version.

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

REQUIRED PEDIATRIC ASSESSMENTS

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

We acknowledge receipt of your request for a full waiver of pediatric studies for this application. Once we have reviewed your request, we will notify you if the full waiver request is denied and a pediatric drug development plan is required.

If you have any questions, call Dawn Williams, Regulatory Project Manager, at (301) 796-5376.

Sincerely,

{See appended electronic signature page}

Jill A. Lindstrom, MD, FAAD
Acting 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/

JILL A LINDSTROM
06/02/2017



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 101389

MEETING MINUTES

Merck Sharp & Dohme Corporation
Attention: Melissa Tice, PhD
Executive Director, Global Regulatory Affairs
126 E. Lincoln Avenue, RY34 B293
Rahway, NJ 07065

Dear Dr. Tice:

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

We also refer to the meeting between representatives of your firm and the FDA on August 31, 2016. The purpose of the meeting was to discuss the content and format of your proposed BLA submission.

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 Dawn Williams, Regulatory Project Manager at (301) 796-5376.

Sincerely,

{See appended electronic signature page}

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

Enclosure:
Meeting Minutes
Sponsor Attachments



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type: Type B
Meeting Category: Pre-BLA

Meeting Date and Time: August 31, 2016; 10:30am
Meeting Location: FDA White Oak Campus, Building 22, Room 1309

Application Number: IND 101389
Product Name: tildrakizumab solution
Proposed Indication: For the treatment of psoriasis
Sponsor Name: Merck Sharp & Dohme Corporation

Meeting Chair: Kendall Marcus, MD
Meeting Recorder: Dawn Williams, BSN

FDA ATTENDEES

Kendall Marcus, MD, Director, DDDP
Julie Beitz, MD, Director, ODE III
Amy Egan, MD, Deputy Director, ODE III
Tatiana Oussova, MD, Deputy Director for Safety, DDDP
Snezana Trajkovic, MD, Clinical Team Leader, DDDP
Melinda McCord, MD, Clinical Reviewer, DDDP
Barbara Hill, PhD, Pharmacology Supervisor, DDDP
Jianyong Wang, PhD, Pharmacology Reviewer, DDDP
Yow Ming Wang, PhD, Clinical Pharmacology Reviewer, DCP III
Jie Wang, PhD, Clinical Pharmacology Reviewer, DCP III
Mohamed Alosch, PhD, Biostatistics Team Leader, DB III
Matt Guerra, PhD, Biostatistics Reviewer, DB III
Jeff Florian, PhD, Pharmacometrics Team Leader, OCP
Fang Li, PhD, Pharmacometrics Reviewer, OCP
Rashmi Rawat, PhD, Product Quality Team Leader, OBP
Will Hallett, PhD, Product Quality Reviewer, OBP
Anand Balakrishnan, PhD, Clinical Pharmacology Reviewer, OCP
Hamid Tabatabai, MD, Clinical Reviewer, DDDP
Dawn Williams, BSN, Regulatory Health Project Manager, DDDP

SPONSOR ATTENDEES

Stuart Green, MD, Vice President, Clinical Research
Carmen LaRosa, MD, Sr. Principal Scientist, Clinical Research

Andrew Tershakovec, MD, Distinguished Scientist, Clinical Research
Azher Hussain, PhD, Principal Scientist, Pharmacokinetics
(b) (4) Contractor, Quantitative Pharmacology & Pharmacometrics
Vinay Girijavallabhan, PhD, Principal Scientist, Global Regulatory Affairs
Melissa Tice, PhD, Executive Director, Global Regulatory Affairs
Michael Santostefano, PhD, DABT, Senior Principal Scientist, Safety Assessment and Laboratory Animal Resources
Denuta Herzyk, PhD, Distinguished Scientist, Safety Assessment and Laboratory Animal Resources
Qing Li, PhD, Associate Principal Scientist, Clinical Biostatistics
Amorjot Kaur, PhD, Executive Director, Clinical Biostatistics
Kathryn Krantz, MD, FACOG, Senior Principal Scientist, Clinical Safety and Risk Management
Dena Ramey, Senior Principal Scientist, Pharmacoepidemiology
Jeffrey Yuan, PhD, Executive Director, Clinical Regulatory Affairs, Sun Pharmaceuticals
Patrick Burnett, MD, PhD, Associate Vice President, Clinical Development, Sun Pharmaceuticals

1.0 BACKGROUND

The purpose of this meeting is to discuss the development program for tildrakizumab solution.

2.0 DISCUSSION

2.1. Chemistry, Manufacturing and Controls

There were no Chemistry, Manufacturing and Controls questions submitted in the briefing package.

2.2. Pharmacology/Toxicology

Question 13:

Based on previous correspondence from the End of Phase 2 meeting (11 APR 2012) and submission of the pre- and post-natal developmental toxicity report (22 OCT 2014), does the Agency agree that the non-clinical toxicology package is complete and sufficient to support licensure of a marketing application for tildrakizumab?

FDA Response to Question 13:

Yes, we agree that no additional nonclinical studies are needed to support a BLA submission.

However, you should submit updated literature references that address the potential carcinogenic risk associated with chronic use of tildrakizumab in the BLA and incorporate appropriate information into Section 13.1 of the label. We reiterate that in order to address the carcinogenic potential of tildrakizumab you should provide data from nonclinical studies conducted with a surrogate monoclonal antibody and in knock-out animal models and all available data regarding the characterization of the IL-23p19 deficient mouse model with the

BLA. Submit full literature articles and complete study reports, not just summary information, to allow an in-depth review.

Question 14:

Does the Agency agree that based on the results from the developmental and reproductive toxicity studies conducted in cynomolgus monkeys, including the pre- and post-natal developmental (PPND) toxicity study, the animal studies do not identify any reproductive (fertility and pregnancy outcome) risk associated with tildrakizumab and no such warning or precaution will be needed in the proposed USPI?

FDA Response to Question 14:

We note a dose dependent increase in infant loss in the PPND study conducted in monkeys. On page 38 of the briefing document the infant loss is 1, 2 and 4 for vehicle, 10 mg/kg and 100 mg/kg tildrakizumab groups, respectively. The infant loss incidence in the high dose group (29%) falls outside the historical control range for the test facility (0 – 20%). We acknowledge that you indicated that two of four infant loss in the high dose group were due to maternal rejection or not nursing and the other two early deaths were likely due to viral infection, which possibly resulted from immunosuppression. It is possible that the maternal rejection was also treatment related. Therefore, we consider the dose dependent increase in infant loss noted in the monkey PPND study to be treatment related and appropriate information should be incorporated in Section 8.1 of the label for tildrakizumab.

Your proposed label should comply with the Pregnancy and Lactation Labeling Rule (PLLR). You are referred to the guidance document, *Pregnancy, lactation, and reproductive potential: labeling for human prescription drug and biological products — content and format*, for detailed information.

Meeting Discussion:

The sponsor stated that they consider the data from the PPND monkey study do not suggest a treatment related increase in the incidence of infant death. The sponsor plans to provide supplemental information regarding historical control data obtained from the testing facility in the BLA submission. The Agency commented that we disagree with the sponsor's conclusion at this time and consider the dose related increase in the incidence of infant deaths a significant signal. Further review will be conducted during the BLA review cycle to make a final determination regarding this issue.

2.3. Clinical Pharmacology

Question 1:

Does the Agency concur

(b) (4)

(b) (4)

FDA Response to Question 1:

(b) (4)

Additional Clinical Pharmacology Comments:

We acknowledge that you have planned to evaluate the impact of immunogenicity on PK, efficacy and safety based on subjects' anti-drug antibodies (ADA) status. Your briefing document indicated that the presence of ADA was associated with increased drug clearance and reduced tildrakizumab exposure in some individuals. As your integrated analysis of the immunogenicity impact on PK, efficacy and safety is ongoing, we have the following general recommendations regarding the immunogenicity assessments:

- For the evaluation of the ADA impact on PK, we recommend that you include between-subject comparison (i.e., between ADA positive subjects and ADA negative subjects) as well as within-subject comparison (i.e., before ADA positive and after ADA positive) of PK data.
- For the ADA positive subjects observed in Phase 3 trials, provide a summary table of study number, study subject ID, serum tildrakizumab concentrations at each PK time-point, sample ADA status at each immunogenicity assessment time-point, and the primary efficacy outcome.

Meeting Discussion:

The sponsor presented PK and ADA measurement schedule in Table 1 of their responses (see attachments). The Agency noted that ADA was not measured at Week 12 which is the timepoint for primary efficacy assessment. The Agency recommended that the sponsor determine ADA status using PK samples at Week 12 or 16 in order to assess the impact of ADA on efficacy. The sponsor will look into the feasibility of the recommended analysis using the PK samples at Week 12 or 16.

The Agency clarified that we will review the modeling analysis results during the BLA review cycle to evaluate the appropriateness of the modeling methodology.

2.1. Clinical/Biostatistics

Question 2:

Does the Agency agree with the proposal to pool the efficacy and safety data from the Phase 2 study P05495 and Phase 3 studies P010 and P011 as outlined in the integrated statistical analysis plan (iSAP)?

FDA Response to Question 2:

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

1. Phase 2 and 3: Placebo-Controlled Safety Pool

Safety data from P05495 (16 weeks) and P010 and P011 (12 weeks) will be summarized in the following columns:

- placebo
- tildrakizumab 100 mg
- tildrakizumab 200 mg,
- tildrakizumab 100 / 200 mg
- all tildrakizumab (5 mg, 25 mg, 100 mg, 200 mg)
- Etanercept 50 mg (P011 only)

For subjects who dropped out during the placebo-controlled period and entered the 20-week follow-up period, adverse events occurring during the follow-up will be included.

2. Phase 3: Placebo-Controlled Safety Pool

Safety data from P010 and P011 (12 weeks) will be summarized in the following columns:

- placebo
- tildrakizumab 100 mg
- tildrakizumab 200 mg,
- tildrakizumab 100 / 200 mg
- Etanercept 50 mg (P011 only)

For subjects who dropped out during the placebo-controlled period and entered the 20-week follow-up period, adverse events occurring during the follow-up will be included for these subjects.

3. Phase 2 and 3: Exposure-Adjusted 1-Year Safety Pool

Safety data through Week 52 for P05495 and P011 and through Week 64 for P010 will be summarized to provide an exposure adjusted rates of adverse events for the base period and will be summarized in the following columns.

- placebo
- tildrakizumab 100 mg
- tildrakizumab 200 mg,
- continuous exposure tildrakizumab 100 mg
- continuous exposure tildrakizumab 200 mg
- tildrakizumab 100 or 200 mg
- continuous exposure tildrakizumab 100 or 200 mg
- all tildrakizumab (5 mg, 25 mg, 100 mg, 200 mg)
- continuous exposure all tildrakizumab (5 mg, 25 mg, 100 mg, 200 mg)
- Etanercept 50 mg (P011 only)

Subjects with multiple treatments will be counted in each treatment received, after exposure adjustment. For subjects who dropped out during the base period or did not enter the extension period, adverse events occurring during follow-up will be included for these subjects and will be attributed to the last treatment received.

4. Phase 3: Partial Responder Dose Increase Safety Pool

Safety data from Week 28 to Week 52 from Trial P010 and P011 will include subjects who were randomized to tildrakizumab 100 mg and who are partial responders at Week 28. Safety data will be summarized in the following columns:

- increased dose to tildrakizumab to 200 mg
- remained on tildrakizumab 100 mg

5. Phase 3: Extension Safety Pool

Safety data from Week 64 to Week 256 from Trial P010 and Week 52 to Week 244 from Trial P011 will be summarized in the following columns:

- tildrakizumab 100 mg
- tildrakizumab 200 mg

For subjects who dropped out during the extension period and entered the 20 week follow-up, adverse events occurring during follow-up period will be included and will be attributed to the last treatment received.

In general, the pooling strategy for safety appears reasonable; however, pooling the 5 mg and 25 mg dosing groups with the 100 and 200 mg dosing groups will not be informative in determining the safety profile for the proposed 100 mg and 200 mg doses. We recommend that you remove 5 mg, 25 mg treatment groups from “all tildrakizumab (5 mg, 25 mg, 100 mg, 200 mg)” columns of “Phase 2 and 3: Placebo-Controlled Safety Pool” and “Phase 2 and 3: Exposure-Adjusted 1-Year Safety Pool”.

It should be noted that the objective of the integrated summary of efficacy (ISE) is to support the analysis results obtained from the individual trials and not to establish a new efficacy claim based on pooling data from the individual trials. Therefore, analyses based on pooled efficacy data are considered exploratory. Establishing an efficacy claim would be based on efficacy data from the individual Phase 3 trials along with a replication of study findings.

We have the following additional comments:

- For the “Placebo-controlled Period through Week 16” pool, provide raw incidence rates for adverse events ($\geq 1\%$) by treatment group.
- You state that the “Partial Responder Dose Increase Safety Pool” data includes AEs from Week 28 to 52. However, Part 3 of Trial P010 extends from Week 28 to 64 while Part 3 of Trial P011 extends from Week 28 to 52. Clarify the data that you intend to include in this pool.

Question 3:

Does the Agency agree with the planned subgroup analyses as described in the iSAP for the efficacy and safety data from the Phase 2b study P05495 and Phase 3 studies P010 and P011?

FDA Response to Question 3:

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. You are encouraged to present results of the subgroup analyses for efficacy and safety for each trial individually as well as for the pooled data.

In your subgroup analysis for the efficacy and safety data by race, add Black/African American to the other racial subgroups (White, Asian, Other Races).

Question 4:

Does the Agency agree with the scope of the iSAP, as well as the presentation of the efficacy and safety data in the proposed table/figure formats?

FDA Response to Question 4:

See response to Questions 2 and 3.

Question 5:

Based on the proposed cut-off date of FEB 2017 for the Safety Update Report (SUR), approximately 8 additional months of safety will be provided, does the Agency agree that the proposed cut-off date and data package is adequate to support this BLA?

FDA Response to Question 5:

For the 120 day safety update submission, you propose a 3 month cut-off date from the date of BLA submission (November 2016) to include 8 additional months of safety data. This appears to be reasonable. Provide narratives in the 120-day safety update for all subjects who died, experienced SAEs, pregnancy outcomes and reported AEs of special interest (serious cardiovascular events, serious events of TB and opportunistic infections, and malignancy). Additionally, submit 7-day and 15-day safety reports to the IND for all ongoing tildrakizumab trials.

Question 6:

Does the Agency concur that a Risk Evaluation and Mitigation Strategy (REMS) is not necessary for tildrakizumab?

FDA Response to Question 6:

Based on our review of the summarized safety information contained in your meeting package, a REMS may not be required for the safe use of tildrakizumab as a treatment for moderate to severe plaque psoriasis. However, our final determination regarding the need for REMS will be based on the overall risk benefit assessment for your product at the time of the BLA review.

Question 7:

Does the Agency agree with the Sponsor's proposal to conduct a prospective, observational study (registry) to assess the long-term safety of tildrakizumab post registration?

FDA Response to Question 7:

Your proposal to support the long-term safety of your product with data from two 4-year extension trials (P010 and P011) and data from a registry appears reasonable at this time.

Question 8:

Does the Agency agree that information pertaining to infections can be adequately and effectively communicated to clinicians in Section 6 (Adverse Reactions) of the proposed US Prescribing Information for tildrakizumab and that, with the exception of preevaluation/pre-treatment for TB, precautionary language in Section 5 (Warnings and Precautions) is not warranted?

FDA Response to Question 8:

It is premature to provide agreements on proposed labeling. It will be necessary for the Agency to complete the review of the safety data to determine whether information regarding

infections can be adequately and effectively communicated to clinicians in Section 6 (Adverse Reactions) of the proposed US Prescribing Information for tildrakizumab.

Question 9:

Based on the core risk profile that has been developed for tildrakizumab, the Sponsor considers that a Medication Guide (MG) (b) (4)

(b) (4)
(b) (4) Does the Agency agree with this proposal?

FDA Response to Question 9:

The need for Medication Guide will be determined following the review of the safety data submitted with your BLA.

Question 10:

- a. Does the Agency agree with the proposed categories for individual electronic Case Report Forms (eCRFs) in the Phase 2 and Phase 3 clinical trials to fulfill the eCRFs requirement for the BLA of tildrakizumab?
- b. Does the Agency require copies of the adjudication packages reviewed by the Clinical Adjudication Committee for cardiovascular events to be submitted as part of the BLA or is acceptable to have them available upon request?

FDA Response to Question 10:

- a. Your proposal to submit electronic Case Report Forms (eCRFs) in the Clinical Study Reports (CSR) for the Phase 2 and Phase 3 clinical trials is acceptable. However, if the eCRFs are located in the CSR, then provide links to the eCRFs in the relevant sections of the Overview of Clinical Safety, Summary of Clinical Safety and Integrated Summary of Safety (ISS).

In addition, provide narratives for all deaths, serious adverse events (SAEs), including all serious infections, subjects who discontinued the study agent due to adverse events (AEs), and AEs of special interest including malignancy, opportunistic infections, active TB, other infections of interest, anaphylaxis/hypersensitivity reactions, serum-sickness or serum-sickness like reactions, elevated liver function (AST or ALT ≥ 3 times upper limit of normal and total bilirubin ≥ 2 times upper limit of normal), and pregnancies. These narratives may also be included in the CSRs with links to the narratives provided in the relevant sections of the Overview of Clinical Safety, Summary of Clinical Safety and Integrated Summary of Safety.

- b. You may provide narratives rather than full adjudication packages for cardiovascular events reviewed by the Clinical Adjudication Committee.

Meeting Discussion:

The sponsor requested clarification regarding the acceptability of providing CIOMS reports for SAEs assessed as unrelated to drug use. The proposal appears reasonable based on the 2 CIOMS reports provided.

Question 11:

Does the Agency agree with the strategy of submitting case report tabulations (CRTs) in both standard (SDTM IG 3.1.1) and nonstandard (legacy) formats?

FDA Response to Question 11:

Yes.

Question 12:

Does the Agency agree with the scope and high-level content of the analysis package?

FDA Response to Question 12:

From the Draft Table of Contents for Module 5, it is not clear what you intend to include in the ISS. 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>)

For the analysis datasets, we have the following comments:

- The protocols for your Phase 3 trials specify using the multiple imputation (MI) approach as a sensitivity analysis for the handling of missing data. Instead of submitting the multiple imputed data within the analysis datasets, submit the SAS code used to implement MI. In addition, submit the SAS code used to analyze the multiple imputed data.
- 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.
- 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.

ESUB's General Comments

From a technical standpoint (not content related) the proposed summary plans for electronic submissions and the table of contents for Key eCTD modules provided, appears acceptable. However, please see additional comments below:

- Do not create additional nodes (e.g. m2.5.1.1 – m2.5.1.6.5; m2.7.1.1 - m2.7.1.5. etc.,) in the eCTD structure beyond what is in the specifications. Please make sure your approach fits the DTD and the “Granularity Annex”, located at:-
<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM073261.pdf>
- Providing Table of Contents in 4.1 and 5.1 is not necessary in the eCTD structure. Instead, it will be helpful to reviewers if sponsors can provide a linked reviewer’s aid/ reviewer’s guide to briefly describe where information can be found throughout the application and place the document in m1.2.
- Case Report Forms need 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”.

Additional comments:

- Conduct a retrospective evaluation of suicidal ideation and behavior using the Columbia Classification Algorithm of Suicide Assessment (C-CASA) for all subjects enrolled in Tildrakizumab clinical trials for all indications.

Meeting Discussion:

The sponsor provided a rationale for not conducting a C-CASA evaluation of their safety database. The Agency reiterated the request and stated that submission of this analysis with the 120-Day Safety Update would be acceptable. Alternatively, the sponsor could provide a proposal for the timing of submission.

2. 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).

Meeting Discussion:

A SAS transport file will be provided that contains this information.

3. Include the full text version of any referenced articles.
4. Provide your rationale/discussion regarding the acceptability of your foreign data. Acceptability of foreign clinical data depends on its ability to be extrapolated to the U.S. population. Refer to the ICH guidance for industry, E5 Ethnic factors in the Acceptability of Foreign Clinical Data, September 2006.

5. Include the following in your pooled analysis (Trial 010 and Trial 011)
 - a. Line listings for all abnormal safety findings (e.g., adverse events, vital signs, laboratory values.)
 - 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.
6. Provide an analysis of ECG data (Trial 010 and Trial 011) 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
7. In addition to the electronic datasets, you should 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).

3.0 ADDITIONAL INFORMATION

DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

As stated in our May 25, 2016 communication granting this meeting, if, at the time of submission, the application that is the subject of this meeting is for a new molecular entity or an original biologic, the application will be subject to “the Program” under PDUFA V. Therefore, at this meeting be prepared to discuss and reach agreement with FDA on the content of a complete application, including preliminary discussions on the need for risk evaluation and mitigation strategies (REMS) or other risk management actions. You and FDA may also reach agreement on submission of a limited number of minor application components to be submitted not later than 30 days after the submission of the original application. These submissions must be of a type that would not be expected to materially impact the ability of the review team to begin its review. All major components of the application are expected to be included in the original application and are not subject to agreement for late submission.

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

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

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

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

PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (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.

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).

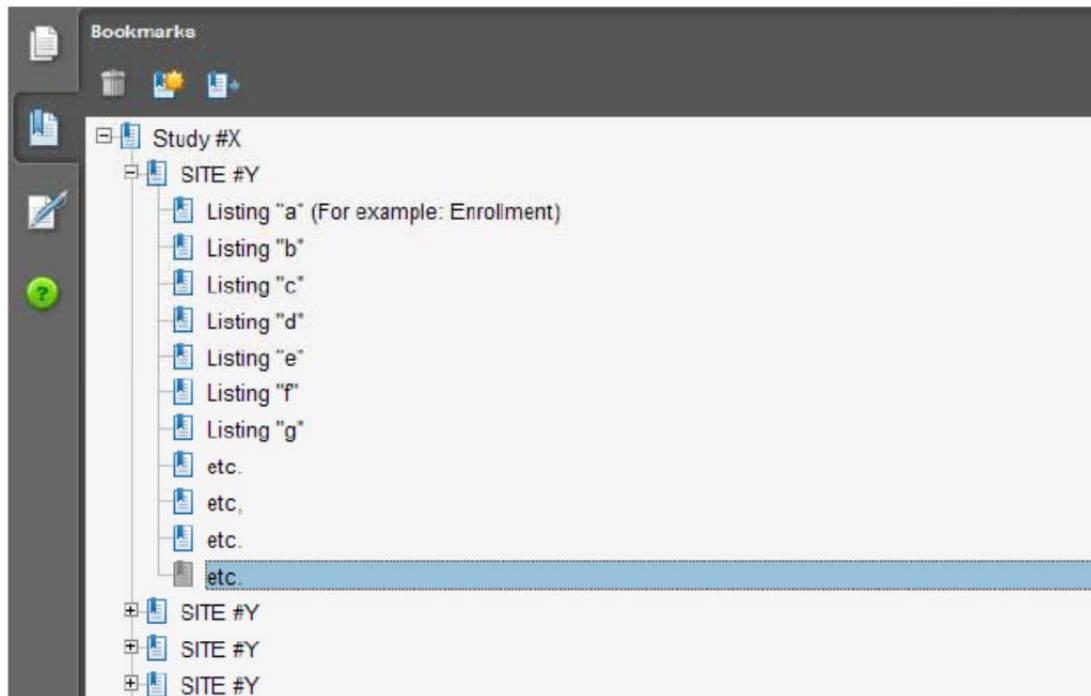
Request for general study related information and comprehensive clinical investigator information (if items are provided elsewhere in submission, describe location or provide link to requested information).

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.

Sponsor Attachments

Merck acknowledges receipt of the FDA preliminary meeting comments on August 26, 2016. Based on the Agency's response, Merck does not require further discussion and acknowledges the FDA recommendations regarding Questions 2,3,4,6,7,8,9, and 11 but does request discussion and/or clarification on the following questions in the proposed order : 5, 13, 14, 1(Additional Clinical Pharmacology Comments), 10a & b, Additional comments 1,2,4 and 6. Merck has provided responses to be discussed at the preBLA meeting on August 31, 2016.

Question 5:

Based on the proposed cut-off date of FEB 2017 for the Safety Update Report (SUR), approximately 8 additional months of safety will be provided, does the Agency agree that the proposed cut-off date and data package is adequate to support this BLA?

FDA Response to Question 5:

For the 120 day safety update submission, you propose a 3 month cut-off date from the date of BLA submission (November 2016) to include 8 additional months of safety data. This appears to be reasonable. Provide narratives in the 120-day safety update for all subjects who died, experienced SAEs, pregnancy outcomes and reported AEs of special interest (serious cardiovascular events, serious events of TB and opportunistic infections, and malignancy). Additionally, submit 7-day and 15-day safety reports to the IND for all ongoing tildrakizumab trials.

Merck response:

Based on the feedback from the FDA on the preBLA CMC comment below, Merck will require 1Q delay and will not submit the BLA until 1Q 2017. Additional safety will be included in the SUR.

Based on FDA feedback received in July 2016, "The manufacturing facility should be ready for inspection at the time of the BLA submission. Based on the proposed facility shutdown schedule indicated in the meeting document, the BLA submission is projected to be submitted while the facility is in a shutdown status. The BLA is not filable if the manufacturing facility is not ready for inspection at the time the application is submitted [e.g., per 21 CFR 600.21, 601.2, 601.20]"

Pharmacology/Toxicology

Question 13:

Based on previous correspondence from the End of Phase 2 meeting (11 APR 2012) and submission of the pre- and post-natal developmental toxicity report (22 OCT 2014), does the Agency agree that the non-clinical toxicology package is complete and sufficient to support licensure of a marketing application for tildrakizumab?

FDA Response to Question 13:

Yes, we agree that no additional nonclinical studies are needed to support a BLA submission. However, you should submit updated literature references that address the potential carcinogenic risk associated with chronic use of tildrakizumab in the BLA and incorporate appropriate information into Section 13.1 of the label. We reiterate that in order to address the carcinogenic potential of tildrakizumab you should provide data from nonclinical studies conducted with a surrogate monoclonal antibody and in knock-out animal models and all available data regarding the characterization of the IL-23p19 deficient mouse model with the BLA. Submit full literature

Attachments

articles and complete study reports, not just summary information, to allow an in-depth review.

Merck response:

We plan to include a comprehensive evaluation of potential carcinogenic risk associated with blockade of IL-23 in the BLA as recommended by the FDA, including submission of complete study reports and full published articles for relevant internal and external studies, as well as discussion of genetically-modified animals. These data support the conclusion that blockade of IL-23 will not be associated with increased tumor risk (and demonstrate reduced tumor incidence or decreased tumor growth) in contrast to increased tumor risk observed following IL-12/IL-23 dual blockade. We will discuss these findings in Section 13.1 of the label, as appropriate. We do not anticipate any further discussion is needed at this time.

Question 14:

Does the Agency agree that based on the results from the developmental and reproductive toxicity studies conducted in cynomolgus monkeys, including the pre- and post-natal developmental (PPND) toxicity study, the animal studies do not identify any reproductive (fertility and pregnancy outcome) risk associated with tildrakizumab and no such warning or precaution will be needed in the proposed USPI?

FDA Response to Question 14:

We note a dose dependent increase in infant loss in the PPND study conducted in monkeys. On page 38 of the briefing document the infant loss is 1, 2 and 4 for vehicle, 10 mg/kg and 100 mg/kg tildrakizumab groups, respectively. The infant loss incidence in the high dose group (29%) falls outside the historical control range for the test facility (0 – 20%). We acknowledge that you indicated that two of four infant loss in the high dose group were due to maternal rejection or not nursing and the other two early deaths were likely due to viral infection, which possibly resulted from immunosuppression. It is possible that the maternal rejection was also treatment related. Therefore, we consider the dose dependent increase in infant loss noted in the monkey PPND study to be treatment related and appropriate information should be incorporated in Section 8.1 of the label for tildrakizumab.

Your proposed label should comply with the Pregnancy and Lactation Labeling Rule (PLLR). You are referred to the guidance document, *Pregnancy, lactation, and reproductive potential: labeling for human prescription drug and biological products — content and format*, for detailed information.

Merck response:

Thank you for the comments, which we would like to further discuss at the pre-BLA meeting since our interpretation of the PPND data appears to be different from the stated interpretation above.

The FDA response implies that the effects on infant loss in the monkey PPND study are related to treatment with tildrakizumab. In our view, the study report and results summarized in the table below do not support this interpretation. In addition, supplemental information from the testing facility, (b) (4) was requested in regards to historical control data. Of note, non-human primate newborns living up to 28 days are defined as neonates. Based on this information, the incidence of neonatal loss in historical controls related to maternal rejection ranges from 0-16.7%, the incidence of neonatal loss not related to maternal rejection ranges from 0-20%, and the incidence of combined fetal/neonatal loss ranges from 20-43%

Attachments

(n=217 pregnancies).

Summary of Pregnancy and Infant Losses in PPND study (TT #12-9004)

Treatment Group (Number of Animals)	Fetal Loss [Abortion and Stillbirths] (Number of Animals)	Neonatal Loss (Number of Animals)	Combined Fetal and Neonatal Loss (Number of Animals)
Placebo (N = 15)	3	1 (due to maternal rejection)	4
Tildrakizumab at 10 mg/kg (N=15)	3	2 (due to maternal rejection)	5
Tildrakizumab at 100 mg/kg (N=15)	1	4 (1 due to maternal rejection, 1 due to inability to nurse; 2 due to potential viral infection)	5

In our study (TT#12-9004), the incidence of each category is listed below:

- 1) *Fetal loss is 20% (3/15) in the placebo control group, 20% (3/15) in the tildrakizumab 10 mg/kg group, and 6.7% (1/15) in the tildrakizumab 100 mg/kg group, which is within the historical control range (0-20%);*
- 2) *Neonatal loss due to maternal rejection is 6.7% (1/15) in the placebo control group, 13% (2/15) in the tildrakizumab 10 mg/kg group, and 6.7% (1/15) in the tildrakizumab 100 mg/kg group, which is within the historical control range (0 – 16.7%);*
- 3) *Neonatal loss not related to maternal rejection is 0% in the placebo control group, 0% in the tildrakizumab 10 mg/kg group, and 20% (3/15) in the tildrakizumab 100 mg/kg group, which is within the historical control range (0-20%);*
- 4) *Combined fetal and neonatal loss is 27% (4/15) in the placebo control group, 33% (5/15) in the tildrakizumab 10 mg/kg group, and 33% (5/15) in the tildrakizumab 100 mg/kg group, which is within the historical control range (20-43%).*

This analysis indicates no tildralizumab-treatment related increase in the incidence of fetal or neonatal losses on the study.

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Among three neonatal deaths from the 100 mg/kg group, one animal was sacrificed on the first day after birth due to an inability to nurse with no tildrakizumab related clinical or histological findings and was considered incidental. Cause of two other neonatal deaths from the 100 mg/kg group was determined based on histopathology examination that suggested viral infection. Since found dead neonates delivered by untreated monkeys are not routinely evaluated histologically, the background incidence of viral infections in monkeys at this age is unknown. In light of the lack of historical control data, the two neonatal deaths associated with viral infection were considered to be of uncertain relationship to the treatment with tildrakizumab despite the weight of evidence indicating the lack of immunosuppression associated with tildrakizumab. Even if these two deaths were related to the treatment with tildrakizumab, they occurred at very high maternal systemic exposure

(AUC_{0-336 hr} of 108,498 µg.day/mL on Gestation Day 120) corresponding to 85-fold the mean clinical exposure at the human recommended dose of 200 mg (AUC_{0-∞} of 1,280 µg.day/mL). In the absence of similar findings in the tildrakizumab 10 mg/kg group (corresponding to maternal systemic exposure AUC_{0-336 hr} of 11,874 µg.day/mL on Gestation Day 120), the safety margin is 9-fold the clinical exposure at human recommended dose of 200 mg. Based on the large safety margin, the neonatal deaths at 100 mg/kg are not considered relevant to human risk.

In summary, the data from the pre-and post-natal development monkey study does not suggest a treatment-related increase in the incidence of fetal or neonatal loss compared to historical controls. For the two neonatal deaths at 100 mg/kg possibly related to viral infections, which may be considered potentially related to the treatment, the NOEL has been established with a robust safety margin and therefore not considered relevant to human risk.

In regards to the comment about proposed label, we plan to communicate animal data in compliance with the Pregnancy and Lactation Labeling Rule (PLLR), including dose levels and exposure margins used on the PPND study.

Clinical Pharmacology

Question 1:

Does the Agency concur

(b) (4)

(b) (4)

FDA Response to Question 1:

(b) (4)

Additional Clinical Pharmacology Comments:

We acknowledge that you have planned to evaluate the impact of immunogenicity on PK, efficacy and safety based on subjects' anti-drug antibodies (ADA) status. Your briefing document indicated that the presence of ADA was associated with increased drug clearance and reduced tildrakizumab exposure in some individuals. As your integrated analysis of the immunogenicity impact on PK, efficacy and safety is ongoing, we have the following general recommendations regarding the immunogenicity assessments:

- For the evaluation of the ADA impact on PK, we recommend that you include between-subject comparison (i.e., between ADA positive subjects and ADA negative subjects) as well as within-subject comparison (i.e., before ADA positive and after

Attachments

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

Merck response:

(b) (4)

In regards to the **Additional Clinical Pharmacology Comments**,

In the Phase 3 trials, the overall ADA incidence in evaluable subjects was 194 out of 1623 (12%). Merck will provide detailed insight in the time-course of ADA (and neutralizing antibodies) development and its potential impact on drug PK, efficacy and safety.

In Phase 3, tildrakizumab was dosed at Week 0, Week 4, and every 12 weeks thereafter up to Week 52 for P011 and Week 64 for P010. In order to make comparisons of drug levels between subjects positive and negative for ADA, the Phase 3 treatment arms will be selected where subjects were treated with 100 mg or 200 mg during the full duration of the clinical trial: Part 1 (Week 0-12), Part 2 (Week 12-28) and Part 3 (Week 28-52 for P010 and P011 and Week 64 for P010 only). The more frequent dosing in Part 1 results in higher PK levels of tildrakizumab after Week 4 with steady state levels observed by Week 16. Merck intends to assess impact of ADA between and within subjects on the PK profile of tildrakizumab. ADA and PK samples were collected at 0, 4, 28, 36 (only P10), 40 (only P010), 52, 64 (only P010) and washout. PK-only time points were also collected at Weeks 12 and 16.

Attachments

Table 1 Sample Collection Time points for PK and ADA in Phase 3 Trials

MK-3222 PK measurements	ADA measurements
Week 0	Week 0
Week 4	Week 4
Week 12	
Week 16	
Week 28	Week 28
Week 36 (P010 only)	Week 36 (P010 only)
Week 40 (P010 only)	Week 40 (P010 only)
Week 52	Week 52
Week 64 (P010 only)	Week 64 (P010 only)
washout	washout

Merck will evaluate the feasibility of the request for a relative comparison of the mean tildrakizumab concentrations over time for different immunogenicity categories. A plot analogous to Figure 1a is being considered (Yow-Ming Wang et al. 2016, AAPS Journal 18(2) 395-402. Likewise inter-subject comparisons will be assessed for feasibility and if feasible provided as part of the BLA.

Figure 1

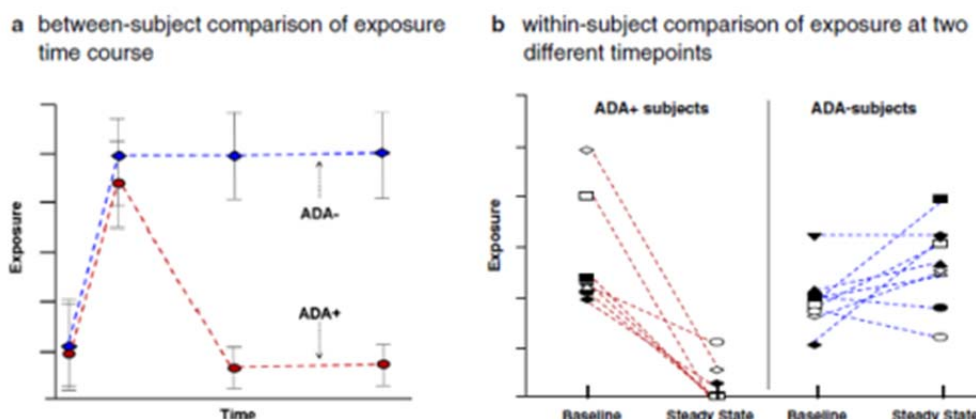


Fig. 3. Schematics for two separate case examples showing the effect of ADA on exposure by between-subject comparison (a), i.e., group average of ADA- subjects vs. group average of ADA+ subjects, at a single time-point or multiple time-points, and within-subject comparison (b) of exposures observed at baseline and at steady state stratified by the subject ADA status at steady state

Various immunogenicity categories will be considered for evaluation (further details in Table 2): Negative, Inconclusive, Treatment emergent positive-NAb negative (TE-POS-NAb NEG), Treatment emergent positive-NAb positive (TE-POS-NAb POS), Non-treatment emergent positive-NAb negative (non-TE-POS NAb NEG) and Non-treatment emergent positive-NAb positive (non-TE-POS NAb POS).

Attachments

Table 2 Immunogenicity Subject Status Definitions Used in the Tildrakizumab Clinical Program

Subject Status	Definition
Negative	All pre-treatment and post-dose samples were negative in the ADA assay and the drug concentration in the last post-dose sample was below the respective DTL for the ADA assay.
Inconclusive	All pre-treatment and post-dose samples were negative in the ADA assay AND the drug concentration in the last post-dose sample was equal or above the respective DTL for the ADA assay.
Treatment-emergent Positive	Pre-treatment sample was negative and at least 1 post-dose sample was positive in the ADA assay (treatment-induced positive).
	Pre-treatment and post-dose samples were both positive in the ADA assay and the titer increased post-dose by ≥ 2 -fold (treatment boosted positive).
Non-treatment-emergent Positive	Pre-treatment sample was positive and post-dose samples were negative in the ADA confirmatory assay.
	Pre-treatment and post-dose samples were positive in the ADA confirmatory assay with a < 2 -fold increase in titer post-dose

The requested data set/table will be prepared to include.

- *study number,*
- *study subject ID*
- *serum tildrakizumab concentrations at each PK time- point*
- *sample ADA status at each immunogenicity assessment time-point*
- *primary efficacy outcome all time points*

Question 10:

- a. Does the Agency agree with the proposed categories for individual electronic Case Report Forms (eCRFs) in the Phase 2 and Phase 3 clinical trials to fulfill the eCRFs requirement for the BLA of tildrakizumab?
- b. Does the Agency require copies of the adjudication packages reviewed by the Clinical Adjudication Committee for cardiovascular events to be submitted as part of the BLA or is acceptable to have them available upon request?

FDA Response to Question 10:

- a. Your proposal to submit electronic Case Report Forms (eCRFs) in the Clinical Study Reports (CSR) for the Phase 2 and Phase 3 clinical trials is acceptable. However, if the eCRFs are located in the CSR, then provide links to the eCRFs in the relevant sections of the Overview of Clinical Safety, Summary of Clinical Safety and Integrated Summary of Safety (ISS).

In addition, provide narratives for all deaths, serious adverse events (SAEs), including all serious infections, subjects who discontinued the study agent due to adverse events (AEs), and AEs of special interest including malignancy, opportunistic infections, active TB, other infections of interest, anaphylaxis/hypersensitivity reactions, serum-sickness or serum-sickness like reactions, elevated liver function (AST or ALT ≥ 3 times upper limit of normal and total bilirubin ≥ 2 times upper limit of normal), and pregnancies. These narratives may also be included in the CSRs with links to the narratives provided in the relevant sections of the Overview of Clinical Safety, Summary of Clinical Safety and Integrated Summary of Safety.

Attachments

- b. You may provide narratives rather than full adjudication packages for cardiovascular events reviewed by the Clinical Adjudication Committee.

Merck response:

- a) *Annotated blank eCRFs will be provided in the CSRs and Module 5 (as part of the CRT package).*

Merck is able to provide narratives for all deaths, and drug-related SAEs resulting in discontinuation, drug related hypersensitivity, drug related severe infections, elevated liver function (AST or ALT ≥ 3 times upper limit of normal and total bilirubin ≥ 2 times upper limit of normal) and pregnancies. Merck request clarification if the FDA would accept Council for International Organizations of Medical Sciences [CIOMS] reports for other all other SAEs and malignancy.

- b) *Merck is planning to provide narratives for all cases of confirmed extended MACE. Is the Agency willing to accept CIOMS reports as narratives for all events reviewed by the Clinical Adjudication Committee?*

Question 12:

Does the Agency agree with the scope and high-level content of the analysis package?

FDA Response to Question 12:

From the Draft Table of Contents for Module 5, it is not clear what you intend to include in the ISS. 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>)

For the analysis datasets, we have the following comments:

- The protocols for your Phase 3 trials specify using the multiple imputation (MI) approach as a sensitivity analysis for the handling of missing data. Instead of submitting the multiple imputed data within the analysis datasets, submit the SAS code used to implement MI. In addition, submit the SAS code used to analyze the multiple imputed data.

Attachments

- 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.
 - 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.

Merck response:

As noted in the FDA guidance on ISE/ISS under Exceptions:

There may be situations in which sections 2.7.3, Summary of Clinical Efficacy, and 2.7.4, Summary of Clinical Safety, would be sufficiently detailed to serve as the narrative portion of the ISE and ISS, respectively, while still concise enough to meet the suggested size limitations for Module 2. This situation is rare but can occur if the application is small and consists of a single study or a number of small studies. In our experience, the narrative portion of the ISE often is more amenable for inclusion in Module 2 than is the ISS. In such situations, the ISE and ISS can be split across Module 2 and Module 5, with the narrative portion located in section 2.7.3 or 2.7.4 and the appendices of tables, figures, and datasets located in section 5.3.5.3. If the ISE or ISS is split across modules in this way, it is critical to include a clear explanation of where the parts are located. This explanation should be placed both in Module 2 (section 2.7.3 or 2.7.4) and in Module 5 (section 5.3.5.3).

Merck does intend to use the Summary of Clinical Safety (Section 2.7.4) as the introductory section of the ISS and will include introductory comments to aid the reviewer on the location of information in the respected documents. Detailed tables and figures, including those not captured in Section 2.7.4, will be provided in Section 5.3.5.3.

Additional comments:

1. Conduct a retrospective evaluation of suicidal ideation and behavior using the Columbia Classification Algorithm of Suicide Assessment (C-CASA) for all subjects enrolled in Tildrakizumab clinical trials for all indications.

Merck response:

Safety information pertaining to suicide-related events (SRE) across the MK-3222 development program was reviewed by the MK-3222 Merck Risk Management Safety Team in 2015 when the presumptive signal for SRE in the brodalumab development program became public knowledge. This review identified no reports describing a completed suicide, and only 2 reports describing non-fatal SREs, across the entire MK-3222 development program. One of these reports, from a Phase 1 study (PN007), described a situational crisis with suicidal ideation in a subject facing substantial gambling debt and other psychosocial stressors; the other, from a Phase 3 study (PN 010), described a suicide attempt by a subject on antipsychotic therapy for a known prior history of schizophrenia. Neither event was considered to be causally related to study therapy by either the investigator or Merck. Information for these 2 reports is provided herewith in CIOMS format

Attachments

(see Attachments 1 and 2).

The small number of SRE cases identified at the time of this review, each of which had clear confounding factors, was not considered to constitute a signal for SRE, particularly in light of the known increased incidence of depression in the target population. Therefore, neither a retrospective C-CASA review nor prospective screening of Phase 3 patients (whose enrollment was already complete at that time)) were considered to be warranted; however, Merck has monitored subsequent Phase 3 base and extension safety data on an ongoing basis for additional events of this nature. No other SREs were identified during the completed base study periods for Phase 3 protocols PN 010 and PN 011. Merck was recently made aware of an additional nonfatal SRE, occurring during the long-term extension phase for Protocol PN011, which was reported by the investigator as “exacerbation of depression with suicide attempt” in a 25-year-old male with a history of depression since the age of 17 and psychosocial stress related to his “labor situation.” The patient had been receiving study therapy for approximately 3 years at the time of the event, and therapy remains ongoing as the event is considered unrelated by the investigator. Additional details have been requested.

In light of the foregoing, Merck would like to respectfully request that the Agency reconsider its request for a retrospective C-CASA review of safety data for MK-3222. Given the small number of SREs identified to date in the MK-3222 program and the low observed rates of adverse events pertaining to anxiety and depression in both the placebo-controlled and exposure-adjusted base period Phase 2/3 safety pools for MK-3222 (please refer to Attachments 3 and 4 appended table extracts displaying Psychiatric Disorders System Organ Class events for the PBO-controlled and base periods), Merck considers that this type of review is extremely unlikely to result in a substantive change in the rate of such events.

2. 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).

Merck response:

Merck will provide a SAS transport file with two columns, one for investigator verbatim AE terms (for all adverse events that happened during P05495, PN010, and PN011) and one for the corresponding preferred AE terms.

Attachments

6. Provide an analysis of ECG data (Trial 010 and Trial 011) 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

Merck response:

Merck would like to request clarification on the ECG data listed above in Question 6. At the End of Phase 2 meeting (April 2012), Merck asked Question 10 (below) and received the response that extensive ECG monitoring would not be required for this monoclonal antibody and we have appropriately adjudicated all CV events as requested. We would propose to provide narratives/CIOMS for the adjudicated events.

Question [10]:

QT prolongation has not been reported with other mAbs and, as a mAb, the size of MK-3222 would be expected to prevent access to the hERG channel via the intracellular side.

Does the Agency agree that a thorough QT/QTc study is not necessary to support review and approval of the application?

Response:

Yes we agree.

We recommend periodic ECG monitoring in clinical trials (at least baseline and steady state) to capture any important cardiovascular effects. If there is evidence of a proarrhythmic signal (e.g. QT prolongation on routine ECG or ventricular arrhythmia)

Attachments

from exposure to your drug product during your trials, then a TQT or additional data maybe 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 include 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.

1. 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

2. Review all of the following SOC's for possible cardiac events, thrombotic and MACE, since cardiac events may be found in several SOC's:

- ☐ 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

3. Have all possible cardiovascular events (rather than only MACE) reviewed by a DMC with expertise in cardiovascular adverse events.

4. Have all TIAs reviewed by the DMC (rather than only those resulting in hospitalization).

5. Evaluate possible thrombotic events alone and MACE alone during the uncontrolled period of the global psoriasis studies.

For both Protocols 010 and 011, ECGs were performed locally by the individual study sites and central reading of was not implemented. Because central reading was not a requirement, waveforms will not be available as part of the data for submission and raw data exists for the following fields: subject number, date of tracing if different from visit date, Time of Tracing (hour and minute), atrial rate, ventricular rate, PR, QRS, QT, QRS axis, QTc, QTcB and QTcF.

Attachments

Additionally, any clinically significant findings were recorded by the sites on the ECG eCRF.

8 Pages have been Withheld in Full as B4 (CCI/TS)
Immediately Following this Page

Subjects With Adverse Events (Incidence > 0% in One or More Treatment Groups)
Phase 2 and 3: Placebo-Controlled Safety Pool
All Subjects as Treated

	Placebo		MK-3222 100mg		MK-3222 200mg		MK-3222 100 / 200 mg		All MK-3222(5 mg, 25 mg, 100 mg, 200 mg)		Etanercept 50mg	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Psychiatric disorders	3	(0.8)	13	(1.8)	14	(2.0)	27	(1.9)	31	(2.0)	5	(1.6)
Alcohol abuse	0	(0.0)	1	(0.1)	0	(0.0)	1	(0.1)	1	(0.1)	0	(0.0)
Anxiety	0	(0.0)	3	(0.4)	1	(0.1)	4	(0.3)	4	(0.3)	0	(0.0)
Depression	0	(0.0)	2	(0.3)	3	(0.4)	5	(0.4)	5	(0.3)	1	(0.3)
Emotional disorder	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.3)
Insomnia	2	(0.6)	4	(0.6)	7	(1.0)	11	(0.8)	11	(0.7)	2	(0.6)
Irritability	0	(0.0)	2	(0.3)	0	(0.0)	2	(0.1)	2	(0.1)	0	(0.0)
Libido decreased	0	(0.0)	1	(0.1)	0	(0.0)	1	(0.1)	1	(0.1)	0	(0.0)
Major depression	0	(0.0)	1	(0.1)	0	(0.0)	1	(0.1)	1	(0.1)	0	(0.0)
Mood swings	0	(0.0)	0	(0.0)	2	(0.3)	2	(0.1)	3	(0.2)	0	(0.0)
Nervousness	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.1)	0	(0.0)
Panic attack	1	(0.3)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Sleep disorder	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.3)
Stress	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.1)	0	(0.0)
Suicide attempt	0	(0.0)	0	(0.0)	1	(0.1)	1	(0.1)	1	(0.1)	0	(0.0)
Renal and urinary disorders	5	(1.4)	10	(1.4)	7	(1.0)	17	(1.2)	18	(1.2)	1	(0.3)
Bladder pain	0	(0.0)	0	(0.0)	1	(0.1)	1	(0.1)	1	(0.1)	0	(0.0)
Calculus ureteric	1	(0.3)	2	(0.3)	0	(0.0)	2	(0.1)	2	(0.1)	0	(0.0)
Haematuria	0	(0.0)	3	(0.4)	3	(0.4)	6	(0.4)	6	(0.4)	0	(0.0)
Hydronephrosis	1	(0.3)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Hypertonic bladder	2	(0.6)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Nephrolithiasis	0	(0.0)	2	(0.3)	1	(0.1)	3	(0.2)	3	(0.2)	0	(0.0)



Subjects with Adverse Events (Incidence > 0% in One or More Treatment Groups)
Exposure Adjusted (Based on 20-Week Follow-Up)
Phase 2 and 3: Base Period Safety Pool
All Subjects as Treated

	Placebo		MK-3222 100 mg		MK-3222 200 mg		MK-3222 100/200 mg		All MK-3222 (5 mg, 25 mg, 100 mg, 200 mg)		Etanercept 50 mg		Continuous exposure MK-3222 100 mg		Continuous exposure MK-3222 200 mg		Continuous exposure MK-3222 100 / 200 mg ^a		Continuous exposure all MK-3222 (5 mg, 25 mg, 100 mg, 200 mg) ^b	
	n	(m†)	n	(m†)	n	(m†)	n	(m†)	n	(m†)	n	(m†)	n	(m†)	n	(m†)	n	(m†)	n	(m†)
Presyncope	2	0.91	1	0.10	2	0.22	3	0.16	4	0.19	2	1.30	1	0.20	1	0.21	3	0.25	4	0.29
Radiculopathy	0	0.00	0	0.00	1	0.11	1	0.05	1	0.05	0	0.00	0	0.00	1	0.21	1	0.08	1	0.07
Restless legs syndrome	0	0.00	1	0.10	0	0.00	1	0.05	1	0.05	0	0.00	0	0.00	0	0.00	1	0.08	1	0.07
Sciatica	0	0.00	3	0.30	7	0.75	10	0.52	13	0.63	1	0.65	1	0.20	3	0.63	7	0.58	10	0.73
Seizure	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	1	0.65	0	0.00	0	0.00	0	0.00	0	0.00
Sinus headache	0	0.00	1	0.10	0	0.00	1	0.05	1	0.05	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Somnolence	1	0.46	2	0.20	2	0.22	4	0.21	4	0.19	1	0.65	0	0.00	1	0.21	3	0.25	3	0.22
Syncope	0	0.00	3	0.30	0	0.00	3	0.16	3	0.15	0	0.00	1	0.20	0	0.00	1	0.08	1	0.07
Tension headache	0	0.00	1	0.10	1	0.11	2	0.10	2	0.10	0	0.00	1	0.20	0	0.00	2	0.17	2	0.15
Thrombotic cerebral infarction	0	0.00	1	0.10	0	0.00	1	0.05	1	0.05	0	0.00	1	0.20	0	0.00	1	0.08	1	0.07
Transient ischaemic attack	0	0.00	1	0.10	1	0.11	2	0.10	2	0.10	0	0.00	1	0.20	0	0.00	1	0.08	1	0.07
Tremor	0	0.00	1	0.10	2	0.22	3	0.16	3	0.15	1	0.65	0	0.00	1	0.21	1	0.08	1	0.07
Vertebrobasilar insufficiency	0	0.00	0	0.00	1	0.11	1	0.05	1	0.05	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Visual field defect	0	0.00	1	0.10	0	0.00	1	0.05	1	0.05	0	0.00	1	0.20	0	0.00	1	0.08	1	0.07
Pregnancy, puerperium and perinatal conditions	0	0.00	1	0.10	3	0.32	4	0.21	5	0.24	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Abortion	0	0.00	1	0.10	0	0.00	1	0.05	1	0.05	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Abortion spontaneous	0	0.00	0	0.00	2	0.22	2	0.10	2	0.10	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Pregnancy	0	0.00	0	0.00	1	0.11	1	0.05	2	0.10	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Psychiatric disorders	4	1.83	34	3.41	38	4.09	71	3.68	79	3.84	8	5.21	20	4.06	15	3.15	45	3.73	51	3.73



Subjects with Adverse Events (Incidence > 0% in One or More Treatment Groups)
Exposure Adjusted (Based on 20-Week Follow-Up)
Phase 2 and 3: Base Period Safety Pool
All Subjects as Treated

	Placebo		MK-3222 100 mg		MK-3222 200 mg		MK-3222 100/200 mg		All MK-3222 (5 mg, 25 mg, 100 mg, 200 mg)		Etanercept 50 mg		Continuous exposure MK-3222 100 mg		Continuous exposure MK-3222 200 mg		Continuous exposure MK-3222 100 / 200 mg ^a		Continuous exposure all MK-3222 (5 mg, 25 mg, 100 mg, 200 mg) ^b	
	n	(m†)	n	(m†)	n	(m†)	n	(m†)	n	(m†)	n	(m†)	n	(m†)	n	(m†)	n	(m†)	n	(m†)
Adjustment disorder	0	0.00	0	0.00	1	0.11	1	0.05	1	0.05	0	0.00	0	0.00	1	0.21	1	0.08	1	0.07
Agitation	1	0.46	1	0.10	1	0.11	2	0.10	2	0.10	0	0.00	1	0.20	1	0.21	2	0.17	2	0.15
Alcohol abuse	0	0.00	2	0.20	0	0.00	2	0.10	2	0.10	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Alcoholism	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	1	0.65	0	0.00	0	0.00	0	0.00	0	0.00
Anxiety	1	0.46	6	0.60	5	0.54	11	0.57	12	0.58	0	0.00	5	1.02	2	0.42	8	0.66	9	0.66
Apathy	0	0.00	0	0.00	1	0.11	1	0.05	1	0.05	0	0.00	0	0.00	0	0.00	1	0.08	1	0.07
Attention deficit/hyperactivity disorder	0	0.00	1	0.10	0	0.00	1	0.05	1	0.05	0	0.00	1	0.20	0	0.00	1	0.08	1	0.07
Bipolar disorder	0	0.00	1	0.10	0	0.00	1	0.05	1	0.05	0	0.00	1	0.20	0	0.00	1	0.08	1	0.07
Borderline personality disorder	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	1	0.65	0	0.00	0	0.00	0	0.00	0	0.00
Depressed mood	0	0.00	1	0.10	0	0.00	1	0.05	1	0.05	0	0.00	1	0.20	0	0.00	1	0.08	1	0.07
Depression	0	0.00	10	1.00	8	0.86	18	0.93	19	0.92	2	1.30	6	1.22	1	0.21	10	0.83	11	0.80
Drug abuse	0	0.00	1	0.10	0	0.00	1	0.05	1	0.05	0	0.00	1	0.20	0	0.00	1	0.08	1	0.07
Emotional disorder	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	1	0.65	0	0.00	0	0.00	0	0.00	0	0.00
Initial insomnia	0	0.00	1	0.10	0	0.00	1	0.05	1	0.05	0	0.00	1	0.20	0	0.00	1	0.08	1	0.07
Insomnia	2	0.91	6	0.60	14	1.51	20	1.04	20	0.97	2	1.30	3	0.61	6	1.26	12	1.00	12	0.88
Irritability	0	0.00	3	0.30	0	0.00	3	0.16	3	0.15	0	0.00	2	0.41	0	0.00	3	0.25	3	0.22
Libido decreased	0	0.00	1	0.10	0	0.00	1	0.05	1	0.05	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Major depression	0	0.00	1	0.10	0	0.00	1	0.05	1	0.05	0	0.00	1	0.20	0	0.00	1	0.08	1	0.07
Mental disorder	0	0.00	1	0.10	0	0.00	1	0.05	1	0.05	0	0.00	0	0.00	0	0.00	1	0.08	1	0.07



Subjects with Adverse Events (Incidence > 0% in One or More Treatment Groups)
Exposure Adjusted (Based on 20-Week Follow-Up)
Phase 2 and 3: Base Period Safety Pool
All Subjects as Treated

	Placebo		MK-3222 100 mg		MK-3222 200 mg		MK-3222 100/200 mg		All MK-3222 (5 mg, 25 mg, 100 mg, 200 mg)		Etanercept 50 mg		Continuous exposure MK-3222 100 mg		Continuous exposure MK-3222 200 mg		Continuous exposure MK-3222 100 / 200 mg ^a		Continuous exposure all MK-3222 (5 mg, 25 mg, 100 mg, 200 mg) ^b	
	n	(m†)	n	(m†)	n	(m†)	n	(m†)	n	(m†)	n	(m†)	n	(m†)	n	(m†)	n	(m†)	n	(m†)
Mood swings	0	0.00	0	0.00	2	0.22	2	0.10	3	0.15	0	0.00	0	0.00	1	0.21	1	0.08	2	0.15
Panic attack	1	0.46	1	0.10	1	0.11	2	0.10	2	0.10	0	0.00	1	0.20	0	0.00	1	0.08	1	0.07
Sleep disorder	0	0.00	2	0.20	4	0.43	6	0.31	7	0.34	1	0.65	1	0.20	1	0.21	4	0.33	5	0.37
Somnambulism	0	0.00	0	0.00	1	0.11	1	0.05	1	0.05	0	0.00	0	0.00	1	0.21	1	0.08	1	0.07
Stress	0	0.00	2	0.20	1	0.11	3	0.16	5	0.24	0	0.00	1	0.20	1	0.21	2	0.17	4	0.29
Suicide attempt	0	0.00	0	0.00	1	0.11	1	0.05	1	0.05	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Renal and urinary disorders	9	4.11	40	4.01	33	3.55	72	3.74	74	3.59	7	4.56	16	3.25	12	2.52	37	3.07	40	2.93
Azotaemia	0	0.00	1	0.10	0	0.00	1	0.05	1	0.05	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Bladder mass	0	0.00	0	0.00	1	0.11	1	0.05	1	0.05	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Bladder pain	0	0.00	0	0.00	1	0.11	1	0.05	1	0.05	0	0.00	0	0.00	0	0.00	1	0.08	1	0.07
Bladder spasm	0	0.00	1	0.10	0	0.00	1	0.05	1	0.05	0	0.00	1	0.20	0	0.00	1	0.08	1	0.07
Calculus ureteric	1	0.46	2	0.20	0	0.00	2	0.10	2	0.10	0	0.00	1	0.20	0	0.00	2	0.17	2	0.15
Calculus urinary	0	0.00	1	0.10	0	0.00	1	0.05	1	0.05	1	0.65	0	0.00	0	0.00	0	0.00	0	0.00
Calyceal diverticulum	0	0.00	1	0.10	0	0.00	1	0.05	1	0.05	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Chronic kidney disease	0	0.00	1	0.10	0	0.00	1	0.05	1	0.05	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Cystitis noninfective	0	0.00	0	0.00	1	0.11	1	0.05	1	0.05	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Glycosuria	1	0.46	2	0.20	8	0.86	10	0.52	10	0.49	1	0.65	1	0.20	2	0.42	4	0.33	4	0.29
Haematuria	1	0.46	12	1.20	8	0.86	20	1.04	20	0.97	2	1.30	4	0.81	2	0.42	8	0.66	9	0.66
Hydronephrosis	1	0.46	1	0.10	1	0.11	2	0.10	2	0.10	0	0.00	0	0.00	1	0.21	1	0.08	1	0.07



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
09/20/2016



IND 101389

MEETING PRELIMINARY COMMENTS

Merck Sharp & Dohme Corporation
Attention: Melissa Tice, PhD
Executive Director, Global Regulatory Affairs
126 E. Lincoln Avenue, RY34 B293
Rahway, NJ 07065

Dear Dr. Tice:

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

We also refer to your correspondence, received and dated May 16, 2016, requesting a meeting to discuss the development plan for tildrakizumab solution.

Our preliminary responses to your meeting questions are enclosed.

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

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

If you have any questions, call me at (301) 796-5376.

Sincerely,

{See appended electronic signature page}

CDR Dawn Williams, RN, BSN, USPHS
Regulatory Health Project Manager
Division of Dermatology and Dental Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

ENCLOSURE:
Preliminary Meeting Comments



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PRELIMINARY MEETING COMMENTS

Meeting Type: B
Meeting Category: Pre-BLA
Meeting Date and Time: August 31, 2016; 10:30 AM – 11:30 AM
Meeting Location: FDA, White Oak Building 22
Application Number: IND 101389
Product Name: tildrakizumab solution
Proposed Indication: For the treatment of psoriasis
Sponsor Name: Merck Sharp & Dohme Corporation

Introduction:

This material consists of our preliminary responses to your questions and any additional comments in preparation for the discussion at the meeting scheduled for August 31, 2016, 10:30 AM at FDA, White Oak Building 22 between Merck Sharp & Dohme Corporation and the Division of Division of Dermatology and Dental Products. We are sharing this material to promote a collaborative and successful discussion at the meeting. The meeting minutes will reflect agreements, important issues, and any action items discussed during the meeting and may not be identical to these preliminary comments following substantive discussion at the meeting. If you determine that discussion is needed for only some of the original questions, you have the option of reducing the agenda and/or changing the format of the meeting (e.g., from face to face to teleconference). Contact the Regulatory Project Manager (RPM) if there are any major changes to your development plan, the purpose of the meeting, or the questions based on our preliminary responses, as we may not be prepared to discuss or reach agreement on such changes at the meeting.

1.0 BACKGROUND

The purpose of this meeting is to discuss the development program for tildrakizumab solution.

2.0 DISCUSSION

2.1. Chemistry, Manufacturing and Controls

There were no Chemistry, Manufacturing and Controls questions submitted in the briefing package.

2.2. Pharmacology/Toxicology

Question 13:

Based on previous correspondence from the End of Phase 2 meeting (11 APR 2012) and submission of the pre- and post-natal developmental toxicity report (22 OCT 2014), does the Agency agree that the non-clinical toxicology package is complete and sufficient to support licensure of a marketing application for tildrakizumab?

FDA Response to Question 13:

Yes, we agree that no additional nonclinical studies are needed to support a BLA submission.

However, you should submit updated literature references that address the potential carcinogenic risk associated with chronic use of tildrakizumab in the BLA and incorporate appropriate information into Section 13.1 of the label. We reiterate that in order to address the carcinogenic potential of tildrakizumab you should provide data from nonclinical studies conducted with a surrogate monoclonal antibody and in knock-out animal models and all available data regarding the characterization of the IL-23p19 deficient mouse model with the BLA. Submit full literature articles and complete study reports, not just summary information, to allow an in-depth review.

Question 14:

Does the Agency agree that based on the results from the developmental and reproductive toxicity studies conducted in cynomolgus monkeys, including the pre- and post-natal developmental (PPND) toxicity study, the animal studies do not identify any reproductive (fertility and pregnancy outcome) risk associated with tildrakizumab and no such warning or precaution will be needed in the proposed USPI?

FDA Response to Question 14:

We note a dose dependent increase in infant loss in the PPND study conducted in monkeys. On page 38 of the briefing document the infant loss is 1, 2 and 4 for vehicle, 10 mg/kg and 100 mg/kg tildrakizumab groups, respectively. The infant loss incidence in the high dose group (29%) falls outside the historical control range for the test facility (0 – 20%). We acknowledge that you indicated that two of four infant loss in the high dose group were due to maternal rejection or not nursing and the other two early deaths were likely due to viral infection, which possibly resulted from immunosuppression. It is possible that the maternal rejection was also treatment related. Therefore, we consider the dose dependent increase in infant loss noted in the monkey PPND study to be treatment related and appropriate information should be incorporated in Section 8.1 of the label for tildrakizumab.

Your proposed label should comply with the Pregnancy and Lactation Labeling Rule (PLLR). You are referred to the guidance document, *Pregnancy, lactation, and reproductive potential: labeling for human prescription drug and biological products — content and format*, for detailed information.

2.3. Clinical Pharmacology

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Question 1:

Does the Agency concur

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(b) (4)

FDA Response to Question 1:

(b) (4)

Additional Clinical Pharmacology Comments:

We acknowledge that you have planned to evaluate the impact of immunogenicity on PK, efficacy and safety based on subjects' anti-drug antibodies (ADA) status. Your briefing document indicated that the presence of ADA was associated with increased drug clearance and reduced tildrakizumab exposure in some individuals. As your integrated analysis of the immunogenicity impact on PK, efficacy and safety is ongoing, we have the following general recommendations regarding the immunogenicity assessments:

- For the evaluation of the ADA impact on PK, we recommend that you include between-subject comparison (i.e., between ADA positive subjects and ADA negative subjects) as well as within-subject comparison (i.e., before ADA positive and after ADA positive) of PK data.
- For the ADA positive subjects observed in Phase 3 trials, provide a summary table of study number, study subject ID, serum tildrakizumab concentrations at each PK time-point, sample ADA status at each immunogenicity assessment time-point, and the primary efficacy outcome.

2.1. Clinical/Biostatistics

Question 2:

Does the Agency agree with the proposal to pool the efficacy and safety data from the Phase 2 study P05495 and Phase 3 studies P010 and P011 as outlined in the integrated statistical analysis plan (iSAP)?

FDA Response to Question 2:

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

1. Phase 2 and 3: Placebo-Controlled Safety Pool

Safety data from P05495 (16 weeks) and P010 and P011 (12 weeks) will be summarized in the following columns:

- placebo
- tildrakizumab 100 mg
- tildrakizumab 200 mg,
- tildrakizumab 100 / 200 mg
- all tildrakizumab (5 mg, 25 mg, 100 mg, 200 mg)
- Etanercept 50 mg (P011 only)

For subjects who dropped out during the placebo-controlled period and entered the 20-week follow-up period, adverse events occurring during the follow-up will be included.

2. Phase 3: Placebo-Controlled Safety Pool

Safety data from P010 and P011 (12 weeks) will be summarized in the following columns:

- placebo
- tildrakizumab 100 mg
- tildrakizumab 200 mg,
- tildrakizumab 100 / 200 mg
- Etanercept 50 mg (P011 only)

For subjects who dropped out during the placebo-controlled period and entered the 20-week follow-up period, adverse events occurring during the follow-up will be included for these subjects.

3. Phase 2 and 3: Exposure-Adjusted 1-Year Safety Pool

Safety data through Week 52 for P05495 and P011 and through Week 64 for P010 will be summarized to provide an exposure adjusted rates of adverse events for the base period and will be summarized in the following columns.

- placebo
- tildrakizumab 100 mg
- tildrakizumab 200 mg,
- continuous exposure tildrakizumab 100 mg
- continuous exposure tildrakizumab 200 mg
- tildrakizumab 100 or 200 mg
- continuous exposure tildrakizumab 100 or 200 mg
- all tildrakizumab (5 mg, 25 mg, 100 mg, 200 mg)
- continuous exposure all tildrakizumab (5 mg, 25 mg, 100 mg, 200 mg)
- Etanercept 50 mg (P011 only)

Subjects with multiple treatments will be counted in each treatment received, after exposure adjustment. For subjects who dropped out during the base period or did not enter the extension period, adverse events occurring during follow-up will be included for these subjects and will be attributed to the last treatment received.

4. Phase 3: Partial Responder Dose Increase Safety Pool

Safety data from Week 28 to Week 52 from Trial P010 and P011 will include subjects who were randomized to tildrakizumab 100 mg and who are partial responders at Week 28. Safety data will be summarized in the following columns:

- increased dose to tildrakizumab to 200 mg
- remained on tildrakizumab 100 mg

5. Phase 3: Extension Safety Pool

Safety data from Week 64 to Week 256 from Trial P010 and Week 52 to Week 244 from Trial P011 will be summarized in the following columns:

- tildrakizumab 100 mg
- tildrakizumab 200 mg

For subjects who dropped out during the extension period and entered the 20 week follow-up, adverse events occurring during follow-up period will be included and will be attributed to the last treatment received.

In general, the pooling strategy for safety appears reasonable; however, pooling the 5 mg and 25 mg dosing groups with the 100 and 200 mg dosing groups will not be informative in determining the safety profile for the proposed 100 mg and 200 mg doses. We recommend that you remove 5 mg, 25 mg treatment groups from “all tildrakizumab (5 mg, 25 mg, 100 mg, 200 mg)” columns of “Phase 2 and 3: Placebo-Controlled Safety Pool” and “Phase 2 and 3: Exposure-Adjusted 1-Year Safety Pool”.

It should be noted that the objective of the integrated summary of efficacy (ISE) is to support the analysis results obtained from the individual trials and not to establish a new efficacy claim based on pooling data from the individual trials. Therefore, analyses based on pooled efficacy data are considered exploratory. Establishing an efficacy claim would be based on efficacy data from the individual Phase 3 trials along with a replication of study findings.

We have the following additional comments:

- For the “Placebo-controlled Period through Week 16” pool, provide raw incidence rates for adverse events ($\geq 1\%$) by treatment group.
- You state that the “Partial Responder Dose Increase Safety Pool” data includes AEs from Week 28 to 52. However, Part 3 of Trial P010 extends from Week 28 to 64 while Part 3 of Trial P011 extends from Week 28 to 52. Clarify the data that you intend to include in this pool.

Question 3:

Does the Agency agree with the planned subgroup analyses as described in the iSAP for the efficacy and safety data from the Phase 2b study P05495 and Phase 3 studies P010 and P011?

FDA Response to Question 3:

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. You are encouraged to present results of the subgroup analyses for efficacy and safety for each trial individually as well as for the pooled data.

In your subgroup analysis for the efficacy and safety data by race, add Black/African American to the other racial subgroups (White, Asian, Other Races).

Question 4:

Does the Agency agree with the scope of the iSAP, as well as the presentation of the efficacy and safety data in the proposed table/figure formats?

FDA Response to Question 4:

See response to Questions 2 and 3.

Question 5:

Based on the proposed cut-off date of FEB 2017 for the Safety Update Report (SUR), approximately 8 additional months of safety will be provided, does the Agency agree that the proposed cut-off date and data package is adequate to support this BLA?

FDA Response to Question 5:

For the 120 day safety update submission, you propose a 3 month cut-off date from the date of BLA submission (November 2016) to include 8 additional months of safety data. This appears to be reasonable. Provide narratives in the 120-day safety update for all subjects who died, experienced SAEs, pregnancy outcomes and reported AEs of special interest (serious cardiovascular events, serious events of TB and opportunistic infections, and malignancy). Additionally, submit 7-day and 15-day safety reports to the IND for all ongoing tildrakizumab trials.

Question 6:

Does the Agency concur that a Risk Evaluation and Mitigation Strategy (REMS) is not necessary for tildrakizumab?

FDA Response to Question 6:

Based on our review of the summarized safety information contained in your meeting package, a REMS may not be required for the safe use of tildrakizumab as a treatment for moderate to severe plaque psoriasis. However, our final determination regarding the need for REMS will be based on the overall risk benefit assessment for your product at the time of the BLA review.

Question 7:

Does the Agency agree with the Sponsor's proposal to conduct a prospective, observational study (registry) to assess the long-term safety of tildrakizumab post registration?

FDA Response to Question 7:

Your proposal to support the long-term safety of your product with data from two 4-year extension trials (P010 and P011) and data from a registry appears reasonable at this time.

Question 8:

Does the Agency agree that information pertaining to infections can be adequately and effectively communicated to clinicians in Section 6 (Adverse Reactions) of the proposed US Prescribing Information for tildrakizumab and that, with the exception of preevaluation/pre-treatment for TB, precautionary language in Section 5 (Warnings and Precautions) is not warranted?

FDA Response to Question 8:

It is premature to provide agreements on proposed labeling. It will be necessary for the Agency to complete the review of the safety data to determine whether information regarding infections can be adequately and effectively communicated to clinicians in Section 6 (Adverse Reactions) of the proposed US Prescribing Information for tildrakizumab.

Question 9:

Based on the core risk profile that has been developed for tildrakizumab, the Sponsor considers that a Medication Guide (MG)

(b) (4)
(u) (4)
(b) (4)

proposal?

FDA Response to Question 9:

The need for Medication Guide will be determined following the review of the safety data submitted with your BLA.

Question 10:

- a. Does the Agency agree with the proposed categories for individual electronic Case Report Forms (eCRFs) in the Phase 2 and Phase 3 clinical trials to fulfill the eCRFs requirement for the BLA of tildrakizumab?
- b. Does the Agency require copies of the adjudication packages reviewed by the Clinical Adjudication Committee for cardiovascular events to be submitted as part of the BLA or is acceptable to have them available upon request?

FDA Response to Question 10:

- a. Your proposal to submit electronic Case Report Forms (eCRFs) in the Clinical Study Reports (CSR) for the Phase 2 and Phase 3 clinical trials is acceptable. However, if the eCRFs are located in the CSR, then provide links to the eCRFs in the relevant sections of the Overview of Clinical Safety, Summary of Clinical Safety and Integrated Summary of Safety (ISS).

In addition, provide narratives for all deaths, serious adverse events (SAEs), including all serious infections, subjects who discontinued the study agent due to adverse events (AEs), and AEs of special interest including malignancy, opportunistic infections, active TB, other infections of interest, anaphylaxis/hypersensitivity reactions, serum-sickness or serum-sickness like reactions, elevated liver function (AST or ALT ≥ 3 times upper limit of normal and total bilirubin ≥ 2 times upper limit of normal), and pregnancies. These narratives may also be included in the CSRs with links to the narratives provided in the relevant sections of the Overview of Clinical Safety, Summary of Clinical Safety and Integrated Summary of Safety.

- b. You may provide narratives rather than full adjudication packages for cardiovascular events reviewed by the Clinical Adjudication Committee.

Question 11:

Does the Agency agree with the strategy of submitting case report tabulations (CRTs) in both standard (SDTM IG 3.1.1) and nonstandard (legacy) formats?

FDA Response to Question 11:

Yes.

Question 12:

Does the Agency agree with the scope and high-level content of the analysis package?

FDA Response to Question 12:

From the Draft Table of Contents for Module 5, it is not clear what you intend to include in the ISS. 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>)

For the analysis datasets, we have the following comments:

- The protocols for your Phase 3 trials specify using the multiple imputation (MI) approach as a sensitivity analysis for the handling of missing data. Instead of submitting the multiple imputed data within the analysis datasets, submit the SAS code used to implement MI. In addition, submit the SAS code used to analyze the multiple imputed data.
- 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.
- 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.

ESUB's General Comments

From a technical standpoint (not content related) the proposed summary plans for electronic submissions and the table of contents for Key eCTD modules provided, appears acceptable. However, please see additional comments below:-

- Do not create additional nodes (e.g. m2.5.1.1 – m2.5.1.6.5; m2.7.1.1 - m2.7.1.5. etc.,) in the eCTD structure beyond what is in the specifications. Please make sure your approach fits the DTD and the “Granularity Annex”, located at:-
<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM073261.pdf>
- Providing Table of Contents in 4.1 and 5.1 is not necessary in the eCTD structure. Instead, it will be helpful to reviewers if sponsors can provide a linked reviewer’s aid/ reviewer’s guide to briefly describe where information can be found throughout the application and place the document in m1.2.
- Case Report Forms need 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”.

Additional comments:

1. Conduct a retrospective evaluation of suicidal ideation and behavior using the Columbia Classification Algorithm of Suicide Assessment (C-CASA) for all subjects enrolled in Tildrakizumab clinical trials for all indications.
2. 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).
3. Include the full text version of any referenced articles.
4. Provide your rationale/discussion regarding the acceptability of your foreign data. Acceptability of foreign clinical data depends on its ability to be extrapolated to the U.S. population. Refer to the ICH guidance for industry, E5 Ethnic factors in the Acceptability of Foreign Clinical Data, September 2006.
5. Include the following in your pooled analysis (Trial 010 and Trial 011)
 - a. Line listings for all abnormal safety findings (e.g., adverse events, vital signs, laboratory values.)
 - 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.

6. Provide an analysis of ECG data (Trial 010 and Trial 011) 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

7. In addition to the electronic datasets, you should 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).

3.0 ADDITIONAL INFORMATION

DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

As stated in our May 25, 2016 communication granting this meeting, if, at the time of submission, the application that is the subject of this meeting is for a new molecular entity or an original biologic, the application will be subject to “the Program” under PDUFA V. Therefore, at this meeting be prepared to discuss and reach agreement with FDA on the content of a complete application, including preliminary discussions on the need for risk evaluation and

mitigation strategies (REMS) or other risk management actions. You and FDA may also reach agreement on submission of a limited number of minor application components to be submitted not later than 30 days after the submission of the original application. These submissions must be of a type that would not be expected to materially impact the ability of the review team to begin its review. All major components of the application are expected to be included in the original application and are not subject to agreement for late submission.

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

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

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

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

PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (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/U>

542 [CM360507.pdf](#). In addition, you may contact the Division of Pediatric and Maternal Health at
543 301-796-2200 or email pdit@fda.hhs.gov. For further guidance on pediatric product
544 development, please refer to:
545 [http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.ht](http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm)
546 [m](#).
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PRESCRIBING INFORMATION

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

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

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

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

MANUFACTURING FACILITIES

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

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

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594 Consider using a table similar to the one below as an attachment to Form FDA 356h. Indicate
595 under Establishment Information on page 1 of Form FDA 356h that the information is provided
596 in the attachment titled, "Product name, NDA/BLA 012345, Establishment Information for Form
597 356h."

598

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.				

599

600 Corresponding names and titles of onsite contact:

601

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

602

603 **Office of Scientific Investigations (OSI) Requests**

604

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

612

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

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

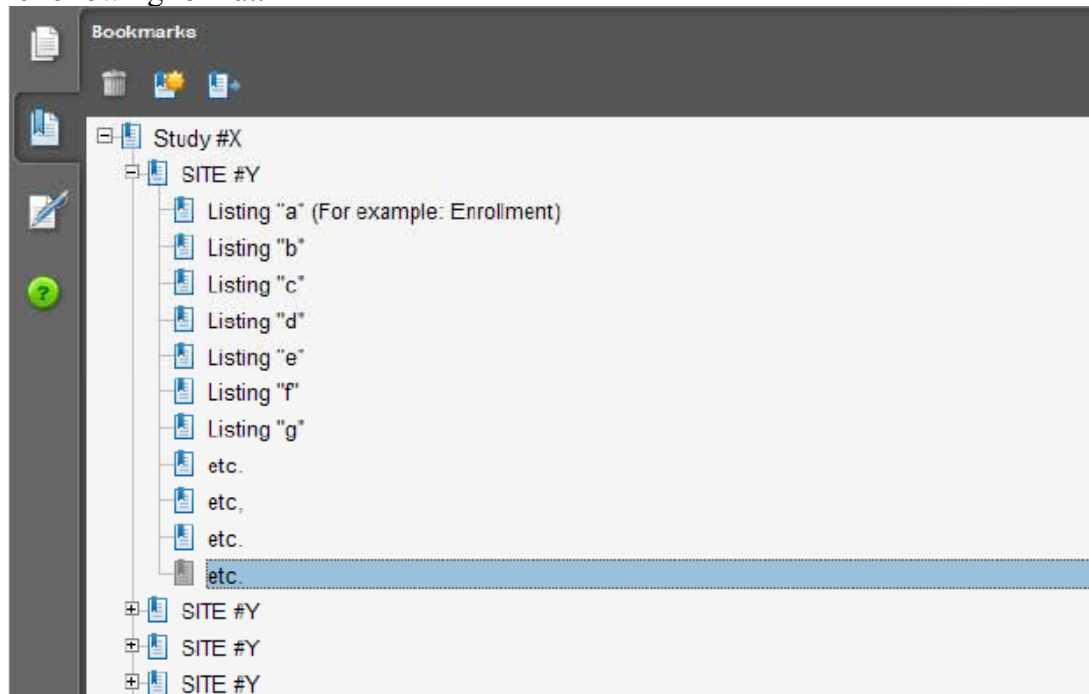
620

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

736 References:

737

738 eCTD Backbone Specification for Study Tagging Files v. 2.6.1

739 ([http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequire](http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM163560.pdf)
740 [ments/ElectronicSubmissions/UCM163560.pdf](http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM163560.pdf))

741

742 FDA eCTD web page

743 ([http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/Elect](http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm153574.htm)
744 [ronicSubmissions/ucm153574.htm](http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm153574.htm))

745

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

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/s/

DAWN WILLIAMS
08/26/2016



IND 101389

**AGREED INITIAL PEDIATRIC STUDY PLAN -
AGREEMENT**

Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc.
Attention: Melissa Tice, PhD
Executive Director, Global Regulatory Affairs
126 E Lincoln Ave; RY34 B293
Rahway, NJ 07065

Dear Dr. Tice:

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

We also refer to your amendment dated May 20, 2016 containing your Agreed Initial Pediatric Study Plan (Agreed iPSP) for the treatment of psoriasis.

We have completed our review of your submission. We agree with your Agreed iPSP and have no further comments at this time. The attached copy of your Agreed iPSP serves as the official copy of this document, and must be included in the appropriate section of an application for marketing approval for tildrakizumab. Your Agreed iPSP may be amended at your initiative or at FDA's initiative at any time before you submit a marketing application. However, FDA must agree to any amendments to an Agreed iPSP.

If you have any questions, contact Dawn Williams, Regulatory Project Manager, at (301) 796-5376.

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: Agreed iPSP

44 Pages have been Withheld in Full as B4(CCI/TS)
Immediately Following This Page

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/s/

KENDALL A MARCUS
06/09/2016



IND 101389

SPECIAL PROTOCOL - AGREEMENT

Merck Sharp and Dohme Corporation
Attention: Frank Seebach, MD
Director, Worldwide Regulatory Affairs
PO Box 2000, RY 33-204
Rahway, NJ 07065

Dear Dr. Seebach:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act (FDCA or the Act) for MK-3222 (Humanized Anti-IL23 monoclonal antibody).

We acknowledge your request dated June 7, 2012, received on June 8, 2012, for a special protocol assessment of a clinical protocol. The protocol is titled, "A 64-Week, Phase 3, Randomized, Double-Blind, Placebo-Controlled, Parallel Design Study to Evaluate the Efficacy and Safety/Tolerability of Subcutaneous SCH 900222/MK-3222, Followed by an Optional Long-Term Safety Extension Study, in Subjects With Moderate-to-Severe Chronic Plaque Psoriasis".

We have completed our review and, based on the information submitted, agree that the design and planned analysis of your study adequately address the objectives necessary to support a regulatory submission. We advise you that, if you make any changes to this protocol, this agreement may be invalidated. If you choose to revise this protocol, submit your modifications as "**Special Protocol Assessment - Amendment**". This agreement is subject to modification only as outlined in section 505(b)(4)(C) of the Act.

As stated on page 9 in the "Guidance for Industry: Special Protocol Assessment," a special protocol assessment documents our agreement that the design and planned analysis of a study can adequately address objectives in support of a regulatory submission. However, final determinations for marketing application approval are made after a complete review of a marketing application and are based on the entire data in the application.

We also have the following responses to your questions.

I. Questions

Question 1:

Does the Agency agree with the proposed Phase III dosing regimen, including the proposed maintenance dose regimen?

Response:

Based on the summary data provided in your submission, the proposed doses and dosing regimen for the Phase 3 trial appears to be acceptable.

Question 2:

Does the Agency agree with the proposed multiplicity strategy?

Response:

Refer to list of agreements.

The following agreements and disagreements pertain to establishing the efficacy claim at Week 12 which you refer to as Part 1 of your protocol.

II. Agreements

1. The proposed study population (subjects 18 years of age and older with moderate-to-severe chronic plaque psoriasis defined as Psoriasis Area and Severity Index (PASI 75) score ≥ 12 , body surface area (BSA) involvement $\geq 10\%$ and Physician Global Assessment (PGA) of at least moderate disease (≥ 3) at Baseline who are considered to be candidates for phototherapy or systemic therapy), is acceptable.
2. Your proposed co-primary endpoints of the proportion of subjects with at least 75% improvement in the PASI 75 at Week 12 and the proportion of subjects with a PGA score of 0 (Clear) or 1 (Minimal) with at least 2-grade reduction from Baseline at Week 12 are acceptable.
3. The proposed safety evaluation is acceptable.
4. Your gate-keeping sequential testing procedure for testing the co-primary and key secondary efficacy endpoints across the two MK-3222 doses (100 mg and 200 mg) is acceptable. It should be noted that the results from endpoints not included in the multiplicity strategy will be considered exploratory.

III. Non-Agreements/Outstanding Issues

5. You proposed to define the full analysis set (FAS) population for Part 1 as all randomized subjects who received at least one dose of Part 1 study treatment. The Agency recommends the intent- to- treat population (ITT) analyses for Part 1 should be planned for all randomized subjects whether or not they received at least one dose of Part 1 study treatment.

6. You plan to enroll approximately 750 subjects from approximately 75 centers, which implies an average of 4 subjects on MK-3222 200 mg, 4 subjects on MK-3222 100 mg, and 2 subjects on placebo per center. With this small number of subjects, it would be difficult to assess center-to-center variability. The Agency reiterates previous comment that you reduce the number of centers and enroll a reasonable number of subjects per arm per center (e.g. 8). In addition, randomization should be stratified by center and the analysis should account for such stratification. If the goal of stratifying by other variables (i.e. body weight and prior exposure to biologics therapy for psoriasis) is to learn about potential differential treatment effects, such information can be gained through subgroup analyses.
7. You stated that missing data will be imputed as non-responders with last observation carried forward (LOCF) as a sensitivity analysis. It should be noted that whether this approach is appropriate or not depends on the magnitude of treatment effect in the various arms. You should provide your rationales for imputing missing data as non-responders and with LOCF as a sensitivity analysis. You stated that an additional sensitivity analysis can be performed if deemed appropriate. In particular, you propose to use pattern mixture model in the event of potential informative missingness. It is not clear how you will determine the appropriateness of an additional sensitivity analysis and why pattern mixture model is limited to informative missingness. To ensure that the efficacy results are not driven by the method of imputation, you should pre-specify sensitivity analyses in the protocol that use an alternate framework from the primary imputation method.

IV. Additional Comments

8. Your definitions for response for the re-randomization at Week 28 and for relapse/rebound during the maintenance period are based only on PASI. For interpretation of trial findings, the Agency reiterates the previous comment from the April 11, 2012 End of Phase 2 Meeting that the same endpoints should be used throughout the trial.
9. Per protocol, at Week 28 subjects who are non-responders in Arm A (MK-3222 200 mg) and Arm B (MK-3222 100 mg) will be discontinued, while subjects who are non-responders in Arm C will remain in the trial. Provide details on how you would maintain blinding for such subjects.
10. You propose to have PGA defined based on an average of three scales corresponding to thickness, erythema, and scaling. This averaging gives equal weight to each of the three scales. In general, the PGA scale should be based on clearly defined descriptions for each category.
11. In addition to a single “key” secondary endpoint, you will evaluate several “other” secondary endpoints at different time points, which lead to over 50 endpoints. Secondary endpoints intended for a labeling claim should be limited in number,

clinically meaningful, and adjusted for multiplicity. Without being specific about the role of these secondary endpoints in labeling, the Agency would consider their findings to be exploratory.

12. We recommend that you collect additional serum pharmacokinetic samples for assessment at Week 16 of your proposed Phase 3 trial, which will be helpful to evaluate the steady state trough serum concentrations of MK-3222 during every 12 week dosing.
13. We recommend that you collect serum samples to evaluate the immunogenicity potential of your product at least every 6 months (24 weeks) during the long-term extension period of your proposed Phase 3 trial.
14. For females of child bearing potential, clarify your rationale for requiring two forms of contraception and your proposed labeling.

If you have any questions, call Dawn Williams, Regulatory Project Manager, at (301) 796-5376.

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

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/s/

GORDANA DIGLISIC
07/18/2012

SUSAN J WALKER
07/18/2012



IND 101389

SPECIAL PROTOCOL - AGREEMENT

Merck Sharp and Dohme Corporation
Attention: Frank Seebach, MD
Director, Worldwide Regulatory Affairs
PO Box 2000, RY 33-204
Rahway, NJ 07065

Dear Dr. Seebach:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act (FDCA or the Act) for MK-3222 (Humanized Anti-IL23 monoclonal antibody).

We acknowledge your request dated June 7, 2012, received on June 8, 2012, for a special protocol assessment of a clinical protocol. The protocol is titled, "A 52-Week, Phase 3, Randomized, Double-Blind, Active Comparator and Placebo-Controlled, Parallel Design Study to Evaluate the Efficacy and Safety/Tolerability of Subcutaneous SCH 900222/MK-3222, Followed by an Optional Long-Term Safety Extension Study, in Subjects With Moderate-to-Severe Chronic Plaque Psoriasis".

We have completed our review and, based on the information submitted, agree that the design and planned analysis of your study adequately address the objectives necessary to support a regulatory submission. We advise you that, if you make any changes to this protocol, this agreement may be invalidated. If you choose to revise this protocol, submit your modifications as "**Special Protocol Assessment - Amendment**". This agreement is subject to modification only as outlined in section 505(b)(4)(C) of the Act.

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Response:

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Question 2:

Does the Agency agree with the proposed multiplicity strategy?

Response:

Refer to list of disagreements.

The following agreements and disagreements pertain to establishing the efficacy claim at Week 12 which you refer to as Part 1 of your protocol.

II. Agreements

1. The proposed study population (subjects 18 years of age and older with moderate-to-severe chronic plaque psoriasis defined as Psoriasis Area and Severity Index (PASI 75) score ≥ 12 , body surface area (BSA) involvement $\geq 10\%$ and Physician Global Assessment (PGA) of at least moderate disease (≥ 3) at Baseline who are considered to be candidates for phototherapy or systemic therapy), is acceptable.
2. Your proposed co-primary endpoints of the proportion of subjects with at least 75% improvement in the PASI 75 at Week 12 and the proportion of subjects with a PGA score of 0 (Clear) or 1 (Minimal) with at least 2-grade reduction from Baseline at Week 12 are acceptable.
3. The proposed safety evaluation is acceptable.

III. Non-Agreements/Outstanding Issues

4. You proposed to define the full analysis set (FAS) population for Part 1 and Part 2 as all randomized subjects who received at least one dose of study medication in Part 1 and Part 2, respectively. The Agency recommends the ITT analyses for Part 1 and Part 2 should be planned for all randomized subjects whether or not they received at least one dose during Part 1 or Part 2.
5. You plan to enroll approximately 1050 subjects from approximately 120 centers, which implies an average of 2 subjects on MK-3222 200 mg, 2 subjects on MK-3222 100 mg, 2 subjects on etanercept, and 1 subject on placebo per center. With this small number of subjects, it would be difficult to assess center-to-center variability. The Agency reiterates previous comment that you reduce the number of centers and enroll a reasonable number of subjects per arm per center (e.g. 8). In addition,

randomization should be stratified by center and the analysis should account for such stratification. If the goal of stratifying by other variables (i.e. body weight and prior exposure to biologics therapy for psoriasis) is to learn about potential differential treatment effects, such information can be gained through subgroup analyses.

6.

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(b) (4)

8. You stated that missing data will be imputed as non-responders with last observation carried forward (LOCF) as a sensitivity analysis. It should be noted that whether this approach is appropriate or not depends on the magnitude of treatment effect in the various arms. You should provide your rationales for imputing missing data as non-responders and with LOCF as a sensitivity analysis. You stated that an additional sensitivity analysis can be performed if deemed appropriate. In particular, you propose to use pattern mixture model in the event of potential informative missingness. It is not clear how you will determine the appropriateness of an additional sensitivity analysis and why pattern mixture model is limited to informative missingness. To ensure that the efficacy results are not driven by the method of imputation, you should pre-specify sensitivity analyses in the protocol that use an alternate framework from the primary imputation method.

IV. **Additional Comments**

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10. Per protocol, at Week 28 subjects who are non-responders in Arm A (MK-3222 200 mg) and Arm B (MK-3222 100 mg) will be discontinued, while subjects who are non-responders in Arm C and Arm D will remain in the trial. In addition, at Week 28 responders in Arm D (etanercept) will be discontinued. Provide details on how you would maintain blinding for such subjects.
11. You propose to have PGA defined based on an average of three scales corresponding to thickness, erythema, and scaling. This averaging gives equal weight to each of the

three scales. In general, the PGA scale should be based on clearly defined descriptions for each category.

12. In addition to a single “key” secondary endpoint, you will evaluate several “other” secondary endpoints at different time points, which lead to over 20 endpoints. Secondary endpoints intended for a labeling claim should be limited in number, clinically meaningful, and adjusted for multiplicity. Without being specific about the role of these secondary endpoints in labeling, the Agency would consider their findings to be exploratory.
13. We recommend that you collect additional serum pharmacokinetic samples for assessment at Week 16 of your proposed Phase 3 trial, which will be helpful to evaluate the steady state trough serum concentrations of MK-3222 during every 12 week dosing.
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15. For females of child bearing potential, clarify your rationale for requiring two forms of contraception and your proposed labeling.

If you have any questions, call Dawn Williams, Regulatory Project Manager, at (301) 796-5376.

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

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/s/

GORDANA DIGLISIC
07/18/2012

SUSAN J WALKER
07/18/2012



IND 101389

SPECIAL PROTOCOL - AGREEMENT

Merck Sharp and Dohme Corporation
Attention: Frank Seebach, MD
Director, Worldwide Regulatory Affairs
PO Box 2000, RY 33-204
Rahway, NJ 07065

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We have completed our review and, based on the information submitted, agree that the design and planned analysis of your study adequately address the objectives necessary to support a regulatory submission. We advise you that, if you make any changes to this protocol, this agreement may be invalidated. If you choose to revise this protocol, submit your modifications as "**Special Protocol Assessment - Amendment**". This agreement is subject to modification only as outlined in section 505(b)(4)(C) of the Act.

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IV. **Additional Comments**

9. You propose to have PGA defined based on an average of three scales corresponding to thickness, erythema, and scaling. This averaging gives equal weight to each of the three scales. In general, the PGA scale should be based on clearly defined descriptions for each category.
10. In addition to the two “key” secondary endpoints, you will evaluate 12 “other” secondary endpoints. Secondary endpoints intended for a labeling claim should be limited in number, clinically meaningful, and adjusted for multiplicity. Without being specific about the role of these secondary endpoints in labeling, the Agency would consider their findings to be exploratory.
11. We recommend that you collect additional serum pharmacokinetic samples for assessment at Week 16 of your proposed Phase 3 trial, which will be helpful to evaluate the steady state trough serum concentrations of MK-3222 during every 12 week dosing.

12. We recommend that you collect serum samples to evaluate the immunogenicity potential of your product at least every 6 months (24 weeks) during the long-term extension period of your proposed Phase 3 trial.

13. For females of child bearing potential, clarify your rationale for requiring two forms of contraception and your proposed labeling.

If you have any questions, call Dawn Williams, Regulatory Project Manager, at (301) 796-5376.

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

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/s/

GORDANA DIGLISIC
07/18/2012

SUSAN J WALKER
07/18/2012



IND 101389

MEETING MINUTES

Merck Sharpe & Dohme Corporation
Attention: Frank Seebach, M.D.
Director, Worldwide Regulatory Affairs
PO Box 2000, RY 33-204
Rahway, NJ 07065

Dear Dr. Seebach:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for MK-3222 (Humanized Anti-IL23 p19 monoclonal antibody).

We also refer to the meeting between representatives of your firm and the FDA on April 11, 2012. The purpose of the meeting was to discuss Merck's late stage development plan for MK-3222.

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 Dawn Williams, Regulatory Project Manager, at (301) 796-5376.

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 B
Meeting Category: End of Phase 2 Meeting

Meeting Date and Time: April 11, 2012; 9:00 a.m.
Meeting Location: White Oak Campus, Building 22, Room 1311

Application Number: 101389
Product Name: MK-3222 (Humanized Anti-IL23 p19 monoclonal antibody)
Proposed Indication: For the treatment of patients with moderate-to-severe chronic plaque psoriasis who are candidates for systemic therapy or phototherapy
Sponsor Name: Merck Sharpe & Dohme Corporation

Meeting Chair: Susan Walker, M.D.
Meeting Recorder: Dawn Williams, B.S.N.

FDA ATTENDEES

Susan J. Walker, M.D., F.A.A.D., Director, DDDP
Barbara Gould, MBAHCM, Chief, Project Management Staff, DDDP
Tatiana Oussova, M.D., Deputy Director for Safety, DDDP
Barbara Hill, Ph.D., Pharmacology Supervisor, DDDP
Jianyong Wang, Ph.D., Pharmacology Reviewer, DDDP
Gordana Diglisic, M.D., Clinical Team Leader, DDDP
Melinda McCord, M.D., Clinical Reviewer, DDDP
Strother Dixon, M.S., Regulatory Health Project Manager, DDDP
Dawn Williams, B.S.N., Regulatory Health Project Manager, DDDP
Barbara Rellahan, Ph.D., Product Quality Team Leader, DMA
Laurie Graham, Ph.D., Product Quality Reviewer, DMA
Yaning Wang, Ph.D., Pharmacometrics Team Leader, DPM
Jeff Florian, Ph.D., Pharmacometrics Reviewer, DPM
Yow-Ming Wang, Ph.D., Clinical Pharmacology Team Leader, DCP III
Jie Wang, Ph.D., Clinical Pharmacology Reviewer, DCP III
Victoria Kusiak, M.D., Deputy Director, ODE III
Mohamed Alosch, Ph.D., Biostatistics Team Leader, DB III
Matthew Guerra, Ph.D., Biostatistics Reviewer, DB III
Patricia Love, M.D., Deputy Director, OCP
Carlos Mena-Grillasca, Ph.D., Safety Evaluator, DMEPA

Quynhnhu Nguyen, Ph.D., Human Factors Specialist, CDRH
Jacqueline Ryan, M.D., Clinical Reviewer, GHDB

SPONSOR ATTENDEES

Frank Seebach, M.D., Director, Worldwide Regulatory Affairs
Martin Himmel, M.D., M.P.H., Senior Director, Worldwide Regulatory Affairs
Sean Curtis, M.D., Vice-President, Project & Pipeline Leader
Annie Chen, M.D., Executive Director, Clinical Research
Richard Shames, M.D., Senior Director, Clinical Research
Kristine Nograles, M.D., M.Sc., Associate Director, Clinical Research
Paul Peloso, M.D., M.D., M.Sc., Senior Director, Clinical Research
Eddie Bowman, Ph.D., Fellow, Biology and Pharmacology
Yagnesh Patel, Ph.D., Manager, Global CMC Regulatory Affairs- Biologics
Lawrence Starke, Ph.D., Senior Director, Global CMC Regulatory Affairs- Biologics
Joost Clerx, Ph.D., Project Manager, Analytical Development & Validation
Ivonne van den Dries, Ph.D., CMC Lead
Janet Mas, M.S., Design Control & Strategic Planning Lead, Device Development
Sauzanne Lhalilieh, Pharm.D., Director, Clinical Pharmacology
Eugene Marcantonio, M.D., Ph.D., Senior Director Clinical Pharmacology
Bo Yang, Ph.D., Senior Director, Late Development Statistics
Yijie Zhou, Ph.D., Biometrics, Late Development Statistics
Anthe Zandvliet, Pharm.D., Ph.D., PK-PD Scientist
Janet Vessotski, Ph.D., Director, Regulatory Policy
Jayanthi Wolf, Ph.D., Associate Director, Biologic Safety Assessment/Toxicological Sciences

Regulatory Correspondence History

We have had the following meetings with you:

- June 1, 2011, Guidance Meeting
- April 1, 2008, Pre-IND Meeting

We have sent the following correspondences:

- March 7, 2011, Advice/Information Request Letter
- December 16, 2010, Advice/Information Request Letter
- January 6, 2010, Advice/Information Request Letter
- June 29, 2009, Advice/Information Request Letter
- October 1, 2008, Advice/Information Request Letter

Chemistry, Manufacturing and Controls (CMC)

Question [23]:

Does the Agency concur that the formal in vitro comparability study results demonstrate comparability between the three Process I DS and the three Process II DS batches, manufactured (b) (4) and therefore there is no need for additional preclinical or clinical studies prior to initiation of Phase III trials?

Response:

Based on the information submitted in the meeting package, in general the data support comparability of the (b) (4) process I and process II lots. The following issues should be addressed when data to support process I and process II comparability is submitted. A final decision on comparability will be made when the full data has been submitted.

- a) Data/information to demonstrate comparable viral clearance/inactivation by the processes should be provided.
- b) Data comparing the level of host cell proteins present in (b) (4) process I and process II drug substance (DS) lots should be provided.
- c) The comparability data should include data from the (b) (4) studies.

Meeting Discussion:

The Agency clarified that the (b) (4) studies were needed to support clinical use of the prefilled syringe presentation.

- d) DS and drug product (DP) batch analyses for all (b) (4) process I lots should be included. Provide the mean $\pm$ standard deviation for tests with quantitative results.

Question [24]:

Does the agency agree with the proposed strategy to introduce site and scale changes for Process II DS during the course of Phase III trials?

Response:

In general your proposal to introduce site and scale changes for process II DS supported by comparability studies during the course of the pivotal trials appears acceptable. However, if changes are observed in the analytical comparability study that could impact product quality, safety or efficacy, additional pre-clinical or clinical studies may be required to support clinical use of material produced by the new process. DP produced from the (b) (4) DS process should not be used clinically until DS and DP comparability studies supporting its use has been submitted for review. A final decision as to whether material from the (b) (4) process is comparable to (b) (4) process II will require full review of the comparability data. It is recommended that DP produced from (b) (4) DS be introduced into the pivotal trials as early as possible to maximize clinical experience with this process. See our response to Question 25 for additional comments.

Question [25]:

Does the agency agree with our proposed comparability protocol to include DP manufactured using (b) (4) to initiate Phase III trials and introduce DP manufactured from (b) (4) DS during the course of Phase III trials?

Response:

In general, based on information provided in the meeting package, the comparability protocol appears acceptable. However, if changes are observed in the analytical comparability study that could impact product quality, safety or efficacy, additional pre-clinical or clinical studies may be required to support clinical use of material produced by the new process. We have the following comments that should be addressed to support the proposed manufacturing changes.

1. As stated above, DP produced from the (b) (4) DS process should not be used clinically until a comparability study supporting its use is submitted for review. A final decision as to whether material from the (b) (4) process is suitable for clinical use will require review of the full comparability data.
2. It was not clear from the meeting package whether (b) (4) DS filled by the intended DP manufacturer would be introduced into the pivotal trial. A comparability study to support use of DP made by a new DP manufacturer needs to be submitted to support its clinical use. It is recommended that the material produced by the intended commercial DS and DP process be used in the pivotal trials so that clinical experience can be gained with the material.

Meeting Discussion:

The sponsor does not plan to use drug product produced by the commercial facility in the phase 3 trials. The Agency indicated that this may be an acceptable approach; however, the adequacy of the analytical comparability data is a BLA review issue.

3. Provide information on the reference standard being used. It is recommended that a reference standard that is representative of (b) (4) process II be implemented for use for the pivotal trials.
4. It is recommended that an assessment of Fc-region activity be performed on product produced by process II to characterize the Fc-region activity of material used in the pivotal trials. (b) (4) this characterization could include an analysis of Fc- and/or FcRn-receptor binding. Depending on changes observed between (b) (4) process II lots and the timeframe when material from the (b) (4) DS process is introduced into the pivotal trials, a comparison of Fc-region activity of the process II (b) (6) processes may be required.
5. The proposed extended characterization testing should include a comparison of process II batches produced (b) (4) (b) (4).
6. It was not clear from the meeting package whether data to support stability of new processes would be included in the comparability packages. Stability data comparing the rate and pathway of degradation of the (b) (4)

(b) (4) process II DS and DP will be required to support comparability of the processes.

8. It was noted that in the process I to process II comparability study there was stated to be some artifacts in the peptide mapping studies that were due to the prolonged digestion procedure. It is recommended that this method be optimized for the late phase comparability studies.

Question [26]:

Does the agency agree with the Sponsor's proposal of establishing the commercial DP shelf life based on stability data generated from the batches manufactured at the clinical (pilot scale) manufacturing site (b) (4), supplemented with the stability data at the commercial site?

Response:

There was not enough information in the meeting package to come to a decision on the acceptability of this approach. It is recommended that the commercial DP shelf-life primarily be established based on data from DP produced from the intended commercial process. Data from DP produced from the phase III clinical process can be used as supportive data. The ability to extrapolate the DP shelf-life from one DP site to another will be a review issue and is dependent on issues such as the similarity of the processes at the different DP sites and the results of comparability studies for DP produced at each site. The Agency has seen unexplained differences in the stability profile of products produced by clinical and commercial processes. It is recommended that as much as possible, data from the intended commercial site and process be used to establish/support DS and DP expiry periods.

Additional CMC comments

1. It is noted that drug substance release allows for the presence of visible particulates. As development continues the composition of the visible particulates and the basis for their formation should be investigated and procedures implemented to control/limit their formation. If visible particulates are present at the time of licensure, a robust control strategy will need to be in place to control for these impurities.
2. It appears that only one unit of DP is being used for assessment of visible particulates. It is unclear whether this is sufficient to assure adequate control over visible particulates. The number of units included in this assay will need to be justified at the time of licensure.

Pharmacology/Toxicology

Question [1]:

Does the Agency agree the nonclinical studies (as described in the background document) will support registration, and no additional nonclinical studies will be required to support registration?

Response:

We agree that no additional nonclinical studies are needed to support registration provided that the planned pre- and post-natal developmental toxicity study in cynomolgus monkeys is conducted prior to registration and the study report is included in the initial submission of the BLA.

Question [2]:

Carcinogenic potential has been assessed in various non-clinical studies, including with a surrogate monoclonal antibody and in knock-out animals.

Does the Agency agree that these data, together with relevant data from the literature, adequately inform clinical risk and no additional nonclinical studies will be required to support registration?

Response:

We agree that no additional nonclinical studies are needed to assess the carcinogenic potential of MK-3222.

The adequacy of the literature data and the nonclinical studies conducted with a surrogate monoclonal antibody and in knock-out animals to address the carcinogenic potential of MK-3222 will be determined after review of the full literature articles and/or complete study reports submitted with the BLA. Submit all available data regarding the characterization of the IL-23p19 deficient mouse model with the BLA. Submit full literature articles and complete study reports, not just summary information, to allow an in-depth review.

Question [3A]:

Does the Agency agree that unlike IL-12/23p40 inhibition, IL-23p19 inhibition is not associated with a signal for carcinogenic potential and that this information can be included in the Non-Clinical Toxicology Section of the label (Section 13.1 Carcinogenesis).

Response:

See below under response to 3B.

Question [3B]:

Independent of the response to Question 3B, does the Agency agree that no further preclinical data are necessary to support omission of the following text which appears in the current, approved labeling for ustekinumab (STELARA®, anti p40 antibody)?

Response to Questions 3A and 3B:

From the summary information you provided it appears that IL-23p19 inhibition may not be associated with an increased carcinogenic risk. However, the final assessment will be made during the BLA review cycle. The information that will be included in the label concerning the carcinogenic potential of MK-3222 will be determined during the BLA review cycle.

Question [4]:

Does the Agency agree that pre-clinical data demonstrate reduced infection risk compared with p40 inhibition, and further studies are not needed?

Response:

We agree that no additional nonclinical studies are needed to address the concern of infection risk associated with MK-3222. The final assessment of infection risk should be made in clinical trials as the relevance of various infection animal models to humans is not clear.

Question [5]:

Does the Agency agree that pre-clinical data (b) (4) can be included in the label, including section 13.2, (b) (4) (b) (4)

Response:

The information that will be included in the labeling concerning (b) (4) MK-3222 will be determined during the BLA review cycle.

Clinical Pharmacology/Biopharmaceutics

Question [6]:

Does the Agency agree that the PK studies as summarized in the background package are adequate to support the review and approval of the application?

Response:

Yes. We agree that the PK studies as summarized in the background package appear to be adequate to support the review of your BLA application; however, the adequacy of the PK trial results to support the approval and labeling of your product will be a review issue following the data submission in the BLA. We acknowledge that you have planned to characterize MK-3222 single dose PK of the to-be-marketed PFS formulation in a frequently-sampled PK trial (P08630) in subjects with moderate-to-severe chronic plaque psoriasis and you will also collect PK samples in the pivotal Phase 3 clinical trials to assess PK of MK-3222 administered as a solution from the prefilled syringe (PFS). These proposed PK studies are required to support the review and approval of your product.

Regarding your PK program related to the formulation transition from lyophilized-in-vial to PFS and PFS in autoinjector (AI), you may consider conducting a 3-arm trial to include the Phase 2 formulation and two Phase 3 formulation/presentations (PFS and PFS in AI). The comparative PK between the Phase 2 formulation and the PFS formulation will facilitate extrapolation of optimal dose from the Phase 2 trial to Phase 3 pivotal trials. The inclusion of a third study arm for PFS-in-AI provides an opportunity for direct comparison of PK data of PFS arm and PFS-in-AI arm in a single dose trial with frequent PK sampling. As such, the trial does not need to be statistically powered.

We may have additional comments on your PK trial design such as blood sampling scheme after review of your final Phase 3 protocols when they are submitted under the IND.

Please refer to response to Question 22A for additional PK comments.

Question [7]:

MRL proposes

(b) (4)

(b) (4)

Does the Agency concur

(b) (4)

(b) (4)

Response:

No.

(b) (4)

(b) (4)

Question [8]:

Population PK will be used to evaluate the effects of: weight, age, race, gender, renal function, hepatic function and disease baseline characteristics, on PK of MK-3222. Does the agency agree with this approach?

Response:

Your approach to use population PK analysis to evaluate the effects of weight, age, race, gender, renal function, hepatic function and disease baseline characteristics on PK of MK-3222 appears to be a reasonable approach at this time. The adequacy of this approach to support the approval and labeling of your product will be a review issue following the submission of BLA. The adequacy of any population pharmacokinetic claims will depend on the number of subjects with various covariates that are enrolled in the Phase 3 trials and will be a review issue. We may have additional comments on your

PK trial design such as blood sampling scheme after review of your final Phase 3 protocols when they are submitted under the IND.

Question [9]:

The effect of immunogenicity status on PK and efficacy of MK-3222 will be assessed using population PK. Does the Agency agree that this approach is adequate to support review and approval of the application?

Response:

While the proposed population PK analysis approach appears reasonable, it is currently considered an exploratory approach for assessing the effect of immunogenicity status on PK and efficacy of MK-3222. The adequacy of this approach to support the approval and labeling of your product will be a review issue following submission of the BLA. Therefore, you must conduct a conventional immunogenicity analysis in addition to the proposed population PK analysis. Both analyses would provide supportive information on the performance of the exploratory approach for future applications.

We may have additional comments on your PK and immunogenicity blood sampling scheme after review of your final Phase 3 protocols submitted under the IND.

Please refer to the responses to Question 14 and Question 15 for additional comments on your immunogenicity assessment plan.

Question [10]:

QT prolongation has not been reported with other mAbs and, as a mAb, the size of MK-3222 would be expected to prevent access to the hERG channel via the intracellular side.

Does the Agency agree that a thorough QT/QTc study is not necessary to support review and approval of the application?

Response:

Yes we agree.

We recommend periodic ECG monitoring in clinical trials (at least baseline and steady state) 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 include 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.

1. 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
2. Review all of the following SOC's for possible cardiac events, thrombotic and MACE, since cardiac events may be found in several SOC's:
 - 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
3. Have all possible cardiovascular events (rather than only MACE) reviewed by a DMC with expertise in cardiovascular adverse events.

4. Have all TIAs reviewed by the DMC (rather than only those resulting in hospitalization).
5. Evaluate possible thrombotic events alone and MACE alone during the uncontrolled period of the global psoriasis studies.

Refer to Appendix 2 for definitions of MACE events and other cardiovascular events.

Question [11]:

The PK of MK-3222 administered as a solution from a pre-filled syringe (PFS) will be assessed using an intensive sampling scheme in the proposed Clinical Pharmacology study (P08630), and using sparse sampling in the Phase 3 studies, as described in the background package.

Does the Agency agree the proposed PK assessments are adequate to support review and approval of the application?

Response:

Yes. Your proposal to characterize PK of MK-3222 administered as a solution from a pre-filled syringe (PFS) appears reasonable; however, the adequacy of the PK trial results to support the approval and labeling of your product will be a review issue following the BLA submission.

Please refer to the responses to Question 6 and Question 22A for additional comments.

Question [12]:

If the Agency considers it necessary to evaluate the PK of MK-3222 administered via autoinjector in clinical studies (based on Agency response to Question 22A), does the Agency agree that the number and timing of PK samples for MK-3222 administered via autoinjector in the long-term extension study described in the background package (b) (4)

Response:

Please refer to responses to Question 6 and Question 22A.

Question [13]:

Does the Agency agree vaccine studies are not needed to support approval of the application?

Response:

We agree that studies of vaccine safety, immunogenicity, or efficacy are not required to support approval of the licensing application for MK-3222. We recommend, however, that the product labeling for MK-3222 include precautions about the potential for reduced efficacy of vaccines in patients taking MK-3222 (drug-vaccine interactions) as well as the potential for increased risk of infectious complications of live vaccines.

The exclusion criteria of the proposed Phase 3 trials prohibit concomitant immunization with live virus vaccines but do not explicitly prohibit other non-virus live vaccines (BCG and live attenuated typhoid vaccine.) Although the risk of serious infections with these vaccines among subjects treated with MK-3222 is probably low, the exclusion criteria should be modified to prohibit concomitant immunization with all live vaccines or provide justification for only prohibiting concomitant immunization with live virus vaccines.

Question [14]:

Does the Agency concur with the proposed bioanalytical testing approach to assess antidrug antibodies in human subjects?

Response:

It is recommended that an immunogenicity assay capable of reliably determining the ADA status of subjects in the presence of drug product levels expected to be present in samples at the time of testing be utilized for pivotal clinical trials. The assay should be capable of determining ADA status during the course of treatment and after the proposed wash-out period. Provide clarification on the anticipated product concentration that will be present in patient samples at the time of sampling for immunogenicity and the ability of your assay to detect ADA at this level.

The proposed screening and confirmatory testing approach to evaluate anti-product antibodies in human subjects appears to be reasonable. However, it is noted that the positive control is a rabbit polyclonal antibody and the immunogen used for generation of the positive control was not described. For example, if the entire MK-3222 antibody was used to immunize animal, it is possible that the positive control would not reflect the anticipated immune response in humans since rabbit would predominantly generate immune responses against the Fc region while human subjects would predominantly generate immune responses against the CDR region. When the immunogenicity assay validation report is submitted it should therefore include information on the immunogen used for generation of the positive control serum and data that demonstrates that the positive control antiserum reacts with both the CDR- and Fc-region of MK-3222.

With regard to the detection of neutralizing antibodies, it is noted that the proposed assay is a competitive ligand binding assay. The Agency recommends the use of a cell based biological assay where feasible as these assays tend to be more reflective of the in vivo situation and are, therefore, important for understanding the impact of patient immune responses.

Question [15]:

Does the Agency agree with the proposal for reporting of ADA incidence in subjects (i.e. definition of a positive ADA response for individual subjects)?

Response:

Because the presence of MK-3222/SCH 900222 in a serum sample with concentration higher than the assay tolerance level can interfere with the detection of an antibody response in your anti-drug antibodies (ADA) assay, you are required to analyze and report drug concentrations in each of your immunogenicity samples. You should report

the subject ADA status using 3-category classification, i.e., positive, negative, or inconclusive, as defined below.

Positive: Samples with detectable ADA are classified as antibody positive, regardless of the drug concentration in these samples. Subjects with at least one positive sample at any time point evaluated are classified as positive ADA status. In the instance that a subject has a positive baseline sample, a post-dose sample may be considered treatment-emergent positives when its titer is higher than the baseline titer by predefined criteria.

Negative: Samples with drug concentration lower than the drug tolerance level and with no detectable ADA are classified as antibody negative. Subjects are designated ADA negative when there is no positive sample at any time up to the time point of ADA assessment and the last sample is negative.

Inconclusive: Samples without detectable ADA but containing drug concentration higher than the drug tolerance level are classified as antibody inconclusive. Subjects were designated inconclusive ADA status when there was no positive sample at any time up to the time point of ADA assessment and the last sample is inconclusive.

We acknowledge that in the immunogenicity assessment of your product, if the result is positive for anti-drug antibodies (ADA), you will characterize whether the ADA are neutralizing or not in nature. We also acknowledge that during your product development, you will evaluate the impact of immunogenicity on PK, efficacy and safety.

Clinical

Question [16A]:

Assuming the proposed Phase 3 studies demonstrate appropriate safety and efficacy in the target population, does the Agency agree that the proposed pivotal program will support an indication for subjects with moderate-to-severe chronic plaque psoriasis who are candidates for systemic therapy or phototherapy?

Response:

Yes, we agree.

Question [16B]:

Does the Agency agree with the proposed endpoints: The primary efficacy objective in all 3 pivotal trials is PASI 75 response at week 12. Key secondary efficacy endpoints include the Physician Global Assessment (PGA) at week 12 and 28, and PASI 75 response at week 28.

Response:

We prefer that you use a primary efficacy endpoint based on a static PGA scale (where success is defined as “clear” or “almost clear” with a 2 grades reduction from baseline) **or** co-primary endpoints that include PGA and PASI 75 because PGA utilizes categories that are easily described in labeling and correspond to disease severity (e.g., moderate to severe disease, clear and almost clear). In contrast, PASI is a calculated score that is not

routinely used in clinical practice and not readily translatable into labeling (e.g. the clinical benefit of a difference in PASI score 75 v PASI 90).

The static PGA scale was not provided with the proposed Phase 3 protocols. Also you did not provide PGA scale that was used in your Phase 2b trial. Without knowing the description of the PGA scale, it is difficult to comment on its adequacy, or concur with its utility for Phase 3 trials.

Meeting Discussion:

The sponsor commits to making the PGA at 12 weeks a co-primary endpoint along with PASI 75. The sponsor will submit a statistical analysis plan to control the multiplicity adjustment along with using the co-primary endpoint.

The Agency recommended that the sponsor propose a definition for the relapse/rebound during the maintenance period based on the PGA as well as the PASI 75 so that the same endpoints are used throughout the various periods of the trial.

The same efficacy scale should be used for all comparisons (e.g. durability of response, relapse, rebound) throughout the trials.

You propose many secondary endpoints (“key” and “other”) which are highly correlated. Secondary endpoints should be limited in number, clinically meaningful and adjusted for multiplicity.

Question [16C]:

Does the Agency agree with the multiplicity adjustments for the primary and secondary endpoints?

Response:

The proposed stepwise method to control multiplicity does not fully control the Type I error rate. To control the Type I error rate, the stepwise method needs to be a series of single steps where clearance to the next step is dependent on if the test or tests within the current step are statistically significant. If a step contains more than one test, then an additional adjustment for multiplicity within the step is needed to control the Type I error rate. You should consider a testing strategy in which success on PGA is the primary (or co-primary) efficacy endpoint.

Question [16D]:

Does the Agency agree with the proposed blinding for the placebo controlled and active comparator controlled studies?

Response:

The blinding for the placebo controlled and active comparator controlled trials appears to be acceptable. For your placebo controlled trials, subjects originally randomized to placebo will be re-randomized to either MK-3222 200 mg or 100 mg at Week 12. Please provide more detail on how blinding of the re-randomization will be maintained.

You state that each pre-filled syringe (PFS) of investigational medicinal product (IMP) contains 50 mg (50 mg/mL) or 100 mg (100 mg/mL) of MK-3222 and each PFS contains 1 mL of solution; however, you do not state the number of injections and concentration of the PFS used for each MK-3222 treatment arm. To maintain blinding, all subjects should receive the same number of injections. In addition, subjects randomized to placebo and etanercept should receive two injections of MK-3222 placebo.

Question [17A]:

The Phase 3 program includes 2 pivotal studies (P011 and P012) comparing safety and efficacy of MK-3222 with etanercept in a double blind, double dummy design. Both pivotal studies will include both EU and US sourced and approved etanercept.

Does the Agency agree with the multiplicity adjustments for etanercept comparison the primary and secondary endpoints?

Response:

See answer to Question 16C.

Question [17B]:

Does the agency agree with the proposed interim futility analysis for comparisons of MK-3222 with etanercept?

Response:

We do not have adequate information to provide concurrence regarding the interim futility analysis. You need to provide more detail on the statistical methodology and statistical software used to obtain the 6.7% futility boundary. You do not indicate which MK-3222 dose will be used in the analysis. In addition, you should consider modifying the interim futility analysis so that success on PGA is the primary (or co-primary) efficacy endpoint. When you submit the full Phase 3 protocols for IND, the protocols should include the external Data Monitoring Committee (eDMC) charter and provide details on how blinding to the eDMC's findings for the interim analysis will be ensured.

Question [17C]:

Does the Agency agree that if these two studies demonstrate superiority of MK-3222 as compared to Enbrel® (etanercept) on the primary endpoint, PASI 75 at 12 weeks, this can be included in product labeling?

Response:

Your proposal appears to be reasonable. However, product labeling will be a review issue.

Although you propose to conduct 2 trials which compare the efficacy of MK-3222 with Enbrel® (etanercept) at week 12 and 28, we are concerned that Protocol P012 does not include a placebo arm in the trial design. By including a placebo arm in Trial P012, you would avoid potential problems in interpreting trial findings. The claim should be specific to a certain dose, otherwise an adjustment for multiplicity will be needed to

control the Type I error rate. In addition, the trials need to be powered for the intended dose comparison.

Your proposal to conduct two trials to demonstrate superiority of MK-3222 compared to etanercept appears reasonable as long as you intend to use the United States (US) approved product in the US trial sites (as labeled) and European Union (EU) approved product in the EU trial sites (as labeled)

Meeting Discussion:

The Agency reiterated the comment that as study P012 does not contain a placebo arm; this might impact interpretability of the study findings if results of this trial turned out to be different from other studies. In addition, having a placebo arm in this trial would help maintain the blinding as otherwise all subjects would be on active treatment that might impact the assessment for this study. If the sponsor decides to include a placebo arm in this trial, they might consider not having equal treatment allocation for all arms.

Question [17D]:

Does the Agency agree that if these two studies demonstrate superiority of MK-3222 compared to etanercept, assuming appropriate strong control for multiplicity among secondary endpoints as outlined in the background package, these superiority data on the key secondary endpoint, PASI 75 at 28 weeks can be included in product labeling?

Response:

The information provided from your Phase 3 trials after Week 12 will be very informative; however, your Phase 3 trials are powered for efficacy assessment at Week 12. Due to possible subject dropout and the inherent branching of the treatment arms in your trial design, it might be difficult to obtain reliable estimates for endpoints related to later parts of your trial. Secondary endpoints related to time-points after Week 12 that you want to be included in labeling will be a review issue.

Question [18]:

Assuming safety and tolerability are consistent with safety and tolerability to date, does the Agency agree that the proposed safety database as detailed in the background package will be adequate to support the review and approval of the proposed dose regimens?

Response:

Your proposal appears to be reasonable. The adequacy of the safety database to support the approval of your drug product will be a review issue.

Question [19A]:

Does the Agency agree with the proposed Phase 3 dosing regimen as detailed in the background package?

Response:

In your Phase 2 program (P05495) you intended to investigate short-term efficacy and the treatment dose/regimen for maintenance. The data provided to support the proposed

Phase 3 dosing regimen is limited and only includes dosing up to 16 weeks. No exposure data beyond 16 weeks has been submitted for review. The 16-week results support further evaluation of the 100 and 200 mg dosage strengths in Phase 3 for short-term efficacy evaluation. However, the trial is ongoing and data regarding the treatment dose/regimen for maintenance are not provided in the briefing package. Therefore, in the absence of data for these dosing parameters from Phase 2 we cannot provide detailed comments on the proposed dosing regimen for Phase 3 trials.

The proposed dosing interval was based on the mean half life (23-30 days), PK/PD modeling and simulation to predict adequate trough levels to maintain a sustained clinical response. These assumptions regarding the optimal dosing interval were not confirmed in a clinical trial and may not reflect actual clinical use.

Your pharmacokinetic and pharmacodynamic model is limited in its ability to evaluate maintenance dosing regimens because it does not include data on the offset of treatment effect. An alternative approach such as using semi-mechanistic model would be more informative. Identifying if lower maintenance doses over a 12-week dosing interval could maintain treatment effect warrants further exploration prior to or during Phase 3.

Meeting Discussion:

The sponsor acknowledged the limitations of the data in the background package to inform maintenance dosing. The sponsor has completed an interim analysis of P05495 and will submit this information with the Phase 3 protocols.

Question [19B]:

Does the Agency agree that the proposed dose escalation for patients with a partial response that is currently planned for the Phase 3 studies (b) (4)?

Response:

The appropriateness of the dose escalation strategy proposed for subjects with a partial response in the Phase 3 trials will be a review issue. (b) (4)

(b) (4) You are also referred to the response to Question 19A.

Question [20]:

Does the Agency agree that the target population as defined by inclusion and exclusion criteria in the study protocols is adequate to demonstrate safety and efficacy of MK-3222 in the proposed indication?

Response:

Yes, we agree.

Question [21]:

Pursuant to 21 CFR 314.55, Merck requests a partial waiver to the pediatric data requirement for pediatric subjects under 6 years of age on the grounds that the disease

does not exist in these young children. Merck further requests a deferral of pediatric data for children 6 years and older per 21 CFR 314.55 until safety and efficacy have been demonstrated in the adult subject population. A pediatric plan will be submitted for the Agency's review prior to BLA submission.

Does the Agency agree that a waiver can be granted for children 6 years of age and younger, and that pediatric studies in children older than 6 years can be deferred until safety and efficacy have been established in the adult population?

Response:

We agree that pediatric trials should be delayed until adult safety and efficacy data have been collected. In addition, progression into the younger pediatric subpopulations would be dependent upon an adequate safety profile (risk/benefit evaluation) in adolescents and adults.

The Agency would consider a deferral of pediatric trials according to section 505B(a)(3)(A)(ii) of the Act with the submission of certification of the reason (s) for deferring the assessments, a description of the planned trials, and evidence that the trials will be conducted with due diligence and at the earliest possible time.

You should submit a partial waiver request that includes evidence that the request meets the statutory reason(s) for waiver of pediatric assessment requirements.

Device Development

(b) (4)



(b) (4)

Question [22B]:

(b) (4)

(u) (u) Does the Agency agree that the proposed Phase 3 studies are adequate to support approval, including self administration, of the pre-filled syringe (b) (4)?

Response:

Refer to the response to Question 22A.

We acknowledge your plan to use the pre-filled syringe in the Phase 3 trials (P010, P011; P012), and your intent to instruct subjects to perform self-administration of the study product after the first 2 injections. (b) (4)

(b) (4)

The information submitted in the meeting package regarding the Human Factors Study includes a test synopsis and risk assessment of delivery by PFS and AI. (b) (4)

(u) (u)

The following are comments regarding the Human Factors Study.

- **Human Factors validation testing**

- The submission does not indicate how you have systematically evaluated use-related risk and how they would validate user-performance based on performance of the highest priority task pertinent to your autoinjector. To complete our review, we will need this information to assess the safety and effectiveness of your device in the hands of representative users. Please provide a comprehensive use-related risks and a HF/usability validation protocol. Please note the following specific comments regarding the protocol and the risk analysis:

1. We recommend that you submit a draft of the test protocol before you implement it for our review and feedback to ensure that your methods will be acceptable.

The purpose of a design validation (human factors) study is to demonstrate that the device can be used by representative users under simulated use conditions without producing patterns of failures that could result in negative

clinical impact to patients or injury to device users. Tasks included in the study should be those identified through completion of a risk assessment of hazards that may be associated with use-related problems and represent greater than minimal risk to users. The study should collect sufficient and appropriate data to facilitate identification and understanding of the root causes of any use failures or problems that do occur. The causes may be related to the design of the device, the device labeling (including instructions for use), and/or the training of test participants. The test report should present a summary of your test results, data analysis, and conclusions regarding safe and effective use and including whether any modifications are indicated; if they are, these modifications should be described and if significant, the modifications should also be validated.

Your **validation study protocol** should include the items listed below.

a. Devices and Labeling Used and Training

For design validation, the devices used in your testing should represent the final design, which includes instructions for use, or any other labeling materials.

The training you provide to your test participants should approximate the training that your actual end users will receive. Please describe the training you plan to provide in your validation study and how it corresponds to realistic training levels.

In the Human Factors/usability validation study, the participants should use the instructions as they desire while interacting with the device. For essential knowledge, users can be asked questions directly. Afterward, you should ask specifically about any errors, problems or hesitations that were observed. The participants should provide subjective feedback regarding any wording in the instructions that they found confusing, misleading or incomplete.

b. User Tasks and Use-Related Risks Analysis

FDA expects to see a clear description of how you determined which user tasks would be included in the testing and how many trials each participant would complete. In order to adequately assess user performance and safety, the tasks selected for testing should be derived from the results of a comprehensive assessment of use-related hazards and risks that consider all functions of the device. The tasks should be prioritized to reflect the relative magnitude and severity of the potential impact of inadequate task performance on the safety of the device and the user.

Please provide a use-related risks analysis, describe and provide a rationale for the tasks you include in your testing and their relative

priority. Please also describe all activities in which your test participants will engage during the test.

c. Use Environment and Conditions

You should conduct your validation testing in an environment that includes or simulates all key aspects of the real-world environments in which you anticipate your device would be used.

Identification of potentially challenging use conditions should be derived through analyses of use hazards prior to conducting validation testing and aspects of use that can be reasonably anticipated, such as use with gloves or wet fingers, dim lighting, noisy situations, etc., should be included in your testing. Please evaluate use of your device under whatever conditions you identify as potentially occurring and hazardous.

Please describe the testing environment and realism of the simulated use in sufficient detail for us and justify how they were appropriate for validation testing.

d. Study Participants

FDA expects you to test a minimum of 15 participants from each major user group for validation of device use. Your test participants should be representative of your intended end-user populations, as described in your indications for use statement. If users with distinctly different characteristics (e.g., age ranges, skill sets, or experience levels, level of disabilities/impairments) will use your device, you should include 15 from each distinct group.

Regardless of the number of groups you test, please provide a rationale that these groups are representative the overall population of users for your device. Note that study participants should not be your own employees, or those that have been exposed to the products prior to the testing.

For devices sold in the United States, FDA has consistently requested that the participants in a validation test to be representative of the U.S. population and to reside in the U.S.

e. Data Collection and Analysis

Any data collected and analyzed in a validation study should be described in terms of how it supports the safety case claim that your device can be used safely and effectively by the indicated users. FDA expects you to collect both empirical and qualitative data in a design validation study.

Empirical Data – Your test participants should be given an opportunity to use the device independently and in as realistic a manner as possible,

without guidance, coaching, praise or critique from the test facilitator/moderator. Some data, such as successful or failed performance of key tasks or time taken to perform tasks – if time is a safety-critical criterion – should be measured directly rather than soliciting participant opinions. Observing participant behavior during the test is also important, in order to assess participants' adherence to protocol and proper technique and especially to assess and understand the nature of any errors or problems that occur.

Qualitative Data – The Agency expects you to ask open-ended questions of participants at the end of a usability validation, such as “ Did you have any difficulty using this device? [If so] can you tell me about that”? The questions should explore performance of each critical task involved in the use of the device and any problems encountered. Note that since the labeling and instructions for use are considered part of the user interface for your device, the questions should cover those components as well.

Your analysis of performance and subjective data should be directed toward understanding user performance and particularly task failures. The analysis should determine the nature of failures, the causes of failures, and the clinical impact. Every test participant who experiences "failure" (does something that would have led to harm under actual conditions of use), should be interviewed about that failure to determine the cause of the failure from the perspective of the participant.

Validation Report: The report should begin with a conclusion that the device is reasonably safe and effective for the intended users, uses and use conditions. A summary of relevant portions of preliminary analyses, evaluations, the validation testing should be used as support of this conclusion. The test results, and particularly failures or patterns of subjective reports of difficulty with the use of the device should be discussed with respect to whether they were caused by aspects of the design of the device, its labeling, the content or proximity of training and whether modifications are required. Residual risk associated with use that cannot be further reduced through modifications of training, labeling, or modifications to the design of the user interface should be discussed and rationale provided for why it cannot be further reduced. Note that stated plans to modify design flaws that could result in clinical impact on patients in future versions of the device are generally unacceptable.

Guidance on human factors procedures to follow can be found in *Medical Device Use-Safety: Incorporating Human Factors Engineering into Risk Management*, available online at:
<http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm094460.htm>.

Additional Comments:

- The Agency is interested in evaluating the center-to-center variability to assess the consistency in your efficacy findings. Therefore, we recommend that randomization be stratified by center and the analysis should account for such stratification; however, the design of your Phase 3 trials does not allow for stratification based on center since you plan to enroll approximately 10 subjects per center. We recommend reducing the number of centers and enrolling more subjects per center. To reduce the chance of empty cells in the analysis, the study should be designed for a minimum number of subjects per treatment arm per center (i.e. 8 subjects) to get reasonable estimates of treatment effect in the centers. In addition, the protocol should pre-specify a strategy for pooling small centers if the actual enrollment does not meet the minimum requirement.
- For long-term trials, it is expected that as the trial progresses, the probability of subjects dropping out increases. To investigate long-term efficacy and maintenance, every effort should be made to minimize missing data. You propose to impute missing data as non-responders. In addition, you propose to conduct a sensitivity analysis where missing data will be imputed using the last observation carried forward (LOCF), with LOCF being applied only within each part of the trial. Since the scientific justification for LOCF is limited, you should either provide a rationale for why LOCF is appropriate in this situation or propose an alternate method that has a reasonable justification. It should be noted that imputing missing data as non-responders and using LOCF will produce similar results. We recommend including a sensitivity analysis that uses an alternate framework from the primary imputation method to ensure that the efficacy results are not driven by the method of imputation.
- For studies P010 and P011, you plan to re-randomize subjects in Parts 2 and 3; however, you did not indicate if the re-randomization will be stratified by body weight and prior exposure to biologics therapy for psoriasis.
- You propose to allow concomitant use of low potency topical corticosteroids. The use of any class of topical steroid products should not be allowed during the trials.
- We can not provide comment on the assessment of joint pain in subjects with PsA in plaque psoriasis trials. (b) (4)
(b) (4)
- The proposed dosing for the Phase 3 trials includes 100 mg and 200 mg of MK-322. However, we note that the CMC section of the briefing package only describe a 100 mg PFS (100 g/mL). Although not explicitly stated in the protocols, the proposed strength of the PFS/AI would require 2 injections to achieve the 200 mg dose. (b) (4)

(b) (4)
(b) (4) we are concerned with the risk of medication errors and recommend that you formulate your product to provide for multiple strengths so that patients have a PFS/AI that provides their dose in one injection (e.g. 100 mg/mL PFS and 200 mg/mL PFS or autoinjectors).

(b) (4)

Meeting Discussion:

The sponsor clarified that a 200 mg/mL prefilled syringe may not be feasible due to product formulation issues (i.e. viscosity). Hence the 200 mg dose in the phase 3 trials will be achieved by administering 2 subcutaneous injections of 100 mg/mL.

(b) (4)

The Agency asked that the Sponsor consider these risks in their Risk Assessment and in the Human Factors studies.

(b) (4)
(b) (4)

Finally, the Agency reiterated our previous recommendation that the Sponsor submit a draft of the HF protocol before implementation for our review and feedback to ensure that your methods will be acceptable.

Post-meeting note:

Patients should be informed of the implications/clinical consequence of not adhering to the prescribed dosing regimen.

- The Phase 3 trials should include a plan on how to capture medication error data. Please include not only the medication errors that occurred (serious and non-serious, including those related to the device), but also near misses, product complaints, etc. All drug product units which HCP and/or patients believe are malfunctioning, should be returned to the sponsor for laboratory evaluation and testing. For all errors that occurred, determine the causality and contributing factors and assess how to address these concerns and minimize the risk of that error. Qualitative data should be collected by asking open ended questions to the HCP and/or patients regarding their impression of the device. All of the medication error related data can be included in Module 5 (Integrated Safety Summary) in a subsection under Medication Error Data from Clinical Trials.

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. 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.
5. You are encouraged to request a Pre-BLA Meeting at the appropriate time.

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>

Note that we recently published a draft guidance document that, while not yet in effect, might also be useful in understanding our current thinking and our approach to human factors. It is titled, *Applying Human Factors and Usability Engineering to Optimize Medical Device Design* and can be found online at:

<http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm259748.htm>.

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/

SUSAN J WALKER
04/27/2012

Executive CAC**Date of Meeting: March 20, 2012**

Committee: David Jacobson-Kram, Ph.D., D.A.B.T, OND IO, Chair
Abby Jacobs, Ph.D., OND IO, Member
Paul Brown, Ph.D., OND IO, Member
Barbara Hill, Ph.D., DDDP, Supervisor
Jianyong Wang, Ph.D., DDDP, Presenting Reviewer

Author of Draft: Jianyong Wang, Ph.D.

Babatunde Akinshola, Ph.D., DGIEP, attending
David Joseph, Ph.D., DGIEP, attending
Anne Pilaro, Ph.D., DHOT, attending

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

IND #: 101,389
Drug Name: MK-3222 (SCH 900222)
Sponsor: Merck Sharp & Dohme Corp., Rahway, NJ

Background:

MK-3222 is a humanized IgG monoclonal antibody that binds to human Interleukin-23 (IL-23). It is a new molecular entity. The sponsor is developing this biologic for the treatment of psoriasis under IND 101389 and for the treatment of Crohn's disease (b) (4). The sponsor submitted a meeting package for an End-of-Phase 2 meeting for IND 101389 scheduled on 04/11/2012. In the meeting package the sponsor raised questions regarding the assessment of carcinogenic potential of MK-3222.

MK-3222 binds to human IL-23 and monkey IL-23 with high affinity but does not bind to rodent IL-23. MK-3222 specifically binds to the subunit p19 of IL-23. It does not bind to human IL-12 or IL-12/23 subunit p40. A mouse anti-mouse IL-23 analog antibody, SCH 900598 (anti-IL-23p19), was developed. SCH 900598 binds relatively weakly to mouse IL-23 and shows lower potency in cell-based assays. This mouse antibody surrogate is not optimal for the assessment of carcinogenic potential of MK-3222.

The sponsor conducted a study in mice to evaluate the impact of IL-23 neutralization on tumor establishment. Antibodies that neutralize IL-23 (SCH 900598), both IL-23 and IL-12 (C17.8, anti-IL-12/23p40), or TNF- α (XT2.2, anti-TNF- α), were administered SC to mice during the immune mediated rejection of transplanted squamous carcinoma of the skin at 48 mg/kg. The results demonstrated a significantly increased risk of tumor persistence upon combined inhibition of IL-12 and IL-23 but reduced tumor persistence following IL-23 specific neutralization. The increased tumor risk imposed by combined inhibition of IL-12 and IL-23 appeared to be much greater than the risk imposed by anti-TNF- α therapy.

In the meeting package the sponsor also provided the following summary information that was obtained from literature to support their position that neutralization of IL-23p19 does not impose a carcinogenic risk.

Human genetic analysis

- 1) Genome-wide SNP association studies did not identify the IL-23R loci or the IL-23p19 loci as associated with cancer risk.
- 2) Cancer chromosomal linkage analysis did not identify the IL-23R loci or the IL-23p19 loci as associated with cancer risk.

Exogenous addition of IL-23 or IL-12

- 1) Using serial intra-dermal administration of IL-23 protein or IL-12 protein in the carcinogen-treated skin of mice, IL-23 caused a decrease of CD8⁺ T cells in the hyperplastic skin, whereas IL-12 led to increased immune-mediated anti-tumor activity.

Tumor induction models

- 1) IL-23p19-deficient mice were resistant to papilloma induction using the chemical carcinogen 7,12 dimethylbenz[a]anthracene (DMBA) followed by tumor promotion with 12-O-tetradecanoyl-phorbol acetate (TPA). In contrast, mice deficient in IL-12 alone (IL-12p35 knockout) showed earlier appearance and developed significantly increased number of papillomas compared to controls. Mice deficient in both IL-23 and IL-12 (IL-12/23p40 knockout) were resistant to papilloma induction.
- 2) IL-23p19-deficient mice were resistant to fibrosarcoma induction using the chemical carcinogen 3-methylcholanthrene (MCA). In contrast, mice deficient in IL-12 and IL-23 (IL-12/23p40 knockout) were more susceptible to fibrosarcoma induction compared to mice deficient only in IL-23.
- 3) Neutralization of IL-23 in mice using anti-IL-23p19 antibody demonstrated delayed tumor appearance following MCA chemical carcinogen application.
- 4) Co-administration of antibodies that blocks the IL-23 receptor and IL-17A (a key IL-23 signature cytokine) inhibited Enterotoxigenic Bacteroides fragilis (ETBF)-induced colonic tumor formation in APC-Min mice.

Tumor transplantation models

- 1) IL-23p19-deficient mice were resistant to tumor growth by transplanted tumor cells, including syngenic PDV squamous carcinoma cells, syngenic B16F10 melanoma cells, and EG7 thymoma cells. In contrast, IL-12 deficient (IL-12p35 knockout) and IL-12+IL-23-deficient mice (IL-12/23p40 knockout) had a dramatically increased tumor growth. The therapeutic benefit observed in IL-23p19-deficient mice was dependent on CD8⁺ T-

cell function implicating that IL-23 action was inhibiting a CD8⁺-mediated anti-tumor activity. IL-23 receptor-deficient mice were also resistant to tumor growth by transplanted syngenic B16F10 melanoma cells or LL/2 lung carcinoma cells.

- 2) Similar to the results in knockout mice, anti-IL-23p19 antibody inhibited tumor growth by transplanted tumor cells in mice, including syngenic PDV squamous carcinoma cells, EP2 mammary tumor cells, EG7 thymoma cells, and B16 melanoma cells. In contrast, anti-IL-12/23p40 antibody that blocks both IL-12 and IL-23 had dramatically increased tumor growth.

Tumor metastases models

- 1) IL-23p19-deficient mice were resistant to intravenous lung metastases of various tumor cells, including B16F10 melanoma cells, 3LL lung carcinoma cells, and RM-1 prostate carcinoma cells. In contrast, IL-12/23p40 deficient mice had increased lung metastases.
- 2) Similar to the results in knockout mice, anti-IL-23p19 antibody treated mice were resistant to intravenous lung metastases of B16F10 melanoma cells and B16 melanoma cells; whereas blockade of both IL-12 and IL-23 with an anti-IL-12/23p40 antibody increased lung metastases.

Executive CAC Recommendations and Conclusions:

- 1) The Committee agreed that no additional nonclinical studies are needed to assess the carcinogenic potential of MK-3222.
- 2) The nonclinical summary information does not suggest an increased carcinogenic risk associated with the use of MK-3222. However, the relevance of various animal models to man is unknown. The recommended wording for labeling regarding the carcinogenic potential of MK-3222 will be determined in the BLA review cycle.
- 3) The Committee recommended that all available characterization data of the IL-23p19 deficient mouse model be requested from the sponsor. These data can be submitted with the BLA.

David Jacobson-Kram, Ph.D., D.A.B.T
Chair, Executive CAC

cc:\ /Division File, DDDP
/D. Jacobson-Kram, OND IO
/A. Jacobs, OND IO
/P. Brown, OND IO
/B. Hill, Supervisor, DDDP
/J. Wang, P/T reviewer, DDDP
/D. Williams, Project Manager, DDDP
/ASeifried, OND IO

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

/s/

ADELE S SEIFRIED

03/21/2012

DAVID JACOBSON KRAM

03/21/2012



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

PIND 101,389

Schering Corporation
Attention: Monique Small, Pharm.D., Senior Manager and Liaison
2000 Galloping Hill Road
Kenilworth, NJ 07033-0530

Dear Dr. Small:

Please refer to your Pre-Investigational New Drug Application (PIND) file for Humanized Anti-IL23 monoclonal antibody.

We also refer to the meeting between representatives of your firm and the FDA on April 1, 2008. The purpose of the meeting was to discuss the sponsor's development plan for their proposed IND.

The official minutes of that meeting are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

Sincerely,

{See appended electronic signature page}

Jill Lindstrom, M.D.
Clinical Team Leader, Dermatology
Division of Dermatology and Dental
Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure

MEMORANDUM OF MEETING MINUTES



Meeting Date: April 1, 2008 **Time:** 3:00 P.M.
Location: Teleconference **Meeting ID:** 23619
Topic: PIND 101,389, Humanized Anti-IL23 monoclonal antibody for psoriasis
Subject: Pre-IND meeting
Sponsor: Schering Corporation
Meeting Chair: Jill Lindstrom, M.D./Clinical Team Leader, Dermatology, DDDP
Meeting Recorder: Melinda Bauerlien, M.S./Regulatory Project Manager, DDDP

FDA Attendees:

Jill Lindstrom, M.D./Team Leader, Clinical, Dermatology, DDDP
Gordana Diglisic, M.D./Clinical Reviewer, DDDP
Barbara Hill, Ph.D./Supervisor, Pharmacology, DDDP
Carmen Booker, Ph.D./Pharmacology Reviewer, DDDP
Melinda Bauerlien, M.S./Regulatory Project Manager, DDDP
Barbara Rellahan, Ph.D./Biologist, OPS, OBP
Laurie Graham, Ph.D./Biologist, OPS, OBP

Sponsor Attendees:

Schering Corporation

Monique Small, Pharm.D./Senior Manager and Liaison, Global Regulatory Affairs
Teresa Perney, Ph.D./Associate Director and Liaison, Global Regulatory Affairs
Gretchen Trout/Director Regulatory Relations and Policy, Global Regulatory Affairs
Robert W. Venezia, Ph.D./Fellow, Drug Safety-Toxicology, Drug Metabolism and Pharmacokinetics Biotechnology Development
Elmer Mirro, D.V.M./Vice President, Drug Safety-Toxicology, Drug Metabolism and Pharmacokinetics Biotechnology Development
Diana Montgomery, Ph.D./Principal Scientist, Drug Safety-Toxicology, Drug Metabolism and Pharmacokinetics Biotechnology Development
Constance Cullen, Ph.D./Principal Scientist, Drug Safety-Toxicology, Drug Metabolism and Pharmacokinetics Biotechnology Development
Zhong Liu/Senior Principal Scientist, CMC, Drug Safety-Toxicology, Drug Metabolism and Pharmacokinetics Biotechnology Development
Usha Barai/M.S., Manager, Biostatistics
Robert A Kastelein, Ph.D./Distinguished Research Fellow, Immunology, Discovery Research

Melinda Marian, M.S./Fellow, Nonclinical Pharmacology, Discovery Research, Early Clinical Research and Experimental Medicine

Hanno Richards, M.D./Associate Director, Nonclinical Pharmacology, Discovery Research, Early Clinical Research and Experimental Medicine

Maria Wiekowski, Ph.D./Director, Clinical Immunology

Christian Antoni, M.D./Senior Director, Clinical Immunology

Purpose:

To provide general guidance on the content and format of the proposed new Investigational New Drug Application under 21CFR 312. The pre-meeting briefing document (submitted March 3, 2008) provides background and questions for discussion. The purpose of the meeting was to discuss the sponsor's development plan for their proposed IND.

Chemistry, Manufacturing and Controls:

Question 7:

Does the Agency concur with this plan to assess ADAs in the monkey?

Response:

Yes, we concur at this time. In the IND, please submit more detailed descriptions of the assays and any available data on their qualification/validation.

Question 8:

Does the Agency concur with this plan to assess ADAs in human subjects?

Response:

Yes, we concur at this time. In the IND, please submit more detailed descriptions of the assays and any available data on their qualification/validation.

Additional CMC comments:

1. A test for sub-visible particulate matter (per USP <788>) should be added to drug product release and stability testing.
2. An assay for drug product excipients (i.e. osmolality) should be added to drug product lot release.
3. The IND submission for a Phase I trial should contain sufficient CMC information as outlined in "Points to Consider in the Manufacture and Testing of Monoclonal Antibodies for Human Use" (1997) (http://www.fda.gov/cber/gdlns/ptc_mab.pdf) and the ICH guidelines (<http://www.fda.gov/cber/ich/ichguid.htm>) to support its use in the proposed trial (s).

Pharmacology/Toxicology:

Question #1:

Does the Agency concur that the proposed nonclinical safety program outlined above supports the FIH Phase I PsO trial?

Response:

These studies appear to be adequate to support the proposed Phase 1 clinical study. However, the adequacy of the studies will be a review issue under the IND. Where possible, toxicology studies should evaluate a range of doses (i.e., at least 3 dose levels) including a high dose that produces frank toxicity or is a maximum feasible dose. Selection of a high dose in a nonclinical study based solely on providing a 10x safety factor to the highest proposed clinical dose may not be acceptable.

Question #2:

Does the Agency concur that the dose-phase data from the 3-month toxicity study, assuming an acceptable safety profile, will be sufficient to support the initiation of the Phase 1 PsO trial?

Response:

If no toxicity has been observed in main study animals in the repeat-dose toxicology study, submission of dose-phase data may be acceptable. Dose-phase data must be comparable to a draft study report after 3 months of treatment that includes complete clinical pathology, histopathology and toxicokinetic analysis for all animals in all dose groups. However, if toxicity is observed, it is recommended that the sponsor wait to submit the IND until data from the recovery animals has been evaluated. In addition, toxicokinetic and anti-SCH 900222 antibody data may be needed to assess the utility of the study. Nonetheless, the adequacy of the data will be a review issue under the IND.

Final quality-assured study reports should be available 120 days after submission of an IND. (See Guidance for Industry Q & A -- Content and Format of INDs for Phase 1 Studies of Drugs, Including Well-Characterized, Therapeutic, Biotechnology-Derived Products; October 2000.)

The sponsor stated that they would submit a quality assured study report after 3 months of dosing in the monkey study and a quality assured report for the 6 month recovery period.

Question #3a:

Assuming an acceptable safety profile, does the Agency concur that the 6-month toxicity study in monkeys is adequate for registration and supports the long-term administration of SCH 900222 (beyond 6 months of duration)?

Response:

A 6-month toxicity study in monkeys is not adequate to support chronic administration of SCH 900222. A chronic toxicity study in monkeys of at least 9 months in duration should be conducted prior to conduct of chronic clinical studies. In addition, chronic toxicity should be addressed in a

second species. The carcinogenic potential of SCH 900222 should be addressed prior to a BLA submission.

The sponsor agreed to conduct a 9 month monkey toxicology study with a 4 month post dose recovery period.

Question #3b:

Does the Agency concur that the dose-phase data provided as a summary report from the 6-month toxicity study will be sufficient to support the Phase 2 trials in PsO?

Response:

If no toxicity has been observed in main study animals in the repeat-dose toxicology study, submission of dose-phase data may be acceptable. Dose-phase data must be comparable to a draft study report after 6 months of treatment that includes complete clinical pathology, histopathology and toxicokinetic analysis for all animals in all dose groups. However, if toxicity is observed, then the sponsor should wait to begin Phase 2 trials until data from the recovery animals has been evaluated and submitted to the IND. In addition, toxicokinetic and anti-SCH 900222 antibody data may be needed to assess the utility of the study. Nonetheless, the adequacy of the data will be a review issue under the IND.

Question #4:

Does the Agency agree that the above plan adequately assesses the immunotoxic potential of SCH 900222?

Response:

This plan appears to be adequate to assess the immunotoxic potential of SCH 900222 provided no immune-related changes are observed in the repeat-dose monkey studies. However, the adequacy of the studies will be a review issue under the IND.

Question #5:

Does the Agency concur with the outlined plan for assessment of reproductive/developmental toxicity?

Response:

Adequate teratology data from two species should be submitted prior to initiation of Phase 3 clinical studies (please see the ICH S5A document, "Detection of Toxicity to Reproduction for Medicinal Products", and related documents). A study in male and female animals for effects upon fertility, reproductive function, or early embryonic development should be submitted to support marketing, and should be included in the initial submission to a BLA. A study to evaluate the effects on prenatal and postnatal development, including maternal function should be submitted to support marketing, and should be included in the initial submission to a BLA. The sponsor may propose modified reproductive/developmental toxicity studies and submit protocols to the Agency for review.

Question #6:

Does the Agency concur that the above information will be adequate to address assessment of the carcinogenic potential of SCH 900222?

Response:

The above information may not be adequate to address the carcinogenic potential of SCH 900222. The Agency recommends that the sponsor consider conducting carcinogenicity studies to assess SCH 900222's carcinogenic potential. The sponsor may propose modified studies to assess the carcinogenic potential of SCH 900222 and submit protocols to the Agency for review.

Question #7:

Does the Agency concur with this plan to assess ADAs in the monkey?

Response:

The Agency concurs that the use of an ECL-based assay is adequate for assessing total antibody levels in the monkey studies. Please thoroughly describe in your IND how you will use an ECL-based assay to assess neutralizing antibodies.

Additional Nonclinical Comment:

It is unclear as to whether the sponsor has evaluated the potential for cytokine release *in vitro* or *in vivo*. The potential for cytokine release should be addressed in the IND.

Clinical:

Question 9:

The sponsor proposes (b) (4)
(b) (4)

Does the Agency concur (b) (4)
(b) (4)

Response:

No, we do not.
(b) (4)

Question 10:

The Phase 3 program for PsO is anticipated to include two or three clinical trials that will be conducted in the US and internationally. The initial filing for the indication [REDACTED] (b) (4) [REDACTED] for SCH 900222 would be based on 6-month efficacy data and safety data from approximately 1500 subjects.

Does the Agency concur with the proposed registration plan for PsO?

Response:

It is premature to discuss your registration plan. However, we have the following general comments.

Psoriasis is a chronic skin disease that is not life threatening. Due to the chronicity of the disease and its often relapsing and remitting course, the safety and efficacy of long-term treatment, duration of response off treatment, potential for rebound, and ability to recapture response upon re-treatment should be studied. Additionally, some adverse drug events may increase in frequency or severity with the time (e.g. malignancy), these events would require a larger and/or longer long-term safety data base.

The sponsor should consult ICH E1A Guidance for Industry the Extend of Population Exposure to assess clinical Safety: for Drugs Intended for Long-term Treatment of Non-Life Threatening Conditions (www.fda.gov/cder/guidance/ichela.pdf).

Additional comments:

- While the sponsor may use PASI 75 for evaluation of subjects in non-pivotal Phase 2 studies, it is recommended that the sponsor also use for the primary efficacy assessment an acceptable static Investigator's Global Assessment Scale (IGA scale).
- The primary efficacy variable should be defined as an Investigator Global Assessment score of 0 or 1 (representing Cleared of Almost Cleared). IGA scale should also be used for study entry criteria.

2.3 Regulatory Questions

Question 11:

The sponsor proposes to submit the IND electronically within the Common Technical Document (CTD) format. The proposed overall Table of Contents of the IND is provided in Appendix 4.

Does the Agency agree that the proposed content and organization of the electronic IND is acceptable?

The proposed content and organization of the electronic IND appears acceptable.

The sponsor should consult Guidance for Industry M4: Organization of the CTD

(<http://www.fda.gov/cder/guidance/index.htm>.)

Question 12:

The sponsor plans to submit an initial IND for the treatment of PsO to the Division of Dermatology and Dental Products. (b) (4)

(b) (4)

Does the Agency agree with the proposal (b) (4) ?

Response:

(b) (4) the sponsor is encouraged to request a Pre-IND meeting at the appropriate time with the specific division to which they will be submitting their IND (e.g. Division of Gastroenterology Products).

Administrative Comments

1. Your pre-IND has been assigned 101,389. Please reference this number on all submissions and correspondence. **Please note, studies in humans may not be conducted under this PIND.** Before you may conduct studies in humans, you must submit an Investigational New Drug Application (IND, see 21 CFR Part 312). When you submit your IND, please submit 2 desk copies in addition to the 3 archival copies.
2. You are encouraged to request and attend an End-of-Phase 2 meeting 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.
4. When you submit your Investigational New Drug application, please provide 5 copies.

Minutes Preparer: _____
Melinda Bauerlien, M.S./Regulatory Project Manager, DDDP

Chair Concurrence: _____
Jill Lindstrom, M.D./Clinical Team Leader, Dermatology, DDDP

Linked Applications

Sponsor Name

Drug Name

IND 101389

Schering-Plough

Anti-interleukin 23 (SCH 900222)

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/s/

JILL A LINDSTROM

04/15/2008

LATE-CYCLE COMMUNICATION
DOCUMENTS



BLA 761067

LATE-CYCLE MEETING MINUTES

Merck Sharp & Dohme Corporation
Attention: Nadine Margaretten, PhD
Director, Global Regulatory Affairs
126 E Lincoln Avenue
PO Box 2000, RY23-B1126
Rahway, NJ 07065

Dear Dr. Margaretten:

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

We also refer to the Late-Cycle Meeting (LCM) between representatives of your firm and the FDA on December 6, 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 Dawn Williams, Regulatory Project Manager at (301) 796-5376.

Sincerely,

{See appended electronic signature page}

Gordana Diglisic, MD
Cross Discipline Team Leader
Division of Dermatology and Dental Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure:
Late Cycle Meeting Minutes



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF LATE-CYCLE MEETING MINUTES

Meeting Date and Time: December 6, 2017; 12:00pm
Meeting Format: Teleconference

Application Number: BLA 761067
Product Name: tildrakizumab
Applicant Name: Merck Sharp & Dohme Corporation

Meeting Chair: Gordana Diglisic, MD
Meeting Recorder: Dawn Williams, BSN

FDA ATTENDEES

Gordana Diglisic, MD, Cross Discipline Team Leader, DDDP
Melinda McCord, MD, Clinical Reviewer, DDDP
Kevin Clark, MD, Clinical Reviewer, DDDP
Dawn Williams, BSN, Regulatory Project Manager, DDDP
Matthew Guerra, PhD, Biostatistics Reviewer, DB III
Tamara Johnson, MD, Clinical Team Leader, DPMH
Christos Mastroyannis, MD, Clinical Reviewer, DPMH
Jie Wang, PhD, Clinical Pharmacology Reviewer, DCP III
Laura Zendel, PhD, Risk Management Analysis, DRISK
Patricia Bright, PhD, Epidemiologist, DEPI I

APPLICANT ATTENDEES

Andrew Tershakovec, MD, Distinguished Scientist, Clinical Research
Carmen La Rosa, MD, Sr. Principal Scientist, Clinical Research
Nadine Margaretten, PhD, Director, Global Regulatory Affairs
Jateh Major, PharmD., Scientist, Global Regulatory Affairs
Diana Montgomery PhD, Principal Scientist, Pharmacokinetics
Qing Li, PhD, Principal Scientist, Clinical Biostatistics
Kathryn Krantz, MD, FACOG, Senior Principal Scientist, Clinical Safety and Risk Management
Ann Strauss, MD, Associate Vice President, Clinical Safety and Risk Management
Dena Ramey B.A. Senior Principal Scientist, Pharmacoepidemiology
Daniel Mines, MD, MSCE, Executive Director, Pharmacoepidemiology, Center for
Observational and Real-World Studies
(b) (4) Contractor, Quantitative Pharmacology & Pharmacometrics
Heather Eurenus, BChE, Director, Regulatory Affairs CMC
Michael Coleman, PhD, Director of Project Leadership, MMD
Deborah Driscoll, M.S., Vice President, MRL Quality Assurance

Karine Julien, M.Sc., M.B.A, Executive Director, MRL Quality Assurance
Larry Puderbach, B.A., MBA, Executive Director, MRL Quality Assurance
Jeffrey Yuan, PhD, Associate Vice President, Global Regulatory Affairs Lead, Sun Pharmaceutical Industries Inc.
Chandrika Kumar, PhD, Senior Director, Global Regulatory Affairs, Sun Pharmaceutical Industries Inc.
Patrick Burnett, MD, PhD, Associate Vice President, Clinical Development, Sun Pharmaceutical Industries Inc.

1.0 BACKGROUND

BLA 761067 was submitted on March 24, 2017 for tildrakizumab.

Proposed indication: For the treatment of adults with moderate-to-severe plaque psoriasis who are candidates for systemic therapy or phototherapy

PDUFA goal date: March 23, 2018

FDA issued a Background Package in preparation for this meeting on December 5, 2017.

2.0 DISCUSSION

1. Introductory Comments

Discussion:

Welcome, Introductions, Ground Rules, Objectives of the meeting

2. Discussion of Substantive Review Issues

Discussion:

No substantive review issues have been identified to date.

3. Discussion of Minor Review Issues

Discussion:

No minor review issues at this time.

4. Information Requests

Discussion:

No pending information requests at this time.

5. Discussion of Upcoming Advisory Committee Meeting

Discussion:

No Advisory Committee planned for this application.

6. REMS or Other Risk Management Actions

Discussion:

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

7. Postmarketing Requirements/Postmarketing Commitments

Discussion:

Postmarketing Requirements Under 505(o): Draft language

- a. A prospective, registry based observational exposure cohort study that compares the maternal, fetal, and infant outcomes of women exposed to tildrakizumab 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 (b) (4) during pregnancy compared to an unexposed control population.

- b. Conduct a prospective, observational study to assess the long-term safety of tildrakizumab 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 tildrakizumab-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 tildrakizumab-exposed and comparator(s) cohorts, clearly define the study drug initiation period and any exclusion and inclusion criteria. Enroll patients over an initial 4 year period and follow for a minimum of 8 years from the time of enrollment.

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 tildrakizumab 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.
- Live vaccinations (MMR, varicella) are usually given in this age group, limiting the treatment of this pediatric population with tildrakizumab.

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.

Meeting Discussion:

The applicant stated that they would propose a timeline for milestone dates associated with the above PREA PMR within one week.

Corrigendum:

As mentioned in the teleconference, you are planning to involve (b) (4) to conduct the pregnancy exposure registry to fulfill the PMR. Provide the Agency with a brief description to inform us of how you and (b) (4) are planning to conduct this pregnancy exposure registry to ensure it meets the requirements of the PMR.

8. Review Plans

Discussion:

- PMC/PMR discussions to firm up language and associated milestone dates
- Manufacturing and clinical site inspection recommendations
- Take action on BLA application

9. Wrap-up and Action Items

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

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/s/

GORDANA DIGLISIC
01/10/2018



BLA 761067

**LATE CYCLE MEETING
BACKGROUND PACKAGE**

Merck Sharp & Dohme Corporation
Attention: Nadine Margaretten, PhD
Director, Global Regulatory Affairs
126 E Lincoln Avenue
PO Box 2000, RY23-B1126
Rahway, NJ 07065

Dear Dr. Margaretten:

Please refer to your Biologic License Application (BLA) submitted under the Public Health Service Act for tildrakizumab.

We also refer to the Late-Cycle Meeting (LCM) scheduled for December 6, 2017 at 11:00am. Attached is our background package, including our agenda, for this meeting.

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

If you have any questions, call Dawn Williams, Regulatory Project Manager, at (301) 796-5376.

Sincerely,

{See appended electronic signature page}

Jill A. Lindstrom, MD, FAAD
Deputy 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: December 6, 2017; 11:00am
Meeting Format: Teleconference

Application Number: BLA 761067
Product Name: Tildrakizumab injection
Indication: For the treatment of adults with moderate to severe plaque psoriasis who are candidates for systemic therapy or phototherapy
Applicant Name: Merck Sharp & Dohme Corporation

INTRODUCTION

The purpose of a Late-Cycle Meeting (LCM) is to share information and to discuss any substantive review issues that we have identified to date, 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

DISCIPLINE REVIEW LETTERS

No Discipline Review letters have been issued to date.

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 – 5 minutes (Williams RPM/Diglisic CDTL)
Welcome, Introductions, Ground rules, Objectives of the meeting
2. Discussion of Substantive Review Issues
No substantive review issues have been identified to date.
3. Discussion of Minor Review Issues
No minor review issues at this time.
4. Information Requests – 5 minutes
Status of pending IRs
5. REMS or Other Risk Management Actions
No issues related to risk management have been identified to date.
6. Postmarketing Requirements/Postmarketing Commitments RPM/Clinical

Postmarketing Requirements Under 505(o): Draft language

- a. A prospective, registry based observational exposure cohort study that compares the maternal, fetal, and infant outcomes of women exposed to tildrakizumab 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 a prospective, observational study to assess the long-term safety of tildrakizumab 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 tildrakizumab-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 tildrakizumab-exposed and comparator(s) cohorts, clearly define the study drug initiation period and any exclusion and inclusion criteria. Enroll patients over an initial 4 year period and follow for a minimum of 8 years from the time of enrollment.

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 tildrakizumab 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.

- Live vaccinations (MMR, varicella) are usually given in this age group, limiting the treatment of this pediatric population with tildrakizumab.

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.

7. Review Plans –RPM

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

8. Wrap-up and Action Items – 5 minutes

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/s/

DAWN WILLIAMS
12/05/2017