

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

761029Orig1s000

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION ¹		
BLA # 761029	NDA Supplement # BLA Supplement #	If NDA, Efficacy Supplement Type: <i>(an action package is not required for SE8 or SE9 supplements)</i>
Proprietary Name: Zinbryta Established/Proper Name: daclizumab Dosage Form: Injection		Applicant: Biogen Agent for Applicant (if applicable):
RPM: Laurie Kelley		Division: Division of Neurology Products
NDA Application Type: <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) Efficacy Supplement: <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) BLA Application Type: <input type="checkbox"/> 351(k) <input checked="" type="checkbox"/> 351(a) Efficacy Supplement: <input type="checkbox"/> 351(k) <input type="checkbox"/> 351(a)		<p><u>For ALL 505(b)(2) applications, two months prior to EVERY action:</u></p> <ul style="list-style-type: none"> Review the information in the 505(b)(2) Assessment and submit the draft² to CDER OND IO for clearance. Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity) <p><input type="checkbox"/> No changes <input type="checkbox"/> New patent/exclusivity (<i>notify CDER OND IO</i>) Date of check:</p> <p><i>Note: If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.</i></p>
❖ Actions		
<ul style="list-style-type: none"> Proposed action User Fee Goal Date is <u>May 27, 2016</u> 		<input checked="" type="checkbox"/> AP <input type="checkbox"/> TA <input type="checkbox"/> CR
<ul style="list-style-type: none"> Previous actions (<i>specify type and date for each action taken</i>) 		<input checked="" type="checkbox"/> None
❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain _____		<input type="checkbox"/> Received
❖ Application Characteristics ³		

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

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

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

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

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

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

NDAs: Subpart H

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

Subpart I

- Approval based on animal studies

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

BLAs: Subpart E

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

Subpart H

- Approval based on animal studies

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

Comments:

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

Action Letters	
❖ Copies of all action letters (<i>including approval letter with final labeling</i>)	Approval 5/27/16
Labeling	
❖ Package Insert (<i>write submission/communication date at upper right of first page of PI</i>)	
<ul style="list-style-type: none"> • Most recent draft labeling (<i>if it is division-proposed labeling, it should be in track-changes format</i>) 	<input checked="" type="checkbox"/> Included
<ul style="list-style-type: none"> • Original applicant-proposed labeling 	<input checked="" type="checkbox"/> Included
❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling (<i>write submission/communication date at upper right of first page of each piece</i>)	<input checked="" type="checkbox"/> Medication Guide <input type="checkbox"/> Patient Package Insert <input checked="" type="checkbox"/> Instructions for Use <input type="checkbox"/> Device Labeling <input type="checkbox"/> None
<ul style="list-style-type: none"> • Most-recent draft labeling (<i>if it is division-proposed labeling, it should be in track-changes format</i>) 	<input checked="" type="checkbox"/> Included
<ul style="list-style-type: none"> • Original applicant-proposed labeling 	<input checked="" type="checkbox"/> Included
❖ Labels (full color carton and immediate-container labels) (<i>write submission/communication date on upper right of first page of each submission</i>)	
<ul style="list-style-type: none"> • Most-recent draft labeling 	<input checked="" type="checkbox"/> Included
❖ Proprietary Name <ul style="list-style-type: none"> • Acceptability/non-acceptability letter(s) (<i>indicate date(s)</i>) • Review(s) (<i>indicate date(s)</i>) 	June 27, 2015 June 10, 2015
❖ Labeling reviews (<i>indicate dates of reviews</i>)	RPM: February 23, 2016 DMEPA: December 31, 2015 DMPP/PLT: May 20, 2016 OPDP: May 20, 2016 SEALD: <input checked="" type="checkbox"/> None CSS: <input checked="" type="checkbox"/> None Product Quality: May 12, 2016
Administrative / Regulatory Documents	
❖ RPM Filing Review ⁴ /Memo of Filing Meeting (<i>indicate date of each review</i>)	May 6, 2015
❖ All NDA 505(b)(2) Actions: Date each action cleared by 505(b)(2) Clearance Committee	<input checked="" type="checkbox"/> Not a (b)(2)
❖ NDAs only: Exclusivity Summary (<i>signed by Division Director</i>)	<input type="checkbox"/> Included
❖ Application Integrity Policy (AIP) Status and Related Documents http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	
<ul style="list-style-type: none"> • Applicant is on the AIP 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
<ul style="list-style-type: none"> • This application is on the AIP <ul style="list-style-type: none"> ○ If yes, Center Director's Exception for Review memo (<i>indicate date</i>) ○ If yes, OC clearance for approval (<i>indicate date of clearance communication</i>) 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> Not an AP action

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

❖ Pediatrics (<i>approvals only</i>)	
<ul style="list-style-type: none"> Date reviewed by PeRC <u>March 9, 2016</u> If PeRC review not necessary, explain: _____ 	
❖ Breakthrough Therapy Designation	<input checked="" type="checkbox"/> N/A
<ul style="list-style-type: none"> Breakthrough Therapy Designation Letter(s) (granted, denied, an/or rescinded) 	
<ul style="list-style-type: none"> CDER Medical Policy Council Breakthrough Therapy Designation Determination Review Template(s) (<i>include only the completed template(s) and not the meeting minutes</i>) 	
<ul style="list-style-type: none"> CDER Medical Policy Council Brief – Evaluating a Breakthrough Therapy Designation for Rescission Template(s) (<i>include only the completed template(s) and not the meeting minutes</i>) <p>(<i>completed CDER MPC templates can be found in DARRTS as clinical reviews or on the MPC SharePoint Site</i>)</p>	
❖ 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>)	
❖ Internal documents: memoranda, telecons, emails, and other documents considered important to include in the action package by the reviewing office/division (e.g., Regulatory Briefing minutes, Medical Policy Council meeting minutes)	
❖ Minutes of Meetings	
<ul style="list-style-type: none"> If not the first review cycle, any end-of-review meeting (<i>indicate date of mtg</i>) 	<input checked="" type="checkbox"/> N/A or no mtg
<ul style="list-style-type: none"> Pre-NDA/BLA meeting 	October 8, 2014
<ul style="list-style-type: none"> EOP2 meeting 	July 24, 2008
<ul style="list-style-type: none"> Mid-cycle Communication 	August 24, 2015
<ul style="list-style-type: none"> Late-cycle Meeting 	February 24, 2016
<ul style="list-style-type: none"> Other milestone meetings (e.g., EOP2a, CMC focused milestone meetings) (<i>indicate dates of mtgs</i>) 	
❖ Advisory Committee Meeting(s)	<input checked="" type="checkbox"/> No AC meeting
<ul style="list-style-type: none"> Date(s) of Meeting(s) 	
Decisional and Summary Memos	
❖ Office Director Decisional Memo (<i>indicate date for each review</i>)	<input type="checkbox"/> None
Division Director Summary Review (<i>indicate date for each review</i>)	<input type="checkbox"/> None
Cross-Discipline Team Leader Review (<i>indicate date for each review</i>)	<input type="checkbox"/> None
PMR/PMC Development Templates (<i>indicate total number</i>)	9
Clinical	
❖ Clinical Reviews	
<ul style="list-style-type: none"> Clinical Team Leader Review(s) (<i>indicate date for each review</i>) 	<input checked="" type="checkbox"/> No separate review
<ul style="list-style-type: none"> Clinical review(s) (<i>indicate date for each review</i>) 	Clinical Efficacy 5/4/16 Clinical Safety 3/24/16

<ul style="list-style-type: none"> • Social scientist review(s) (if OTC drug) (indicate date for each review) 	<input checked="" type="checkbox"/> None
<ul style="list-style-type: none"> ❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here <input type="checkbox"/> and include a review/memo explaining why not (indicate date of review/memo) 	Located in Clinical Efficacy Review
<ul style="list-style-type: none"> ❖ Clinical reviews from immunology and other clinical areas/divisions/Centers (indicate date of each review)⁵ 	<u>CDRH</u> Device Review 7/29/15 Compliance Memo 3/31/16 <u>OSE</u> Hepatology Consult Review (Dr. Senior) 1/18/16 Hepatology Consult Review (Dr. Avigan) 11/9/15 Division of Epidemiology Consult Review 3/11/16 <u>OBP/Immunogenicity</u> 3/4/16 <u>DMPH</u> 4/22/16
<ul style="list-style-type: none"> ❖ Controlled Substance Staff review(s) and Scheduling Recommendation (indicate date of each review) 	<input type="checkbox"/> N/A
<ul style="list-style-type: none"> ❖ Risk Management <ul style="list-style-type: none"> • REMS Documents and REMS Supporting Document (indicate date(s) of submission(s)) • REMS Memo(s) and letter(s) (indicate date(s)) • Risk management review(s) and recommendations (including those by OSE and CSS) (indicate date of each review and indicate location/date if incorporated into another review) 	
<ul style="list-style-type: none"> ❖ OSI Clinical Inspection Review Summary(ies) (include copies of OSI letters to investigators) 	12/8/15
Clinical Microbiology <input checked="" type="checkbox"/> None	
<ul style="list-style-type: none"> ❖ Clinical Microbiology Team Leader Review(s) (indicate date for each review) 	<input type="checkbox"/> No separate review
<ul style="list-style-type: none"> <ul style="list-style-type: none"> Clinical Microbiology Review(s) (indicate date for each review) 	<input type="checkbox"/> None
Biostatistics <input type="checkbox"/> None	
<ul style="list-style-type: none"> ❖ Statistical Division Director Review(s) (indicate date for each review) 	<input checked="" type="checkbox"/> No separate review
<ul style="list-style-type: none"> <ul style="list-style-type: none"> Statistical Team Leader Review(s) (indicate date for each review) 	<input checked="" type="checkbox"/> No separate review
<ul style="list-style-type: none"> <ul style="list-style-type: none"> Statistical Review(s) (indicate date for each review) 	3/18/16
Clinical Pharmacology <input type="checkbox"/> None	
<ul style="list-style-type: none"> ❖ Clinical Pharmacology Division Director Review(s) (indicate date for each review) 	<input checked="" type="checkbox"/> No separate review
<ul style="list-style-type: none"> <ul style="list-style-type: none"> Clinical Pharmacology Team Leader Review(s) (indicate date for each review) 	<input checked="" type="checkbox"/> No separate review
<ul style="list-style-type: none"> <ul style="list-style-type: none"> Clinical Pharmacology review(s) (indicate date for each review) 	5/2/16
<ul style="list-style-type: none"> ❖ OSI Clinical Pharmacology Inspection Review Summary (include copies of OSI letters) 	<input checked="" type="checkbox"/> None requested

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

Nonclinical <input type="checkbox"/> None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) (<i>indicate date for each review</i>)	
• Supervisory Review(s) (<i>indicate date for each review</i>)	
• Pharm/tox review(s), including referenced IND reviews (<i>indicate date for each review</i>)	2/24/16
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
❖ Statistical review(s) of carcinogenicity studies (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> No carc
❖ ECAC/CAC report/memo of meeting	<input checked="" type="checkbox"/> None Included in P/T review, page
❖ OSI Nonclinical Inspection Review Summary (<i>include copies of OSI letters</i>)	<input checked="" type="checkbox"/> None requested
Product Quality <input type="checkbox"/> None	
❖ Product Quality Discipline Reviews ⁶	
• Tertiary review (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
• Secondary review (e.g., Branch Chief) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
• Integrated Quality Assessment (contains the Executive Summary and the primary reviews from each product quality review discipline) (<i>indicate date for each review</i>)	4/28/16
❖ Reviews by other disciplines/divisions/Centers requested by product quality review team (<i>indicate date of each review</i>)	<input checked="" type="checkbox"/> None
❖ Environmental Assessment (check one) (original and supplemental applications)	
<input checked="" type="checkbox"/> Categorical Exclusion (<i>indicate review date</i>)(<i>all original applications and all efficacy supplements that could increase the patient population</i>)	4/28/16
<input type="checkbox"/> Review & FONSI (<i>indicate date of review</i>)	
<input type="checkbox"/> Review & Environmental Impact Statement (<i>indicate date of each review</i>)	
❖ Facilities Review/Inspection	
<input checked="" type="checkbox"/> Facilities inspections (<i>action must be taken prior to the re-evaluation date</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>)	<input checked="" type="checkbox"/> Acceptable Re-evaluation date: <input type="checkbox"/> Withhold recommendation <input type="checkbox"/> Not applicable

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

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

Kelley, Laurie

From: Kelley, Laurie
Sent: Tuesday, May 17, 2016 4:38 PM
To: Tammy Phinney
Cc: Kelley, Laurie
Subject: FW: Preferred Terms for Immune-Mediated Events for Daclizumab

Follow Up Flag: Follow up
Flag Status: Flagged

Tammy

In reference to the list of terms I sent this morning for immune-mediated events, please see the update below.

In reference to the list of preferred terms that we sent this morning for immune-mediated events, we note that in our search we used the STDM datasets. In addition, the MedDRA query used preferred terms from MedDRA 16.1, although the AEs in Study 201 were coded using MedDRA 14.1.

Thank you,

Laurie

Kelley, Laurie

From: Kelley, Laurie
Sent: Tuesday, May 17, 2016 8:54 AM
To: Tammy Phinney
Cc: Kelley, Laurie
Subject: Preferred Temrs for Immune-Mediated Events for Daclizumab



Potential immune
mediated AE C...

Hi Tammy

This is the list of terms we used for the immune-mediated events.

Thanks,

Laurie

Kelley, Laurie

From: Kelley, Laurie
Sent: Monday, May 16, 2016 3:23 PM
To: 'Tammy Phinney'
Cc: Kelley, Laurie
Subject: REMS Discussion BLA 761029

Tammy

DRISK would like to propose a tcon on Weds if you are amenable to it. I have a tentative time of 2:30 PM EST. Would that be acceptable to you.

Best regards,
Laurie

Laurie Kelley, PA-C
Regulatory Project Manager
Food and Drug Administration
Office of Drug Evaluation – Division of Neurology Products
Bldg. 22, Room 4200
10903 New Hampshire Ave.
Silver Spring, Maryland 20993-0002

Kelley, Laurie

From: Kelley, Laurie
Sent: Monday, May 16, 2016 1:58 PM
To: 'Tammy Phinney'
Cc: Kelley, Laurie
Subject: BLA 761029
Attachments: FDA proposed BW WP 16May2016.doc

Tammy

Please find attached the label with our edits and comments for our meeting today at 4PM.

Please confirm receipt.

Regards,
Laurie

Laurie Kelley, PA-C
Regulatory Project Manager
Food and Drug Administration
Office of Drug Evaluation – Division of Neurology Products
Bldg. 22, Room 4200
10903 New Hampshire Ave.
Silver Spring, Maryland 20993-0002

Kelley, Laurie

From: Kelley, Laurie
Sent: Monday, May 16, 2016 12:19 PM
To: 'Tammy Phinney'
Cc: Kelley, Laurie
Subject: PMR/PMC BLA 761029

Tammy

Regarding PMC # 9, our CMC reviewers would like to propose a change to the language (see edits in red below):

Conduct microbial spiking studies of the (b) (4) product intermediates in a small-scale-study to demonstrate that the product intermediates do not support significant microbial growth under the proposed hold conditions.

Does Biogen agree to this change?

Best regards,
LAurie

Laurie Kelley, PA-C
Regulatory Project Manager
Food and Drug Administration
Office of Drug Evaluation – Division of Neurology Products
Bldg. 22, Room 4200
10903 New Hampshire Ave.
Silver Spring, Maryland 20993-0002

Kelley, Laurie

From: Kelley, Laurie
Sent: Thursday, May 12, 2016 7:11 PM
To: 'Tammy Phinney'
Cc: Kelley, Laurie
Subject: FW: DAC enrollment form attestations
Attachments: ZINBRYTA REMS Program Patient Enrollment Form Attestations TRACKED.doc;
ZINBRYTA REMS Program Pharmacy Enrollment Form Attestations TRACKED.doc;
ZINBRYTA REMS Program Prescriber Enrollment Form Attestations TRACKED.doc

Hi Tammy

We've prepared and attached tracked changes attestation documents for clarity. Again, these are under review and may require additional revision.

Thanks
Laurie

From: Tammy Phinney [mailto:tammy.phinney@biogen.com]
Sent: Thursday, May 12, 2016 3:09 PM
To: Kelley, Laurie
Subject: RE: DAC enrollment form attestations

Dear Laurie,
I'm told by my team that they see 1 very slight difference in the pharmacy form but the other 2 are exactly the same. Is this correct?

Tammy

From: Kelley, Laurie [mailto:Laurie.Kelley@fda.hhs.gov]
Sent: Wednesday, May 11, 2016 9:40 AM
To: Tammy Phinney
Cc: Kelley, Laurie
Subject: DAC enrollment form attestations

Tammy

The attached enrollment form attestations have undergone a few revisions compared with what was sent to you last week. The REMS document and the enrollment form attestations are being reviewed by at this time and may require further revision. Also, could you let me know when you expect to have the various training materials available for our review?

Thanks!
Laurie

Laurie Kelley, PA-C
Regulatory Project Manager
Food and Drug Administration
Office of Drug Evaluation – Division of Neurology Products
Bldg. 22, Room 4200
10903 New Hampshire Ave.
Silver Spring, Maryland 20993-0002

Kelley, Laurie

From: Kelley, Laurie
Sent: Wednesday, May 11, 2016 9:40 AM
To: 'Tammy Phinney'
Cc: Kelley, Laurie
Subject: DAC enrollment form attestations
Attachments: ZINBRYTA REMS Program Patient Enrollment Form Attestations.doc; ZINBRYTA REMS Program Pharmacy Enrollment Form Attestations.doc; ZINBRYTA REMS Program Prescriber Enrollment Form Attestations.doc

Tammy

The attached enrollment form attestations have undergone a few revisions compared with what was sent to you last week. The REMS document and the enrollment form attestations are being reviewed by at this time and may require further revision. Also, could you let me know when you expect to have the various training materials available for our review?

Thanks!

Laurie

Laurie Kelley, PA-C
Regulatory Project Manager
Food and Drug Administration
Office of Drug Evaluation – Division of Neurology Products
Bldg. 22, Room 4200
10903 New Hampshire Ave.
Silver Spring, Maryland 20993-0002

Kelley, Laurie

From: Kelley, Laurie
Sent: Monday, May 09, 2016 3:30 PM
To: 'Tammy Phinney'
Cc: Kelley, Laurie
Subject: daclizumab nonclinical IR

Tammy

There is an apparent discrepancy in reporting of the incidence of microglial aggregates. In the Toxicology Written Summary, it is stated that there was 1 LD animal affected in the 39-week study, as well as 1 LD animal in the 9-month study. However, we are unable to find a listing for the affected LD animal in the 39-week study report. We ask that you clarify whether or not there was an affected animal in the 39-week study.

Please provide a response as soon as possible. Please confirm receipt.

Best regards,
Laurie

Laurie Kelley, PA-C
Regulatory Project Manager
Food and Drug Administration
Office of Drug Evaluation – Division of Neurology Products
Bldg. 22, Room 4200
10903 New Hampshire Ave.
Silver Spring, Maryland 20993-0002

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

/s/

LAURIE A KELLEY
05/12/2016

Kelley, Laurie

From: Kelley, Laurie
Sent: Tuesday, May 10, 2016 10:04 AM
To: 'Tammy Phinney'
Cc: Kelley, Laurie
Subject: RE: container carton Daclizumab BLA 761029

Tammy

Since the dosing issue is also part of the PI the dosing recommendation will need to be part of the labeling negotiation.

Laurie

From: Tammy Phinney [mailto:tammy.phinney@biogen.com]
Sent: Monday, May 09, 2016 4:37 PM
To: Kelley, Laurie
Subject: RE: container carton Daclizumab BLA 761029

Hi Laurie,
Biogen will remove (b) (4) from the (b) (4) on the carton labeling, per the noted attached request. However, we would like to note that we have requested information from Anita Brown about whether FDA intends to apply a (b) (4) to daclizumab according to the August 2015 guidance on naming biologics. We note that we may want to revisit the established name for Zinbryta in the post-approval environment.

Additionally, we propose retaining the monthly language on the carton labeling (b) (4). We believe monthly is supported by the dosing used in the clinical protocols which allowed a tolerance of +/- 4 days around the 4 week visit schedule. Furthermore, we believe that using the term "monthly" with respect to dosing will be clearer to patients since the monitoring is described as monthly. Please confirm if this is acceptable and if so, we will resubmit the carton labeling to the BLA accordingly.

Thank you,
Tammy

Tammy Phinney Vice President, Regulatory Affairs | Advertising, Labeling & Promotion
Biogen | 133 Boston Post Road, Weston MA 02493 | Email: tammy.phinney@biogen.com
Office: (781) 464 5687 | Cell: (b) (6)



From: Kelley, Laurie [<mailto:Laurie.Kelley@fda.hhs.gov>]
Sent: Tuesday, May 03, 2016 8:11 AM
To: Tammy Phinney
Cc: Kelley, Laurie
Subject: container carton Daclizumab BLA 761029

Tammy

Please send the following container label and carton labeling comments for BLA 761029 Zinbryta (daclizumab).

Please provide a response by 5/6.

Thanks,

Laurie

Kelley, Laurie

From: Kelley, Laurie
Sent: Tuesday, May 10, 2016 8:06 AM
To: 'Tammy Phinney'
Cc: Kelley, Laurie
Subject: Up dated Zinbryta PI
Attachments: 9May16-FDAedits2clean-BLA 761029 daclizumab.doc

Tammy

The attached version of the PI has 2 small changes that had been missed in our editing session (Table 4:the p value for Proportion Relapse Free has been removed, as well as the sentence above table 4 which has been changed to "the nominal p-value"). Please disregard the previous version. Apologies for the inconvenience.

Laurie

Kelley, Laurie

From: Kelley, Laurie
Sent: Monday, May 09, 2016 8:23 PM
To: Tammy Phinney
Cc: Kelley, Laurie
Subject: Fw: nDA 761029 daclizumab
Attachments: 9May16-FDAedits-clean-BLA 761029 daclizumab.doc

Tammy

The attached is the clean proposed label for BLA 761029.

Please confirm receipt.

Regards
Laurie

Kelley, Laurie

From: Kelley, Laurie
Sent: Monday, May 09, 2016 12:55 PM
To: 'Tammy Phinney'
Subject: RE: Daclizumab REMS Comments and Forms

Hi Tammy

The comments were based on a thorough review.

L

From: Tammy Phinney [mailto:tammy.phinney@biogen.com]
Sent: Thursday, May 05, 2016 1:36 PM
To: Kelley, Laurie
Subject: RE: Daclizumab REMS Comments and Forms

Hi Laurie,
The team will meet to discuss and I will get back to you ASAP as to when to expect the submission. A vendor does our forms so we will have to seek their input as well.

Regarding the Supporting Document – were these initial comments or was a thorough review made?

Thank you,
Tammy

From: Kelley, Laurie [mailto:Laurie.Kelley@fda.hhs.gov]
Sent: Thursday, May 05, 2016 1:16 PM
To: Tammy Phinney
Cc: Kelley, Laurie
Subject: Daclizumab REMS Comments and Forms

Tammy

The comments below are with regards to the REMS forms that were emailed to me on April 29, 2016, and April 30, 2016. Please note that there are additional comments and questions within the attached documents that we would like addressed. The updated REMS goals should be ready to provide to you in the next few days.

Can you tell me when you may anticipate being able to respond to these comments and/or submit a complete REMS (Document, all appended materials, website, and supporting document)?

Thank you!
Laurie

ZINBRYTA REMS Program Prescriber Enrollment Form

- Decrease the font size of the title of the form and consolidate to one line. Decrease the height of the red box header. Consider removing the additional red, green, and blue lines below the header to allow for more room for content. Increase the font size of all content below the title in document. As it stands now, the font size is too small for readability.

We do not require [REDACTED] (b) (4) The process may be described in the REMS supporting document, but please remove from form.

- Provide rationale on the need to collect additional Office Contact Information.
- Account for the redline deletions and the comments found in sticky notes, highlighting, and strikethrough text.

ZINBRYTA REMS Program Pharmacy Enrollment Form

- Decrease the font size of the title of the form and consolidate to one line. Decrease the height of the red box header. Increase the font size of all content below the title in document. As it stands now, the font size is too small for readability.
- Consider removing the additional red, green, and blue lines below the header to allow for more room for content. It is acceptable to move content to the back page of the form in order for font size to be larger.
- Account for the redline deletions and the comments found in sticky notes, highlighting, and strikethrough text.

ZINBRYTA REMS Patient Enrollment Form

- Decrease the font size of title of form and move to one line. Decrease the height of the red box header. Increase font size of all content below the title in document. As it stands now, the font size is too small for readability. Consider removing the additional red, green, and blue lines below the header to allow for more room for content. It is acceptable to move content to the back page of the form to accommodate for larger font size.
- Account for the redline deletions and the comments found in sticky notes, highlighting, and strikethrough text.

ZINBRYTA REMS Patient Status Form

- Decrease the font size of title of form and move to one line. Decrease the height of the red box header. Consider removing the additional red, green, and blue lines below the header to allow for more room for content. Increase font size of all content below the title in document. As it stands now, the font size is too small for readability. It is acceptable to move content to the back page of the form to accommodate for larger font size.
- Remove [REDACTED] (b) (4) from title.
- Account for the redline deletions and the comments found in sticky notes, highlighting, and strikethrough text.
- Include additional conditions in the Patient Status section, as listed below. To make use of space, we suggest using two columns.

(b) (4)



ZINBRYTA REMS Website (pre-submission comments)

Ensure the REMS website is independent of the link to the promotional and/or commercial website and non-REMS materials about the product. Do not include a link from the REMS website back to the www.ZINBRYTA.com website. The REMS website should also be accessible directly through a search engine.

All REMS materials on the REMS website; i.e., *REMS Forms, Guides* should be downloadable from the REMS website and made available on the website for the duration of the REMS.

We recommend that you include a prominent link on the product website's homepage (www.ZINBRYTA.com) for REMS materials. This link should direct users to the ZINBRYTAREMS website on which the REMS Program is described. The site should include only FDA-approved REMS materials.

We ask you to use bullets, moderate white space, short line lengths, and few lines of text when possible when developing your website.

Submit all screen shots, and actual layout and content for the ZINBRYTA REMS website.

By way of example, the Agency recommends you review a recently approved REMS website such as the LEMTRADA REMS website in public domain.

Kelley, Laurie

From: Kelley, Laurie
Sent: Thursday, May 05, 2016 1:16 PM
To: Tammy Phinney
Cc: Kelley, Laurie
Subject: Daclizumab REMS Comments and Forms
Attachments: FDA-Comments-Zinbryta-Supporting-Doc.docx; ZINBRYTA REMS Program Patient Status Form.pdf; ZINBRYTA REMS Program Pharmacy Enrollment Form.pdf; ZINBRYTA REMS Program Prescriber Enrollment Form.pdf

Tammy

The comments below are with regards to the REMS forms that were emailed to me on April 29, 2016, and April 30, 2016. Please note that there are additional comments and questions within the attached documents that we would like addressed. The updated REMS goals should be ready to provide to you in the next few days.

Can you tell me when you may anticipate being able to respond to these comments and/or submit a complete REMS (Document, all appended materials, website, and supporting document)?

Thank you!
Laurie

ZINBRYTA REMS Program Prescriber Enrollment Form

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- Provide rationale on the need to collect additional Office Contact Information.
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ZINBRYTA REMS Program Pharmacy Enrollment Form

- Decrease the font size of the title of the form and consolidate to one line. Decrease the height of the red box header. Increase the font size of all content below the title in document. As it stands now, the font size is too small for readability.
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- Account for the redline deletions and the comments found in sticky notes, highlighting, and strikethrough text.

ZINBRYTA REMS Patient Enrollment Form

- Decrease the font size of title of form and move to one line. Decrease the height of the red box header. Increase font size of all content below the title in document. As it stands now, the font size is too small for readability. Consider removing the additional red, green, and blue lines below the header to allow for more room for content. It is acceptable to move content to the back page of the form to accommodate for larger font size.
- Account for the redline deletions and the comments found in sticky notes, highlighting, and strikethrough text.

ZINBRYTA REMS Patient Status Form

- Decrease the font size of title of form and move to one line. Decrease the height of the red box header. Consider removing the additional red, green, and blue lines below the header to allow for more room for content. Increase font size of all content below the title in document. As it stands now, the font size is too small for readability. It is acceptable to move content to the back page of the form to accommodate for larger font size.
- Remove (b) (4) from title.
- Account for the redline deletions and the comments found in sticky notes, highlighting, and strikethrough text.
- Include additional conditions in the Patient Status section, as listed below. To make use of space, we suggest using two columns.



ZINBRYTA REMS Website (pre-submission comments)

Ensure the REMS website is independent of the link to the promotional and/or commercial website and non-REMS materials about the product. Do not include a link from the REMS website back to the www.ZINBRYTA.com website. The REMS website should also be accessible directly through a search engine.

All REMS materials on the REMS website; i.e., *REMS Forms, Guides* should be downloadable from the REMS website and made available on the website for the duration of the REMS.

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We ask you to use bullets, moderate white space, short line lengths, and few lines of text when possible when developing your website.

Submit all screen shots, and actual layout and content for the ZINBRYTA REMS website.

By way of example, the Agency recommends you review a recently approved REMS website such as the LEMTRADA REMS website in public domain.

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/s/

LAURIE A KELLEY
05/05/2016

**PeRC Meeting Minutes
March 9, 2016**

PeRC Members Attending:

Lynne Yao

Hari Cheryl Sachs

Linda Lewis

Thomas Smith

Meshaun Payne

Michelle Roth-Kline

Wiley Chambers

George Greeley

Peter Starke (Did not review **Non-Responsive**)

Dionna Green

Barbara Buch

Adrienne Hornatko-Munoz

Andrew Mulberg (Did not review **Non-Responsive**)

Lisa Faulcon (**Non-Responsive** reviews only)

Raquel Tapia

John Alexander

Shrikant Pagay

Freda Cooner

Belinda Hayes

Agenda

9:00	Non-Responsive				
9:15					
9:30					
9:45					
10:05					
10:20					
10:30					
10:40					
11:00					
11:10					
11:20					
11:35	Non-Responsive				

6 Pages have been Withheld in Full as Non Responsive immediately following this page

Non-Responsive

Zinbryta (daclizumab) Partial Waiver/Deferral/Plan (with Agreed iPSP)

- Proposed Indication: Relapsing Multiple Sclerosis
- The division noted that the pediatric plan presented for the NDA is consistent with the plan in the Agreed iPSP for the proposed indication.
- This product triggered PREA as a new indication.
- The division noted that additional significant safety concerns have been identified in adults, which included hepatotoxicity, autoimmune diseases, permanent skin reactions, as well as a death in a patient with a serious skin reaction. As a result, the division no longer agrees that this drug should be studied in pediatric patients with MS for safety reasons and plans to allow full waivers for pediatric MS. The division also clarified that this product would only be indicated in adult patients that have failed to see a response in other two products for multiple sclerosis and that this pediatric population would also be impossible or highly impracticable to study.
- PeRC recommends contacting the EMA to amend the PIP because of the safety concerns. The division is planning to discuss this product in April with the EMA.
- *PeRC Recommendations:*
 - The PeRC agreed with the division to grant a full waiver in pediatric patients because of safety concerns and that label will indicate that this product is not recommended for use in the pediatric population

Non-Responsive

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/s/

GEORGE E GREELEY
04/13/2016

Kelley, Laurie

From: Kelley, Laurie
Sent: Tuesday, April 12, 2016 10:10 AM
To: Tammy Sarnelli (tammy.sarnelli@biogen.com)
Cc: Kelley, Laurie
Subject: Tentative PMRs for Daclizumab

Tammy

The attached are the tentative PMRs/PMCs for BLA 761029. Please note that these are tentative. Please provide milestone dates by April 29th.

Best Regards,
Laurie



BLA 761029
tentative: PMRs, P...

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/s/

LAURIE A KELLEY
04/12/2016

Kelley, Laurie

From: Kelley, Laurie
Sent: Wednesday, April 06, 2016 3:45 PM
To: Tammy Sarnelli (tammy.sarnelli@biogen.com)
Cc: Kelley, Laurie
Subject: FW: BLA 761029 Daclizumab Information Request

Tammy

Our Clinical Team Leader has a request for information regarding BLA 761029:

Please explain how the number of patients who received prior MS therapy excluding steroids in Table 150 (Trial 301 CSR page 878 of 3937) can be reconciled with the numbers reported in Table 24 (page 151). Likewise, please reconcile number of patients for Table 18, page 101, and Table 87, page 349 of 1641 in the CSR for Trial 201. We are looking at treatment response for patients who had prior treatment with MS drugs excluding steroids prior to randomization.

Please provide a response by April 7, 2016. Please also confirm receipt.

Best Regards,
Laurie

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/s/

LAURIE A KELLEY
04/06/2016

Kelley, Laurie

From: Kelley, Laurie
Sent: Wednesday, March 30, 2016 7:24 AM
To: Tammy Phinney
Cc: Kelley, Laurie
Subject: FW: Skeleton Daclizumab REMS Document
Attachments: DACSkeletonREMSDocumentTOBIOGEN.doc

Importance: High

Tammy

Please see attached a “skeleton” REMS document. This document is a draft, and subject to change as it continues internal clearance within the Agency. Also, we are willing to receive the individual components of the REMS via email to review as you have them completed. Once all of the pieces of the REMS developed, you can then submit an entire REMS to the gateway.

Best regards,
Laurie

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/s/

LAURIE A KELLEY
03/30/2016

Kelley, Laurie

From: Kelley, Laurie
Sent: Wednesday, March 30, 2016 2:28 PM
To: Tammy Phinney
Cc: Kelley, Laurie
Subject: RE: Skeleton Daclizumab REMS Document

Tammy

While I can make no promises, my hope is to have, if not the entire label, at least portions of it, to you by next week.

Best regards,
Laurie

From: Tammy Phinney [<mailto:tammy.phinney@biogen.com>]
Sent: Wednesday, March 30, 2016 9:36 AM
To: Kelley, Laurie
Subject: RE: Skeleton Daclizumab REMS Document

Thank you Laurie. We are quite anxious to get the draft label. Can you provide any update as to when we might expect to receive the redline label from the Agency?

Thank you.
Tammy

Tammy Phinney Vice President, Regulatory Affairs | Advertising, Labeling & Promotion

Biogen | 133 Boston Post Road, Weston MA 02493 | Email: tammy.phinney@biogen.com

Office: (781) 464 5687 | Cell: (b) (6)



From: Kelley, Laurie [<mailto:Laurie.Kelley@fda.hhs.gov>]
Sent: Wednesday, March 30, 2016 7:24 AM
To: Tammy Phinney
Cc: Kelley, Laurie
Subject: FW: Skeleton Daclizumab REMS Document
Importance: High

Tammy

Please see attached a "skeleton" REMS document. This document is a draft, and subject to change as it continues internal clearance within the Agency. Also, we are willing to receive the individual

components of the REMS via email to review as you have them completed. Once all of the pieces of the REMS developed, you can then submit an entire REMS to the gateway.

Best regards,
Laurie

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/s/

LAURIE A KELLEY
03/30/2016

Kelley, Laurie

From: Kelley, Laurie
Sent: Thursday, March 24, 2016 10:59 AM
To: Tammy Phinney
Cc: Kelley, Laurie
Subject: FW: DAC Follow up teleconference

Tammy

In response to your queries, DRISK hopes to have a REMS document by early next week, which I will then forward to you. With regards to the question about autoimmune disorders:

1. How is the FDA defining autoimmune disorders?

FDA response: We are including as autoimmune disorders those that are recognized in the published literature to be autoimmune disorders.

Please let me know if there are any further questions. Best Regards,
Laurie

From: Tammy Phinney [<mailto:tammy.phinney@biogen.com>]
Sent: Thursday, March 24, 2016 7:47 AM
To: Kelley, Laurie
Subject: RE: Follow up teleconference

Good morning Laurie

I have followed up with the team and we do not have specific questions to discuss with the Agency at this point in time except for:

1. How is the FDA defining autoimmune disorders?
 2. Do you have an update on when you will be sending us the draft REMS and redline label

Thank you Laurie.
Tammy

Tammy Phinney Vice President, Regulatory Affairs | Advertising, Labeling & Promotion
Biogen | 133 Boston Post Road, Weston MA 02493 | Email: tammy.phinney@biogen.com
Office: (781) 464 5687 | Cell: (b) (6)



From: Kelley, Laurie [<mailto:Laurie.Kelley@fda.hhs.gov>]
Sent: Monday, March 21, 2016 12:55 PM

To: Tammy Phinney
Cc: Kelley, Laurie
Subject: RE: Follow up teleconference

Tammy

DRISK has said that if Biogen has particular questions we can have a tcon. Are there any questions or need for clarification? I do not believe they will have a document to send to you until late this week.

Thanks
Laurie

From: Tammy Phinney [<mailto:tammy.phinney@biogen.com>]

Sent: Monday, March 21, 2016 11:59 AM

To: Kelley, Laurie

Subject: Follow up teleconference

Hi Laurie,

I am just checking in to see if the Agency is still planning a short teleconference with us this week regarding the Zinbryta REMS and to see if we have any questions. If yes, I'm wondering if Thursday could be a possibility.

Thank you,
Tammy

Tammy Phinney Vice President, Regulatory Affairs | Advertising, Labeling & Promotion

Biogen | 133 Boston Post Road, Weston MA 02493 | Email: tammy.phinney@biogen.com

Office: (781) 464 5687 | Cell: (b) (6)



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/s/

LAURIE A KELLEY
03/24/2016

Kelley, Laurie

From: Kelley, Laurie
Sent: Wednesday, March 16, 2016 7:05 PM
To: Tammy Phinney
Cc: Kelley, Laurie
Subject: BLA 761029 Daclizumab REMS Mtg
Attachments: Daclizumab REMS Mtg March 16 Final.pptx

Tammy

The attached are the slides as discussed in our teleconference of earlier today. In addition, a list of FDA attendees is below. Please let me know if you have any questions.

Best Regards,
Laurie

Office of New Drugs (OND), Office of Drug Evaluation I (ODEI), Division of Neurology Products DNP

Billy Dunn, M.D., Director
Alice Hughes, M.D., Deputy Director for Safety
John Marler, M.D., Clinical Team Leader
Lawrence Rodichok, M.D., Clinical Reviewer
Sally Yasuda, PharmD. Safety Team Leader
Lourdes Villaba, M.D., Safety Reviewer
Christine Phipps, PharmD., Safety Regulatory Project Manager
Laurie Kelley, PA-C, Regulatory Project Manager

Office of Surveillance and Epidemiology (OSE), Office of Medication Error Prevention and Risk Management (OMEPRM), Division of Risk Management (DRISK)

Kellie Taylor, PharmD., MPH, Office Deputy Director, OSE/OMEPRM
Cynthia LaCivita, PharmD., MPH, Division Director, OSE/DRISK
Jamie Wilkins-Parker, PharmD, Risk Management Analyst, Team Lead, OSE/DRISK
Robert Pratt, PharmD, DRISK Risk Management Analyst,, OSE/DRISK
Doris Auth, PharmD, Safety Evaluator Team Lead, OSE/DRISK
Corwin Howard, PharmD, RPh, Safety Regulatory Project Manager, OSE

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/s/

LAURIE A KELLEY
03/16/2016

Kelley, Laurie

From: Kelley, Laurie
Sent: Monday, March 07, 2016 9:52 AM
To: Tammy Sarnelli (tammy.sarnelli@biogen.com)
Cc: Kelley, Laurie
Subject: Daclizumab 761029

Tammy

The daclizumab Risk Management team has a request for information. Could you please provide us with the Risk Management Program being used for daclizumab in Europe?

Regards,
Laurie

Laurie Kelley, PA-C
Regulatory Project Manager
Food and Drug Administration
Office of Drug Evaluation – Division of Neurology Products
Bldg. 22, Room 4200
10903 New Hampshire Ave.
Silver Spring, Maryland 20993-0002

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/s/

LAURIE A KELLEY
03/07/2016

Kelley, Laurie

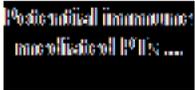
From: Kelley, Laurie
Sent: Thursday, February 18, 2016 9:17 AM
To: Tammy Sarnelli (tammy.sarnelli@biogen.com)
Cc: Kelley, Laurie
Subject: Daclizumab Safety Information Request

Categories: With Sponsor

Tammy

Our Safety reviewer has the following request for information. Please provide a response by March 8, 2016.

Best regards,
Laurie



1. The proposed labeling (under Section 6. ADVERSE REACTIONS. 6.1, Clinical Trial Experience) states: (b) (4)
Please clarify which patients the label is referring to and whether data from the ongoing studies 203 and 302 was included.
2. Please include analyses of alternative medications for MS in study 301 and the Total DAC HYP database. Please confirm that alternative medications for DAC HYP treated patients were used only after DAC HYP was discontinued and provide analysis of the time elapsed between the last dose of DAC HYP and the start of an alternative medication for MS.
3. Your Table 32 of the SUR includes tacrolimus and immunoglobulins. Please clarify what were tacrolimus and immunoglobulins used for, and whether tacrolimus was topical or systemic.
4. Please submit AE datasets for patients who had potential immune related disorders (see preferred terms in the attached excel file, plus any skin and angioedema type reaction that you consider may be immune related), for the controlled trials and the Total DAC HYP database. Include the same variables you already have in the ADEM AE datasets plus
 - a) the number of DAC HYP doses received prior to the event
 - b) number of DAC HYP doses received after the event
 - c) variables for the MedDRA alternative path for HLTG and SOC (e.g. for psoriasis the primary SOC is Skin and SC tissues, the secondary is Immune System disorders)
 - d) variables for the MedDRA SMQ(s)

e) treatment received for the immune mediated event, specify whether systemic corticosteroids or immunosuppressive medications were needed (include name of drug, e.g. prednisone, methylprednisolone, azathioprine). Include variables for route, dose and duration of corticosteroid or immunosuppressor treatment.

f) outcome of immune mediated event (resolved, ongoing, resolved with sequelae, death or unknown) as of December 2015. If a patient is still receiving corticosteroids or immunosuppressants the event should be considered ongoing. Be clear as to what the date and relative day for the last dose of DAC HYP (relative the first day on DAC HYP).

g) Invasive procedures that the patients underwent because of workup or treatment of potential immune mediated disorders. This include but is not limited to duodenoscopy, sigmoidoscopy, colonoscopy, bronchoscopy, mediastinoscopy, any major organ biopsy (e.g. lung, liver, renal, bone marrow), skin and lymph node biopsy (specify if it was fine needle aspiration or lymphadenectomy; specify if lymphadenopathy was mediastinal/abdominal or peripheral), endotracheal intubation, tracheostomy, transfusions and plasmapheresis.

h) Prior history of drug allergy (if so, to which drug).

i) Pre-existent condition at baseline for a similar event (e.g. for patients with events in the Dermatitis and eczema HLT and Psoriatic conditions HLT, whether the patient had a prior history of eczema or psoriasis; for patients with thyroid related events whether the patient already had hypo or hyperthyroidism; for patients with events in the Colitis (excl infective) HLT specify whether the patients had Ulcerative Colitis or Crohn's disease).

5. Please provide clarification/follow up for the following patients

- a) 202/509-014 diagnosed as central pontine myelinolysis. How was the diagnosis made? Patient had no sodium measurements. Provide outcome of the patient.
- b) 303/611-015 with non-fatal aspiration pneumonia. Is the patient still in the study?
- c) 202/758-023 was treated with neostigmine. Clarify what was neostigmine used for.
- d) 303/600-010 with Myasthenia Gravis had a thymectomy. Please provide pathology report of thymic tissue.
- e) 301/133-004 had temporal artery biopsy. Clarify the reason and whether the patient was treated with corticosteroids
- f) 301/453-041 had ALT 18x ULN and BR elevation <2xULN, treated with prednisone for elevated liver enzymes. Clarify how long he received systemic corticosteroids and outcome of the event.
- g) 203/501-013 and 303/622-016 (this one with a prior history of Crohn's disease) were diagnosed with Clostridium Difficile infection after antibiotic treatment but both had negative stool culture for C Difficile Toxins A and B. Treatment included prednisone and mesalazine. As of last follow up enteritis in 203/501-013 was ongoing; information on whether 303/622-016 was still in the trial or not was not available. Please clarify why you think these are active infections vs. DAC HYP related immune mediated colitis and provide outcome for these patients.
- h) 303/747-005 had granulomatous inflammation of the lungs, diagnosed as tuberculosis. She also had severe anemia, leukocytosis, hypoalbuminemia, and hyponatremia. Differential diagnosis included aspergillus infection. She was treated empirically with antibiotic, antiviral, antifungal and anti-tuberculosis medications, blood transfusion and bromocriptine among other treatments. As of last follow up the

event was ongoing. Please clarify what is the evidence that this patient had tuberculosis if all cultures for TB were negative. Clarify why the patient was treated with bromocriptine. Provide current status of this patient.

6. It is unclear whether the cases of Hepatitis B, C, CMV in this application were de novo or reactivation of chronic infections. Please clarify for each of the cases.
7. Two patients with serious AE of infectious mononucleosis (202/500-009 [hospitalized, no ALT or BR values provided at time of hospitalization] and 203/ 508-013 [ALT up to 12xULN, normal BR; positive Anti-Smooth muscle antibody 1:160]) were IgM negative. Please clarify why you think they represent an acute viral infection versus a DAC HYP related effect.
8. We request that you provide a Kaplan Meir curve for the development of drug-induced liver injury (DILI) in subjects with one or more ALT levels > 3X ULN for Study 201, Study 301, and for Total DAC

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/s/

LAURIE A KELLEY
03/07/2016

Kelley, Laurie

From: Kelley, Laurie
Sent: Wednesday, February 24, 2016 1:52 PM
To: Tammy Sarnelli (tammy.sarnelli@biogen.com)
Cc: Kelley, Laurie
Subject: daclizumab BLA 761029 Request for Information

Categories: With Sponsor

Tammy

Our Safety Reviewer has the following request for information:

Please provide the location of the AE coding datafile (an xpt file). If this information is not in the application, please provide it for the controlled studies and the SUR AE dataset.

Please respond by COB today.

Best regards,
Laurie

Laurie Kelley, PA-C
Regulatory Project Manager
Food and Drug Administration
Office of Drug Evaluation – Division of Neurology Products
Bldg. 22, Room 4200
10903 New Hampshire Ave.
Silver Spring, Maryland 20993-0002

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/s/

LAURIE A KELLEY
03/07/2016

Kelley, Laurie

From: Kelley, Laurie
Sent: Monday, February 08, 2016 12:48 PM
To: Tammy Sarnelli (tammy.sarnelli@biogen.com)
Cc: Kelley, Laurie
Subject: BLA 761029 Clinical IR

Tammy

Our Clinical reviewer has the following information request with regards to BLA 761029. Please provide a response by 2/9/16.

Please provide the number of subjects enrolled in Study 205MS301 when protocol version 4 was implemented in April, 2013.

Regards,
Laurie

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/s/

LAURIE A KELLEY
02/09/2016

Kelley, Laurie

From: Kelley, Laurie
Sent: Thursday, February 04, 2016 2:12 PM
To: Tammy Sarnelli (tammy.sarnelli@biogen.com)
Cc: Kelley, Laurie
Subject: BLA 761029 Clinical IR supplemental analyses 26Jan2016.doc
Attachments: IR supplemental analyses 26Jan2016.doc

Importance: High

Tammy

Our Clinical reviewer has an information request regarding BLA 761029, the details of which are in the attachment to this email. Please provide a response by 2/11/16.

Regards,
Laurie

Laurie Kelley, PA-C
Regulatory Project Manager
Food and Drug Administration
Office of Drug Evaluation – Division of Neurology Products
Bldg. 22, Room 4200
10903 New Hampshire Ave.
Silver Spring, Maryland 20993-0002

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/s/

LAURIE A KELLEY
02/09/2016

Kelley, Laurie

From: Tammy Sarnelli <tammy.sarnelli@biogen.com>
Sent: Thursday, January 28, 2016 1:19 PM
To: Kelley, Laurie
Subject: RE: Information Request for Daclizumab BLA 761029

Categories: With Sponsor

Many thanks, Laurie. It will allow the team to use the weekend.

Tammy Sarnelli
Senior Director, Regulatory Affairs
Biogen, 225 Binney Street, Cambridge MA 02142
Tel (617) 679-3513 Mobile (b) (6)

From: Kelley, Laurie [<mailto:Laurie.Kelley@fda.hhs.gov>]
Sent: Thursday, January 28, 2016 1:02 PM
To: Tammy Sarnelli
Subject: RE: Information Request for Daclizumab BLA 761029

That will be fine

From: Tammy Sarnelli [<mailto:tammy.sarnelli@biogen.com>]
Sent: Thursday, January 28, 2016 12:56 PM
To: Kelley, Laurie
Subject: RE: Information Request for Daclizumab BLA 761029

Hi Laurie:

I can confirm that we have received this request and my team is working on it. May I request that we submit the response on Monday February 1 in order to assess the associated adverse events as requested?

Kind regards
Tammy

Tammy Sarnelli
Senior Director, Regulatory Affairs
Biogen, 225 Binney Street, Cambridge MA 02142
Tel (617) 679-3513 Mobile (b) (6)

From: Kelley, Laurie [<mailto:Laurie.Kelley@fda.hhs.gov>]
Sent: Thursday, January 28, 2016 8:47 AM
To: Tammy Sarnelli
Cc: Kelley, Laurie
Subject: Information Request for Daclizumab BLA 761029
Importance: High

Hi Tammy

Our Safety reviewer has the following information request for regarding daclizumab (BLA761029):

Please provide a listing of all patients with hematologic parameters meeting the definition of NCI CTCAE ≥ 3 using the unique patient ID (rather than the Dummy ID provided in the SUR). For each subject, please identify any associated adverse event. Please provide this information by close of business on Friday, January 29th.

Thank you,

Laurie

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/s/

LAURIE A KELLEY
02/01/2016

Kelley, Laurie

From: Kelley, Laurie
Sent: Thursday, January 28, 2016 10:48 AM
To: Tammy Sarnelli (tammy.sarnelli@biogen.com)
Cc: Kelley, Laurie
Subject: Safety Information Request for daclizumab BLA 761029

Tammy

Our Safety reviewer has the following request for information for BLA 761029.

Thanks
Laurie

Please provide the listing of patients with breast cancer in the DAC HYP program including those that occurred after 180 days post dose. Include age, gender and country, along with the number of doses received at the time of the breast cancer diagnosis. Include estrogen, progesterone and Her-2 receptor tests and staging, whether they had mastectomy or not, chemotherapy or not, and whether they are receiving tamoxifen or other hormonal therapy. Also provide the reporting rate in the DAC HYP program as of December 2015, and compare to the rate expected in the background population adjusted by age, gender and region. Please provide this information by February 8, 2016.

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/s/

LAURIE A KELLEY
02/01/2016

Kelley, Laurie

From: Kelley, Laurie
Sent: Monday, February 01, 2016 1:27 PM
To: Tammy Sarnelli (tammy.sarnelli@biogen.com)
Cc: Kelley, Laurie
Subject: Safety request for daclizumab BLA 761029

Categories: With Sponsor

Tammy

Our Safety reviewer has the following request for information:

In reference to IND safety report 2016BI00176395, for patient # 303/622-106 with a working diagnosis of sarcoidosis, please provide follow up as soon as available. Additionally, your report indicates that there is one case of renal sarcoidosis in the DAC HYP database. DNP is not aware of that case. Please submit (or re-submit) the original IND safety report on that case. As per our account there are at least 7 patients with sarcoidosis in the DAC HYP database, including the recently submitted case.

Please provide a brief narrative of all cases with diagnosis of sarcoidosis in the DAC HYP database including age, gender and race/ethnicity, country, clinical presentation, the number of doses of DAC HYP received, diagnostic tests, treatment (with specific dose and duration of systemic corticosteroid treatment or other immunosuppression) and current status (if the condition resolved, specify how long the patient has been off DAC HYP and off any other corticosteroid or immunosuppressive therapy).

Provide the reporting rate of sarcoidosis in the DAC HYP program as of December 2015, and compare to the rate expected in the background population adjusted by age, gender and region.

Provide this information by February 8, 2016.

Thank you
Laurie

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/s/

LAURIE A KELLEY
02/01/2016

Kelley, Laurie

From: Kelley, Laurie
Sent: Friday, December 04, 2015 11:07 AM
To: Mary Geissler
Cc: Kelley, Laurie
Subject: Safety IR for daclizumab

Mary,

Our Safety reviewer has the following information request:

Please provide the exposure in terms of subject years on treatment for placebo, DAC HYP 150 mg, and DAC HYP 300 mg for Study 201. Please provide the response by COB today.

Thank you,

Laurie

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/s/

LAURIE A KELLEY
12/04/2015

Kelley, Laurie

From: Kelley, Laurie
Sent: Friday, November 20, 2015 9:39 AM
To: Mary Geissler
Cc: Kelley, Laurie
Subject: BLA 761029 Clinical Information Request

Good Morning Mary

Our Clinical Reviewer has an information request (see below). Please provide a response by November 23, 2016.

Regards,
Laurie

Please reference your response to a request for additional information that you submitted in sequence e0020.

Please also reference the document in the above submission entitled "clinical-response-to-d74-communication-dated-13may2015".

In "Response 3" of the above document you indicate that the "Suspected MS Relapse Questionnaire" was completed "whenever a subject first reported possible relapse symptoms". You also indicate that the completed questionnaire was maintained in the sites' files but that the components of the questionnaire were only entered into the clinical database after completion of an unscheduled relapse assessment visit. For study 205MS301, please provide all original Suspected Relapse Questionnaires, whether or not the subject report resulted in an unscheduled relapse visit, from the following sites:

Site 606 – Dr. Hermanowska
Site 667 – Dr. Obradovic
Site 609 – Dr. Fryze
Site 554 – Dr. Malkova
Site 311 – Dr. Sharrack
Site 441 – Dr. Al Khedr
Site 459 – Dr. Centonze
Site 476 – Dr. Izquierdo
Site 136 – Dr. Freedman
Site 102 – Dr. Twyman
Site 141 – Dr. Lynch
Site 101 – Dr. Ford

Please also provide a dataset that includes the results of the questionnaires that is comparable to the dataset entitled (205MS301) RL.

Laurie Kelley, PA-C
Regulatory Project Manager
Food and Drug Administration
Office of Drug Evaluation – Division of Neurology Products

Bldg. 22, Room 4380
10903 New Hampshire Ave.
Silver Spring, Maryland 20993-0002

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/s/

LAURIE A KELLEY
11/20/2015



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug
Administration Silver
Spring MD 20993

BLA 761029

MID-CYCLE COMMUNICATION

Biogen
Attention:

Dear Dr. Cohen:

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

We also refer to the teleconference between representatives of your firm and the FDA on August 24, 2015. The purpose of the teleconference was to provide you an update on the status of the review of your application.

A record of the teleconference is enclosed for your information.

If you have any questions, contact Laurie Kelley, Regulatory Project Manager, by phone or email at (301) 796-5068 or laurie.kelley@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

John Marler, M.D.
Clinical Team Leader
Division of Neurology Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosure:
Mid-Cycle Communication



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND

MID-CYCLE COMMUNICATION

Meeting Date and Time: August 24, 2015, 2:00 p.m. – 3:00 p.m. EDT

Application Number: BLA 761029

Product Name: daclizumab

Indication: Treatment of relapsing multiple sclerosis

Applicant Name: Biogen

Meeting Chair: John Marler, MD

FDA ATTENDEES

Division of Neurology Products

John Marler, MD, Clinical Team Leader
Lawrence Rodichok, MD, Clinical Reviewer
Sally Jo Yasuda, MS, PharmD, Safety Team Leader
Lourdes Villalba, MD, Clinical Safety Reviewer
Laurie Kelley, PA-C, Regulatory Project Manager

Eastern Research Group

Marc Goldstein, Independent Assessor

APPLICANT ATTENDEES

Biogen

Mary Geissler, Associate Director, Regulatory Affairs
Paula Sandler, Vice President, Regulatory Affairs
Tammy Sarnelli, Senior Director, Regulatory Affairs
Anna Williams, Senior Manager, Regulatory Affairs ALP
Tammy Phinney, Vice President, Regulatory Affairs ALP
Steven Sparks, Director, Regulatory Affairs ALP
Shannon Holmes, Associate Director, Regulatory Affairs CMC
Jacob Elkins, Senior Director, Clinical Development
Katherine Riester, Senior Principal Biostatistician
Peter McCroskery, Senior Medical Director, Drug Safety
Agata Tofil-Kaluza, Senior Medical Director, Drug Safety

Gary Bloomgren, Vice President, Drug Safety

1.0 INTRODUCTION

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

2.0 SIGNIFICANT ISSUES

Clinical

- Ongoing review to determine if there is substantial evidence of efficacy
 - Safety concerns regarding drug-induced liver injury, immune-mediated events, and seizures.
 - Ongoing review to determine if there is substantial evidence of efficacy.

Discussion: There are no specific issues requiring responses from the sponsor that haven't been apparent in requests for information from FDA. Further requests are likely because the safety and efficacy reviews are ongoing. FDA extended the review period to allow time to complete review of all the material submitted.

3.0 MAJOR SAFETY CONCERNS/RISK MANAGEMENT

- At this time, the Office of New Drugs and the Office of Surveillance and Epidemiology continue to evaluate whether a risk evaluation and mitigation strategy (REMS) would be necessary to ensure that the benefits of daclizumab (if approved) outweigh the risks.

Discussion: FDA reviewers are currently assessing the seriousness of known risks and what actions can mitigate them. The information requests reflect the questions that arise during the review.

4.0 LATE-CYCLE MEETING /OTHER PROJECTED MILESTONES

- Late Cycle Meeting: Tentative scheduled on October 15, 2015, 10 – 11 am
Face-to-face (or teleconference if requested by sponsor): 1 hour

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/s/

JOHN R MARLER
09/28/2015

Kelley, Laurie

From: Kelley, Laurie
Sent: Monday, September 28, 2015 7:35 AM
To: Mary Geissler
Cc: Kelley, Laurie
Subject: BLA 761029

Mary

Please see the information request below regarding BLA 761029:

1. Your September 15, 2015 response to our August 25, 2015 request for information includes a listing in pdf format. Please provide the data in a format that allows searching and sorting, such as an xpt or excel file. Of note, some events have an end date under the column "End date in current clinical database entered by statistician" but are listed as "Not Resolved" under the Outcome variable column. Please confirm that this means that the event was ongoing at the time of the last visit and there is no available information after that date.

Please provide a response for the above request by Wednesday, September 30, 2015.

2. Please submit digitalized images of the liver biopsies for all patients who had a liver biopsy or postmortem histopathology in the Daclizumab HYP database, using software that is Aperio compatible. We are aware of the following cases

301/624-012

301/670-035

202/909-001

203/508-012

201/454 019

302/622 103

Please include any additional cases that may have had a liver biopsy in this database.

3. In reference to patients 203/453-003 (T cell lymphoma), and 203/761-004 (B cell lymphoma), please provide the histopathology, immunohistochemistry and gene rearrangement reports, staging and treatment received.
4. 303/600-010 developed Myasthenia Gravis at the end of study 301. She was found to have a thymoma and stabilized after thymectomy. Please provide the histopathology report and available immunohistochemistry/genetic studies.
5. At least six patients were diagnosed with sarcoidosis in this application (including 3 with pulmonary sarcoidosis). These cases are 303/611-029, 302/463-105, 303/659-001, 301/659-014, 303/659-116 and 302/622-502 (the latter submitted as an initial IND safety report in July 2015). The narratives for the events of sarcoidosis in patients 302/463-105, 303/659-001 and 301/659-014 contain very limited information. Please provide information about the clinical presentation, extent of involvement (lung, skin and/or other organ) and how the diagnoses were made. Additionally, for each of the cases, specify whether the patient was treated with corticosteroids or other immunosuppressor including the dose and duration of treatment and whether the event has resolved.

6. Separate from the patients with diagnosis of pulmonary sarcoidosis, at least five patients had bilateral lung nodules/fibrosis coded as interstitial lung disease (ILD) (n=3), idiopathic pulmonary fibrosis (n=1) or pulmonary granuloma (“inflammatory granulocytosis pulmonis”) (n=1) in this application. (ID# 301/447-001, 203/751-015, 203/563-001, 301/554-001 and 303/611-049; the latter was later coded as atypical pneumonia, under the Infections and Infestations SOC). Additionally, the narrative for patient 303/609-013 with a SAE of “peripheral edema” mentions that he had exfoliative rash, lung nodules and generalized lymphadenopathy. No infectious agent was identified in any of these cases, although some were treated empirically with antibiotics.
 - a. At least two of these patients had thoracoscopy and lung biopsy; some had bronchoscopy and bronchoalveolar lavage (BAL) and/or biopsy. Please provide the histopathology report of both lung biopsies as well as the histopathology report for any lymph node biopsy that may have been done in any of these patients, and results of BAL cytology.
 - b. Provide chest CT scan report for each patient
 - c. List the laboratory testing and results of studies conducted to rule out immune mediated lung diseases (e.g. sarcoidosis, vasculitis, eosinophilic pneumonia) in each of these cases.
 - d. For patients treated with systemic corticosteroids or other immunosuppressor specify the name, dose and duration of treatment.
7. Three patients reported vitiligo in this application (203/453-011, 303/104-002, 303/603-003) and one had a skin biopsy consistent with morphea (203/312-007). Please provide additional information about these cases, such as the location and extent of lesions, whether the diagnosis was made by a dermatologist and whether they were associated with other manifestations of autoimmunity.
8. Please provide follow up information for the following IND safety reports submitted on 9/23/15
 - a. Patient 303/539-010 presented bloody diarrhea and was suspected to have Chron’s disease with duodenal involvement, later coded as “duodenal ulcer”. Please provide full biopsy results, as well as treatment received and outcome.
 - b. Patient 303/657-017 presented axillary lymphadenopathy and underwent lymph node biopsy on (b) (6) which was read as “abnormal.” Please provide full histopathology results.
9. In reference to your responses to the FDA request for information submitted on September 24, 2015
 - a. For patient 203/553-005, please clarify the dates of sertraline use in study 201/202.
 - b. For patient 203/100-002, who had hemolytic anemia, please clarify whether the source of interference with blood cross matching was identified.

Please provide a response for items 2 – 9 by October 12, 2015.

Regards,
Laurie

Laurie Kelley, PA-C
Regulatory Project Manager
Food and Drug Administration
Office of Drug Evaluation – Division of Neurology Products
Bldg. 22, Room 4380
10903 New Hampshire Ave.
Silver Spring, Maryland 20993-0002

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/s/

LAURIE A KELLEY
09/28/2015

Kelley, Laurie

From: Kelley, Laurie
Sent: Tuesday, September 22, 2015 1:03 PM
To: Mary Geissler
Cc: Kelley, Laurie
Subject: RE: BLA 761029: Information Requests due September 22nd

Mary

With regards to the email below we have the following response:

September 15th – Narrative Information Request:

While the team is working to prepare the new narratives as soon as possible with the comprehensive details and format requested, we expect the new narratives will be available for submission on October 13th. Can you confirm whether this would be acceptable to the review team?

If you cannot respond earlier, October 13th is acceptable. However, we believe that the response to the September 17th request could be submitted earlier than October 13th.

September 17th- eDISH Information Request:

With reference to the excel file with the data requirements, we confirm we can provide datasets requested on the 'liver data' and 'demography' tabs for Studies 205MS201, 205MS301 and the Total DAC HYP experience. We believe the 'viral load' tab is not applicable to DAC HYP so this would not be included in the response.

As per the Excel file with eDISH data requirements, viral load applies only for agents to treat Hepatitis B and C, therefore it does not apply to daclizumab.

Regarding the narratives, we are seeking clarification regarding the content and format requested by the Review team:

-'the narrative pdf files' tab indicates that narratives are requested in pdf format. Does the review team accept PDF narratives in place of providing narrative text in SAS dataset, or are both narrative text in a SAS dataset and PDF files required?

As per the Excel file with eDISH data requirements, narrative text in the SAS dataset is required; narratives in pdf are optional. Please note that eDISH requires narratives only for the cases with ALT>3xULN and total BR>2xULN.

-The provision of the narratives as datasets will be linked to completion of the updated narratives requested on September 15th (and referenced above). In order to facilitate ongoing review, would the review team accept datasets for 'liver data' and 'demography' on September 22nd, with a follow-up submission of the narratives datasets on October 13th?

We request that the text narratives in sas dataset be provided along with the liver data and demography at once, preferably before October 13, 2015.

Please let me know if you have any further questions. Please also confirm receipt.

Thanks
Laurie

From: Mary Geissler [mailto:mary.geissler@biogen.com]
Sent: Monday, September 21, 2015 10:31 AM
To: Kelley, Laurie
Subject: RE: BLA 761029: Information Requests due September 22nd

Thank you, Laurie.

From: Kelley, Laurie [mailto:Laurie.Kelley@fda.hhs.gov]
Sent: Monday, September 21, 2015 10:23 AM
To: Mary Geissler
Subject: RE: BLA 761029: Information Requests due September 22nd

Mary

I received your voicemail, as well as the email below. I will discuss this with the review team and provide a response as soon as possible.

Regards,
Laurie

From: Mary Geissler [mailto:mary.geissler@biogen.com]
Sent: Monday, September 21, 2015 10:07 AM
To: Kelley, Laurie
Subject: BLA 761029: Information Requests due September 22nd

Dear Laurie,

As per my voice message today, I wanted to follow-up regarding two recent Information Requests for BLA 761029: the September 15th and September 17th information requests, which relate to submission of narratives for hepatobiliary events and submission of new eDISH datasets, respectively. The team feels that we can provide the requested information; however, we are seeking some minor clarification regarding the content of the eDISH datasets and are kindly requesting an extension to the September 22nd response deadline in order to comply with these requests.

September 15th – Narrative Information Request:

While the team is working to prepare the new narratives as soon as possible with the comprehensive details and format requested, we expect the new narratives will be available for submission on October 13th. Can you confirm whether this would be acceptable to the review team?

September 17th- eDISH Information Request:

With reference to the excel file with the data requirements, we confirm we can provide datasets requested on the 'liver data' and 'demography' tabs for Studies 205MS201, 205MS301 and the Total DAC HYP experience. We believe the 'viral load' tab is not applicable to DAC HYP so this would not be included in the response.

Regarding the narratives, we are seeking clarification regarding the content and format requested by the Review team:

-‘the narrative pdf files’ tab indicates that narratives are requested in pdf format. Does the review team accept PDF narratives in place of providing narrative text in SAS dataset, or are both narrative text in a SAS dataset and PDF files required?

-The provision of the narratives as datasets will be linked to completion of the updated narratives requested on September 15th (and referenced above). In order to facilitate ongoing review, would the review team accept datasets for ‘liver data’ and ‘demography’ on September 22nd, with a follow-up submission of the narratives datasets on October 13th?

Please let me know if I can provide any further clarification.

Kind Regards,
Mary

Mary L. Geissler, MPH

Associate Director, Regulatory Affairs

Biogen

300 Binney Street

Cambridge MA 02142

Tel: 617.679.6474

Email: mary.geissler@biogen.com

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/s/

LAURIE A KELLEY
09/22/2015

Kelley, Laurie

From: Kelley, Laurie
Sent: Thursday, September 17, 2015 9:59 AM
To: Mary Geissler
Cc: Kelley, Laurie
Subject: BLA 761029
Attachments: eDISHDataRequirements.xlsx

Mary

Please submit data sets following the eDISH Data Requirements attached in this Excel file for studies 205MS201, 205MS301 and the Total DAC HYP experience by September 22nd, 2015.

Please confirm receipt.

Thank you
Laurie

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/s/

LAURIE A KELLEY
09/17/2015

Kelley, Laurie

From: Kelley, Laurie
Sent: Tuesday, September 15, 2015 1:26 PM
To: Mary Geissler
Cc: Kelley, Laurie
Subject: BLA 761029 Safety Information Request

Mary,

Regarding BLA 761029, please submit narratives for the following serious adverse events and events leading to DAC HYP discontinuation in the Hepatobiliary SOC and Hepatobiliary Investigations HLG.T.

1. 201-763-004
2. 202-909-001 (fatal case...any new study or lab data not previously submitted)
3. 201-454-019
4. 201-763-011
5. 301-624-012
6. 301-453-026
7. 301-110-006
8. 301-604-040
9. 301-670-024
10. 301-670-035
11. 203-506-011
12. 302-622-103
13. 303-649-009
14. 202-765-003
15. 303-680-001
16. 203-508-016
17. 203-508-012
18. 203-759-008
19. 201-763-005
20. 201-460-010
21. 201-903-025
22. 201-908-005
23. 201-509-007
24. 301-517-003
25. 301-649-006
26. 301-660-007
27. 301-611-007
28. 301-605-002
29. 301-148-004
30. 301-205-006
31. 301-592-001
32. 301-622-005
33. 301-539-013
34. 301-668-013
35. 301-554-008
36. 301-611-048
37. 301-741-001

38. 301-228-003
39. 301-161-006
40. 301-670-001
41. 301-311-020
42. 301-110-002
43. 301-612-004
44. 301-254-007
45. 301-136-008
46. 301-517-003
47. 301-649-006
48. 301-660-007
49. 301-611-007
50. 301-148-004
51. 301-605-002
52. 301 453-041

Please follow the model of the narrative in IND safety report 2014BI032793 (for patient 670 024). The narratives should be organized in a timeline by dates of the key clinical events, the drug exposure history (with dates and doses of treatment, including steroids), clinical data, results of imaging studies, biopsy and all other labs (dates of serum sampling) and all long-term follow-up findings (at 6 months and even later to exclude late post-treatment relapses of underlying AIH not induced by daclizumab) after resolution of the liver injury to the most recent visit. The date of the last patient encounter and testing should be provided, including those lost to follow-up or who discontinued the study. Also, an attached timeline table of all lab results, such as that appended at the end of the IND safety report 2014BI032793 should be provided in all the cases.

Please provide updated narratives for the following cases by *(1 week from request)* September 22nd, 2015.

Regards,
Laurie

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/s/

LAURIE A KELLEY
09/15/2015

Kelley, Laurie

From: Kelley, Laurie
Sent: Friday, September 11, 2015 1:38 PM
To: Mary Geissler
Cc: Laurie Kelley
Subject: Daclizumab request for information regarding clinical safety
Attachments: Additional request SEPT 11 2015 final.doc

Mary

Please find attached a word doc comprising an information request daclizumab. Please confirm receipt.

Regards
Laurie

Sent from my BlackBerry 10 smartphone.

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/s/

LAURIE A KELLEY
09/14/2015

Kelley, Laurie

From: Kelley, Laurie
Sent: Tuesday, August 25, 2015 2:39 PM
To: Mary Geissler
Cc: Kelley, Laurie
Subject: Daclizumab HYP (August 25, 2015) Information REquest

Dear Mary

Please see our additional requests for clarification for with regards to Daclizumab HYP.

1. Patient 303/606-010 developed a rash around the ankles in study 301 and colitis in study 303. A colonoscopy was consistent with chronic active inflammation. This patient also developed disseminated lymphadenopathy after the cut-off of the SUR. Information of study status and outcome was not available. Please provide follow up for this patient.
2. Two cases of angioedema were reported in study 301 (441-021 and 552-014). One case of vasculitis was reported in study 301 (301/660-008). Please provide information about the clinical and laboratory workup conducted in these patients.
3. One patient had DRESS in study 301 (patient 512-006). As per the patient profile the patient had a “central catheter dialysis” placement. However, the patient was treated with plasmapheresis. Please clarify if the patient did have dialysis or not.
4. Patient 202/ 363 008 received DAC HYP 150 in study 201 and placebo in study 202. Last dose of DAC in 201 was on Day 340. An adverse event of aseptic meningitis was reported on Day 407 of study 201 while the patient was on placebo, leading to study withdrawal. The event of meningitis was preceded by a maculopapular rash, which was biopsied. This patient was treated empirically with ampicillin, ceftriaxone and acyclovir and the event is reported as resolved on Day 420. Labs showed mild eosinophilia. Anti-DAC antibodies were positive in all three measurements in study 202. Please clarify the infectious disease workup that this patient had, which led to a diagnosis of aseptic meningitis, as well as other immunologic work up she may have had (e.g. ANA, DsDNA), along with the result of the skin biopsy.
5. Patient 203/751-012 presented ALT and AST elevation in study 203, up to 7x ULN on Day 1053. Repeated labs on 1059 showed improvement but was still >5xULN. Please clarify how long the patient was followed and whether there was full recovery.
6. Patient 303/141-008 received DAC HYP 150 in study 301 and had elevated ALT and AST soon after starting study 303. Patient was withdrawn from the study with diagnosis of celiac disease. Please clarify whether the patient had autoimmune disease panel workup (e.g. ANA, liver specific autoantibodies) and provide any results.
7. Patient 201/752-018 was diagnosed with “hepatic form of yersiniosis” after 11 doses of DAC HYP 300 mg. The patient also had a toxic skin eruption that led to drug withdrawal and reported ALT/AST above 30x ULN. Neither the narrative nor the patient profile provides information about the work up done in this patient to support a diagnosis of hepatic yersiniosis. Please provide additional information to support such a diagnosis and whether an autoimmune disease workup was conducted.

8. 201/509-007 had ALT elevation up to 40xULN along with AST, LDH and GGT elevation after 12 doses of DAC HYP 150. She was diagnosed with hepatic arteriovenous malformation and did not enter the extension study. Liver enzymes improved after drug discontinuation. Neither the narrative nor the patient profile mentions whether hepatitis serology, ANA and specific liver antibodies were measured. Please provide any such supporting data.
9. 301/649-006 was diagnosed with biliary dyskinesia and idiopathic chronic hepatitis. She was taking diclofenac, ibuprofen and meloxicam during the study. Last dose of DAC was Day 701. ALT was 11xULN, AST 6xULN and BR 2.9x ULN on Day 737. She was Anti DAC ab positive. ALT and AST were normal by Day 805 but BR persisted elevated. The patient profile does not include the ANA and liver autoantibody panel. Please confirm the date for concomitant analgesics used during the study and provide liver autoantibody panel results.
10. In regard to your July 28 response that includes the July 24, 2014, Hepatic Adjudication Committee (HAC) evaluation of additional cases of hepatotoxicity reported with daclizumab HYP, we note that the HAC was presented case 303/543-010. This potential case of liver injury is not in the AE datasets and it is not discussed in the safety update report. Please clarify why.
11. In response to a DNP request for additional information regarding two reported cases of lymphoma (patients 303/678 004 and 203/500 003) on July 28, 2015, you responded that as per assessment of an independent hematopathologist, the available data are not supportive/do not provide unequivocal evidence of lymphoma. Please provide the biopsy report along with the information that your consultant has reviewed.
12. Please provide follow up of all cases with serious AEs or AE that led to study drug withdrawal whose outcome is listed as "not resolved" or "unknown" in the Safety Update Report AE datasets which had a cut-off date of November 2014.

For items 1 to 11 please submit information by September 2nd, 2015. For item # 12 please submit information by September 15, 2015.

Regards,
Laurie

Laurie Kelley, PA-C
Regulatory Project Manager
Food and Drug Administration
Office of Drug Evaluation – Division of Neurology Products
Bldg. 22, Room 4380
10903 New Hampshire Ave.
Silver Spring, Maryland 20993-0002

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/s/

LAURIE A KELLEY
08/25/2015



BLA 761029

**REVIEW EXTENSION –
MAJOR AMENDMENT**

Biogen
Attention: Nadine D. Cohen, Ph.D.
Senior Vice President, Regulatory Affairs
14 Cambridge Center
Cambridge, MA 02142

Dear Dr. Cohen:

Please refer to your Biologics License Application (BLA) dated February 27, 2015, received February 27, 2015, submitted under section 351(a) of the Public Health Service Act for daclizumab High Yield Process (DAC HYP) 150 mg/mL Injection.

Please also refer to your additional submissions dated March 9, 2015, March 12, 2015, April 2, 2015, April 6, 2015, April 8, 2015, April 8, 2015, April 20, 2015, May 7, 2015, May 11, 2015, May 14, 2015, May 18, 2015, May 20, 2015, May 26, 2015, July 1, 2015, July 14, 2015, July 21, 2015, July 22, 2015, July 29, 2015, and August 3, 2015.

We consider your April 2, 2015, submission to be a major amendment to this application. Therefore, we are extending the goal date by three months to provide time for a full review of the submission. The extended user fee goal date is May 27, 2016.

In addition, we are establishing a new timeline for communicating labeling changes and/or postmarketing requirements/commitments in accordance with “BIOSIMILAR BIOLOGICAL PRODUCT AUTHORIZATION PERFORMANCE GOALS AND PROCEDURES FOR FISCAL YEARS 2013 THROUGH 2017.” If major deficiencies are not identified during our review, we plan to communicate proposed labeling and, if necessary, any postmarketing requirement/commitment requests by February 9, 2016.

If you have any questions, please contact Laurie Kelley, PA-C, Regulatory Project Manager, by email laurie.kelley@fda.hhs.gov or by phone at (301) 796-5068.

Sincerely,

{See appended electronic signature page}

Billy Dunn, M.D.
Director
Division of Neurology Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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/s/

LAURIE A KELLEY
08/20/2015

WILLIAM H Dunn
08/20/2015

Kelley, Laurie

From: Kelley, Laurie
Sent: Tuesday, July 28, 2015 12:07 PM
To: Mary Geissler
Cc: Kelley, Laurie
Subject: BLA 761029 Clinical Information Request

Categories: With Sponsor

Mary

Our Clinical Reviewer has the following request for information (see below). Please provided a response by COB today.

Regards,
Laurie

Please refer to you BLA 761029. Please also refer to the following communication: "FILING COMMUNICATION NO FILING REVIEW ISSUES IDENTIFIED" sent on 5/13/15.

Please address the following issues related to the occurrence of relapses in trial 205MS301: We note that Section 14.3.8 of the protocol states that the "Protocol defined interval to the relapse assessment by the treating neurologist should be no more than 3 days and to the assessment by the examining neurologist to confirm that there was a new objective deficit and to record the EDSS should be no more than 5 days."

1. In our analysis of the results for trial 205MS301 we estimate that 40% of relapses were evaluated by the treating neurologist more than 3 days after relapse symptom onset, 20% after 7 days and 2% (22 relapses) after 30 days or more had elapsed. We believe that the assessments of a relapse are likely to be affected by the duration of time since the relapse started. Please provide analyses to assess the impact of the interval from relapse symptom onset to the time of evaluation by the treating neurologist on the efficacy results from this trial. This should include an assessment of whether there was any imbalance between the two treatment arms in the decision by the investigator and/or the Independent Neurology Evaluation Committee (INEC) to include relapses in the analyses of efficacy.
2. In the "FILING COMMUNICATION/NO FILING REVIEW ISSUES IDENTIFIED" the following request for further information was included:

3) Section 14.3.8 of the protocol (Unscheduled Relapse Assessment Visit(s)) states that "subjects who experience new neurological symptoms must contact the Treating Nurse or Treating Neurologist as soon as possible and within no more than 48 hours of the onset of symptoms. A standardized Suspected Relapse Questionnaire will be completed to determine the necessity of an Unscheduled Relapse Assessment Visit." We located a "Suspected MS Relapse Questionnaire – INEC Alert" form in the site operations manual. However, the instructions for this form state that it "should only be completed if the suspected MS relapse case is sent to INEC for review". Please indicate whether this questionnaire is the standardized questionnaire used to document all subject reports of possible relapses including those that did not require an unscheduled relapse visit. If not, then indicate where we can find all subject reports of a potential relapse in the CRFs and datasets you submitted.

We are unable to locate your response to this question. Please indicate where we may find your response or provide a response at this time. In your response please indicate whether there is documentation of patient reports of new symptoms that were deemed to not merit an unscheduled visit.

Laurie Kelley, PA-C
Regulatory Project Manager
Food and Drug Administration
Office of Drug Evaluation – Division of Neurology Products
Bldg. 22, Room 4380
10903 New Hampshire Ave.
Silver Spring, Maryland 20993-0002

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/s/

LAURIE A KELLEY
07/29/2015

Kelley, Laurie

From: Kelley, Laurie
Sent: Tuesday, July 21, 2015 6:57 AM
To: 'Mary Geissler'
Cc: Kelley, Laurie
Subject: FW: BLA 761029 daclizumab IR

Mary

We received your response to our June 30, 2015 information request, but the Safety Reviewer states that the information was not sent as an Excel file. Could you please resend with the information in Excel. Please provide a response by COB today if possible.

Thanks
Laurie

From: Kelley, Laurie
Sent: Tuesday, June 30, 2015 1:47 PM
To: Mary Geissler
Cc: Kelley, Laurie
Subject: BLA 761029 daclizumab IR

Mary,

Our Safety reviewer has the following request for information. Please confirm receipt.

Please provide a table (preferably an Excel file) that lists all patients referred for evaluation by the central dermatologist, including: Study ID, patient IUSUBJID, verbatim term used by investigator, preferred term used in the safety analyses, treatment group, number of doses received [specify if there was placebo washout] before the event onset, action taken with drug, treatment given for the event [specify if topical or systemic], duration of event, nomenclature used by the central dermatologist for that event, and the category in which the event was classified by the central dermatologist, along with attribution of causality by the central dermatologist. Also indicate whether a biopsy or photographs were available for review of that case. If a biopsy was available, please describe the result.

Provide this information by July 14, 2015.

Regards,
Laurie

Laurie Kelley, PA-C
Regulatory Project Manager
Food and Drug Administration

Office of Drug Evaluation – Division of Neurology Products
Bldg. 22, Room 4380
10903 New Hampshire Ave.
Silver Spring, Maryland 20993-0002

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/s/

LAURIE A KELLEY
07/21/2015

Kelley, Laurie

From: Kelley, Laurie
Sent: Tuesday, July 21, 2015 6:59 AM
To: 'Mary Geissler'
Cc: Kelley, Laurie
Subject: daclizumab NBLA 761029

Mary

Our Safety Reviewer has an additional requests for information.

1. Patient #301&303/678-004 diagnosed with non-Hodgkin's lymphoma had a bone marrow biopsy (b) (6) Patient 500-003 from study 203 was diagnosed with Peripheral T cell lymphoma after the cut-off date of the safety update report (SUR). Please provide additional information about these patients including, but not limited to, dose and duration of DAC HYP treatment, prior immunosuppressor treatment, biopsy results, EBV testing of the tissue, treatment given, and outcome.
2. As per the Safety Update Report (SUR), patients 508-012 and 512-013 presented elevated liver enzymes leading to drug withdrawal in an extension study after the cut-off for analyses. A biopsy was planned for patient 508-012. Clarify the study in which these events occurred. Provide follow up of these cases including results of work-up, treatment received, and outcome.
3. Provide the evaluation of the Hepatic Adjudication Committee (HAC) for patient 759-008 from study 203 as well as other cases of hepatotoxicity that may have been referred to the HAC after cut-off of the original BLA submission.
4. As per Table 29 in the Summary of Clinical Safety of the original BLA application, a total of 111 patients received alternative therapy in the Total DAC experience including IFN beta-1a. However, as per Table 41, AE after alternative MS medication, in the original BLA, a total of 125 patients received alternative MS therapy in the Total DAC population. Please clarify the discrepancy.
5. The Data Analysis Plan for the ISS indicated that sensitivity analysis might be conducted that censored subjects after use of alternative MS medications. Please direct the reviewer to the location of those sensitivity analyses for serious AEs and AE of interest.
6. Laboratory analyses show a higher percentage of patients with atypical lymphocytes in DAC treated patients as compared to placebo and Avonex. Please provide a potential explanation and discuss the significance of these atypical lymphocytes among DAC HYP treated patients.
7. In a previous request for information sent on 7/10/15 we asked for location and biopsy results of all cases of lymphadenopathy/lymphadenitis submitted in the original application. That information is still pending. If not included in the response to our previous request, please provide the same information for cases reported in the SUR and after the cut-off of analysis of the SUR. Please provide follow up of patients who do not show an end date in the SUR AE datasets.

Patient 301&303/453-048 had a diagnosis of brucellosis. This patient had a lymph node biopsy that showed atypical lymphoid proliferation. Please provide follow up on this patient. Did he have lymphoma? How was the diagnosis of brucellosis made in this patient? Which risk factors did he have for brucellosis?

Please provide a response by July 29, 2015.

Regards,
Laurie

Laurie Kelley, PA-C
Regulatory Project Manager
Food and Drug Administration
Office of Drug Evaluation – Division of Neurology Products
Bldg. 22, Room 4380
10903 New Hampshire Ave.
Silver Spring, Maryland 20993-0002

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/s/

LAURIE A KELLEY
07/21/2015

Kelley, Laurie

From: Kelley, Laurie
Sent: Friday, July 10, 2015 7:35 AM
To: 'Mary Geissler'
Cc: Kelley, Laurie
Subject: BLA 761029

Categories: With Sponsor

Mary

Out Safety reviewer has the following request for information. Please provide a response to the following by July 22, 2015.

1. The Hepatic Adjudication Committee (HAC) report states that the committee reviewed all cases fulfilling Hy's Law biochemical criteria (defined as concurrent ALT or AST >3x ULN and total bilirubin >2x ULN) as well as additional cases of interest at the discretion of the sponsor. The HAC report mentions a total of 25 cases, including five in which bilirubin was either <2xULN or transaminase and bilirubin elevation were non concurrent (did not occur within 30 days of each other). We note that there were several reports of SAEs with highly elevated transaminases without bilirubin elevation that are not mentioned in the HAC report, such as 201 763-004 (ALT 48x ULN), 201 763-011 (ALT 17x ULN), 301 453-026 (ALT 18x ULN) and 301 670-035 (ALT 15x ULN) (all in controlled studies) and 506-011 and 608-001 (from study 203 and 202, respectively).
 - a. Please clarify what the criteria were for referring non-Hy's law cases to the HAC .
 - b. Please clarify whether the HAC reviewed any of the non Hy's law cases mentioned above. We request that these cases be evaluated by the HAC if this was not previously done.
2. The narrative for case 301 624-012 (non-fatal acute hepatic failure with biopsy consistent with drug induced hepatitis) suggests that the last dose of DAC HYP 150 was on Day 169 and the diagnosis of liver failure was on Day 197. However, the patient profile indicates that the last dose was on Day 197. Please clarify when the last dose was for this patient. Additionally, an Anti Smooth muscle (ASMA) antibody is reported to be 1:40. Please comment on this finding.
3. Some patients presented low titers of liver specific autoantibodies such as ASMA (patient 301 624-012 mentioned under #2), Anti-liver kidney microsomal-1 (anti-LKM-1) (patients 301 453-026 diagnosed as drug induced hepatitis and 301 670-035 diagnosed as autoimmune hepatitis, [neither referred to the HAC] and patient 301 604 040 diagnosed with acute hepatitis), and Anti Soluble L A (SLA Ig) (patient 301 604 040). What was the HAC interpretation of the presence of such autoantibodies in these cases? We request that these cases be reviewed by the HAC if this was not previously done. Were liver autoantibodies found in any patient treated with Avonex?
4. Patient 301 670 024 was initially adjudicated by the HAC as a possible Hy's Law Case and changed to "unlikely" after unblinding and review of the aggregate data. As per the HAC the most likely diagnosis was bacterial cholangitis "because of MRI findings, enlarged lymph node and dramatic improvement after starting antibiotics." Could you please clarify the basis for a diagnosis of bacterial cholangitis in a patient without fever and abdominal pain and with a normal WBC? Please note that the ALT was already at half of the peak value by the time that cephalexin was started on Day 856. Moreover, this patient was treated with IV methylprednisolone followed by oral prednisone taper down to 10

mg/day on Day 903, suggesting treatment for autoimmune hepatitis. Please clarify whether prednisone was completely tapered off and provide information about the outcome of the patient after prednisone discontinuation.

5. Patient 622-103 from study 302 developed autoimmune hepatitis after 5 doses of DAC HYP 150 mg. She was treated with prednisone and azathioprine for unclear duration. The event is reported to have resolved. Please clarify whether the patient was tapered off prednisone and azathioprine and what the outcome was after being off immunosuppressors.

6. Patient 506-011 from study 203 also reported autoimmune hepatitis and was treated with corticosteroids. Please clarify the dose and duration of prednisone treatment, as well as outcome after discontinuation of prednisone.

7. Patient 649-009 from study 303 developed liver disease consistent with drug induced autoimmune hepatitis versus spontaneous autoimmune hepatitis. This patient is not in the datasets because the event occurred after data cutoff for the BLA. As of the last available information (September 2014) patient was improved but still on prednisone. Please clarify whether this patient was able to get off corticosteroid treatment. Also clarify whether a diagnosis of concurrent glomerulonephritis was confirmed.

8. Please have the HAC reassess the liver toxicity of DAC HYP after they have seen the additional cases identified in items # 1 and 3 above.

9. Please provide an analysis of characteristics that could predict the risk of liver disease in individual patients. This should include a discussion how HLA testing could be used to predict the risk and a discussion of any HLA testing done to date.

10. Please provide a table of patients with lymphadenopathy, lymphadenitis or lymphoproliferative disease, and for each patient provide the location of the abnormal lymph nodes and the results of lymph node biopsies, if done.

11. Two patients with SAEs of lymphadenitis were diagnosed with “salivary gland neoplasm” and one patient with a SAE of lymphadenopathy was diagnosed with “benign neoplasm” in study 301. Please clarify the histopathology of these neoplasms, the location of the neoplasms, and any additional testing done in the tumor tissues or lymph nodes.

Regards,
Laurie

Laurie Kelley, PA-C
Regulatory Project Manager
Food and Drug Administration
Office of Drug Evaluation – Division of Neurology Products
Bldg. 22, Room 4380
10903 New Hampshire Ave.
Silver Spring, Maryland 20993-0002

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/s/

LAURIE A KELLEY
07/13/2015

Kelley, Laurie

From: Kelley, Laurie
Sent: Tuesday, June 30, 2015 1:47 PM
To: 'Mary Geissler'
Cc: Kelley, Laurie
Subject: BLA 761029 daclizumab IR

Mary,

Our Safety reviewer has the following request for information. Please confirm receipt.

Please provide a table (preferably an Excel file) that lists all patients referred for evaluation by the central dermatologist, including: Study ID, patient IUSUBJID, verbatim term used by investigator, preferred term used in the safety analyses, treatment group, number of doses received [specify if there was placebo washout] before the event onset, action taken with drug, treatment given for the event [specify if topical or systemic], duration of event, nomenclature used by the central dermatologist for that event, and the category in which the event was classified by the central dermatologist, along with attribution of causality by the central dermatologist. Also indicate whether a biopsy or photographs were available for review of that case. If a biopsy was available, please describe the result.

Provide this information by July 14, 2015.

Regards,
Laurie

Laurie Kelley, PA-C
Regulatory Project Manager
Food and Drug Administration
Office of Drug Evaluation – Division of Neurology Products
Bldg. 22, Room 4380
10903 New Hampshire Ave.
Silver Spring, Maryland 20993-0002

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LAURIE A KELLEY
06/30/2015



BLA 761029

**PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE**

Biogen Inc.
300 Binney Street
Cambridge, MA 02142

ATTENTION: Mary L. Geissler, MPH
Associate Director, Regulatory Affairs,

Dear Ms. Geissler:

Please refer to your Biologics License Application (BLA) dated and received February 27, 2015, submitted under section 351(a) of the Public Health Service Act for Daclizumab, 150 mg/ mL.

We also refer to your correspondence, dated and received April 10, 2015, requesting review of your proposed proprietary name, Zinbryta.

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

If any of the proposed product characteristics as stated in your April 10, 2015, submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

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

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

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Ermias Zerislassie, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-0097. For any other information regarding this application, contact Laurie Kelley, Regulatory Project Manager in the Office of New Drugs, at 301-796-5068.

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/

TODD D BRIDGES
06/27/2015

Kelley, Laurie

From: Kelley, Laurie
Sent: Thursday, May 21, 2015 12:40 PM
To: Mary Geissler
Cc: Choy, Fannie (Yuet); Kelley, Laurie
Subject: BLA761029

Hi Mary

Our Clinical reviewer has the following request for information:

For Study 205MS301 the Disposition dataset includes a "Reported Term for the Disposition Event" (DSTERM) and a "Standardized Disposition Term" (DSDCOD) of "Randomization Date Site Entered". We are unable to locate where in the Case Report Form (CRF) the date and time of this event was recorded by the site. Please indicate where this was recorded in the CRF.

Please indicate whether the date of randomization as entered by the site corresponds to the date of randomization as recorded by the Interactive Voice Response System (IVRS). If these do not necessarily correspond please indicate which date was used as the randomization date for analyses of study results. In addition, even if the dates are the same, provide a revised Disposition dataset that includes the date and time of randomization reported from the IVRS as a separate field.

Please respond by May 28, 2015.

Regards,
Laurie

Laurie Kelley, PA-C
Regulatory Project Manager
Food and Drug Administration
Office of Drug Evaluation – Division of Neurology Products
Bldg. 22, Room 4380
10903 New Hampshire Ave.
Silver Spring, Maryland 20993-0002

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/s/

LAURIE A KELLEY
05/21/2015

Kelley, Laurie

From: Kelley, Laurie
Sent: Tuesday, May 19, 2015 9:47 AM
To: Mary Geissler
Cc: Kelley, Laurie
Subject: FW: BLA761029 additional request for clarification

Good Morning Mary

Our Safety reviewer has the following information request:

BLA 761029 includes two feeder studies (205MS201 and 205MS301) and three FU studies (205MS202, 205MS203 and 205MS303). Please submit a mapping table linking the FU USUBJIDs with the USUBJIDs in the feeder studies so we can pool the SDTM individual files.

Please provide this information by May 21, 2015.

Regards,
Laurie

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/s/

LAURIE A KELLEY
05/19/2015

Kelley, Laurie

From: Kelley, Laurie
Sent: Tuesday, May 19, 2015 10:12 AM
To: Mary Geissler
Cc: Kelley, Laurie; Choy, Fannie (Yuet)
Subject: BLA761029 Information Request

Mary

Our Clinical Reviewer has the following request for information:

For studies 205MS201 and 205MS301 please provide the following analyses:

1. An analysis of the primary endpoint which includes patients randomized at all sites at which any investigator reported any financial interest as listed in the Financial Disclosure document submitted with the application. Please provide a listing of the sites included as having reported any financial interest.
2. An analysis of the primary endpoint which includes patients randomized at all sites at which no investigator reported a financial interest as listed in the Financial Disclosure document submitted with the application. A listing of these sites is not necessary.
3. Analyses of the proportion with 12 week confirmed disability progression comparable to 1 and 2 above.

Please provide a response by May 26, 2015. Also, I will be out of the office May 26, 2015 – June 5, 2015. During that time my colleague, Fannie Choy, will be covering me for anything regarding daclizumab, NDA 761029. Please send your response to her as well as myself.

Thanks,
Laurie

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/s/

LAURIE A KELLEY
05/19/2015



BLA 761029

**FILING COMMUNICATION
NO FILING REVIEW ISSUES IDENTIFIED**

AbbVie Inc.
Attention: Mahlaqa Patel
Director, Regulatory Affairs
1 North Waukegan Road
North Chicago, IL 60064

Dear Ms. Patel:

Please refer to your Biologics License Application (BLA) dated February 27, 2015, received February 27, 2015, submitted under section 351(a) of the Public Health Service Act for ZINBRYTA™ [daclizumab high yield process (DAC HYP)].

We also refer to your amendments dated March 9, 2015, March 12, 2015, March 26, 2015, April 2, 2015, April 6, 2015, April 8, 2015, April 20, 2015, and May 7, 2015.

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 February 28, 2016. This application is also subject to the provisions of “the Program” under the Prescription Drug User Fee Act (PDUFA) V (refer to <http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm272170.htm>).

We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, mid-cycle, team, and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If we do not identify major deficiencies during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing commitment requests by November 9, 2015. In addition, the planned date for our internal mid-cycle review meeting is July 27, 2015.

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. Please note that our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that we may identify during our review.

Please submit the information described in the requests for further information below in response to this letter by June 7, 2015. Please respond only to the requests for information listed below in your reply to this communication. 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.

Submit responses to the requests below regarding Prescribing Information by June 2, 2015, in a separate submission.

REQUESTS FOR FURTHER INFORMATION

Clinical

1. For studies 205MS201 and 205MS301 in the tabulation dataset for disposition (“DS”), the Start Date for the Disposition Event “End of Treatment” is blank. Please explain what this disposition event represents and why it blank for all subjects in both studies.
2. Please indicate where the date and study day for the End of Treatment are located in the tabulation datasets. The reviewer’s guides do not explain the Rule ID relevant to this issue (SD1118 for studies 205MS201 and 205MS301).
3. Section 14.3.8 of the protocol (Unscheduled Relapse Assessment Visit(s)) states that “subjects who experience new neurological symptoms must contact the Treating Nurse or Treating Neurologist as soon as possible and within no more than 48 hours of the onset of symptoms. A standardized Suspected Relapse Questionnaire will be completed to determine the necessity of an Unscheduled Relapse Assessment Visit.” We located a “Suspected MS Relapse Questionnaire – INEC Alert” form in the site operations manual. However, the instructions for this form state that it “should only be completed if the suspected MS relapse case is sent to INEC for review”. Please indicate whether this questionnaire is the standardized questionnaire used to document all subject reports of possible relapses including those that did not require an unscheduled relapse visit. If not, then indicate where we can find all subject reports of a potential relapse in the CRFs and datasets you submitted.
4. You have provided data on the occurrence of protocol deviations in study 205MS301 (dataset DV and SUPPDV). Although we note the submission of a listing of all protocol deviations for study 205MS201 in the Clinical Study Report - Appendix 16.2.2, we are unable to locate a dataset for study 205MS201 comparable to that submitted for study 205MS301. Please indicate the location of the DV dataset and any SUPPDV datasets for study 205MS201. If you have not submitted data on the occurrence of protocol deviations for study 205MS201, please do so.

5. Please provide the following information:

- a. A comprehensive map linking the USUBJIDs for the same patients included in any feeder and follow-up study, in the SDTM, ADaM, and ISS datasets, in the text of narratives, and in any report for the submitted studies.
- b. Analyses by treatment group of clinically significant abnormalities (outlier analyses) of eosinophil counts for study 205MS301 and the total DAC HYP experience. For each patient with clinically significant eosinophil abnormalities in all studies, provide a brief narrative that includes a possible explanation of the finding and a description of any associated immune mediated adverse events.
- c. Missing outlier analyses of vital signs using specific BP and weight values requested at the pre-BLA meeting:
 - Systolic Blood Pressure: <90 mmHg, >140 mmHg, >160 mmHg
 - Diastolic Blood Pressure: <50 mmHg, >90 mmHg, >100 mmHg
 - Pulse Rate: <60 bpm, >100 bpm
 - Body Weight: 7% or more increase or decrease from baseline
 - Temperature: >38.0 °C, <36.0 °C
 - Respiratory rate: <12 breaths/min, > 20 breaths/min

For instance, the BP analyses are missing in Study 205MS201; weight analyses are missing in individual studies 205MS201 and 205MS301. We also expected there to be analyses of change from baseline and change from pre-dose for vital signs in study 205MS201. We see a listing of actual values for vital signs but no analyses of change from baseline values or change from pre-dose values for this trial.

- d. A table of all patients who underwent antibody testing (antinuclear antibody, DsDNA antibody, specific autoantibodies [e.g., antithyroid antibody, anti-mitochondrial antibody, anti-smooth muscle antibody, etc.] in this application (other than protocol mandated DAC anti-drug and neutralizing antibody testing), the reason for testing (if available), treatment group, date relative to initiation of treatment, and the result of each test. Please also indicate whether these patients were DAC anti-drug or neutralizing antibody positive (or if these antibody tests were not done).
- e. A description of the duration of treatment interruption (mean, median, and range in days, by treatment group) in all patients who interrupted study treatment (other than patients randomized to placebo washout in study 205MS202).

- f. An evaluation of the incidence of allergic and autoimmune reactions for the entire duration of treatment and not just 24 hours after the first dose. Evaluate these reactions for all trials by treatment group. In your analyses, use the lists of preferred terms included in your application with the addition of gastrointestinal immune mediated reactions to all the lists. Perform an additional analysis of allergic and autoimmune reactions in any patient who missed more than two consecutive doses of the study drug and then restarted treatment.
6. We remind you of the request for revised datasets that we sent you on April 30, 2015. We are expecting a response by May 14, 2015.

Biostatistics

Please describe the location in your application of SAS macros setup.sas, var.txt, and any other files that you used to create the derived datasets; otherwise, provide the files and describe the locations of the new files.

Office of Product Quality

1. You provided only one requalification study (b) (4).
In addition, we cannot determine which (b) (4) you used for daclizumab production. We ask you to:
 - a. Identify all (b) (4)
 - b. Describe the daclizumab production loads and explain (b) (4)
 - c. Provide (b) (4) (a): summary reports, acceptance criteria, and (b) (4) data from the three most recent annual requalification studies relevant to daclizumab manufacturing. Identify the requalification loads relevant to daclizumab manufacturing. We expect the summary reports to describe (b) (4)
2. Please provide the description of the procedure for drug product endotoxin testing by the LAL kinetic turbidimetric method.
3. Please provide the document that describes the procedure for drug product sterility testing.
4. The characterization of the charge variant profile includes substantial information about (b) (4) variants but minimal information about (b) (4) variants. Submit additional information on the characterization of (b) (4) charge variants, their potential impact on product performance, and the control strategy.

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](#) website including:

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

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

General

- Remove all page numbers throughout the labeling.

Highlights

- In the Product Title, add a comma after “ZINBRYTA (daclizumab) injection” and before “for subcutaneous use”.
- If a product belongs to an established pharmacologic class, we require the following statement under the Indications and Usage heading: “(Product) is a (name of established pharmacologic class) indicated for (indication)”. Please include the established pharmacologic class.

Table of Contents

- Remove all periods after the numbers for the section and subsection headings.

Full Prescribing Information

- Underline the title of each subheading in a section (for example, “General” under Section 12.3) rather than using italicized or bold font.
- In Section 4, include a description of the observed or anticipated consequence of the contraindicated use.
- In Section 6.1, use clinical terms to describe adverse reactions. For example, use “allergic dermatitis” rather than (b) (4).
- In Section 6.1, remove (b) (4) in Table 1 and 2 and list the adverse reactions in order of highest to lowest frequency.

- Move the immunogenicity information from Section 6.1 to a new Section 6.2 titled “Immunogenicity”.
- Section 7 provides a description of the clinical implications of clinically significant interactions with other drugs. Do not include the details of a clinical or drug interaction study. Instead, you may provide a cross-reference to a clinical study description in another section.
- In Section 7, do not include the results of drug interaction studies that show no interaction unless this information is clinically relevant for the prescriber; for example, if two drugs are commonly used together or if a drug does not have the same interaction as other drugs in the same class.
- In Section 12.3, include information only about specific populations that you have assessed.

We request that you resubmit labeling (in Microsoft Word format) that addresses these issues by June 2, 2015. The resubmitted labeling will be used for further labeling discussions. Use the SRPI checklist to correct any formatting errors to ensure conformance with the format items in regulations and guidances.

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

PROMOTIONAL MATERIAL

You may request advisory comments on proposed introductory advertising and promotional labeling. Please submit, in triplicate, a detailed cover letter requesting advisory comments (list each proposed promotional piece in the cover letter along with the material type and material identification code, if applicable), the proposed promotional materials in draft or mock-up form with annotated references, and the proposed package insert (PI), Medication Guide, patient PI, and Instructions for Use (IFU). Submit consumer-directed, professional-directed, and television advertisement materials separately and send each submission to:

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

Do not submit launch materials until you have received our proposed revisions to the package insert (PI), Medication Guide, patient PI, and IFU, 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 reference the partial waiver granted on December 1, 2014, for the pediatric study requirement for this application for pediatric patients less than 10 years old.

We reference the partial deferral granted on December 1, 2014, for the pediatric study requirement for this application for pediatric patients from 10 to 17 years old.

If you have any questions, please contact Laurie Kelley, PA-C, Regulatory Project Manager, by email laurie.kelley@fda.hhs.gov or by phone at (301) 796-5068.

Sincerely,

{See appended electronic signature page}

Billy Dunn, M.D.
Director
Division of Neurology Products
Office of Drug Evaluation I
Office of New Drugs
Center for Drug Evaluation and Research

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/s/

WILLIAM H Dunn
05/13/2015

Kelley, Laurie

From: Kelley, Laurie
Sent: Wednesday, May 06, 2015 11:04 AM
To: Kuntz, Matthew (matthew.kuntz@abbvie.com)
Cc: Kelley, Laurie
Subject: Daclizumab Information request

Importance: High

Dear Matt,

We have the following request with regards to BLA 761029:

- In Section 2.2.2 of the MRI charter for study 205MS301 it is stated that “(b) (4) will send an MRI eligibility report to sites”. Please indicate whether the data from these reports are included the datasets submitted and, if so, please indicate where the data are located. If the results of these reports were not submitted, please submit a dataset that includes the results of the eligibility report for each subject.
- For Study 205MS201 please indicate whether the central MRI reader played a role in the determination of eligibility of patients for the study. If the central MRI reader did provide an assessment of eligibility please provide a dataset with the results of those determinations for each subject in the trial.

Please provide a response by 7am tomorrow (5/7/15).

Regards,
Laurie

Laurie Kelley, PA-C
Regulatory Project Manager
Food and Drug Administration
Office of Drug Evaluation – Division of Neurology Products
Bldg. 22, Room 4380
10903 New Hampshire Ave.
Silver Spring, Maryland 20993-0002

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/s/

LAURIE A KELLEY
05/06/2015

From: Kelley, Laurie
Sent: Thursday, April 30, 2015 2:04 PM
To: Kuntz, Matthew (matthew.kuntz@abbvie.com)
Cc: Kelley, Laurie
Subject: BLA 761029 Information Request

Matt,

We have the following request with regards to the datasets for individual studies and for the Integrated Summary of Safety submitted to BLA 761029.

1. Information on treatment period and outcome is important when conducting AE analyses.
 - a. Please include an EPOCH variable in the AE, SUPPAE and LB domains. Within the treatment period, please distinguish between the period up to the last dose of DAC HYP, the 180-day follow up period and the period beyond 180 days post last dose. Please include detailed explanations for missing EPOCH values in an updated Study Data Reviewers Guide (SDRG) and update the define to reflect the changes.
 - b. Please fill out the null values for the Outcome variable in the adverse event datasets for the variable AEOUT. Please provide a "RECOVERED/RESOLVED" value for AEOUT where the value is available; otherwise specify if the data is Missing. If an adverse event resulted in the death of a subject, please provide a "FATAL" value for AEOUT.
 - c. Please re-code your datasets using controlled CDISC terminology in the LB domain for the following labs:-

Liver Function

LBCAT like '%CHEMISTRY%' AND actual value and Baseline value
LBTESTCD ='ALT' Alanine Aminotransferase
LBTESTCD ='AST' Aspartate Aminotransferase
LBTESTCD ='BILI' Total Bilirubin
LBTESTCD ='ALP' Alkaline Phosphatase

Renal Function

LBCAT like '%CHEMISTRY%' or like '%ELECTROLYTE%' AND actual value and Baseline value
LBTESTCD ='CREAT' Serum Creatinine
LBTESTCD ='CRCLREST' Creatinine Clearance Estimation
LBTESTCD ='BUN' Blood Urea Nitrogen
LBTESTCD ='K' Potassium

Electrolytes

LBCAT like '%CHEMISTRY%' or like '%ELECTROLYTE%') AND actual value and Baseline value

LBTESTCD ='HCO3' Bicarbonate
LBTESTCD ='CA' Calcium
LBTESTCD ='CAION' Calcium Ion
LBTESTCD ='CL' Chloride
LBTESTCD ='CO2' Carbon Dioxide
LBTESTCD ='FE' Iron
LBTESTCD ='K' Potassium
LBTESTCD ='POT' Potassium
LBTESTCD ='MG' Magnesium
LBTESTCD ='PHOS' Phosphorus
LBTESTCD ='SODIUM' Sodium

LIPIDS

LBCAT like '%CHEMISTRY%' or like '%LIPIDS%' AND actual value and Baseline value

LBTESTCD ='CHOL' Cholesterol
LBTESTCD ='HDL' High Density Lipoprotein
LBTESTCD ='LDL' Low Density Lipoprotein
LBTESTCD ='TRIG' Triglycerides

Hematology

LBCAT like '%HEMATOLOGY%' AND actual value and Baseline value

LBTESTCD ='BASO' Basophils
LBTESTCD ='EOS' Eosinophils
LBTESTCD ='HGB' Hemaglobin
LBTESTCD ='HCT' Hematocrit
LBTESTCD ='LYM' Lymphocytes
LBTESTCD ='PLAT' Platelets
LBTESTCD ='RBC' Erythrocytes
LBTESTCD ='WBC' Leukocytes

Some of these requests are part of the recently issued Technical Conformance Guide of March 2015 and they would greatly help expedite our review.

(<http://www.fda.gov/downloads/ForIndustry/DataStandards/StudyDataStandards/UCM384744.pdf>). The dictionary for the controlled terminology can be found in the following link: <http://evs.nci.nih.gov/ftp1/CDISC/SDTM/SDTM%20Terminology.xls>

Please provide this information by May 14, 2015.

Regards,

Laurie

Laurie Kelley, PA-C
Regulatory Project Manager
Food and Drug Administration
Office of Drug Evaluation – Division of Neurology Products
Bldg. 22, Room 4380
10903 New Hampshire Ave.
Silver Spring, Maryland 20993-0002

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/s/

LAURIE A KELLEY
04/30/2015

Kelley, Laurie

From: Kelley, Laurie
Sent: Friday, April 17, 2015 3:24 PM
To: Kuntz, Matthew
Cc: Kelley, Laurie
Subject: RE: New AbbVie Contact for IND 12120, BLA 761029 and IND 123455

Matt

Please refer to BLA 761029 submitted February 27, 2015

Please confirm that you have submitted and provide the location for the following items requested at the pre-BLA meeting for Daclizumab DYP:

1. Narratives, CRFs and patient profiles for:
 - a. All discontinuations for the following reasons:
 - Lost to follow-up
 - Other
 - Physician decision
 - Patient decision (subject choice, subject withdrew consent)
 - b. All non-serious adverse events of MS relapse for cases that had not been included in the efficacy analyses
2. Autopsy reports for all patients who died.
3. Tables with the reference ranges for normal laboratory values used in data analyses for each study.

Please respond by 5:00 PM EST today

Thank you
Laurie

Laurie Kelley, PA-C
Regulatory Project Manager
Food and Drug Administration
Office of Drug Evaluation – Division of Neurology Products
Bldg. 22, Room 4380
10903 New Hampshire Ave.
Silver Spring, Maryland 20993-0002

Tel: 301-796-5068

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/s/

LAURIE A KELLEY
04/17/2015

Sun, Su-Lin

From: Sun, Su-Lin
Sent: Wednesday, April 08, 2015 9:02 AM
To: 'Patel, Mahlaqa'
Cc: Kelley, Laurie
Subject: RE: BLA 761029 response to FDA's IR confirmation and change of PM contact

Dear Mahlaqa:

Yes, thank you, we receive your official submission this morning. I already forward it to our review team.

Also I would like to inform you that this BLA project will be managed by Ms. Laurie Kelley from this point on. Laurie told me that you two worked together with other applications previously, so you already know each other. :-)

It has been a great pleasure to work with you for the past few years.

Thanks,
Sulin

-----Original Message-----

From: Patel, Mahlaqa [<mailto:mahlaqa.patel@Abbvie.com>]
Sent: Wednesday, April 08, 2015 8:34 AM
To: Sun, Su-Lin
Subject: Re: BLA 761029 FDA's IR

Dear Sulin,
The response was transmitted through the gateway. Please can you confirm receipt?
Regards,
Mahlaqa

Sent from my iPhone

> On Apr 7, 2015, at 8:27 AM, Sun, Su-Lin <Su-Lin.Sun@fda.hhs.gov> wrote:

>

> Dear Mahlaqa:

>

> Below are information request from our review team:

>

> Please indicate the locations in the submission of the following PK analysis datasets (RAW data and/or PK analysis) for each individual study and the bioanalytical reports for in-study assay performance:

>

- > · Study 205MS201 -- both concentration-time data and PK parameters in SAS transport file (.xpt)
- > · Study 205MS202 -- both concentration-time data and PK parameters in SAS transport file (.xpt)
- > · Study 205MS203 -- PK parameters in SAS transport file (.xpt)
- > · Study 205MS301 -- both concentration-time data and PK parameters in SAS transport file (.xpt)
- > · Study 205MS302 -- PK datasets for the interim week 44 could not be opened. Since hyperlinks are not available, please clarify whether those datasets in Module 5 under Orphaned Files are the pertinent datasets for this study.

- > · The output listings for all models/analyses in Report CPP-14-008-BIIB019. Submit these files as ASCII text files with *.txt extension
- >
- > · The bioanalytical reports for the in-study assay performance for Studies DAC-1015 (listed in Reference #7-13), DAC-1012, 205MS301, 205MS302 Interim (clarify whether they are the same as those for 205MS302 Interim Week-44), and 205MS303 (when they become available). For clarity, please provide a tabular listing of all the in-study bioanalytical reports.
- >
- > Please respond before 8:30 am tomorrow.
- >
- > Thanks
- > Sulin

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/s/

SU-LIN SUN
04/08/2015

Sun, Su-Lin

From: Sun, Su-Lin
Sent: Monday, April 06, 2015 1:28 PM
To: 'Patel, Mahlaqa'
Subject: RE: 761029_Information request

OK, thanks ☺

From: Patel, Mahlaqa [mailto:mahlaqa.patel@Abbvie.com]
Sent: Monday, April 06, 2015 1:18 PM
To: Sun, Su-Lin
Subject: RE: 761029_Information request

Dear Sulin,

Please find our responses to the Information Request below. We sincerely apologize for the delay. We are preparing this response for formal submission as well which will contain hyperlinks to the appropriate BLA sections referenced in the response.

Please do not hesitate to let me know if you need any additional information or if you have additional requests.

Kind Regards,
Mahlaqa

FDA Question #1

Provide the location of the information from your completed clinical trials regarding any tracking or analysis of device malfunctions, device failures, and adverse events related to the device.

Sponsor Response

In clinical studies, DAC HYP was supplied as a vial or a prefilled syringe (PFS) for subcutaneous (SC) delivery. The PFS is the proposed commercial delivery device.

(b) (4)

Tracking or Analysis of Adverse Events related to the PFS:

Completed clinical trial data are provided in the BLA for Studies 205MS201, 205MS202, and 205MS301. In these studies, DAC HYP or Placebo was supplied as vials. No device was used to deliver DAC HYP via subcutaneous (SC) injections.

In the 3 ongoing studies (205MS203, 205MS302, 205MS303) during which PFS were used to deliver DAC HYP SC, no adverse events considered as “related to the device or device use” by the investigator were reported.

Tracking or Analysis of Malfunction or Failures related to the PFS:

There has only been one complaint during the clinical program which was potentially related to the use of the PFS combination product. Information regarding pre-filled syringe device malfunctions or failures from clinical trials is provided in [Section 3.2.P.2.4; Container Closure System](#), subsection 4.3 (Pre-filled Syringe Combination Product Development).

There were two reported events for unsuccessful administration with the autoinjector in Study 203 (Appendix 16.2.6, [Table 4](#), CSR 205MS203). No adverse events were associated with these administrations.

FDA Question #2

Provide the location of the biocompatibility information and the method information.

Sponsor Response

As the pre-filled syringe (PFS) container closure system comes fully sterilized and ready to use at the drug product manufacturing site, biocompatibility and sterilization/validation method information for the PFS is located in component manufacturers’ DMFs (b) (4), which are referenced in [Section 3.2.P.7; Container Closure System](#). The letters of authorizations for the DMFs are provided in [Module 1.4.1](#). A summary of the biocompatibility evaluation performed by the PFS manufacturer (b) (4) is also provided in [Section 3.2.P.2.4; Container Closure System](#), subsection 4.3 (Pre-filled Syringe Combination Product Development). Additionally, the compatibility of the DAC HYP formulation with the container closure system is demonstrated through long-term stability studies described in [Section 3.2.P.8.1; Stability Summary and Conclusions](#).

Sterilization/validation information for all other equipment used in the drug product manufacturing process (i.e., (b) (4) etc.) is located in [Section 3.2.P.3.5; Process Validation and/or Evaluation](#) per the FDA Information Request dated March 4, 2015.

MAHLAQA PATEL
Director, Regulatory Affairs
Area & Affiliate; US & Canada



AbbVie, Inc.
1 Waukegan Road
North Chicago, IL 60064
OFFICE + 1 847-937-2724
FAX + 1 847-938-8476
CELL + (b) (6)
EMAIL mahlaqa.patel@abbvie.com

abbvie.com

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From: Toure, Hamet [<mailto:Hamet.Toure@fda.hhs.gov>]
Sent: Friday, April 03, 2015 3:15 PM
To: Patel, Mahlaqa
Subject: 761029_Information request

Dear Ms. Patel,

We refer to BLA 761029. We have the following requests:

1. Provide the location of the information from your completed clinical trials regarding any tracking or analysis of device malfunctions, device failures, and adverse events related to the device.
2. Provide the location of the biocompatibility information and the sterilization/validation method information.

Please respond today by email.

Best regards,

Hamet Touré, PharmD MPH
CDR, United States Public Health Service
Regulatory Project Manager
Food and Drug Administration
Office of Drug Evaluation – Division of Neurology Products
Bldg. 22, Room 4202
10903 New Hampshire Ave
Silver Spring, MD 20993
Office: 301-796-7534
Fax: 301-796-9842
hamet.toure@fda.hhs.gov

Sun, Su-Lin

From: Sun, Su-Lin
Sent: Monday, April 06, 2015 11:21 AM
To: 'Patel, Mahlaqa'
Subject: RE: daclizumab BLA 761029 - Information Request



From: Patel, Mahlaqa [mailto:mahlaqa.patel@Abbvie.com]
Sent: Monday, April 06, 2015 11:20 AM
To: Sun, Su-Lin
Subject: RE: daclizumab BLA 761029 - Information Request

Thank you!

MAHLAQA PATEL
Director, Regulatory Affairs
Area & Affiliate; US & Canada

abbvie

AbbVie, Inc.

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From: Sun, Su-Lin [mailto:Su-Lin.Sun@fda.hhs.gov]
Sent: Monday, April 06, 2015 10:12 AM
To: Patel, Mahlaqa; Shiber, Andrew J
Subject: RE: daclizumab BLA 761029 - Information Request

Andrew:

I will forward Mahlaqa's email to OBP team 😊

From: Patel, Mahlaqa [mailto:mahlaqa.patel@Abbvie.com]
Sent: Monday, April 06, 2015 11:03 AM
To: Shiber, Andrew J
Cc: Sun, Su-Lin
Subject: FW: daclizumab BLA 761029 - Information Request

Dear Andrew,

I am forwarding my email below to you, based on Ms. Brown's out of office message. Please do not hesitate to let me know if you have any additional questions or need more information.

Kind Regards,
Mahlaqa

MAHLAQA PATEL
Director, Regulatory Affairs
Area & Affiliate; US & Canada

abbvie

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EMAIL mahlaqa.patel@abbvie.com

abbvie.com

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From: Patel, Mahlaqa
Sent: Monday, April 06, 2015 9:57 AM
To: 'Brown, Anita'
Cc: Sun, Su-Lin (Su-Lin.Sun@fda.hhs.gov)
Subject: RE: daclizumab BLA 761029 - Information Request

Dear Anita,

In reference to your Information Request below, we would like to request clarification for Request #2:

FDA Request #2:

From Module 1.1.2., FDA Form 356h Attachment, please correct the FEI number for the following facility:

(b) (4)



Function: DP Visual Inspection

FEI: (b) (4)

FEI should be (b) (4)

AbbVie/Biogen Response:

We reviewed the 356h Attachment and followed up with the site. The FEI number (b) (4) for the (b) (4) facility located in (b) (4) is listed correctly in the Form 356h Attachment according to the FDA Drug Establishments Current Registration Site. The requested change in FEI number to (b) (4) is actually the identifier for the (b) (4) facility located in (b) (4). Can the Agency clarify which FEI number is incorrect, if any, or if there are errors introduced through the Drug Establishments Registration site?

Please do not hesitate to let me know if you need more information or have follow up questions.

Kind Regards,
Mahlaqa

MAHLAQA PATEL
Director, Regulatory Affairs
Area & Affiliate; US & Canada

abbvie

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From: Brown, Anita [<mailto:Anita.Brown@fda.hhs.gov>]
Sent: Wednesday, April 01, 2015 1:20 PM
To: Patel, Mahlaqa
Subject: daclizumab BLA 761029 - Information Request

Good Afternoon Mahlaqa,

In reference to your February 27, 2015 submission for daclizumab (BLA 761029), please find attached a CMC Information Request. A written response is requested by April 9, 2015. Please forward me a PDF copy of the official submission.

Kindly acknowledge receipt of this request.

Regards,
Anita

Anita N. Brown
Regulatory Business Process Manager

Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research
10309 New Hampshire Ave.
WO-Bldg 71 Room 2029
Silver Spring, Maryland 20993-0002
Anita.Brown@fda.hhs.gov
301-796-2066

Sun, Su-Lin

From: Sun, Su-Lin
Sent: Friday, March 27, 2015 3:10 PM
To: 'Patel, Mahlaqa'
Cc: Toure, Hamet
Subject: RE: FYI



From: Patel, Mahlaqa [<mailto:mahlaqa.patel@Abbvie.com>]
Sent: Friday, March 27, 2015 3:05 PM
To: Sun, Su-Lin
Cc: Toure, Hamet
Subject: Re: FYI

Thank you. I sincerely appreciate the follow up.
Kind Regards,
Mahlaqa

Sent from my iPhone

On Mar 27, 2015, at 1:54 PM, Sun, Su-Lin <Su-Lin.Sun@fda.hhs.gov> wrote:

Dear Mahlaqa:

Sorry that I missed your phone call. I did received your voice mail. Our review is informed that you are waiting for their comments. As soon as I receive their comments, Hamet or I will follow up with you. 😊

Thanks,
Sulin

Sun, Su-Lin

From: Sun, Su-Lin
Sent: Thursday, March 26, 2015 5:21 PM
To: 'Patel, Mahlaqa'
Subject: RE: BLA 761029 Daclizumab-FDA's information request

Thanks ☺

From: Patel, Mahlaqa [mailto:mahlaqa.patel@Abbvie.com]
Sent: Thursday, March 26, 2015 5:17 PM
To: Sun, Su-Lin
Cc: Toure, Hamet
Subject: Re: BLA 761029 Daclizumab-FDA's information request

Thank you Sulin! And have a great holiday :)

On Mar 26, 2015, at 4:11 PM, Sun, Su-Lin <Su-Lin.Sun@fda.hhs.gov> wrote:

Let me double check with them, as soon as I receive their comment, I will follow up with you. ☺

By the way, I will be on annual leave starting 3/29 to 4/5/15 without email access. Hamet has kindly agree to cover me for this application during that week. So any correspondence please send to him and cc me.

Thanks,
Sulin

From: Patel, Mahlaqa [mailto:mahlaqa.patel@Abbvie.com]
Sent: Thursday, March 26, 2015 5:05 PM
To: Sun, Su-Lin
Subject: RE: BLA 761029 Daclizumab-FDA's information request

Hi Sulin,

Just checking to see if you've had a chance to speak with your review team and if they find our response acceptable and/or do they have any additional questions?

Kind Regards,
Mahlaqa

MAHLAQA PATEL
Director, Regulatory Affairs
Area & Affiliate; US & Canada

<image001.gif>

AbbVie, Inc.
1 Waukegan Road
North Chicago, IL 60064

OFFICE + 1 847-937-2724
FAX + 1 847-938-8476
CELL + [REDACTED] (b) (6)
EMAIL mahlaqa.patel@abbvie.com

abbvie.com

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From: Sun, Su-Lin [<mailto:Su-Lin.Sun@fda.hhs.gov>]
Sent: Wednesday, March 25, 2015 4:01 PM
To: Patel, Mahlaqa
Subject: RE: BLA 761029 Daclizumab-FDA's information request

Let me check with my review team first, and I will follow up with you as soon as I receive their comment.

Thanks,
Sulin

From: Patel, Mahlaqa [<mailto:mahlaqa.patel@Abbvie.com>]
Sent: Wednesday, March 25, 2015 4:53 PM
To: Sun, Su-Lin
Subject: RE: BLA 761029 Daclizumab-FDA's information request

Dear Sulin,

Regarding the question from the review team below, here is the AbbVie/Biogen response. Please let me know if you would like to discuss further or have any follow up questions for us.

As discussed at the pre-BLA meeting on October 8, 2014, relevant information from patient profiles and other data sources (where available) is included within the submitted patient safety narratives to provide a synthesis of the available clinical data and an informed discussion of the case.

As requested, the Sponsor will provide patient profiles for all subjects who met the criteria for a safety narrative during Studies 205MS201, 205MS202, 205MS203, 205MS301, 205MS302, and 205MS303, and that are included in the BLA. The clinical reviewer will be able to access a subject's patient profile using a hyperlink from the index of subject safety narratives. Each subject's patient profile will include the subject's available data from the study clinical database, including the following:

- Age, gender.
- Dates of randomization, and starting therapy. Date of screening is not captured in the clinical database and therefore is not included.
- Duration of study participation, whether the patient completed or did not complete the study, dates for starting and stopping treatment, and reason for withdrawal.
- Adverse events (reported term, preferred term, start and stop date [with relative study day from initiation of treatment within each study protocol]), seriousness, outcome, whether it resolved or not, and action taken with study drug. For serious hypersensitivity

and injection reactions that occur within 24 hours of dosing, if applicable, the time in minutes or hours after dosing is included in the narrative.

- Prior medications and concomitant medications with dates of start and end relative to study initiation.
- Vital signs and laboratories, sorted by date. Abnormal laboratory values are flagged within the subject profiles. Reference ranges for lab values and criteria for abnormal vital signs are provided in the individual Clinical Study Reports.
- Antidrug and neutralizing antibody test results with time after first dose and study visit.

This information will be supplied to the Agency by Thursday 02 April 2015.

With respect to relevant results obtained outside of clinical trial visits, including those obtained during hospitalization or emergency room visits, those results are not readily accessible by the Sponsor and therefore are not part of the patient profiles. For example, although sites are queried for copies of hospital discharge reports, biopsy reports and other source documents, the information is often not available and not routinely provided to Sponsor. If any pertinent information is provided, a description of the information is included in the narrative. However, the Sponsor would try to obtain this information on a case-by-case basis.

Kind Regards,
Mahlaqa

MAHLAQA PATEL
Director, Regulatory Affairs
Area & Affiliate; US & Canada

<image001.gif>

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1 Wakuegan Road
North Chicago, IL 60064
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EMAIL mahlaqa.patel@abbvie.com

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From: Sun, Su-Lin [<mailto:Su-Lin.Sun@fda.hhs.gov>]
Sent: Tuesday, March 24, 2015 3:21 PM
To: Patel, Mahlaqa
Subject: BLA 761029 Daclizumab-FDA's information request
Importance: High

Dear Mahlaqa:

Below are our review team's information request for your BLA 761029 Daclizumab:

Please refer to the pre-BLA meeting minutes under Q5. We have taken an initial look at some of the patient narratives and found that some of the information we requested is missing and there is no link to a patient profile. We were unable to locate any patient profiles in the database. Could you please direct the clinical reviewer to the location of the patient profiles for all patients for which a narrative has been submitted. Please respond by COB 3/25/15.

Thanks,
Sulin

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/s/

SU-LIN SUN
04/06/2015

Toure, Hamet

From: Toure, Hamet
Sent: Friday, April 03, 2015 4:15 PM
To: Patel, Mahlaqa
Subject: 761029_Information request

Dear Ms. Patel,

We refer to BLA 761029. We have the following requests:

1. Provide the location of the information from your completed clinical trials regarding any tracking or analysis of device malfunctions, device failures, and adverse events related to the device.
2. Provide the location of the biocompatibility information and the sterilization/validation method information.

Please respond today by email.

Best regards,

Hamet Touré, PharmD MPH
CDR, United States Public Health Service

Regulatory Project Manager
Food and Drug Administration
Office of Drug Evaluation – Division of Neurology Products
Bldg. 22, Room 4202
10903 New Hampshire Ave
Silver Spring, MD 20993
Office: 301-796-7534
Fax: 301-796-9842
hamet.toure@fda.hhs.gov

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/s/

HAMET M TOURE
04/04/2015

Toure, Hamet

From: Toure, Hamet
Sent: Friday, April 03, 2015 11:54 AM
To: Patel, Mahlaqa
Cc: Sun, Su-Lin
Subject: 761029_Information request

Dear Ms. Patel,

We refer to BLA 761029. We are unable to locate information regarding the functional performance of the device constituent of the combination product (testing of the glass syringe with biologic already filled into it) for our engineering device review. Please notify us today where this information is in the submission.

Best regards,

Hamet Touré, PharmD MPH
CDR, United States Public Health Service

Regulatory Project Manager
Food and Drug Administration
Office of Drug Evaluation – Division of Neurology Products
Bldg. 22, Room 4202
10903 New Hampshire Ave
Silver Spring, MD 20993
Office: 301-796-7534
Fax: 301-796-9842
hamet.toure@fda.hhs.gov

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/s/

HAMET M TOURE
04/03/2015



BLA 761029

INFORMATION REQUEST

AbbVie, Inc.
Attention: Mahlaqa Patel
Director, US Regulatory Affairs
1 North Waukegan Road
Dept PA77/Bldg AP30-1
North Chicago, IL 60064

Dear Ms. Patel:

Please refer to your Biologics License Application (BLA) dated February 27, 2015, received February 27, 2015, submitted under section 351(a) of the Public Health Service Act for ZINBRYTA™ (daclizumab High Yield Process).

We are reviewing the CMC section of your submission and have the following comments and information requests. We request a prompt written response by April 9, 2015 in order to continue our evaluation of your BLA.

- 1). For the facilities identified below, provide a summary of testing to be performed at each location. Additionally, clarify if they will use identical validated methods at each location specified.

1. Biogen Indec, Inc

[Redacted] (b) (4)

FEI [Redacted] (b) (4)

Function: Drug Product QC Testing

2. Biogen Idec

[Redacted] (b) (4)

Function: Drug Product QC Testing

FEI [Redacted] (b) (4)

3. [Redacted] (b) (4)

(b) (4)
Function: Drug Product (b) (4) Testing
Drug Product QC Testing
FEI: (b) (4)

4. (b) (4)
Function: Drug Product (b) (4) Testing
Drug Product QC Testing
FEI: (b) (4)

5. (b) (4)
Function: Drug Product (b) (4) Testing
Drug Product QC Testing
FEI: (b) (4)

1. Biogen Indec, Inc
(b) (4)
FEI (b) (4)
Function: Drug Substance (b) (4) Testing; Drug Substance QC Testing

2. Biogen Indec, Inc.
14 Cambridge
Cambridge, MA
Function: Drug Substance (b) (4) Testing
FEI: 1220951

3. Biogen Idec (b) (4)
(b) (4)
Function: Drug Substance QC Testing
FEI: (b) (4)

2). From Module 1.1.2., FDA Form 356h Attachment, please correct the FEI number for the following facility:

(b) (4)

(b) (4)
Function: DP Visual Inspection
FEI: (b) (4)
FEI should be (b) (4)

If you have any questions, please contact me at 301-796-2066 or Anita.Brown@fda.hhs.gov.

Sincerely,

Joel T. Welch - S

Digitally signed by Joel T. Welch - S
DN: c=US, o=U.S. Government,
ou=HHS, ou=FDA, ou=People,
cn=Joel T. Welch - S,
0.9.2342.19200300.100.1.1=200044
3745
Date: 2015.04.01 12:49:36 -0400

Joel Welch, Ph.D.
CMC/Product Quality Team Leader
Division of Biotechnology Review and Research II
Office of Biotechnology Products
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research

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/s/

ANITA N BROWN
04/01/2015

Sun, Su-Lin

From: Sun, Su-Lin
Sent: Friday, March 27, 2015 3:10 PM
To: 'Patel, Mahlaqa'
Cc: Toure, Hamet
Subject: RE: FYI



From: Patel, Mahlaqa [<mailto:mahlaqa.patel@Abbvie.com>]
Sent: Friday, March 27, 2015 3:05 PM
To: Sun, Su-Lin
Cc: Toure, Hamet
Subject: Re: FYI

Thank you. I sincerely appreciate the follow up.
Kind Regards,
Mahlaqa

Sent from my iPhone

On Mar 27, 2015, at 1:54 PM, Sun, Su-Lin <Su-Lin.Sun@fda.hhs.gov> wrote:

Dear Mahlaqa:

Sorry that I missed your phone call. I did received your voice mail. Our review is informed that you are waiting for their comments. As soon as I receive their comments, Hamet or I will follow up with you. ☺

Thanks,
Sulin

Sun, Su-Lin

From: Sun, Su-Lin
Sent: Monday, April 06, 2015 11:21 AM
To: 'Patel, Mahlaqa'
Subject: RE: daclizumab BLA 761029 - Information Request



From: Patel, Mahlaqa [mailto:mahlaqa.patel@Abbvie.com]
Sent: Monday, April 06, 2015 11:20 AM
To: Sun, Su-Lin
Subject: RE: daclizumab BLA 761029 - Information Request

Thank you!

MAHLAQA PATEL
Director, Regulatory Affairs
Area & Affiliate; US & Canada

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From: Sun, Su-Lin [mailto:Su-Lin.Sun@fda.hhs.gov]
Sent: Monday, April 06, 2015 10:12 AM
To: Patel, Mahlaqa; Shiber, Andrew J
Subject: RE: daclizumab BLA 761029 - Information Request

Andrew:

I will forward Mahlaqa's email to OBP team ☺

From: Patel, Mahlaqa [mailto:mahlaqa.patel@Abbvie.com]
Sent: Monday, April 06, 2015 11:03 AM
To: Shiber, Andrew J
Cc: Sun, Su-Lin
Subject: FW: daclizumab BLA 761029 - Information Request

Dear Andrew,

I am forwarding my email below to you, based on Ms. Brown's out of office message. Please do not hesitate to let me know if you have any additional questions or need more information.

Kind Regards,
Mahlaqa

MAHLAQA PATEL
Director, Regulatory Affairs
Area & Affiliate; US & Canada

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From: Patel, Mahlaqa
Sent: Monday, April 06, 2015 9:57 AM
To: 'Brown, Anita'
Cc: Sun, Su-Lin (Su-Lin.Sun@fda.hhs.gov)
Subject: RE: daclizumab BLA 761029 - Information Request

Dear Anita,

In reference to your Information Request below, we would like to request clarification for Request #2:

FDA Request #2:

From Module 1.1.2., FDA Form 356h Attachment, please correct the FEI number for the following facility:

(b) (4)

Function: DP Visual Inspection

FEI: (b) (4)

FEI should be (b) (4)

AbbVie/Biogen Response:

We reviewed the 356h Attachment and followed up with the site. The FEI number (b)(4) for the (b)(4) facility located in (b)(4) is listed correctly in the Form 356h Attachment according to the FDA Drug Establishments Current Registration Site. The requested change in FEI number to (b)(4) is actually the identifier for the (b)(4) facility located in (b)(4). Can the Agency clarify which FEI number is incorrect, if any, or if there are errors introduced through the Drug Establishments Registration site?

Please do not hesitate to let me know if you need more information or have follow up questions.

Kind Regards,
Mahlaqa

MAHLAQA PATEL
Director, Regulatory Affairs
Area & Affiliate; US & Canada

abbvie

AbbVie, Inc.
1 Waukegan Road
North Chicago, IL 60064
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EMAIL mahlaqa.patel@abbvie.com

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From: Brown, Anita [<mailto:Anita.Brown@fda.hhs.gov>]
Sent: Wednesday, April 01, 2015 1:20 PM
To: Patel, Mahlaqa
Subject: daclizumab BLA 761029 - Information Request

Good Afternoon Mahlaqa,

In reference to your February 27, 2015 submission for daclizumab (BLA 761029), please find attached a CMC Information Request. A written response is requested by April 9, 2015. Please forward me a PDF copy of the official submission.

Kindly acknowledge receipt of this request.

Regards,
Anita

Anita N. Brown
Regulatory Business Process Manager

Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research
10309 New Hampshire Ave.
WO-Bldg 71 Room 2029
Silver Spring, Maryland 20993-0002
Anita.Brown@fda.hhs.gov
301-796-2066

Sun, Su-Lin

From: Sun, Su-Lin
Sent: Thursday, March 26, 2015 5:21 PM
To: 'Patel, Mahlaqa'
Subject: RE: BLA 761029 Daclizumab-FDA's information request

Thanks ☺

From: Patel, Mahlaqa [mailto:mahlaqa.patel@Abbvie.com]
Sent: Thursday, March 26, 2015 5:17 PM
To: Sun, Su-Lin
Cc: Toure, Hamet
Subject: Re: BLA 761029 Daclizumab-FDA's information request

Thank you Sulin! And have a great holiday :)

On Mar 26, 2015, at 4:11 PM, Sun, Su-Lin <Su-Lin.Sun@fda.hhs.gov> wrote:

Let me double check with them, as soon as I receive their comment, I will follow up with you. ☺

By the way, I will be on annual leave starting 3/29 to 4/5/15 without email access. Hamet has kindly agree to cover me for this application during that week. So any correspondence please send to him and cc me.

Thanks,
Sulin

From: Patel, Mahlaqa [mailto:mahlaqa.patel@Abbvie.com]
Sent: Thursday, March 26, 2015 5:05 PM
To: Sun, Su-Lin
Subject: RE: BLA 761029 Daclizumab-FDA's information request

Hi Sulin,

Just checking to see if you've had a chance to speak with your review team and if they find our response acceptable and/or do they have any additional questions?

Kind Regards,
Mahlaqa

MAHLAQA PATEL
Director, Regulatory Affairs
Area & Affiliate; US & Canada

<image001.gif>

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North Chicago, IL 60064

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From: Sun, Su-Lin [<mailto:Su-Lin.Sun@fda.hhs.gov>]
Sent: Wednesday, March 25, 2015 4:01 PM
To: Patel, Mahlaqa
Subject: RE: BLA 761029 Daclizumab-FDA's information request

Let me check with my review team first, and I will follow up with you as soon as I receive their comment.

Thanks,
Sulin

From: Patel, Mahlaqa [<mailto:mahlaqa.patel@Abbvie.com>]
Sent: Wednesday, March 25, 2015 4:53 PM
To: Sun, Su-Lin
Subject: RE: BLA 761029 Daclizumab-FDA's information request

Dear Sulin,

Regarding the question from the review team below, here is the AbbVie/Biogen response. Please let me know if you would like to discuss further or have any follow up questions for us.

As discussed at the pre-BLA meeting on October 8, 2014, relevant information from patient profiles and other data sources (where available) is included within the submitted patient safety narratives to provide a synthesis of the available clinical data and an informed discussion of the case.

As requested, the Sponsor will provide patient profiles for all subjects who met the criteria for a safety narrative during Studies 205MS201, 205MS202, 205MS203, 205MS301, 205MS302, and 205MS303, and that are included in the BLA. The clinical reviewer will be able to access a subject's patient profile using a hyperlink from the index of subject safety narratives. Each subject's patient profile will include the subject's available data from the study clinical database, including the following:

- Age, gender.
- Dates of randomization, and starting therapy. Date of screening is not captured in the clinical database and therefore is not included.
- Duration of study participation, whether the patient completed or did not complete the study, dates for starting and stopping treatment, and reason for withdrawal.
- Adverse events (reported term, preferred term, start and stop date [with relative study day from initiation of treatment within each study protocol]), seriousness, outcome, whether it resolved or not, and action taken with study drug. For serious hypersensitivity

and injection reactions that occur within 24 hours of dosing, if applicable, the time in minutes or hours after dosing is included in the narrative.

- Prior medications and concomitant medications with dates of start and end relative to study initiation.
- Vital signs and laboratories, sorted by date. Abnormal laboratory values are flagged within the subject profiles. Reference ranges for lab values and criteria for abnormal vital signs are provided in the individual Clinical Study Reports.
- Antidrug and neutralizing antibody test results with time after first dose and study visit.

This information will be supplied to the Agency by Thursday 02 April 2015.

With respect to relevant results obtained outside of clinical trial visits, including those obtained during hospitalization or emergency room visits, those results are not readily accessible by the Sponsor and therefore are not part of the patient profiles. For example, although sites are queried for copies of hospital discharge reports, biopsy reports and other source documents, the information is often not available and not routinely provided to Sponsor. If any pertinent information is provided, a description of the information is included in the narrative. However, the Sponsor would try to obtain this information on a case-by-case basis.

Kind Regards,
Mahlaqa

MAHLAQA PATEL
Director, Regulatory Affairs
Area & Affiliate; US & Canada

<image001.gif>

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From: Sun, Su-Lin [<mailto:Su-Lin.Sun@fda.hhs.gov>]
Sent: Tuesday, March 24, 2015 3:21 PM
To: Patel, Mahlaqa
Subject: BLA 761029 Daclizumab-FDA's information request
Importance: High

Dear Mahlaqa:

Below are our review team's information request for your BLA 761029 Daclizumab:

Please refer to the pre-BLA meeting minutes under Q5. We have taken an initial look at some of the patient narratives and found that some of the information we requested is missing and there is no link to a patient profile. We were unable to locate any patient profiles in the database. Could you please direct the clinical reviewer to the location of the patient profiles for all patients for which a narrative has been submitted. Please respond by COB 3/25/15.

Thanks,
Sulin

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/s/

SU-LIN SUN
04/06/2015

Sun, Su-Lin

From: Sun, Su-Lin
Sent: Tuesday, March 10, 2015 12:01 PM
To: 'Patel, Mahlaqa'
Subject: RE: FDA's IR

: -)

-----Original Message-----

From: Patel, Mahlaqa [<mailto:mahlaqa.patel@Abbvie.com>]
Sent: Tuesday, March 10, 2015 11:53 AM
To: Sun, Su-Lin
Subject: Re: FDA's IR

Thank you.

Sent from my iPhone

> On Mar 10, 2015, at 10:37 AM, "Sun, Su-Lin" <Su-Lin.Sun@fda.hhs.gov> wrote:

>
> Per our review team they are looking for a document that simply describes where the datasets are located within the eCTD.

>
> Thanks,

> Sulin

>
> -----Original Message-----

> From: Patel, Mahlaqa [<mailto:mahlaqa.patel@Abbvie.com>]
> Sent: Tuesday, March 10, 2015 11:06 AM
> To: Sun, Su-Lin
> Subject: RE: FDA's IR

>
> Dear Sulin,

>
> Would it be possible for you to clarify with the reviewers that they are looking for a document that simply describes where the datasets are located within the eCTD: i.e. instructions for location, and NOT anything additional as seen in a typical "reviewer guide" such as an explanation for how the data were derived?

>
> Best Regards,

> Mahlaqa

>

>
> MAHLAQA PATEL
> Director, Regulatory Affairs
> Area & Affiliate; US & Canada

>

>

> AbbVie, Inc.
> 1 Waukegan Road
> North Chicago, IL 60064
> OFFICE + 1 847-937-2724
> FAX + 1 847-938-8476
> CELL + [REDACTED] (b) (6)
> EMAIL mahlaqa.patel@abbvie.com

>
> abbvie.com

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> notify the sender immediately by telephone or by return e-mail and delete it from his or her computer.

>

>
> -----Original Message-----

> From: Sun, Su-Lin [<mailto:Su-Lin.Sun@fda.hhs.gov>]

> Sent: Tuesday, March 10, 2015 8:04 AM

> To: Patel, Mahlaqa

> Subject: FDA's IR

>

> Dear Mahlaqa:

> Here is the information request from our review team for your BLA 761029:

>

> Please provide a reviewer guide to the location of the datasets described in the Efficacy Data section on pages 23-25 of the meeting minutes for the October 8 pre-BLA meeting. So far, we have been unable to identify the datasets in the submission or find a description of them in the reviewer guides. Please provide a response by COB Thursday, March 12, 2015.

>

> Thanks

> Sulin

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/s/

SU-LIN SUN
03/24/2015

Sun, Su-Lin

From: Sun, Su-Lin
Sent: Tuesday, March 10, 2015 1:08 PM
To: 'Patel, Mahlaqa'
Subject: RE: FDA's Information request

Sure ☺

From: Patel, Mahlaqa [<mailto:mahlaqa.patel@Abbvie.com>]
Sent: Tuesday, March 10, 2015 12:22 PM
To: Sun, Su-Lin
Subject: Re: FDA's Information request

We will prepare this for you. Is March 12 COB acceptable for a response?

Regards,
Mahlaqa

On Mar 10, 2015, at 11:03 AM, "Sun, Su-Lin" <Su-Lin.Sun@fda.hhs.gov> wrote:

Dear Mahlaqa:

For BLA 761029, our review team also would like me to ask you which company has the original records of all the studies (AbbVie or Biogen).

Please list each study and its corresponding study record holder.

Thanks,
Sulin

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/s/

SU-LIN SUN
03/24/2015

Sun, Su-Lin

From: Patel, Mahlaqa <mahlaqa.patel@Abbvie.com>
Sent: Tuesday, March 24, 2015 4:30 PM
To: Sun, Su-Lin
Subject: RE: BLA 761029 Daclizumab-FDA's information request

Dear Sulin,

I have forwarded your request to the team and will respond shortly.

Kind Regards,
Mahlaqa

MAHLAQA PATEL
Director, Regulatory Affairs
Area & Affiliate; US & Canada

abbvie

AbbVie, Inc.

1 Waukegan Road
North Chicago, IL 60064
OFFICE + 1 847-937-2724
FAX + 1 847-938-8476
CELL + (b) (6)
EMAIL mahlaqa.patel@abbvie.com

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From: Sun, Su-Lin [<mailto:Su-Lin.Sun@fda.hhs.gov>]
Sent: Tuesday, March 24, 2015 3:21 PM
To: Patel, Mahlaqa
Subject: BLA 761029 Daclizumab-FDA's information request
Importance: High

Dear Mahlaqa:

Below are our review team's information request for your BLA 761029 Daclizumab:

Please refer to the pre-BLA meeting minutes under Q5. We have taken an initial look at some of the patient narratives and found that some of the information we requested is missing and there is no link to a patient profile. We were unable to locate any patient profiles in the database. Could you please direct the clinical reviewer to the location of the patient profiles for all patients for which a narrative has been submitted. Please respond by COB 3/25/15.

Thanks,

APPEARS THIS WAY ON ORIGINAL

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/s/

SU-LIN SUN
03/24/2015

Sun, Su-Lin

From: Patel, Mahlaqa <mahlaqa.patel@Abbvie.com>
Sent: Thursday, March 19, 2015 3:54 PM
To: Sun, Su-Lin
Subject: RE: BLA 761029 FDA"s information request

Hi Su-Lin,

Thank you for the request. I will send it to the team and respond by the due date.

Kind Regards,
Mahlaqa

MAHLAQA PATEL
Director, Regulatory Affairs
Area & Affiliate; US & Canada

abbvie

AbbVie, Inc.

1 Waukegan Road

North Chicago, IL 60064

OFFICE + 1 847-937-2724

FAX + 1 847-938-8476

CELL + (b) (6)

EMAIL mahlaqa.patel@abbvie.com

abbvie.com

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From: Sun, Su-Lin [<mailto:Su-Lin.Sun@fda.hhs.gov>]

Sent: Thursday, March 19, 2015 2:51 PM

To: Patel, Mahlaqa

Subject: BLA 761029 FDA"s information request

Importance: High

Dear Mahlaqa:

Below are information request from our review team for your BLA 761029 daclizumab:

Please refer to your Biologics License Application number 761029. For studies 205MS201 and 205MS301 please provide (or locate in the submission) the Manual of Operations or equivalent document and training materials which document the instructions to the investigators and site personnel regarding execution of the protocol. Please provide by 3/26/2015.

Thanks,
Sulin

APPEARS THIS WAY ON
ORIGINAL

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

/s/

SU-LIN SUN
03/19/2015



BLA 761029

BLA ACKNOWLEDGMENT

AbbVie Inc.
Attention: Mahlaqa Patel
Director, Regulatory Affairs
1 North Waukegan Road
North Chicago, IL 60064

Dear Ms. Patel:

We have received your Biologics License Application (BLA) submitted under section 351(a) of the Public Health Service Act (PHS Act) for the following:

Name of Biological Product: ZINBRYTA™ [daclizumab High Yield Process (DAC HYP)]
150 mg/mL Injection

Date of Application: February 27, 2015

Date of Receipt: February 27, 2015

Our Reference Number: BLA 761029

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on April 28, 2015, in accordance with 21 CFR 601.2(a).

If you have not already done so, promptly submit the content of labeling [21 CFR 601.14(b) in structured product labeling (SPL) format as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action. The content of labeling must conform to the content and format requirements of revised 21 CFR 201.56-57.

You are also responsible for complying with the applicable provisions of sections 402(i) and 402(j) of the Public Health Service Act (PHS Act) [42 USC §§ 282 (i) and (j)], which was amended by Title VIII of the Food and Drug Administration Amendments Act of 2007 (FDAAA) (Public Law No. 110-85, 121 Stat. 904).

The BLA number provided above should be cited at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Neurology Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

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

If you have any questions, please contact Su-Lin Sun, PharmD, Regulatory Project Manager, by email su-lin.sun@fda.hhs.gov or by phone at (301) 796-0036.

Sincerely,

{See appended electronic signature page}

Su-Lin Sun, PharmD
Senior Regulatory Project Manager
Division of Neurology Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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/s/

SU-LIN SUN
03/03/2015

Sun, Su-Lin

From: Sun, Su-Lin
Sent: Wednesday, March 04, 2015 5:01 PM
To: 'Patel, Mahlaqa'
Subject: RE: BLA 761029 FDA's information request

Thanks ☺

From: Patel, Mahlaqa [<mailto:mahlaqa.patel@Abbvie.com>]
Sent: Wednesday, March 04, 2015 4:58 PM
To: Sun, Su-Lin
Subject: RE: BLA 761029 FDA's information request

Dear Su-Lin,
Thank you. I will send this to the team and we will prepare a response by the due date.
Kind Regards,
Mahlaqa

MAHLAQA PATEL
Director, Regulatory Affairs
Area & Affiliate; US & Canada

abbvie

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From: Sun, Su-Lin [<mailto:Su-Lin.Sun@fda.hhs.gov>]
Sent: Wednesday, March 04, 2015 3:54 PM
To: Patel, Mahlaqa
Subject: BLA 761029 FDA's information request
Importance: High

Dear Mahlaqa:

Below are our review team's information request for your BLA 761029 daclizumab, please send your response as soon as possible, no later than COB on March 9, 2015:

1. Information that should be provided in the drug product quality module (3.2.P) of the application was provided in the appendix. Please update the BLA file by moving the following items to section 3.2.P.3.5 and removing them from the appendix.
 - a. Environmental and personnel monitoring information. Provide the limits, monitoring frequencies, and brief descriptions of the methods used.
 - b. Equipment and component sterilization and data, including the associated validation reports.

2. Information that should be provided in the drug substance quality module (3.2.S) of the application was provided in the appendix. Please update the BLA file by moving the following items to the indicated sections and removing them from the appendix.
 - c. (b) (4) hold time validation (3.2.S.2.5).
 - d. Intermediate hold time validation (3.2.S.2.5).
 - e. Endotoxin recovery studies (3.2.S.4.3).

Thanks,

Sulin

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/s/

SU-LIN SUN
03/05/2015



IND 012120

MEETING MINUTES

AbbVie Inc.
Attention: Mahlaqa Patel
Director, Regulatory Affairs
1 North Waukegan Road
North Chicago, IL 60064

Dear Ms. Patel:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for daclizumab high yield process (DAC HYP).

We also refer to the meeting between representatives of your firm and the FDA on October 8, 2014. The purpose of the meeting was to discuss the content and format of the planned Biologics License Application (BLA) for the treatment of multiple sclerosis.

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 Hamet Touré, PharmD MPH, Regulatory Project Manager at (301) 796-7534.

Sincerely,

{See appended electronic signature page}

Billy Dunn, MD
Acting Director
Division of Neurology Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes



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

MEMORANDUM OF MEETING MINUTES

Meeting Type: B
Meeting Category: Pre-BLA meeting

Meeting Date and Time: October 8, 2014, 1:00 – 2:30 PM EST
Meeting Location: 10903 New Hampshire Avenue
White Oak Building 22, Conference Room: 2205
Silver Spring, Maryland 20903

Application Number: IND 012120
Product Name: Daclizumab high yield process (DAC HYP)
Indication: Multiple sclerosis
Sponsor/Applicant Name: AbbVie Inc.

Meeting Chair: Billy Dunn, MD
Meeting Recorder: LCDR Hamet Touré

FDA ATTENDEES

Biotech Manufacturing Assessment Branch
Bo Chi, PhD, Reviewer

Center for Devices and Radiological Health,
Office of Drug Evaluation
Ryan McGowan, Combo Products Team
Lead

Controlled Substance Staff
Chad Reissig, PhD, Reviewer

Division of Medical Policy Programs
Sharon Williams, RN, MSN, Patient
Labeling Reviewer
Aman Sarai, Patient Labeling Reviewer

Division of Monoclonal Antibodies
Michele Dougherty, PhD, Team Leader
Chen Sun, PhD, Reviewer

Division of Neurology Products
Billy Dunn, MD, Acting Director
Eric Bastings, MD, Deputy Director
Nicole Bradley, PharmD, Acting Associate
Director for Labeling
John Marler, MD, Acting Team Leader
Lawrence Rodichok, MD, Medical
Reviewer
Sally Jo Yasuda, PharmD, Safety Team
Leader
Lourdes Villalba, MD, Safety Reviewer
Aaron Sherman, Consumer Safety
Technician
Kinbo Lee, PharmD Candidate
Hamet Touré, PharmD, Project Manager

Division of Risk Management
Jamie Wilkins-Parker, PharmD, Team
Leader
Nyedra Booker, PharmD, Reviewer

Barbrakaryne NchindaFobi, PharmD
Candidate

Office of Biostatistics
Kun Jin, PhD, Team Leader
Sharon Yan, PhD, Reviewer

Office of Clinical Pharmacology
Hristina Dimova, PhD, Clinical
Pharmacology

Office of Combination Products
Bindi Nikhar, MD, Associate Clinical
Director

Office of Drug Evaluation I
Ellis Unger, MD, Director
Robert Temple, MD, Deputy Director

Office of Pediatric and Maternal Health
Donna Snyder, MD, Medical Officer
Lori Gorski, Senior Regulatory Project
Manager

Office of Prescription Drug Promotion
Aline Moukhtara, RN, Regulatory Review
Officer

EASTERN RESEARCH GROUP ATTENDEES

Patrick Zhou, Independent Assessor

SPONSOR ATTENDEES

AbbVie

Steven Greenberg, MD, Sr. Medical Director, Medical Research
Douglas Feltner, MD, VP, Neuroscience Development
Joan Holman, MD, Sr. Medical Director, Pharmacovigilance and Patient
Safety
Randy Robinson, PhD, Project Director, Program Management
Mahlaqa Patel, BA Director, US Regulatory Affairs
Ratna Lingamaneni, PhD Director, Global Regulatory Affairs
David Schisla, PhD, CMC Program Management

Biogen Idec

Jacob Elkins, MD, Sr. Director, Clinical Development
Gilmore O'Neill, MB, MRCPI, M Med Sci, VP, Clinical Development
Marianne Sweetser, MD, PhD, Sr. Medical Director, Safety and Benefit Risk Management
Priya Singhal, MD, PhD, VP, Global Head, Safety and Benefit Risk Management
Katherine Riester, PhD, Sr. Principal Biostatistician, Biostatistics
Stacy Lindborg, PhD, VP, Biostatistics
Lynn Difinizio, Sr. Director, Statistical Programming and Operations
Varia Cartledge, Principal Analyst, Statistical Data Standards
Prafulla Girase, Sr. Analyst III, Statistical Submissions Management
Ketan Shah, PhD, Director, Quality Control Stability
Atul Patel Director, Technical Development, Protein Formulation Development
Kimberly Hocknell, MBA, Director, CMC Management
Brett Johnston, Staff Associate, Product Quality Management
Bina Keshavan, PhD, Director, Program Leadership and Management
Paula Sandler, PhD, VP, Regulatory Affairs
Tammy Sarnelli, Sr. Director, Regulatory Affairs

Mary Geissler, MPH, Associate Director, Regulatory Affairs
Shannon Holmes, PhD, Sr. Manager, Regulatory Affairs CMC
Suzanne Stella, Sr. Director, Regulatory Affairs CMC
Suzette Roan, JD, Associate Director, Regulatory Affairs CMC

1. BACKGROUND

The purpose of this meeting is to discuss the content and format of the planned Biologic License Application (BLA) for the treatment of multiple sclerosis.

2. MEETING QUESTIONS

Format and Content of the BLA

Question 1. Does the Agency agree that the two pivotal studies (Study 201 and Study 301), together with the long-term extension studies and other safety data, are adequate to establish DAC HYP safety and effectiveness for the treatment of multiple sclerosis (MS) (Section 4)?

Preliminary response to question 1:

Subject to a full review of a complete application, we agree that studies 201 and 301 appear to be adequate to contribute to and potentially provide a demonstration of substantial evidence of effectiveness of DAC HYP for the treatment of relapsing MS.

From the safety perspective, the exposure of a total of over 2200 subjects with MS, 1485 subjects for more than 1 year, 1193 subjects for more than 2 years, and 447 subjects for more than 3 years at or above the proposed commercial dose is generally adequate in terms of exposure. However, the BLA submission should indicate compliance with the monthly regimen by indicating how many patients received treatment at each month. Adequacy of the safety data to establish safety for treatment of MS is a review issue.

On October 2, 2014, we requested that you provide a preliminary exposure table by dose and number of doses similar to a table you will present in your submission, for FDA comment. We will provide comments to you in the meeting minutes for the pre-BLA meeting. When you submit your BLA application please also provide the estimated exposure in patient years by treatment group (including placebo and interferon) for individual studies and for Pool A.

Meeting Discussion:

The Sponsor submitted an exposure table on October 3, 2014, that specifies the number of doses received, pooled in bins of 5 months. FDA agreed that this presentation along with the estimated exposure in patient years as requested above will be acceptable for the BLA submission.

Question 2. Does the Agency agree with the proposed approach to summarizing and presenting efficacy data in the BLA (Section 7.2)?

Preliminary response to question 2:

In general, the general plan for presentation of the efficacy data appears to be adequate. See additional comments.

Please include in the main body of the clinical study report tables and figures for the efficacy analysis of the primary endpoint in subpopulations (by demographic and baseline characteristics, regions, and other important factors) with point estimates, confidence intervals, and nominal p-values of the treatment difference.

Meeting Discussion:

The sponsor noted that some of the requested information related to MRI datasets, for example, the date the MRI was received and when it was reviewed at the MRI Central Reading Center, was not available. FDA asked the sponsor to indicate in its application instances where the requested information was not available.

FDA reiterated that it would be useful for the review team to receive a single dataset of important trial events for each patient with one row per patient per event.

Question 3. Does the Agency agree with the overall safety database (Table 24 and Table 26), the proposed safety data integration plan (Section 7.3), and approach to integrate the DAC HYP RMS safety information and to present supportive safety data separately (Section 7.3)?

Preliminary response to question 3:

The proposal to present studies 201 (1-year, placebo-controlled) and 301 (2-3 year, INF controlled) separately and an overall DAC HYP experience (“Pool A”) involving these studies and their extensions plus study 302 with the proposed cut-off dates for analyses of ongoing trials (January/February 2014) is acceptable. Please confirm that your 120-day Safety Update Report will include an integrated summary of safety with cut-off of November 2014 (assuming that your BLA will be submitted in the first quarter of 2015). Depending on the format you chose to present the different pools, we may ask for separate efficacy databases for the pools.

It is acceptable not to pool safety data from the Phase 1 studies with the data from the Phase 2/3 studies; however, please submit a single dataset for adverse events in all the Phase 1 trials. At a minimum, the dataset should include patient ID, study ID, demographics, PT, SOC, relative date of the event, duration, treatment group, whether the event was serious or fatal, and whether the event led to drug discontinuation or not.

The elimination half life of dacluzimab is approximately 3 weeks, but the pharmacodynamic effects are longer (for example, reversion of NK expansion takes approximately 6 months). The Data Analysis Plan (DAP) submitted in November 2013 stated that safety analyses would be done up to 6 months after last dose of daclizumab. However, the briefing package is not clear about follow-up of patients after last dose. Please specify the cut-off after daclizumab discontinuation that will be used for analyses of adverse events and other safety evaluations for each study and for Pool A.

Meeting Discussion:

The sponsor confirmed that the 120-day Safety Update Report will include an integrated summary of safety with a cut-off on November 2014. In addition, the sponsor confirmed that it had follow-up data for 6 months after the last dose of daclizumab and that it will include safety analyses of these follow-up data in the submission.

Question 4. Does the Agency concur with the proposed approach to not include the clinical study reports for the exploratory studies with DAC Penzberg or DAC Nutley in non-MS subjects and with the proposed literature review of other drugs targeting CD25 (Section 7.3.4)?

Preliminary response to question 4:

No. For the exploratory studies conducted with DAC Penzberg or DAC Nutley (table 28 of your briefing document [healthy volunteers, psoriasis, ulcerative colitis, and asthma]) please submit the complete study reports and a summary of safety results from each study and overall and that describes major findings and safety differences with the DAC HYP studies.

Also include a summary of safety for Zenapax from the BLA and postmarketing exposure.

The safety summaries for DAC Penzberg and Nutley in non-MS subjects and in the renal transplant population may be appended to the ISS.

Meeting Discussion: The sponsor confirmed that it will include the information requested for the exploratory studies. The sponsor agreed to provide a summary of publically available information about the safety of Zenapax.

Question 5. Does the Agency concur with the proposed provision for case report forms (CRFs) and safety narratives in the BLA (Section 7.1)?

Preliminary response to question 5:

- Your proposal is acceptable provided that the ISS includes hyperlinks to narratives and CRFs. Please also submit the CRF and narratives for pregnancies and adverse events of MS relapse whether serious or not.

Also submit narratives and CRFs for all discontinuations for the following reasons: Lost to follow-up, Other, Physician decision, and Patient decision (subject choice, subject withdrew consent) including as much information as possible regarding the cause of discontinuation.

Please include in your submission an index listing of all submitted narratives and an index of all submitted CRFs. The listing should include columns for study number, treatment group,

unique subject ID, and primary reason why the narrative/CRF has been included (for example, serious AE, discontinuation, and AE of special interest).

- Narratives

Narrative summaries should provide a complete synthesis of all available clinical data and an informed discussion of the case, preferably using a common template that is easy to review.

The narratives should be comprehensive enough for the reader to come to a reasonable conclusion regarding the subject and the adverse event. The following items should be included (but not limited to):

- Patient age and gender
- Adverse event onset and stop dates (presented as relative Study Day number)
- Signs and symptoms related to the adverse event being discussed
- An assessment of the relationship of exposure duration to the development of the AE
- Pertinent medical history
- Concomitant medications with start dates relative to the adverse event
- Pertinent physical exam findings
- Pertinent test results (e.g., lab data, ECG data, biopsy data, autopsy results)
- Discussion of the diagnosis as supported by available clinical data
- For events without a definitive diagnosis, a list of the different possible diagnoses you considered
- Administered treatment
- Re-challenge results (if performed)
- Outcomes and follow-up information

If more than one event is contained in a single narrative, then each item should appear in a line listing. We prefer, however, to have separate narratives for each event, especially if the events for an individual occurred 6 months or more apart.

- Patient profiles

It is expected that all the information listed above will be in the narratives. If some of this information is not in the narrative, we request that you include an hyperlink to a place where this information can be easily gathered, such as the individual patient file (also referred to as patient profile). The patient profile should include

- Age, gender
- Dates of screening, randomization, and starting therapy
- Duration of study participation, whether the patient completed or did not complete the study, dates for starting and stopping treatment, and reason for withdrawal.
- Adverse events (reported term, preferred term, start and stop date [with relative study day from initiation of treatment and dose cycle (for example, “day 60 of treatment, day 20 of 2nd month dose”)], seriousness, outcome, whether it resolved or not, and action taken with study drug. For hypersensitivity and injection reactions that occur within 24 hours of dosing, please specify the time in minutes or hours after dosing and the dose month (for example, 45 minutes after second dose).

- Prior medications and concomitant medications with dates of start and end relative to study initiation
- Vital signs and laboratories, sorted by date, with reference ranges *
- Antidrug and neutralizing antibody test results with time after dose and dose month
- Full reports for radiological studies, ECG, MRI, pathology results, and special studies with dates and reference ranges *
- Autopsy reports for all deaths. (If an autopsy report is not available, state this explicitly.)

* Relevant results obtained outside of clinical trial visits, including those obtained during hospitalization or emergency room visits, should be included in each patient file. Available baseline study results should also be included.

- For those patients who had an IND safety report, please include dates when the initial and follow-up safety reports were submitted to the IND. Please provide a listing of patients who had IND safety reports.
- Please include updated listings of narratives, CRFs, patient profiles, and IND safety reports and the corresponding links, in the 120-day Safety Update Report.
- Additional requests/comments:

The Data Analysis Plan (DAP) for the ISS submitted to the IND in November 2013 mentions that the following events might be included as events of interest

- Infections, including serious infections and potential opportunistic infections
- Cutaneous events, including serious events
- Hepatic events
- Gastrointestinal events
- Autoimmune disorders
- Injection site reactions
- Depression and suicide
- Malignancies, potential and those confirmed upon medical review

Please include all the events mentioned in your DAP (plus adverse events of MS relapse) as well as cytopenias and autoimmune disorders as events of special interest in your BLA submission.

We note that your briefing package does not specifically mention autoimmune disorders as a group. A review of the adverse event tables suggests a potential for immune-mediated reactions (rash, hepatitis, colitis, lymphadenopathy/lymphadenitis, and two cases of hemolytic anemia have been recently reported as 15-day reports). Although the tables do not state whether these events occurred in the same patient, the presence of adverse events of lymphadenopathy and cutaneous reactions and events such as hepatitis raises the possibility of Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS). Therefore, please also include a search for and an analysis of potential cases of DRESS. We suggest that you use the REGISCAR criteria (http://www.regiscar.org/Diseases_HSS_DRESS.html) but without requiring hospitalization or suspected relationship to study drug.

Moreover, the labeling for Zenapax includes serious hypersensitivity reactions within 24 hours of administration, including anaphylaxis and cytokine release syndrome. Notwithstanding that DAC HYP may have different immunogenicity than Zenapax, please assess the possibility of hypersensitivity reactions and anaphylaxis with first and subsequent doses of daclizumab. In particular, address the possibility of hypersensitivity reactions upon re-administration after interruption of treatment.

Please include analyses of potential immune-mediated disorders as an event of special interest in your BLA submission. Provide a list of preferred terms with corresponding HLT, HLGT, and SOC that will be used for potential immune-mediated disorders. We suggest that your search include the Hypersensitivity, Anaphylactic reactions, and Angioedema SMQs along with the Allergic conditions HLGT and Autoimmune disorders HLGT. Include additional analyses of immune-mediated events as deemed necessary.

- Provide time to event analyses of infections, serious infections, discontinuations due to adverse events of infection, and opportunistic infections in the Phase 2 and 3 trials.
- Please include an assessment of the effects of immunogenicity on safety in your clinical trials. Provide analyses of incidence of AEs with special attention to potential immune-mediated events among patients who developed anti-drug antibodies and neutralizing antibodies, after each dose and overall, at any time up to 180 days after last dose.
- For those trial populations with the available data, include analyses of changes in lymphocyte subpopulations, NK cells, and immunoglobulin levels over time. If possible, explore the relationship between AEs and the extent of CD25 T cell receptor saturation as well as NK cell expansion, particularly for infectious and immune-mediated AEs.
- At the time of the DAP for the ISS submitted in November 2013, a substudy to assess the impact of DAC HYP on response to the seasonal flu vaccine was ongoing (205MS203). If the study has been completed, please submit the complete study report to the BLA application.
- In reference to liver toxicity, please be sure that the narratives include all the necessary details for evaluation of cases of potential drug induced liver injury cases, including liver enzyme and serum bilirubin, detailed history of symptoms and prior or concurrent disease, history of concomitant drug use, alcohol use, recreational drug use, special diets, tests to rule out viral hepatitis A,B, C, D, and E, autoimmune or alcoholic hepatitis, non-alcoholic hepatitis, hypoxic-ischemic hepatopathy, biliary tract disease, history of exposure to environmental chemical agents, supporting tests to evaluate liver function, copies of gastroenterology or hepatology consults, biopsy results, tests for autoantibodies, and the assessment of the hepatologist who evaluated the case. Include a listing of patients who fulfill Hy's law criteria with links to these narratives, CRFs, and patient profiles.
- Regarding Laboratory and Vital Sign Measurements:

Include a table with all of the reference ranges for normal laboratory values used in data analyses.

All outlier data should have the normative values clearly indicated as well as the thresholds for analysis of outliers. This should include laboratory data, vital signs data, and ECG data.

When available, we request that you use the National Institutes of Health (NIH) Common Terminology Criteria for Adverse Events (CTCAE) for shift tables documenting changes in laboratory values from baseline.

We also request the following outlier analyses of vital sign data. Report the number and percentage of subjects with at least one post-treatment vital sign measurement meeting any of these criteria:

- Systolic Blood Pressure: <90 mmHg, >140 mmHg, >160 mmHg
- Diastolic Blood Pressure: <50 mmHg, >90 mmHg, >100 mmHg
- Pulse Rate: <60 bpm, >100 bpm
- Body Weight: 7% or more increase or decrease from baseline
- Temperature: >38.0 °C, <36.0 °C
- Respiratory rate: <12 breaths/min, > 20 breaths/min

Please provide tables of vital sign and body weight analyses using Tables A and B in the Appendix.

Meeting Discussion:

FDA requested narratives, CRFs, and patient profiles for all MS relapse adverse events, whether serious or not. The sponsor explained that the proposed adverse event tables included all cases of relapse and not only those that were particularly severe or atypical. For adverse events of MS relapse that were non-serious there would be little or no description of the case. After discussion, the sponsor and FDA agreed that the sponsor would submit narratives, CRFs, and patient profiles for all serious AEs and AEs leading to discontinuation including cases reported as adverse events but not included as MS relapse in the efficacy analyses (if any).

Question 6. Does the Agency agree with the proposed presentation of electronic data, which includes datasets for key studies (Section 7.1, Table 24, and Table 25)?

Preliminary response to question 6:

Please label each variable clearly. Describe key information for each variable in relevant columns and in the comment column in the define document for each dataset. Data with imputation for missing values should use a separate variable with a clear label. An additional document is recommended for descriptions of complicated derivations for variables.

Include SAS programs for analysis of the primary and key secondary endpoints.

EDATA TEAM:

Your approach regarding dataset formats seems acceptable. Please note that if the SDTM datasets are not traceable back to CRFs, please include the raw data that serves as the intermediary to allow reviewers to check traceability of data elements.

We recommend that you submit for our review an eCTD sample prior to submitting the actual BLA submission. For information about eCTD and the process of submitting a sample, please refer to the first link on the FDA eCTD web page located at <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm153574.htm> for eCTD Basics, Getting Started, and the eCTD sample process.

Regarding safety, we request that the submitted datasets contain verbatim terms and MedDRA coding with all levels of the MedDRA hierarchy. For each adverse event, MedDRA coding should be provided for the primary MedDRA path, as well as all alternate MedDRA coding paths.

Please provide anti-drug antibody and neutralizing antibody data that will allow us to analyze the relationship of antibodies to safety and efficacy.

Meeting Discussion: None.

Question 7. Would the Agency be willing to provide any considerations on potential hepatic risk management actions, in general, and/or be willing to interact with AbbVie and Biogen Idec as risk management actions are being considered for DAC HYP (Section 7.3.5) prior to the submission of the BLA?

Preliminary response to question 7:

We are unable to comment on potential hepatic risk management actions or other risk management actions prior to submission of the BLA because that requires a review of the data in the submission. Please submit your own recommendations for our review.

Meeting Discussion: None.

Question 8. Does the Agency agree that AbbVie and Biogen Idec have adequately assessed the potential impact of DAC HYP on the cytochrome P450 (CYP) enzymes (Section 4.4.1)?

Preliminary response to question 8:

Clinical Pharmacology:

On face, you have adequately assessed the potential impact. Final acceptability will be a matter of review. In addition, please provide a discussion of whether you expect any PK interactions between DAC HYP and medications commonly used in MS patients.

Meeting Discussion: None.

Question 9. Does the Agency agree with the Sponsor's population PK analysis plan for submission (Section 4.4.3)?

Preliminary response to question 9: Yes. Please follow the instructions below for submission of datasets and codes related to your analyses of population PK and exposure-response:

- Submit all datasets used for model development and validation as SAS transport files (*.xpt). Describe each data item in a define.pdf file. Flag any concentrations or subjects in the datasets that you exclude from analysis.
- Provide model codes, control streams, and output listings for all major model building steps including the base structural model, covariates models, the final model, and the validation model. Submit these files as ASCII text files with *.txt extension (e.g., myfile_ctl.txt, myfile_out.txt).
- Provide a model development table which gives an overview of modeling steps.

Meeting Discussion: None.

Question 10. Based on the available data for DAC HYP, the Sponsor believes that no additional nonclinical studies of abuse liability are required. Does the Agency agree (Section 5.3.3)?

Preliminary response to question 10:

Yes, we agree. No additional abuse potential assessment studies are required.

Meeting Discussion: None.

Question 11. Does the Agency agree that the information planned for inclusion in the BLA is sufficient to allow for substantive review (Appendix A)?

Preliminary response to question 11:

Efficacy:

See the additional comments below for additional analyses that we request.

Safety:

We request additional safety analyses as noted above in our preliminary response to Question 5.

Clinical Pharmacology:

Please provide the Bioanalytical Study Report (sample analysis report) for each clinical study in which PK samples were collected. Please provide the Clinical Pharmacology summary using the attached Review Aid template.

Combination Products:

Following are comments regarding eCTD submission for combination products.

Other than data analogous to batch records, all data pertaining to the device constituent and other combination product information should be integrated within the standard electronic Common Technical Document (eCTD) sections together with conceptually similar drug constituent information. The data should be organized based on the following principles:

1. For eCTD format and use of the electronic submission system, please adhere to eCTD headings as defined per ICH and FDA specifications. In the specifications, these may be identified as leaf nodes or elements. Specifically, any title that is associated with a numerical item should not change; i.e., Item 3.2.P.7 should say “Container Closure System.”
2. Do not use "node extensions" to create new elements. Although this is described in the eCTD specification, and may be acceptable in some regions, it is not acceptable in submissions to FDA.
3. When including and referencing device information, we recommend the following:
 - a) You may reference files under 3.2.P.7, which are not currently listed as numerical items in ICH and FDA specifications and guidance.
 - b) In Module 3.2.P.7, you could include a leaf titled similar to the following, “Table of Contents for Drug-Device Autoinjector”. This leaf/document could provide reference links to the other files in module 3.2.P.7.
 - c) The leaf titles should be clear, concise, and indicative of the document's content.
4. Module 1.4.4 “Cross-reference to other applications” is a location where you can provide references to other applications and you can include copies of an application’s table of contents, reference tables, or other similar documents. If you are cross referencing another company's application or master file, include the appropriate letters of authorization from the other companies in modules 1.4.1 - 1.4.3 (1.4.1 “Letter of authorization”, 1.4.2 “Statement of right of reference”, 1.4.3 “List of authorized persons to incorporate by reference”). If there are standards you will reference in the Performance Specifications that also meet these criteria, then please put them in module 1.4.4. The Performance Specifications section should link to this information.
5. All device information pertaining to manufacturing or assembly of the finished combination product and documents necessary to demonstrate compliance with 21

CFR Part 4 and the applicable 21 CFR part 820 regulations should be located in Section 3.2.P.3.

- a) The list of manufacturing facilities provided on the Form FDA 356h, or as an attachment to the form, should explicitly describe the manufacturing, assembly, or testing processes taking place at each site involved with the device constituent part.
 - b) Suggestions on the types of documents to submit for review of required sections of 21 CFR Part 820 (based upon the combination product 21 CFR Part 4 GMP operating system at the facility) can be found in the guidance document titled “Quality System Information for Certain Premarket Application Reviews; Guidance for Industry and FDA Staff,” issued on February 3, 2003. The complete document may be found at <http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm070897.htm>.
6. We recommend that you provide an "Information to Reviewers" or "Reviewers' Guide" document in Module 1.2 Cover letters. This document would be separate from the cover letter and placed after the cover letter and should provide a high level overview (with reference links) of the submission's content and list where the information is located in the eCTD. For example, it should identify where drug, device, and combination product information is located.

Please see Section 3, “additional FDA comments”, below for additional information.

Meeting Discussion: FDA agreed to provide post-meeting comments regarding item 5 above. After the meeting, the sponsor submitted a comment and question for FDA to consider that are copied below. The FDA post-meeting response is immediately below the sponsor's request.

Sponsor's October 9, 2014, questions:

We confirm that we will be providing a guide to the review of the combination product/device information in the eCTD as part of Module 1.2 as requested. Regarding the request to include the documents necessary to demonstrate compliance with 21 CFR Part 4 and the applicable 21 CFR Part 820 regulations in Section 3.2.P.3, we have two questions:

1. As this request is specific to the US and the CTD Regional module is for country specific requests, we would like to propose to place this information in the Regional module (3.2.R) to facilitate our global filing. Can the Agency confirm whether this approach would be acceptable?

FDA post-meeting response: No, the approach is not acceptable. As discussed at the meeting, you should place all documents necessary to demonstrate compliance of your combination product with 21 CFR Part 4 and 21 CFR Part 820 regulations in Section 3.2.P.3 along with other manufacturing information for the product.

2. If this approach is not acceptable, the concern we have with placing the information in Section 3.2.P.3 is that this section is normally considered part of the regulatory commitment and subject to post-approval submission updates. As quality systems evolve, this information is likely to involve changes during the lifecycle of the application. Can we confirm that this information would not be subject to submission updates in the post-approval setting, but would instead be assessed during routine site inspections?

FDA post-meeting response: No, we disagree with your conclusion. Your combination product is subject to post-approval regulatory commitments and subject to post-approval submission requirements which should be provided to FDA as outlined in the following draft Guidance: *Submissions for Postapproval Modifications to a Combination Product Approved under a BLA, NDA, or PMA* accessible at

<http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM336230.pdf>.

Specifically, for changes to the combination product design (including a change to either constituent part) or for changes to quality systems of the device constituent of the combination product, information on the changes should be submitted to FDA for approval and should ensure that the approved combination product has remained intact without any safety or effectiveness concerns. Overall, all changes during the lifecycle of the application as quality systems evolve will need to be submitted to the Agency, and will be subject to post-market inspections as appropriate.

Question 12. Does the Agency concur with Sponsor's proposal to waive clinical trials in children less than 10 years old and defer clinical studies in children 10-17 years old until the product has been approved in the adult population (Section 8)?

Preliminary response to question 12:

We agree with your plan to request a waiver for studies in pediatric patients less than 10 years of age. Depending on when you submit your NDA, a deferral of studies in pediatric patients 10 to 17 years of age may be reasonable; however, pediatric studies should commence once sufficient data has been collected to support study in the pediatric population and should not be tied to the submission and approval of your NDA. Please refer to comments provided to you on your initial Pediatric Study Plan. We remind you that waivers and deferrals for pediatric studies under the Pediatric Research and Equity Act (PREA) are granted at the time of approval of the NDA and the final decision to grant any waivers or deferrals will be made during the NDA review.

Note that FDA requires that an "Agreed Initial Pediatric Study Plan" be in place prior to submission of your NDA. Timelines must be included in your Agreed iPSP. Subsection 505B(e)(3) requires the sponsor to document agreement on the initial PSP in a submission to FDA marked "Agreed Initial Pediatric Study Plan". The Agreed iPSP must be submitted no later than 90 calendar days after the meeting with FDA or after the sponsor receives FDA's written response. FDA must confirm agreement in writing no later than 30 calendar days after receipt of the submission.

Meeting Discussion: None.

CMC

Question 13. The Sponsor intends to submit the stability data as outlined in Table 15 and Table 16 for drug substance and pre-filled syringe (PFS) drug product, respectively, in the initial BLA to support expiry assignment. Based on the totality of the data to be provided:

- a. Does the Agency agree that the data planned for inclusion in the BLA is sufficient to allow for substantive review?

Preliminary response to question 13a:

The stability data package that will be included in the BLA submission is sufficient to allow for substantive review. We have the following recommendations regarding the proposed stability testing.

Regarding the PFS stability protocols provided in tables 17 through 19 of the meeting package, syringe functionality testing should be added to the stability protocols. This testing should cover any element of essential PFS performance and safety including physical inspection, leakage testing, force to activate and sustain plunger movement, and any other evaluations necessary to verify the PFS will perform as intended after aging. Similar functionality testing should also be incorporated into the DP lot release testing.

- b. Does the Agency agree that the Sponsor's proposed expiry (refer to Section 6.2) may be assigned based on the available clinical and pre-process consistency validation stability study data?

Meeting Discussion:

With respect to the stability data package to support the syringe functionality testing, the sponsor proposed submitting data to support syringe functionality during the shelf life generated with an alternate product presented in the same PFS configuration currently used for daclizumab (DAC-HYP). FDA stated that the proposed approach appeared acceptable and that final concurrence on adequacy of the data would be a review issue.

Preliminary response to question 13b:

Concurrence with the proposed expiry period will depend on review of the stability data provided in the BLA submission. We note that the clinical process used to manufacture the 2020 and 2011 campaigns is stated to be representative of the commercial manufacturing process. The determination that the clinical process is representative of the commercial manufacturing process and determination of expiry for drug substance and drug product will be a review issue.

Meeting Discussion: None.

[Redacted] (b) (4)

Based on this, does the Agency agree that:

Question 14. [Redacted] (b) (4)

Preliminary response to question 14:

[Redacted] (b) (4)

Meeting Discussion:

The sponsor asked [Redacted] (b) (4)
[Redacted] (b) (4)
FDA stated that this was not acceptable [Redacted] (b) (4)
[Redacted] (b) (4)
(b) (4) . The sponsor then proposed [Redacted] (b) (4)
[Redacted] (b) (4)
FDA did not agree to the proposal [Redacted] (b) (4)
[Redacted] (b) (4)

Question 15.

(b) (4)

Preliminary response to question 15:

(b) (4)

Meeting Discussion: None.

During the BLA review additional stability data (from clinical and process consistency validation batches/lots) will be generated to support expiry assignment.

Question 16. Does the Agency agree that the Sponsor may submit a stability update to the BLA three (3) months prior to the PDUFA date to further support the requested expiry assignments of the drug substance, PFS drug product and PFP?

Preliminary response to question 16:

Regarding the proposed timing of the stability data submission described in the PDUFA V legislation, agreement must be reached regarding data to be submitted subsequent to the submission of the BLA, and these data must be submitted within 30 days of the submission of the complete BLA. With respect to the timeline for submission of a drug substance and/or drug product stability update described in the meeting package, we have the following comments: FDA may request a "simple stability update." A simple stability update is defined as stability data and analyses performed under the same conditions and for the same drug product batches in the same container closure systems as described in the stability protocol provided in the original submission; it will use the same tabular presentation as in the original submission as well as the same mathematical or statistical analysis methods (if any) and will not contain any matrix or bracketing approaches that deviate from the stability protocol in the original BLA. If FDA requests this information, the simple stability update would need to be submitted within 4 months of the submission of the final portion of the BLA or, if designated standard review, within 7 months of the submission of the final portion of the BLA. A simple stability update submitted at FDA's request within these timeframes may be reviewed and considered in shelf life determinations.

Meeting Discussion: FDA noted that no formal agreement could be made to accept additional stability data, including a simple stability update, beyond the 30 day time point. FDA emphasized that it is the practice of the Office of Biotechnology Products to request simple stability updates to support adequate assessment of the sponsor's proposed expiry in cases where the stability update would be meaningful. FDA acknowledged that the sponsor has provided sufficient information to indicate that such stability data would be available during the BLA review and that the data could be requested as a simple stability update if the data would be necessary to support the sponsor's proposed expiry.

BLA Review Process

Question 17. At this time, does the Agency anticipate convening an Advisory Committee meeting for this application?

Preliminary response to question 17: We will make a determination on the need for an Advisory Committee meeting for this application during the filing period.

Meeting Discussion: None.

Question 18. DAC HYP is a new treatment option that has demonstrated superior efficacy to a current standard of MS care, that can be dosed infrequently and at-home, and which has a manageable safety profile. Does the Agency agree that the product should be considered for priority review based on this rationale?

Preliminary response to question 18: We will make a determination on your request for priority review during the filing period.

Meeting Discussion: None.

Question 19. In accordance with PDUFA V, does the Agency intend to issue a Day 74 Filing Communication letter?

Preliminary response to question 19: We must issue a Day 60 Filing Communication letter for all Biological License Applications. A Day 74 Filing Communication letter may or may not be issued depending on whether deficiencies have been identified and whether they are included in the Day 60 Filing Communication letter.

Meeting Discussion: None.

3. ADDITIONAL FDA COMMENTS

Human Factors

We are currently reviewing your submission, dated August 19, 2014, providing a revised human factors summative validation protocol [REDACTED] (b) (4) We will provide additional comments after completion of our review. In the meantime, we have the following general comments:

- Ensure that you also include a complete human factors validation study report along with a comprehensive use-related risk analysis at the time of the BLA filing.
- Please see the following guidance references on human factors:
- 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>
- There is a more recent draft guidance document that includes the current thinking on human factors at CDRH and recommended approaches to human factors evaluation and testing: Applying Human Factors and Usability Engineering to Optimize Medical Device Design:
<http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm259748.htm>

Meeting Discussion: None.

CDRH

1. [REDACTED] (b) (4)
2. Within the briefing package, you do not specify whether you intend to submit all [REDACTED] (b) (4) PFS information to the BLA record or if you intend to rely on master file (MAF) submissions to provide design and design verification and validation information for Agency review. If you do intend to rely on one or more master files for the referenced BLA, you should clearly identify what type of information is presented within each submission and the location of that information. Additionally, submit any information intended to support safety and efficacy of the final combination product to the BLA submission and be aware that any MAF documentation will be reviewed in the context of the intended use as described in the BLA.

3. Within the briefing package, you do not appear to reference the submission of biocompatibility, toxicology, or sterility information for the device constituent parts of the (b) (4) PFS combination products. We expect that you will submit this information for review at the time of the BLA submission. If you intend to provide this information through a master file submission, you should clearly indicate why further processing of the combination product as part of final assembly, filling, and packaging procedures does not necessitate further testing or assessment.

Meeting Discussion: None.

CMC product quality microbiology

All facilities should be registered with FDA at the time of the BLA submission and ready for inspection in accordance with 21 CFR 600.21 and 601.20(b)(2). The facility should be in operation and manufacturing the product during the inspection. A preliminary manufacturing schedule for the drug substance and drug product should be provided to facilitate the planning of the pre-license inspections under Module 1 of the BLA. Please include in the BLA submission a complete list of manufacturing and testing sites with their corresponding FEI numbers under sections S.2.1 and P.3.1 of Module 3.

The CMC Drug Substance section of the BLA (Section 3.2.S) should contain the following product quality microbiology information:

- Evidence of monitoring of bioburden and endotoxin levels at critical manufacturing steps using qualified bioburden and endotoxin tests. Pre-determined bioburden and endotoxin limits should be provided (3.2.S.2.4).
- Three successful product intermediate hold time validation runs at manufacturing scale. Bioburden and endotoxin levels before and after the maximum allowed hold time should be monitored and bioburden and endotoxin limits provided (3.2.S.2.5).
- (b) (4) storage validation data and information (3.2.S.2.5).
- Bioburden and endotoxin data obtained during manufacture of the three conformance lots (3.2.S.2.5).
- Data summaries of shipping validation studies (3.2.S.2.5).
- Drug substance bioburden and endotoxin release specifications. The bioburden limit should be < (b) (4) CFU/10 mL (b) (4) (3.2.S.4).
- Qualification data for bioburden and endotoxin test methods performed for (b) (4) drug substance (3.4.S.4).
- (b) (4) the effect of hold time on endotoxin recovery should be assessed by spiking a known amount of endotoxin into undiluted drug substance and then testing for recoverable endotoxin over time. The studies should be conducted using containers of similar composition as those used for drug substance during hold. Effects of sampling containers on endotoxin recovery should also be evaluated.

The CMC Drug Product section of the BLA (Section 3.2.P) should contain validation data summaries supporting the (b) (4) sterility assurance. For guidance on the type of data and information that should be submitted, refer to the 1994 “FDA Guidance for Industry, Submission Documentation for Sterilization Process Validation in Applications for Human and Veterinary Drug Products”.

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

- Bacterial (b) (4) retention study (b) (4)
- Sterilization (b) (4) of equipment and components that contact the sterile drug product. The equipment requalification program should be described.
- (b) (4) microbial controls and hold times. Hold times should be validated at manufacturing scale. (b) (4) bioburden limits should be monitored and should be less than (b) (4) CFU/100 mL.
- (b) (4)
- Three successful consecutive media fill runs, including summary environmental monitoring data obtained during the runs. Media fill and environmental monitoring procedures should be described.
- A description of the routine environmental monitoring program.
- Shipping validation studies.

The following method validation information should be provided:

- Container closure integrity testing (3.2.P.2.5). System integrity (including maintenance of the microbial barrier) should be demonstrated for the complete manufacturing process. Container closure integrity methods validation should demonstrate that the assay is sensitive enough to detect breaches that could allow microbial ingress. We recommend that container closure integrity testing be performed in lieu of sterility testing for stability samples every 12 months (annually) and at expiry (3.2.P.8.2). Shipping validation studies should also include an assessment of shipping conditions on the maintenance of integrity of the PFS and autoinjector from a sterility assurance perspective. Maintenance of sterility of the prefilled syringes during the autoinjector assembly process should be demonstrated with container closure integrity studies.
- Qualification data for bioburden, sterility, and endotoxin test methods performed for (b) (4) the drug product, as appropriate (3.2.P.5).
- Rabbit Pyrogen Test results from three batches of drug product in accordance with 21 CFR 610.13(b).
- (b) (4) the effect of hold time on endotoxin recovery should be assessed by spiking a known amount of endotoxin into undiluted drug product and then testing for recoverable endotoxin over time. The studies should be conducted using containers of similar composition as those used for drug product during hold. Effects of sampling containers on endotoxin recovery should also be evaluated.

Meeting Discussion: None.

Efficacy data

1. Describe the detailed sequence used for identification of relapses from the initial subject report to confirmation by the Independent Neurology Evaluation Committee (INEC). Provide complete accounting and analysis of all potential relapse events. The datasets should include the times that the potential relapse events were first reported by the subject, the time that the event was first evaluated by the treating and examining neurologist, and the time the event was reported to and evaluated by the INEC. Include an analysis for any potential bias in the determination made by the treating investigator in referring the event for further evaluation as well as for any bias in the INEC confirmation process. Provide sensitivity analyses based on relapses as reported by subjects and as determined by the treating and examining neurologist in addition to the pre-specified primary analysis based on determination by the INEC. Discuss the impact of any differences in the results of these analyses. Provide a clear indication of any values that were imputed for these analyses.
2. Provide a complete accounting of all EDSS determinations. Include documentation of the process used to arrive at the final EDSS score. Provide a dataset that has one row per subject and which includes a column for each EDSS determination by visit (including screening, baseline, and unscheduled visits) and the time interval between the time of randomization and the EDSS determination. Indicate the EDSS assessment used as the baseline. Identify those EDSS scores that met the protocol-defined criteria for progression of disability and those which contributed to the determination of confirmed/sustained progression of disability. Provide an analysis of the impact of a missing baseline EDSS and missing confirmatory EDSS values. Describe the process for the EDSS certification. Flag EDSS scores that were from an assessment by a non-certified examiner. Describe the process for assessment of the internal consistency of the determination of EDSS scores and any process for assessment of the consistency of the EDSS score with other clinical assessments.
3. In the documentation of inclusion criteria, include a column for which of the two criteria for disease activity (inclusion criterion #5 in study 201 and 301) were met. Provide an analysis of the impact of these two sub-criteria on key outcome analyses.
4. For each study include a CONSORT diagram of patient disposition with an indication of populations used in analyses of efficacy and safety. Indicate the number of subjects who did not receive the treatment to which they were randomized and how these subjects were handled.
5. Provide complete accounting of all discontinuations and withdrawals from study treatment and withdrawals from the trial including the reason(s) for discontinuation or withdrawal. Identify those discontinuations due to a relapse or worsening MS. Provide an analysis of the impact of including these events in the analyses of the annual relapse rate and disability progression.
6. Provide an accounting of subjects whose relapse and EDSS outcomes you exclude from the analysis following the use of alternative MS treatment. Provide an analysis in which these subjects are included as “treatment failures”.
7. Provide an analysis of injection-related adverse events as a potential factor unblinding subjects or investigators to treatment assignment.

8. Include a dataset of important trial events for each patient with one row per patient per event. Columns should include the patient identifier, trial name, description of event, and event-specific remark (such as reason for discontinuation, reason for unscheduled visit, EDSS score, and name of medication). For events marked with an asterisk, provide a table with one row per patient and two columns for each event, the date and the days from randomization. The events should include:
 - a. Sign consent form*
 - b. Randomization*
 - c. Start study medication*
 - d. Discontinue study medication*
 - e. Start treatment for acute relapse*
 - f. Scheduled visits
 - g. EDSS determinations
 - h. Start first alternative MS medication.*
 - i. Patient reports of relapses to clinic (remark for each if confirmed by INEC)
 - j. Relapse evaluation visits
 - k. Unscheduled visits (not for relapse)
 - l. MRI scan performed
 - m. Last subject contact*
9. Include in the MRI datasets and tables the following:
 - a. Date the MRI was performed
 - b. Date the MRI was received and when it was reviewed at the MRI Central Reading Center
 - c. Detail the imputation method(s) employed.
 - d. Describe the MRI scan protocols for sites and reviewing center and the extent of deviation from the protocol-defined MRI methods. Describe the process for assessment of the reliability and reproducibility of the central reader(s). Describe the methods for determination of MRI lesion volume.
 - e. Provide a detailed accounting of all missing primary and key secondary endpoint values. Provide a detailed accounting of all missing MRI scan values. Flag all imputed endpoint values. Identify the extent of missing data in all tables, figures, and graphs.
10. Include a table that identifies the time of key milestones in the 201 and 301 trials and their corresponding extensions. Milestones should include:
 - a. Protocol approvals
 - b. Protocol amendments
 - c. Statistical Analysis Plan (SAP) approvals
 - d. SAP amendments
 - e. First subject randomized
 - f. Last subject randomized
 - g. First subject completes follow-up
 - h. Last subject completes follow-up
 - i. Database lock
 - j. Interim analyses (labeled as blinded or not, and for efficacy and/or safety).
 - k. DSMC meetings and teleconferences
 - l. INEC meetings and teleconferences

11. Describe the site monitoring process and document when monitoring visits occurred and the personnel who conducted the visit. Document the extent of source data verification.
12. Provide a dataset with a row for each site with fields in each row that are needed to evaluate the extent of participation at the different sites. The fields to include in the table are the following: (Unique)SiteID, contact individual, address, city, (state/territory/province), country, mail code, region, telephone number, fax number, email address for contact individual, fields for the number of subjects randomized to each arm of the 205MS201 and 205MS 301 trials, the number enrolled in the 202, 203, and 303 extension trials, fields showing the number of randomized patients in each arm of the 201 and 301 trials who experienced SAD events and relapses, fields to list the total number of SAD events and total number of relapses for all 201 and 301 patients, fields with the number of patients who did not complete the trial in each of the treatment arms, fields to provide the number of patients who completed each required MRI study with acceptable quality for each arm.
13. Document any fields that were collected in the CRF but which were not included in the datasets.
14. Includes a sample of active treatment and placebo packaged and labeled as received at study sites.
15. Provide an analysis and a summary addressing the extent to which the sites with clinical investigators who disclosed financial interests contributed to the outcome of the trial. The analysis and summary should include a comparison of the primary outcome for the 201 and 301 trials at sites that had investigators who disclosed financial interests with those sites that did not. Also, please discuss the significance of the percentage of U.S. sites with investigators who made disclosures compared to non-U.S. sites. Provide comparable analyses of the high level safety results (e.g., overall incidence of serious adverse events, discontinuations due to adverse events, and the incidence of any adverse events of special interest such as liver toxicity).

Meeting Discussion:

The sponsor indicated that the date and time of receipt and review of MRI scans may not be available. The sponsor indicated that all imputed endpoint values would be identifiable.

DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

- The content of a complete application was discussed. Major components of the application are expected to be submitted with the original application and are not subject to agreement for late submission. You stated you intend to submit a complete application and therefore, there are no agreements for late submission of application components.
- All applications are expected to include a comprehensive and readily located list of all clinical sites and manufacturing facilities included or referenced in the application.

- As indicated in our communication of October 8, 2014, the Office of New Drugs and the Office of Surveillance and Epidemiology have insufficient information to determine whether a risk evaluation and mitigation strategy (REMS) will be necessary to ensure that the benefits of the drug outweigh the risks, and if it is necessary, what the required elements will be. We will determine the need for a REMS during the review of your application.

If you plan to submit a Risk Evaluation and Mitigation Strategy (REMS) with the original BLA submission, please submit all planned materials identified within the plan that will be necessary to implement your proposal. Education provided as part of a REMS should emphasize the safety messages important for the safe use of the product. Product marketing materials generally are not appropriate to educate about product risks.

For information on the Agency's position on REMS, please refer to the following Guidance for Industry:

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM184128.pdf>.

Please also see the REMS Standardization Report for more information:

<http://www.fda.gov/downloads/ForIndustry/UserFees/PrescriptionDrugUserFee/UCM415751.pdf>.

PREA REQUIREMENTS

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

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

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

PRESCRIBING INFORMATION

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

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

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

MANUFACTURING FACILITIES

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

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

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

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

Corresponding names and titles of onsite contact:

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

Appendix 1:

Table A – Incidence of Abnormal Vital Signs During Treatment

Abnormal Vital Sign (VS) Parameters Relative to Baseline/Pre-treatment VS	Dose 1	Dose 2	Placebo or INF
Supine			
SBP increment ≥ 20 mm Hg			
SBP increment ≥ 40 mm Hg			
SBP decrement ≥ 20 mm Hg			
SBP decrement ≥ 40 mm Hg			
DBP increment ≥ 10 mm Hg			
DBP increment ≥ 20 mm Hg			
DBP decrement ≥ 10 mm Hg			
DBP decrement ≥ 20 mm Hg			
Pulse increment ≥ 15 bpm			
Pulse increment ≥ 30 bpm			
Pulse decrement ≥ 15 bpm			
Pulse decrement ≥ 30 bpm			
Standing			
SBP increment ≥ 20 mm Hg			
SBP increment ≥ 40 mm Hg			
SBP decrement ≥ 20 mm Hg			
SBP decrement ≥ 40 mm Hg			
DBP increment ≥ 10 mm Hg			
DBP increment ≥ 20 mm Hg			
DBP decrement ≥ 10 mm Hg			
DBP decrement ≥ 20 mm Hg			
Pulse increment ≥ 15 bpm			
Pulse increment ≥ 30 bpm			
Pulse decrement ≥ 15 bpm			
Pulse decrement ≥ 30 bpm			
Change from Supine to Standing			
SBP increment ≥ 20 mm Hg			
SBP increment ≥ 40 mm Hg			
SBP decrement ≥ 20 mm Hg			
SBP decrement ≥ 40 mm Hg			
DBP increment ≥ 10 mm Hg			
DBP increment ≥ 20 mm Hg			
DBP decrement ≥ 10 mm Hg			
DBP decrement ≥ 20 mm Hg			
Pulse increment ≥ 15 bpm			
Pulse increment ≥ 30 bpm			
Pulse decrement ≥ 15 bpm			
Pulse decrement ≥ 30 bpm			

SBP = systolic blood pressure
DBP = diastolic blood pressure

Patients are counted once during treatment regardless of number of times achieving the threshold change.

Table B – Summary of changes from baseline in vital sign measurements and body weight

Parameter	Dose 1			Dose 2			Placebo or IFN
	n	mean	SD	n	mean	SD	
SBP (mmHg)							
baseline							
Δ end of treatment							
DBP (mmHg)							
baseline							
Δ end of treatment							
Pulse rate (bpm)							
baseline							
Δ end of treatment							
Weight (kg)							
baseline							
Δ end of treatment							

CLINICAL PHARMACOLOGY SUMMARY AID

1. Goal

The goal of this Aid is to facilitate the creation of an optimal Clinical Pharmacology Summary that summarizes the relevant Clinical Pharmacology findings and focuses sponsor and reviewer on the critical review issues of a submission. To guide sponsors in creating the Clinical Pharmacology Summary in NDA and BLA submissions the Aid provides a generic questionnaire that covers the entire Clinical Pharmacology realm. The aggregate answers provided by sponsors generate the desired Clinical Pharmacology Summary in NDA and BLA submissions. Where needed instructions are added to the questions to clarify what the answers should address. The questions and instructions included in this guide are not intended to be either inclusive of all or exclusive of any questions that specific reviews will address. A special Section of the Clinical Pharmacology Summary should identify and discuss the critical findings and issues and indicate how the unresolved issues are addressed.

The Clinical Pharmacology Summary generated by sponsors is a **stand-alone document**, i.e. the answers to the questions including supporting evidence should be self-sufficient. Appropriate use of complementary tables and figures should be made. The sponsors' answers to the questions should be annotated with links to the detailed information in the study reports and the raw data located in SAS transport files.

2. Question Based Review

2.1 What are the *in vitro* and *in vivo* Clinical Pharmacology and Biopharmaceutics studies and the clinical studies with PK and/or PD information submitted in the NDA or BLA?

All performed Clinical Pharmacology studies (*in vitro* studies with human biomaterials and *in vivo* studies) and clinical studies with PK and/or PD information along with report numbers should be tabulated. Study titles, objectives, treatments (single or multiple doses, size of the dose/interval), demographics (sex, age, race/ethnicity, body weight, creatinine clearance) and numbers of study participants should be listed. Studies whose results support the label should be marked.

2.2 General Attributes of the Drug

2.2.1 What are the highlights of the chemistry and physical-chemical properties of the drug substance and the formulation of the drug product?

Provide background information on the drug substance (description, chemical name, molecular formula, molecular weight, structure), physical characteristics (Log D, solubility, pKa if applicable). Provide tabular information on the drug products, strengths, quantitative composition of ingredients and lot numbers for all formulations used in all *in vivo* studies and indicate corresponding study report numbers.

2.2.2 What are the proposed mechanism of action and therapeutic indications?

2.2.3 What are the proposed dosages and routes of administration?

2.2.4 What drugs (substances, products) indicated for the same indication are approved in the US?

2.3 General Clinical Pharmacology

2.3.1 What are the design features of the clinical pharmacology and biopharmaceutics studies and the clinical studies used to support dosing or claims?

Provide a tabular description of the designs, methodology and salient findings of the clinical pharmacology-, dose-ranging-, and pivotal studies and other clinical studies with PK and/or PD information in brief for each indication. Indicate duration of study, subjects' demographics, dose regimens, endpoints (clinical/biomarkers) and study report numbers.

2.3.2 What is the basis for selecting the response endpoints and how are they measured in clinical pharmacology studies?

Provide a rationale for the selected clinical endpoints and biomarkers. For biomarkers indicate relationship to effectiveness and safety endpoints.

2.3.3 Are the active moieties in plasma and clinically relevant tissues appropriately identified and measured to assess pharmacokinetic

parameters and exposure response relationships?

Indicate circulating active moieties and their plasma and-tissue concentration range after therapeutic doses of the drug of interest. Provide evidence that sensitivity of the assay method(s) used is (are) sufficient to determine apparent terminal $t_{1/2}$ and AUC.

2.4 Exposure-Response

2.4.1 Does the exposure-response relationship support evidence of effectiveness?

Describe briefly the method(s) used to determine the exposure-effectiveness relationship from randomized and well controlled trials (RCT) and other appropriate studies. Provide evidence that the exposure-response analysis supports evidence of effectiveness: e.g. a significant slope in the E-R relationship or a clear separation in effectiveness at different drug levels and placebo.

Indicate whether the selected effectiveness endpoints are continuous, categorical or event driven variables. Indicate the number of pooled subjects studied and identify the trials they were enrolled in. Provide the results of the analysis of the dose- and/or concentration-effectiveness relationship. Indicate major covariates (e.g. age, body weight, sex, race/ethnicity, creatinine clearance, disease severity, genetic factors, hormonal status see also 2.6/2.7) impacting the exposure-effectiveness relationship. If not identifiable by commonly known covariates, evaluate different strategies, for example therapeutic drug monitoring, to maximize effectiveness for patients with a sub-therapeutic exposure.

Provide point estimate as well as a measure of the inter-subject variability for applicable. Indicate minimum and maximum effective dose- and concentration levels (major active moieties). Provide evidence that with the proposed regimens clinically meaningful effectiveness is maintained throughout the entire dose interval or alternatively provide evidence that maintenance of effectiveness during the entire dose interval is not important. Indicate the magnitude of the effect at peak and trough concentrations with the tested dose regimens. Indicate steady-state trough and peak plasma concentrations of the major active moieties with the proposed dose regimens. Indicate whether AUC, C_{max} or C_{min} is more correlated with effectiveness. Show the distribution of the effect size for each dose/concentration level tested.

Justify if an analysis of the exposure-effectiveness relationship was not done.

2.4.2 What are the characteristics of the exposure-response relationships for safety?

Describe briefly the method(s) used to determine the exposure-safety relationship. The analysis should focus on adverse events responsible for

discontinuations and other drug related toxicities. Indicate whether the safety endpoints are continuous, categorical or event driven variables. Indicate the number of pooled subjects studied and identify the trials they were enrolled in. Provide the results of the analysis of the dose- and/or concentration-safety relationship. Indicate the major covariates (e.g. age, body weight, sex, race/ethnicity, creatinine clearance, disease severity, genetic factors, hormonal status) impacting the exposure-safety relationship. Provide point estimate as well as a measure of the inter-subject variability for relevant safety endpoints. Indicate magnitude and/or frequency of relevant adverse events at the tested dose/concentration levels. Indicate proportion of subjects with an excessive adverse response. Indicate whether AUC, C_{max} or C_{min} is more related to clinically relevant adverse effects. Add information on the maximum tolerated single and multiple dose regimens and the corresponding plasma levels [mean (SD) C_{max} and AUC] of the circulating major active moieties.

Justify if an analysis of the exposure-safety relationship was not done.

2.4.3 Does this drug prolong QT/QTc Interval?

Provide a brief description of the study design, regimens, population and data analysis used. Indicate whether plasma concentrations of the drug and the relevant metabolites and the positive control were measured. Give a rationale for the chosen supra-therapeutic dose regimen. Report the findings on the relationship between dose/concentration and QTc interval. Indicate point estimate and 95% confidence interval for the increase of the QTc- interval at the supra-therapeutic dose level. Discuss the relevance of the findings for safety. Provide support for the appropriateness of the selected supra-therapeutic dose, if applicable. Indicate whether the pharmacokinetics of the drug of interest at supra-therapeutic levels is different from that at therapeutic levels.

2.4.4 Is the dose and dosing regimen selected consistent with the known E-R relationship?

Provide information on the criteria used to select the dose regimen (doses, dose intervals) used in the RCTs. Indicate the therapeutic dose and/or concentration range for the drug and provide evidence that the proposed dose regimens are optimal given the effectiveness/safety profile of the drug.

2.5 What are the PK characteristics of the drug?

2.5.1 What are the single and multiple dose PK parameters of parent drug and relevant metabolites in healthy adults?

Briefly describe methods (two-stage and/or population approaches, compartment model dependent or-independent methods) in healthy subjects and in patients with the target disease used to determine the pharmacokinetic parameters of parent drug and relevant metabolites (pharmacologically active or

impacting the exposure to parent drug or co-administered drugs). Provide mean, median (SD, CV%) pharmacokinetic parameters of parent drug and relevant metabolites after single doses and multiple doses at steady-state [C_{max} , t_{max} , AUC, $C_{max,ss}$, $C_{min,ss}$, $C_{max,ss}/C_{min,ss}$, $t_{max,ss}$, $AUC_{0-\tau}$, CL/F, V/F and $t_{1/2}$ (half-life determining accumulation factor), accumulation factor, fluctuation, time to steady-state]. Indicate how attainment of steady-state is determined. Provide evidence for attainment of steady-state.

2.5.2 How does the PK of the drug and its relevant metabolites in healthy adults compare to that in patients with the target disease?

Compare the pharmacokinetic parameters of the drug of interest and relevant metabolites in healthy subjects and patients with the target disease. Provide a rationale for observed significant differences between healthy subjects and patients with the target disease.

2.5.3 What is the inter- and intra-subject variability of the PK parameters in volunteers and patients with the target disease?

Provide mean/median (SD, coefficient of variation, range within 5% to 95% confidence interval bracket for concentrations) about mean AUC, C_{max} , C_{min} , CL/F and $t_{1/2}$ of the parent drug and relevant metabolites after single doses and at steady-state.

2.5.4 What are the characteristics of drug absorption?

Indicate absolute and relative bioavailability, lag time, t_{max} , $t_{max,ss}$, C_{max} , $C_{max,ss}$ and extent of systemic absorption of parent drug and relevant metabolites in healthy subjects and patients with the target disease. Indicate mean (SD) for these parameters.

2.5.5 What are the characteristics of drug distribution?

Indicate mean (SD) V/F for the drug of interest in healthy subjects and patients with target disease. Provide mean (SD) blood/ plasma ratio for parent drug in healthy subjects. Briefly describe method and pH- and temperature conditions used for determining plasma protein binding for parent drug and relevant metabolites. Provide mean (SD) values of the plasma protein binding of the drug of interest and relevant metabolites measured over the therapeutic range in healthy subjects and patients with target disease and special populations.

2.5.6 Does the mass balance study suggest renal or hepatic as the major route of elimination?

Present total, renal and fecal recoveries as percent of the administered total radioactivity. Indicate the percentage of radioactivity excreted as unchanged parent drug in urine and feces and the percent of radioactivity excreted as metabolites in urine and feces.

2.5.7 What is the percentage of total radioactivity in plasma identified as parent drug and metabolites?

Provide identification for $\geq 90\%$ of the circulating total radioactivity (AUC). If multiple small peaks are present whose individual radioactivity is too small to be assignable to individual metabolites provide an estimate for their contribution to circulating total radioactivity.

2.5.8 What are the characteristics of drug metabolism?

Present the metabolic scheme for the drug. Provide an estimate for the contribution of metabolism to the overall elimination of the drug of interest. Indicate mean (SD) values for the non-renal clearance in healthy subjects and patients with the target disease. Indicate whether active metabolites constitute major circulating moieties and if so how much they contribute to effectiveness and/or whether they affect safety.

2.5.9 Is there evidence for excretion of parent drug and/or metabolites into bile?

If appropriate provide *in vitro* and/or *in vivo* evidence suggesting that parent drug and/or metabolites are excreted into bile (*in vitro*: parent drug and/or metabolites are substrates of BCRP, *in vivo*: recovery of unchanged parent drug in mass balance- and absolute bioavailability studies suggest excretion into bile)

2.5.10 Is there evidence for enterohepatic recirculation for parent and/or metabolites?

Indicate whether there are secondary peaks and humps in the plasma concentration profile correlating with food intake.

2.5.11 What are the characteristics of drug excretion in urine?

Provide an estimate of the contribution of renal excretion to the overall elimination of parent drug in healthy volunteers. Present mean values (SD) for the renal clearance (mL/min or mL/min/1.73m²) in healthy subjects and in the target population. Using mean plasma protein binding and renal clearance values in healthy subjects estimate the respective contributions of glomerular filtration and net tubular secretion or re-absorption to renal clearance.

2.5.12 Based on PK parameters, what is the degree of the proportionality of the dose-concentration relationship?

Briefly describe the statistical methods used to determine the type of pharmacokinetics of the drug and its relevant metabolites (linearity, dose

proportionality, non-linearity, time dependency) in healthy subjects and patients with the target disease. Identify the doses tested after single and multiple dose administrations of the drug of interest and the respective dose normalized mean (SD) C_{max} and AUC values in healthy subjects and patients with the target disease. Indicate whether the kinetics of the drug is linear, dose proportionate or nonlinear within the therapeutic range. In case of nonlinear or time dependent pharmacokinetics provide information on the suspected mechanisms involved.

2.5.13 How do the PK parameters change with time following chronic dosing?

Indicate whether the mean ratio of AUC_{0-τ} at steady-state to AUC after the first dose for the circulating major active moieties deviates statistically significantly from 1.0 in healthy subjects and patients with the target disease. Discuss the relevance of the findings and indicate whether an adjustment of the dose regimen is required. If the pharmacokinetics of the drug of interest changes with time provide a rationale for the underlying mechanism.

2.5.14 Is there evidence for a circadian rhythm of the PK?

Indicate whether C_{max} and C_{min} of the parent drug after the morning and evening dose differ significantly. Discuss the relevance of the findings and whether an adjustment of the dose regimen is required for the drug of interest. Provide a rationale for the underlying mechanism for the observed circadian rhythm of the pharmacokinetics of the drug of interest. Indicate whether the dose regimens in the pivotal studies were adjusted for circadian rhythm.

2.6 Intrinsic Factors

2.6.1 What are the major intrinsic factors responsible for the inter-subject variability in exposure (AUC, C_{max}, C_{min}) in patients with the target disease and how much of the variability is explained by the identified covariates?

Provide for all studies investigating the impact of the intrinsic factors (age, sex, body weight, ethnicity/race, renal and hepatic impairment) demographics and number of study subjects, and dose regimens. Provide summaries of the results and indicate intrinsic factors that impact significantly exposure and/or efficacy and safety of the drug of interest. Provide for each major identified covariate an estimate for its contribution to the inter-subject variability and indicate how much of the inter-subject variability is explained by the identified covariates.

Provide mean (SD) parameters for AUC, C_{max}, clearance, volume of distribution and t_{1/2} for pairs studied (e.g. elderly vs. young, male vs. female,

normal body weight vs. obese, race/ethnicity(x) vs. race/ethnicity (y), mild vs. severe target disease)

2.6.2 Based upon what is known about E-R relationships in the target population and their variability, what dosage regimen adjustments are recommended for each group?

Characterize the populations (age, sex, body weight, ethnicity/race) used to determine the impact of each intrinsic factor on variability in exposure and exposure-response. Indicate for each intrinsic factor whether a dose adjustment (change of dose or dose interval or both) is required or not and provide a rationale for either scenario.

2.6.2.1 Severity of Disease State

2.6.2.2 Sex

2.6.2.3 Body Weight

2.6.2.4 Elderly

2.6.2.5 Pediatric Patients

If available provide mean (SD, range) pharmacokinetic parameters, biomarker activity, effectiveness and safety in the pediatric sub-populations (neonates (birth-1 month), infants (1 month- 2 years), children (2-12 years) and adolescents (12- < 16 years) and define the target disease. If no information is available in the pediatric population indicate age groups to be investigated in future studies. Provide a summary stating the rationale for the studies proposed and the endpoints and age groups selected. Include a hyperlink to the development plan of the drug of interest in children.

2.6.2.6 Race/Ethnicity

2.6.2.7 Renal Impairment

Characterize the demographics for each subgroup (normal renal function, mild, moderate and severe renal impairment, on and off dialysis). Indicate mean (SD, range) for creatinine clearance estimated by the Cockcroft-Gault- and MDRD equations for the stages of renal impairment investigated. Provide arithmetic mean (SD) AUC, C_{max} and t_{1/2} of parent drug and relevant metabolites in the different sub-groups assessed by 2-stage or population PK approaches. Show regressions including 90% confidence intervals of AUC, C_{max} and CL/F on Cl_{cr} for parent drug and relevant metabolites. If a population approach is used provide evidence supporting that statistical power was sufficient to determine impact of creatinine clearance.

Indicate mean (SD) for total and renal clearance of the drug in the different sub-groups and provide estimates of the contribution of glomerular filtration and net tubular secretion or re-absorption to the renal excretion of the drug of interest. Indicate whether plasma protein binding of the active moieties is significantly altered in renal impairment and whether the change in the unbound fraction is clinically relevant. Indicate whether a dose adjustment (dose or dose interval, or both) is required or not for each of the sub-groups of patients with impaired renal function and provide a rationale for either scenario.

2.6.2.8 Hepatic Impairment

Characterize the demographics for each subgroup (normal hepatic function, mild, moderate and severe hepatic impairment based on Child-Pugh scores). Provide information on arithmetic mean (SD) AUC, C_{max}, t_{max} and t_{1/2} of parent drug and relevant metabolites in the different hepatic function sub-groups assessed by two-stage or population PK approaches. Show regressions including 90% confidence intervals of C_{max}, AUC or CL/F on the Child-Pugh score for parent drug and relevant metabolites. Indicate whether plasma protein binding of the active moieties is significantly altered in hepatic impairment and whether the change in the unbound fraction is clinically relevant. Indicate whether a dose adjustment is required or not for each of the subgroups of patients with impaired hepatic function and provide a rationale for either scenario. If a population approach is used provide evidence supporting that statistical power was sufficient to determine impact of Child-Pugh score.

2.6.2.9 What pregnancy and lactation use information is available?

2.6.3 Does genetic variation impact exposure and/or response?

Describe the studies in which DNA samples have been collected. If no DNA samples were collected state so. Include a table with links to the studies in which DNA was analyzed and genomic/genetic information is reported. In the description of these studies include demographics, purpose of DNA analysis (effectiveness, safety, drug metabolism, rule in-out of patients, etc.), rationale

for the analysis, procedures for bio-specimen sample collection and DNA isolation, genotyping methods, genotyping results in individual subjects, statistical procedures, genotype-phenotype association analysis and results, interpretation of results, conclusions. If genomic polymorphism impacts either exposure and/or response indicate the measures to be taken to safeguard efficacy and safety of the drug in subjects with varying genotypes. Indicate the contribution of genetic factors to inter-subject variability.

2.6.4 Immunogenicity (NOT applicable to small molecule drugs)

2.6.4.1 What is the incidence (rate) of the formation of the anti-product antibodies (APA), including the rate of pre-existing antibodies, the rate of APA formation during and after the treatment, time profiles and adequacy of the sampling schedule?

2.6.4.2 Does the immunogenicity affect the PK and/or PD of the therapeutic protein?

2.6.4.3 Do the anti-product antibodies have neutralizing activity?

2.6.4.4 What is the impact of anti-product antibodies on clinical efficacy?

2.6.4.5 What is the impact of anti-product antibodies on clinical safety?
Provide information on the incidence of infusion-related reactions, hypersensitivity reactions, and cross-reactivity to endogenous counterparts.

2.7 Extrinsic Factors

2.7.1 Is there an in vitro basis to suspect in vivo drug-drug interactions?

Summarize the results of the in vitro studies performed with the drug of interest as substrate, inhibitor or inducer of relevant CYP and non-CYP enzymes and transporters. Give rationale for why based on the *in vitro* results an interaction study in humans is required or is not required

2.7.2 Is the drug a substrate of CYP enzymes?

Briefly describe the methods used (specific chemicals/antibodies, human recombinant CYP enzymes, human microsomes). Indicate incubate, initial rate conditions, concentration range tested relative to K_m , controls etc. Provide a summary of the results of the *in vitro* studies investigating the drug of interest as a substrate of CYP 450 and non-CYP 450 enzymes. Provide for each of the relevant enzymes a mean estimate for the % contribution to the metabolism of the drug of interest. Discuss the relevance of the in vitro findings for the drug of

interest as a substrate for deciding which drug-drug interactions should be or need not be performed in humans. For each situation provide supporting evidence.

2.7.3 Is the drug an inhibitor and/or an inducer of enzymes?

Briefly describe the methods used (type and source of liver tissue, concentration range tested for the drug of interest as substrate, inhibitor and inducer, experimental conditions, pre-incubation, probe substrates, positive/negative controls. Provide summary results of the *in vitro* studies with human liver tissues for the drug of interest as a potential inhibitor or inducer of enzymes. Indicate whether the drug is a reversible inhibitor (competitive, non-competitive or un-competitive) or an irreversible inhibitor (mechanism based) and supportive evidence. Provide mean (SD) values for K_i , IC_{50} and V_{max} for each relevant enzyme and probe substrate. Indicate the anticipated maximum total and unbound concentration of the drug of interest as inhibitor ($[I]$). Provide the mean (SD) % activity relative to the positive control for the drug of interest as inducer. Discuss the relevance of the *in vitro* findings for the drug of interest as an inhibitor or inducer for deciding which drug-drug interactions should be or need not be performed *in vivo* in humans. If appropriate use the $[I]/K_i$ ratio as a means to assess the likelihood of an *in vitro* result to be clinically relevant. For each situation provide supporting evidence.

2.7.4 Is the drug a substrate, an inhibitor and/or an inducer of transporter processes?

See 2.7.2.2 and 2.7.2.3. The instructions for the interactions of the drug of interest as substrate, inhibitor or inducer of transporters are analogous to those for enzymes.

2.7.5 Are there other metabolic/transporter pathways that may be important?

2.7.6 What extrinsic factors influence exposure and/or response, and what is the impact of any differences in exposure on effectiveness or safety responses?

Indicate extrinsic factors that impact significantly exposure and/or effectiveness and safety of the drug. Indicate extent of increase or decrease in exposure and/or response caused by extrinsic factors. State whether an adjustment of the dose is or is not required and provide supporting evidence for either case.

2.7.7 What are the drug-drug interactions?

Provide a list of the drug-drug interaction studies (PK or PD based mechanism) performed and give a rationale for conducting the listed studies. Indicate the suspected mechanism responsible for the interaction. For each of the *in vivo* studies performed provide a rationale for the design selected (single or multiple dose regimens, randomized/non-randomized cross-over or parallel design for

perpetrator and/or victim).

a) Drug of interest is impacted by co-administered other drugs

Provide information on the demographics of populations, number of subjects, dose levels, and design of the studies performed in humans. Justify the magnitude of the equivalence interval selected if it is greater than the default interval. Report $t_{1/2}$, point estimates and 90% confidence intervals of the geometric mean ratios of AUC and C_{max} for the drug of interest in the presence and absence of each of the co-administered drugs. Provide a summary statement on the drug interaction liability of the drugs as victim. Indicate whether a dose adjustment is required or not. In either case provide a rationale. Define the required adjusted dose regimens.

b) Drug of interest impacts other co-administered drugs

Provide information on the demographics of populations, number of subjects, dose levels, and design of the studies performed in humans. Justify the magnitude of the equivalence interval selected if it is greater than the default interval. Provide a summary statement on the drug interaction liability of the drug as a perpetrator. Report $t_{1/2}$, point estimates and 90% confidence intervals of the geometric mean ratios of AUC and C_{max} for each of the co-administered drugs in the presence and absence of the drug of interest.

2.7.8 Does the label specify co-administration of another drug?

2.7.9 What other co-medications are likely to be administered to the target population?

2.7.10 Is there a known mechanistic basis for pharmacodynamic drug-drug interactions?

2.8 General Biopharmaceutics

For all *in vivo* studies performed in this section indicate study design, demographics and number of subjects enrolled, and type, composition, strength and lot number of the formulations used. Provide summary results with estimates for mean and inter-subject variability on AUC and C_{max} after single and multiple dose administration and peak to trough fluctuation after multiple dose administration.

IR Product

2.8.1 Based on the biopharmaceutical classification system principles, in what class is this drug and formulation? What solubility, permeability and dissolution data support this classification?

2.8.2 How is the proposed to-be-marketed formulation linked to the clinical service formulation?

2.8.2.1 What are the safety or effectiveness issues, if any, for BE studies that fail to meet the 90% CI using equivalence limits of 80-125%?

2.8.2.2 If the formulation does not meet the standard criteria for bioequivalence, what clinical pharmacology and/or safety and efficacy data support the approval of the to-be-marketed product?

2.8.3 What is the effect of food on the bioavailability of the drug when administered as solution or as drug product?

Indicate composition and calories of the food administered, and length of the pre-dose fasting period. State whether the impact of food is on the drug substance or the inactive ingredients of the formulation. Indicate the clinical relevance of findings. Indicate the temporal relationship between drug intake and food intake in the pivotal studies.

2.8.4 Was the bioequivalence of the different strengths of the to be marketed formulation tested? If so were the strengths bioequivalent or not?

2.8.5 If unapproved products or altered approved products were used as active controls, how is BE to the to be marketed product demonstrated? What is the link between the unapproved/altered and to be marketed products?

MR product (if an IR is already marketed)

2.8.6 What is the bioavailability of the MR product relative to the approved IR product? How does the plasma concentration time profile of the MR formulation compare to that of the IR formulation after single and multiple doses?

Indicate whether or not the pharmacokinetics of the drug of interest is linear, dose proportional or nonlinear after administration of the MR formulation. Summarize data on C_{max}, AUC and C_{min} of the IR and MR formulations after a single dose and multiple doses at steady-state. Provide information on the fluctuation factor at steady-state.

2.8.7 What is evidence that MR formulation *in vivo* consistently shows claimed MR characteristics?

2.8.8 What is evidence that MR formulation displays less variability in C_{max}, AUC and C_{min} than IR formulation?

2.8.9 Does the MR product show dose dumping *in vivo*?

Describe design, demographics and number of subjects participating in the studies performed to determine whether dose dumping occurs with the MR formulation when given in the fed state or when given together with alcohol. Present summaries of results.

2.8.10 Does ethanol *in vitro* have a dose-dumping effect on the MR product?

Provide the results of the *in vitro* dissolution testing of the various strengths of the ER product in pH 1.2, 4.5 and 6.8 media containing 0, 5, 10, 20 and 40% alcohol. Discuss any dose dumping observed. If an *in vivo* study was performed report the clinical relevance of the findings.

2.8.11 Are the MR and IR products marketed simultaneously?

If the intention is to market both the MR and IR products, indicate how patients are converted from the IR to the MR product and vice versa.

2.8.12 If the NDA is for an MR formulation of an approved IR product without supportive safety and effectiveness studies, what dosing regimen changes are necessary, if any, in the presence or absence of a PKPD relationship?

2.8.13 In the absence of effectiveness and safety data what data support the NDA for a MR formulation of an approved IR product?

2.9 Analytical Section

2.9.1 How are parent drug and relevant metabolites identified and what are the analytical methods used to measure them in plasma and other matrices?

List all assays used and briefly describe the individual methods.

2.9.2 Which metabolites have been selected for analysis and why?

2.9.3 For all moieties measured, is free, bound, or total measured?

Indicate whether free, bound or total (bound+unbound) concentrations of the drug of interest and relevant metabolites are measured and give a rationale for your selection.

2.9.4 What bioanalytical methods are used to assess concentrations of the measured moieties?

Identify all studies that used a particular assay method. For each assay report indicate the corresponding assay validation report.

2.9.5 What is the range of the standard curve? How does it relate to the requirements for clinical studies? What curve fitting techniques were used?

For each method and analyte provide concentration range of calibration curve and indicate respective concentration range for relevant moieties with therapeutic regimens. Indicate fit type of the calibration curves.

2.9.5.1 What are the lower and upper limits of quantitation?

For each method and analyte indicate LLOD, LLOQ and ULOQ for undiluted and diluted samples.

2.9.5.2 What are the accuracy, precision, and selectivity at these limits?

For each method and analyte indicate inter-day and intra-day precision (CV%) and inter-day and intra-day accuracy (RE%).

2.9.5.3 What is the sample stability under conditions used in the study?

For all studies in which concentrations of the drug of interest and relevant metabolites were measured provide information on initiation date of study, date of last sample analyzed and total sample storage time. For each method and matrix provide information on the stability of the analytes, i.e. number of freeze-thaw cycles, benchtop stability at room temperature and stability during long term storage at $\leq -20^{\circ}$ C.

2.9.5.4 What is the plan for the QC samples and for the reanalysis of the incurred samples?

For each study, method and analyte indicate precision (CV%) and accuracy (%RE) using the QC samples measured alongside samples with unknown concentrations. Indicate the concentrations of the QC and incurred samples used.

2.9.5.5 What evidence is available demonstrating that neither the assay

of the drug on interest is impacted by co-administered other drugs and vice versa?

Applicable to therapeutic proteins only

2.9.5.6 What bioanalytical methods are used to assess therapeutic protein concentrations?

Briefly describe the methods and summarize the assay performance.

2.9.5.7 What bioanalytical methods are used to assess the formation of the anti-product antibodies?

Briefly describe the methods and assay performance including sensitivity, specificity, precision, cut point, interference and matrix, etc.

2.9.5.8 What is the performance of the neutralizing assay(s)?

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

/s/

WILLIAM H Dunn
11/07/2014



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

IND 12,120

PDL BioPharma, Inc.
Attention: Jill A. Henrich
Executive Director, Regulatory Affairs
1400 Seaport Blvd.
Redwood City, CA 94063

Dear Ms. Henrich:

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

We also refer to the End of Phase 2 meeting between representatives of your firm and the FDA on July 24, 2008. The purpose of the meeting was to discuss the proposed registration plan for treatment of multiple sclerosis.

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

If you have any questions, call James H. Reese, Ph.D., RAC, Regulatory Project Manager, at (301) 796-1136.

Sincerely,

{See appended electronic signature page}

Russell Katz, M.D.
Director
Division of Neurology Products
Office of Drug Evaluation 1
Center for Drug Evaluation and Research

Enclosure

MEMORANDUM OF MEETING MINUTES

MEETING DATE: July 24, 2008
TIME: 3:30 PM
LOCATION: White Oak Bldg 22
APPLICATION: IND 12,120
DRUG NAME: Daclizumab
TYPE OF MEETING: End of Phase 2

MEETING CHAIR: Russell Katz, M.D.

MEETING RECORDER: James H. Reese, Ph.D., RAC

FDA ATTENDEES:

Russell Katz
Billy Dunn
Eric Bastings
Barbara Wilcox
Lois Freed
Kun Jin
Ram Sihag
Barbara Rellahan
Tim Robison
Veneeta Tandon
Sripal Mada
Richard Houghtling
Teresa Podruchny

PDL BioPharma, Inc. ATTENDEES:

Michael Panzara
Paula Sandler
Joanne Gibbons
Marianne Sweetser
Tammy Sarnelli
Alice Fong
Lisa Beebe
Gilmore O'Neill
Ann Dodds-Frerichs
Brian Schmidt
Nancy Teasdale
Ingrid Caras
Surekha Akella

Janice Lansita
Mark McCarish
Jacob Elkins
Doug Cecchini

Questions

Non-clinical

1. Does the Agency concur that the non-clinical toxicology studies are adequate to support the registration of daclizumab?

FDA RESPONSE: No. The finding of microglial aggregations in the CNS of monkeys presents a safety concern that needs to be addressed. No neurologic assessments were conducted in any of the nonclinical toxicology studies in monkeys in which microglial aggregates were detected. Therefore, the potential behavioral effects of this finding have not been adequately assessed. In addition, there is concern that, due to the relatively late histopathological evaluation of brain (i.e., after 5 to 20 bi-weekly doses), additional microscopic findings may have been missed. Therefore, we recommend that you conduct additional studies in monkeys that focus on earlier time points and include expanded microscopic examination (e.g., special stains, step sectioning) of the brain. The in-life examinations should include a comprehensive neurological evaluation (e.g., Functional Observation Battery).

Meeting Discussion:

The sponsor indicated that since the incidence or severity of the microglial aggregates did not increase with duration of dosing, a 10-13 week study in monkey was planned in order to further assess the potential neurotoxicity of daclizumab; an FOB will be incorporated into that study. FDA recommended that neurohistopathology be evaluated earlier than 10-13 weeks. There is concern that early damage to vulnerable areas may be cleared and, therefore, be undetectable by 10-13 weeks. A focused neurohistopathology evaluation, to include special stains (to detect neurodegeneration, inflammation) and step sectioning, should be conducted at each sampling time.

2. Does the Agency concur that a peri- and post-natal toxicity study using DAC HYP is not required to support the registration of daclizumab?

FDA RESPONSE: No. If the DAC Nutley material used in the completed peri-and post-natal study cannot be demonstrated to be comparable to the DAC HYP material to be used in the Phase 3 clinical studies (and intended for marketing), you will need to conduct a peri- postnatal study using the DAC HYP material.

Meeting Discussion: None

CMC

3. Does the agency agree with the overall plans for assessing comparability for the changes described?

FDA RESPONSE: Comparability studies should conform to the principles outlined in ICH Q5E. Each time a manufacturing change is made, a risk assessment should be performed to evaluate the potential of the change to affect the drug product. While in general, the information provided on the proposed (b) (4) changes for the production process of the daclizumab drug substance is reasonable, a final determination as to whether the data are adequate to determine comparability will require complete review of the results. In addition, please note the following comments in regard to the comparability assessments in general and in particular for the proposed (b) (4) change to a pre-filled syringe format (PFS).

1. Comparability studies should include an assessment of product stability. This assessment should include product stored at both the recommended storage condition and under accelerated/stressed conditions that induce product degradation within a relatively short period of time. This allows comparison of the degradation pathways of the pre- and post-change batches. This will be particularly important for the proposed change in drug substance (b) (4) to 150 mg/ml and for the move to a pre-filled syringe format (see below).
2. PFS formats have the potential to introduce impurities such as tungsten and silicone that are not normally present in a vial format and which can affect product stability and immunogenicity. Potential leachables from the PFSs should be identified and data on the level of these impurities in the PFS drug product reported. Comparability studies between vial and PFS drug product formats should include a thorough comparison of the degradation pathways of product stored in each format as mentioned above, and should include spiking studies with new impurities found in the PFS drug product to assess their impact on product stability. In addition, an analysis of the immunogenicity of the PFS DP compared to that of the vial DP will be required if new impurities are present. This includes an assessment of the percent of patients who develop anti-product antibody responses as well as the percent that develop neutralizing responses. A comparison of the relative titer of neutralizing antibody between patients who receive the PFS compared to the vial drug product may also be needed.
3. The cover letter of IND submission 12120/113 mentions (b) (4) but no information (b) (4) could be found in that submission. The current package also contains no mention of this (b) (4). Please clarify your plans (b) (4).
4. It is unclear how many lots from a new process will be included in the comparability studies. Data from more than one lot may be required particularly if differences between pre- and post-change lots are observed.

Meeting Discussion:

- 3.1 and 3.2 The sponsor stated that they understand that the Agency needs to know about leachables and stability in regard to the new prefilled syringes. They asked whether they would need to perform an immunogenicity analysis if they showed that new impurities present in the PFS DP are not a concern. FDA responded that with the information available, it is difficult to know whether an analysis of immunogenicity of the PFS DP compared to that of vial DP is needed. The Agency reiterated that it requires some data on immunogenicity when the submission is made. The sponsor asked if the concern was anti-product antibodies. FDA responded in the affirmative.
- 3.3 The sponsor stated that mention (b) (4) in the cover letter was a clerical error. The sponsor enquired if an amendment needed to be filed for correcting the error. FDA responded that the minutes of this meeting should be sufficient to address the error.

Clinical

4. Does the Agency agree that demonstration of a statistically significant effect on the primary endpoint in Study A at 1 year and in Study B at 2 years with at least 2 years of controlled safety data from each study will support registration of daclizumab?

FDA RESPONSE: Yes, keeping in mind the other comments we have made with regard to the proposed studies. As described in your submission, the primary endpoints and durations are acceptable.

Meeting Discussion: None

5. Does the Agency agree that if a superiority analysis of the primary endpoint after a median of 24 months and after all subjects have had a minimum of 18 months of treatment demonstrates statistical significance, then the blinded portion of Study B could be terminated and these data will support registration of daclizumab?

FDA RESPONSE: Yes.

Meeting Discussion: None

6. Does the Agency concur that the proposed clinical development plan would support the following indication statement, if adequate safety and statistically significant efficacy are demonstrated in the proposed Phase 3 studies?

(b) (4)

FDA RESPONSE: Yes.

Meeting Discussion: None

7. Does the Agency agree that the proposed dosing regimen is appropriate for Study A and Study B?

FDA RESPONSE: No. Nonclinical and CMC issues (see answers and comments for those disciplines regarding the need for additional animal studies and demonstration of comparability) may preclude immediate initiation of clinical studies with your proposed dosing regimen. In addition, the adequacy of your proposed safety margin of exposure will be a matter of review. Your proposal to inform the choice of dose for Study B based on an interim futility analysis of Study A appears acceptable.

Meeting Discussion:

The sponsor enquired whether the additional nonclinical study could be performed concurrently with the clinical study. FDA indicated this would be unacceptable as the nonclinical issues need to be resolved prior to starting additional clinical investigations. The sponsor enquired about submitting the proposed protocol as an SPA prior to completion of the required nonclinical study. FDA indicated that such an SPA submission would likely result in a hold and recommended the sponsor wait until the nonclinical issues are resolved. Additionally, FDA noted that nonclinical information informs clinical decisions made during the review process (such as assessment of safety margins for the dose).

8. Does the Agency concur that the projected overall safety database is adequate for registration?

FDA RESPONSE: For products intended for long-term treatment of non-life-threatening conditions, the ICH and FDA have generally recommended that 1500 subjects be exposed to the investigational product (with 300 to 600 exposed for 6 months, and 100 exposed for 1 year). It appears that the total expected exposure to daclizumab at the time of registration falls below our general recommendation. The eventual adequacy of such a safety package will be a matter of review upon submission.

Meeting Discussion: None

Clinical Pharmacology

9. Does the Agency agree that no additional QTc studies are necessary, assuming that these analyses do not show an effect of daclizumab on the QT interval?

FDA RESPONSE: Yes.

Meeting Discussion: None

10. Does the Agency agree that no formal drug-drug interaction studies are necessary?

FDA response: Monoclonal antibodies targeted to interleukins have the potential to affect CYP systems. We recommend that you conduct an *in vitro* study using human hepatocytes to assess

the potential for drug interactions. If the findings are positive, *in vivo* drug interaction studies may be necessary.

Additional Clinical Pharmacology comment: In addition to the trough samples planned for study A, you should take intensive PK sampling in about 15-20 subjects in a subgroup of population to adequately characterize PK, and include a POP PK analysis plan in the protocol. You should also determine the impact of CD25 expression on the PK/PD on daclizumab.

Meeting Discussion:

The sponsor clarified that the daclizumab was targeted to the IL- receptor and not to the IL itself, and as such may not affect the CYP systems based on current knowledge. The agency agreed that *in vitro* studies to assess the potential of drug-drug interactions may not be necessary in that case.

The sponsor sought clarification of the agency expectation on assessing the impact of CD25 expression on the PK/PD of daclizumab and whether the agency expectation was to collect CD25 expression data at baseline and evaluate its impact on the PK/PD. The Agency agreed to this.

The sponsor indicated that they do not intend to take intensive PK samples in Study A, but plan to do so in Study B. They also indicated that Study DAC 1012 was conducted in patients, but the Agency emphasized that Study DAC1012 did not use the DAC HYP product. The Agency agreed that it was acceptable to take intensive samples in Study B, as the intent was the adequate characterization of the PK in patients.

Post meeting comment:

Upon discussion with the biologics experts within the Agency it was felt that even though the current literature does not suggest a potential for drug interaction with monoclonal antibodies targeted to the IL-receptor, our understanding of the mechanistic basis of interleukin based interactions with biologics is limited at this time. Given this, the Agency recommends that the sponsor conduct the *in vitro* study using human hepatocytes to assess the potential of drug interactions.

11. Does the Agency concur that a pediatric waiver is appropriate for daclizumab?

FDA RESPONSE: No. The Division is currently reviewing the policy regarding pediatric drug development of MS products. You should explore a pediatric development plan with pediatric MS experts. We will inform you when we make a determination of what studies will be required (if any).

Meeting Discussion:

The sponsor noted that this represents a change from previous experience with the Agency and asked about additional background. FDA stated that the Agency's consideration of a change in policy with respect to pediatric waivers in MS is ongoing and in an early phase. While deferral to the post-marketing phase for any required pediatric studies is likely, FDA strongly

recommended the sponsor seek advice from MS experts and start developing a plan. The sponsor indicated they understood these comments and will begin discussions with experts in the field.

Statistics Comments and Requests

- Study A will be modified from a trial that is currently ongoing in Europe. We have no information about the ongoing study, its primary endpoint, or its modifications. We would like to review the protocol of the ongoing study.
Meeting Discussion: None
- There are some inconsistencies in the wording of the primary endpoint for Study A. On pages 11 and 91, you stated that the primary endpoint will be the annualized relapse rate after 1 year. On page 121, you stated that the primary objective is to determine the effect ... on reducing the number of relapses between baseline and Week 52. Please clarify if the primary endpoint will be the annualized relapse rate at the end of Week 52.
Meeting Discussion:
Biogen Idec will clarify the primary endpoints relative to week 52.
- The protocol concept for Study A states that subjects who switch to an alternative MS therapy will be censored at the time they switch or add treatment. Since subjects are allowed to add IFN- β after 6 months with 1 relapse, the protocol should add information about whether or not those subjects will be censored.
Meeting Discussion: None
- A futility analysis is planned for Study A. You need to submit detailed information regarding the plan for such an analysis before it is conducted.
Meeting Discussion:
The SAP should be sent to the Agency before the final analysis begins. FDA needs the criteria by which the effect will be determined. A firewall should be included. If possible, provide the SAP with the protocol.

Meeting Discussion: None

Linked Applications

Sponsor Name

Drug Name

IND 12120

PDL BIOPHARMA INC

Daclizumab, [humanized monoclonal antibody, anti-CD25 (recombinant, Hoffmann-La Roche) to ^{(b) (4)} subunit of the interleukin-2 receptor]

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/s/

ERIC P BASTINGS

08/22/2008

LATE-CYCLE COMMUNICATION
DOCUMENTS



BLA 761029

LATE-CYCLE MEETING MINUTES

Biogen
Attention: Trevor Mill,
Senior Vice President, Regulatory Affairs
14 Cambridge Center
Cambridge, MA 02142

Dear Mr. Mill:

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

We also refer to the Late-Cycle Meeting (LCM) between representatives of your firm and the FDA on February 24, 2016.

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

If you have any questions, contact Laurie Kelley, PA-C, Regulatory Project Manager at laurie.kelley@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

John Marler, M.D.
Clinical Team Leader
Division of Neurology Products
Office of Drug Evaluation I
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: February 24, 2016, 10 AM – 12 PM EST
Meeting Location: Teleconference

Application Number: BLA 761029
Product Name: daclizumab
Indication: Relapsing forms of multiple sclerosis
Sponsor/Applicant Name: Biogen

FDA ATTENDEES

Ellis Unger, M.D., Director, OND/Office of Drug Evaluation I
Billy Dunn, M.D., Director, Division of Neurology Products
Eric Bastings, M.D., Deputy Director, Division of Neurology Products
Laurie Kelley, PA-C, Regulatory Project Manager, Division of Neurology Products
Heather Fitter, M.D., Clinical Team Leader, Division of Neurology Products
Lawrence Rodichok, M.D., Clinical Reviewer, Division of Neurology Products
Alice Hughes, Deputy Director for Safety, Division of Neurology Products
Sally Yasuda, PharmD., Division of Neurology Products
Lourdes Villalba, M.D., Division of Neurology Products
Tracy Peters, PharmD., Associate Director for Labeling, Division of Neurology Products
Jamie Wilkins-Parker, PharmD., Office of Surveillance and Epidemiology, Division of Risk Management
Robert Pratt, PharmD., Office of Surveillance and Epidemiology, Division of Risk Management

EASTERN RESEARCH GROUP ATTENDEES

Marc Goldstein, Independent Assessor

APPLICANT ATTENDEES

Gary Bloomgren, Vice President Safety and Benefit Risk (Biogen)
Peter McCroskery, Senior Director, Safety and Benefit Risk (Biogen)
Joan Holman, Safety (Abbvie)
Jacob Elkins, Senior Director, Medical Research (Biogen)
Tammy Sarnelli, Senior Director, Regulatory Affairs (Biogen)
Paula Sandler, Vice President, Regulatory Affairs (Biogen)

1.0 BACKGROUND

BLA 761029 was submitted on February 27, 2015 for Zinbryta (daclizumab HYP).

Proposed indication(s): Relapsing forms of multiple sclerosis

PDUFA goal date: May 27, 2016

FDA issued a Background Package in preparation for this meeting on February 18, 2016.

2.0 DISCUSSION

1. Introductory Comments

Welcome, Introductions, Ground rules, and Objectives of the meeting were presented.

Discussion: FDA welcomed the sponsor to the late cycle meeting and expressed their plan to follow the agenda closely and to share substantive review issues identified.

2. Discussion of Substantive Review Issues

- Drug-induced liver injury
- Immune-mediated and autoimmune conditions
- Cutaneous reactions
- Lymphadenopathy
- Infections
- Systemic inflammatory conditions with multi-organ failure
- Malignancies
- Acute hypersensitivity reactions

Discussion:

Specific points were highlighted for each of the review issues, reflecting the data in the submission.

FDA noted that with respect to the comparison of malignancies (non-Hodgkin lymphoma and breast cancer in females), it is difficult to characterize the risk from daclizumab without a comparator in the total daclizumab pool and it is difficult to determine the most appropriate background rate.

A discussion of immune-mediated autoimmune conditions included acute hypersensitivity reactions, and other immune and autoimmune diseases. The Agency clarified that this review issue heading was meant to be a topical heading, recognizing that not all of the adverse reactions noted under this category would necessarily be considered autoimmune.

3. Additional Applicant Data

Discussion: There was no additional discussion.

4. Information Requests

Discussion: The Sponsor noted that they were working towards providing a response to pending safety information requests by March 3, 2016.

5. REMS or Other Risk Management Actions

Discussion: FDA stated that they had not yet determined whether a REMS or other risk management strategy in addition to appropriate labeling would be required, and clarified that we are considering options ranging from no REMS to REMS with elements to assure safe use.

6. Postmarketing Requirements/Postmarketing Commitments

We are considering the following post-marketing requirements if the drug is approved:

- A pregnancy registry.
- An observational registry to further characterize the risk and outcomes of specific safety signals.
- A study to identify predictive biomarkers for serious skin reactions.

Other postmarketing requirements or commitments remain to be determined but will be provided as quickly as possible.

Discussion: No further clarifications were discussed.

7. Major Labeling Issues

We anticipate that labeling would include a boxed warning for at least the significant safety issue of hepatotoxicity if the drug is approved.

Discussion: FDA noted that labeling for the safety issues was complex and clarified that the period of labeling negotiations would begin at the earliest opportunity.

8. Review Plans

There is no change in review plans.

Discussion:

9. Wrap-up and Action Items

Discussion:

The Sponsor is working towards providing responses to outstanding information requests by March 3, 2016.

The Agency will act as quickly as we can to provide labeling, REMS, and PMRs.

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/

JOHN R MARLER
04/06/2016