

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

761053Orig1s000

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION ¹		
BLA # 761053		If NDA, Efficacy Supplement Type: N/A <i>(an action package is not required for SE8 or SE9 supplements)</i>
Proprietary Name: OCREVUS Established/Proper Name: Ocrelizumab Dosage Form: Injectable Solution		Applicant: Genentech, Inc. Agent for Applicant (if applicable): Sonali Patel, PharmD
RPM: LCDR Nahleen Lopez		Division: Division of Neurology Products
NDA Application Type: ☐ 505(b)(1) ☐ 505(b)(2) Efficacy Supplement: ☐ 505(b)(1) ☐ 505(b)(2) BLA Application Type: ☐ 351(k) ☒ 351(a) Efficacy Supplement: ☐ 351(k) ☐ 351(a)		<u>For ALL 505(b)(2) applications, two months prior to EVERY action:</u> - Review the information in the 505(b)(2) Assessment and submit the draft² to CDER OND IO for clearance. - Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity) ☐ No changes ☐ New patent/exclusivity <i>(notify CDER OND IO)</i> Date of check: <i>Note: If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.</i>
❖ Actions		
- Proposed action - User Fee Goal Date is <u>03/28/17</u>		☒ AP ☐ TA ☐ CR
Previous actions <i>(specify type and date for each action taken)</i>		☒ None
❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain _____		☐ Received ☒ N/A
❖ Application Characteristics ³		

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

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

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

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

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

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

NDAs: Subpart H

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

Subpart I

- ☐ Approval based on animal studies

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

BLAs: Subpart E

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

Subpart H

- ☐ Approval based on animal studies

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

Comments:

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

Action Letters	
❖ Copies of all action letters (including approval letter with final labeling)	Action(s) and date(s): AP 03/28/17
Labeling	
❖ Package Insert (write submission/communication date at upper right of first page of PI)	
Most recent draft labeling (if it is division-proposed labeling, it should be in track-changes format)	☒ Included
Original applicant-proposed labeling	☒ Included
❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling (write submission/communication date at upper right of first page of each piece)	☒ Medication Guide ☒ Patient Package Insert ☐ Instructions for Use ☐ Device Labeling ☐ None
Most-recent draft labeling (if it is division-proposed labeling, it should be in track-changes format)	☒ Included
Original applicant-proposed labeling	☒ Included
❖ Labels (full color carton and immediate-container labels) (write submission/communication date on upper right of first page of each submission)	
Most-recent draft labeling	☒ Included
❖ Proprietary Name	☒ Included
- Acceptability/non-acceptability letter(s) (indicate date(s)) - Review(s) (indicate date(s))	Dates: 07/22/16 and 07/29/16
❖ Labeling reviews (indicate dates of reviews)	RPM: ☐ None DMEPA: ☒ 10/18/16; 11/01/16; 02/14/17 DMPP: ☒ 03/16/17 OPDP: ☒ 03/16/17 SEALD: ☒ None CSS: ☒ None Product Quality: ☒ 11/02/16 Other: ☒ None
Administrative / Regulatory Documents	
❖ RPM Filing Review ⁴ /Memo of Filing Meeting (indicate date of each review)	RPM: 08/18/16
❖ All NDA 505(b)(2) Actions: Date each action cleared by 505(b)(2) Clearance Committee	☒ Not a (b)(2)
❖ NDAs/NDA supplements only: Exclusivity Summary (signed by Division Director)	☐ Completed
❖ Application Integrity Policy (AIP) Status and Related Documents http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	
Applicant is on the AIP	☐ Yes ☒ No

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

- This application is on the AIP - If yes, Center Director's Exception for Review memo (<i>indicate date</i>) - If yes, OC clearance for approval (<i>indicate date of clearance communication</i>)	☐ Yes ☐ No ☐ Not an AP action
❖ Pediatrics (<i>approvals only</i>) Date reviewed by PeRC <u>03/01/17</u> If PeRC review not necessary, explain: <u>N/A</u>	☒ Included
❖ Breakthrough Therapy Designation	☐ N/A
Breakthrough Therapy Designation Letter(s) (granted, denied, an/or rescinded)	Granted 02/01/16
CDER Medical Policy Council Breakthrough Therapy Designation Determination Review Template(s) (<i>include only the completed template(s) and not the meeting minutes</i>)	☒ Included
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>) (completed CDER MPC templates can be found in DARRTS as clinical reviews or on the MPC SharePoint Site)	☒ Included
❖ 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	
If not the first review cycle, any end-of-review meeting (<i>indicate date of mtg</i>)	☒ N/A or no mtg
Pre-NDA/BLA meeting (<i>indicate date of mtg</i>)	☒ 12/08/16 and 02/04/16
EOP2 meeting (<i>indicate date of mtg</i>)	☒ 12/05/08 and 09/22/10
Mid-cycle Communication (<i>indicate date of mtg</i>)	☒ 08/09/16
Late-cycle Meeting (<i>indicate date of mtg</i>)	☒ 10/18/16
Other milestone meetings (e.g., EOP2a, CMC focused milestone meetings) (<i>indicate dates of mtgs</i>)	Meeting Minutes CMC (4)
❖ Advisory Committee Meeting(s)	☒ No AC meeting
Date(s) of Meeting(s)	N/A
Decisional and Summary Memos	
❖ Office Director Decisional Memo (<i>indicate date for each review</i>)	☒ 03/28/17
Division Director Summary Review (<i>indicate date for each review</i>)	☒ 03/28/17
Cross-Discipline Team Leader Review (<i>indicate date for each review</i>)	☒ 11/28/16
PMR/PMC Development Templates (<i>indicate total number</i>)	☒ 03/28/17 (13)
Clinical	

❖ Clinical Reviews	
• Clinical Team Leader Review(s) (indicate date for each review)	☒ SEE CDTL 11/28/16
• Clinical review(s) (indicate date for each review)	☒ 12/12/16
• Clinical Safety Team Leader Review(s) (indicate date for each review)	☒ 10/25/16
• Clinical Safety review(s) (indicate date for each review)	☒ 09/14/16
• Social scientist review(s) (if OTC drug) (indicate date for each review)	☒ None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here ☐ and include a review/memo explaining why not (indicate date of review/memo)	YES (see page 187 of clinical reviewer)
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers (indicate date of each review) ⁵	☒ Oncology 06/28/16 ☒ Hematology 07/05/16 ☒ Epidemiology 07/18/16; 11/17/16 ☒ DPMH 11/10/16
❖ Controlled Substance Staff review(s) and Scheduling Recommendation (indicate date of each review)	☒ 04/08/16
❖ Risk Management • REMS Documents and REMS Supporting Document (indicate date(s) of submission(s)) • REMS Memo(s) and letter(s) (indicate date(s)) 09/26/16 • 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)	☒ 09/26/16
❖ OSI Clinical Inspection Review Summary(ies) (include copies of OSI letters to investigators)	☒ Included
Clinical Microbiology ☒ None	
❖ Clinical Microbiology Team Leader Review(s) (indicate date for each review)	☐ No separate review
Clinical Microbiology Review(s) (indicate date for each review)	☐ None
Biostatistics ☐ None	
❖ Statistical Division Director Review(s) (indicate date for each review)	☒
Statistical Team Leader Review(s) (indicate date for each review)	☒
Statistical Review(s) (indicate date for each review)	☒ Included with Addendum 10/27/16 and 02/10/17
Clinical Pharmacology ☐ None	
❖ Clinical Pharmacology Division Director Review(s) (indicate date for each review)	☒ No separate review
Clinical Pharmacology Team Leader Review(s) (indicate date for each review)	☒ No separate review
Clinical Pharmacology review(s) (indicate date for each review)	☒ 09/16/16
❖ OSI Clinical Pharmacology Inspection Review Summary (include copies of OSI letters)	☒ 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 ☐ None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) (indicate date for each review)	☒ 12/13/16
• Supervisory Review(s) (indicate date for each review)	☒ 12/05/16
• Pharm/tox review(s), including referenced IND reviews (indicate date for each review)	☒ 11/17/16
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer (indicate date for each review)	☒ None
❖ Statistical review(s) of carcinogenicity studies (indicate date for each review)	☒ No carc
❖ ECAC/CAC report/memo of meeting	☒ None Included in P/T review, page
❖ OSI Nonclinical Inspection Review Summary (include copies of OSI letters)	☒ None requested
Product Quality ☐ None	
❖ Product Quality Discipline Reviews ⁶	
• Tertiary review (indicate date for each review)	☒ None
• Secondary review (e.g., Branch Chief) (indicate date for each review)	☒ None
• Integrated Quality Assessment (contains the Executive Summary and the primary reviews from each product quality review discipline) (indicate date for each review)	☒ Primary CMC 11/28/16 Addendum #1 11/23/16 Addendum #2 03/20/17
❖ Reviews by other disciplines/divisions/Centers requested by product quality review team (indicate date of each review)	☒ Micro CMC 10/28/16 ☒ Sterility CMC 10/29/16
❖ Environmental Assessment (check one) (original and supplemental applications)	
☐ Categorical Exclusion (indicate review date)(all original applications and all efficacy supplements that could increase the patient population)	N/A
☐ Review & FONSI (indicate date of review)	N/A
☐ Review & Environmental Impact Statement (indicate date of each review)	N/A
❖ Facilities Review/Inspection	
☒ Facilities inspections (indicate date of recommendation; within one week of taking an approval action, confirm that there is an acceptable recommendation) (only original applications and efficacy supplements that require a manufacturing facility inspection(e.g., new strength, manufacturing process, or manufacturing site change)	☒ Acceptable Re-evaluation date: ☐ Withhold recommendation ☐ Not applicable

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

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

Lopez, Nahleen (FDA)

From: Ware, Jacqueline H
Sent: Monday, March 27, 2017 5:22 PM
To: Sonali Patel
Cc: Tiffany Wan; Michelle Rohrer; Eric Olson; Lopez, Nahleen (FDA); Ware, Jacqueline H
Subject: RE: Sponsor proposed labeling for BLA 761053 - March 27, 2017
Attachments: OCREVUS MG FDAedits_27Mar17v3.docx

Dear Sonali,

We have reviewed your proposed Medication Guide. It is acceptable except for 2 sentences. Please see the attached and let me know if our revisions are acceptable.

With regard to the carton and container labeling, please confirm that:

1. The carton change is to certain numbers in the solution ingredient list. Specifically the trailing zeros have been removed (i.e., 0.20mg is now 0.2 mg; 40.00 mg is now 40 mg).
2. With the exception of the change described in item 1 above, the carton labeling is unchanged and identical to carton labeling submitted October 31, 2016.
3. Ocrevus container labels are unchanged and identical to container labeling submitted October 31, 2016.

If items 1-3 above are correct, a formal resubmission of draft carton and container labeling is not required.

Best regards,
Jackie

Jacqueline H. Ware, Pharm.D.
Captain, United States Public Health Service
Chief, Project Management Staff

Center for Drug Evaluation and Research
Office of Drug Evaluation I, Division of Neurology Products
U.S. Food and Drug Administration
Tel: 301-796-1160
Jacqueline.ware@fda.hhs.gov



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From: Sonali Patel [<mailto:patel.sonali@gene.com>]
Sent: Monday, March 27, 2017 3:25 PM
To: Ware, Jacqueline H
Cc: Tiffany Wan; Michelle Rohrer; Eric Olson; Lopez, Nahleen (FDA)
Subject: Sponsor proposed labeling for BLA 761053 - March 27, 2017

Dear Jackie,

Medication Guide

Attached is the Sponsor's rebuttal. All edits were accepted, aside from a minor editorial edit from us. This document is now only pending the confirmation of "recommendation".

USPI

In the interest of time, I've attached a document with the Sponsor's proposal of substantive changes to Section 14.1 and 14.2. In parallel, we are editing the USPI in tracked changes and will get that off to you as soon as possible.

Carton and Container Labeling Change (Based on USPI update)

Based on the editorial change to the numbers for the contents of the solution in Section 11, the Carton and Container labeling was also updated. Please let me know if a formal resubmission is also required for this change.

Kindly,

Sonali

--

Sonali Patel, Pharm.D.
Associate Program Director
Product Development Regulatory
Genentech, A Member of the Roche Group
Phone: (650) 580-3613
Email: patel.sonali@gene.com

This email and any and all attachments contain information that is confidential and may not be disclosed without prior written consent from Genentech/Roche

2 Pages of Draft Labeling have been Withheld in Full as B4 (CCI/TS) immediately following this page

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

/s/

REBECCA N LOPEZ
03/31/2017

Lopez, Nahleen (FDA)

From: Ware, Jacqueline H
Sent: Thursday, March 23, 2017 2:00 PM
To: Sonali Patel
Cc: Michelle Rohrer (rohrer.michelle@gene.com); wan.tiffany@gene.com; Lopez, Nahleen (FDA); Eric Olson (olson.eric@gene.com); Ware, Jacqueline H
Subject: RE: BLA 761053 - additional postmarketing requirement

Dear Dr. Patel,

The Division's review team has provided the following response to your March 21, 2017, question regarding the nonclinical PMR.

The PMR for an expanded pre- and postnatal development study in monkey, to include an assessment of immune function, is necessary because:

- The completed embryofetal development study in monkey was conducted using ocrelizumab (v 0.1 DS) manufactured by a different manufacturing process than that used in the pivotal clinical studies (v 0.4 DS). There are insufficient data to conclude that v 0.1 DS and v 0.4 DS are comparable.
- In the completed pre- and postnatal development study, the TDAR evaluation was inadequate because of methodological problems. Therefore, there was no assessment of potential long-term effects of ocrelizumab on immune function.

If you have additional questions, please let me know.

Best regards,

Jackie

Jacqueline H. Ware, Pharm.D.

*Captain, United States Public Health Service
Chief, Project Management Staff*

Center for Drug Evaluation and Research
Office of Drug Evaluation I, Division of Neurology Products
U.S. Food and Drug Administration
Tel: 301-796-1160
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From: Sonali Patel [<mailto:patel.sonali@gene.com>]
Sent: Tuesday, March 21, 2017 5:54 PM
To: Ware, Jacqueline H

Cc: Michelle Rohrer (rohrer.michelle@gene.com); wan.tiffany@gene.com; Lopez, Nahleen (FDA); Eric Olson (olson.eric@gene.com)

Subject: Re: BLA 761053 - additional postmarketing requirement

Dear Dr. Ware,

The team have reviewed the proposed PMR, and taking into consideration the completed Pre- and Postnatal Development (PPND) study in Cynomolgus Monkeys (Study No. 06-1260) and the ongoing Developmental Immunotoxicity study (including TDAR) in Juvenile Cynomolgus Monkeys (Study No. 15-1309), we are unclear about what new information could be gathered by the conduct of an additional expanded PPND study.

Can the Agency please clarify the intent of this PMR and provide additional insight on the major design elements to support the study objective?

If this is more easily addressed via a quick call with nonclinical reviewers, we can certainly make ourselves available. The nonclinical team is located in (b) (4) so we have a bit more flexibility in terms of timing than usual.

Thank you.

Kind regards,

Sonali

On Mon, Mar 20, 2017 at 3:53 PM, Sonali Patel <patel.sonali@gene.com> wrote:
Dear Dr. Ware,

I acknowledge receipt and will respond as soon as possible.

Kindly,

Sonali

On Mon, Mar 20, 2017 at 3:49 PM, Ware, Jacqueline H <Jacqueline.Ware@fda.hhs.gov> wrote:

Dear Dr. Patel,

Reference is made to BLA 761053/ocrelizumab. Provided below is an additional FDAAA PMR. Please review and provide a formal submission that includes your proposed milestone dates and confirmation of your agreement to this PMR. It is acceptable for you to email your responses in advance of a formal, archival submission as long as both communications (email & archive) contain identical information. We ask that you submit your responses by 4:30pm EST, Thursday, March 23, 2017.

Postmarketing Requirement

An expanded pre-and postnatal development study (including T-cell dependent antibody response [TDAR]) of Ocrevus in nonhuman primate.

Draft Protocol Submission:	MM/DD/YYYY
Final Protocol Submission:	MM/DD/YYYY
Study/Trial Completion:	MM/DD/YYYY
Final Report Submission:	MM/DD/YYYY

If you have any questions regarding this request, please let me know.

Best regards,

Jackie

Jacqueline H. Ware, Pharm.D.
Captain, United States Public Health Service
Chief, Project Management Staff

Center for Drug Evaluation and Research

Office of Drug Evaluation I, Division of Neurology Products

U.S. Food and Drug Administration

10903 New Hampshire Avenue; WO22 Rm. 4346
Silver Spring, MD 20993-0002

Tel: [301-796-1160](tel:301-796-1160)
Jacqueline.ware@fda.hhs.gov

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<image002.jpg> <image003.jpg> <image004.jpg> <image005.jpg> <image006.jpg>

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--

Sonali Patel, Pharm.D.

Associate Program Director

Product Development Regulatory

Genentech, A Member of the Roche Group

Phone: [\(650\) 580-3613](tel:(650)580-3613)

Email: patel.sonali@gene.com

This email and any and all attachments contain information that is confidential and may not be disclosed without prior written consent from Genentech/Roche

--

Sonali Patel, Pharm.D.

Associate Program Director

Product Development Regulatory

Genentech, A Member of the Roche Group

Phone: [\(650\) 580-3613](tel:(650)580-3613)

Email: patel.sonali@gene.com

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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/

REBECCA N LOPEZ
03/26/2017

Lopez, Nahleen (FDA)

From: Ware, Jacqueline H
Sent: Monday, March 20, 2017 6:50 PM
To: patel.sonali@gene.com
Cc: Michelle Rohrer (rohrer.michelle@gene.com); wan.tiffany@gene.com; Lopez, Nahleen (FDA); Eric Olson (olson.eric@gene.com); Ware, Jacqueline H
Subject: BLA 761053 - additional postmarketing requirement

Dear Dr. Patel,

Reference is made to BLA 761053/ocrelizumab. Provided below is an additional FDAAA PMR. Please review and provide a formal submission that includes your proposed milestone dates and confirmation of your agreement to this PMR. It is acceptable for you to email your responses in advance of a formal, archival submission as long as both communications (email & archive) contain identical information. We ask that you submit your responses by 4:30pm EST, Thursday, March 23, 2017.

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Draft Protocol Submission:	MM/DD/YYYY
Final Protocol Submission:	MM/DD/YYYY
Study/Trial Completion:	MM/DD/YYYY
Final Report Submission:	MM/DD/YYYY

If you have any questions regarding this request, please let me know.

Best regards,
Jackie

Jacqueline H. Ware, Pharm.D.
Captain, United States Public Health Service
Chief, Project Management Staff

Center for Drug Evaluation and Research
Office of Drug Evaluation I, Division of Neurology Products
U.S. Food and Drug Administration
10903 New Hampshire Avenue; WO22 Rm. 4346
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REBECCA N LOPEZ
03/26/2017

Lopez, Nahleen (FDA)

From: Ware, Jacqueline H
Sent: Tuesday, March 14, 2017 5:51 PM
To: patel.sonali@gene.com
Cc: Michelle Rohrer (rohrer.michelle@gene.com); wan.tiffany@gene.com; Lopez, Nahleen (FDA); Eric Olson (olson.eric@gene.com); Ware, Jacqueline H
Subject: FDA proposed labeling for BLA 761053/Ocrelizumab
Attachments: Ocrevus PI- FDAedits to sponsor 14Mar17.docx

Follow Up Flag: Follow up
Flag Status: Flagged

Dear Dr. Patel,

Attached please find FDA's proposed draft labeling for the above referenced application (clean version). The base document is the Genentech's proposed labeling submitted on July 8, 2016. Comments, where applicable, are also included.

Please share this proposed labeling with the appropriate people on your team and let me know if it is acceptable. If you wish to send a counter-proposal, please provide it via email as a tracked-changes WORD document using our proposed labeling as the base.

We ask that you respond request as soon as possible but no later than 4:30pm EST Monday, March 20, 2017.

If you have any questions, please don't hesitate to contact me.

Best regards,
Jackie

Jacqueline H. Ware, Pharm.D.
Captain, United States Public Health Service
Chief, Project Management Staff

Center for Drug Evaluation and Research
Office of Drug Evaluation I, Division of Neurology Products
U.S. Food and Drug Administration
10903 New Hampshire Avenue; WO22 Rm. 4346
Silver Spring, MD 20993-0002

Tel: 301-796-1160
Jacqueline.ware@fda.hhs.gov



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19 Page(s) of Draft Labeling have been Withheld in Full as B4 (CCI/TS) immediately following this page

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

/s/

REBECCA N LOPEZ
03/26/2017

Lopez, Nahleen (FDA)

From: Ware, Jacqueline H
Sent: Thursday, March 09, 2017 12:18 PM
To: Sonali Patel
Cc: Nguyen, Anhtu (Annie); rohrer.michelle@gene.com; wan.tiffany@gene.com; Jennifer Sexton; Bauerlien, Melinda; Lopez, Nahleen (FDA); Ware, Jacqueline H
Subject: RE: Information request for Ocrelizumab BLA 761053

Follow Up Flag: Follow up
Flag Status: Flagged

Dear Dr. Patel,

Thank you for providing the below PMC information via email and a formal BLA amendment (received March 8, 2017). In follow-up, the team has one additional request.

With regard to PMC 6, a submission date for the final qualification report was not included. As such, we ask that you agree to providing this report and commit to a submission date. Our proposal is below, shown in red, underline text. We are basing this report submission date on timeframes provided by Jennifer Mercer of Genentech in her November 25, 2016, electronic communication. We are open to a minor adjustment in the report submission date given that Genentech has adjusted the protocol submission date to the next quarter (as compared to the November 25, 2016 communication).

6	To manufacture, qualify, and implement new primary and secondary reference standards that are representative of the pivotal clinical study materials. The qualification protocol will be submitted as a PAS, and the final qualification report will be submitted to the BLA. The qualification protocol will be submitted by May 31, 2017. <u>The reference standard qualification report will be submitted by December 31, 2017.</u>
---	---

Please review and provide a formal submission that restates your proposed milestone dates and agreement to all eight PMCs outlined in your March 8, 2017, BLA amendment with the additional report submission date included under PMC 6. It is acceptable for you to email your responses in advance of a formal, archival submission as long as both communications (email & archive) contain identical information. We ask that you submit your responses by 4:30pm EST, Wednesday, March 15, 2017.

In addition, I will be sending a separate communication later today in response to your March 7, 2017, question regarding PMR 1. I do not yet have any update regarding labeling.

Best regards,
Jackie

Jacqueline H. Ware, Pharm.D.
Captain, United States Public Health Service
Chief, Project Management Staff

Center for Drug Evaluation and Research
Office of Drug Evaluation I, Division of Neurology Products
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From: Sonali Patel [mailto:patel.sonali@gene.com]
Sent: Tuesday, March 07, 2017 5:15 PM
To: Ware, Jacqueline H
Cc: Nguyen, Anhtu (Annie); rohrer.michelle@gene.com; wan.tiffany@gene.com; Jennifer Sexton; Bauerlien, Melinda; Lopez, Nahleen (FDA)
Subject: Re: Information request for Ocrelizumab BLA 761053

Dear Dr. Ware,

We plan to formally submit this information tomorrow to the BLA as a Response to Request for Information.

Please let me know if you have any comments regarding this approach.

Kindly,

Sonali

On Tue, Mar 7, 2017 at 1:49 PM, Ware, Jacqueline H <Jacqueline.Ware@fda.hhs.gov> wrote:

Dear Dr. Patel,

Kindly confirm that the information provided below will be submitted officially to the BLA.

Best regards,

Jackie

Jacqueline H. Ware, Pharm.D.
Captain, United States Public Health Service
Chief, Project Management Staff

Center for Drug Evaluation and Research

Office of Drug Evaluation I, Division of Neurology Products

U.S. Food and Drug Administration

Tel: [301-796-1160](tel:301-796-1160)
Jacqueline.ware@fda.hhs.gov



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From: Sonali Patel [mailto:patel.sonali@gene.com]

Sent: Tuesday, March 07, 2017 4:40 PM

To: Nguyen, Anhtu (Annie)

Cc: rohrer.michelle@gene.com; wan.tiffany@gene.com; Jennifer Sexton; Bauerlien, Melinda; Lopez, Nahleen (FDA); Ware, Jacqueline H

Subject: Re: Information request for Ocrelizumab BLA 761053

Dear Dr. Nguyen,

The Sponsor accepts the PMC's proposed. Please find below the commitment dates as requested.

1	To perform a shipping study to confirm validation of the commercial ocrelizumab drug product shipping conditions. The study will be performed using representative shipping routes and drug product that has been stored for an extended period. The study will include testing of pre- and post-shipping samples for product quality (purity by SE-HPLC, reduced and non-reduced CE-SDS, IE-HPLC, sub-visible particles, visible particles, clarity/opalescence, and potency) and confirmation that the commercial shipping configuration minimizes physical damage to drug product containers. The final validation study report will be submitted by August 31, 2017.
2	To confirm validation of the Antibody-Dependent Cellular Cytotoxicity assay (Method Q12764). The validation study will be performed to demonstrate suitability of the method to be used as a potency assay for drug substance release testing. The final validation report will be provided by June 30, 2017.
3	To confirm validation of the Capillary Electrophoresis Glycan Analysis assay (Method Q12756). The validation study will be performed to demonstrate suitability of the method to be used to assess levels of high-mannose 5 glycan (Man-5) for drug substance release testing. The final validation report will be provided by June 30, 2017.
4	To confirm validation of the Reversed-Phase Ultra-High-Performance Liquid Chromatography assay (Method Q13406). The validation study will be performed to demonstrate suitability of the method to

	be used to assess levels of Fc oxidation for drug substance release testing. The final validation report will be provided by June 30, 2017.
5	To confirm validation of the Polysorbate 20 assay (Method SAM-0106429) or develop, validate, and implement an alternative assay to evaluate Polysorbate 20. The validation study will be performed to demonstrate suitability of the method for use in detecting degradation of polysorbate 20 during drug product storage and to be included in the drug product release specifications. The final validation report and updated specifications, if applicable, will be submitted to the BLA. The final validation report and updated specifications, if applicable, will be provided by May 31, 2017.
6	To manufacture, qualify, and implement new primary and secondary reference standards that are representative of the pivotal clinical study materials. The qualification protocol will be submitted as a PAS, and the final qualification report will be submitted to the BLA. The qualification protocol will be submitted by May 31, 2017.
7	To perform a leachable study to evaluate the drug product container closure system through the end of shelf-life when stored under the recommended conditions. Testing will be performed at regular intervals and will include appropriate methods to detect, identify, and quantify organic non-volatile (e.g., HPLC-UV-MS), volatile (e.g., headspace GC-MS) and semi-volatile (e.g., GC-MS) species and metals (e.g., ICP-MS). Study results will be updated annually in the BLA Annual Report. The complete data and risk evaluation for potential impact of leachables on product safety and quality will be submitted to the BLA. The final report, including 24 month study time point, will be submitted by May 31, 2019. (NOTE: Study duration extends beyond the current shelf life)
8	To confirm that the updates to the ocrelizumab drug substance manufacturing process and controls lead to the manufacturing of drug substance with critical product quality attributes consistent with those of the drug substance used to manufacture pivotal clinical study drug product. The process validation protocol will be submitted by April 7, 2017. The final validation report will be submitted by March 30, 2018.

Feel free to reach out with any questions you might have.

Warm regards,

Sonali

On Mon, Feb 27, 2017 at 12:04 PM, Sonali Patel <patel.sonali@gene.com> wrote:

Dear Annie,

I acknowledge receipt of these PMC's and will follow-up with you with the dates as requested.

Kindly,

Sonali

On Mon, Feb 27, 2017 at 11:47 AM, Nguyen, Anhtu (Annie) <Anhtu.Nguyen@fda.hhs.gov> wrote:

Dear Dr. Patel,

Please refer to BLA 761053.

The CMC team has prepared the following list of PMCs for your acceptance and request that you provide commitment dates by COB **March 7, 2017**:

1. To perform a shipping study to confirm validation of the commercial ocrelizumab drug product shipping conditions. The study will be performed using representative shipping routes and drug product that has been stored for an extended period. The study will include testing of pre- and post-shipping samples for product quality (purity by SE-HPLC, reduced and non-reduced CE-SDS, IE-HPLC, sub-visible particles, visible particles, clarity/opalescence, and potency) and confirmation that the commercial shipping configuration minimizes physical damage to drug product containers.

The final validation study report will be submitted by XXX, XX, 2017 (Genentech to provide date).

2. To confirm validation of the Antibody-Dependent Cellular Cytotoxicity assay (Method Q12764). The validation study will be performed to demonstrate suitability of the method to be used as a potency assay for drug substance release testing.

The final validation report will be provided by XXX, XX, 2017 (Genentech to provide date).

3. To confirm validation of the Capillary Electrophoresis Glycan Analysis assay (Method Q12756). The validation study will be performed to demonstrate suitability of the method to be used to assess levels of high-mannose 5 glycan (Man-5) for drug substance release testing.

The final validation report will be provided by XXX, XX, 2017 (Genentech to provide date).

4. To confirm validation of the Reversed-Phase Ultra-High-Performance Liquid Chromatography assay (Method Q13406). The validation study will be performed to demonstrate suitability of the method to be used to assess levels of Fc oxidation for drug substance release testing.

The final validation report will be provided by XXX, XX, 2017 (Genentech to provide date).

5. To confirm validation of the Polysorbate 20 assay (Method SAM-0106429) or develop, validate, and implement an alternative assay to evaluate Polysorbate 20. The validation study will be performed to demonstrate suitability of the method for use in detecting degradation of polysorbate 20 during drug product storage and to be included in the drug product release specifications. The final validation report and updated specifications, if applicable, will be submitted to the BLA.

The final validation report and updated specifications, if applicable, will be provided by XXX, XX, XXXX (Genentech to provide date).

6. To manufacture, qualify, and implement new primary and secondary reference standards that are representative of the pivotal clinical study materials. The qualification protocol will be submitted as a PAS, and the final qualification report will be submitted to the BLA.

The qualification protocol will be submitted by XXX, XX, 2017 (Genentech to provide date).

The final qualification report will be submitted by XXX, XX, 2017 (Genentech to provide date).

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

The final report will be submitted by XXX, XX, XXXX (Genentech to provide date).

8. To confirm that the updates to the ocrelizumab drug substance manufacturing process and controls lead to the manufacturing of drug substance with critical product quality attributes consistent with those of the drug substance used to manufacture pivotal clinical study drug product.

The process validation protocol will be submitted by XXX, XX, 2017 (Genentech to provided date).

The final validation report will be submitted by XXX, XX, 20XX (Genentech to provide date).

Warm regards,

Annie

Annie Nguyen, RPh
Regulatory Project Manager

Division of Neurology Products
Office of Drug Evaluation I

Center for Drug Evaluation and Research
U.S. Food and Drug Administration
Tel: [240-402-4460](tel:240-402-4460)
anhtu.nguyen@fda.hhs.gov



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--

Sonali Patel, Pharm.D.
Associate Program Director

Product Development Regulatory

Genentech, A Member of the Roche Group

Phone: [\(650\) 580-3613](tel:6505803613)

Email: patel.sonali@gene.com

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--

Sonali Patel, Pharm.D.
Associate Program Director

Product Development Regulatory

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Phone: [\(650\) 580-3613](tel:(650)580-3613)

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Sonali Patel, Pharm.D.
Associate Program Director
Product Development Regulatory
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Phone: [\(650\) 580-3613](tel:(650)580-3613)
Email: patel.sonali@gene.com

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APPEARS THIS WAY ON ORIGINAL

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/s/

REBECCA N LOPEZ
03/26/2017

Lopez, Nahleen (FDA)

From: Ware, Jacqueline H
Sent: Thursday, March 23, 2017 3:26 PM
To: patel.sonali@gene.com
Cc: Michelle Rohrer (rohrer.michelle@gene.com); wan.tiffany@gene.com; Eric Olson (olson.eric@gene.com); Lopez, Nahleen (FDA); Ware, Jacqueline H
Subject: RE: BLA 761053 - Postmarketing requirements

Dear Sonali,

Thank you for your message. My apologies for the confusion. You are correct. We have agreed upon dates for the PREA PMR, as submitted on March 10, 2017. Another BLA submission regarding these dates is not required.

Best regards,
Jackie

Jacqueline H. Ware, Pharm.D.
Captain, United States Public Health Service
Chief, Project Management Staff

Center for Drug Evaluation and Research
Office of Drug Evaluation I, Division of Neurology Products
U.S. Food and Drug Administration
10903 New Hampshire Avenue; WO22 Rm. 4346
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From: Sonali Patel [<mailto:patel.sonali@gene.com>]
Sent: Thursday, March 23, 2017 1:40 PM
To: Ware, Jacqueline H
Cc: Michelle Rohrer (rohrer.michelle@gene.com); wan.tiffany@gene.com; Lopez, Nahleen (FDA); Eric Olson
Subject: Re: BLA 761053 - Postmarketing requirements

Dear Jackie,

Quick clarification question. On our phone call yesterday, you requested that the pediatric requirement dates be formally submitted to the application.

I know we have had some discussion about the pediatric dates of Part B; however, based on the feedback from reviewers, I believe that we have agreed on the same dates as those submitted on March 10, 2017. Given this, can you confirm you require another submission to the BLA with these dates?

Thanks,

Sonali

On Fri, Mar 10, 2017 at 12:32 PM, Sonali Patel <patel.sonali@gene.com> wrote:
Dear Dr. Ware,

This is a courtesy notification to inform you that the Sponsor response to the proposed PMRs has been formally submitted to the BLA. I have attached a copy here for your reference.

Please let me know if you have any questions.

Hope you have a nice weekend,

Sonali

On Mon, Mar 6, 2017 at 5:14 PM, Sonali Patel <patel.sonali@gene.com> wrote:
Dear Dr. Ware,

I acknowledge receipt of these PMR's on behalf of our team and will aim to get you our responses by the date requested.

Kindly,

Sonali

On Mon, Mar 6, 2017 at 4:44 PM, Ware, Jacqueline H <Jacqueline.Ware@fda.hhs.gov> wrote:
Dear Dr. Rohrer:

Reference is made to BLA 761053/ocrelizumab and to the late cycle meeting held on October 18, 2016, during which we discussed with you possible postmarketing requirements and commitments (PMRs and PMCs) for this application. Provided below are four PMRs that we plan to issue. Please review and provide a formal submission that includes your proposed milestone dates and confirmation of your agreement to the PMRs. It is acceptable for you to email your responses in advance of a formal, archival submission as long as both communications (email & archive) contain identical information. We ask that you submit your responses by 4:30pm EST, Friday, March 10, 2017.

When determining your "Final Protocol Submission" dates for these PMRs, please take into account the time required to reach agreement on final protocol designs. Also, for PMR 4 (a deferred pediatric trial under PREA), please propose milestone dates in alignment with those described in ocrelizumab's Agreed Initial Pediatric Study Plan (AiPSP) for multiple sclerosis (see October 2, 2015, Agency Agreement Letter under IND 100593).

Postmarketing Requirements

1. Conduct a prospective longitudinal observational study in adult patients with relapsing multiple sclerosis and primary progressive multiple sclerosis exposed to Ocrevus (ocrelizumab) to determine the incidence and mortality rates of breast cancer and all malignancies. All patients enrolled in the study should be followed for a minimum of 5 years or until death following their first exposure to Ocrevus. The protocol must specify two appropriate populations to which the observed incidence and mortality rates will be compared.

Draft Protocol Submission:	MM/DD/YYYY
Final Protocol Submission:	MM/DD/YYYY
Study/Trial Completion:	MM/DD/YYYY
Final Report Submission:	MM/DD/YYYY

2. Conduct prospective pregnancy exposure registry cohort analyses in the United States that compare the maternal, fetal, and infant outcomes of women with multiple sclerosis exposed to ocrelizumab during pregnancy with two unexposed control populations: one consisting of women with multiple sclerosis who have not been exposed to ocrelizumab before or during pregnancy and the other consisting of women without multiple sclerosis. The registry will identify and record pregnancy complications, major and minor congenital malformations, spontaneous abortions, stillbirths, elective terminations, preterm births, small-for-gestational-age births, and any other adverse outcomes, including postnatal growth and development. Outcomes will be assessed throughout pregnancy. Infant outcomes, including effects on postnatal growth and development, will be assessed through at least the first year of life.

Draft Protocol Submission:	MM/DD/YYYY
Final Protocol Submission:	MM/DD/YYYY
Study/Trial Completion:	MM/DD/YYYY
Final Report Submission:	MM/DD/YYYY

3. Conduct a pregnancy outcomes study using a different study design than provided for in PMR 2 (for example a retrospective cohort study using claims or electronic medical record data or a case control study) to assess major congenital malformations, spontaneous abortions, stillbirths, and small for gestational age in women exposed to ocrelizumab during pregnancy compared to an unexposed control population.

Draft Protocol Submission:	MM/DD/YYYY
Final Protocol Submission:	MM/DD/YYYY
Study/Trial Completion:	MM/DD/YYYY
Final Report Submission:	MM/DD/YYYY

4. Conduct a two-part study of ocrelizumab in pediatric patients with RMS at least 10 years and less than 17 years of age. Part A is an open-label study of the safety, tolerability, pharmacokinetics (PK) and pharmacodynamics (PD) of ocrelizumab in pediatric patients. Part A will include two cohorts, one with body weights less than 40 kg and the other with body weights 40 kg or more. The objective of Part A is to determine a dose of ocrelizumab that will result in PK and PD effects that are comparable to those of a 600 mg dose (300 mg given twice 14 days apart) in adult patients with RMS. Safety assessments will continue for at least 2 years after the last dose of ocrelizumab. Part B is a randomized, double-blind, parallel-group study to evaluate the efficacy and safety of ocrelizumab compared to an appropriate comparator.

Draft Protocol Submission:	MM/DD/YYYY
Final Protocol Submission:	MM/DD/YYYY
Study/Trial Completion:	MM/DD/YYYY
Final Report Submission:	MM/DD/YYYY

Lastly, I expect to have a first draft of proposed FDA labeling to share with you by the end of this week.

If you have questions, please let me know.

Best regards,

Jackie

Jacqueline H. Ware, Pharm.D.
Captain, United States Public Health Service
Chief, Project Management Staff

Center for Drug Evaluation and Research

Office of Drug Evaluation I, Division of Neurology Products

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Sonali Patel, Pharm.D.
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Phone: (650) 580-3613
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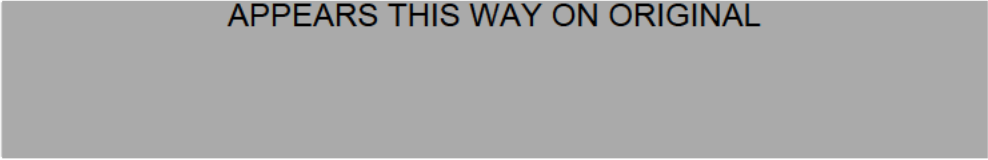
Sonali Patel, Pharm.D.
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Phone: (650) 580-3613
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Sonali Patel, Pharm.D.
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Product Development Regulatory
Genentech, A Member of the Roche Group
Phone: (650) 580-3613
Email: patel.sonali@gene.com

APPEARS THIS WAY ON ORIGINAL



PeRC Meeting Minutes
March 1, 2017

PeRC Members Attending:

Lynne Yao
John Alexander
Gettie Audain
Jacqueline Yancy
Donna Snyder
Lily Mulugeta
Robert "Skip" Nelson
Dionna Green
Victor Baum
Rosemary Addy
Hari Cheryl Sachs
Kevin Krudys
Barbara Buch
Wiley Chambers
Gil Burkhart
Gerri Baer
Adrienne Hornatko-Munoz
Maura O'leary
Julia Pinto
Tom Smith
Greg Reaman
Freda Cooner
Daiva Shetty
Susan McCune

Agenda

[illegible]

Non Responsive

Ocrevus (ocrelizumab) Full Waiver/Partial Waiver/Deferral/Plan (with Agreed iPSP)

- Proposed indication: Primary Progressive Multiple Sclerosis (PPMS) and (b) (4)
- The PREA trigger is new active ingredient and indication with a PDUFA date of March 28, 2017.
- The division clarified that the sponsor is requesting a full waiver is for PPMS and a partial waiver for (b) (4)
- The PeRC recommends that the timeline reflect specific study dates that the division would like the sponsor to complete. The division clarified that the studies may all be included in a single PMR.
- The PeRC acknowledged that there is still insufficient evidence to agree to pediatric extrapolation at this time, but there may be additional data based on programs in progress for other MS drugs that can be evaluated that could potentially increase the knowledge available and support consideration of pediatric extrapolation. The PeRC encouraged the

division to consider what information would be needed to increase the confidence in pediatric extrapolation (b) (4)

- PeRC pharmacologist recommends that a PK study sampling scheme should be evaluated when the protocol is submitted so that the sampling scheme can be optimized.
- *PeRC Recommendations:*
 - The PeRC concurs with the division to grant a full waiver for PPMS and for (b) (4) a partial waiver from birth to less than 10 years of age because the studies are highly impractical.
 - The PeRC concurs with the division to grant a deferral in pediatric studies for ages 10 to 17 years of age until adult studies are completed as agreed upon in the Agreed iPSP.

Non Responsive

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

/s/

GETTIE AUDAIN
03/22/2017

Ware, Jacqueline H

From: Ware, Jacqueline H
Sent: Monday, March 06, 2017 7:44 PM
To: Michelle Rohrer (rohrer.michelle@gene.com)
Cc: wan.tiffany@gene.com; Lopez, Nahleen (FDA); patel.sonali@gene.com; Eric Olson; patel.sonali@gene.com; Ware, Jacqueline H
Subject: BLA 761053 - Postmarketing requirements

Dear Dr. Rohrer:

Reference is made to BLA 761053/ocrelizumab and to the late cycle meeting held on October 18, 2016, during which we discussed with you possible postmarketing requirements and commitments (PMRs and PMCs) for this application. Provided below are four PMRs that we plan to issue. Please review and provide a formal submission that includes your proposed milestone dates and confirmation of your agreement to the PMRs. It is acceptable for you to email your responses in advance of a formal, archival submission as long as both communications (email & archive) contain identical information. We ask that you submit your responses by 4:30pm EST, Friday, March 10, 2017.

When determining your "Final Protocol Submission" dates for these PMRs, please take into account the time required to reach agreement on final protocol designs. Also, for PMR 4 (a deferred pediatric trial under PREA), please propose milestone dates in alignment with those described in ocrelizumab's Agreed Initial Pediatric Study Plan (AiPSP) for multiple sclerosis (see October 2, 2015, Agency Agreement Letter under IND 100593).

Postmarketing Requirements

1. Conduct a prospective longitudinal observational study in adult patients with relapsing multiple sclerosis and primary progressive multiple sclerosis exposed to Ocrevus (ocrelizumab) to determine the incidence and mortality rates of breast cancer and all malignancies. All patients enrolled in the study should be followed for a minimum of 5 years or until death following their first exposure to Ocrevus. The protocol must specify two appropriate populations to which the observed incidence and mortality rates will be compared.

Draft Protocol Submission:	MM/DD/YYYY
Final Protocol Submission:	MM/DD/YYYY
Study/Trial Completion:	MM/DD/YYYY
Final Report Submission:	MM/DD/YYYY

2. Conduct prospective pregnancy exposure registry cohort analyses in the United States that compare the maternal, fetal, and infant outcomes of women with multiple sclerosis exposed to ocrelizumab during pregnancy with two unexposed control populations: one consisting of women with multiple sclerosis who have not been exposed to ocrelizumab before or during pregnancy and the other consisting of women without multiple sclerosis. The registry will identify and record pregnancy complications, major and minor congenital malformations, spontaneous abortions, stillbirths, elective terminations, preterm births, small-for-gestational-age births, and any other adverse outcomes, including postnatal growth and development. Outcomes will be assessed throughout pregnancy. Infant outcomes, including effects on postnatal growth and development, will be assessed through at least the first year of life.

Draft Protocol Submission:	MM/DD/YYYY
Final Protocol Submission:	MM/DD/YYYY
Study/Trial Completion:	MM/DD/YYYY

Final Report Submission:	MM/DD/YYYY
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3. Conduct a pregnancy outcomes study using a different study design than provided for in PMR 2 (for example a retrospective cohort study using claims or electronic medical record data or a case control study) to assess major congenital malformations, spontaneous abortions, stillbirths, and small for gestational age in women exposed to ocrelizumab during pregnancy compared to an unexposed control population.

Draft Protocol Submission:	MM/DD/YYYY
Final Protocol Submission:	MM/DD/YYYY
Study/Trial Completion:	MM/DD/YYYY
Final Report Submission:	MM/DD/YYYY

4. Conduct a two-part study of ocrelizumab in pediatric patients with RMS at least 10 years and less than 17 years of age. Part A is an open-label study of the safety, tolerability, pharmacokinetics (PK) and pharmacodynamics (PD) of ocrelizumab in pediatric patients. Part A will include two cohorts, one with body weights less than 40 kg and the other with body weights 40 kg or more. The objective of Part A is to determine a dose of ocrelizumab that will result in PK and PD effects that are comparable to those of a 600 mg dose (300 mg given twice 14 days apart) in adult patients with RMS. Safety assessments will continue for at least 2 years after the last dose of ocrelizumab. Part B is a randomized, double-blind, parallel-group study to evaluate the efficacy and safety of ocrelizumab compared to an appropriate comparator.

Draft Protocol Submission:	MM/DD/YYYY
Final Protocol Submission:	MM/DD/YYYY
Study/Trial Completion:	MM/DD/YYYY
Final Report Submission:	MM/DD/YYYY

Lastly, I expect to have a first draft of proposed FDA labeling to share with you by the end of this week.

If you have questions, please let me know.

Best regards,
Jackie

Jacqueline H. Ware, Pharm.D.
Captain, United States Public Health Service
Chief, Project Management Staff

Center for Drug Evaluation and Research
Office of Drug Evaluation I, Division of Neurology Products
U.S. Food and Drug Administration
10903 New Hampshire Avenue; WO22 Rm. 4346
Silver Spring, MD 20993-0002

Tel: 301-796-1160
Jacqueline.ware@fda.hhs.gov



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/s/

JACQUELINE H WARE
03/06/2017



BLA 761053

MEETING MINUTES

Genentech, Inc.
Attention: Jennifer Sexton
Pharma Technical Regulatory
1 DNA Way
South San Francisco, CA 94080

Dear Ms. Sexton:

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

We also refer to the meeting between representatives of your firm and the FDA on December 14, 2016. The purpose of the meeting was to discuss the pending BLA.

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 Melinda Bauerlien, Senior Regulatory Business Process Manager at (301) 796-0906.

Sincerely,

{See appended electronic signature page}

Steven Kozlowski, Ph.D.
Office Director
Office of Biotechnology Products
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes

MEMORANDUM OF MEETING MINUTES

Meeting Type: C
Meeting Category: CMC

Meeting Date and Time: December 14, 2016 at 9:00 AM
Meeting Location: Teleconference

Application Number: BLA 761053

Product Name: ocrelizumab
Indication: For the treatment of patients with PPMS
Sponsor/Applicant Name: Genentech, Inc.

Meeting Chair: Steven Kozlowski, Ph.D.
Meeting Recorder: Melinda Bauerlien, M.S.

FDA ATTENDEES

Steven Kozlowski, Ph.D., Office Director, OBP
Kathleen Clouse, Ph.D., Division Director, Division of Biotechnology Review and Research I
Milos Dokmanovic, Ph.D., Product Reviewer, Division of Biotechnology Review and Research I
Sarah Kennett, Ph.D., Review Chief, Division of Biotechnology Review and Research I
Billy Dunn, M.D., Director, Division of Neurology Products, OND/ODEI/DNP
Robert Temple, M.D., Deputy Director, Office of Drug Evaluation I, OND/ODEI
Eric Bastings, M.D., Deputy Director, Division of Neurology Products, OND/ODEI/DNP
John Marler, M.D., Medical Officer, OND/ODEI/DNP
Jacqueline Ware, Chief Project Manager, OND/ODEI/DNP
Nahleen Lopez, Regulatory Project Manager, DNP
Melinda Bauerlien, M.S., Senior Regulatory Business Process Manager, OPRO

SPONSOR ATTENDEES

Damian Cunningham, Ph.D., Technical Development Leader
Jennifer Sexton, Technical Regulatory Leader
John Joly, Ph.D., Senior Director, Analytical Development and Quality Control
Pin Yee Wong, M.S., Director, Biological Technologies
Robert Kiss, Ph.D., Senior Director, Late Stage Cell Culture
Jennifer Mercer, Senior Director, Pharma Technical Regulatory
Lynne Krummen, Ph.D., Vice President, Pharma Technical Development
Michelle Rohrer, Ph.D., Senior Vice President, Pharma Development Regulatory
Ralf Altenburger, Ph.D., Senior Vice President, Pharma Technical Regulatory
Patricia Hancock, Senior Director of Quality, Vacaville
Jamie Moore, Ph.D., Senior Director, Late Stage Pharmaceutical Development
Hideki Garren M.D., Group Medical Director, Clinical Science Leader
Fabian Model, Ph.D., Biostatistics Leader

Ann Santen, Global Operations Program Leader
Erica Evans, Ph.D., Senior Global Regulatory Leader
Simona Skerjanec, MBA, Lifecycle Leader
Sonali Patel, Pharm.D., Associate Program Director, US Regulatory
Tiffany Wan, Associate Program Director, US Regulatory

1.0 BACKGROUND

To discuss the pending BLA.

2.0 DISCUSSION

The sponsor acknowledged the concerns regarding process validation, robustness, and proposed control strategy and stated that it is fully committed to resolving any outstanding issues. The sponsor recognizes the challenge posed by this complex application and appreciates the specific feedback that was provided by the Agency. The sponsor stated they have not received feedback regarding the most recent information request responses or proposed PMCs. The sponsor believes that the manufacturing process control is appropriate and would like to understand the Agency's concerns and receive guidance regarding the next steps.

The Agency responded that one of the ongoing concerns is related to the difference in potency between ocrelizumab manufactured using the proposed commercial process and the pivotal clinical material and the lack of understanding of the root cause of the difference. The sponsor believes that the process performance is now consistent with that of the commercial process and it is convinced that it can control any potential sources of variation. The Agency stated that sponsor's interpretation regarding the sources of variability is still under discussion and noted that (b) (4). The sponsor stated that it believes that (b) (4). The sponsor reiterated that it understands the concerns and the issues for which the Agency needed further clarification. The Agency acknowledged that some lots are where they should be with respect to potency; however, the sponsor needs to show that it can consistently produce batches. The sponsor stated that data from additional lots are in line with the pivotal material (b) (4).

Regarding the drug product stability issue, the sponsor stated that it will include polysorbate 20 testing in the stability study for the 15 month shelf life. The sponsor clarified that currently it has sufficient supply to get to market. The Agency responded that the concern with the 15 month shelf life is that without better understanding of the mechanism of polysorbate 20 degradation, it will be hard to assure that the batches that have not yet been produced will not be out of specification at time points earlier than 15 months. The sponsor stated that it is working on solutions to reduce degradation that it has generated new information regarding polysorbate degradation of the early (pivotal) material, and that it plans to submit the information to the Agency. The sponsor stated that it is committed to understanding the sources of degradation.

The Agency responded that there is a big difference in degradation of the early (pivotal) material compared to the later (commercial) material and it would be useful to understand the difference.

The sponsor stated that they have a consistency report for 2016 and a process qualification protocol that they can provide along with the new drug product data. The Agency responded that they will review any data the sponsor can provide.

The sponsor asked if any new data would extend the clock. The Agency responded that any new information that arises that could affect the approvability of the BLA will likely extend the clock.

The sponsor asked if there were any additional issues or only the CMC issues discussed. The Agency responded that the issues are primarily CMC but the other reviews are under discussion. The Agency stated that the CMC issues are being discussed in the context of the breakthrough designation. The Agency will review the additional information that the sponsor provides and respond as to whether the clock will be extended.

3.0 ATTACHMENTS AND HANDOUTS

A copy of the slides presented during the meeting are attached.

APPEARS THIS WAY ON ORIGINAL

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/s/

MELINDA J BAUERLIEN
02/27/2017

STEVEN KOZLOWSKI
02/27/2017



BLA 761053

MEETING MINUTES

Genentech, Inc.
Attention: Jennifer Sexton
Pharma Technical Regulatory
1 DNA Way
South San Francisco, CA 94080

Dear Ms. Sexton:

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

We also refer to the meeting between representatives of your firm and the FDA on January 31, 2017. The purpose of the meeting was to discuss the pending BLA.

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 Melinda Bauerlien, Senior Regulatory Business Process Manager at (301) 796-0906.

Sincerely,

{See appended electronic signature page}

Steven Kozlowski, Ph.D.
Office Director
Office of Biotechnology Products
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes

MEMORANDUM OF MEETING MINUTES

Meeting Type: C
Meeting Category: CMC

Meeting Date and Time: January 31, 2017 at 1:00 PM
Meeting Location: Teleconference

Application Number: BLA 761053

Product Name: ocrelizumab
Indication: For the treatment of patients with PPMS
Sponsor/Applicant Name: Genentech, Inc.

Meeting Chair: Steven Kozlowski, Ph.D.
Meeting Recorder: Melinda Bauerlien, M.S.

FDA ATTENDEES

Steven Kozlowski, Ph.D., Office Director, OBP
Kathleen Clouse, Ph.D., Division Director, Division of Biotechnology Review and Research I
Milos Dokmanovic, Ph.D., Product Reviewer, Division of Biotechnology Review and Research I
Sarah Kennett, Ph.D., Review Chief, Division of Biotechnology Review and Research I
Billy Dunn, M.D., Director, Division of Neurology Products, OND/ODEI/DNP
Eric Bastings, M.D., Deputy Director, Division of Neurology Products, OND/ODEI/DNP
Lawrence Rodichok, M.D., Medical Officer, OND/ODEI/DNP
Jacqueline Ware, Chief Project Manager, OND/ODEI/DNP
Nahleen Lopez, Regulatory Project Manager, DNP
Melinda Bauerlien, M.S., Senior Regulatory Business Process Manager, OPRO

SPONSOR ATTENDEES

Michelle Rohrer, Head of Product Development Regulatory
Ralf Altenburger, Head of Global Pharma Technical Regulatory
Lynne Krummen, Vice President, Pharma Technical Development
Patricia Hancock, Senior Director, Vacaville Site Quality Head
Andrea Goddard, Vice President, Drug Substance Quality Head
Benedicte Lebreton, Vice President, Pharma Technical Regulatory
Jennifer Mercer, Senior Director, Pharma Technical Regulatory
Damian Cunningham, Technical Development Leader
Jennifer Sexton, Technical Regulatory Leader
Jamie Moore, Senior Director, Late Stage Pharmaceutical Development
John Joly, Senior Director, Analytical Development & QC
Jesse Bergevin, Associate Director, Manufacturing Sciences, Vacaville
Simona Skerjanec, Ocrevus Life Cycle Team Leader
Erica Evans, Global Regulatory Leader

Anne-Marie Li-Kwai-Cheung, Global Development Team Leader
Paulo Fontoura, Head of Clinical Science, Neuroscience
Lesley Luginbill, Technical Regulatory Program Manager
Sonali Patel, Associate Regulatory Program Director

1.0 BACKGROUND

To discuss the pending BLA.

2.0 DISCUSSION

The Agency sent the following to the sponsor prior to the teleconference:

If all indications can be approved, we will work toward resolving remaining CMC issues through post-marketing commitments (e.g., those noted in an email from Jennifer Mercer), including those to perform appropriate drug product shipping and leachables studies, to perform method validation for the ADCC potency assay and other product quality assays included in the updated release and stability specifications, and to implement more appropriate reference standards.

Other CMC issues have been partially mitigated through the control strategy changes that were implemented during the initial portion of the BLA review cycle. Post-approval adjustments to those changes (e.g., manufacturing process parameters, in-process testing, release testing, the post-approval lifecycle management plan, and expiry periods) can be proposed in post-approval submissions to the BLA. These adjustments should be submitted as prior-approval supplements that include an appropriate amount of supporting data.

We expect that the Genentech quality unit will perform continued process verification to ensure that the materials manufactured and released to the market remain representative of the drug product used in the pivotal clinical studies and that quality product will be able to be continually supplied to the market. The CPV strategies and data will be reviewed during routine FDA cGMP inspections of the current and any future ocrelizumab manufacturing facilities.

We also expect that Genentech will continue to investigate the polysorbate and potential drug product degradation issues and to implement appropriate corrective and preventative actions to ensure that drug product of appropriate quality reaches the patients and that these actions and/or additional stability and product quality shipping data will be provided (b) (4)

[REDACTED]

[REDACTED] (b) (4)

The sponsor responded with the following:

As referenced in the email dated January 27, 2017 from Melinda Bauerlien to Michelle Rohrer, we understand that in addition to those post marketing commitments (PMCs) previously communicated to the Agency and noted below, if all indications can be approved, the remaining CMC items can be managed as post marketing commitments (PMCs). Below we provide a summary of commitments and updated PMCs. In addition at the teleconference, we would like to discuss if there are any outstanding clinical issues and when we might expect further discussion on the potential draft labeling.

With regard to CMC, we commit to the following:

- We will submit any future changes relevant to manufacturing process (b) (4) as prior approval supplements to the license.
- We will perform (b) (4) and oversight to ensure that product released to the market remains representative of product used in pivotal trials (e.g., updated control system) and that data are available during routine GMP inspections at Vacaville or other future Ocrevus manufacturing sites.
- We agree to continue our investigation of polysorbate degradation. As actions are identified to ensure that drug product of appropriate quality reaches patients, the appropriate Quality system will be used for implementation.
- We commit to (b) (4)

In reference to an email dated November 25, 2017 from Jennifer Mercer to FDA, the following PMCs are provided below and include an updated PMC for the process validation protocol.

1	Genentech commits to qualify a new primary and secondary reference standard using Drug Substance from the 2016 campaign. The reference standard protocol will be submitted by Q2 2017 and the new reference standard will be qualified and submitted by Q4 2017.
2	Genentech commits to perform method validation for Method Q12764, (Antibody-Dependent Cellular Cytotoxicity Potency) by Q3 2017
3	Genentech commits to perform method validation for Method Q13406 (Purity by Reversed-Phase Ultra-High-Performance Liquid Chromatography) to assess Fc oxidation by Q3 2017.
4	Genentech commits to update method validation for Method Q12756 (Glycan Analysis by Capillary Electrophoresis) to include Man-5 by Q3 2017.
5	Genentech commits to perform a supplemental shipping validation study that will include drug product stored (b) (4) and that will include the impact of commercial shipping conditions through representative shipping

	routes on drug product quality attributes by Q2 2017.
6	Genentech commits to perform a leachable study using the drug product container closure system. Genentech will evaluate the impact of leachables to product safety and quality using methods to detect, identify, and quantify organic non-volatile compounds using liquid chromatography –mass spectrometry (LC-MS), volatile compounds using gas chromatography –mass spectrometry (GC-MS), and semi-volatile compounds using GC-MS, and metal species using inductively coupled plasma –mass spectrometry (ICP-MS). Data will be collected throughout the shelf-life of the product and will be provided in the Annual Report until the study is completed.
7	Genentech commits to [REDACTED] (b) (4)
8	Genentech commits to [REDACTED] (b) (4)

Meeting Discussion:

The Agency noted that many of the CMC PMCs are not specific to ocrelizumab and that the studies should have been included as part of the drug development program and are expected for any similar product that the Agency approves. The Agency stated that when it is time to have PMCs agreed upon, we will send PMC language to Genentech. The PMC 7 included on the list generated by Genentech will not be requested [REDACTED] (b) (4)

However, an additional PMC will be requested; this PMC is related to the assay for polysorbate 20 testing that was added to the DP stability specifications. It has not been demonstrated that the ELSD assay is suitable for this purpose, and the data provided in the BLA indicate that the fluorescent micelle assay is more sensitive to polysorbate degradation (Table 3.2.P.2.2-49). The sponsor acknowledged the Agency's concern and clarified that as was indicated previously, the polysorbate assay is currently under evaluation and that a commitment was made to continue the studies. The Agency reiterated that they will be including a PMC regarding the polysorbate testing.

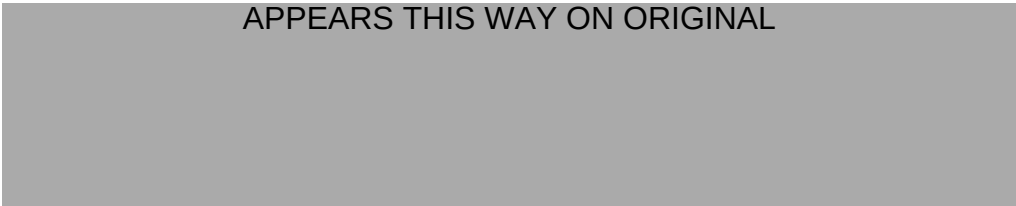
The Agency inquired about the timing of the submission [REDACTED] (b) (4)

(b) (4)



The Agency stated that they will contact the sponsor if any additional discussion needs to take place. The reviews are continuing and the Agency will be in touch regarding labeling discussions and proposed PMC language.

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/s/

MELINDA J BAUERLIEN
02/27/2017

STEVEN KOZLOWSKI
02/27/2017



BLA 761053

**REVIEW EXTENSION –
MAJOR AMENDMENT**

Genentech, Inc.
Attention: Sonali Patel, Pharm.D.
Associate Program Director, Product Development Regulatory
1 DNA Way
South San Francisco, CA 94080-4990

Dear Dr. Patel:

Please refer to your Biologics License Application (BLA) dated and received on April 28, 2016, submitted under section 351(a) of the Public Health Service Act for Ocrevus (ocrelizumab) intravenous injection, 300mg/10mL.

On December 16, 2016, we received your December 16, 2016, major amendment to this application. Therefore, we are extending the goal date by three months to provide time for a full review of the submission. The extended user fee goal date is March 28, 2017.

In addition, we are establishing a new timeline for communicating labeling changes and/or postmarketing requirements/commitments in accordance with “PDUFA REAUTHORIZATION PERFORMANCE GOALS AND PROCEDURES – FISCAL YEARS 2013 THROUGH 2017.” If major deficiencies are not identified during our review, we plan to communicate proposed labeling and, if necessary, any postmarketing requirement/commitment requests by March 1, 2017.

If you have any questions, call LCDR Nahleen Lopez, Regulatory Project Manager, at (240) 402-2659.

Sincerely,

{See appended electronic signature page}

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

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/s/

ERIC P BASTINGS on behalf of WILLIAM H Dunn
12/16/2016



BLA 761053

MID-CYCLE COMMUNICATION

Genentech, Inc.
Attention: Sonali Patel, Pharm.D.
Associate Program Director
1 DNA Way
South San Francisco, CA 94080-4990

Dear Dr. Patel:

Please refer to your Biologic License Application (BLA) submitted under section 351(a) of the Public Health Service Act for Ocrevus (ocrelizumab) intravenous injection, 300mg/10mL.

We also refer to the teleconference between representatives of your firm and the FDA on August 9, 2016. The purpose of the teleconference was to provide you an update on the status of the review of your application.

A record of the teleconference is enclosed for your information.

If you have any questions, call LCDR Nahleen Lopez, Regulatory Project Manager at (240) 402-2659.

Sincerely,

{See appended electronic signature page}

John Marler, MD
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 RESEARCH**

MID-CYCLE COMMUNICATION

Meeting Date and Time: Tuesday, August 9, 2016 (1500-1600 EST)

Application Number: 761053
Product Name: Ocrelizumab
Indication: Multiple Sclerosis
Applicant Name: Genentech, Inc.

Meeting Chair: John Marler, MD
Meeting Recorder: LCDR Nahleen Lopez, PharmD

FDA ATTENDEES

Division of Neurology Products:

Billy Dunn, MD, Director
John Marler, MD, Clinical Team Leader
Sally Jo Yasuda, MS, PharmD, Safety Team Leader
Gerard Boehm, MD, Clinical Safety Reviewer
Nahleen Lopez, PharmD, Regulatory Project Manager
Heather Fitter, MD, Clinical Team Leader
Laura Jawidzik, MD, Clinical Reviewer

Office of Surveillance and Epidemiology:

Jacqueline Sheppard, PharmD, DRISK Reviewer

Office of Biotechnology Products:

Milos Dokmanovic

Eastern Research Group:

Marc Goldstein, Independent Assessor

APPLICANT ATTENDEES

Sonali Patel, Associate Program Director, US Regulatory
Erica Evans, Senior Global Regulatory Leader (incoming)
Annemarie Likwaicheung, Senior Global Regulatory Leader (outgoing)
Tiffany Wan, Associate Program Director, US Regulatory
Jennifer Sexton, Regulatory Program Director, Pharma Technical Regulatory
Damian Cunningham, Technical Development Leader, Pharma Technical Development
Hideki Garren, Group Medical Director, Clinical Science Leader
Fabian Modal, Associate Director, CNS Biostatistics
Gaelle Klingelschmitt, Project Lead Statistician
Ann Santen, Global Operations Program Leader
Heidi Kletzl, Clinical Pharmacology
Jean-Paul Pfefen, Global Development Team Leader
Nicole Mairon, Senior Safety Science Leader
Thomas Gelzeichter, Toxicology
David Wormser, Senior Epidemiologist
Lindsay Ham, Global Franchise Head, Regulatory
Kathy Francissen, Senior Director, Pharma Technical Regulatory



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

1. INTRODUCTION

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

2. SIGNIFICANT ISSUES

All review issues have been or are being addressed with information requests as soon as we identify them. Primary review is ongoing.

Regarding the changes to the (b) (4) manufacturing process (b) (4) we will review and discuss these during the inspection. We will be requesting all available commercial scale data when they become available.

3. INFORMATION REQUESTS

There is one outstanding request for information regarding CMC microbiology.

4. MAJOR SAFETY CONCERNS/RISK MANAGEMENT

Safety concerns include the risk of breast cancer, in addition to the safety issues identified in Section 5 of your proposed labeling. At this time we believe that risk mitigation strategies will include labeling and a Medication Guide. Postmarketing requirements for a long-term observational study and for a pregnancy registry are under consideration. Based on the information currently available, we do not believe that a REMS will be necessary, at this time. We will make a final determination for the need for a REMS at the completion of the review cycle.

5. ADVISORY COMMITTEE MEETING

There are no plans at this time for an AC meeting.

6. LATE-CYCLE MEETING /OTHER PROJECTED MILESTONES

We are planning for a Late-Cycle Meeting between you and the review team October 18, 2016 (3:00-4:00pm EST). We intend to send the briefing package to you approximately 2 days in advance of the meeting. If these timelines change, we will communicate updates to you during the course of review.

7. DISCUSSION

We will begin labeling negotiations as soon as possible after the primary reviews are completed. We refer you to the CMC project manager for an answer to your inquiry about the deadline for submitting the amendment with the at-scale data from the (b) (4) commercial manufacturing process. We are currently considering whether to include breast cancer in labeling and, if so, where.

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/s/

JOHN R MARLER
09/07/2016



DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

BLA 761053

**PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE**

Genentech Inc.
1 DNA Way
South San Francisco, CA 94080-4990

ATTENTION: Tiffany Wan
Regulatory Program Manager

Dear Ms. Wan:

Please refer to your Biologics License Application (BLA) dated and received April 28, 2016, submitted under section 351(a) of the Public Health Service Act for ocrelizumab, 30mg/mL.

We also refer to your correspondence, dated and received June 13, 2016, requesting review of your proposed proprietary name, Ocrevus.

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

If any of the proposed product characteristics as stated in your June 13, 2016, 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 Ruth Maduro, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (240) 402-4232. For any other information regarding this application, contact Rebecca Lopez, Regulatory Project Manager in the Office of New Drugs at (240) 402-2659.

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
07/29/2016

Treatment IND/Protocol Summary Review

Receipt Date	April 12, 2016	30-day Action Date	May 12, 2016
IND#/Amendment #	100593	Related INDs/NDAs	BLA761053
Drug	Ocrelizumab		
Sponsor	Genentech, Inc.		
Indication for Treatment Use	<i>Primary Progressive Multiple Sclerosis</i>		
IND/Protocol Summary	<i>The protocol is for an open label study of ocrelizumab, 600 mg every 24 weeks given as two infusions of 300mg two weeks apart. Dosing of ocrelizumab, eligibility criteria and safety assessments are comparable to those in the ongoing open label extension of the completed pivotal trial WA25046.</i>		

Does the submission meet the criteria for authorizing treatment use under a treatment IND/protocol (21 CFR 312.305 and 312.320)?

1. Is the disease for which this drug is intended:	☒ serious	☐ immediately life-threatening
2. Is there a comparable or satisfactory alternative drug or other therapy available to treat, diagnose, or monitor the disease in the intended patient population?	☐ Yes ☒ No If yes, name the comparable or satisfactory alternative drug or other therapy.	
3. Is the drug under investigation in a controlled clinical trial designed to support marketing approval of the access use under an IND that is in effect (i.e., not on clinical hold) or have all such clinical trials of the drug been completed?	☒ Yes ☐ No	
4. Is the sponsor actively pursuing marketing approval of the investigational drug for the expanded access use with due diligence?	☒ Yes ☐ No	
5. If the answer to the above question is yes, has an NDA/BLA been submitted?	☒ Yes, NDA/BLA Number: BLA761053 ☐ No	
6. The potential patient benefits justify the potential risks of treatment and the potential risks are not unreasonable in the context of the disease to be treated?	☒ Yes ☐ No	
7. Providing the investigational drug for this use will not interfere with the initiation, conduct, or completion of clinical trials that could support marketing approval of the use or otherwise compromise development of the use	☒ Yes ☐ No	
8. The evidentiary standard has been met per the criteria described under 312.320(a)(3) for a serious or life-threatening disease or condition, depending upon which standard applies	☒ Yes ☐ No	
9. Have all the submission requirements described under 312.305(b)(2) been met?	☒ Yes ☐ No	
10. Is there assurance that the informed consent requirements of Part 50 will be met?	☒ Yes ☐ No	
11. Is there assurance that IRB review of the use will be obtained in a manner consistent with the requirements of Part 56 prior to the start of treatment?	☒ Yes ☐ No	

Brief Summary of Medical Review:	<i>The protocol and informed consent form were reviewed and are adequate. The data reviewed include efficacy and safety data from a single pivotal trial included in the breakthrough therapy request that was granted. The primary and key secondary endpoints all demonstrate a reduction in the accumulation of disability. There are no apparent major safety concerns.</i>
Pharmacological, Microbiological, and Manufacturing Review:	Are there pharmacological, microbiological, and/or manufacturing and control reasons for placing the IND on hold? ☐ Yes ☒ No Explain:
Recommendation	<i>The proposed protocol should be allowed to proceed.</i>

Division Director Signature: *{See appended electronic signature page}*

Office Director: *{See appended electronic signature page}*

Note: Nonconcurrence by Office Director should be documented in a separate review.

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/s/

REBECCA N LOPEZ
05/05/2016

WILLIAM H Dunn
05/06/2016

ROBERT TEMPLE
05/06/2016



IND 100593

STUDY MAY PROCEED

Genentech, Inc.
Attention: Tiffany Wan
Regulatory Program Management
1 DNA Way
South San Francisco, CA 94080

Dear Ms. Wan:

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

We have completed our safety review of your protocol, received April 12, 2016, and entitled "An Open-Label, Multicenter, Expanded Access Program for Ocrelizumab in Patients with Primary Progressive Multiple Sclerosis." We have concluded that you may proceed with your proposed treatment use for Primary Progressive Multiple Sclerosis (PPMS).

ADDITIONAL IND RESPONSIBILITIES

As sponsor of this IND, you are responsible for compliance with the FDCA (21 U.S.C. §§ 301 et. seq.) as well as the implementing regulations [Title 21 of the Code of Federal Regulations (CFR)]. A searchable version of these regulations is available at <http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm>. Your responsibilities include:

- Reporting any unexpected fatal or life-threatening suspected adverse reactions to this Division no later than 7 calendar days after initial receipt of the information [21 CFR 312.32(c)(2)].

If your IND is in eCTD format, submit 7-day reports electronically in eCTD format via the FDA Electronic Submissions Gateway (ESG). To obtain an ESG account, see information at the end of this letter.

If your IND is not in eCTD format:

- you should submit 7-day reports by a rapid means of communication, preferably by facsimile or email. You should address each submission to the Regulatory Project Manager and/or to the Chief, Project Management Staff;

- if you intend to submit 7-day reports by email, you should obtain a secure email account with FDA (see information at the end of this letter);
- if you also send copies of these reports to your IND, the submission should have the same date as your facsimile or email submission and be clearly marked as “Duplicate.”
- Reporting any (1) serious, unexpected suspected adverse reactions, (2) findings from other clinical, animal, or in-vitro studies that suggest significant human risk, and (3) a clinically important increase in the rate of a serious suspected adverse reaction to this Division and to all investigators no later than 15 calendar days after determining that the information qualifies for reporting [21 CFR 312.32(c)(1)]. If your IND is in eCTD format, submit 15-day reports to FDA electronically in eCTD format. If your IND is not in eCTD format, you may submit 15-day reports in paper format; and
- Submitting annual progress reports within 60 days of the anniversary of the date that the IND became active (the date clinical studies were permitted to begin) [21 CFR 312.33].

PATIENT-FOCUSED ENDPOINTS

An important component of patient-focused drug development is describing the patient’s perspective of treatment benefit in labeling based on data from patient-focused outcome measures [e.g., patient-reported outcome (PRO) measures]. Therefore, early in product development (i.e, phase 1 or 2), we encourage sponsors to consider incorporating well-defined and reliable patient-focused outcome measures as key efficacy endpoints in clinical trials, when appropriate, and to discuss those measures with the Agency in advance of confirmatory trials. For additional information, refer to FDA’s guidance for industry *Patient-Reported Outcome Measures: Use in Medical Product Development to Support Claims*, available at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM193282.pdf>.

SUBMISSION REQUIREMENTS

Cite the IND number listed above at the top of the first page of any communications concerning this application. Each submission to this IND must be provided in triplicate (original plus two copies). Please include three originals of all illustrations that do not reproduce well. 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

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however,

it may occasionally be necessary to use individual pages larger than standard paper size. Non-standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission. For additional information, see <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/DrugMasterFilesDMFs/ucm073080.htm>.

Secure email between CDER and sponsors 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 (except for 7-day safety reports for INDs not in eCTD format).

The FDA Electronic Submissions Gateway (ESG) is the central transmission point for sending information electronically to the FDA and enables the secure submission of regulatory information for review. If your IND is in eCTD format, you should obtain an ESG account. For additional information, see <http://www.fda.gov/ForIndustry/ElectronicSubmissionsGateway/>.

If you have any questions, contact Nahleen Lopez, Regulatory Project Manager, at (240) 402-2659.

Sincerely,

{See appended electronic signature page}

Robert Temple, MD
Deputy Director
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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/s/

ROBERT TEMPLE
05/05/2016

Clinical (Medical Officer Review for Treatment IND/Protocol

Type of Submission	☐ New Treatment IND ☒ New Treatment Protocol	Serial Number	0692
Receipt Date	April 12, 2016	30-day Action Date	May 12, 2016
IND#/Amendment #	100593	Related INDs/NDAs	BLA761053
Drug	Ocrelizumab		
Sponsor	Genentech		
Indication for Treatment Use	Primary Progressive Multiple Sclerosis		

Medical Officer Assigned	Lawrence Rodichok MD
Date Assigned	

1.	Is the disease for which this drug is intended: ☒ serious ☐ immediately life-threatening
2.	Is there a comparable or satisfactory alternative drug or other therapy available to treat, diagnose, or monitor the disease in the intended patient population? ☐ Yes ☒ No
3.	Is the drug under investigation in a controlled clinical trial designed to support marketing approval of the access use under an IND that is in effect (i.e., not on clinical hold) or have all such clinical trials of the drug been completed? ☒ Yes ☐ No
4.	Is the sponsor actively pursuing marketing approval of the investigational drug for the expanded access use with due diligence? ☒ Yes ☐ No
5.	If the answer to the above question is yes, has an NDA/BLA been submitted? ☒ Yes, NDA/BLA Number: BLA761053 ☐ No
6.	If this Treatment IND/Protocol is for treatment of a serious disease, is there sufficient evidence of safety and effectiveness to support the drug's use? ☒ Yes ☐ No
7.	If for treatment of immediately life-threatening disease, does the available scientific evidence provide a reasonable basis to conclude that the drug may be effective for the access use and would not expose patients to an unreasonable and significant risk of illness or injury? ☐ Yes ☐ No N/A
8.	The potential patient benefits justify the potential risks of treatment and the potential risks are not unreasonable in the context of the disease to be treated? ☒ Yes ☐ No
9.	Providing the investigational drug for this use will not interfere with the initiation, conduct, or completion of clinical trials that could support marketing approval of the use of otherwise compromise development of the use? ☒ Yes ☐ No
10.	Have all the submission requirements described under 312.305(b)(2) been met? ☒ Yes ☐ No

11. Is there assurance that the informed consent requirements of Part 50 will be met?	
☒ Yes	☐ No
12. Is there assurance that IRB review of the use will be obtained in a manner consistent with the requirements of Part 56 prior to the start of treatment?	
☒ Yes	☐ No
13. Will the investigator's brochure for the drug (if one exists) be provided to the investigators?	
☒ Yes	☐ No
14. Will the treatment protocol be monitored to ensure that licensed physicians comply with the protocol and regulations applicable to investigators?	
☒ Yes	☐ No

Comments by Medical Officer	The protocol and informed consent were reviewed and are acceptable. Drug administration and safety surveillance are essentially the same as in the pivotal trial WA25046. See attached review.
Recommendation	To allow the Treatment IND/Protocol to proceed, the answers to questions 3-4 and 6-14 must be "Yes" and the answer to question 2 must be "No." ☒ 1) Treatment IND or Protocol may proceed ☐ 2) Treatment IND or Protocol should be placed on hold. Reason for hold recommendation:

Version: 01/21/2014

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/s/

LAWRENCE D RODICHOK
05/04/2016

REVQuality (Chemistry) Review for Treatment IND/Protocol

Type of Submission	☐ New Treatment IND ☒ New Treatment Protocol	Serial Number	
Receipt Date	April 12, 2016	30-day Action Date	May 12, 2016
IND#/Amendment #	IND 100593/SDN702	Related INDs/NDAs	
Drug	Ocrelizumab		
Sponsor	Genentech		
Indication for Treatment Use	primary progressive multiple sclerosis (PPMS)		

Chemist Assigned	Milos Dokmanovic
Date Assigned	April 12, 2016

Date EER Entered into EES (for a drug)	N/A
Date TB- EER is Submitted to OMPQ (for a biologic)	April 27, 2016

Compliance Overall Recommendation	Acceptable
Date of Compliance Recommendation	May 2, 2016

Chemical Name and Structure	Ocrelizumab: a recombinant humanized IgG1κ monoclonal antibody against CD20
Comments by Chemist	From a product quality perspective, this study is safe to proceed. From a facility perspective, there are no pending or ongoing compliance actions that prevent this IND Treatment Protocol.

Recommendation	☒ 1) Treatment IND or Protocol may proceed ☐ 2) Treatment IND or Protocol should be placed on hold. Reason for hold recommendation:
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Revised: 11/04/2011

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/s/

MILOS DOKMANOVIC
05/02/2016

LINAN HA
05/02/2016

ZHIHAO PETER QIU
05/03/2016

Nonclinical (Pharm-Tox) Review for Treatment IND/Protocol

Type of Submission	☐ New Treatment IND ☒ New Treatment Protocol	Serial Number	0679
Receipt Date	2/25/2016	30-day Action Date	5/12/2016
IND#/Amendment #	100593/ SDN689	Related INDs/NDAs	BLA 761053
Drug	Ocrelizumab		
Sponsor	Genentech		
Indication for Treatment Use	Primary Progressive Multiple Sclerosis		

Pharmacologist Assigned	Barbara J Wilcox, Ph.D.
Date Assigned	2/25/2016

Comments by Pharmacologist	The nonclinical program is adequate to support safety of this treatment IND.
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Recommendation	☒ 1) Treatment IND or Protocol may proceed ☐ 2) Treatment IND or Protocol should be placed on hold. Reason for hold recommendation:
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/s/

BARBARA J WILCOX
04/29/2016

LOIS M FREED
04/29/2016

**Review and Evaluation of Clinical Data
Review of Expanded Access Protocol**

IND	100593
Supporting Document Number:	702
Sponsor:	Genentech
Drug:	Ocrelizumab
Proposed Indication:	Treatment of PPMS
Correspondence Date:	4/12/16
Date Received / Agency:	4/12/16
Date Review Completed	4/29/16
Reviewer:	Lawrence Rodichok MD, ODEI, DNP
Materials Reviewed	Protocol ML29972 for Expanded Access for PPMS

FDA text, *reviewer comment*, extracted from sponsor documents

1. Introduction

1.1. Executive Summary

This is a review of a proposed expanded access protocol for treatment of PPMS with ocrelizumab. BLA 761053 is a rolling submission and some nonclinical data has been submitted. There is no approved treatment for PPMS. The protocol and ICF were reviewed. In general the initial protocol was adequate with the exception of the frequency of collection of safety labs and adverse events. We had informed that sponsor that we expected the protocol to mirror that of the pivotal trial protocol WA25046 which did have more frequent (every 12 week) monitoring (b) (4)

The protocol also (b) (4)

An IR was sent to the sponsor on 4/19/16 – it is included at the end of the review. It was also noted that the requirement for male contraception was not included in the protocol whereas it was an inclusion criterion in the pivotal trial.

Based on a review of nonclinical data it was determined by the nonclinical reviewers that removal of the requirement for male use of contraception was acceptable. An email confirming that is included in the review.

In response to an information request the sponsor revised the protocol to address the above issues. The sponsor (b) (4)

An email to that effect was sent to the sponsor (b) (4) – that email is at the end of the review. The sponsor indicates that those (b) (4) will be removed in the final protocol.

The sponsor has addressed each of the above issues. I believe that the protocol can now be approved from a clinical point of view. There are no further comments for the sponsor.

1.2. Scientific and Regulatory Background

1.2.1 Scientific Background

Ocrelizumab (OCR) is a recombinant humanized monoclonal antibody (mAb) that selectively targets CD20-expressing B cells. CD20 is a cell surface antigen found on pre-B cells, mature B cells, and memory B cells but is not expressed on lymphoid stem cells and plasma cells. While OCR selectively depletes CD20-expressing B cells, the capacity of B-cell reconstitution and pre-existing humoral immunity are preserved. In addition, innate immunity and total T-cell numbers are not affected (clinical study report [CSR] Study WA21493/ACT4422G).

1.2.2 Regulatory Background

Pre-IND meeting: 6/14/07
Original IND: 1/9/08
Full HOLD: 2/8/08
Remove HOLD: 5/21/08
EOP2 meeting: 12/5/08
End of Phase 2: September 22, 2010
SPA request: 3/23/11
SPA no Agreement: 4/25/11
Grant Fast Track (for PPMS): 3/6/13
Type C meeting (WRO): 8/19/15
IPSP agreed (RMS): 10/2/15
Pre-BLA (RMS): 12/8/15
Pre-BLA (PPMS): 2/4/16
Breakthrough Therapy Designation (PPMS): 2/1/16

1.3 Overall development plan

2. Background

2.1. CMC

Ocrelizumab is a humanized glycosylated monoclonal antibody to CD20 based on the human IgG1 subarm-III variable heavy and κ subarm-I variable light consensus sequences. CD20 is a B-cell surface molecule that is restricted in expression to pre-B-cells and mature B-cells, but not expressed earlier in the development of B-cells or on mature plasma cells. Ocrelizumab demonstrated enhanced antibody-dependent cell-mediated cytotoxicity (ADCC) and decreased complement-dependent cytotoxicity (CDC) in vitro (in comparison to rituximab). These differences are theorized to provide an increase in potency and improved safety profile compared with rituximab with regard to immunogenicity.

- **Drug Substance**

Generic Name: ocrelizumab
Chemical Name: Recombinant humanized anti-human CD20 monoclonal antibody
Alternative Name: RO4964913; PRO70769
Molecular Formula:

Chemical Structure: H2L2 polypeptide structure consisting of 2 light chains and 2 heavy chains held together by disulfide bonds. Each light and heavy chain consists of 213 and 452 amino acids, respectively.

Molecular Weight: 148KDa

- **Drug Product**

Ocrelizumab is supplied as a single-use liquid formulation containing 30 mg/mL ocrelizumab in (b) (4) mM sodium acetate at pH 5.3, with 4% trehalose dihydrate and 0.02% polysorbate 20. The drug product is provided as a single-use liquid formulation containing nominal (b) (4) ocrelizumab. The (b) (4) drug product is supplied at a nominal volume of (b) (4) mL in a 15 cc Type I glass vial. Vials are fitted with a 20 mm (b) (4) stopper and an aluminium seal with a flip-off plastic cap. No preservative is used, as each vial is designed for single use.

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2.2. Nonclinical Findings – see previous reviews

From Lois Freed, 4/28/16

Based on the information provided by you and Barbara, I think we're comfortable with lifting the restrictions on males in the ocrelizumab clinical studies, with the caveat that repro and developmental studies in monkey are limit in their utility because of the very small n's.

According to Barbara, the only adverse developmental effects observed were neonatal morbidity, leading to premature sacrifice, in offspring, presumably resulting from infections. Barbara assumes that the B-cell depletion caused by ocrelizumab may have contributed to the infections, which is perfectly reasonable. At the NOAEL, the lowest mean Cmax in monkey is □500 ug/mL. That in humans at the recommended dose of 600 mg is 212 ug/mL.

With those data, it is estimated that males would be responsible for a plasma concentration of 0.212 ug/mL in a female partner. That concentration is orders of magnitude lower than the plasma level at the NOAEL for offspring morbidity and death in female monkey.

2.3. Previous clinical experience– see previous reviews

3. Protocol Review - Clinical Protocol

Title of Study:

**AN OPEN-LABEL, MULTICENTER, EXPANDED ACCESS PROGRAM FOR
OCRELIZUMAB IN PATIENTS WITH PRIMARY PROGRESSIVE MULTIPLE SCLEROSIS**

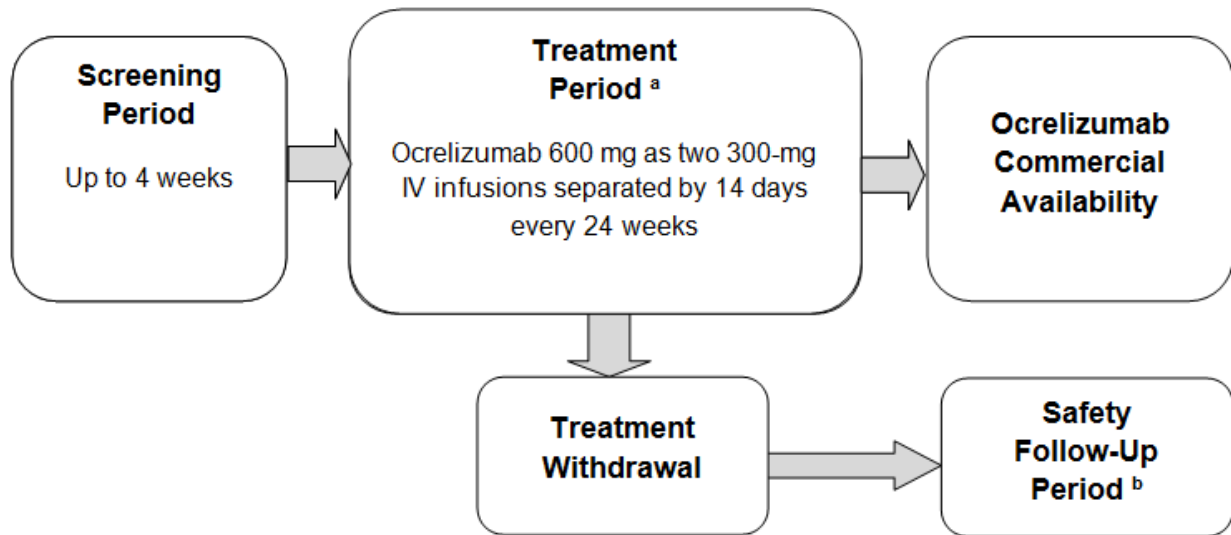
Protocol version 1, 12April 2016

3.1. Design/objectives of study

This is an open-label, multicenter EAP designed to provide ocrelizumab to eligible patients with PPMS. This EAP is not randomized nor does it have an active comparator drug.

The EAP is designed to provide ocrelizumab to eligible patients until ocrelizumab can be prescribed, meaning that ocrelizumab will be available for prescription (i.e., commercially available). If a patient received ocrelizumab as part of the EAP, he/she will receive study drug until ocrelizumab can be prescribed or until the patient withdraws from the EAP.

Figure 1 Program Schema



3.1.1 Objectives

3.1.1.1 Primary objective

The primary objective of this EAP is to provide ocrelizumab as treatment for eligible patients with PPMS before it is commercially available in the U.S. for the indication of PPMS.

3.1.1.2 Secondary objective(s)

The secondary objectives of this EAP are to collect safety data and to monitor the clinical condition of patients with PPMS who are taking ocrelizumab based on MRI, EDSS score, or clinical judgement.

3.1.2 Sites

3.1.3 Estimated timeline

3.2. Study conduct/schedule

3.2.1. Study procedures

3.2.1.1. Screening

Screening will occur over a 4-week period, after which eligible patients may begin treatment with ocrelizumab.

3.2.1.2. Randomization procedure

3.2.1.3. Treatment

3.2.1.3.1. Investigational products

4.3.1.1 Ocrelizumab

Ocrelizumab will be supplied by the Sponsor as a liquid formulation containing 30-mg/mL ocrelizumab in (b) (4) mM sodium acetate at pH 5.3, with 4% trehalose dehydrate and 0.02% polysorbate 20. The drug product is provided as a single-use liquid formulation in a 15-cc, type I USP, glass vial fitted with a 20-mm, (b) (4) laminated stopper and an aluminum seal with a flip-off plastic cap and contains a nominal 300 mg ocrelizumab.

3.2.1.3.2. Treatment regimen

Ocrelizumab 600 mg will be administered as two 300-mg IV infusions separated by 14 days at a scheduled interval of every 24 weeks.

Reviewer Comment: We had provided a comment that until all of the data from the pivotal studies in RMS and PPMS could be reviewed, ocrelizumab should be administered as it was in study WA25046. The above regimen is the same as in that study.

Although ocrelizumab may be administered on an outpatient basis, patients may be hospitalized for observation at the discretion of the investigator. Ocrelizumab infusions should always be administered in a hospital or clinic environment under close supervision of the investigator or a medically qualified staff member.

Each ocrelizumab infusion should be given as a slow IV infusion over approximately 150 minutes (2.5 hours) for the 300-mg dose. To reduce potential IRRs, all patients will receive prophylactic treatment with 100 mg of methylprednisolone (or equivalent IV steroid), administered by slow IV infusion, to be completed approximately 30 minutes before the start of each ocrelizumab infusion.

It is also strongly recommended that the infusion is accompanied by prophylactic treatment with an analgesic/antipyretic such as acetaminophen/paracetamol (1 g) and/or an IV or oral antihistamine (such as IV diphenhydramine 50 mg or equivalent dose of alternative) 30 – 60 minutes prior to the start of an infusion to reduce potential IRRs. Patients administered a sedating antihistamine for the treatment or prevention of IRRs should be given appropriate warnings concerning drowsiness and potential impairment of ability to drive or operate machinery.

Since transient hypotension may occur during ocrelizumab infusion, the investigator may wish to withhold anti-hypertensive medications 12 hours prior to ocrelizumab infusion.

After completion of the infusion, the IV cannula should remain in situ for at least 1 hour to allow for administration of drugs intravenously, if necessary, in the event of a delayed reaction. If no adverse events occur during this period of time, the IV cannula may be removed and the patient may be discharged.

Table 2 Overview of Ocrelizumab Dosing

Group	1 st Dose (Weeks 1 – 24)		Subsequent Dose(s)	
	Day 1 Infusion	Day 15 Infusion	First Infusion	Next Infusion (14 days later)
Ocrelizumab	300 mg IV	300 mg IV	300 mg IV	300 mg IV

IV = intravenous.

Note: Before each infusion of ocrelizumab, 100 mg of methylprednisolone IV (or equivalent IV steroid) will be administered to reduce the potential for infusion-related reactions. Each treatment cycle has a duration of 24 weeks.

Treatment with ocrelizumab will continue until:

- Lack of clinical benefit
- Unacceptable toxicity
- Withdrawal of consent
- Patient or physician decision to discontinue treatment
- Death
- Ocrelizumab becomes commercially available in the U.S. following approval of ocrelizumab for the indication of PPMS by the U.S. Food and Drug Administration (FDA) or the Sponsor decides to close the trial, whichever occurs first.

3.2.1.4. Assessments

Potential relapses must be recorded throughout the treatment period. Protocol-defined relapse is the occurrence of new or worsening neurological symptoms attributable to MS. Symptoms must persist for > 24 hours and should not be attributable to confounding clinical factors (e.g., fever, infection, injury, adverse reactions to medications) and immediately preceded by a stable or improving neurological state for least 30 days. The new or worsening neurological symptoms must be accompanied by objective neurological worsening consistent with an increase of at least half a step on the EDSS, or 2 points on one of the appropriate FS scales, or 1 point on two or more of the appropriate FS scales. The change must affect the selected FS (i.e., pyramidal, ambulation, cerebellar, brainstem, sensory, or visual). Episodic spasms, sexual dysfunction, fatigue, mood change, or bladder or bowel urgency or incontinence will not suffice to establish a relapse. Sexual dysfunction and fatigue will not be scored.

(Note: **Adjudication of protocol-defined relapses will be performed by the Sponsor** based on pre-specified criteria, applied to data collected by investigator, in a blinded fashion.)

Reviewer Comment: Physical and neurologic examination, vital signs, pregnancy test and review of concomitant medications are done at every visit. Cerebrospinal fluid will be collected at baseline only if this had not been done previously.

In Study 25046 there was an additional in person assessment mid-way between each treatment cycle. These have been omitted in the proposed study. In an email response to sponsor request for advice regarding this protocol we had advised the sponsor as follows: FDA Response to Question 4: Conduct clinical and safety assessments in all patients as you did in study WA25046. The sponsor should add an assessment midway between dose cycles, e.g. at weeks 12, 37, 61 and comparable times for additional treatment cycles.

29-Apr-16

Appendix 1 Schedule of Activities - revised

(b) (4)

Reviewer Comment: The additional visits at weeks 13 and 37 are added. Safety labs are being collected at those visits. See email at the end of the review notifying the sponsor

(b) (4)

3.2.1.5. Follow-up – see Table above

3.2.2. Blinding – N/A

3.2.3. Randomization method – N/A

3.2.4. Discontinuation

When a patient discontinues ocrelizumab due to transition to commercially available ocrelizumab, a visit will be completed at the time of transition or within 6 months of the last dose of ocrelizumab in this EAP (whichever is earlier; see Section 4.6.2).

If a patient switches to another treatment or discontinues from the EAP, the patient will be followed for safety for 24 weeks after the last dose of ocrelizumab in this EAP, providing the patient consents to participate in follow-up. Otherwise, patients will be followed for safety for 24 weeks after their last dose of ocrelizumab in this EAP

4.6.2 Treatment Discontinuation

Patients must discontinue ocrelizumab treatment if they experience any of the following:

- Ongoing pregnancy: Please note that the pregnancy should be followed up to determine outcome, including spontaneous or voluntary termination, details of birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and newborn complications. The health status of any infant born to patients or their partners may be followed until the child is 1 year of age.
- Life-threatening IRR or serious hypersensitivity reaction
- Active hepatitis B infection
- PML
- Active tuberculosis, either new onset or reactivation

The primary reason for ocrelizumab treatment discontinuation should be documented on the appropriate eCRF. Patients who discontinue ocrelizumab treatment prematurely will not be replaced.

When a patient discontinues ocrelizumab due to transition to commercially available ocrelizumab, a visit will be completed at the time of transition or within 6 months of the last dose of ocrelizumab in this EAP (whichever is earlier). The following assessments will be conducted:

1. Review of adverse events/serious adverse events (recording of new or changed information since the previous visit and prior to start of dosing with ocrelizumab)
2. Recording of reason for discontinuation of ML29972 EAP as “transition to commercial ocrelizumab”
3. Neurological examination (for patients who return to the clinic)

3.2.5. Concomitant medications and other treatments

4.4.2 Prohibited Therapy

Use of the following therapies is prohibited during the program and for at least 7 days prior to initiation of ocrelizumab, unless otherwise specified below:

- Therapies for MS other than systemic corticosteroids
- Immunosuppressants, lymphocyte-depleting agents, or lymphocyte-trafficking blockers while patient is B-cell depleted
-

3.2.6. Number of patients/subjects

4.1 PATIENTS

Approximately 900 – 1000 patients with PPMS in accordance with the revised 2010 McDonald criteria (Polman et al. 2011) are estimated to enter this EAP (see Appendix 2).

Reviewer Comment: In the March 30 email we indicated that the proposed size of the study population was acceptable.

3.3. Eligibility criteria

3.3.2 Rationale for Patient Population

This program will admit patients with PPMS according to revised 2010 McDonald criteria (Polman et al. 2011) who also have present or documented history of cerebrospinal fluid oligoclonal bands by isoelectric focusing or elevated IgG index and an EDSS score of 2.0 – 6.5 points.

Although the patient population studied in the Phase III PPMS trial included patients with a lower age upper limit (55 years) and a higher lower limit for EDSS (3.0), it is considered that eligibility in this EAP can be expanded in order to allow access in a broadly defined clinical population.

Reviewer Comment: In our comments sent on March 30 by email was indicated that the proposed changes to the inclusion and exclusion criteria were acceptable:

1. The inclusion and exclusion criteria of the EAP are similar to those used in Study WA25046. Does the Agency have any comments?

Based on the safety and efficacy results from Study WA25046, the eligibility criteria for the EAP have been closely aligned with those of Study WA25046.

Inclusion and exclusion criteria for Study WA25046 addressed the need for the selection of a population adequate for a Phase III placebo-controlled study. Some modifications have introduced in the EAP to allow eligibility in the context of expanded access and are described below.

- a) PPMS diagnosis: the 2010 McDonald criteria (Pollman et al. 2011) will be used for eligibility to the EAP. Study WA25046 used the 2005 McDonald criteria as the study was conducted before introduction of this revised criteria.

- b) Expanded Disability Status Scale (EDSS) range: the lower limit of the range in the EAP will be 2.00 compared to 3.00 in Study WA25046. This will allow access to the EAP to a broader PPMS population.
- c) Score on the Functional System Scale: a score of ≥ 2.0 involving the pyramidal system that was due to lower extremity involvement was an inclusion criterion for Study WA25046, however has not been considered necessary for the EAP to enable a broader population to be treated.
- d) Duration of disease: duration of disease (less than 15 years for $EDSS > 5.0$ and less than 10 years for $EDSS \leq 5.0$) was an inclusion criterion for Study WA25046 to enable a broader population to be treated.
- e) Exclusion criteria: In the absence of approved therapies for PPMS, physicians may use existing disease-modifying therapy (DMT). Although previously excluded from Study WA25046, the EAP will enable use of ocrelizumab in patients previously treated with some DMTs with appropriate wash out, as well as previous treatment with B-cell targeted therapies. Alemtuzumab will continue to be an excluded DMT. A complete description is provided in the EAP in Appendix C (Section 4.1.2).

FDA Response to Question 1: We assume that you plan to eliminate the inclusion criterion d) above. If so, that is acceptable. If that is not correct, please advise us accordingly. The proposed modifications a), b), and c) are clear and acceptable. The intent of modification e) is acceptable but we prefer that you replace "disease modifying therapy" with "therapies approved for relapsing forms of MS" because "disease modifying therapy".

3.4.1 Key Inclusion Criteria

- Age 18 – 55 years (inclusive)
- Diagnosis of PPMS in accordance with the revised 2010 McDonald criteria (Polman et al. 2011) and the presence or documented history of cerebrospinal fluid oligoclonal bands by isoelectric focusing or elevated IgG index
- EDSS score of 2.0 – 6.5 points at screening

3.4.2 Key Exclusion Criteria

- Treatment with therapies approved for relapsing forms of MS, including: β interferons, glatiramer acetate, fingolimod (Gilenya®), teriflunomide (Aubagio®), dimethyl fumarate (Tecfidera®), IV immunoglobulin, plasmapheresis, or other immunomodulatory therapies within 12 weeks prior to enrollment
 - o Patients should not be excluded from the EAP due to previous treatment with rituximab.
- Patients who have received fingolimod (Gilenya®) or dimethyl fumarate (Tecfidera®) if their lymphocyte count is not within normal values
- Previous treatment with natalizumab (Tysabri®) within 6 months of screening
 - o Patients are not eligible for the EAP if they have been treated with natalizumab (Tysabri) for more than 1 year.
- Any previous treatment with alemtuzumab (Lemtrada®)
- Certain laboratory abnormalities or findings at the time of treatment initiation, including the following:
 - o Positive serum β -hCG at screening

- o Positive for hepatitis B (hepatitis B surface antigen [HBsAg] positive or hepatitis B core antibody [total HBcAb] confirmed by positive viral DNA polymerase chain reaction [PCR]) or hepatitis C antibody (HepCAb) at screening
- o Positive rapid plasma reagin (RPR), confirmed by microhemagglutination assay (MHA-TP) or fluorescent treponemal antibody absorption (FTA-ABS) test
- o CD4 count < 300/ μ L
- o Serum creatinine > 1.4 mg/dL (>124 μ mol/L) for women or > 1.6 mg/dL (>141 μ mol/L) for men
- o AST or ALT $\geq$ 2.0 upper limit of normal (ULN)
- o Platelet count < 100,000/ μ L (< 100 $\times$ 10⁹/L)
- o Hemoglobin < 8.5 g/dL (< 5.15 mmol/L)
- o ANC < 1.5 $\times$ 10³/ μ L
- o Serum immunoglobulin (Ig) G 18% below the lower limit of normal (LLN)
- o Serum IgM 8% below the LLN
- Pregnant or lactating, or intending to become pregnant during the program
 - o Women of childbearing potential must have a negative serum pregnancy test result within 7 days prior to initiation of ocrelizumab.

3.4. Safety measures and considerations

3.4.1. Adverse event definitions and collection

Reviewer Comment: The adverse event definitions are standard but the frequency of collection does not correspond to that in WA25046 – see IR sent to the sponsor on 4/19/16 below

3.4.2. Adverse events of special interest

3.4.3. Laboratory studies

Pre-infusion laboratory samples should be drawn up to 14 days before the start of infusion so that routine laboratory test results are available for review before the infusion, unless otherwise specified.

3.4.3.1. Hematology

Hematology (CD4 count, hemoglobin, hematocrit, RBCs, WBC absolute and differential, ANC, and quantitative platelet count)

3.4.3.2. Chemistry

Serum chemistry (AST, ALT, GGT, alkaline phosphatase, amylase, lipase, total protein, albumin, cholesterol, total bilirubin, urea, uric acid, creatinine, random glucose, potassium, sodium, calcium, phosphorus, LDH, creatine phosphokinase, and triglycerides)

3.4.3.3. Pregnancy tests

All women of childbearing potential will have a serum pregnancy test at screening. Urine pregnancy tests will be performed at specified subsequent visits. If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test.

3.4.3.4. Suicidality

Reviewer Comment: Not being monitored

3.4.3.5. Other laboratory studies

- Viral serology
- Hepatitis screening
 - Must be negative for HBsAg and HepCAb prior to enrollment; if HBcAb is positive at screening, HBN DNA by PCR must be negative. For those patients enrolled with negative HBsAg and positive total HBcAb, HBV DNA (PCR) must be repeated every 24 weeks during the treatment period.
- RPR assessment (must be negative for syphilis)
- Quantitative immunoglobulin: Ig levels (including total Ig, IgG, IgM, and IgA isotypes)
- CSF specimen as part of PPMS diagnosis, if no previous specimen has been collected and reported (i.e., when there is no history of CSF measurement).
 - If a patient has been diagnosed with PPMS according to a CSF specimen in the past, another CSF specimen is not needed.
 - If a patient has been diagnosed with PPMS according to revised 2010 McDonald criteria (Polman et al. 2011) or MRI criteria, another CSF specimen is not needed.
 - However, if a patient meets only one of the two MRI criteria required for diagnosis of PPMS, a CSF specimen must be obtained.
- Fluorescence activated cell sorter (FACS) sample to screen for CD19 and other circulating B-cell subsets, T cells, natural killer cells, and other leukocytes

3.4.4. ECG

A 12-lead electrocardiogram (ECG) is required at screening and when clinically indicated.

ECG recordings must be performed after the patient has been resting in a supine position for at least 10 minutes.

3.4.5. Vital signs

3.4.6. Physical examination

3.4.7. Other

3.4.8. Safety monitoring

5.3.5.7 Abnormal Liver Function Tests

The finding of an elevated ALT or AST ($> 3 \times \text{ULN}$) in combination with either an elevated total bilirubin ($> 2 \times \text{ULN}$) or clinical jaundice in the absence of cholestasis or other causes of hyperbilirubinemia is considered to be an indicator of severe liver injury (as defined by Hy's law). Therefore, investigators must report as an adverse event the occurrence of either of the following:

- Treatment-emergent ALT or AST $> 3 \times \text{ULN}$ in combination with total bilirubin $2 \times \text{ULN}$
- Treatment-emergent ALT or AST $> 3 \times \text{ULN}$ in combination with clinical jaundice

3.5. Safety issues with related drugs in pharmacologic class

3.6. Study endpoint – safety endpoints only

3.7. Compliance – monitored during the infusion at the site

3.8. Informed Consent – reviewed and adequate – the added visit will need to be added to the ICF

3.9. Investigational Brochure – see previous reviews

3.10. Investigator's Qualifications – N/A

3.11. Statistical considerations/analyses – all statistical analyses will be descriptive only

3.11.1. Sample size/power

The main objective of the EAP is to provide access to ocrelizumab; thus, the total number of patients enrolled into the EAP is based on the prevalence of PPMS in the U.S. and the estimated willingness to participate in an expanded access program. It is anticipated that approximately 900 – 1000 patients will be enrolled in the EAP.

3.11.2. Analysis population(s) – N/A

3.11.3. Control of Type 1 error– N/A

3.11.4. Interim Analyses– N/A

3.11.5. Primary analysis methods- descriptive

3.11.6. Secondary analyses– N/A

3.11.7. Subgroup analyses– N/A

3.11.8. Missing data – to be addressed in SAP

3.12. Study monitoring plan

3.12.1. Safety monitoring

3.12.2. Data integrity monitoring

Site visits will be conducted by the Sponsor or an authorized representative for inspection of program data, subjects' medical records, and eCRFs. The investigator will permit national and local health authorities; Sponsor monitors, representatives, and collaborators; and the IRBs/ECs to inspect facilities and records relevant to this program.

4. Recommended Regulatory Action

- As the protocol stands, is the study REASONABLY safe to proceed? YES

6. Comments to the Sponsor

The following request was sent on 4/19/16

- In protocol ML29972 you propose to assess subjects (b) (4) and to collect safety laboratory studies (b) (4). However, in Study WA25046 subjects were assessed every 12 weeks including collection of safety laboratory tests. As we indicated

29-Apr-16

in our March 30, 2016, email response to your request for advice regarding this protocol (refer to response to Question 4) we request that you perform the same clinical and safety assessments as in study WA25046. This includes an in person assessment midway between treatment cycles. At a minimum, these mid-cycle visits should include a determination of adverse events and safety laboratory tests.

2. We also note that the Informed Consent Form includes reference to a phone call to the subject every 4 weeks to assess for new neurologic symptoms or other adverse events that may warrant an unscheduled visit. We agree it is important to continue the same safety monitoring used in the trial during BLA review. Please revise protocol ML29972 to include these telephone interviews.

The following information request was sent to the sponsor:

On Tue, Apr 19, 2016 at 6:17 AM, Lopez, Nahleen (FDA) <Nahleen.Lopez@fda.hhs.gov> wrote:

Dear Ms. Wan,

Please refer to IND 100593 and the Expanded Access Protocol you submitted on April 12, 2016.

1. In protocol ML29972 you propose to assess subjects (b) (4) and to collect safety laboratory studies (u) (4). However, in Study WA25046 subjects were assessed every 12 weeks including collection of safety laboratory tests. As we indicated in our March 30, 2016, email response to your request for advice regarding this protocol (refer to response to Question 4) we request that you perform the same clinical and safety assessments as in study WA25046. This includes an in person assessment midway between treatment cycles. At a minimum, these mid-cycle visits should include a determination of adverse events and safety laboratory tests.
2. We also note that the Informed Consent Form includes reference to a phone call to the subject every 4 weeks to assess for new neurologic symptoms or other adverse events that may warrant an unscheduled visit. We agree it is important to continue the same safety monitoring used in the trial during BLA review. Please revise protocol ML29972 to include these telephone interviews.

Please respond by COB Tuesday, April 26, 2016.

The following changes were made to protocol ML29972 – version 2

1. Visits were added at Week 13, 37 that include collection of safety labs – see Appendix 1.
2. A telephone interview was added for the assessment of adverse events and any new neurologic symptoms that might merit an unscheduled visit. These will occur every 4 weeks starting at week 9. See Protocol Section 4.5.10
3. ECG's were added at baseline and week 49.
4. The fluorescence activated cell sorter (FACS) assessment has been changed to screen for total B cells (CD19⁺), total T cells (CD3⁺), and T-helper cells (CD3⁺ and CD4⁺) and will be conducted at baseline and then only prior to the first infusion of the dual-infusion study treatment

29-Apr-16

5. The timing of the brain magnetic resonance imaging (MRI) assessments has been changed to be consistent with the WA25046 study (Section 4.5.6 and Appendix 1).
6. Clarification that the safety follow-up period will begin when the patient receives their final infusion as part of this EAP as opposed at the time of discontinuation from the EAP.
7. [REDACTED] (b) (4)

The following email was sent [REDACTED] (b) (4) since these are not necessary.

From: Lopez, Nahleen (FDA)
Sent: Wednesday, April 27, 2016 1:00 PM
To: wan.tiffany@gene.com
Cc: Tammy Rose; patel.sonali@gene.com

Subject: IND 100593_Information
Dear Ms. Wan,

Please refer to IND 100593 and the Draft protocol ML29972 version 2 which we received by email on April 26, 2016.

[REDACTED] (b) (4)
Section 4.5.6 of the protocol ("Brain Magnetic Resonance Imaging") was acceptable as it was in version 1, i.e. that "Brain MRI scans will be obtained at baseline and if requested by the investigator , as needed".

This change can be made in the next version of the protocol to be submitted.

Please let me know if you have any questions.

Kind Regards,
Nahleen Lopez, PharmD
LCDR, United States Public Health Service
Regulatory Project Manager
Food and Drug Administration
Office of Drug Evaluation – Division of Neurology Products

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/s/

LAWRENCE D RODICHOK
04/29/2016

JOHN R MARLER
04/29/2016

Lopez, Nahleen (FDA)

From: Lopez, Nahleen (FDA)
Sent: Wednesday, April 27, 2016 1:00 PM
To: wan.tiffany@gene.com
Cc: Tammy Rose; patel.sonali@gene.com
Subject: IND 100593_Information

Dear Ms. Wan,

Please refer to IND 100593 and the Draft protocol ML29972 version 2 which we received by email on April 26, 2016.

Please note [REDACTED] (b) (4)
[REDACTED] Section 4.5.6 of the protocol ("Brain Magnetic Resonance Imaging") was acceptable as it was in version 1, i.e. that "Brain MRI scans will be obtained at baseline and if requested by the investigator , as needed".

This change can be made in the next version of the protocol to be submitted.

Please let me know if you have any questions.

Kind Regards,

Nahleen Lopez, PharmD
LCDR, 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: 240-402-2659
Fax: 301-796-9842
Nahleen.Lopez@fda.hhs.gov

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/s/

REBECCA N LOPEZ

04/27/2016



IND 100593

**TREATMENT PROTOCOL
ACKNOWLEDGEMENT**

Genentech, Inc.
Attention: Tiffany Wan
Regulatory Program Management
1 DNA Way
South San Francisco, CA 94080

Dear Ms. Wan:

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

We acknowledge our April 12, 2016, receipt, of your treatment protocol titled “An Open-Label, Multicenter, Expanded Access Program For Ocrelizumab In Patients With Primary Progressive Multiple Sclerosis,” dated April 12, 2016.

Use of this investigational drug in humans, under this treatment protocol, may not be initiated until 30 days after the date of receipt shown above or on earlier notification by FDA, as per 21 CFR 312.305(d)(2)(ii). Therefore, unless we notify you otherwise, you may not initiate your proposed treatment protocol before May 12, 2016. If, within the 30-day period, we find that your submission is deficient under 21 CFR 312.42(b)(3), we will immediately notify you by telephone that the study may not proceed (“partial clinical hold”). In that event, it is understood that you will not proceed with the treatment use of this investigational drug until FDA notifies you that treatment use under this protocol may proceed.

It has not been our policy to object to a sponsor, upon receipt of this acknowledgement letter, either obtaining supplies of the investigational drug or shipping it to investigators listed in the IND. However, if the drug is shipped to investigators, they should be reminded that treatment with the investigational drug may not begin under the IND until 30 days after the IND receipt date or later if the IND is placed on clinical hold.

Prior to use of each new lot of the investigational biologic in clinical studies, submit the lot number, the results of all tests performed on the lot, and the specifications when established (i.e., the range of acceptable results).

We remind you that, under 21 CFR 312.8(a)(3), you may not charge for this investigational drug without prior written authorization from FDA.

PATIENT-FOCUSED ENDPOINTS

An important component of patient-focused drug development is describing the patient’s perspective of treatment benefit in labeling based on data from patient-focused outcome measures [e.g., patient-reported outcome (PRO) measures]. Therefore, early in product development (i.e., phase 1 or 2), we encourage sponsors to consider incorporating well-defined and reliable patient-focused outcome measures as key

efficacy endpoints in clinical trials, when appropriate, and to discuss those measures with the Agency in advance of confirmatory trials. For additional information, refer to FDA's guidance for industry *Patient-Reported Outcome Measures: Use in Medical Product Development to Support Claims*, available at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM193282.pdf>.

DATA STANDARDS FOR STUDIES

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

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

PEDIATRIC ASSESSMENTS

As amended by the Food and Drug Administration Safety and Innovation Act (Public Law 112-144, 126 Stat. 993) of July 9, 2012, the Pediatric Research Equity Act (PREA) requires any sponsor who plans to file a marketing application for a drug or biological product (FDCA section 505 or PHSA section 351, respectively) that includes a new active ingredient, new indication, new dosage form, new dosing regimen, and/or new route of administration to submit an initial Pediatric Study Plan (PSP) (21 U.S.C. 355c). The intent of the PSP is to identify needed pediatric studies and begin planning for these studies. The timing and content of an initial PSP, including a template, can be found at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM360507.pdf>. Review this guidance and the PREA requirements to determine if your application must contain an assessment (pediatric clinical data), waiver request, and/or deferral request (21 U.S.C. 355c).

If you have any questions, you may contact the Division of Pediatric and Maternal Health at 301-796-2200 or email pdit@fda.hhs.gov.

ABUSE POTENTIAL ASSESSMENT

Drugs that affect the central nervous system, are chemically or pharmacologically similar to other drugs with known abuse potential, or produce psychoactive effects such as mood or cognitive changes (e.g., euphoria, hallucinations) need to be evaluated for their abuse potential and a proposal for scheduling will be required at the time of the NDA submission [21 CFR 314.50(d)(5)(vii)]. For information on the abuse potential evaluation and information required at the time of your NDA submission, see the draft guidance for industry, "Guidance for Industry Assessment of Abuse Potential of Drugs", available at: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM198650.pdf>.

SUBMISSION REQUIREMENTS

Cite the IND number listed above at the top of the first page of any communications concerning this application. Each submission to this IND must be provided in triplicate (original plus two copies). Please

include three originals of all illustrations that do not reproduce well. 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

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size. Non-standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission. For additional information, see <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/DrugMasterFilesDMFs/ucm073080.htm>.

If you have any questions, call me at (240) 402-2659.

Sincerely,

{See appended electronic signature page}

Nahleen Lopez, PharmD
Regulatory Project Manager
Division of Neurology Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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/s/

REBECCA N LOPEZ
04/19/2016

Lopez, Nahleen (FDA)

From: Lopez, Nahleen (FDA)
Sent: Tuesday, April 19, 2016 9:18 AM
To: wan.tiffany@gene.com
Cc: Tammy Rose; 'patel.sonali@gene.com'
Subject: IND 100593_Information Request

Dear Ms. Wan,

Please refer to IND 100593 and the Expanded Access Protocol you submitted on April 12, 2016.

1. In protocol ML29972 you propose to assess subjects (b) (4) and to collect safety laboratory studies (b) (4). However, in Study WA25046 subjects were assessed every 12 weeks including collection of safety laboratory tests. As we indicated in our March 30, 2016, email response to your request for advice regarding this protocol (refer to response to Question 4) we request that you perform the same clinical and safety assessments as in study WA25046. This includes an in person assessment midway between treatment cycles. At a minimum, these mid-cycle visits should include a determination of adverse events and safety laboratory tests.
2. We also note that the Informed Consent Form includes reference to a phone call to the subject every 4 weeks to assess for new neurologic symptoms or other adverse events that may warrant an unscheduled visit. We agree it is important to continue the same safety monitoring used in the trial during BLA review. Please revise protocol ML29972 to include these telephone interviews.

Please respond by **COB Tuesday, April 26, 2016.**

Kind Regards

Nahleen Lopez, PharmD
LCDR, 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: 240-402-2659
Fax: 301-796-9842
Nahleen.Lopez@fda.hhs.gov

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/s/

REBECCA N LOPEZ
04/19/2016



IND 100593

MEETING MINUTES

Genentech, Inc.
Attention: Jennifer Sexton
Regulatory Program Director
Genentech, Inc.
1 DNA Way MS# 241A
South San Francisco, CA 94080-4990

Dear Ms. Sexton:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Ocrelizumab (rhuMAb 2H7).

We also refer to the meeting between representatives of your firm and the FDA on February 29, 2016. The purpose of the meeting was to obtain feedback from the Agency on key components of the CMC strategy.

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

If you have any questions, call Melinda Bauerlien, Senior Regulatory Business Process Manager at (301) 796-0906.

Sincerely,

{See appended electronic signature page}

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

Enclosure:
Meeting Minutes

MEMORANDUM OF MEETING MINUTES

Meeting Type: C
Meeting Category: CMC

Meeting Date and Time: February 29, 2016 at 12:00 PM
Meeting Location: 10903 New Hampshire Avenue
White Oak Building 71, Conference Room: 1206
Silver Spring, Maryland 20903

Application Number: IND 100593

Product Name: Ocrelizumab (rhuMAb 2H7)
Indication: Treatment of patients with relapsing-forms of multiple sclerosis (RMS) and primary progressive multiple sclerosis (PPMS)

Sponsor/Applicant Name: Genentech, Inc.

Meeting Chair: Linan Ha, Ph.D.
Meeting Recorder: Melinda Bauerlien, M.S.

FDA ATTENDEES

Milos Dokmanovic, Ph.D., Product Reviewer, Division of Biotechnology Review and Research I
Linan Ha, Ph.D., Team Leader, Division of Biotechnology Review and Research I
Sarah Kennett, Ph.D., Review Chief, Division of Biotechnology Review and Research I
Patricia Hughes, Ph.D., Acting Branch Chief, Division of Microbiology Assessment/Branch IV
Reyes Candauchacon, Ph.D., Microbiology Team Lead, Division of Microbiology Assessment/Branch IV
Melinda Bauerlien, M.S., Senior Regulatory Business Process Manager, OPRO

SPONSOR ATTENDEES

Anthony Chen, Ph.D., QC Principal Scientist, IMP Product Quality, Pharma Technical Development
Damian Cunningham, Ph.D., Technical Development Leader, Pharma Technical Development
Lisa deCardenas, Associate Regulatory Program Director, Pharma Technical Regulatory
Kathy Francissen, Ph.D., Senior Director, Pharma Technical Regulatory
Ryan Hamilton, Ph.D., Senior Engineer, Late Stage Cell Culture, Pharma Technical Development
Basim Hilal, Associate Group Director, Pharma Technical Regulatory
Yung-Hsiang Kao, Ph.D., Associate Director, Analytical Development, Pharma Technical Development
Michele Libonati, Lifecycle Leader, Global Product Strategy
Anne-Marie Li-Kwai-Cheung, Senior Global Regulatory Leader, Pharma Development Regulatory

Jamie Moore, Ph.D., Director, Late Stage Pharmaceutical Development, Pharma Technical Development

Melissa Mun, M.S., Senior Engineer, Late Stage Cell Culture, Pharma Technical Development

Jennifer Sexton, Regulatory Program Director, Pharma Technical Regulatory

Vikas Sharma, Ph.D., Group Leader, Late Stage Pharmaceutical Development, Pharma Technical Development

John Stults, Ph.D., Director, Analytical Development and Quality Control, Pharma Technical Development

Pin Yee Wong, M.S., Director, Biological Technologies, Pharma Technical Development

1.0 BACKGROUND

To obtain feedback from the Agency on key components of the CMC strategy.

2.0 DISCUSSION

Question 1:

Appreciating that the agreement on specifications is a review issue, can the Agency comment on the following:

- a) Proposed commercial Drug Substance release and stability specifications.
- b) Proposed commercial Drug Product release and stability specifications.

Agency's Response:

As the sponsor noted, it is premature to agree on the adequacy of the proposed commercial ocrelizumab drug substance (DS) and drug product (DP) release and stability specifications; these are a review issue. Based on the information provided in the meeting package, we have the following comments:

- The lot release and stability acceptance criteria for the commercial product should be linked to the material used in the pivotal clinical studies to support the BLA application, i.e., the pivotal clinical studies conducted in patients with primary progressive multiple sclerosis (PPMS) and relapsing multiple sclerosis (RMS), rather than in patients with rheumatoid arthritis.
- Genentech previously stated that the available literature and Genentech's historical experience strongly suggest that the activity driving B-cell depletion is Fc receptor-mediated (i.e., ADCC and ADCP), while CDC plays a lesser role in B-cell depletion (Type C pre-meeting package, page 19, submitted on September 23, 2015). However, the proposed acceptance criterion for normalized G0-F (b) (4) % area, Table 2), a surrogate quality attribute for ADCC, is quite wide, and it is not clear that this criterion will provide adequate control over ADCC-mediated potency. The statement that the ADCC range calculated using the correlation equation (55%-206%) overlaps the range of clinical experience (66%-235%) is based on clinical studies of rheumatoid arthritis patients (Pages 33 and 37). Additionally, data presented in the previous meeting package (Figure 3, Type C pre-meeting package, submitted on September 23, 2015) indicated a much

narrower range of ADCC activity for both v0.4 DS lots (lots used in pivotal studies) and v1.0 DS lots (proposed commercial material) than the 55-206% range derived from the proposed limit for G0-F. An adequate and comprehensive control strategy for ADCC activity, and supporting data obtained from materials used in the pivotal clinical studies conducted with PPMS and RMS patients should be provided in the BLA.

Meeting Discussion:

The sponsor acknowledged the Agency's concern regarding the wide acceptance criterion proposed for %G0-F ((b) (4) %). The sponsor clarified that only materials used in Phase II and Phase III clinical studies in MS patients were used for setting the proposed release and stability specifications for commercial ocrelizumab DS and DP. The sponsor further presented the overall control strategies used for setting specifications, which included considerations relevant to both clinical experience and process capability (Slides #6-9). The Sponsor requested Agency comment on this approach.

The Agency indicated agreement with the major considerations for the upper and lower limits of the %G0-F acceptance criterion being safety and efficacy, respectively. However, it is premature to agree on the commercial DS and DP release and stability acceptance criteria. The adequacy of the proposed specifications will be determined during the BLA review based on the entirety of the BLA submission. Additionally, the Agency stated that the appropriateness of using data from Phase II MS studies as a critical component of setting commercial specifications may be discussed with the clinical review team. The Agency further emphasized that the proposed specifications should be supported by pivotal clinical studies in MS patients and that the $\pm 3SD$ approach may not be appropriate for certain product quality attributes.

- The proposed commercial DS and DP lot release and stability specifications include a number of acceptance criteria that are wider than the current clinical acceptance criteria; these criteria include those for HMWS by SE-HPLC, G0% by CE-Glycan analysis, and acidic region by IE-HPLC. In addition, the controls specific to main peak and basic region by IE-HPLC and LMWS by SE-HPLC were eliminated from the release and stability specifications for both DS and DP. The BLA should include scientifically sound justifications for these proposed changes.
- The proposed DS and DP release and stability specifications do not include a test conducted under denatured and reduced conditions, such as reduced CE-SDS, for size variants. Information to demonstrate that adequate control over potential product degradation is in place should be provided in the BLA. The degradation products of concern includes fragments that might arise during the DS and DP manufacturing processes or storage that cannot be evaluated using the currently proposed size-based assays, SE-HPLC and non-reduced CE-SDS.
- To facilitate the evaluation of the adequacy of the proposed release and stability specifications for commercial ocrelizumab DS and DP, the release and stability data used

to support the justification of the proposed specifications should be clearly identified with respect to the clinical studies in which the material was used and the version of the processes by which the lots were manufactured.

- Please clarify if the (b) (4) is equivalent to (b) (4). Provide a justification (b) (4)

Meeting Discussion:

(b) (4) *For consistency and clarification in the BLA, "Drug Product Solution" will be used to define the material after dilution has taken place. Information on bacterial endotoxins testing (b) (4) will be provided in the BLA.*

- The endotoxin DS and DP specifications ($\leq$ (b) (4) EU/mL) appears to be acceptable based on an infused volume of 20 mL of product (please confirm that this is the maximum volume per dosage); however, endotoxin coming from the saline solution should also be considered.

Question 2:

Does the Agency agree that the data provided supports the Sponsor's conclusions that Drug Substance and Drug Product release testing as currently performed, using kinetic chromogenic assay (KCA) with limulus amoebocyte lysate reagent water (LRW), does not exhibit low endotoxin recovery (LER) and masking, and therefore is suitable as a commercial release assay?

Agency's Response:

The conclusion from your LER studies appears to be adequate and they will be assessed during the BLA review. Please clarify if the studies were conducted at the hold temperature.

Meeting Discussion:

Endotoxin Recovery Studies (ERS) were performed at 2-8°C because of a concern for the stability of the spiked Control Standard Endotoxin, which has a recommended storage temperature of 2-8°C. The samples in the ERS were held for 7 days prior to testing as the applicant has observed endotoxin masking at 1-2 days or earlier at 2-8°C. Studies performed by the applicant have shown that samples which do not show endotoxin masking when the ERS is performed at 2-8°C, also do not show endotoxin masking when the ERS is performed

(b) (4)

The Agency stated that the acceptability of this approach will be a review issue. They commented that the study was performed at 2 – 8°C while manufacturing occurs (b) (4)

Temperature may affect the kinetics of endotoxin masking. The Agency inquired

(b) (4)

The sponsor stated

(b) (4)

Question 3:

Does the Agency agree with the Sponsor's (b) (4) validation study strategy, specifically that (b) (4) ocrelizumab is considered representative and suitable for use in the study?

Agency's Response:

(b) (4)

In general the strategy appears to be acceptable, but it will be assessed during the BLA review. Include data demonstrating bactericidal effects of ocrelizumab on the challenge microorganism and data on the viability of *B. diminuta* in ocrelizumab solution (b) (4)

Question 4:

Given the Sponsor's product knowledge, does the Agency agree that the stability data to be submitted at time of BLA submission, including those data provided during the review period of the BLA, will support a Drug Product shelf life of (b) (4) months?

Agency's Response:

It is premature to make a determination regarding the adequacy of the data to support the proposed (b) (4) month shelf life for commercial ocrelizumab DP. It may be acceptable to establish the DP shelf-life by leveraging stability data obtained from v0.4-derived Phase III clinical DP batches, if these batches are determined to be fully representative of the commercial material. In addition, the increased opalescence/visible particles observed in all three DP validation batches at 3 months of storage at 25°C/60% RH is of concern. Genentech's investigation identified that the increased opalescence/visible particles is related to polysorbate 20 degradation. Although no increase in opalescence/visible particles was observed in the validation lots through 9 months of real time storage at 2-8°C, a visible particle associated increase in opalescence was observed in v0.4-derived DP lots stored under real time conditions at the 5 year time point. To support assurance that the commercial DP lots will stay within the proposed acceptance criterion of practically free from visible particles through the end of the shelf-life, the following should be provided in the BLA:

- Data to clarify whether the increased opalescence/visible particles were observed in v0.4-derived representative DP lots in a time course consistent with the validation lot observations, e.g., if opalescence/visible particles were increased in the v0.4 lots after 3 months of storage under 25°C/60% RH conditions.
- Data and the control strategy implemented to ensure that the validation lots and subsequent commercial lots will remain within the acceptance criterion for visible particles through the end of the shelf-life.
- A comprehensive control strategy for the polysorbate 20 raw material.

Meeting Discussion:

The sponsor provided information on opalescence for clinical batches (v0.4) and validation batches (v1.0). The data indicate that through the current time points, the increased opalescence was only observed in validation batches stored at the accelerated condition of 25°C and clinical batches stored under the recommended condition of 2-8°C for 5 years (Slides #11 and 12). The sponsor stated the increased opalescence is associated with the increased level of free fatty acid (FFA) resulting from polysorbate 20 degradation. Polysorbate 20 appeared to be degrading via a similar catalytic hydrolytic mechanism in both clinical and validation batches. The difference in the level of opalescence observed between clinical batches and validation batches may be caused by the subtle differences in polysorbate 20 raw material used. The sponsor further presented the proposed mitigation and control strategies for the observed increasing level of opalescence (Slides #14 and 15).

The Agency stated that the adequacy of the control strategy to mitigate the increasing level of opalescence will be determined during the BLA review. In addition to the control strategy proposed by the sponsor, the Agency requested the following information be submitted in the BLA:

- 1. detailed information on visible particles/opalescence for all DP lots under stability monitoring***
- 2. all available stability data for other lots with increased opalescence (i.e., analytical data for lots that are not on official stability programs)***
- 3. data to demonstrate that the observed visible particles are not proteinaceous***
- 4. formulation development data to demonstrate the robustness of the polysorbate 20 concentration and ensure that the decrease in polysorbate 20 concentration as a result of degradation will not impact the stability of the product (e.g., aggregation)***
- 5. assessment of potential safety concerns, such as hypersensitivity, that may be associated with degraded Polysorbate 20.***

The sponsor agreed to provide the information in the BLA submission.

Question 5:

Does the Agency agree with the proposed timing for the stability amendment to be submitted during the review period?

Agency's Response:

It is acceptable to provide a simple stability update within 30 days of submission of the completed BLA package. "Simple stability update" refers to stability data and analyses performed under the same conditions and for the same drug product batches in the same container closure system(s) as described in the stability protocol provided in the original

submission. In addition, the simple stability update should use the same tabular presentation as in the original submission and the same mathematical or statistical analysis method(s) (if any) and should not contain any matrix or bracketing approaches that deviate from the stability protocol in the original BLA. Alternatively, if deemed necessary, this information may be requested as an information request during the review cycle.

Question 6:

Does the Agency agree to the approach for PALM of critical process parameters supported by multivariate acceptable ranges and/or proven acceptable ranges?

Agency's Response:

It is premature to make a determination regarding the adequacy of the approach and proposed MAR/PAR ranges to support lifecycle management of ocrelizumab. Agreement with the approach will require a comprehensive review of the entirety of the data submitted in the BLA.

Question 7:

Ocrelizumab Drug Substance is manufactured at the Genentech facility in Vacaville, CA and Drug Product at (b) (4). A proposal for an inspection timeframe based on manufacturing dates scheduled at each facility is provided in Section 7. Can the Agency comment on the acceptability of this timeframe for the proposed pre-license inspection(s)?

Agency's Response:

The Vacaville facility should be in operations manufacturing ocrelizumab during the review timeline (ideally between filing and mid-cycle). (b) (4) facility should be in operation during the review timeline for ocrelizumab or another product.

Meeting Discussion:

The sponsor stated that (b) (4) will be in production between BLA filing and the anticipated mid-cycle meeting to accommodate the PLI.

The sponsor clarified the timing of the Drug Substance manufacturing schedule in Vacaville, with first harvest occurring on (b) (4). The Agency concurred that the proposed time frame for PLI is acceptable.

Question 8:

Would the Agency like to have an Applicant Orientation/Technical Walk-Through meeting with the Sponsor after the submission of the BLA to outline major components for Module 3?

Agency's Response:

No, an applicant orientation following the submission of the BLA to outline major components of Module 3 is not necessary.

Meeting Discussion:

The sponsor stated that a Technical Walk through Meeting has been planned to orient the review team to the general format of all modules of the BLA and to specific components requested at the pre-BLA meeting.

The Agency noted that a CMC technical walk through meeting is not needed, if the purpose of the meeting is only for the orientation of the information provided in module 3.

9.2 CONTENT FOR MICROBIAL CONTROL STRATEGY IN THE BLA

We have the following comments:

- Provide data demonstrating effectiveness (b) (4)
[REDACTED]
- Provide data demonstrating effectiveness of the storage solution (b) (4)
[REDACTED]

3.0 ATTACHMENTS AND HANDOUTS

A copy of the slides presented during the meeting are attached.

22 Pages have been Withheld in Full as B4 (CCI/TS) immediately following this page

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

/s/

LINAN HA
03/11/2016



IND 100593

MEETING MINUTES

Genentech, Inc.
Attention: Tiffany Wan
Regulatory Program Management
1 DNA Way
South San Francisco, CA 94080

Dear Ms. Wan:

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

We also refer to the meeting between representatives of your firm and the FDA on February 4, 2016. The purpose of the meeting was to discuss reaching an agreement on the acceptability of the study to support the proposed indication, primary progressive multiple sclerosis (PPMS)

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 Nahleen Lopez, Regulatory Project Manager at (240) 402-2659.

Sincerely,

{See appended electronic signature page}

Billy Dunn, MD
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 Date and Time: Thursday, February 4, 2016, 1230 to 1400 EST
Meeting Location: White Oak Building 22, Conference Room: 1309

Application Number: 100593
Product Name: Ocrelizumab
Indication: Multiple Sclerosis
Sponsor/Applicant Name: Genentech, Inc.

Meeting Chair: Billy Dunn, MD
Meeting Recorder: Nahleen Lopez, PharmD

FDA ATTENDEES

Division of Neurology Products

Billy Dunn, MD, Director
Heather Fitter, MD, Acting Clinical Team Leader
Larry Rodichok, MD, Clinical Reviewer
Laura Jawidzik, MD, Clinical Reviewer
Sally Jo Yasuda, PharmD, Safety Team Leader
Gerard Boehm, MD, Safety Reviewer
Jacqueline Ware, PharmD, Chief Project Management Staff
Nahleen Lopez, PharmD, Project Manager

Office of Clinical Pharmacology
Jagan Parepally, PhD, Reviewer

Office of Biostatistics
Xiang Ling, PhD, Reviewer

Office of Surveillance and Epidemiology
Jasminder Kumar, PharmD, Risk Management Analyst

Division of Pediatric and Maternal Health
Donna Snyder, MD, Acting Pediatrics Team Leader
Denise Johnson-Lyles, PhD, Project Manager

SPONSOR ATTENDEES

Ann Santen, Global Operations Program Leader
Anne-Marie Li-Kwai-Cheung, Senior Global Regulatory Leader
Fabian Model, Associate Director, CNS Biostatistics
Gaelle Klingelschmitt, Project Lead Statistician
Heidemarie Kletzl, Clinical Pharmacology
Hideki Garren, Group Medical Director, Clinical Science Leader
Jean-Paul Pfefen, Global Development Team Leader

Michele Libonati, Lifecycle Leader, Global Product Strategy
Nicole Mairon, Senior Safety Science Leader
Paulo Fontoura, Vice President, Global Head Clinical Development Neuroscience
Peter Chin, Principal Medical Director, Clinical Science
Sophie Banzet, Therapeutic Area Head Safety Science CNS
Tammy Rose, US Global Regulatory Lead
Tiffany Wan, US Regulatory Program Manager

1. BACKGROUND

Genentech is requesting a pre-BLA meeting to discuss their plans to submit a standalone BLA for the treatment of PPMS.

FDA sent Preliminary Comments to Genentech, Inc. on February 2, 2016.

2. DISCUSSION

The sponsor plans on filing the BLA in April, 2016. They received the grant breakthrough therapy letter for PPMS issued on February 2, 2016.

2.1 CLINICAL AND STATISTICAL

Question 1: Does the Agency agree that the outcomes from the single pivotal Phase III Study WA25046 in patients with primary progressive MS with supportive evidence from related Studies WA21092 and WA21093 in the RMS patient population provides sufficient clinical evidence to support the review of the BLA for patients with primary progressive MS?

FDA Preliminary Response to Question 1: In principle, yes, the PPMS study and the RMS studies appear appropriate for mutual support, but recognize that this is a preliminary assessment and a formal filing decision for the PPMS indication can only be made after receipt of the application. Also, note that the adequacy of the clinical data from study WA25046 in PPMS and studies WA21092 and WA21093 in RMS to support an indication for PPMS will be determined following full review of the clinical trial results from these studies.

Sponsor's Response to FDA Preliminary Response to Question 1: No further discussion is necessary.

Meeting Discussion: No discussion.

Question 2: Does the Agency have any comments on the proposed indication based on the clinical trial conducted?

FDA Preliminary Response to Question 2: Discussion of specific language to be included in labeling is premature.

Sponsor's Response to FDA Preliminary Response to Question 2: No further discussion is necessary.

Meeting Discussion: FDA stated that the indication described in labeling would reflect the study population enrolled. If the patients enrolled in the PPMS trial actually had many relapses and appeared more consistent with a diagnosis of RMS than PPMS, then an indication of PPMS would presumably not be adequately supported by this trial. FDA plans to review the relapses identified in the trial to determine the effect of relapses on the classification of the study population and on the disability outcome endpoint.

Question 3: Based on the initial review of the PPMS safety data, the Sponsor believes that the information included in the US prescribing information (USPI) will be sufficient to convey the benefits and risks of ocrelizumab and that additional REMS measures are not deemed necessary. Does the Agency agree?

FDA Preliminary Response to Question 3: At this time, we have insufficient information to determine whether a risk evaluation and mitigation strategy (REMS) will be necessary to ensure that the benefits of ocrelizumab outweigh the risks. We will determine the need for a REMS during the review of your application.

Sponsor's Response to FDA Preliminary Response to Question 3: No further discussion is necessary.

Meeting Discussion: No discussion.

Question 4: To support the PPMS BLA, the presentation of safety data will utilize the same approach agreed with the Division for the RMS indication on 08 December 2015. Does the Agency agree with presentation of safety data as described in Section 8.3?

FDA Preliminary Response to Question 4: Yes.

Sponsor's Response to FDA Preliminary Response to Question 4: No further discussion is necessary.

Meeting Discussion: No discussion.

2.2 REGULATORY

Question 5: The Sponsor would like to further discuss the options for filing BLAs to support both the RMS and PPMS indications. Consideration is given to the Division's ability to take action on the indications separately with clear review timelines associated to each indication.

a. The Sponsor proposes to submit in parallel, two standalone BLAs, containing the clinical evidence described below. Does the Agency agree with the proposed clinical content to support the PPMS BLA?

i. RMS BLA containing clinical data from RMS studies WA21092 and WA21093.

ii. PPMS BLA containing clinical data from PPMS study WA25046 and RMS studies WA21092 and WA21093.

b. The Sponsor understands filing a single BLA to support both indications is also an option and would like further clarity on the expectations for the review of the application and applicable timelines for each indication.

i. In consideration of the unmet medical need in PPMS and the significant improvement in efficacy and safety demonstrated in the RMS trials, the Sponsor intends to request priority review. Does the Agency agree priority review could be considered for both indications?

ii. Recognizing the unmet medical need and potential for breakthrough therapy designation in the PPMS population, would a single BLA enable an earlier action date for this indication?

FDA Preliminary Response to Question 5: We recommend that you file a single BLA. Review classification (priority or standard) is determined at the time of filing. We agree that priority review appears to be a consideration for an application for the treatment of PPMS. While submission of a single original BLA allows for different action dates for multiple indications proposed in that BLA, we note that consideration of a PPMS indication in a single application preliminarily appears to require review of the studies supporting the RMS indication.

Sponsor's Response to FDA Preliminary Response to Question 5: The Sponsor acknowledges the Agency's feedback to submit a single BLA to include PPMS and RMS and would like to further understand the Agency's recommendation. The Sponsor would like to clarify the review milestones for a single BLA specifically if PPMS is classified as priority review.

Meeting Discussion: FDA recommends filing a single BLA for both the PPMS and RMS indications. Inclusion of the RMS and the PPMS data in a single application should not delay the review timeline for the PPMS indication. Additionally, since the data for RMS would appear to require review in order to take an action on the PPMS indication, submitting as a single application likely will shorten the timeline for the RMS indication compared to submitting the RMS indication as a separate application. The review period will be determined upon submission of the application. FDA stated that submitting a single application would result in only one user fee and one PDUFA date even if two indications were requested. If, during the review period, the application was split by indication for any reason, another user fee would not need to be submitted at that time.

FDA also stated that any recommendations previously provided for the December 8, 2015, pre-BLA meeting with respect to components of the safety submission are applicable for the PPMS submission. In addition to the responses to the questions in the minutes from the December 8, 2015, meeting, FDA reminded the sponsor of the general recommendations for submission of safety data included in the Meeting Request Denied communication of March 13, 2015; these will be applicable for the PPMS submission.

Question 6: Does the Agency agree with:

- a. The proposed BLA Table of Contents to support the PPMS indication including clinical evidence from PPMS study WA25046 and RMS studies WA21092 and WA21093 as described in Appendix 1?
- b. The structure of one Summary of Clinical Efficacy (SCE) to cover both the RMS and PPMS indications as described in Appendix 1?

FDA Preliminary Response to Question 6: The approach is acceptable assuming the application meets the standard data submission requirements.

Sponsor's Response to FDA Preliminary Response to Question 6: No further discussion is necessary.

Meeting Discussion: No discussion.

Question 7: Based on the preliminary review of the data, does the Agency foresee that the PPMS application will be reviewed by an Advisory Committee?

FDA Preliminary Response to Question 7: The need for an Advisory Committee review will be determined following submission of the BLA.

Sponsor's Response to FDA Preliminary Response to Question 7: The Sponsor would like to better understand the timing of when we would be notified of the need for an Advisory Committee.

Meeting Discussion: In general, a decision is made around the time of the filing meeting and is communicated in the 74 day letter. If an application receives priority review this decision may be communicated earlier. A decision to take an application to an Advisory Committee may also occur later in the review cycle and would be communicated at that time.

3. ADDITIONAL FDA COMMENTS

With regard to the clinical pharmacology sections of the BLA, we have the following suggestions for format.

1. Please provide a “review aid” for Clinical Pharmacology in the BLA submission. A template is attached as an appendix. Relevant information should be provided per the template. Please note the summary template is just to provide an idea of what we look for in the submission, and the Sponsor should add and summarize additional aspects or questions that are pertinent to Biologics for the application.

Sponsor's Response to FDA Preliminary Response to Additional Comment 1: The Sponsor agrees to structure the Clinical Pharmacology section in the BLA according to the provided guidance.

2. For submitting findings from population pharmacokinetic data :
 - a. All datasets used for model development and validation should be submitted as a SAS transport files (*.xpt). A description of each data item should be provided in a Define.pdf file. Any concentrations and/or subjects that have been excluded from the analysis should be flagged and maintained in the datasets.
 - b. Model codes or control streams and output listings should be provided for all major model building steps, e.g., base structural model, covariates models, final model, and validation model. These files should be submitted as ASCII text files with *.txt extension (e.g.: myfile_ctl.txt, myfile_out.txt).
 - c. A model development decision tree and/or table which gives an overview of modeling steps. For the population analysis reports we request that you submit, in addition to the standard model diagnostic plots, individual plots for a representative number of subjects. Each individual plot should include observed concentrations, the individual predication line and the population prediction line. In the report, tables should include model parameter names and units. For example, oral clearance should be presented as CL/F (L/h) and not as THETA(1). Also provide in the summary of the report a description of the clinical application of modeling results.
 - d. In terms of where the code and data should be submitted, the following folders can be used as one xample for population PK related codes and data. The codes should be submitted under "module5/datasets/poppk/analysis/programs/" folder (such as run1.ct1.txt, run1.lst.txt, plot1.R.txt) with a define pdf file to explain the role of each file and sometimes with a pdf file as the revieweraid.pdf to explain the flow of running the code if necessary. The datasets should be submitted under "module5/datasets/poppk/analysis/datasets/" folder (such as poppk.xpt, pkpd.xpt) with a define pdf file to explain the variables within each data file.

Sponsor's Response to FDA Preliminary Response to Additional Comment 2: The Sponsor agrees to provide the population pharmacokinetics data files in the BLA as specified.

4. ADDITIONAL SPONSOR COMMENTS

The Sponsor would like to discuss several additional points with the Agency.

1. The Sponsor would like feedback from the Agency on the approach to investigate

the imbalance in malignancy seen with ocrelizumab in the MS indication.

Meeting Discussion:

FDA requested the following in the submission:

- 1) A justification of the use of the comparator databases.
- 2) A comparison of sponsor data to SEER data.
- 3) Comparisons to appropriate gender and age range.
- 4) An evaluation of malignancy in the other ocrelizumab indications.
- 5) A complete discussion of malignancy, especially breast cancer risk, for other biologics in this class of drugs.
- 6) For each individual subject with a malignancy, provide the time from starting ocrelizumab to when the malignancy was identified.

FDA agreed with an ongoing update regarding incidence throughout the review period.

2. One consideration for the Dosage and Administration section in the USPI is to harmonize the infusion regimen for the PPMS and RMS indications. Could the Agency provide initial thoughts on this proposal (dual infusion for the first dose; single infusion for subsequent doses)?

Meeting Discussion: After discussion, FDA stated that it understood the sponsor's general rationale for harmonization of the infusion regimen and recommended the sponsor provide a proposal including supportive PK/PD, safety, tolerability, and efficacy data comparing both regimens for review in the BLA.

3. Based on the positive outcome of Study WA25046, the Sponsor is proposing an expanded access treatment protocol. The Sponsor would like the Agency's feedback on the patient population, estimated study size of up to 1000 patients, and infusion regimen (dual infusion for the first dose; single infusion for subsequent doses).

Meeting Discussion: FDA suggested submitting the plan to the IND in draft form for Agency feedback. On face, it appeared that the patient population and size of the study would be acceptable, but consideration of which infusion regimen to use may require further review of data on those two regimens.

4. We note the Agency's recommendation for the inclusion of multiple components in the RMS BLA. The Sponsor proposes to provide items detailed in RMS feedback for the PPMS trial, with the exception of items specific to relapses (FDA Additional Comment 8):

- survival curves (FDA Additional Comment 7 from RMS preliminary comments)
- a complete accounting of all EDSS determinations (FDA Additional Comment 9 from RMS preliminary comments)
- a CONSORT diagram of patient disposition (FDA Additional Comment 10 from RMS preliminary comments)

- an assessment of potential sources of bias in consideration of the Study WA25046 design (FDA Additional Comments 11 and 12 from RMS preliminary comments)
- a log of clinical events for each patient (FDA Additional Comment 13 from RMS preliminary comments)
- MRI tables (FDA Additional Comment 14 from RMS preliminary comments)
- a table identifying key milestones in the study (FDA Additional Comment 15 from RMS preliminary comments)
- a description of site monitoring process (FDA Additional Comment 16 from RMS preliminary comments)
- datasets with a row for each site to evaluate extent of participation (FDA Additional Comment 17 from RMS preliminary comments)
- fields collected in the CRF but not included in the dataset (FDA Additional Comment 18 from RMS preliminary comments)
- a sample of active treatment and placebo packaged and labeled as received at study sites (FDA Additional Comment 19 from RMS preliminary comments)
- 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 (FDA Additional Comment 20 from RMS preliminary comments)

Does the Agency have any comments?

Meeting Discussion:

If there are subjects in the ITT who have had relapses during the period for analysis of 12 and 24 week confirmed disability progression, then the sponsor should plan to provide the following:

1. Data on the relapses themselves similar to those data submitted for relapses in the trials of RMS (e.g., date of onset, date of evaluation, date of EDSS score).
2. The relative impact of relapses on the primary endpoint (e.g., the proportion of first progressions that started at a relapse, the primary endpoint analysis after removing progressions that started at a relapse).

Additional FDA Comments:

The sponsor should plan to provide the following:

1. The Neurostatus Scoring Manual
2. The MSFC scoring manual
3. Data on the disposition of EDSS scores through the Neurostatus edit check process and the EDSS Assessment Check process described in Appendix 1 of the Statistical Analysis Plan for Study WA25046. If this process was initiated after subjects had been randomized, please differentiate these results before and after the process was initiated.

4. Data from the results of the telephone interviews as described in Appendix 4 of the WA25046 protocol. Submission of the telephone interview forms is not necessary but should be available for submission if requested.
5. Information on the timing of EDSS scores in relationship to administration of investigational product if there were EDSS scores that contributed to the baseline EDSS from assessments conducted after randomization.

5. **PREA REQUIREMENTS**

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

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

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

PRESCRIBING INFORMATION

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

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

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

(<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM425398.pdf>).

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

ABUSE POTENTIAL ASSESSMENT

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

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

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.				

6. ATTACHMENTS AND HANDOUTS

No attachments or handouts for the meeting minutes.

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW AID

This is only an example of the requested review aid. This can also replace the summary section of Clinical Pharmacology and Biopharmaceutics:

- **Please fill the headings as it applies to your drug**
- **Additional specific headings can be included to suit the development of your drug/ dosage form (for e.g. For extended release products, headings like comparability of the ER to IR product, for transdermal products section on effect of application site on the PK and adhesiveness of the product etc should be included)**
- **All statements in this summary section should be annotated with links similar to your “annotated label” that would allow the reader to locate all relevant data supporting the statement. Additional links should be provided, whenever possible, for the study report and any raw data located in a SAS transport file or other format that supports the QBR statement.**
- **Within the summary section text, relevant Tables and Figures to understand the data should be included and should not be referred to some Appendix.**
- **Results from various studies, pop pk analyses should be pooled to provide information under each heading, so that consistencies across studies can be determined. If results from two similar studies are different, plausible explanations of these differences should be included.**
- **If different formulations were used during the development, the section should mention what formulation was used (to-be marketed vs. clinical service formulation)**

1.0 GENERAL ATTRIBUTES OF THE DRUG

This section contains background information about the drug and drug product to provide a context for assessing the results of the clinical pharmacology and biopharmaceutics studies.

1.1 Drug/Drug Product Information:

Dosage Form/Strengths:

Pharmacologic Class:

Chemical Name:

Physical Characteristics:

Formulation: Quantitative formula for all the dose strengths

Ingredients	Wt (mg/capsule)							
	Formulation #/Capsule Strength							
Total Size								

1.2 Proposed mechanism(s) of action and indication(s)

1.3 Proposed dosage(s) and route(s) of administration?

2.0 GENERAL CLINICAL PHARMACOLOGY

2.1 Design features of the clinical pharmacology and clinical studies used to support dosing or claims:

Here describe the type of pivotal clinical studies in brief for each indication.

For treatment of A: For e.g.

The efficacy of Drug X in patients was established in X Phase 3 randomized, double-blind, parallel, placebo-controlled multi-center trials of Y weeks duration conducted as Z treatment of patients. Of these Z studies only Y studies used the proposed dosing

regimen. The X mg/day dose was not replicated in any study. Should use key studies and supportive studies that are used for labeling the product.

Short tabular descriptions may be useful here, for example:

Protocol	N	Duration	Population	X Dose
101				PER DAY AND OR BID OR TID
102				e.g., X MG/DAY
103				

Should repeat this information for each indication if multiple indications are proposed.

2.2. Clinical endpoints (i.e., clinical or surrogate endpoints) or biomarkers (collectively called pharmacodynamics (PD)) and how are they measured in clinical pharmacology and clinical studies

For treatment of A: For e.g.

The primary criterion to establish the efficacy of Drug X was the

The primary efficacy parameter was:

The secondary efficacy parameters were:

2.3 Exposure-response relationships

2.3.1 Characteristics of exposure/effectiveness relationship

For Efficacy in patients with Y:

An exposure (dose)-response analysis was conducted in Y patients pooled from X studies (Study numbers). Provide exposure or dose/response analyses data. This section should include information on all proposed doses and should also include relevant Tables and Figures of dose-response or exposure-response either from the PK-PD study conducted or from pivotal clinical trials that were used to label the drug product.

This section should also include information on any differences of exposure/dose – response for covariates such as dose, regimen, gender, age, race etc.

2.3.2 Characteristics of the exposure-response relationships for safety (dose-response, concentration-response)

If relevant, indicate the time to the onset and offset of the undesirable pharmacological response or clinical endpoint.

This section should include relevant safety information on all proposed doses and should also include relevant Tables and Figures.

This section should also include information on any differences of exposure/dose – response relationship for safety in covariates such as dose, regimen, gender, age, race etc.

e.g. Dizziness and somnolence were the most prevalent adverse events associated with treatment.

The probability for a subject to experience dizziness (AE1) increased with the dose. At the X mg/day, the incidence of AE1 averaged to be approximately 30% (range: from >20% to <50%). Female patients apparently reported higher incidence of dizziness. It is clear that the variability was high among various trials as shown in the following figure (). The ED₅₀ for incidence of dizziness was estimated to be $X \pm Z$ mg/day. ED₅₀ for severity of somnolence was estimated to be $Y \pm Z$ mg/day.

The incidence and severity of AE1 can also be depicted by the following figures that differentiate the incidence of adverse events for the BID and TID regimens.

2.3.3 Effect on QT or QTc interval

Should include relevant Tables and figure showing Concentration-QTc relationship.

2.3.4 Justification of dose and dosing regimen based on known relationship between dose-concentration-response (In some cases, it may be possible to combine this with 2.3.2 and 2.3.3.)

The following are the sponsor proposed dosage regimen for patients:

Patient Population	Age Group	Starting Dose	Maximum Dose	Increments
A				
B				

Age Group:

This section should include what information is available for justifying the dose in a particular age group.

Regimen:

From a pharmacokinetic perspective:

Based on a half-life of x hours, ...appears to be suitable for the Y regimen. However, the sponsor has conducted pharmacokinetic studies to show that X mg q8h vs. Y mg q12h showed similar pharmacokinetic profiles.

Include figure where possible

Figure: Pharmacokinetics over one dosing interval

Differences in steady state plasma concentration versus time profiles for q8h and q12h dosing regimens can also be evaluated by comparing the differences in C_{maxss} and C_{minss} for these two dosing regimens. As the dosing interval is increased from q8h to q12h, the fluctuation between C_{maxss} and C_{minss} would be expected to increase, while C_{ave} would be expected to remain constant. The following figure illustrates that the differences between regimens are small when individual and mean steady-state C_{maxss} , C_{minss} , and C_{ave} values are compared following a dose of Y mg/day administered q8h and q12h in healthy subjects.

Include figures and Tables as necessary

From a pharmacodynamic perspective:

Include figures and Tables justifying the dose and regimen from a efficacy standpoint. Should include information on other regimens studied, but not selected for dosing recommendations and reasons why. This information can be obtained from efficacy studies, PK-PD analysis if conducted or simulation performed.

Conclusions from such analyses must be included. For e.g
These figures show that doses Y mg and above may perform better than the lowest recommended dose in patients based on the EC50 values. However, titrating with a lower dose is desirable for tolerability reasons.

These also show that both X/day and Y/day doses may be acceptable, however, for practical administration reasons X/day may be the preferred choice.

Summary efficacy Tables such as the following should be included.

Study - Summary of RRatio analysis (ITT)				
Treatment group	N	Treatment differences**		P value***
		Mean (SE)	95% CI	

* Statistically significant based on Hochberg's procedure (p = 0.049).

** Based on treatment means for the raw RRatio

*** Hochberg procedure applied to the ranked RRatio

Summary of secondary endpoints (ITT)		
Study	Placebo	X dose and regimen

		BID	BID	TID	BID	BID	TID

*statistical significance for difference between X dose and placebo (and/or 95% CI exclude zero for Median change figures)

**subject numbers for ITT population are constant across secondary parameters in this table

From a safety perspective:

The two main adverse events of dizziness and somnolence was evaluated in terms of various doses given X/day and Y/day conditioned on severity of the adverse event. The following plots show that Y/day regimen had higher percent of observation for both dizziness and somnolence. This could be due to sustained concentration of Drug X with Y dosing.

Titration Scheme:

If a titration scheme is recommended information relevant to its selection should be included.

2.4 PK characteristics of the drug and its major metabolite?

2.4.1 Single dose and multiple dose PK pharmacokinetics?

Here Provide tables and figures on mean pharmacokinetic parameters and refer to them in the subsequent sections.

Also include in this section whether the pharmacokinetics of the drug change with chronic dose. And information on whether the multiple dose PK is predicted from single dose PK, accumulation ratio, time to reach steady state etc

2.4.2 General ADME characteristics of the drug

Absorption: may include information on transporter as well

Distribution: include information on protein binding etc

Metabolism:

Elimination:

2.4.3 Fate of drug as seen in mass balance studies

Include tables and figures from the mass balance study, also state whether these studies suggest renal or hepatic as the major route of elimination.

2.4.4 Comparison on PK between healthy subjects and patients

This section should also include information obtained from population analysis if conducted along with any definitive PK study conducted. Table and figures showing the differences in the two population should be included.

2.4.5 Degree of linearity or nonlinearity in the dose-concentration relationship

The non-linearity can be due to multiple dosing or due to increase of doses. Both should be described in this section.

This section must include Tables showing dose proportionality with statistical evaluation of the data using power model analysis.

This section should also include figures of dose normalized PK parameters versus dose for all relevant PK parameters.

An example Table given below:

Multiple dosing Day 1 vs Day 10 —X-Y mg/day.

Table	Study - Summary Results of the Assessment of Dose Proportionality Using the Power Model Analysis			
PK Parameter	Day	AUC	β Estimate (95% CI)*	R- Estimate of the Increase in Doses Required for Doubling the AUC (95% CI)**
* ANOVA (SAS GLM Procedure)				

The results of the analysis demonstrate dose proportionality in AUC.

2.4.5 Inter-subject variability in PK parameter

Include Tables to show variability, information from different studies should be included. This section should also mention the possible causes of this variability.

3.0 INTRINSIC FACTORS

In the introductory paragraph of this section highlight the key intrinsic factors that influence exposure and/response and what is the impact of such differences in efficacy and safety.

The following intrinsic factors should be discussed:

3.1 Effect of Renal Impairment:

This section should include information on the type of data available, can be presented in Tables such as....

Group Creatinine Clearance*	Renal function	N
1 > 80 mL/min	Normal	8
2 50-80 mL/min	Mildly	8
3 30-49 mL/min	Moderately impaired	8

* according to Cockcroft and Gault

Include relevant figures and Tables showing the renal clearance with change of creatinine clearance. Include 90% CI in the Tables.

Dosage Adjustment: State if needed or not, If yes then what

Dosing recommendations should be provided in Tabulate format

Sponsor's Proposal for Dosage Adjustment Based on Renal Function			
Creatinine Clearance (CLcr) (mL/min)	Total X Daily Dose ^a		Dose Regimen
	Starting dose (mg/day)	Maximum dose (mg/day)	

BID = Two divided doses; QD = Single daily dose.

^a Total daily dose (mg/day) should be divided as indicated by dose regimen to provide mg/dose.

^b Supplementary dose is a single additional dose.

3.2 Effect of Hepatic Impairment:

information same as above should be included

3.3 Effect of age:

Elderly:

Describe the data available to draw conclusions, definitive or pop pk, number of subjects in this population. Include Tables and figures to show the differences as compared to young subjects. Also describe if any differences in efficacy or safety are observed in this population.

Dosage Adjustment: State if needed or not, If yes then what

Pediatrics:

Describe the data available to draw conclusions, definitive or pop pk, number of subjects in this population. Include Tables and figures to show the differences as compared to young subjects. Also describe if any differences in efficacy or safety are observed in this population.

Dosage Adjustment: State if needed or not, If yes then what

3.4 Effect of Gender:

Describe the data available to draw conclusions, definitive or pop pk, number of subjects in this population. Include Tables and figures to show the differences as compared to young subjects. Also describe if any differences in efficacy or safety are observed in this population.

Dosage Adjustment: State if needed or not, If yes then what

3.5 Effect of Race:

Describe the data available to draw conclusions, definitive or pop pk, number of subjects in this population. Include Tables and figures to show the differences as compared to young subjects. Also describe if any differences in efficacy or safety are observed in this population.

Dosage Adjustment: State if needed or not, If yes then what

3.6 . Effect of pregnancy or lactation:

Similar information as above, if no information available state so.

4.0 EXTRINSIC FACTORS

In the introductory paragraph of this section highlight the key extrinsic factors (such as herbal, diet, smoking, alcohol) that influence exposure and/response and what is the impact of such differences in efficacy and safety.

Also indicate in brief whether there are any in-vivo drug-drug interaction studies that indicate the exposure alone and/or exposure response relationships are different when drugs are coadministered.

4.1 In vitro basis of drug interactions

Include information on the following, this section should not be descriptive only but should include relevant Tables to show the results and indicate which of these can lead to possible in vivo drug interactions under each of these sub headings:

- Drug as substrate of CYP 450
- Drug as inhibitor of CYP 450
- Drug as inducer of CYP 450
- Drug interaction based on protein binding
- Drug as substrate of p-glycoprotein
- Drug as inhibitor of p-glycoprotein
- Any other transporter involved

This section can also include information from mass balance studies that suggest possible interaction, for e.g if totally renally eliminated then there is a possibility of an interaction with drugs that are also renally eliminated.

Also indicate whether the in vitro studies are conducted at relevant therapeutic concentrations (in the same units as for the plasma data (e.g. ng/ml as opposed to μM or $\mu\text{mole/liter}$)).

4.2 In vivo drug interactions

Give a tabular listing of all drugs and indicate whether a dosage adjustment is necessary. This section can be subdivided into pharmacokinetic and pharmacodynamic interactions.

Pharmacokinetic Interactions:

For e.g. Influence of Drug X on the pharmacokinetics of concomitant drugs and the influence of these drugs on the pharmacokinetics of Drug X is summarized in the following Table:

Concomitant Medication	doses evaluated	Drug X on Co-Med PK	Co-Med on Drug X PK	Evaluation Method	Dosage Adjustment

Pharmacodynamic interactions:

List any pharmacodynamic interactions observed, if any.

5.0 GENERAL BIOPHARMACEUTICS

5.1 BCS Classification of the drug

This section should include information on solubility, permeability and dissolution of the drug product, which are the basis of classifying the drug and formulation. All relevant Tables and figures should be included.

5.2 Relative Bioavailability of the to-be marketed formulation to those used in the clinical studies

This section should include Tables showing the test and reference comparisons, geometric mean of PK parameters, geometric mean ratios and 90% CI.

If the formulations are not bioequivalent this section should also indicate what safety and efficacy issues may arise, if any. In case of failed BE studies, this section should provide other supporting data regarding the to-be-marketed formulation that would aid in the decision making for the approval of the product.

5.3 Absolute Bioavailability and Relative Bioavailability to other dosage forms/route of administrations

This section should include Tables showing the test and reference comparisons, geometric mean of PK parameters, geometric mean ratios and 90% CI.

5.4 Food effect

Provide Tables as well showing the ratios and 90% CI. Also indicate if type of meal (light, medium, high) has an effect, if necessary.

Also provide the dosing recommendations based on the results of the Food Effect study. Indication if clinical trials were done with or without regard to food. If different across studies tabular listing of clinical studies and their dosing administration in relation to meals. Include any population analysis data if available.

If a fed BE study was conducted, provide justification for doing so, that will help reviewers in decision making.

5.5 Dissolution and IVIVC if appropriate

This section should include dissolution method and specifications and justification for selecting the method (for example stirring speed, media etc).

5.6 Alcohol Effect (for ER products):

This is to rule out dose dumping. Should provide the data in tabular format based on in vitro dissolution in different concentrations of alcohol. If in vivo data are available, include in this section as well.

6.0 ANALYTICAL

This section should highlight the method used in analytical assays and provide its validation parameters. This can be done in a tabular format.

Parameter	parent	-metabolite
Method	LC/MS/MS	LC/MS/MS
LLOQ		
Linear range		
QC samples		
Inter-day accuracy and precision		
Intra-day accuracy and precision		
Freeze-thaw stability		
Benchtop Stability at RT		
Long term at -70° C		

Recovery Low Med High		
--------------------------------	--	--

If several different analytical methods were used, the difference in method and the LLOQs should be given, for example in a Table

Analyte	Method	Assay Sensitivity ng/ml
340	LC/MS	X
344	LC/MS	Y

Assay cross validation results should also be provided.

In this section in Tabular format also provide the assay performance from each study (QC data).

Immunogenicity (May not be applicable to small molecule drugs)

- o Are the assays adequate to test binding antibodies and neutralizing antibodies (based on CMC assessment)?
- o Is the sampling plan adequate to capture the baseline, the early onset and the dynamic profile (transient or persistent) of the APA formation and to minimize the interference from the presence of the product in the samples?
- o What is the incidence (rate) of the anti-product antibodies (APAs)? (Provide the rate of pre-existing antibodies at baseline and the rate of development of APAs during and after the treatment)
- o Do the APAs have neutralizing activity?
- o What is the impact of the APAs on the PK, PD and efficacy of the therapeutic protein?
- o What is the impact of APAs on clinical safety? (Provide information on the incidence of infusion-related reactions, hypersensitivity reactions, and cross-reactivity to endogenous counterparts.)

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
02/26/2016



IND 100593

**GRANT –
BREAKTHROUGH THERAPY DESIGNATION**

Genentech, Inc.
Attention: Tiffany Wan
Regulatory Program Management
1 DNA Way
South San Francisco, CA 94080-4990

Dear Ms. Wan:

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

We also refer to your December 4, 2015, request for Breakthrough Therapy designation. We have reviewed your request and have determined that ocrelizumab for the treatment of primary progressive multiple sclerosis (PPMS) meets the criteria for Breakthrough Therapy designation. Therefore, we are granting your request for Breakthrough Therapy designation. Please note that if the clinical development program does not continue to meet the criteria for Breakthrough Therapy designation, we may rescind the designation.

FDA will work closely with you to provide guidance on subsequent development of ocrelizumab for PPMS to help you design and conduct a development program as efficiently as possible. For further information regarding Breakthrough Therapy designation and FDA actions to expedite development of a designated product, please refer to section 902 of the Food and Drug Administration Safety and Innovation Act (FDASIA) and the *Guidance for Industry: Expedited Programs for Serious Conditions – Drugs and Biologics*.¹

When breakthrough therapy designation is granted, sponsors are asked to submit a Type B meeting request for a multidisciplinary comprehensive discussion of the drug development program, including planned clinical trials and plans for expediting the manufacturing development strategy. We note your pre-Biologic Licensing Application (BLA) meeting is scheduled for February 4, 2016; therefore, if this pre-BLA discussion includes the issues generally covered in the initial breakthrough therapy meeting, a separate Type B meeting request may not be necessary. Please refer to the MAPP 6025.6 - *Good Review Practice: Management of Breakthrough Therapy-Designated Drugs and Biologics*, Attachment 1, for potential topics for discussion at an initial breakthrough therapy meeting.²

¹ <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM358301.pdf>

²

If the breakthrough therapy designation for ocrelizumab for PPMS is rescinded, submission of portions of the BLA will not be permitted under this program. However, if you have Fast Track designation you will be able to submit portions of your application under the Fast Track program.

If you have any questions, contact Nahleen Lopez, Regulatory Project Manager, at (240) 402-2659.

Sincerely,

{See appended electronic signature page}

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

<http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ManualofPoliciesProcedures/default.htm>.

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
02/01/2016

Benton, Sandra J

From: Benton, Sandra J
Sent: Monday, January 25, 2016 3:39 PM
To: Temple, Robert; Jenkins, John K; Woodcock, Janet; Dal Pan, Gerald; Moscicki, Richard; Marcus, Kendall; Kehoe, Theresa
Cc: Jarow, Jonathan; Hinton, Denise; Sacks, Leonard V; Raggio, Miranda; Wedlake, Lauren; Cox, Edward M; Unger, Ellis; Beitz, Julie G; Ganley, Charles J; Pazdur, Richard; Rosebraugh, Curtis; Throckmorton, Douglas C; Lopez, Nahleen (FDA); Marler, John; Rodichok, Lawrence; Bastings, Eric; Dunn, Billy
Subject: RE: January 27, 2016 Medical Policy Council – Breakthrough Therapy Designation - IND 100593

As the Council agrees with DNP's recommendation to grant Genentech's breakthrough therapy designation request and does not believe a Council discussion is needed, this request will be cancelled from the January 27, 2016 meeting agenda.

Please let me know if you have any questions. Thanks!

Sandy Benton
Senior Policy Analyst
CDER/Office of Medical Policy
301-796-1042
sandra.benton@fda.hhs.gov

From: Benton, Sandra J
Sent: Wednesday, January 13, 2016 10:19 AM
To: Temple, Robert; Jenkins, John K; Woodcock, Janet; Dal Pan, Gerald; Moscicki, Richard; Marcus, Kendall; Kehoe, Theresa
Cc: Jarow, Jonathan; Hinton, Denise; Sacks, Leonard V; Raggio, Miranda; Wedlake, Lauren; Benton, Sandra J; Cox, Edward M; Unger, Ellis; Beitz, Julie G; Ganley, Charles J; Pazdur, Richard; Rosebraugh, Curtis; Throckmorton, Douglas C; Lopez, Nahleen (FDA); Marler, John; Rodichok, Lawrence; Bastings, Eric; Dunn, Billy
Subject: January 27, 2016 Medical Policy Council – Breakthrough Therapy Designation - IND 100593

Hi! OMP has scheduled a Medical Policy Council discussion on January 27, 2016 regarding the breakthrough therapy designation request from Genentech for its IND 100593, Ocrelizumab (RO4964913) for the treatment of Primary Progressive Multiple Sclerosis (PPMS).

DNP recommends that this breakthrough therapy request be granted. Attached is DNP's background on the breakthrough therapy designation with its rationale for granting the request.

DNP has asked if this request can be reviewed by email.

Would you please review DNP's recommendation and let me know by COB Friday, January 22 if –

- You agree with DNP's recommendation regarding this breakthrough therapy request and you do not believe a Council discussion is needed.
- You agree with DNP's recommendation regarding this breakthrough therapy request. However, you would like a Council discussion regarding any questions you have.
- You disagree with DNP's recommendation regarding this breakthrough therapy request.

If the Council agrees with bullet 1, I will cancel the discussion for this IND.

Please let me know if you have any questions. Thank you.

Sandy Benton
Senior Policy Analyst
CDER/Office of Medical Policy
301-796-1042
sandra.benton@fda.hhs.gov

<< File: IND 100593 SDN 672 5-7-15CDER-MPC Breakthrough Therapy Designation Dete....doc >> << File: 100593
btdr.pdf >>

APPEARS THIS WAY ON ORIGINAL

CDER Breakthrough Therapy Designation Determination Review Template

IND/NDA/BLA #	100593
Request Receipt Date	December 4, 2015
Product	Ocrelizumab (RO4964913)
Indication	Primary Progressive Multiple Sclerosis (PPMS)
Drug Class/Mechanism of Action	Monoclonal antibody/target CD 20 on B-cells
Sponsor	Genentech
ODE/Division	ODE1/DNP
Breakthrough Therapy Request Goal Date (within <u>60</u> days of receipt)	February 2, 2016

Note: This document should be uploaded into CDER's electronic document archival system as a clinical review and will serve as the official Clinical Review for the Breakthrough Therapy Designation Request (BTDR). Note: Signatory Authority is the Division Director.

Section I: Provide the following information to determine if the BTDR can be denied without Medical Policy Council (MPC) review.*Section I to be completed within 14 days of receipt for all BTDRs*

1. Briefly describe the indication for which the product is intended (Describe clearly and concisely since the wording will be used in the designation decision letter): Primary Progressive Multiple Sclerosis

2. Are the data supporting the BTDR from trials/IND(s) which are on Clinical Hold?

☐ YES ☒ NO

If 2 above is checked "Yes," the BTDR can be denied without MPC review. Skip to number 5 for clearance and sign-off. If checked "No", proceed with below:

3. Consideration of Breakthrough Therapy Criteria:

a. Is the condition serious/life-threatening¹?

☒ YES ☐ NO

If 3a is checked "No," the BTDR can be denied without MPC review. Skip to number 5 for clearance and sign-off. If checked "Yes", proceed with below:

b. Are the clinical data used to support preliminary clinical evidence that the drug may demonstrate substantial improvement over existing therapies on 1 or more clinically significant endpoints adequate and sufficiently complete to permit a substantive review?

- ☒ YES the BTDR is adequate and sufficiently complete to permit a substantive review
☐ Undetermined
☐ NO, the BTDR is inadequate and not sufficiently complete to permit a substantive review; therefore the request must be denied because (check one or more below):

¹ For a definition of serious and life threatening see Guidance for Industry: "Expedited Programs for Serious Conditions—Drugs and Biologics"

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM358301.pdf>

- i. Only animal/nonclinical data submitted as evidence ☐
- ii. Insufficient clinical data provided to evaluate the BTDR
(e.g. only high-level summary of data provided, insufficient information about the protocol[s]) ☐
- iii. Uncontrolled clinical trial not interpretable because endpoints are not well-defined and the natural history of the disease is not relentlessly progressive (e.g. multiple sclerosis, depression) ☐
- iv. Endpoint does not assess or is not plausibly related to a serious aspect of the disease (e.g., alopecia in cancer patients, erythema chronicum migrans in Lyme disease) ☐
- v. No or minimal clinically meaningful improvement as compared to available therapy²/ historical experience (e.g., <5% improvement in FEV1 in cystic fibrosis, best available therapy changed by recent approval) ☐

4. Provide below a brief description of the deficiencies for each box checked above in Section 3b:

If 3b is checked “No”, BTDR can be denied without MPC review. Skip to number 5 for clearance and sign-off (Note: The Division always has the option of taking the request to the MPC for review if the MPC’s input is desired. If this is the case, proceed with BTDR review and complete Section II). If 3b is checked “Yes” or “Undetermined”, proceed with BTDR review and complete Section II, as MPC review is required.

5. Clearance and Sign-Off (no MPC review)

Deny Breakthrough Therapy Designation ☐

Reviewer Signature: {See appended electronic signature page}
 Team Leader Signature: {See appended electronic signature page}
 Division Director Signature: {See appended electronic signature page}

Section II: If the BTDR cannot be denied without MPC review in accordance with numbers 1-3 above, or if the Division is recommending that the BTDR be granted, provide the following additional information needed by the MPC to evaluate the BTDR.

6. A brief description of the drug, the drug’s mechanism of action (if known), the drug’s relation to existing therapy(ies), and any relevant regulatory history. Consider the following in your response.

Primary progressive multiple sclerosis (PPMS) is a form of Multiple sclerosis (MS) that is characterized by continuous progression of disability over a year or more with evidence of lesions affecting primarily CNS white matter disseminated in space and/or time¹. While all forms of MS are serious and disabling, progression of disability and mortality are both greater for PPMS as compared to relapsing forms of MS². The pathophysiology that leads to a steadily progressive course as opposed to the more typical relapsing course of MS (RMS) is not understood.

Ocrelizumab is a humanized monoclonal antibody that targets the CD20 surface antigen found on B-cells. Although a trial of rituximab, a chimeric monoclonal antibody that also targets CD20, for the treatment of PPMS did not show a statistically significant benefit³, there was a suggestion of benefit in selected

² For a definition of available therapy refer to Guidance for Industry: “Expedited Programs for Serious Conditions—Drugs and Biologics”

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM358301.pdf>

subgroups. The sponsor chose the humanized antibody to CD20 for further development. Two large pivotal trials of ocrelizumab for the treatment of RMS have been completed and a pre-BLA meeting has been completed for that indication. A single trial was completed of ocrelizumab for the treatment of PPMS and a pre-BLA meeting is scheduled.

7. Information related to endpoints used in the available clinical data:

- a. Describe the endpoints considered by the sponsor as supporting the BTDR and any other endpoints the sponsor plans to use in later trials. Specify if the endpoints are primary or secondary, and if they are surrogates.

The primary endpoint of the trial submitted in support of the BTDR is the time to onset of confirmed disability progression. Progression was defined as an increase of ≥ 1.0 point from baseline EDSS, if the baseline EDSS was less than or equal to 5.5 points, or an increase of ≥ 0.5 point, if the baseline EDSS was > 5.5 points. Confirmation required that the increase had to meet the same criteria 12 weeks later.

- b. Describe the endpoint(s) that are accepted by the Division as clinically significant (outcome measures) for patients with the disease. Consider the following in your response:

DNP considers the primary endpoint employed in the trial submitted in support of the BTDR to be acceptable.

- c. Describe any other biomarkers that the Division would consider likely to predict a clinical benefit for the proposed indication even if not yet a basis for accelerated approval.

There are no acceptable biomarkers for this indication.

8. A brief description of available therapies, if any, including a table of the available Rx names, endpoint(s) used to establish efficacy, the magnitude of the treatment effects (including hazard ratio, if applicable), and the specific intended population. Consider the following in your response:

There are no therapies for PPMS that are approved in the US. There is off label use of treatments approved for RMS in patients with PPMS, in particular treatments targeting the immune system such as mitoxantrone⁴, mycophenolate and rituximab³.

9. A brief description of any drugs being studied for the same indication, or very similar indication, that requested breakthrough therapy designation³.

There have been no other requests for BTDR for this indication.

10. Information related to the preliminary clinical evidence:

- a. Table of clinical trials supporting the BTDR (only include trials which were relevant to the designation determination decision), including study ID, phase, trial design⁴, trial endpoints, treatment group(s), number of subjects enrolled in support of specific breakthrough indication, hazard ratio (if applicable), and trial results.

³ Biweekly reports of all BTDRs, including the sponsor, drug, and indication, are generated and sent to all CPMSs.

⁴ Trial design information should include whether the trial is single arm or multi-arm, single dose or multi-dose, randomized or non-randomized, crossover, blinded or unblinded, active comparator or placebo, and single center or multicenter.

Study WA25046 is the single trial submitted in support of this BTDR. This study was a randomized (2:1), double-blind, placebo-controlled trial that compared ocrelizumab 600mg to placebo. The treatment period was 120 weeks or until 253 Confirmed Disability Progression (CDP) events occurred.

The primary endpoint was the time to 12 week CDP. The proportion with CDP was estimated using the Kaplan-Meier model. The overall hazard ratio was estimated using the Cox proportional hazards model.

A key secondary endpoint was the time to 24 week CDP. Other key specified secondary endpoints were the change in the timed 25-foot walk test from baseline to 120 weeks of treatment, and the change in total volume of T2 lesions on MRI scan from baseline to Week 120.

The study enrolled 732 subjects randomized 2:1 to ocrelizumab or placebo. Demographic and baseline disease characteristics were typical of a population with PPMS and were balanced between treatment groups. Eighty five of 731 subjects had been treated previously with a “disease modifying” therapy.

There was a 24% reduction in the risk of 12 week CDP in the group treated with ocrelizumab compared to those treated with placebo. The hazard ratio was 0.76 (95% CI: 0.59 to 0.98, p=0.0321).

There was a similar reduction of 25% in the proportion of subjects with 24 week CDP in the ocrelizumab group as compared to placebo. The hazard ratio was 0.76 (95%CI: 0.59, 0.98, p=0.0321).

The ratio of the time to complete the timed 25 foot walk test (T25WT) at 120 weeks compared to baseline was superior in the ocrelizumab group vs. placebo by 29% (p=0.0404).

Results for each of the above endpoints were generally similar between treatment groups across subgroup analyses by gender, age group, baseline EDSS and duration of PPMS.

There was a significant reduction in the volume of T2 lesions on MRI in the ocrelizumab group as compared to placebo.

- b. Include any additional relevant information. Consider the following in your response:

No treatment studied previously for this indication has shown a significant benefit on disability progression. Preliminary data suggests that ocrelizumab is also effective in the treatment of RMS.

11. Division’s recommendation and rationale (pre-MPC review):

☒ GRANT :

There are no approved therapies for the treatment of PPMS. A number of clinical trials of drugs targeting the immune system that demonstrated efficacy in RMS have shown no benefit in PPMS⁵. The preliminary results for measures of disability from Study WA25046 suggest that ocrelizumab may be the first drug to show a reduction in the progression of disability in PPMS. Preliminary data on safety indicate that adverse events are not significantly different from placebo, suggesting a favorable benefit to risk comparison.

☐ DENY:

Provide brief summary of rationale for denial:

12. Division's next steps and sponsor's plan for future development:

DNP has scheduled a pre-BLA with the sponsor for this indication and will work closely with the sponsor to expedite the review of this product.

13. List references, if any:

1. Polman CH, Reingold SC, Banwell B, et al. Diagnostic criteria for multiple sclerosis: 2010 revisions to the McDonald criteria. Ann Neurol 2011;69:292-302.
2. Cottrell DA, Kremenchutzky M, Rice GP, et al. The natural history of multiple sclerosis: a geographically based study. 5. The clinical features and natural history of primary progressive multiple sclerosis. Brain 1999;122 (Pt 4):625-39.
3. Hawker K, O'Connor P, Freedman MS, et al. Rituximab in patients with primary progressive multiple sclerosis: results of a randomized double-blind placebo-controlled multicenter trial. Ann Neurol 2009;66:460-71.
4. Grey Nee Cotte S, Salmen Nee Stroet A, von Ahsen N, et al. Lack of efficacy of mitoxantrone in primary progressive Multiple Sclerosis irrespective of pharmacogenetic factors: a multi-center, retrospective analysis. J Neuroimmunol 2015;278:277-9.
5. Hartung HP, Aktas O. Bleak prospects for primary progressive multiple sclerosis therapy: downs and downs, but a glimmer of hope. Ann Neurol 2009;66:429-32.

14. Is the Division requesting a virtual MPC meeting via email in lieu of a face-to-face meeting?

YES ☒ NO ☐

15. Clearance and Sign-Off (after MPC review):

Grant Breakthrough Therapy Designation ☐
Deny Breakthrough Therapy Designation ☐

Reviewer Signature: {See appended electronic signature page}
Team Leader Signature: {See appended electronic signature page}
Division Director Signature: {See appended electronic signature page}

5-7-15/M. Raggio

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

/s/

SANDRA J BENTON
01/27/2016

WILLIAM H Dunn
01/27/2016



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 100593

MEETING MINUTES

Genentech, Inc.
Attention: Sonali Patel, Pharm.D.
Regulatory Program Manager
1 DNA Way
South San Francisco, CA 94080

Dear Dr. Patel:

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

We also refer to the meeting between representatives of your firm and the FDA on December 8, 2015. The purpose of the meeting was to discuss the acceptability of the Phase III studies (WA21092 and WA21093) to support a BLA and align with the Agency on the proposed content and format to support the proposed indication for relapsing forms of multiple sclerosis (RMS).

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 Nahleen Lopez, Regulatory Project Manager at (240) 402-2659.

Sincerely,

{See appended electronic signature page}

Eric Bastings, MD
Deputy Director
Division of Neurological Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes
Sponsor's Comments



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type: B
Meeting Category: Pre-BLA

Meeting Date and Time: Tuesday, December 8, 2015, 1400 to 1500 EST
Meeting Location: White Oak Building 22, Conference Room: 1315

Application Number: 100593
Product Name: Ocrelizumab
Indication: Multiple Sclerosis
Sponsor/Applicant Name: Genentech, Inc.

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

FDA ATTENDEES

Division of Neurology Products

Billy Dunn, MD, Director
Eric Bastings, MD, Deputy Director
John Marler, MD, Clinical Team Leader
Larry Rodichok, MD, Clinical Reviewer
David Hosford, MD, Clinical Reviewer
Sally Jo Yasuda, PharmD, Safety Team Leader
Gerard Boehm, MD, Safety Reviewer
Jacqueline Ware, PharmD, Chief Project Management Staff
Nahleen Lopez, PharmD, Project Manager
Hamet Touré, PharmD, Project Manager

Office of Clinical Pharmacology

Jagan Parepally, PhD, Reviewer

Controlled Substance Staff

Katherine Bonson, PhD

Office of Biostatistics

Kun Jin, PhD, Team Leader

Xiang Ling, PhD, Reviewer

Office of Business Informatics

Douglas Warfield, eData Team Regulatory Specialist
Valerie Gooding, eSub Team Regulatory Specialist

Office of Surveillance and Epidemiology

Jamie Wilkins-Parker, PharmD, Team Leader
Jasminder Kumar, Risk Management Analyst

Office of Biotechnology Products

Sarah Kennett, PhD, Review Chief
Linan Ha, PhD, Team Leader
Milos Dokmanovic, PhD, Biologist

Division of Pediatric and Maternal Health

Denise Johnson-Lyles, Project Manager

SPONSOR ATTENDEES

An Song, PhD, Director and Senior Scientist, BioAnalytical Sciences and Pharmacology Subteam Leader
Anne-Marie Li-Kwai-Cheung, Senior Global Regulatory Leader
Fabian Model, Associate Director, CNS Biostatistics,
Gaëlle Klingelschmitt, Project Lead Statistician
Heidemarie Kletzl, Clinical Pharmacology
Jean-Paul Pfefen, Global Development Team Leader
Michele Libonati, Lifecycle Leader, Global Product Strategy
Nicole Mairon, MD, Senior Safety Science Leader
Paulo Fontoura, MD, PhD, Vice President, Global Head Clinical Development Neuroscience
Peter Chin, MD, MSHS, Principal Medical Director, Clinical Science
Sonali Patel, US Regulatory Program Manager
Sophie Banzet, MD, Therapeutic Area Head Safety Science CNS
Tammy Rose, US Global Regulatory Lead

1. BACKGROUND

Genentech is requesting a pre-BLA meeting to discuss ocrelizumab, a recombinant humanized monoclonal antibody against the CD20 antigen present on human B-cells. It is currently in development for the treatment of patients with relapsing forms of multiple sclerosis (RMS) and primary progressive multiple sclerosis (PPMS). The sponsor plans to submit a BLA for RMS based on the results from the pivotal studies WA21092 and WA21093 for safety and efficacy. The sponsor would like to reach an agreement on the acceptability of the studies to support the BLA and align with the FDA on the proposed content and format to support the proposed indication.

FDA sent Preliminary Comments to Genentech, Inc. on December 4, 2015

2. DISCUSSION

2.1 NON-CLINICAL

Question 1: Does the Agency agree that the completed and planned nonclinical studies are sufficient to support filing a BLA for registration of ocrelizumab?

FDA Preliminary Response to Question 1:

Your nonclinical plan is acceptable, except that the carcinogenicity study waiver request (with all supportive data) should be submitted during clinical development so that a decision can be made prior to BLA submission regarding the need for the studies.

Sponsor's Response to FDA Preliminary Response:

No further discussion is necessary. The Sponsor will submit to IND 100593 the carcinogenicity study waiver request, with all supportive data, prior to submission of the BLA.

Meeting Discussion: None.

Question 2: The Sponsor plans to initiate a pharmacokinetics (PK)/pharmacodynamics (PD) study in pediatric patients aged 10 – 17 years prior to the conclusion of the FDA requested juvenile immunotoxicology study (which will assess immune system function at the end of dosing and at the end of recovery). Does the Agency agree that results from this toxicology study are not required before the start of the pediatric PK/PD study?

FDA Preliminary Response to Question 2:

The juvenile animal toxicology study will not be required prior to initiation of the pediatric PK/PD study. As previously mentioned, we strongly encourage you to submit the final protocol for the juvenile animal study for feedback prior to study initiation.

Sponsor's Response to FDA Preliminary Response:

No further discussion is necessary. The Sponsor plans to submit to IND 100593 the final protocol for the juvenile animal study as a Type C Meeting – request for written response only, prior to the end of 2015.

Meeting Discussion: None.

Question 3: The Sponsor does not believe that ocrelizumab has abuse potential and therefore a full assessment or proposed scheduling is not required in the RMS or PPMS BLA. Does the Agency agree?

FDA Preliminary Response to Question 3:

There is insufficient information in the meeting package to for us to determine the need for an abuse potential assessment. If ocrelizumab has central nervous system (CNS) activity, it will need an abuse potential assessment.

Sufficient evidence that ocrelizumab does not have CNS activity may be based on full protocols and summary data from the following studies:

- Pharmacokinetic distribution studies with radiolabelled ocrelizumab that demonstrate that the drug does not significantly penetrate the brain.
- Receptor binding studies showing that ocrelizumab does not have activity at typical abuse-related sites (such as dopamine, GABA, NMDA, opioid, and cannabinoid receptors or monoamine transporters).

- Animal toxicology studies showing that ocrelizumab does not alter behavior (e.g., induce changes in locomotion suggestive of stimulation or sedation).
- Clinical studies showing that abuse-related adverse events such as euphoria, hallucinations, sedation, or stimulation do not occur at therapeutic or supratherapeutic doses of ocrelizumab.

We will evaluate whether ocrelizumab appears to have CNS activity. If it does not, then dedicated abuse-related studies are not necessary. If we determine that ocrelizumab does have CNS activity, additional abuse-related studies are necessary (refer to the 2010 *Guidance for Industry: Assessment of the Abuse Potential of Drugs*).

Sponsor's Response to FDA Preliminary Response:

The Sponsor plans to provide the following evidence to support the assessment of ocrelizumab CNS activity:

1. Pharmacokinetic distribution studies with radiolabelled ocrelizumab that demonstrate that the drug does not significantly penetrate the brain.

Study 03-0431-0349, entitled “Tissue Distribution of 125I-ocrelizumab in Normal Mice and a Transgenic Mouse Model”

Conclusion: Tissue distribution was examined using 125I-ocrelizumab in normal mice and in a transgenic mouse model, in which human CD20 was transfected to be expressed on murine B cells. The results suggest that a significant amount of 125I-ocrelizumab is bound to B cells in the systemic lymphoid organs of the spleen and mesenteric lymph nodes in CD20 transgenic mice. In comparison, normal mice had much more radioactivity in their plasma and cleared 125I-ocrelizumab more slowly than CD20 transgenic mice.

Like most monoclonal antibodies, there was no evidence that 125I-ocrelizumab significantly penetrates the brain.

Study 15-0538, entitled “PET Biodistribution Imaging of Cu-64 Labeled Anti-CD20 2H7 Variants (v511, v16) in B-Cell Depleted Cynomolgus Monkeys”

Conclusion: PET images in cynomolgus monkeys given ocrelizumab indicated presence of the labeled ocrelizumab within blood pool and distribution to organs having high levels of B cells (e.g., spleen and lymphoid tissues).

There was no evidence that labeled ocrelizumab significantly penetrates the brain.

3. Animal toxicology studies showing that ocrelizumab does not alter behavior (e.g., induce changes in locomotion suggestive of stimulation or sedation).

Multiple repeat-dose GLP toxicology studies were conducted in cynomolgus monkeys to

evaluate the safety of ocrelizumab at different dose levels and by different dosing regimen (Studies 03-0113-0349, 03-0114-0349, 03-0684-0134, 04-0192-0134, 07-0171). In addition, reproductive and developmental toxicity were evaluated in cynomolgus monkeys in studies 12-0524, 12-0525, 04-1272-1342, and 06-1260. In all these studies, clinical signs were evaluated including twice daily cage side observations and predose and postdose observations on all animals. In most studies, other physical (e.g. abdominal palpation and observations of the condition of integument, respiratory and cardiovascular systems) and physiological evaluations (blood pressure, heart rate, respiration rate and body temperature, etc.) were also conducted. There were no observations that ocrelizumab altered animal behavior (e.g., induced changes in locomotion suggestive of stimulation or sedation).

In Study 12-0524, entitled “Ocrelizumab 9-Week Intravenous Administration Male Fertility Study in the Cynomolgus Monkey with a 16-Week Recovery Phase”, physical examinations and neurobehavioral battery were assessed and no abnormal behavioral effects were detected.

4. Clinical studies showing that abuse-related adverse events such as euphoria, hallucinations, sedation, or stimulation do not occur at therapeutic or supratherapeutic doses of ocrelizumab.

The clinical evidence planned to support the assessment of ocrelizumab CNS activity will utilize the Medical Dictionary for Regulatory Activities (MedDRA) Query 'Standardized MedDRA Query (SMQ) drug abuse and dependence (narrow)' to evaluate MS All Exposure and RA All Exposure populations. This SMQ was applied to the controlled period of the RMS Phase III studies WA21092 and WA21093, and the adverse event (AE) profile was not suggestive of abuse potential. In addition, an evaluation will be presented for specific terms such as euphoria, hallucinations, sedation, and stimulation.

Due to the high degree of specificity associated with a monoclonal, off target binding would not be expected with ocrelizumab and receptor-binding studies beyond CD20 have not been completed. Therefore, we intend to submit details and protocols about the three outlined components to demonstrate lack of CNS activity associated with abuse potential.

Can the Agency provide initial feedback if this is sufficient?

Meeting Discussion: FDA expects the Sponsor to submit for CSS review all available information to support their claim that ocrelizumab does not have CNS activity. If CSS concludes that the drug does not have CNS activity, no dedicated abuse-related studies will be necessary.

2.1. CLINICAL

Question 4: Does the Agency agree that the outcomes from pivotal Phase III studies WA21092 and WA21093 in RMS patients provide sufficient clinical evidence to support the review of the BLA in patients with relapsing forms of MS?

FDA Preliminary Response to Question 4:

Subject to a full review of a complete application, we agree that studies WA21092 and WA21093 appear to potentially provide substantial evidence of effectiveness of ocrelizumab for the treatment of patients with relapsing MS.

Sponsor's Response to FDA Preliminary Response:

No further discussion is necessary.

Meeting Discussion: None.

Question 5: Does the Agency have any comments on the proposed indication based on the clinical trials conducted?

FDA Preliminary Response to Question 5:

If we approve the application, we anticipate the indication will be for the treatment of patients with relapsing forms of multiple sclerosis.

Sponsor's Response to FDA Preliminary Response:

No further discussion is necessary.

Meeting Discussion: None.

Question 6: Based on the initial review of the RMS safety data, the Sponsor believes that the information included in the US prescribing information will be sufficient to convey the benefits and risks of ocrelizumab and that additional REMS measures are not deemed necessary Does the Agency agree?

FDA Preliminary Response to Question 6:

At this time, we have insufficient information to determine whether a risk evaluation and mitigation strategy (REMS) will be necessary to ensure that the benefits of ocrelizumab outweigh the risks. We will determine the need for a REMS during the review of your application.

Sponsor's Response to FDA Preliminary Response:

No further discussion is necessary.

Meeting Discussion: None.

Question 7: The Sponsor is seeking feedback on the acceptability of potential mechanisms for collecting real world safety data on the use of ocrelizumab, specifically:

a) Does the Agency agree (b) (4) could contribute to support post-approval US requirements, if determined to be necessary?

b) Would the FDA consider pregnancy studies based on pre-planned review of existing population-based registers or healthcare databases (b) (4)? Would the FDA consider (b) (4) to support any post-approval US requirements, if determined necessary?

FDA Preliminary Response to Question 7:

a) Review of the design of any post-approval studies is not part of the BLA review. In general, (b) (4) we would need to review a more detailed proposal that includes information on the specific data that could be collected, the validity of the data collected, and information regarding completeness of follow up. We would also need to assess your proposal for collecting US data. We will not be able to determine the specific data you will need to collect until after the BLA review is complete.

b) See our reply to question 7a, above.

Sponsor's Response to FDA Preliminary Response:

No further discussion is necessary.

Meeting Discussion: None.

Question 8: A summary of the process and analyses for identifying and reporting relapse events from the Phase III clinical studies WA21092 and WA21093 will be provided in Module 5, Section 5.3.5.3 of the RMS BLA. Does the Agency agree that the assessment provided within Appendix 3 adequately addresses this request?

FDA Preliminary Response to Question 8:

The adequacy of the process for identification of relapses will depend on a full review of the data collected for each step of the process. In general the protocol-defined process for identification of a potential relapse provided in Appendix 3 of this submission has the potential to adequately document the process from the point at which it was determined that a subject report should be evaluated further. Documentation of the process prior to that point is less well defined. You should be prepared to submit information on all subject reports of a potential relapse collected at any of the 4 sources listed in Section 4 of Appendix 3. You should submit data on spontaneous reports of a relapse or relapses detected at the monthly telephone interviews including those that were not referred to the treating investigator. You should submit data on determinations made by the treating investigator to conduct relapse

assessments. You indicate that the results of the subject interviews were not included in the eCRF. You should be prepared to submit the forms used to collect this information.

Sponsor's Response to FDA Preliminary Response:

The Sponsor would like to further discuss the requested information during the pre-BLA meeting.

Meeting Discussion:

The sponsor and FDA agreed that monthly subject interviews will not be included in the BLA. However, FDA expects that the sponsor will submit subject monthly interviews upon request.

Question 9: Does the Agency agree with the overall approach for inclusion and evaluation of safety data, including the proposed pooling strategy and analyses for the integrated safety summary specifically the:

- a) Proposed inclusion of all individual study reports as described in Section 9.3.1?
- b) Proposed pooling strategy for 1) MS studies 2) Rheumatoid Arthritis (RA) studies and 3) the proposal to not pool data from any of the Systemic Lupus Erythematosus(SLE) and Lupus Nephritis (LN) and Non-Hodgkin's Lymphoma (NHL) studies, but inclusion of CSRs only as described in Section 9.3.2?
- c) Proposed analyses planned for the MS and RA Pools and presentation within the integrated summary of safety, as described in Section 9.3.3.

FDA Preliminary Response to Question 9:

- a) Yes.
- b) Comparative data is particularly useful in assessing safety. In your proposal, the controlled data from the PPMS trial would not be available separately, but only pooled with RMS data. The data from the PPMS trial would be available separately in the CSR, but it would facilitate the review to have it included as part of the presentation of safety data. Therefore, we request the following pools for presentation of safety data:
 - Pool A: Phase III RMS Controlled Treatment
 - *Pool B: MS PPMS Controlled Treatment*
 - Pool C: MS All Exposure (RMS and PPMS)
 - Pool D: Phase III RMS All Exposure
 - Pool E: Phase II and Phase III RA Controlled Treatment
 - Pool F: RA All Exposure
- c) Yes, but we also request the following information:

- i) You reported a death in trial WA21493 that was due to SIRS. In addition to a detailed review of this case, we ask that you search all available ocrelizumab safety data for similar cases of SIRS or potential SIRS.
- ii) Please also provide a discussion of the known safety issues of approved anti-CD20 monoclonal antibodies with comparisons to the safety profile of ocrelizumab.

Additional FDA Comment:

Provide a summary of any protocol amendments and changes to the informed consent document or Investigator's Brochure that occurred as a result of an adverse event or potential safety signal within your Clinical Summary of Safety. Include a description of the rationale for these changes and corresponding minutes from the Data Safety Monitoring Board.

Sponsor's Response to FDA Preliminary Response:

Question 9a

No further discussion is necessary.

Question 9b

The Sponsor agrees to include the pools as requested by the Division; however, the description of the pools for display purposes will be identified as in Appendix 1. The analyses for the pools have been expanded based on FDA feedback and are described in the table below.

GNE Response to Additional Request 9c(i)

The Sponsor will search all available ocrelizumab safety data for cases of SIRS using a company basket (sepsis terms including SIRS) as part of the overall assessment of infections.

GNE Response to Additional Request 9c(ii)

The Sponsor acknowledges the Division's request to provide a discussion of the known safety issues of approved anti-CD20 monoclonal antibodies with comparisons to the safety profile of ocrelizumab. Approved anti-CD20 monoclonal antibodies include Rituxan, Gazyva and Arzerra in oncology (all) and autoimmune (Rituxan) indications.

Given the approved use of Rituxan in autoimmune indications, the Sponsor proposes an evaluation of all identified and potential safety risks from the Rituxan Rheumatoid Arthritis indication for assessment of relevance to the ocrelizumab MS patient population. This assessment will be provided in Integrated Summary of Safety in the BLA.

Does the Agency agree?

GNE Response to Additional FDA Comment:

No further discussion is necessary.

Meeting Discussion:

The sponsor agreed to provide a discussion of the known safety issues of approved anti-CD20 monoclonal antibodies with comparisons to the safety profile of ocrelizumab.

Question 10: Does the Agency agree with the proposed safety package, including:

- a) The patient exposure to assess clinical safety is sufficient to support the use of ocrelizumab for the treatment of RMS (see Section 9.3.1)
- b) Proposed clinical cutoff dates and content of the 120-Day Safety Update Report as described in Section 9.3.6.
- c) Proposed categories for individual patient narratives, electronic case report forms and individual patient profiles as described in Section 9.3.8?
- d) Specific analyses for DRESS (Drug Reaction with Eosinophilia and Systemic Symptoms) as described within Section 9.3.7.

FDA Preliminary Response to Question 10:

- a) Yes, based on the information provided, the exposure appears adequate.
- b) Yes.
- c) Yes.
- d) Yes.

Sponsor's Response to FDA Preliminary Response:

No further discussion is necessary.

Meeting Discussion: None.

2.2. REGULATORY

Question 11: The Sponsor intends to submit two BLAs to support registration of ocrelizumab in relapsing forms of MS and primary progressive MS respectively. Does the Agency agree with the overall content of the RMS BLA, as described in the Table of Contents, provided in Appendix 4, and the proposed approach for submission of two BLAs to include, indication specific Module 1 content and identical Module 2-5?

FDA Preliminary Response to Question 11:

We would like to discuss your submission plans at the meeting. Also, it is not clear to us how Module 2-5 could be identical. From a technical standpoint (not content related), the proposed format for the planned RMS BLA is generally acceptable. We have the following specific requests:

1. If you are utilizing “The eCTD Backbone Files Specification For Module 1 v2.3”, FDA Form 3674 should reside in m1.1.7; otherwise, it should reside in m1.2 (cover letter section), with a clear leaf title.
2. Please make sure leaf titles are clear and indicative of the content Appendix 1 is not a proper leaf title.
3. 1.6.3 Correspondence regarding meetings: you may provide a single pdf file instead of separate pdf files for each document if you also provide proper bookmarks of all correspondence, table of contents, and hyperlinks.
4. For archival purposes, also submit a pdf file of the labeling document you submit in Microsoft Word format. When you submit MS Word documents, make sure the leaf title includes "word", so reviewers can quickly identify the word version of the document.
5. Do not create additional nodes in the eCTD structure beyond what is in the specifications (3.2.p.5.2.1 – 7; 3.2.p.5.3.1 – 7; etc.,). Please make sure your approach fits the DTD and the “Granularity Annex,” located at:-
<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM073261.pdf>
6. Please note that we require Study Tagging Files (STF) for submissions to the FDA when providing study information in modules 4 and 5 with the exception of modules 4.3 Literature References, 5.2 Tabular Listing, 5.4 Literature References, and 5.3.6 if the Periodic Report is a single PDF document. Each study should have an STF and all components regarding that study should be properly file tagged and placed under the study’s STF, including case report forms. Reference case report forms under the appropriate study's STF to which they belong, organized by site, as per the specifications and tagged as “case report form.” Subject Data Listings (16.4) should be file tagged as “data-listing-dataset”. For documents with no specific file tags, you can apply the “study-report-body” or “legacy-clinical-study-report” file tag. Please refer to The eCTD Backbone File Specification for Study Tagging Files 2.6.1 (PDF - 149KB) (6/3/2008).¹
 - Regarding use of the m5-3-7 heading element, FDA does not use module 5.3.7 CRFs. Instead, reference case report forms in the appropriate study's STF to which they belong organized by site as per the specifications and tagged as “case report form”. Do not use 5.3.7 as a heading element in the index.xml.
7. Provide the tabular listing in module 5.2 and synopsis of individual studies in m2.7.6 in tabular format and linked to the referenced studies in m5.

1

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

Sponsors options for cross referencing information submitted to another application, would be to either place a cross reference document under module m1.4.4 (cross reference to other applications), or use cross application links.

1. To use the first option (placing a cross reference document in m1.4.4), a table formatted document can be submitted in section 1.4.4 of the eCTD, detailing previously submitted information (paper and/or non- eCTD format) that is being referenced by the current application. The information in the document should include (1) the application number, (2) the date of submission (e.g., letter date), (3) the file name, (4) the page number (if necessary), (5) the eCTD sequence number, (6) the eCTD heading location (e.g., m3.2.p.4.1 Control of Excipients – Specifications), (7) the document leaf title and (8) the submission identification (e.g., submission serial number, volume number, electronic folder, file name, etc.,) of the referenced document along with a hypertext link to the location of the information, when possible.
2. To use the second option (cross application links), both applications must be in eCTD format. The applications must include the appropriate prefix in the href links (e.g., xlink:href "../ind900000/0009/m2/24-nonclin-over/nonclinical-overview.pdf"). In the leaf titles of the documents, we recommend that the leaf title indicate the word “cross reference to” and the application number (e.g. Cross Ref to nda XXXXXX). The cross reference information in the leaf title allows the reviewer to know that the document resides in another application.

Prior to using cross application linking in an application, we recommend that you submit an "eCTD cross application links" sample to ensure successful use of cross application links.

To submit an eCTD cross application links sample, request two sample application numbers from the ESUB team (esub@fda.hhs.gov). For more information on eCTD samples, please refer to the Sample Process web page.²

Sponsor's Response to FDA Preliminary Response:

GNE Response to Question 11

The Sponsor plans to file two BLA applications to support the review and approval of the RMS and PPMS indication. One of the two cross-referencing options as described in the Division's response will be utilized for the second BLA application.

The Sponsor believes the RMS and PPMS studies will both be important to discuss in the Summary of Clinical Efficacy (SCE) and proposes to file a single SCE. This will be included in the first BLA and cross-referenced in the second BLA.

Does the Agency agree with the attached table of contents in Appendix 2?

²<http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM315023.pdf>

Meeting Discussion:

The sponsor noted that it plans to submit its two applications a few weeks apart in the second quarter of 2016. The sponsor has not yet determined which application they will submit first. The second BLA will cross-reference the first one. The sponsor proposed a single comprehensive ISS and a single ISE for both applications. The safety data will be the same for both applications. The Final study reports and final pharmacokinetic reports will be indication-specific and different for the two applications. FDA asked for the full study reports not just the summary of effectiveness.

FDA found the proposed structure of the RMS application in Appendix 2 acceptable. FDA noted that the structure of the PPMS application would be the subject of further discussion during the upcoming pre-BLA meeting for the PPMS indication. FDA mentioned that another possibility to consider is a single BLA submission for both indications.

GNE Response to Question 11 Part 1-7

No further discussion is necessary.

GNE Response to Question 11, additional comments 1 and 2

No further discussion is necessary.

Meeting Discussion: None.

Question 12: Prior to the BLA submission, the Sponsor would like to review the navigation, formatting of electronic files and specifically the layout of the RMS application to ensure it is acceptable for filing. Does the Agency recommend proceeding with an electronic pre-submission meeting?

FDA Preliminary Response to Question 12:

Yes. We would like to become familiar with the navigation features of the application. Because the data formats and SAS programs appear acceptable, we recommend that you submit a test submission. The Edata and Esub team can review the submission formatting and layout and provide comments. For the test submission, please follow the test submission guide.³

Sponsor's Response to FDA Preliminary Response:

No further discussion is necessary.

Meeting Discussion: None.

³<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm174459.htm>

Question 13: Would the Agency like to have an Applicant Orientation/Technical Walk-Through meeting with the Sponsor after the submission of the BLA to outline major components for BLA?

FDA Preliminary Response to Question 13:

Yes.

Sponsor's Response to FDA Preliminary Response:

No further discussion is necessary.

Meeting Discussion: None.

Question 14: Based on the preliminary review of the data, does the Agency foresee that the proposed BLA will be reviewed by an Advisory Committee?

FDA Preliminary Response to Question 14:

We will make a determination on the need for an Advisory Committee meeting for this application during the filing period.

Sponsor's Response to FDA Preliminary Response:

No further discussion is necessary.

Meeting Discussion: None.

Question 15: Does the Agency agree that ocrelizumab represents a significant improvement in efficacy or safety and therefore the proposed BLA could be considered for priority review?

FDA Preliminary Response to Question 15:

We will make a determination on your request for priority review during the filing period. Please provide your justification for priority review with the application.

Sponsor's Response to FDA Preliminary Response:

No further discussion is necessary.

Meeting Discussion: None.

Question 16: Are there any other recommendations the Agency can provide to help the Sponsor prepare an acceptable BLA for review, or to facilitate the review process?

FDA Preliminary Additional Comments:

1) The facilities should be ready for inspection at the time of the BLA submission and in operation manufacturing ocrelizumab drug substance. We noted that amendment 0645 received on October 30, 2015, indicates that the proposed manufacturing campaign for ocrelizumab is scheduled for August 2016; please ensure that the manufacturing schedule complies with GRMP timelines.

2) For the CMC Drug Substance section of the BLA (Section 3.2.S), provide the following product quality microbiology information:

- a) (b) (4) at critical manufacturing steps (b) (4) (3.2.S.2.4).
- b) Provide microbial data from three successful product validation runs at manufacturing scale. Monitor (b) (4) hold time (b) (4) (3.2.S.2.5). Collect (b) (4)
- c) Data demonstrating microbial control (b) (4) (3.2.S.2.5).
- d) (b) (4) data obtained during manufacture of the three process qualification batches (3.2.S.2.5).
- e) Summary of shipping validation studies and data (3.2.S.2.5).
- f) Drug substance bioburden and endotoxin release specifications (3.2.S.4). The bioburden limit should be (b) (4)
- g) Summary report with summary results from (b) (4) qualification performed for in-process (b) (4) and drug substance (3.4.S.4).

3) 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 we expect, refer to the 1994 "FDA Guidance for Industry, Submission Documentation for Sterilization Process Validation in Applications for Human and Veterinary Drug Products".

4) Provide information and validation data summaries in Section 3.2.P.3.5 for the following:

- a) (b) (4) study report (b) (4).
- b) Sterilization and depyrogenation of equipment and components that contact the sterile drug product. Provide summary data for the three most recent requalification studies and describe the equipment requalification program.
- c) At-scale data from three product (b) (4) hold times to support hold times. Monitor (b) (4)
- d) (b) (4) if applicable.
- e) Three successful consecutive media fill runs, including summary environmental monitoring data obtained during the runs. Describe media fill and environmental monitoring procedures.

- f) A description of the routine environmental monitoring program.
 - g) A summary of shipping validation studies and data.
- 5) Provide the following method validation information:
- a) Container closure integrity testing (3.2.P.2.5). Demonstrate system integrity (including maintenance of the microbial barrier) initially to qualify the container closure system and process and during stability. Container closure integrity methods validation must demonstrate that the assay is sensitive enough to detect breaches that could allow microbial ingress. Perform container closure integrity testing *in lieu* of sterility testing for stability samples every 12 months (annually) and at expiry (3.2.P.8.2).
 - b) Qualification data (b) (4) performed for in-process (b) (4) and the drug product, as appropriate (3.2.P.5).
 - c) Rabbit Pyrogen Test results from three lots of drug product in accordance with 21 CFR 610.13(b).
 - d) Because formulations with certain excipient and polysorbate combinations may interfere with endotoxin recoverability in the USP LA test methods over time, it is necessary to assess the effect of hold time on endotoxin recovery by spiking a known amount of endotoxin standard into undiluted drug product and testing for recoverable endotoxin over time using containers of similar composition to those used for drug product during hold.
- 6) All facilities should be registered with FDA at the time of the BLA submission and ready for inspection in accordance with 21 CFR 600.21 and 601.20(b)(2). Please include in the BLA submission a complete list of manufacturing and testing sites with their corresponding FEI numbers. An updated manufacturing schedule for the bulk drug substance and drug product fill finish sites should be included in Module 1 of the BLA.
- 7) For survival curves, the Y-axis should start with zero and end with 1 or 100%. The X-axis labels should include the time from 0 and the number of subjects in each treatment arm for each tick mark. The final proportion surviving and treatment should be indicated clearly.
- 8) Provide complete accounting and analysis of all potential relapse events. The dataset should include the date that the potential relapse events were first reported by the subject and the date that the events were first evaluated by the treating and by the examining investigators. Please include a column for the criteria that confirmed that there was a new objective neurologic deficit. Please include documentation of the blinded adjudication process used by the sponsor. Please include a calculation of the time intervals (in days) from the onset of symptoms to the various points in the relapse assessment process. Include an analysis for any potential bias in the determination made by the treating investigator in referring the event for further evaluation by the examining investigator and for adjudication by the sponsor. Provide sensitivity analyses based on relapses as reported by subjects and as determined by the treating and examining investigators in addition to the pre-specified primary analysis based on sponsor adjudication. Discuss the impact of any differences in the results of these analyses. Provide a clear indication of any imputed values used for these analyses.

9) 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 which includes the time interval between the time of randomization and the EDSS determination. Please place all scheduled EDSS assessments, e.g. screening, baseline, week 12, etc, in the same column for all subjects. Please identify and assign sequential identification numbers for those EDSS assessments that were performed at unscheduled relapse assessments and place each of them in the same column for all subjects, e.g., “unscheduled relapse assessment #1, etc.. The identification term used should map to the same events if they appear in other datasets. 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. If there are missing baseline EDSS values, explain how this could have happened. Describe the process for the certification of EDSS examiners. Flag EDSS scores that were from an assessment by a noncertified 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.

Meeting Discussion:

FDA agreed to review and provide feedback on a sample table of the dataset. FDA requested the dataset in a table format that is easy to review, with one row per patient, and formatted to allow easy subtraction without conversion.

10) 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 randomized treatment and how data from these subjects were handled. 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 accounting of subjects whose relapse and EDSS outcomes you exclude from the analysis following the use of alternative MS treatment.

11) Provide an analysis of injection-related adverse events as a potential factor unblinding subjects and/or investigators to treatment assignment.

12) Provide an analysis of the use of anti-inflammatory agents as a potential factor in the unblinding of subjects and/or investigators to treatment assignment.

13) To assist review of outcome events, relapses and sustained disability, a log of events relevant to these clinical events for each patient is required for a full understanding. Include a dataset of important trial events for each patient with one row per patient per event. The dataset should have few columns and many rows. Columns should include the patient identifier, trial name, name of event, treatment arm, event-specific comment (such as reason

for discontinuation, reason for unscheduled visit, EDSS score, name of new medication, preferred term for adverse event). There should be a column for the date and time of the event, and a column for the time since randomization. The events must include:

- Sign consent form (date and time)
- Randomization (date and time)
- Start study medication (medication, date and time)
- Discontinue study medication (reason, date and time)
- Start treatment for acute relapse (medication, date and time)
- Scheduled visits (visit number, date and time)
- Every EDSS determinations (EDSS Visit Number Indicator, total score, type of EDSS, scheduled or not, etc, and date and time, rater)
- EDSS score entered into data system, EDSS Visit Indicator)
- EDSS score changed in audit trail (date and time, previous score, new score)
- Start alternative MS medication (medication name and date and time).
- Patient reports of relapses to clinic (type of contact: patient calls site, during clinic visit, clinic calls patient, date and time)
- Relapse evaluation visits (date and time, evaluator, confirmed relapse or not)
- Unscheduled visits (reason, date and time)
- MRI scan performed (lesion count)
- Last subject contact (date and time)
- Adverse event (preferred term, date and time)
- Use of steroids (date and time)
- Relapse event confirmed (date and time of relapse)

Meeting Discussion:

FDA asked the sponsor to provide MRI datasets in chronological order. FDA asked the sponsor to specify in the datasets whether the use of steroids and NSAIDs was for pre-medication or for other reasons.

14) Include in the MRI datasets and tables the following:

- Date and time the MRI was performed
- Date the MRI was received and when it was reviewed at the MRI Centralized Reading Center
- Detail the imputation method(s) employed.

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 volumes.

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.

15) Include a table that identifies the time of key milestones in the WA21092 and WA21093 trials and their corresponding extensions. Milestones should include:

- Protocol approvals
- Protocol amendments
- Statistical Analysis Plan (SAP) approvals
- SAP amendments
- First subject randomized
- Any interim analysis
- Last subject randomized
- First subject completes follow-up
- Last subject completes follow-up
- Database lock
- DMC meetings and teleconferences

16) 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.

17) 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 WA21092 and WA21093 trials, the number enrolled in the corresponding extension trials, fields showing the number of randomized patients in each arm of the WA21092 and WA21093 trials who experienced relapses and progression of disability events, fields to list the total number of progression of disability events and total number of relapses for all WA21092 and WA21093 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.

18) List any fields that were collected in the CRF but which were not included in the datasets.

19) Include a sample of active treatment and placebo packaged and labeled as received at study sites.

20) 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 WA21092 and WA21093 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).

Sponsor's Response to FDA Preliminary Response:

GNE Response Question 16 Part 1-6

Comments will be addressed by the Sponsor in the CMC-only pre-BLA meeting planned for February 2016.

GNE Response Question 16 Part 7

Similar to previous MS applications, the Sponsor proposes to present a cumulative event curve for CDP as a cumulative plot of probability of having an event and number of patients at risk at regular 12-week intervals, with a Y-axis ranging from 0 to 20%. We propose to present the final proportion of patients who progress at 673 days [starting on day 1].

If a survival curve [proportions of event free patients] is preferred, the Sponsor could submit it in addition to the cumulative event curve described above. Can the Division provide further clarification on the timepoint for “final proportion surviving” (eg. day 673) and for which endpoints this presentation should be included?

Meeting Discussion:

FDA provided an example of a survival curve. FDA requested confidence intervals for the survival curve.

GNE Response Question 16 Part 8

The Sponsor acknowledges the Division’s requests and would like to discuss further during the pre-BLA meeting.

Meeting Discussion:

FDA asked the sponsor to complete an assessment of possible uncertainties in the data including bias. For example, the primary outcome event requires a complex process for determination. FDA requested that the sponsor estimate the potential for patients, investigators, and raters to introduce bias at each step in the process. This should include any bias in the selection of potential relapses for further evaluation following the telephone interviews. FDA recommended an analysis of the use of NSAIDs as an indicator that subjects and/or investigators had become aware of treatment assignment. FDA is interested in knowing whether knowledge of the previous EDSS scores may have influenced the determination of current EDSS scores.

GNE Response Question 16 Part 9

No further discussion is necessary. Please see Additional Comment 13.

GNE Response Question 16 Part 10

No further discussion is necessary.

GNE Response Question 16 Part 11

Genentech acknowledges the comment. In the filing, we will provide the proportion of flu-like symptoms, injection site reactions, and infusion related reactions across both ocrelizumab and interferon arms.

Does the Agency agree?

GNE Response Question 16 Part 12

Genentech acknowledges the comment. In the filing, we will provide the proportion of the use of NSAIDS across both ocrelizumab and interferon arms.

Does the Agency agree?

GNE Response Question 16 Part 13

The Sponsor agrees to provide a dataset of clinical events for each patient, as described in Question 16 Part 13.

Regarding MRI endpoints, the Sponsor proposes to provide data, including T1 Gd lesions, new and enlarging T2 lesions, T2 volume and T1 hypointense lesions. Clinical events related to steroid use will be provided for those given for treatment of relapse and will not include protocol-mandated pre-medication for infusions (methylprednisolone or equivalent).

The Sponsor would like to further discuss the EDSS audit trail and reasons for unscheduled visits at the meeting.

Meeting Discussion:

FDA asked the sponsor to provide an explanation in the BLA application for duplicate EDSS scores for the same assessment. FDA also noted that changes in the initial recorded EDSS scores several months later may not be acceptable.

GNE Response Question 16 Part 14

The Sponsor has not imputed missing values for any primary or key secondary endpoints. For MRI lesion count endpoints, analyses were based on a negative binomial regression model using all observed data including the number of MRI assessment per patient as an off-set variable.

The Sponsor plans to present the number of observed data points by visit in tables, figures and graphs shown below (see Appendix 3). Together with the baseline patient numbers, the Division will be able to assess the impact of missingness.

Meeting Discussion:

FDA stated that the sponsor's plan was acceptable.

GNE Response Question 16 Part 15

No further discussion is necessary.

GNE Response Question 16 Part 16

No further discussion is necessary.

GNE Response Question 16 Part 17

No further discussion is necessary.

GNE Response Question 16 Part 18

For Studies WA21092 and WA21093, the Sponsor will provide a list of fields collected in the CRF, but which were not included in the datasets.

GNE Response Question 16 Part 19

No further discussion is necessary.

GNE Response Question 16 Part 20

No further discussion is necessary.

DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

As stated in our October 22, 2015, communication granting this meeting, if, at the time of submission, the application that is the subject of this meeting is for a new molecular entity or an original biologic, the application will be subject to "the Program" under PDUFA V. Therefore, at this meeting be prepared to discuss and reach agreement with FDA on the content of a complete application, including preliminary discussions on the need for risk evaluation and mitigation strategies (REMS) or other risk management actions. You and FDA may also reach agreement on submission of a limited number of minor application components to be submitted not later than 30 days after the submission of the original application. These submissions must be of a type that would not be expected to materially impact the ability of the review team to begin its review. All major components of the application are expected to be included in the original application and are not subject to agreement for late submission.

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

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

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

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

DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

- The content of a complete application was discussed.

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

- A preliminary discussion on the need for a REMS was not held.
- 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.

PREA REQUIREMENTS

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

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

plans with other regulatory authorities. The PSP should be submitted in PDF and Word format. Failure to include an agreed iPSP with a marketing application could result in a refuse to file action.

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

PRESCRIBING INFORMATION

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

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

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

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

MANUFACTURING FACILITIES

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

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

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

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

Corresponding names and titles of onsite contact:

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

Office of Scientific Investigations (OSI) Requests

The Office of Scientific Investigations (OSI) requests that the following items be provided to facilitate development of clinical investigator and sponsor/monitor/CRO inspection assignments, and the background packages that are sent with those assignments to the FDA field investigators who conduct those inspections (Item I and II). This information is requested for all major trials

used to support safety and efficacy in the application (i.e., phase 2/3 pivotal trials). Please note that if the requested items are provided elsewhere in submission in the format described, the Applicant can describe location or provide a link to the requested information.

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

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

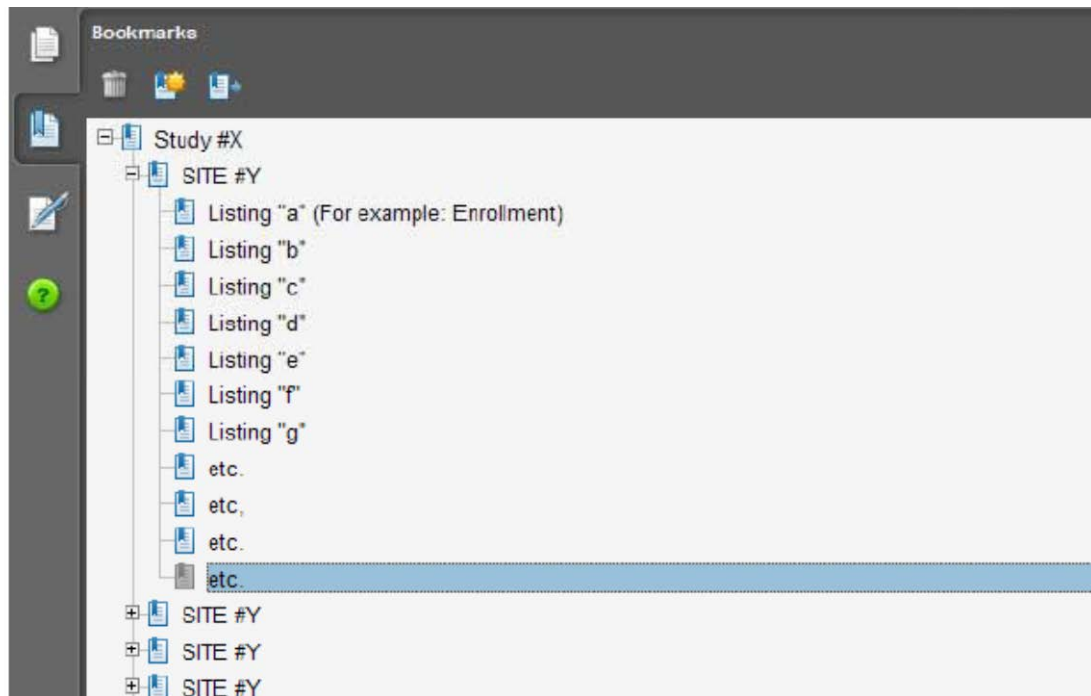
I. Request for general study related information and comprehensive clinical investigator information (if items are provided elsewhere in submission, describe location or provide link to requested information).

1. Please include the following information in a tabular format in the original NDA for each of the completed pivotal clinical trials:
 - a. Site number
 - b. Principal investigator
 - c. Site Location: Address (e.g., Street, City, State, Country) and contact information (i.e., phone, fax, email)
 - d. Location of Principal Investigator: Address (e.g., Street, City, State, and Country) and contact information (i.e., phone, fax, email). If the Applicant is aware of changes to a clinical investigator's site address or contact information since the time of the clinical investigator's participation in the study, we request that this updated information also be provided.
2. Please include the following information in a tabular format, *by site*, in the original NDA for each of the completed pivotal clinical trials:
 - a. Number of subjects screened at each site
 - b. Number of subjects randomized at each site
 - c. Number of subjects treated who prematurely discontinued for each site by site
3. Please include the following information in a tabular format in the NDA for each of the completed pivotal clinical trials:
 - a. Location at which sponsor trial documentation is maintained (e.g., , monitoring plans and reports, training records, data management plans, drug accountability records, IND safety reports, or other sponsor records as described ICH E6, Section 8). This is the actual physical site(s) where documents are maintained and would be available for inspection
 - b. Name, address and contact information of all Contract Research Organization (CROs) used in the conduct of the clinical trials and brief statement of trial related functions transferred to them. If this information has been submitted in eCTD format

- previously (e.g., as an addendum to a Form FDA 1571, you may identify the location(s) and/or provide link(s) to information previously provided.
- c. The location at which trial documentation and records generated by the CROs with respect to their roles and responsibilities in conduct of respective studies is maintained. As above, this is the actual physical site where documents would be available for inspection.
 4. For each pivotal trial, provide a sample annotated Case Report Form (or identify the location and/or provide a link if provided elsewhere in the submission).
 5. For each pivotal trial provide original protocol and all amendments ((or identify the location and/or provide a link if provided elsewhere in the submission).

II. Request for Subject Level Data Listings by Site

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



III. Request for Site Level Dataset:

OSI is piloting a risk based model for site selection. Voluntary electronic submission of site level datasets is intended to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process. If you wish to voluntarily provide a dataset, please refer to the draft Guidance for Industry Providing Submissions in Electronic Format – Summary Level Clinical Site Data for CDER’s Inspection Planning” (available at the following link <http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/UCM332468.pdf>) for the structure and format of this data set.

Attachment 1
Technical Instructions:
Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format

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

DSI Pre-NDA Request Item⁴	STF File Tag	Used For	Allowable File Formats
I	data-listing-dataset	Data listings, by study	.pdf
I	annotated-crf	Sample annotated case report form, by study	.pdf
II	data-listing-dataset	Data listings, by study (Line listings, by site)	.pdf
III	data-listing-dataset	Site-level datasets, across studies	.xpt
III	data-listing-data-definition	Define file	.pdf

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



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

⁴ Please see the OSI Pre-NDA/BLA Request document for a full description of requested data files

References:

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

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

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

APPEARS THIS WAY ON ORIGINAL

ROCHE – GENENTECH RESPONSE
TO PRELIMINARY MEETING COMMENTS

Meeting Type: B / Face to Face
Meeting Category: Pre-BLA

Meeting Date and Time: Tuesday, December 8, 2015, 1400 to 1500 EST
Meeting Location: White Oak Building 22, Conference Room: 1315

Application Number: 100593
Product Name: Ocrelizumab
Indication: Multiple Sclerosis
Sponsor/Applicant Name: Genentech, Inc.

1. BACKGROUND

On December 4, 2015 preliminary responses to the Sponsor's questions and additional comments were provided in preparation for the pre-BLA meeting scheduled for December 8, 2015 between Genentech and the Division of Neurology Products. Provided within, the Sponsor provides response to the Division's comments.

Based on the preliminary comments the Sponsor would like to focus the meeting discussion on the following topics:

1. GNE Question 8 and the Division's Additional Comment 8 – regarding the requested information on the process and analyses for identifying and reporting relapse
2. Additional Comment 9 – EDSS Analyses
3. GNE Question 11 – Format of the BLAs

Further clarification is needed on the following topics:

1. GNE Question 3: Abuse potential requirements
2. GNE Question 9c(ii): Comparison of approved anti-CD20 molecules to the safety profile of ocrelizumab
3. FDA Additional Comment 11 and 12: Provide an analyses of injection related adverse events and anti-inflammatory agents
4. Additional comment 13: Log of events relevant to clinical effects (Assume that Ph III ONLY)
5. Additional comment 7 & 14: Efficacy data

2. **DISCUSSION**

2.1 NON-CLINICAL

Question 1: Does the Agency agree that the completed and planned nonclinical studies are sufficient to support filing a BLA for registration of ocrelizumab?

FDA Response to Question 1:

Your nonclinical plan is acceptable, except that the carcinogenicity study waiver request (with all supportive data) should be submitted during clinical development so that a decision can be made prior to BLA submission regarding the need for the studies.

GNE Response to Question1:

No further discussion is necessary.

The Sponsor will submit to IND 100593 the carcinogenicity study waiver request, with all supportive data, prior to submission of the BLA.

Question 2: The Sponsor plans to initiate a pharmacokinetics (PK)/pharmacodynamics (PD) study in pediatric patients aged 10 – 17 years prior to the conclusion of the FDA requested juvenile immunotoxicology study (which will assess immune system function at the end of dosing and at the end of recovery). Does the Agency agree that results from this toxicology study are not required before the start of the pediatric PK/PD study?

FDA Response to Question 2:

The juvenile animal toxicology study will not be required prior to initiation of the pediatric PK/PD study. As previously mentioned, we strongly encourage you to submit the final protocol for the juvenile animal study for feedback prior to study initiation.

GNE Response to Question2:

No further discussion is necessary.

The Sponsor plans to submit to IND 100593 the final protocol for the juvenile animal study as a Type C Meeting – request for written response only, prior to the end of 2015.

Question 3: The Sponsor does not believe that ocrelizumab has abuse potential and therefore a full assessment or proposed scheduling is not required in the RMS or PPMS BLA. Does the Agency agree?

FDA Response to Question 3:

There is insufficient information in the meeting package for us to determine the need for an abuse potential assessment. If ocrelizumab has central nervous system (CNS) activity, it will need an abuse potential assessment.

Sufficient evidence that ocrelizumab does not have CNS activity may be based on full protocols and summary data from the following studies:

1. Pharmacokinetic distribution studies with radiolabelled ocrelizumab that demonstrate that the drug does not significantly penetrate the brain.
2. Receptor binding studies showing that ocrelizumab does not have activity at typical abuse-related sites (such as dopamine, GABA, NMDA, opioid, and cannabinoid receptors or monoamine transporters).
3. Animal toxicology studies showing that ocrelizumab does not alter behavior (e.g., induce changes in locomotion suggestive of stimulation or sedation).
4. Clinical studies showing that abuse-related adverse events such as euphoria, hallucinations, sedation, or stimulation do not occur at therapeutic or supratherapeutic doses of ocrelizumab.

We will evaluate whether ocrelizumab appears to have CNS activity. If it does not, then dedicated abuse-related studies are not necessary. If we determine that ocrelizumab does have CNS activity, additional abuse-related studies are necessary (refer to the 2010 *Guidance for Industry: Assessment of the Abuse Potential of Drugs*).

GNE Response to Question 3

The Sponsor plans to provide the following evidence to support the assessment of ocrelizumab CNS activity:

1. Pharmacokinetic distribution studies with radiolabelled ocrelizumab that demonstrate that the drug does not significantly penetrate the brain.**Study 03-0431-0349, entitled “Tissue Distribution of 125I-ocrelizumab in Normal Mice and a Transgenic Mouse Model”**

Conclusion: Tissue distribution was examined using 125I-ocrelizumab in normal mice and in a transgenic mouse model, in which human CD20 was transfected to be expressed on murine B cells. The results suggest that a significant amount of 125I-ocrelizumab is bound to B cells in the systemic lymphoid organs of the spleen and mesenteric lymph nodes in CD20 transgenic mice. In comparison, normal mice had much more radioactivity in their plasma and cleared 125I-ocrelizumab more slowly than CD20 transgenic mice.

Like most monoclonal antibodies, there was no evidence that 125I-ocrelizumab significantly penetrates the brain.

Study 15-0538, entitled “PET Biodistribution Imaging of Cu-64 Labeled Anti-CD20 2H7 Variants (v511, v16) in B-Cell Depleted Cynomolgus Monkeys”

Conclusion: PET images in cynomolgus monkeys given ocrelizumab indicated presence of the labeled ocrelizumab within blood pool and distribution to organs having high levels of B cells (e.g., spleen and lymphoid tissues).

There was no evidence that labeled ocrelizumab significantly penetrates the brain.

3. Animal toxicology studies showing that ocrelizumab does not alter behavior (e.g., induce changes in locomotion suggestive of stimulation or sedation).

Multiple repeat-dose GLP toxicology studies were conducted in cynomolgus monkeys to evaluate the safety of ocrelizumab at different dose levels and by different dosing regimen (Studies 03-0113-0349, 03-0114-0349, 03-0684-0134, 04-0192-0134, 07-0171). In addition, reproductive and developmental toxicity were evaluated in cynomolgus monkeys in studies 12-0524, 12-0525, 04-1272-1342, and 06-1260. In all these studies, clinical signs were evaluated including twice daily cage side observations and predose and postdose observations on all animals. In most studies, other physical (e.g. abdominal palpation and observations of the condition of integument, respiratory and cardiovascular systems) and physiological evaluations (blood pressure, heart rate, respiration rate and body temperature, etc.) were also conducted. There were no observations that ocrelizumab altered animal behavior (e.g., induced changes in locomotion suggestive of stimulation or sedation).

In Study 12-0524, entitled “Ocrelizumab 9-Week Intravenous Administration Male Fertility Study in the Cynomolgus Monkey with a 16-Week Recovery Phase”, physical examinations and neurobehavioral battery were assessed and no abnormal behavioral effects were detected.

4. Clinical studies showing that abuse-related adverse events such as euphoria, hallucinations, sedation, or stimulation do not occur at therapeutic or supratherapeutic doses of ocrelizumab.

The clinical evidence planned to support the assessment of ocrelizumab CNS activity will utilize the Medical Dictionary for Regulatory Activities (MedDRA) Query 'Standardized MedDRA Query (SMQ) drug abuse and dependence (narrow)' to evaluate MS All Exposure and RA All Exposure populations. This SMQ was applied to the controlled period of the RMS Phase III studies WA21092 and WA21093, and the adverse event (AE) profile was not suggestive of abuse potential. In addition, an evaluation will be presented for specific terms such as euphoria, hallucinations, sedation, and stimulation.

Due to the high degree of specificity associated with a monoclonal, off target binding would not be expected with ocrelizumab and receptor-binding studies beyond CD20 have not been completed. Therefore, we intend to submit details and protocols about the three outlined components to demonstrate lack of CNS activity associated with abuse potential.

Can the Agency provide initial feedback if this is sufficient?

2.1. CLINICAL

Question 4: Does the Agency agree that the outcomes from pivotal Phase III studies WA21092 and WA21093 in RMS patients provide sufficient clinical evidence to support the review of the BLA in patients with relapsing forms of MS?

FDA Response to Question 4:

Subject to a full review of a complete application, we agree that studies WA21092 and WA21093 appear to potentially provide substantial evidence of effectiveness of ocrelizumab for the treatment of patients with relapsing MS.

GNE Response to Question 4:

No further discussion is necessary.

Question 5: Does the Agency have any comments on the proposed indication based on the clinical trials conducted?

FDA Response to Question 5:

If we approve the application, we anticipate the indication will be for the treatment of patients with relapsing forms of multiple sclerosis.

GNE Response to Question5:

No further discussion is necessary.

Question 6: Based on the initial review of the RMS safety data, the Sponsor believes that the information included in the US prescribing information will be sufficient to convey the benefits and risks of ocrelizumab and that additional REMS measures are not deemed necessary Does the Agency agree?

FDA Response to Question 6:

At this time, we have insufficient information to determine whether a risk evaluation and mitigation strategy (REMS) will be necessary to ensure that the benefits of ocrelizumab outweigh the risks. We will determine the need for a REMS during the review of your application.

GNE Response to Question6:

No further discussion is necessary.

Question 7: The Sponsor is seeking feedback on the acceptability of potential mechanisms for collecting real world safety data on the use of ocrelizumab, specifically:

a) Does the Agency agree

(b) (4)

(b) (4) could contribute to support post-approval US requirements, if determined to be necessary?

b) Would the FDA consider pregnancy studies based on pre-planned review of existing population-based registers or healthcare databases (b) (4)

(b) (4) ? Would the FDA consider (b) (4) to support any post-approval US requirements, if determined necessary?

FDA Response to Question 7:

a) Review of the design of any post-approval studies is not part of the BLA review. In general, (b) (4) we would need to review a more detailed proposal that includes information on the specific data that could be collected, the validity of the data collected, and information regarding completeness of follow up. We would also need to assess your proposal for collecting US data. We will not be able to determine the specific data you will need to collect until after the BLA review is complete.

b) See our reply to question 7a, above.

GNE Response to Question 7a and 7b:

No further discussion is necessary.

Question 8: *A summary of the process and analyses for identifying and reporting relapse events from the Phase III clinical studies WA21092 and WA21093 will be provided in Module 5, Section 5.3.5.3 of the RMS BLA. Does the Agency agree that the assessment provided within Appendix 3 adequately addresses this request?*

FDA Response to Question 8:

The adequacy of the process for identification of relapses will depend on a full review of the data collected for each step of the process. In general the protocol-defined process for identification of a potential relapse provided in Appendix 3 of this submission has the potential to adequately document the process from the point at which it was determined that a subject report should be evaluated further. Documentation of the process prior to that point is less well defined. You should be prepared to submit information on all subject reports of a potential relapse collected at any of the 4 sources listed in Section 4 of Appendix 3. You should submit data on spontaneous reports of a relapse or relapses detected at the monthly telephone interviews including those that were not referred to the treating investigator. You should submit data on determinations made by the treating investigator to conduct relapse assessments. You indicate that the results of the subject interviews were not included in the eCRF. You should be prepared to submit the forms used to collect this information.

GNE Response to Question 8:

The Sponsor would like to further discuss the requested information during the pre-BLA meeting.

Question 9: *Does the Agency agree with the overall approach for inclusion and evaluation of safety data, including the proposed pooling strategy and analyses for the integrated safety summary specifically the:*

- a) Proposed inclusion of all individual study reports as described in Section 9.3.1?*
- b) Proposed pooling strategy for 1) MS studies 2) Rheumatoid Arthritis (RA) studies and 3) the proposal to not pool data from any of the Systemic Lupus Erythematosus (SLE) and Lupus Nephritis (LN) and Non-Hodgkin's Lymphoma (NHL) studies, but inclusion of CSRs only as described in Section 9.3.2?*
- c) Proposed analyses planned for the MS and RA Pools and presentation within the integrated summary of safety, as described in Section 9.3.3.*

FDA Response to Question 9:

- a) Yes.
- b) Comparative data is particularly useful in assessing safety. In your proposal, the controlled data from the PPMS trial would not be available separately, but only pooled with RMS data. The data from the PPMS trial would be available separately in the CSR, but it would facilitate the review to have it included as part of the presentation of safety data. Therefore, we request the following pools for presentation of safety data:
 - Pool A: Phase III RMS Controlled Treatment
 - Pool B: MS PPMS Controlled Treatment
 - Pool C: MS All Exposure (RMS and PPMS)
 - Pool D: Phase III RMS All Exposure
 - Pool E: Phase II and Phase III RA Controlled Treatment
 - Pool F: RA All Exposure
- c) Yes, but we also request the following information:
 - i) You reported a death in trial WA21493 that was due to SIRS. In addition to a detailed review of this case, we ask that you search all available ocrelizumab safety data for similar cases of SIRS or potential SIRS.
 - ii) Please also provide a discussion of the known safety issues of approved anti-CD20 monoclonal antibodies with comparisons to the safety profile of ocrelizumab.

Additional FDA Comment:

Provide a summary of any protocol amendments and changes to the informed consent document or Investigator's Brochure that occurred as a result of an adverse event or potential safety signal within your Clinical Summary of Safety. Include a description of the rationale for these changes and corresponding minutes from the Data Safety Monitoring Board.

GNE Response to Question 9:

Question 9a

No further discussion is necessary.

Question 9b

The Sponsor agrees to include the pools as requested by the Division; however, the description of the pools for display purposes will be identified as in Appendix 1. The analyses for the pools have been expanded based on FDA feedback and are described in the table below.

GNE Response to Additional Request 9c(i)

The Sponsor will search all available ocrelizumab safety data for cases of SIRS using a company basket (sepsis terms including SIRS) as part of the overall assessment of infections.

GNE Response to Additional Request 9c(ii)

The Sponsor acknowledges the Division's request to provide a discussion of the known safety issues of approved anti-CD20 monoclonal antibodies with comparisons to the safety profile of ocrelizumab. Approved anti-CD20 monoclonal antibodies include Rituxan, Gazyva and Arzerra in oncology (all) and autoimmune (Rituxan) indications.

Given the approved use of Rituxan in autoimmune indications, the Sponsor proposes an evaluation of all identified and potential safety risks from the Rituxan Rheumatoid Arthritis indication for assessment of relevance to the ocrelizumab MS patient population. This assessment will be provided in Integrated Summary of Safety in the BLA.

Does the Agency agree?

GNE Response to Additional FDA Comment:

No further discussion is necessary.

Question 10: Does the Agency agree with the proposed safety package, including:

- a) The patient exposure to assess clinical safety is sufficient to support the use of ocrelizumab for the treatment of RMS (see Section 9.3.1)*
- b) Proposed clinical cutoff dates and content of the 120-Day Safety Update Report as described in Section 9.3.6.*
- c) Proposed categories for individual patient narratives, electronic case report forms and individual patient profiles as described in Section 9.3.8?*
- d) Specific analyses for DRESS (Drug Reaction with Eosinophilia and Systemic Symptoms) as described within Section 9.3.7.*

FDA Response to Question 10:

- a) Yes, based on the information provided, the exposure appears adequate.
- b) Yes.
- c) Yes.
- d) Yes.

GNE Response to Question 10a, b, c and d:

No further discussion is necessary.

2.2. REGULATORY

Question 11: The Sponsor intends to submit two BLAs to support registration of ocrelizumab in relapsing forms of MS and primary progressive MS respectively. Does the Agency agree with the overall content of the RMS BLA, as described in the Table of Contents, provided in Appendix 4, and the proposed approach for submission of two BLAs to include, indication specific Module 1 content and identical Module 2-5?

EDA Response to Question 11:

We would like to discuss your submission plans at the meeting. Also, it is not clear to us how Module 2-5 could be identical. From a technical standpoint (not content related), the proposed format for the planned RMS BLA is generally acceptable. We have the following specific requests:

GNE Response to Question 11

The Sponsor plans to file two BLA applications to support the review and approval of the RMS and PPMS indication. One of the two cross-referencing options as described in the Division's response will be utilized for the second BLA application.

The Sponsor believes the RMS and PPMS studies will both be important to discuss in the Summary of Clinical Efficacy (SCE) and proposes to file a single SCE. This will be included in the first BLA and cross-referenced in the second BLA.

Does the Agency agree with the attached table of contents in Appendix 2?

1. If you are utilizing "The eCTD Backbone Files Specification For Module 1 v2.3", FDA Form 3674 should reside in m1.1.7; otherwise, it should reside in m1.2 (cover letter section), with a clear leaf title.
2. Please make sure leaf titles are clear and indicative of the content Appendix 1 is not a proper leaf title.
3. 1.6.3 Correspondence regarding meetings: you may provide a single pdf file instead of separate pdf files for each document if you also provide proper bookmarks of all correspondence, table of contents, and hyperlinks.
4. For archival purposes, also submit a pdf file of the labeling document you submit in Microsoft Word format. When you submit MS Word documents, make sure the leaf title includes "word", so reviewers can quickly identify the word version of the document.
5. Do not create additional nodes in the eCTD structure beyond what is in the specifications (3.2.p.5.2.1 – 7; 3.2.p.5.3.1 – 7; etc.). Please make sure your approach fits the DTD and the "Granularity Annex," located at:
<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM073261.pdf>
6. Please note that we require Study Tagging Files (STF) for submissions to the FDA when providing study information in modules 4 and 5 with the exception of modules 4.3 Literature References, 5.2 Tabular Listing, 5.4 Literature References,

and 5.3.6 if the Periodic Report is a single PDF document. Each study should have an STF and all components regarding that study should be properly file tagged and placed under the study's STF, including case report forms. Reference case report forms under the appropriate study's STF to which they belong, organized by site, as per the specifications and tagged as "case report form." Subject Data Listings (16.4) should be file tagged as "data-listing-dataset". For documents with no specific file tags, you can apply the "study-report-body" or "legacy-clinical-study-report" file tag. Please refer to The eCTD Backbone File Specification for Study Tagging Files 2.6.1 (PDF - 149KB) (6/3/2008).¹

- Regarding use of the m5-3-7 heading element, FDA does not use module 5.3.7 CRFs. Instead, reference case report forms in the appropriate study's STF to which they belong organized by site as per the specifications and tagged as "case report form". Do not use 5.3.7 as a heading element in the index.xml.
7. Provide the tabular listing in module 5.2 and synopsis of individual studies in m2.7.6 in tabular format and linked to the referenced studies in m5.

[GNE Response to Question 11 Part 1-7](#)

[No further discussion is necessary.](#)

Sponsors options for cross referencing information submitted to another application, would be to either place a cross reference document under module m1.4.4 (cross reference to other applications), or use cross application links.

1. To use the first option (placing a cross reference document in m1.4.4), a table formatted document can be submitted in section 1.4.4 of the eCTD, detailing previously submitted information (paper and/or non- eCTD format) that is being referenced by the current application. The information in the document should include (1) the application number, (2) the date of submission (e.g., letter date), (3) the file name, (4) the page number (if necessary), (5) the eCTD sequence number, (6) the eCTD heading location (e.g., m3.2.p.4.1 Control of Excipients – Specifications), (7) the document leaf title and (8) the submission identification (e.g., submission serial number, volume number, electronic folder, file name, etc.) of the referenced document along with a hypertext link to the location of the information, when possible.
2. To use the second option (cross application links), both applications must be in eCTD format. The applications must include the appropriate prefix in the href links (e.g., xlink:href".../ind900000/0009/m2/24-nonclin-over/nonclinical-overview.pdf"). In the leaf titles of the documents, we recommend that the leaf title indicate the word "cross reference to" and the application number (e.g. Cross Ref to nda XXXXXX). The cross reference information in the leaf title allows the reviewer to know that the document resides in another application.

Prior to using cross application linking in an application, we recommend that you submit an "eCTD cross application links" sample to ensure successful use of cross application links.

To submit an eCTD cross application links sample, request two sample application numbers from the ESUB team (esub@fda.hhs.gov). For more information on eCTD samples, please refer to the Sample Process web page.²

GNE Response to Question 11, additional comments 1 and 2

No further discussion is necessary.

Question 12: *Prior to the BLA submission, the Sponsor would like to review the navigation, formatting of electronic files and specifically the layout of the RMS application to ensure it is acceptable for filing. Does the Agency recommend proceeding with an electronic pre-submission meeting?*

FDA Response to Question 12:

Yes. We would like to become familiar with the navigation features of the application. Because the data formats and SAS programs appear acceptable, we recommend that you submit a test submission. The Edata and Esub team can review the submission formatting and layout and provide comments. For the test submission, please follow the test submission guide.³

GNE Response to Question 12

No further discussion is necessary.

Question 13: *Would the Agency like to have an Applicant Orientation/Technical Walk-Through meeting with the Sponsor after the submission of the BLA to outline major components for BLA?*

FDA Response to Question 13:

Yes.

GNE Response to Question 13

No further discussion is necessary.

Question 14: *Based on the preliminary review of the data, does the Agency foresee that the proposed BLA will be reviewed by an Advisory Committee?*

FDA Response to Question 14:

We will make a determination on the need for an Advisory Committee meeting for this application during the filing period.

GNE Response to Question 14

No further discussion is necessary.

Question 15: *Does the Agency agree that ocrelizumab represents a significant improvement in efficacy or safety and therefore the proposed BLA could be considered for priority review?*

FDA Response to Question 15:

We will make a determination on your request for priority review during the filing period. Please provide your justification for priority review with the application.

GNE Response to Question 15

No further discussion is necessary.

Question 16: *Are there any other recommendations the Agency can provide to help the Sponsor prepare an acceptable BLA for review, or to facilitate the review process?*

FDA Additional Comments:

1) The facilities should be ready for inspection at the time of the BLA submission and in operation manufacturing ocrelizumab drug substance. We noted that amendment 0645 received on October 30, 2015, indicates that the proposed manufacturing campaign for ocrelizumab is scheduled for August 2016; please ensure that the manufacturing schedule complies with GRMP timelines.

2) For the CMC Drug Substance section of the BLA (Section 3.2.S), provide the following product quality microbiology information:

- a) (b) (4) at critical manufacturing steps (b) (4)
(3.2.S.2.4).
- b) Provide microbial data from three successful product (b) (4) hold time (b) (4)
validation runs at manufacturing scale. Monitor (b) (4)
(3.2.S.2.5). Collect (b) (4)
- c) Data demonstrating microbial control (b) (4)
(3.2.S.2.5).
- d) (b) (4) data obtained during manufacture of the three process
qualification batches (3.2.S.2.5).
- e) Summary of shipping validation studies and data (3.2.S.2.5).
- f) Drug substance bioburden and endotoxin release specifications (3.2.S.4). The
bioburden limit should be (b) (4)
- g) Summary report with summary results from (b) (4)
qualification performed for in-process (b) (4) and drug substance (3.4.S.4).

3) 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 we expect, refer to the 1994 "FDA Guidance for Industry, Submission Documentation for Sterilization Process Validation in Applications for Human and Veterinary Drug Products".

- 4) Provide information and validation data summaries in Section 3.2.P.3.5 for the following:
 - a) (b) (4) study report (b) (4)
 - b) Sterilization and depyrogenation of equipment and components that contact the sterile drug product. Provide summary data for the three most recent requalification studies and describe the equipment requalification program.
 - c) At-scale data from three product (b) (4) hold times to support hold times. Monitor (b) (4)
 - d) (b) (4) if applicable.
 - e) Three successful consecutive media fill runs, including summary environmental monitoring data obtained during the runs. Describe media fill and environmental monitoring procedures.
 - f) A description of the routine environmental monitoring program.
 - g) A summary of shipping validation studies and data.
- 5) Provide the following method validation information:
 - a) Container closure integrity testing (3.2.P.2.5). Demonstrate system integrity (including maintenance of the microbial barrier) initially to qualify the container closure system and process and during stability. Container closure integrity methods validation must demonstrate that the assay is sensitive enough to detect breaches that could allow microbial ingress. Perform container closure integrity testing *in lieu* of sterility testing for stability samples every 12 months (annually) and at expiry (3.2.P.8.2).
 - b) Qualification data (b) (4) performed for in-process (b) (4) and the drug product, as appropriate (3.2.P.5).
 - c) Rabbit Pyrogen Test results from three lots of drug product in accordance with 21 CFR 610.13(b).
 - d) Because formulations with certain excipient and polysorbate combinations may interfere with endotoxin recoverability in the USP LA test methods over time, it is necessary to assess the effect of hold time on endotoxin recovery by spiking a known amount of endotoxin standard into undiluted drug product and testing for recoverable endotoxin over time using containers of similar composition to those used for drug product during hold.
- 6) All facilities should be registered with FDA at the time of the BLA submission and ready for inspection in accordance with 21 CFR 600.21 and 601.20(b)(2). Please include in the BLA submission a complete list of manufacturing and testing sites with their corresponding FEI numbers. An updated manufacturing schedule for the bulk drug substance and drug product fill finish sites should be included in Module 1 of the BLA.

GNE Response Question 16 Part 1-6

Comments will be addressed by the Sponsor in the CMC-only pre-BLA meeting planned for February 2016.

- 7) For survival curves, the Y-axis should start with zero and end with 1 or 100%. The X-axis labels should include the time from 0 and the number of subjects in each treatment arm for each tick mark. The final proportion surviving and treatment should be indicated clearly.

GNE Response Question 16 Part 7

Similar to previous MS applications, the Sponsor proposes to present a cumulative event curve for CDP as a cumulative plot of probability of having an event and number of patients at risk at regular 12-week intervals, with a Y-axis ranging from 0 to 20%. We propose to present the final proportion of patients who progress at 673 days [starting on day 1].

If a survival curve [proportions of event free patients] is preferred, the Sponsor could submit it in addition to the cumulative event curve described above. Can the Division provide further clarification on the timepoint for “final proportion surviving” (eg. day 673) and for which endpoints this presentation should be included?

8) Provide complete accounting and analysis of all potential relapse events. The dataset should include the date that the potential relapse events were first reported by the subject and the date that the events were first evaluated by the treating and by the examining investigators. Please include a column for the criteria that confirmed that there was a new objective neurologic deficit. Please include documentation of the blinded adjudication process used by the sponsor. Please include a calculation of the time intervals (in days) from the onset of symptoms to the various points in the relapse assessment process. Include an analysis for any potential bias in the determination made by the treating investigator in referring the event for further evaluation by the examining investigator and for adjudication by the sponsor. Provide sensitivity analyses based on relapses as reported by subjects and as determined by the treating and examining investigators in addition to the pre-specified primary analysis based on sponsor adjudication. Discuss the impact of any differences in the results of these analyses. Provide a clear indication of any imputed values used for these analyses.

GNE Response Question 16 Part 8

The Sponsor acknowledges the Division’s requests and would like to discuss further during the pre-BLA meeting.

9) 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 which includes the time interval between the time of randomization and the EDSS determination. Please place all scheduled EDSS assessments, e.g. screening, baseline, week 12, etc, in the same column for all subjects. Please identify and assign sequential identification numbers for those EDSS assessments that were performed at unscheduled relapse assessments and place each of them in the same column for all subjects, e.g., “unscheduled relapse assessment #1, etc.. The identification term used should map to the same events if they appear in other datasets. 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. If there are missing baseline EDSS values, explain how this could have happened. Describe the process for the certification of EDSS examiners. Flag EDSS scores that were from an assessment by a noncertified 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.

GNE Response Question 16 Part 9

No further discussion is necessary. Please see Additional Comment 13.

10) 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 randomized treatment and how data from these subjects were handled. 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 accounting of subjects whose relapse and EDSS outcomes you exclude from the analysis following the use of alternative MS treatment.

GNE Response Question 16 Part 10

No further discussion is necessary.

11) Provide an analysis of injection-related adverse events as a potential factor unblinding subjects and/or investigators to treatment assignment.

GNE Response Question 16 Part 11

Genentech acknowledges the comment. In the filing, we will provide the proportion of flu-like symptoms, injection site reactions, and infusion related reactions across both ocrelizumab and interferon arms.

Does the Agency agree?

12) Provide an analysis of the use of anti-inflammatory agents as a potential factor in the unblinding of subjects and/or investigators to treatment assignment.

GNE Response Question 16 Part 12

Genentech acknowledges the comment. In the filing, we will provide the proportion of the use of NSAIDS across both ocrelizumab and interferon arms.

Does the Agency agree?

13) To assist review of outcome events, relapses and sustained disability, a log of events relevant to these clinical events for each patient is required for a full understanding. Include a dataset of important trial events for each patient with one row per patient per event. The dataset should have few columns and many rows. Columns should include the patient identifier, trial name, name of event, treatment arm, event-specific comment (such as reason for discontinuation, reason for unscheduled visit, EDSS score, name of new medication, preferred term for adverse event). There should be a column for the date and time of the event, and a column for the time since randomization. The events must include:

- Sign consent form (date and time)
- Randomization (date and time)
- Start study medication (medication, date and time)
- Discontinue study medication (reason, date and time)

- Start treatment for acute relapse (medication, date and time)
- Scheduled visits (visit number, date and time)
- Every EDSS determinations (EDSS Visit Number Indicator, total score, type of EDSS, scheduled or not, etc, and date and time, rater)
- EDSS score entered into data system, EDSS Visit Indicator)
- EDSS score changed in audit trail (date and time, previous score, new score)
- Start alternative MS medication (medication name and date and time).
- Patient reports of relapses to clinic (type of contact: patient calls site, during clinic visit, clinic calls patient, date and time)
- Relapse evaluation visits (date and time, evaluator, confirmed relapse or not)
- Unscheduled visits (reason, date and time)
- MRI scan performed (lesion count)
- Last subject contact (date and time)
- Adverse event (preferred term, date and time)
- Use of steroids (date and time)
- Relapse event confirmed (date and time of relapse)

GNE Response Question 16 Part 13

The Sponsor agrees to provide a dataset of clinical events for each patient, as described in Question 16 Part 13.

Regarding MRI endpoints, the Sponsor proposes to provide data, including T1 Gd lesions, new and enlarging T2 lesions, T2 volume and T1 hypointense lesions. Clinical events related to steroid use will be provided for those given for treatment of relapse and will not include protocol-mandated pre-medication for infusions (methylprednisolone or equivalent).

The Sponsor would like to further discuss the EDSS audit trail and reasons for unscheduled visits at the meeting.

14) Include in the MRI datasets and tables the following:

- Date and time the MRI was performed
- Date the MRI was received and when it was reviewed at the MRI Centralized Reading Center
- Detail the imputation method(s) employed.

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 volumes.

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.

GNE Response Question 16 Part 14

The Sponsor has not imputed missing values for any primary or key secondary endpoints. For MRI lesion count endpoints, analyses were based on a negative binomial regression model using all observed data including the number of MRI assessment per patient as an off-set variable.

The Sponsor plans to present the number of observed data points by visit in tables, figures and graphs shown below (see Appendix 3). Together with the baseline patient numbers, the Division will be able to assess the impact of missingness.

15) Include a table that identifies the time of key milestones in the WA21092 and WA21093 trials and their corresponding extensions. Milestones should include:

- Protocol approvals
- Protocol amendments
- Statistical Analysis Plan (SAP) approvals
- SAP amendments
- First subject randomized
- Any interim analysis
- Last subject randomized
- First subject completes follow-up
- Last subject completes follow-up
- Database lock
- DMC meetings and teleconferences

GNE Response Question 16 Part 15

No further discussion is necessary.

16) 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.

GNE Response Question 16 Part 16

No further discussion is necessary.

17) 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 WA21092 and WA21093 trials, the number enrolled in the corresponding extension trials, fields showing the number of randomized patients in each arm of the WA21092 and WA21093 trials who experienced relapses and progression of disability events, fields to list the total number of progression of disability events and total number of relapses for all WA21092 and WA21093 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.

GNE Response Question 16 Part 17

No further discussion is necessary.

18) List any fields that were collected in the CRF but which were not included in the datasets.

GNE Response Question 16 Part 18

For Studies WA21092 and WA21093, the Sponsor will provide a list of fields collected in the CRF, but which were not included in the datasets.

19) Include a sample of active treatment and placebo packaged and labeled as received at study sites.

GNE Response Question 16 Part 19

No further discussion is necessary.

20) 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 WA21092 and WA21093 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).

GNE Response Question 16 Part 20

No further discussion is necessary.

Appendix 1. Description of Data Pools for Assessment of Safety Data

FDA REQUESTED POOLS	GNE DATA POOL	Analyses
“Pool A: Phase III RMS Controlled Treatment”	POOL A RMS Phase III Controlled Treatment	As described in the PMP
“Pool B: MS PPMS Controlled Treatment”	Study WA25046 PPMS Phase III Controlled Treatment	Propose to include the same level of analyses as Pool A.
“Pool C: MS All Exposure (RMS and PPMS)”	Pool B MS All Exposure (RRMS Phase II + RMS Phase III + PPMS Phase III)	As described in the PMP
“Pool D: Phase III RMS All Exposure”	Pool C RMS Phase III All Exposure	Analyses will be expanded from IRRs and general laboratory evaluations, to include all the analyses described by MS All Exposure.
“Pool E: Phase II and Phase III RA Controlled Treatment”	Pool D RA Phase II and III Controlled Treatment	As described in the PMP
“Pool F: RA All Exposure”	Pool E RA Phase II and III all exposure	As described in the PMP
Other Populations	Summary of safety profile in systemic lupus erythematosus, lupus nephritis, follicular non-Hodgkin’s lymphoma.	As described in the PMP

Appendix 2
Module 1: Table of Contents for RMS and PPMS BLA

Section	BLA #1 eg. RMS ¹	BLA #2 eg. PPMS ¹
Module 1: Administrative and Prescribing Information		
1.1. Forms	Forms FDA 356h, 3397, 2567	Forms FDA 356h, 3397, 2567
1.2 Cover Letter Appendix 1 Appendix 2	Certificate of Compliance FDA Form 3674 - Request for Priority Review -Reviewers Guide	Certificate of Compliance FDA Form 3674 - Request for Priority Review -Reviewers Guide
1.3 Administrative Information	Included	Included
1.3.1.4 Transfer of Obligation		
1.3.3 Debarment Certification	Included	Included
1.3.4 Financial Disclosure	Will be provided for studies WA21092, WA21093, WA21493	Will be provided for study WA25046.
1.3.5 Patent and Exclusivity 1.3.5.3 Exclusivity Request	Will be identical in each BLA	Will be identical in each BLA
1.4 References	Cross reference to IND 100,593	Cross reference to IND 100,593
1.4.4 Cross Reference to Other Applications		*Cross reference to BLA #1
1.6 Meetings 1.6.3 Correspondence Regarding Meetings	Single .pdf file of Correspondence for RMS and PPMS	Single .pdf file of Correspondence for RMS and PPMS
1.7 Fast Track 1.7.1 Fast track designation request 1.7.4 Correspondence regarding fast track/rolling review	N/A	GNE fast track request dated 21-Dec-2012, SN 0509 Fast track designation received 06-Mar-2013
1.9 Pediatric administrative information	N/A	03 October 2015 Agreed iPSP
1.9.1 Request for Waiver of Pediatric Studies		
1.9.2 Request for Deferral of Pediatric Studies	03 October 2015 Agreed iPSP	n/a
1.12 Other Correspondence 1.12.4 Request for Comment and Advice 1.12.14 Environmental Analysis	Included	Request for Breakthrough Therapy Designation cross-reference

1.14 Labeling 1.14.1 Draft Labeling 1.14.1.1. Draft carton and container labels 1.14.1.2 Annotated draft labeling text 1.14.1.3 Draft labeling text (Word and SPL)	Only RMS indication proposed labeling will be included, Draft carton and container labels RMS Annotated draft labeling text RMS Draft labeling text (Word,.PDF and SPL)	Only PPMS indication proposed labeling will be included Draft carton and container labels PPMS Annotated draft labeling text PPMS Draft labeling text (Word, .PDF and SPL)
1.16 Risk Management Plans 1.16.1 Risk Management (Non-REMS)	Included	Included
1.18 Proprietary Name	Request for Proprietary Name: Ocrevus	Request for Proprietary Name: Ocrevus

Order of submission the RMS and PPMS is to be confirmed ie. BLA #1 or BLA #2

*To be determined: “Cross-reference” may refer to M 1.4.4 OR as cross application links and will be applied as recommended.

Module 2: Table of Contents for RMS BLA and PPMS BLA

Section	BLA #1 eg. RMS ¹	BLA #2 eg. PPMS ¹
2. Common Technical Document Summaries		
2.2 Introduction	included	cross-reference
2.3 Quality Overall Summary		
2.3.S Drug Substance	included	cross-reference
2.3.P Drug Product	included	cross-reference
2.3.A Appendices	included	cross-reference
2.3.R Regional Information	included	cross-reference
2.4 Nonclinical Overview	included	cross-reference
2.5 Clinical Overview	Clinical Overview: RMS+PPMS	cross-reference
2.6 Nonclinical Written and Tabulated Summary	included	cross-reference
2.6.1 Introduction	included	cross-reference
2.6.2 Pharmacology Written Summary	included	cross-reference
2.6.3 Pharmacology Tabulated Summary	included	cross-reference
2.6.4 Pharmacokinetic Written Summary	included	cross-reference
2.6.5 Pharmacokinetic Tabulated Summary	included	cross-reference
2.6.6 Toxicology Written Summary	included	cross-reference
2.6.7 Toxicology Tabulated Summary	included	cross-reference
2.7 Clinical Summary		
2.7.1 Summary of Biopharmaceutic Studies and Associated Analytical Methods	Included RMS and PPMS	cross-reference
2.7.2 Summary of Clinical Pharmacology	Discussion of RMS and PPMS	cross-reference
2.7.3 Summary of Clinical Efficacy	Discussion of RMS and PPMS	cross-reference
2.7.4 Summary of Clinical Safety	included	cross-reference
2.7.5 Literature References	included	cross-reference
2.7.6 Synopses of Individual Studies	included	cross-reference

Order of submission the RMS and PPMS is to be confirmed ie. BLA #1 or BLA #2

To be determined: “Cross-reference” may refer to M 1.4.4 OR as cross application links and will be applied as recommended.

Module 3: Table of Contents for RMS BLA and PPMS BLA

Section	BLA #1 eg. RMS ¹	BLA #2 eg. PPMS ¹
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	All Module 3 documents are identical for both indications	
3.2.S Drug Substance	Included	cross-reference
3.2.S.1 General Information	Included	cross-reference
3.2.S.1.1 Nomenclature	Included	cross-reference
3.2.S.1.2 Structure	Included	cross-reference
3.2.S.1.3 General Properties	Included	cross-reference
3.2.S.2 Manufacture	Included	cross-reference
3.2.S.2.1 Manufacturer(s)	Included	cross-reference
3.2.S.2.2 Description of Manufacturing Process and Process Controls	Included	cross-reference
3.2.S.2.2.1 Batch and Scale Definition	Included	cross-reference
3.2.S.2.2.2 Cell Culture and Harvest	Included	cross-reference
3.2.S.2.2.3 Purification and Modification Reactions	Included	cross-reference
3.2.S.2.2.4 Filling, Storage, and Transportation	Included	cross-reference
3.2.S.2.3 Control of Materials	Included	cross-reference
3.2.S.2.3.1 Source, History, and Generation of the Cell Substrate	Included	cross-reference
3.2.S.2.3.2 Cell Banking System, Characterization, and Testing	Included	cross-reference
3.2.S.2.4 Controls of Critical Steps and Intermediates	Included	cross-reference
3.2.S.2.5 Process Validation and/or Evaluation	Included	cross-reference
3.2.S.2.5.1 Introduction	Included	cross-reference
3.2.S.2.5.2 Site-Specific Validation	Included	cross-reference
3.2.S.2.5.3 Process Consistency	Included	cross-reference
3.2.S.2.5.4 Removal of Process-Related Impurities and Product Variants	Included	cross-reference
3.2.S.2.5.5 Process Hold Times	Included	cross-reference
3.2.S.2.5.6 (b) (4)	Included	cross-reference
3.2.S.2.5.7 Evaluation — Qualification of Scale-Down Models	Included	cross-reference
3.2.S.2.5.8 Site- and Scale-Independent Characterization and Validation of the (b) (4)	Included	cross-reference
3.2.S.2.5.9 Site- and Scale-Independent Characterization and Validation of the Purification Process	Included	cross-reference

3.2.S.2.5.10 Process Linkage	Included	cross-reference
3.2.S.2.5.11 Determination of the Process Impact Scores for Critical Quality Attributes	Included	cross-reference
3.2.S.2.6 Manufacturing Process Development	Included	cross-reference
3.2.S.3 Characterization	Included	cross-reference
3.2.S.3.1 Elucidation of Structure and Other Characteristics	Included	cross-reference
3.2.S.3.2 Impurities	Included	cross-reference
3.2.S.4 Control of Drug Substance	Included	cross-reference
3.2.S.4.1 Specification	Included	cross-reference
3.2.S.4.2 Analytical Procedures	Included	cross-reference
3.2.S.4.2.1 Methods Performed According to Pharmacopeia	Included	cross-reference
3.2.S.4.2.2 Peptide Map	Included	cross-reference
3.2.S.4.2.3 Purity by Non-Reduced Capillary Electrophoresis Sodium Dodecyl Sulfate	Included	cross-reference
3.2.S.4.2.4 Purity by Size-Exclusion High-Performance Liquid Chromatography	Included	cross-reference
3.2.S.4.2.5 Purity by Ion-Exclusion High-Performance Liquid Chromatography	Included	cross-reference
3.2.S.4.2.6 Glycan Analysis by Capillary Electrophoresis	Included	cross-reference
3.2.S.4.2.7 CDC Potency	Included	cross-reference
3.2.S.4.2.8 Ultraviolet-Visible Spectrophotometric Scan Using Gravimetric Sample Preparation	Included	cross-reference
3.2.S.4.2.9 Determination of Polysorbate 20 Content by Fluorescent Micelle Assay	Included	cross-reference
3.2.S.4.3 Validation of Analytical Procedures	Included	cross-reference
3.2.S.4.3.1 Clarity, Opalescence, and Color of Liquids and Appearance of Liquids/ (b) (4) Vials	Included	cross-reference
3.2.S.4.3.2 Peptide Map	Included	cross-reference
3.2.S.4.3.3 Bioburden	Included	cross-reference
3.2.S.4.3.4 Bacterial Endotoxins	Included	cross-reference
3.2.S.4.3.5 Purity by Non-Reduced Capillary Electrophoresis Sodium Dodecyl Sulfate	Included	cross-reference

3.2.S.4.3.6	Purity by Size-Exclusion High-Performance Liquid Chromatography	Included	cross-reference
3.2.S.4.3.7	Purity by Ion-Exclusion High-Performance Liquid Chromatography	Included	cross-reference
3.2.S.4.3.8	Glycan Analysis by Capillary Electrophoresis	Included	cross-reference
3.2.S.4.3.9	CDC Potency	Included	cross-reference
3.2.S.4.3.10	Ultraviolet-Visible Spectrophotometric Scan Using Gravimetric Sample Preparation	Included	cross-reference
3.2.S.4.3.11	pH Determination	Included	cross-reference
3.2.S.4.3.12	Osmolality Determination	Included	cross-reference
3.2.S.4.3.13	Determination of Polysorbate 20 Content (b) (4)	Included	cross-reference
3.2.S.4.3.14	Determination of Product Titer in (b) (4) High-Performance Liquid Affinity Chromatography	Included	cross-reference
3.2.S.4.4	Batch Analyses	Included	cross-reference
3.2.S.4.5	Justification of Specification	Included	cross-reference
3.2.S.5	Reference Standards or Materials	Included	cross-reference
3.2.S.6	Container Closure Systems	Included	cross-reference
3.2.S.7	Stability	Included	cross-reference
3.2.S.7.1	Stability Summary and Conclusions	Included	cross-reference
3.2.S.7.2	Post-Approval Stability Protocol and Stability Commitment	Included	cross-reference
3.2.S.7.3	Stability Data	Included	cross-reference
3.2.P	Drug Product	Included	cross-reference
3.2.P.1	Description and Composition of the Drug Product	Included	cross-reference
3.2.P.2	Pharmaceutical Development	Included	cross-reference
3.2.P.2.1	Components of the Drug Product	Included	cross-reference
3.2.P.2.2	Formulation Development	Included	cross-reference
3.2.P.2.3	Manufacturing Process Development	Included	cross-reference
3.2.P.2.4	Container Closure System	Included	cross-reference
3.2.P.2.5	Microbiological Attributes	Included	cross-reference
3.2.P.2.6	Compatibility	Included	cross-reference
3.2.P.3	Manufacture	Included	cross-reference

3.2.P.3.1 Manufacturer(s)	Included	cross-reference
3.2.P.3.2 Batch Formula	Included	cross-reference
3.2.P.3.3 Description of Manufacturing Process and Process Controls	Included	cross-reference
3.2.P.3.4 Control of Critical Steps and Intermediates	Included	cross-reference
3.2.P.3.5 Process Validation and/or Evaluation	Included	cross-reference
3.2.P.3.5.1 Transport Validation	Included	cross-reference
3.2.P.3.5.2 Drug Product, Equipment Validation	Included	cross-reference
3.2.P.4 Control of Excipients	Included	cross-reference
3.2.P.4.5 Excipients of Human or Animal Origin	Included	cross-reference
3.2.P.4.6 Novel Excipients	Included	cross-reference
3.2.P.5 Control of Drug Product	Included	cross-reference
3.2.P.5.1 Specification(s)	Included	cross-reference
3.2.P.5.2 Analytical Procedures	Included	cross-reference
3.2.P.5.2.1 Physical State	Included	cross-reference
3.2.P.5.2.2 Extractable Volume	Included	cross-reference
3.2.P.5.2.3 Identity by Capillary Zone Electrophoresis	Included	cross-reference
3.2.P.5.2.4 Visible Particles	Included	cross-reference
3.2.P.5.2.5 Subvisible Particles	Included	cross-reference
3.2.P.5.2.6 Sterility	Included	cross-reference
3.2.P.5.2.7 Bacterial Endotoxins	Included	cross-reference
3.2.P.5.3 Validation of Analytical Procedures	Included	cross-reference
3.2.P.5.3.1 Extractable Volume	Included	cross-reference
3.2.P.5.3.2 Visible Particles	Included	cross-reference
3.2.P.5.3.3 Subvisible Particles	Included	cross-reference
3.2.P.5.3.4 Bacterial Endotoxins	Included	cross-reference
3.2.P.5.3.5 Sterility	Included	cross-reference
3.2.P.5.3.6 Identity by Capillary Zone Electrophoresis	Included	cross-reference
3.2.P.5.3.7 Low Endotoxin Recovery	Included	cross-reference
3.2.P.5.4 Batch Analyses	Included	cross-reference

3.2.P.5.5 Characterization of Impurities	Included	cross-reference
3.2.P.5.6 Justification of Specification(s)	Included	cross-reference
3.2.P.6 Reference Standards of Materials	Included	cross-reference
3.2.P.7 Container Closure System	Included	cross-reference
3.2.P.8 Stability	Included	cross-reference
3.2.P.8.1 Stability Summary and Conclusion	Included	cross-reference
3.2.P.8.2 Post-Approval Stability Protocol and Stability Commitment	Included	cross-reference
3.2.P.8.3 Stability Data	Included	cross-reference
3.2.A Appendices	Included	cross-reference
3.2.A.1 Facilities and Equipment	Included	cross-reference
3.2.A.1.1 Drug Substance	Included	cross-reference
3.2.A.1.2 Drug Product	Included	cross-reference
3.2.A.2 Adventitious Agents Safety Evaluation	Included	cross-reference
3.2.A.2.1 Safety of Materials of Biological Origin	Included	cross-reference
3.2.A.2.2 Safety of Cell Banks	Included	cross-reference
3.2.A.2.3 Testing at Appropriate Stages of Production	Included	cross-reference
3.2.A.2.4 Virus Clearance Studies	Included	cross-reference
3.3 Literature References	Included	cross-reference

Order of submission the RMS and PPMS is to be confirmed ie. BLA #1 or BLA #2

To be determined: "Cross-reference" may refer to M 1.4.4 OR as cross application links and will be applied as recommended.

Module 4: Table of Contents for RMS BLA and PPMS BLA

CTD Section	Title	BLA #1 eg. RMS ¹	BLA #2 eg. PPMS1
4	Nonclinical Study Reports		
4.2	Study Reports		
4.2.1	Pharmacology		
4.2.1.1	Primary Pharmacodynamics		
	Report 03-0387-0349. In Vitro Binding and Activity of Humanized Anti-CD20 2H7. November 2013.	Included	cross-reference
	Report 14-1579. In Vitro Evaluation of Ocrelizumab for Antibody Dependent Cell Mediated Phagocytosis Activity. August 2014.	Included	cross-reference
	Report 06-1069. Fc Gamma Receptor Binding and ADCC Analysis of Ocrelizumab (2H7) Samples Produced from the 2006 Process. September 2006.	Included	cross-reference
	Report 02-182-0352. A Two-Week (Non GLP) Pharmacokinetic and Pharmacodynamic Study of Two Humanized 2H7 Monoclonal Antibodies In Cynomolgus Monkeys with an 8 Week Recovery Period. October 2003.	Included	cross-reference
	Report 03-0235-0349. A Pharmacokinetic and Pharmacodynamic Study of rhuMAb 2H7 in Cynomolgus Monkeys with a 12 Week Recovery Period. October 2003.	Included	cross-reference
4.2.1.2	Secondary Pharmacodynamics		
4.2.1.3	Safety Pharmacology		
4.2.1.4	Pharmacodynamic Drug Interactions		
4.2.2	Pharmacokinetics		
4.2.2.1	Analytical Methods and Validation Reports		
	Validation Report 4.2H7.2.AVR_1. 2H7.002 PRO70769 rhuMAb 2H7 Antigen ELISA. March 2012.	Included	cross-reference
	Validation Report 4.2H7.4.AVR_1. 4.2H7.4 rhuMAb 2H7 Antibody ECLA. January 2012.	Included	cross-reference

	Validation Report 4.2H7.5.AVR_0. 4.2H7.5 rhuMAB 2H7 Antibody ECLA. May 2007.	Included	cross-reference
	Validation Report BA.MET.4.2H7.13.AVR_0: 2H7.013 Anti-2H7 ELISA for Detecting Anti-Therapeutic Antibodies to PRO# (PRO70769). January 2014.	Included	cross-reference
4.2.2.2	Absorption		
	Report 03-0155-0349. Pharmacokinetics of rhuMAB 2H7 in mice. October 2003.	Included	cross-reference
	Report 03-0157-0349. Pharmacokinetics of rhuMAB 2H7 in rats. October 2003.	Included	cross-reference
4.2.2.3	Distribution		
	Report 03-0431-0349. Tissue Distribution of Rituximab and rhuMAB 2H7 (PRO70769) in Normal and Human CD20 Transgenic Mice. March 2004.	Included	cross-reference
	Report 15-0538. PET Biodistribution Imaging of Cu-64 Labeled Anti-CD20 2H7 Variants (v511,v16) in B-cell Depleted Cynos (in progress). June 2015.	Included	cross-reference
	Report 14-3756. Whole-Body Imaging and Radiation Dosimetry in Nonhuman Primates of [111In] Ocrelizumab. June 2015.	Included	cross-reference
4.2.2.4	Metabolism		
4.2.2.5	Excretion		
4.2.2.6	Pharmacokinetics Drug Interactions		
4.2.2.7	Other Pharmacokinetic Studies		
4.2.3	Toxicology		
4.2.3.1	Single-Dose Toxicity		
4.2.3.2	Repeat-Dose Toxicity		
	Report 03-0113-0349. A Toxicity and Toxicokinetic Evaluation of Humanized Anti-CD20 Antibody (rhuMAB 2H7) by Intravenous Administration in Cynomolgus Monkeys. October 2003.	Included	cross-reference
	Report 03-0114-0349. A Toxicity and Toxicokinetic Evaluation of Re-treatment with a Humanized Anti-CD20 Antibody (rhuMAB 2H7) by Intravenous Administration in Cynomolgus Monkeys. July 2004.	Included	cross-reference
	Report 03-0684-0134. A Repeated Dose (x4) Toxicity and Toxicokinetic Evaluation of rhuMAB 2H7 Antibody (PRO70769) by Intravenous Administration in Cynomolgus Monkeys. December 2004.	Included	cross-reference

	Report 04-0192-0134. A Repeat-Dose (Once Every 3 Weeks for 8 Doses) Toxicity and Toxicokinetic Evaluation of rhuMAB 2H7 (PRO70769) by Intravenous Administration in Cynomolgus Monkeys, with a 23-Week Recovery Period. June 2005.	Included	cross-reference
	Report 07-0171. Ocrelizumab (b) (4) vs. (b) (4): A Four-Week Toxicity and PK/PD Comparison by Intravenous Administration in Cynomolgus Monkeys (GLP). September 2007.	Included	cross-reference
4.2.3.3	Genotoxicity		
4.2.3.3.1	in vitro		
4.2.3.3.2	In vivo		
4.2.3.4	Carcinogenicity		
4.2.3.4.1	Long-term Studies		
4.2.3.4.2	Short- or Medium-term Studies		
4.2.3.4.3	Other Studies		
	Cross-reference leaf to Section 5.3.5.4: Summary and assessment of mechanistic considerations, preclinical and clinical data, including an assessment of cancer outcomes from Phase III clinical trials	Included	cross-reference
4.2.3.5	Reproductive and Developmental Toxicity		
4.2.3.5.1	Fertility and Early Embryonic Development		
	Report 12-0524. Ocrelizumab 9-Week Intravenous Administration Male Fertility Study in the Cynomolgus Monkey with a 16 Week Recovery Phase. August 2014.	Included	cross-reference
	Report 12-0525. A Study of the Effect of Ocrelizumab, Administered by Intravenous Injection, on Female Fertility in Cynomolgus Monkeys (Seg I). October 2014.	Included	cross-reference
4.2.3.5.2	Embryo-fetal Development		
	Report 04-1272-1342. An Assessment of the Effects of PRO70769 (rhuMAB 2H7) on Embryo-Fetal Development when Administered Weekly by Intravenous Injection to Pregnant Cynomolgus Monkeys. March 2006.	Included	cross-reference
4.2.3.5.3	Prenatal and Postnatal Development		
	Report 06-1260. An Assessment of the Effects of Ocrelizumab (rhuMAB 2H7) on Pre-and Postnatal Development When Administered Weekly by Intravenous	Included	cross-reference

	Injection to Pregnant Cynomolgus Monkeys. December 2011.		
4.2.3.5.4	Further Juvenile Animal Studies		
4.2.3.6	Local Tolerance		
	Report 05-0025-1466. A Pharmacokinetic, Pharmacodynamic and Local Tolerance Study of rhuMAb 2H7 (PRO70769) Administered by Subcutaneous Injection to Cynomolgus Monkeys as a Single or Divided Dose. July 2006.	Included	cross-reference
4.2.3.7	Other Toxicity Studies		
4.2.3.7.1	Antigenicity		
4.2.3.7.2	Immunotoxicity		
4.2.3.7.3	Mechanistic studies		
4.2.3.7.4	Dependence		
4.2.3.7.5	Metabolites		
4.2.3.7.6	Impurities		
4.2.3.7.7	Other		
	Report 03-0236-0349. Hemolytic Potential and Blood Compatibility of rhuMAb 2H7. September 2003.	Included	cross-reference
	Report 03-0216-0349. Cross-Reactivity of PRO70769 With Human and Cynomolgus Monkey Tissues. September 2003.	Included	cross-reference
4.3	Literature references		
	<i>will be added</i>	Included	cross-reference

Order of submission the RMS and PPMS is to be confirmed ie. BLA #1 or BLA #2

To be determined: "Cross-reference" may refer to M 1.4.4 OR as cross application links and will be applied as recommended.

Module 5: Table of Contents for RMS BLA and PPMS BLA

CTD Section	Title	BLA #1 eg. RMS ¹	BLA #2 eg. PPMS1
5	Clinical Study Reports		
5.2	Tabular listing		
	Tabular listing of all Clinical studies	included	cross-reference
5.3	Clinical Study Reports and Related Info		
5.3.1	Reports of Biopharmaceutic Studies		
5.3.1.1	Bioavailability (BA) Study Reports		
5.3.1.2	Comparative BA and Bioequivalence (BE) Study Reports		
5.3.1.3	In vitro - In vivo Correlation Study Reports		
5.3.1.4	Reports of Bioanalytical and Analytical Methods for Human Studies		
	Assay Validation Report, 4.2H7.2 PRO70769 rhuMAb 2H7 Antigen ELISA (Genentech Study No. 4.2H7.2.AVR), Report 1035235, December 3, 2007	Included	cross-reference
	Assay Validation Report 4.2H7.4 rhuMAb 2H7 Antibody ECLA (Genentech Study No. 4.2H7.4.AVR_0), Report 1035236, September 18, 2006	Included	cross-reference
	Assay Validation Report 4.2H7.12 PRO70769 rhuMAb 2H7 Human Serum ATA DIG ELISA (Genentech Study No. BA.MET.4.2H7.12.AVR_0), September 13, 2010	Included	cross-reference
	Assay Validation Report 2H7.014.AVR_0 - Cell-based Assay to Detect Anti-Ocrelizumab Neutralizing Antibodies in Human Serum, September 8, 2015	Included	cross-reference
	WA21493 ADA Bioanalytical Report (Phase II, multicenter, randomized, parallel-group, partially blinded, placebo and Avonex® controlled dose finding study to evaluate the efficacy as measured by brain MRI lesions, and safety of 2 dose regimens of ocrelizumab in patients with RRMS), Report number WA21493_ATA_BAR_0, 25 November 2014	Included	cross-reference
	WA21493 ADA Bioanalytical Report_Interim Bioanalytical Report, Analysis of Samples using an enzyme linked immunosorbent Assay (ELISA) for the detection of anti-ocrelizumab antibodies in Human Serum, (Phase II, multicenter, randomized, parallel-group, partially blinded, placebo and Avonex® controlled dose finding study to evaluate the efficacy as measured by brain MRI lesions, and safety of 2 dose regimens of ocrelizumab in patients with RRMS), 02 July 2015	Included	cross-reference

	WA21493 PK Bioanalytical Report (Phase II, multicenter, randomized, parallel-group, partially blinded, placebo and Avonex® controlled dose finding study to evaluate the efficacy as measured by brain MRI lesions, and safety of 2 dose regimens of ocrelizumab in patients with RRMS), Report number WA21493_PK_BAR_1, 17 October 2014	Included	cross-reference
	WA21493 PK Bioanalytical Report (Phase II, multicenter, randomized, parallel-group, partially blinded, placebo and Avonex® controlled dose finding study to evaluate the efficacy as measured by brain MRI lesions, and safety of 2 dose regimens of ocrelizumab in patients with RRMS)	Included	cross-reference
	WA21092 ADA BAR report,(Randomized, double-blind, double-dummy, parallel-group study to evaluate the efficacy and safety of ocrelizumab in comparison to interferon (Rebif) in patients with relapsing multiple sclerosis)	included	N/A
	WA21092 PK BAR report, (Randomized, double-blind, double-dummy, parallel-group study to evaluate the efficacy and safety of ocrelizumab in comparison to interferon (Rebif) in patients with relapsing multiple sclerosis)	included	N/A
	WA21092 Nab BAR report, (Randomized, double-blind, double-dummy, parallel-group study to evaluate the efficacy and safety of ocrelizumab in comparison to interferon (Rebif) in patients with relapsing multiple sclerosis)	included	N/A
	WA21093 ADA BAR report, (Randomized, double-blind, double-dummy, parallel-group study to evaluate the efficacy and safety of ocrelizumab in comparison to interferon (Rebif) in patients with relapsing multiple sclerosis)	included	N/A
	WA21093 PK BAR report, (Randomized, double-blind, double-dummy, parallel-group study to evaluate the efficacy and safety of ocrelizumab in comparison to interferon (Rebif) in patients with relapsing multiple sclerosis)	included	N/A
	WA21093 Nab BAR report, (Randomized, double-blind, double-dummy, parallel-group study to evaluate the efficacy and safety of ocrelizumab in comparison to interferon (Rebif) in patients with relapsing multiple sclerosis)	included	N/A
	WA25046 ADA BAR report, (A Phase III, multicentre, randomized, parallel-group, double blinded, placebo controlled study to evaluate the efficacy and safety of ocrelizumab in adults with Primary Progressive Multiple Sclerosis)	N/A	included
	WA25046 PK BAR report, (A Phase III, multicentre, randomized, parallel-group, double blinded, placebo controlled study to evaluate the efficacy and safety of ocrelizumab in adults with Primary Progressive Multiple Sclerosis)	N/A	included

	WA25046 Nab BAR report, (A Phase III, multicentre, randomized, parallel-group, double blinded, placebo controlled study to evaluate the efficacy and safety of ocrelizumab in adults with Primary Progressive Multiple Sclerosis)	N/A	included
	ACT2847g ADA Bioanalytical Report, (A randomized, placebo-controlled, multicenter, blinded Phase I/II study of the safety of escalating doses of ocrelizumab (PRO70769) in subjects with moderate to severe rheumatoid arthritis receiving stable doses of concomitant methotrexate), Report ACT2847g_ATA_BAR_0, 11 November 2014	Included	cross-reference
	ACT2847g PK Bioanalytical Report, (A randomized, placebo-controlled, multicenter, blinded Phase I/II study of the safety of escalating doses of ocrelizumab (PRO70769) in subjects with moderate to severe rheumatoid arthritis receiving stable doses of concomitant methotrexate), Report ACT2847g_BAR_PK_0, 8 March 2011	Included	cross-reference
	WA18230 ADA Bioanalytical Report, (A randomized placebo-controlled, multicenter, Phase I/II study of the safety of escalating single intravenous doses of ocrelizumab (rhuMAb 2H7, RO4964913, PRO70769) in patients with moderate to severe rheumatoid arthritis receiving stable doses of concomitant methotrexate but with unsatisfactory clinical response), Report WA18230_ATA_BAR_1, 27 October 2014	Included	cross-reference
	WA18230 PK Bioanalytical Report , (A randomized placebo-controlled, multicenter, Phase I/II study of the safety of escalating single intravenous doses of ocrelizumab (rhuMAb 2H7, RO4964913, PRO70769) in patients with moderate to severe rheumatoid arthritis receiving stable doses of concomitant methotrexate but with unsatisfactory clinical response), Report WA18230_PK_BAR_1, 24 March 2015	Included	cross-reference
	WA20494 ADA Bioanalytical Report, (A randomized, double-blind, parallel group, international study to evaluate the safety and efficacy of ocrelizumab compared to placebo in patients with active rheumatoid arthritis continuing methotrexate treatment), Report WA20494_ATA_BAR_0),12 September 2014	Included	cross-reference
	WA20494 ADA Bioanalytical Report, (A randomized, double-blind, parallel group, international study to evaluate the safety and efficacy of ocrelizumab compared to placebo in patients with active rheumatoid arthritis continuing methotrexate treatment), Report TNJR09-208, 09 November 2011	Included	cross-reference

	WA20494 PK Bioanalytical Report, (A randomized, double-blind, parallel group, international study to evaluate the safety and efficacy of ocrelizumab compared to placebo in patients with active rheumatoid arthritis continuing methotrexate treatment), TNJR07-249, 29 November 2010	Included	cross-reference
	WA20495 ADA Bioanalytical Report, (A randomized, double-blind, parallel group, international study to evaluate the safety and efficacy of ocrelizumab compared to placebo in patients with active rheumatoid arthritis who have an inadequate response to at least one anti-TNF- α therapy.), Report WA20495_ATA_BAR_0 , 12 September 2014	Included	cross-reference
	WA20495 ADA Bioanalytical Report, (A randomized, double-blind, parallel group, international study to evaluate the safety and efficacy of ocrelizumab compared to placebo in patients with active rheumatoid arthritis who have an inadequate response to at least one anti-TNF- α therapy), Report TNJS09-209 , 21 November 2011	Included	cross-reference
	WA20495 PK Bioanalytical Report, (A randomized, double-blind, parallel group, international study to evaluate the safety and efficacy of ocrelizumab compared to placebo in patients with active rheumatoid arthritis who have an inadequate response to at least one anti-TNF- α therapy), Report TNJR07-250 , 29 November 2010	Included	cross-reference
	WA20496 ADA Bioanalytical Report, (A Randomized, Double-Blind, Parallel-Group, International Study to Evaluate the Safety and Efficacy of Ocrelizumab Given as a Single Infusion or Dual Infusion Compared with Placebo in Patients with Active Rheumatoid Arthritis Who Have an Inadequate Response to Methotrexate Therapy), Report WA20496_ATA_BAR_0, 3 October 2014	Included	cross-reference
	WA20496 ADA Bioanalytical Report , (A Randomized, Double-Blind, Parallel-Group, International Study to Evaluate the Safety and Efficacy of Ocrelizumab Given as a Single Infusion or Dual Infusion Compared with Placebo in Patients with Active Rheumatoid Arthritis Who Have an Inadequate Response to Methotrexate Therapy), Report TNJS09-211, 21 November 2011	Included	cross-reference
	WA20496 PK Bioanalytical Report, (A Randomized, Double-Blind, Parallel-Group, International Study to Evaluate the Safety and Efficacy of Ocrelizumab Given as a Single Infusion or Dual Infusion Compared with Placebo in Patients with Active Rheumatoid Arthritis Who Have an Inadequate Response to Methotrexate Therapy), Report TNJS08-039, 29 November 2010	Included	cross-reference

	WA20497 ADA Bioanalytical Report, (A randomized, double-blind, parallel group, international study to evaluate the safety and efficacy of ocrelizumab in combination with methotrexate (MTX) compared to MTX alone in methotrexate naïve patients with active rheumatoid arthritis), WA20497_ATA_BAR_0, 03 October 2014	Included	cross-reference
	WA20497 ADA Bioanalytical Report , (A randomized, double-blind, parallel group, international study to evaluate the safety and efficacy of ocrelizumab in combination with methotrexate (MTX) compared to MTX alone in methotrexate naïve patients with active rheumatoid arthritis), Report TNJS09-207, 10 November 2011	Included	cross-reference
	WA20497 PK Bioanalytical Report , (A randomized, double-blind, parallel group, international study to evaluate the safety and efficacy of ocrelizumab in combination with methotrexate (MTX) compared to MTX alone in methotrexate naïve patients with active rheumatoid arthritis.),Report TNJR07-251, 29 November 2010	Included	cross-reference
	JA21963 ADA BAR report, Detection Confirmation and Titration of Antibodies to rhuMAb in Human Serum by an Enzyme-Linked Immunosorbent Assay (ELISA) in Support of Chugai Pharmaceutical Co., Ltd. Protocol Number JA21963, ReportTNJR09-027, 31 May 2012	Included	cross-reference
	JA21963 PK BAR report , Quantitation of rhuMAb 2H7 in Human Serum n support of Chugai Pharmaeutical Co.,Ltd. Protocol Number JA21963, Report TNJR9-026, 01 June 2012	Included	cross-reference
	JA22003 ADA BAR report, Detection, Confirmation and Titration of Antibodies to rhuMAb 2H7 in Human Serum by an Enzyme-Linked Immunosorben Assay (ELISA) in Support of Chugai Pharmaceutical Co., Ltd. Protocol Number JA22003 , Report TNJR09-097, 02 November 2011	Included	cross-reference
	JA22003 PK BAR report , Quantitation of rhuMAb 2H7 in Human Serum in support of Chugai Pharmaeutical Co.,Ltd. Protocol Number JA22003, Report TNJR09-096 ,19 April 2012	Included	cross-reference
	WA20499 ADA Bioanalytical Report– A randomised, double-blind, placebo controlled, parallel-group, multicenter study to evaluate the efficacy and safety of two doses of ocrelizumab in patients with active systemic lupus erythematosus _TNJS09-269- 05 August 2010	Included	cross-reference

	WA20499 PK Bioanalytical Report– A randomised, double-blind, placebo controlled, parallel-group, multicenter study to evaluate the efficacy and safety of two doses of ocrelizumab in patients with active systemic lupus erythematosus _TNJR08-037- 17 October 2011	Included	cross-reference
	WA20500 ADA Bioanalytical Report , (A randomized, double-blind, placebo controlled, parallel group, multicenter study to evaluate the efficacy and safety of two doses of ocrelizumab in patients with WHO or ISN Class III or IV nephritis due to systemic lupus erythematosus), TNJR09-210), 02 November 2011	Included	cross-reference
	WA20500 PK Bioanalytical Report, (A randomized, double-blind, placebo controlled, parallel group, multicenter study to evaluate the efficacy and safety of two doses of ocrelizumab in patients with WHO or ISN Class III or IV nephritis due to systemic lupus erythematosus), Report TNJR08-038, 20 October 2011	Included	cross-reference
	BO18414 ADA Bioanalytical Report, (An open-label, multicentre, dose-escalating phase I/II trial of 3-weekly ocrelizumab in patients with follicular non-Hodgkin's lymphoma), Report BO18414_ATA_BAR_0 , 4 December 2014	Included	cross-reference
	BO18414 PK Bioanalytical Report , (An open-label, multicentre, dose-escalating phase I/II trial of 3-weekly ocrelizumab in patients with follicular non-Hodgkin's lymphoma), Report BO18414_PK_BAR_0, 17 March 2015	Included	cross-reference
5.3.2	Reports of Studies Pertinent to Pharmacokinetics using Human Biomaterials		
5.3.2.1	Plasma Protein Binding Study Reports		
5.3.2.2	Reports of Hepatic Metabolism and Drug Interaction Studies		
5.3.2.3	Reports of Studies using Other Human Biomaterials		
	Non-Clinical overview (section 2.4)	<i>Cross-reference leaf to 2.4</i>	cross-reference
5.3.3	Reports of Human Pharmacokinetic (PK) Studies		
5.3.3.1	Healthy Subject PK and Initial Tolerability Study Reports		
5.3.3.2	Patient PK and Initial Tolerability Study Reports		

	Cross-reference to the following report (from 5.3.5.4 section) WA18230 Clinical Study Report – A randomized placebo-controlled, multicenter, Phase I/II study of the safety of escalating single intravenous doses of ocrelizumab (rhuMAb 2H7, RO4964913, PRO70769) in patients with moderate to severe rheumatoid arthritis receiving stable doses of concomitant methotrexate but with unsatisfactory clinical response. Interim Report. Report no. 1029664, February 2009.	Included	cross-reference
	Cross-reference to the following report (from 5.3.5.4 section) ACT2847g Clinical Study Report - A randomized, placebo-controlled, multicenter, blinded Phase I/II study of the safety of escalating doses of ocrelizumab (PRO70769) in subjects with moderate to severe rheumatoid arthritis receiving stable doses of concomitant methotrexate. Report No. 1059784 February 2008.	Included	cross-reference
5.3.3.3	Intrinsic Factors PK Study Reports		
5.3.3.4	Extrinsic Factors PK Study Reports		
5.3.3.5	Population PK Study Reports		
	Development of a population pharmacokinetic model for ocrelizumab in patients with relapsing-remitting multiple sclerosis. March 2 2010	included	cross-reference
	WA21092 and WA21093 - Population Pharmacokinetic Report RMS	included	N/A
	Population PK analysis and graphical exposure-safety and efficacy analyses of WA20494, WA20495 and WA20496. ICON 165/118. Version 3.0. 11 May 2011.	included	N/A
	WA25046 Population Pharmacokinetic Report PPMS	N/A	included
5.3.4	Reports of human pharmacodynamic (PD) studies		
5.3.4.1	Healthy Subject PD and PK-PD Study Reports		
5.3.4.2	Patient PD and PK-PD Study Reports		
	Cross-reference leaf to the following report (from 5.3.5.4 section) WA18230 Clinical Study Report – A randomized placebo-controlled, multicenter, Phase I/II study of the safety of escalating single intravenous doses of ocrelizumab (rhuMAb 2H7, RO4964913, PRO70769) in patients with moderate to severe rheumatoid arthritis receiving stable doses of concomitant methotrexate but with unsatisfactory clinical response. Interim Report. Report no. 1029664, February 2009.>	cross-reference leaf to ACT2847g	cross-reference leaf to ACT2847g

	Cross-reference leaf to the following report (from 5.3.5.4 section) <ACT2847g Clinical Study Report - A randomized, placebo-controlled, multicenter, blinded Phase I/II study of the safety of escalating doses of ocrelizumab (PRO70769) in subjects with moderate to severe rheumatoid arthritis receiving stable doses of concomitant methotrexate. Report No. 1059784 February 2008.	cross-reference leaf to ACT2847g	cross-reference leaf to ACT2847g
5.3.5	Reports of Efficacy and Safety Studies		
5.3.5.1	Reports of Controlled Clinical Studies Pertinent to the Claimed Indication		
	WA21493 Clinical Study Report - Phase II, multicenter, randomized, parallel-group, partially blinded, placebo and Avonex® controlled dose finding study to evaluate the efficacy as measured by brain MRI lesions, and safety of 2 dose regimens of ocrelizumab in patients with RRMS. Report No. 1034917, November 2012.	Included	cross-reference
	WA21493 Update Clinical Study Report - Phase II, multicenter, randomized, parallel-group, partially blinded, placebo and Avonex controlled dose finding study to evaluate the efficacy as measured by brain MRI lesions, and safety of 2 dose regimens of ocrelizumab in patients with RRMS (Open Label Extension Phase)	Included	cross-reference
	WA21493 Addendum Clinical study Report - Phase II, multicenter, randomized, parallel-group, partially blinded, placebo and Avonex controlled dose finding study to evaluate the efficacy as measured by brain MRI lesions, and safety of 2 dose regimens of ocrelizumab in patients with RRMS	Included	cross-reference
	WA21493 Patient Profiles	Included	cross-reference
	WA21493 Case Report Forms	Included	cross-reference
	WA21092 Primary Clinical Study Report - Randomized, double-blind, double-dummy, parallel-group study to evaluate the efficacy and safety of ocrelizumab in comparison to interferon (Rebif) in patients with relapsing multiple sclerosis	included	N/A
	WA21092 Patient Profiles	included	N/A
	WA21092 Case Report Forms		N/A
	WA21093 Primary Clinical Study Report - Randomized, double-blind, double-dummy, parallel-group study to evaluate the efficacy and safety of ocrelizumab in comparison to interferon (Rebif) in patients with relapsing multiple sclerosis	included	N/A
	WA21093 Patient Profiles	included	N/A
	WA21093 Case Report Forms	included	N/A

	WA25046 Primary Clinical Study Report – Multicentre, randomized, parallel group, double blinded, placebo controlled study to evaluate the efficacy and safety of ocrelizumab in adults with primary progressive multiple sclerosis	N/A	included
	WA25046 patient profiles	N/A	included
	WA25046 Case Report Forms		
5.3.5.2	Study Reports of Uncontrolled Clinical Studies		
5.3.5.3	Reports of Analyses of Data from More than One Study		
	ISS		
	RMS and PPMS Integrated Summary of Safety	Included	cross-reference
	ISE : not applicable		
	Integrated Summary of Efficacy	cross-reference leaf to Module 2: Summary of Clinical Efficacy –	cross-reference leaf to Module 2: Summary of Clinical Efficacy –
	Other reports		
	WA21092 and WA21093 Primary Pooled Efficacy Clinical Study Report - Randomized, double-blind, double-dummy, parallel-group studies to evaluate the efficacy and safety of ocrelizumab in comparison to interferon (Rebif) in patients with relapsing multiple sclerosis	included	N/A
	A summary of the process and analyses for identifying and reporting relapse events from the Phase III clinical studies WA21092 and WA21093	included	N/A
	Comparison of safety results from ocrelizumab and Real World Data from Clinical Trials Studies WA21092 and WA21093	included	N/A
	Safety update for serious adverse events in non-multiple sclerosis indications based on spontaneous reports (update on SAEs/death that were not in the non-MS CSRs but reported after DBL).	included	cross-reference
	Summary of pregnancy cases reported in clinical trials with ocrelizumab	included	cross-reference
	Integrated risk assessment for malignancy: risk assessment of mechanistic considerations, preclinical and clinical data, including an assessment of cancer outcomes from Phase III clinical trials	included	cross-reference
5.3.5.4	Other study reports		

	Bioresearch Monitoring Clinical Data – RMS Investigator List (Studies WA21092, WA21093 and Study WA21493)	Included	N/A
	Bioresearch Monitoring Clinical Data – PPMS Investigator List (Study WA25046)	N/A	Included
	Independent Data Monitoring Committee (IDMC) for RMS and PPMS studies: List of IDMC meetings, IDMC meeting presentations, Open/Closed Meeting Minutes and IDMC recommendations, Open/Closed Reports produced by IDCC	Included	cross-reference
	ACT2847g Clinical Study Report - A randomized, placebo-controlled, multicenter, blinded Phase I/II study of the safety of escalating doses of ocrelizumab (PRO70769) in subjects with moderate to severe rheumatoid arthritis receiving stable doses of concomitant methotrexate. Report No. 1059784 February 2008.	Included	cross-reference
	ACT2847g additional narratives (safety - non safety) (narratives not included in CSRs)	included	cross-reference
	ACT2847g patient profiles	included	cross-reference
	ACT2847g Case Report Forms	included	cross-reference
	ACT4562g Clinical Study Report – A Phase II, randomized, double-blind, parallel-group study to evaluate the efficacy and safety of ocrelizumab in combination with methotrexate compared with infliximab plus methotrexate in patients with active rheumatoid arthritis currently responding inadequately to etanercept or adalimumab. Report No. 1048133. August 2012.	included	cross-reference
	ACT4562g Final Clinical Study Report – A phase II, randomized, double-blind, parallel-group study to evaluate the efficacy and safety of ocrelizumab in combination with methotrexate compared with infliximab plus methotrexate in patients with active rheumatoid arthritis currently responding inadequately to etanercept or adalimumab. Report No. 1054693. February 2013.	included	cross-reference
	ACT4562g additional narratives (safety - non safety) (narratives not included in CSRs)	included	cross-reference
	ACT4562g patient profiles	included	cross-reference
	ACT4562g Case Report Forms	included	cross-reference
	WA18230 Clinical Study Report – A randomized placebo-controlled, multicenter, Phase I/II study of the safety of escalating single intravenous doses of ocrelizumab (rhuMAb 2H7, RO4964913, PRO70769) in patients with moderate to severe rheumatoid arthritis receiving stable doses of concomitant methotrexate but with unsatisfactory clinical response. Interim Report. Report no. 1029664, February 2009.	included	cross-reference

	WA18230 Clinical Study Report – A randomized placebo-controlled, multicenter, Phase I/II study of the safety of escalating single intravenous doses of ocrelizumab (rhuMAb 2H7, RO4964913, PRO70769) in patients with moderate to severe rheumatoid arthritis receiving stable doses of concomitant methotrexate but with unsatisfactory clinical response. Interim Report. Report no. 1037662 / September 2010. [Update CSR: results up to 104 weeks]	included	cross-reference
	WA18230 Clinical Study Report – A randomized placebo-controlled, multicenter, Phase I/II study of the safety of escalating single intravenous doses of ocrelizumab (rhuMAb 2H7, RO4964913, PRO70769) in patients with moderate to severe rheumatoid arthritis receiving stable doses of concomitant methotrexate but with unsatisfactory clinical response. Report No. 1047412, June 2012. [Update CSR: safety data for 72 weeks of follow-up after last infusion]	included	cross-reference
	WA18230 Final Clinical Study Report - A randomized placebo-controlled, multicenter, Phase I/II study of the safety of escalating single intravenous doses of ocrelizumab (rhuMAb 2H7, RO4964913, PRO70769) in patients with moderate to severe rheumatoid arthritis receiving stable doses of concomitant methotrexate but with unsatisfactory clinical response. Report No. 1055105, May 2013. [Final CSR: safety data to last patient last visit]	included	cross-reference
	WA18230 Addendum Clinical Study Report – A randomized placebo-controlled, multicenter, Phase I/II study of the safety of escalating single intravenous doses of ocrelizumab (rhuMAb 2H7, RO4964913, PRO70769) in patients with moderate to severe rheumatoid arthritis receiving stable doses of concomitant methotrexate but with unsatisfactory clinical response. Report No. 1060283, April 2015.	included	cross-reference
	WA18230 additional narratives (safety - non safety) (narratives not included in CSRs)	included	cross-reference
	WA18230 patient profiles	included	cross-reference
	WA18230 case report forms	included	cross-reference
	WA20494 Clinical Study Report - A randomized, double-blind, parallel group, international study to evaluate the safety and efficacy of ocrelizumab compared to placebo in patients with active rheumatoid arthritis continuing methotrexate treatment. Report No. 1035307, September 2010. This clinical study report covers the double-blinded treatment phase of the study (Day 1 to Week 48). [Primary CSR]	included	cross-reference
	WA20494 additional narratives (safety - non safety) (narratives not included in CSRs)	included	cross-reference

	WA20494 patient profiles	included	cross-reference
	WA20494 case report forms	included	cross-reference
	WA20495 Clinical Study Report – A randomized, double-blind, parallel group, international study to evaluate the safety and efficacy of ocrelizumab compared to placebo in patients with active rheumatoid arthritis who have an inadequate response to at least one anti-TNF- α therapy. Research Report 1037893. December 2010. This clinical study report covers the double-blinded treatment phase of the study (Day 1 to Week 48). [Primary CSR]	included	cross-reference
	WA20495 additional narratives (safety - non safety) (narratives not included in CSRs)	included	cross-reference
	WA20495 patient profiles	included	cross-reference
	WA20495 case report forms	included	cross-reference
	WA20496 Clinical Study Report – A Randomized, Double-Blind, Parallel-Group, International Study to Evaluate the Safety and Efficacy of Ocrelizumab Given as a Single Infusion or Dual Infusion Compared with Placebo in Patients with Active Rheumatoid Arthritis Who Have an Inadequate Response to Methotrexate Therapy / Report No. 1035248. [Primary CSR: 24-week double-blind period]	included	cross-reference
	WA20496 additional narratives (safety - non safety) (narratives not included in CSRs)	included	cross-reference
	WA20496 patient profiles	included	cross-reference
	WA20496 case report forms	included	cross-reference
	WA20497 Clinical Study Report – A randomized, double-blind, parallel group, international study to evaluate the safety and efficacy of ocrelizumab in combination with methotrexate (MTX) compared to MTX alone in methotrexate naïve patients with active rheumatoid arthritis. Report No. 1035249, September 2010. [Primary CSR: 52-week double-blind period]	included	cross-reference
	WA20497 additional narratives (safety - non safety) (narratives not included in CSRs)	included	cross-reference
	WA20497 patient profiles	included	cross-reference
	WA20497 case report forms	included	cross-reference

	WA20494, WA20495, WA20496, WA20497 Clinical Study Report – Four randomized, double-blind, parallel group, international studies to evaluate the safety of ocrelizumab compared to placebo in patients with active rheumatoid arthritis continuing methotrexate treatment.– Report No. 1045332, April 2012. [Update CSR: safety data for 72 weeks of follow-up after last infusion]	included	cross-reference
	WA20494, WA20495, WA20496, WA20497 Clinical Study Report — Four randomized, double-blind, parallel group, international studies to evaluate the safety of ocrelizumab compared to placebo in patients with active rheumatoid arthritis continuing methotrexate treatment.– Report No. 1058114, December 2013. [Update CSR: safety data follow-up to last patient last visit]	included	cross-reference
	WA20494, WA20495, WA20496, WA20497 – Four randomized, double-blind, parallel group, international studies to evaluate the safety of ocrelizumab compared to placebo in patients with active rheumatoid arthritis continuing methotrexate treatment. Report No. 1059619, June 2015. Addendum CSR	included	cross-reference
	JA21963 Clinical Study Report (Japanese study translated in English) — Dose-response study of ocrelizumab for rheumatoid arthritis - 13 January 2011	included	cross-reference
	Clinical Study Report of JA21963* and JA22003**, May 2 2014 *Dose-response study of ocrelizumab for rheumatoid arthritis ** Long term study of ocrelizumab for rheumatoid arthritis (Open label extension study to JA21963)) - May 2,2014	included	cross-reference
	JA21963/JA22003 additional narratives (safety - non safety) (narratives not included in CSRs)	included	cross-reference
	JA21963/JA22003 patient profiles	included	cross-reference
	JA21963/JA22003 case report forms		
	WA20499/ACT4071g Clinical Study Report — A randomised, double-blind, placebo controlled, parallel-group, multicenter study to evaluate the efficacy and safety of two doses of ocrelizumab in patients with active systemic lupus erythematosus – Research Report No. 1037328. June 2010. [Abbreviated CSR: safety data to Week 20]	included	cross-reference
	WA20499/ACT4071g Clinical Study Report (Safety Update Addendum)– – A randomized, double-blind, placebo controlled, parallel-group, multicenter study to evaluate the efficacy and safety of two doses of ocrelizumab in patients with active systemic lupus erythematosus – Research Report No. 1048322. May 2012. [Final CSR: safety data follow-up to last patient last observation]	included	cross-reference

	WA20499 additional narratives (safety - non safety) (narratives not included in CSRs)	included	cross-reference
	WA20499 patient profiles	included	cross-reference
	WA20499 case report forms	included	cross-reference
	WA20500 Clinical Study Report — A randomized, double-blind, placebo controlled, parallel group, multicenter study to evaluate the efficacy and safety of two doses of ocrelizumab in patients with WHO or ISN Class III or IV nephritis due to systemic lupus erythematosus – Report No. 1044373 – October 2011. [Primary CSR: up to Week 48]	included	cross-reference
	WA20500/ACT4072g (BELONG) Clinical Study Report — A Randomised, double-blind, placebo controlled, parallel-group, multicenter study to evaluate the efficacy and safety of two doses of ocrelizumab in patients with WHO or ISN Class III or IV nephritis due To systemic lupus erythematosus – Report No. 1058167, January 2014. [Final CSR: safety data follow-up to last patient last visit]	included	cross-reference
	WA20500/ACT4072g (BELONG) – A Randomised, Double-Blind, Placebo Controlled, Parallel-Group, Multicenter Study To Evaluate The Efficacy and Safety of Two Doses of Ocrelizumab in Patients With WHO or ISN Class III or IV Nephritis Due To Systemic Lupus Erythematosus – Report No. 1060284, February 2015.	included	cross-reference
	WA20500 additional narratives (safety - non safety) (narratives not included in CSRs)	included	cross-reference
	WA20500 patient profiles	included	cross-reference
	WA20500 case report forms	included	cross-reference
	BO18414 Clinical Study Report — An open-label, multicentre, dose-escalating phase I/II trial of 3-weekly ocrelizumab in patients with follicular non-Hodgkin's lymphoma. Roche Report No 1023122; December 2008.	included	cross-reference
	BO18414 additional narratives (safety - non safety) (narratives not included in CSRs)	included	cross-reference
	BO18414 Patient profiles	included	cross-reference
	BO18414 case report forms	included	cross-reference
5.4	Literature references		
	All provided references	included	cross-reference

Order of submission the RMS and PPMS is to be confirmed ie. BLA #1 or BLA #2

To be determined: "Cross-reference" may refer to M 1.4.4 OR as cross application links and will be applied as recommended.

Appendix 3

Time to Event example

Confirmed Disability Progression (12 Weeks)

	IFN beta-1a (N=411)	OCR 600mg (N=410)
Time Point Analysis		
12 Weeks		
Patients at risk	385	384
Event rate (%)	2.01	2.02
95% CI	(0.63, 3.39)	(0.63, 3.40)
24 Weeks		
Patients at risk	360	375
Event rate (%)	5.12	3.05
95% CI	(2.93, 7.31)	(1.35, 4.75)
36 Weeks		
Patients at risk	349	365
Event rate (%)	6.46	4.87
95% CI	(4.01, 8.90)	(2.73, 7.00)
48 Weeks		
Patients at risk	335	361
Event rate (%)	8.08	5.65
95% CI	(5.35, 10.81)	(3.36, 7.94)

MRI Lesion Count example

	IFN beta-1a (N=411)	OCR 600mg (N=410)
WEEK 24		
n	372	382
Mean (SD)	0.28 (1.10)	0.03 (0.23)
Median	0.00	0.00
Min - Max	0.0 - 12.0	0.0 - 3.0
Number of Lesions		
0	325 (87.4%)	373 (97.6%)
1	25 (6.7%)	7 (1.8%)
2	11 (3.0%)	1 (0.3%)
3	4 (1.1%)	1 (0.3%)
>3	7 (1.9%)	0
WEEK 48		
n	357	377
Mean (SD)	0.23 (0.82)	0.01 (0.07)
Median	0.00	0.00
Min - Max	0.0 - 5.0	0.0 - 1.0
Number of Lesions		
0	318 (89.1%)	375 (99.5%)
1	23 (6.4%)	2 (0.5%)
2	3 (0.8%)	0
3	4 (1.1%)	0
>3	9 (2.5%)	0

DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

As stated in our October 22, 2015, communication granting this meeting, if, at the time of submission, the application that is the subject of this meeting is for a new molecular entity or an original biologic, the application will be subject to “the Program” under PDUFA V. Therefore, at this meeting be prepared to discuss and reach agreement with FDA on the content of a complete application, including preliminary discussions on the need for risk evaluation and mitigation strategies (REMS) or other risk management actions. You and FDA may also reach agreement on submission of a limited number of minor application components to be submitted not later than 30 days after the submission of the original application. These submissions must be of a type that would not be expected to materially impact the ability of the review team to begin its review. All major components of the application are expected to be included in the original application and are not subject to agreement for late submission.

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

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

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

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

PREA REQUIREMENTS

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

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

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

PRESCRIBING INFORMATION

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

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

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

ABUSE POTENTIAL ASSESSMENT

Drugs that affect the central nervous system, are chemically or pharmacologically similar to other drugs with known abuse potential, or produce psychoactive effects such as mood or cognitive changes (e.g., euphoria, hallucinations) need to be evaluated for their abuse potential and a proposal for scheduling will be required at the time of the NDA submission [21 CFR 314.50(d)(5)(vii)]. For information on the abuse potential evaluation and information required at the time of your NDA submission, see the draft guidance for industry, *Guidance for Industry Assessment of Abuse Potential of Drugs*, available at: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM198650.pdf>.

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.				

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/s/

REBECCA N LOPEZ
12/04/2015

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/s/

ERIC P BASTINGS
01/05/2016



IND 100593

MEETING MINUTES

Genentech, Inc.
Mr. Kieran O'Donoghue
Associate Regulatory Program Director
1 DNA Way
South San Francisco, California 94080-4990

Dear Mr. O'Donoghue:

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

We also refer to the meeting between representatives of your firm and the FDA on September 10, 2014. The purpose of the meeting was to discuss and obtain agreement with the Agency on the following: (1) Mechanism(s) of action (MOAs) and potency. (2) Assessment of critical quality attributes (CQAs), (3) Cell banking (4) A strategy to establish the Drug Product shelf life.

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

If you have any questions, contact me.

Sincerely,

{See appended electronic signature page}

Marjorie Shapiro, Ph.D.
Chief, Laboratory of Molecular and
Developmental Immunology
Division of Monoclonal Antibodies
Office of Biotechnology Products
Office of Pharmaceutical Science
Center for Drug Evaluation and Research

Enclosure: Meeting Minutes



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type: Type C
Meeting Category: CMC Only

Meeting Date and Time: September 10, 2014 1:30 PM
Meeting Format: Teleconference

Application Number: 100593
Product Name: ocrelizumab
Sponsor/Applicant Name: Genentech, Inc.

Meeting Chair: Marjorie Shapiro, Ph.D.
Meeting Recorders: Andrew Shiber, Pharm.D.

FDA ATTENDEES:

Center for Drug Evaluation and Research

Office of Biotechnology Products (OBP)

Marjorie Shapiro, Ph.D. Team Leader, Division of Monoclonal Antibodies (DMA)
Sean Fitzsimmons, Ph.D. Product Quality, DMA

SPONSOR ATTENDEES

Damian Cunningham, Ph.D.	Technical Development Leader, Pharma Technical Development
Kathy Francissen, Ph.D.	Senior Director, Pharma Technical Regulatory
Dan Hewitt, M.S.	Technical Development Scientist, Analytical Development, Pharma Technical Development
Basim Hilal	Senior Regulatory Program Director, Pharma Technical Regulatory
Kim Latimer	Senior Product Specialist, Pharma Technical Quality
Lori McCaig, Ph.D.	Associate Director, Stability Program Management
Melissa Mun, M.S.	Senior Engineer, Late Stage Cell Culture, Pharma Technical Development
Kieran O'Donoghue	Associate Regulatory Program Director, Pharma Technical Regulatory

Nicole Piros	Regulatory Program Manager, Pharma Technical Regulatory
Melody Trexler Schmidt, Ph.D.	Technical Development Senior Scientist, Purification Development, Pharma Technical Development
Max Tejada	Quality Control Senior Scientist, Analytical Development and Quality Control, Pharma Technical Development
Rita Wong	Technical Development Leader, Pharma Technical Development
Taylor Yonghua Zhang, Ph.D.	Technical Development Senior Scientist, Analytical Development, Pharma Technical Development

1.0 BACKGROUND

Name of drug: ocrelizumab

Objectives: To discuss and obtain agreement with the Agency on the following: (1) Mechanism(s) of action (MOAs) and potency. (2) Assessment of critical quality attributes (CQAs), (3) Cell banking (4) A strategy to establish the Drug Product shelf life.

Pre Meeting Correspondence:

On September 5th, preliminary comments were sent to the sponsor. Based on the preliminary comments, the Sponsor requested a teleconference. The Agency received responses to the preliminary comments on September 8th. The Agency responded to the sponsor responses on September 9th. Based on this response, agreement with the Agency had been reached on four of the five questions. For the last question, the Agency provided a recommendation regarding the stressed comparability study conditions and duration. On September 9th, the Sponsor provided a table listing historical stressed stability data for multiple quality attributes that supported the stressed stability study design proposed in the PMP.

Preliminary Comments:

Question 1a)

Does the Agency agree with, or have comments on, the Sponsor's selection of biological activity methods to reflect mechanism(s) of action used during the assessment of ocrelizumab critical quality attributes?

FDA Response to Question 1a:

We agree with your proposal us use the CDC and ADCC methods as tools to assess ocrelizumab critical quality attributes, however, data should be included in the BLA that include a complete characterization using functional methods such as binding to CD20, FcγR's and FcRn in addition to CDC and ADCC.

Question 1b)

Does the Agency agree with, or have comments on, the Sponsor's proposed control system strategy to monitor potency?

FDA Response to Question 1b:

In general, we agree with your strategy to use the CDC assay and the CE-glycan assay (as a surrogate for ADCC activity) as part of the control system for ocrelizumab drug substance, drug product and stability testing, but we have the following comments:

- a. Regarding your definition of normalized G0-F, how does the calculation account for other glycan structures that lack fucose?
- b. Your high mannose data (lower ADCC for high mannose forms) is contradictory to published data showing higher ADCC activity for high mannose forms (Yu M, Brown D, Reed C, Chung S, Lutman J, et al. (2012) Production, characterization, and pharmacokinetic properties of antibodies with N-linked mannose-5 glycans. MAbs 4:475-487.) Please comment.

Question 2a:

Does the Agency agree with, or have comments on, the Sponsor's approach to the identification and current assessment of ocrelizumab critical quality attributes, including the identification of non-critical quality attributes?

FDA Response to Question 2a:

In general, we agree with your approach to the identification and assessment of CQA's and non-CQA's, but a final determination of the acceptability of the CQA assessment will be a review issue. In the BLA, provide a justification for the derivation of the moderate and low impact ranges for bioactivity and PK. For example, we note that in Table A-1, low impact ratings are given for both biological activity and PK changes of (b) (4) %. How are these ranges determined? Why, for instance, was (b) (4) % not considered as the top end of the low impact rating for bioactivity and PK? Regarding immunogenicity risk ranking and filtering, we agree that those attributes ranked as low risk may indeed be low, but uncertainty should be rated higher until ADA have been analyzed and shown not to be directed against variants (b) (4)

Question 2b)

Does the Agency agree with, or have comments on, the Sponsor's additional assessment approach to capture the potential interactions and stability of quality attributes?

FDA Response to Question 2b:

We agree with your approach for assessing potential interactions and stability of quality attributes. However, new information that may suggest additional potential interactions should be included in the assessment.

Question 3:

Minor process modifications were implemented between the 2009 Drug Substance process used to generate material for the Multiple Sclerosis Phase 3 clinical trials and the 2014 Drug Substance process used to produce the validation batches.

Does the Agency agree with the Sponsor's approach to demonstrate comparability and suitability of the process for registration?

FDA Response to Question 3:

In general the drug substance comparability strategy appears to be acceptable, but we have the following comments:

- a. In addition to CDC, the analysis should include a comparison of ADCC activity and binding to CD20, FcγR's and FcRn.
- b. You should justify the use of tolerance intervals, which result in larger ranges with fewer lots. If the 2014 Drug Substance lots are within the TI range but appear to be out of trend when compared with the 2009 Drug Substance lots, we may not consider the processes to be comparable.
- c. We recommend that you extend the stressed stability protocols from one month to at least 3 months. Changes are likely to occur beyond one month and obtaining additional data will strengthen the statistical comparisons of the degradation rates. Where possible, we recommend that you provide a statistical comparison of degradation rates for each assay that is used for assessing drug product comparability.

Meeting Discussion:

At the beginning of the teleconference, the Agency stated that we reviewed the information submitted on September 9, 2014 regarding historical stressed stability data for multiple quality attributes that supported the stressed stability study design for both drug substance and drug product and found it to be acceptable.

Question 4a:

To ensure a continuous supply of ocrelizumab, new Working Cell Bank (WCB) No. (b) (4) was implemented in the 2014 Drug Substance validation campaign in addition to the use of existing Working Cell Bank (WCB) No. (b) (4). Drug Substance batches derived from both the new and existing Working Cell Banks were placed on stability. WCB No. (b) (4) was created from the same Master Cell Bank (MCB No. (b) (4)) as WCB No. (b) (4) using the same procedures and materials. Because of the late introduction of WCB No. (b) (4) in the development program, the Sponsor intends to provide an enhanced data package in the BLA. Does the Agency agree with the Sponsor's approach to support the implementation of WCB No. (b) (4)?

FDA Response to Question 4A:

We agree with your approach to support implementation of WCB No. (b) (4); however we have the following comments:

- a. The general viral screening assay (b) (4) is listed as (b) (4) assay. It should include (b) (4).
- b. Provide information on the viability of both WCB (b) (4) and WCB (b) (4). If there are issues with the ocrelizumab WCBs similar to that of pertuzumab, you should inform us prior to filing the BLA.

Question 4b:

The maximum (b) (4) duration and limit of in vitro cell age will be established (b) (4). Does the Agency agree that the planned approach supports establishing the limit of in vitro cell age and maximum (b) (4) duration?

FDA Response to Question 4B:

Yes, we agree with your planned approach for establishing the limit of in vitro cell age.

Question 5:

The Sponsor intends to establish comparability between the 300 mg/vial configuration proposed for commercial Drug Product filled at (b) (4)

(b) (4) A (b) (4) month shelf life for the commercial Drug Product will be proposed based on 12 months of real-time stability data from the 300 mg/vial validation batches and will be supported by up to (b) (4) 20 months of real-time stability data from a representative 300 mg/vial batch.

Assuming comparability is established and stability results meet acceptance criteria, does the Agency agree with the Sponsor's proposal that the available data will be sufficient to establish a commercial shelf life of (b) (4) months?

FDA Response to Question 5:

A determination of the commercial shelf life will be a BLA review issue. In general, shelf life is based on real-time data from lots manufactured using the proposed commercial process, while data from development lots or clinical lots that use the same container closure system, formulation and fill volume can be used to support the commercial shelf life. You may submit data from the (b) (4) lots, which will be reviewed and taken into consideration. In addition, if the BLA undergoes a standard review, you should be able to provide a stability update with data from the 18-month time point.

The response to Question 3a regarding the drug substance accelerated stress study also applies to drug product. Additional stressed conditions other than temperature should be also included in the drug product comparability protocol. The drug product comparability assessment also includes a stressed stability study at 25°C, but details of the study are not clear, such as the lots that will be used, the duration of the study and the sampling time points.

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/s/

MARJORIE A SHAPIRO
12/12/2014



IND 100593

MEETING MINUTES

Genentech
Attention: Kathleen Winson
1 DNA Way
South San Francisco
California, 94080

Dear Ms. Winson:

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

We also refer to the meeting between representatives of your firm and the FDA on September 22, 2010. The purpose of the meeting was to discuss your overall clinical development plan for the proposed indication, the design of proposed phase 3 studies, and the risk/benefit profile of ocrelizumab for the treatment of patients with relapsing multiple sclerosis (RMS).

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

Sincerely,

{See appended electronic signature page}

Russell Katz, M.D.
Director
Division of Neurology Products
Center of Drug Evaluation I
Center of Drug Evaluation and Research



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type: [Type B]
Meeting Category: [End of Phase 2]

Meeting Date and Time: [September 22, 2010]
Meeting Location: [White Oak; Building 22, room 1309]

Application Number: [IND 100593]
Product Name: [Ocrelizumab]
Indication: [Multiple Sclerosis]
Sponsor/Applicant Name: [Genentech]

Meeting Chair: [Dr. Russell Katz]
Meeting Recorder: [LT Hamet Touré]

FDA ATTENDEES

Russell Katz, MD, Division of Neurology Products Director
Billy Dunn, MD, Team Leader
John Marler, MD, Clinical Reviewer
Ta-Chen Wu, PhD, Clinical Pharmacology Reviewer
Kun Jin, PhD, Biostatistics Team Leader
Sean Fitzsimmons, PhD, Quality Reviewer
LT Hamet Touré, PharmD MPH, Regulatory Project Manager

SPONSOR ATTENDEES

Genentech/Roche:

Kathie Winson
Nathan Winslow
Denise Morgan
Sarah Fabes, PhD
Robert Glanzman, MD
David Leppert, MD
Wolfgang Dummer MD, PhD
Marianne Gerber, MD
David Zhang, PhD
Jiameng Zhang, PhD
Heidi Kletzl
Anu Vaidyanathan

Biogen:

Kimi DeNoble
Marianne Sweetser, MD, PhD
John Richert

1.0 BACKGROUND

The purpose of the meeting was to discuss your overall clinical development plan for the proposed indication, the design of proposed phase 3 studies, and the risk/benefit profile of ocrelizumab for the treatment of patients with relapsing multiple sclerosis (RMS). FDA provided its preliminary comments on September 20, 2010. In turn, the sponsor provided feedback to the comments on September 21, 2010.

2. DISCUSSION

Nonclinical Question

A fertility study will be conducted in parallel with the Phase III studies. Provided no unique and/or unexpected toxicity is observed in this study, no additional nonclinical studies are planned to support the filing of a Biologics License Application (BLA) for the proposed indication. Does the Agency agree with this plan?

FDA Response: We agree that the male and female fertility study(ies) may be completed in parallel with the Phase 3 clinical trials.

Your completed and planned nonclinical studies appear, on face, to be sufficient to support the filing of a BLA; however, the adequacy of the nonclinical data will be a matter of review.

Discussion:

None

Clinical Questions

QUESTION 1

The Sponsor intends to conduct two identical Phase III superiority studies versus interferon beta-1a (Rebif) to evaluate the efficacy and safety of ocrelizumab for the treatment of patients with RMS.

a. Does the Agency agree that the clinical development plan as outlined supports the following proposed indication if adequate safety and statistically persuasive evidence of efficacy are demonstrated?

(b) (4)

FDA Response: Yes, we agree the indication is supported by the endpoints you propose.

Discussion:

None

b. Does the Agency agree with the proposed study design?

FDA Response: No. The study design will not provide persuasive evidence of efficacy because of the lack of double blinding of patients and treating physicians. We reiterate the importance of double blinding in our response to question 3.

Discussion:

None

c. Does the Agency agree with the overall safety plan; in particular, the proposed plan for monitoring for PML and other infection related diseases in the Phase III study?

FDA Response: Yes.

Discussion:

None

d. Does the Agency agree that the estimated effect sizes for reduction in relapse rate and disease progression used in powering the studies are clinically meaningful to demonstrate superiority of ocrelizumab and support a superiority claim over Rebif?

FDA Response: Ultimately, this will be a matter of review. A 50% reduction in the 96-week ARR compared to Rebif seems reasonable. We didn't see a specific discussion of the effect size for 12- and 24-week sustained disability progression in the SAMPLE SIZE AND STATISTICAL ANALYSES section of the protocol synopsis.

Sponsor's response:

We appreciate the Agency's response. The estimated effect size of 30% for sustained disease progression confirmed at 12 weeks over 96 weeks vs. Rebif (see page 47 of the PMP) is based on published data from other disease modifying therapies and the estimated 50% reduction in 96-week ARR vs. Rebif. Does the Agency have any further questions regarding these assumptions?

Discussion:

FDA agreed that a 30% reduction in 12 week sustained disease progression was reasonable and mentioned the particular importance of complete data collection for all time points with this endpoint. The advantages and disadvantages of reminding

examiners of prior EDSS scores were considered. Reminding examiners would reduce variability; not reminding them would reduce the chances of introducing bias and increase the credibility of the results. More rigorous training of examiners as an alternative to reminding was also discussed as a way to reduce variability in the EDSS scores.

e. Does the Agency agree with the proposed doses of ocrelizumab to be tested in the Phase III RMS clinical program?

FDA Response: No. We encourage you to consider a second dose (b) (4)
The high dose seems appropriate since there is little difference between the 600 mg and higher doses. Considering the similarity between the effects of the 600 and 1000mg doses, (b) (4)

As we have stressed to you in the past, we strongly encourage you to make every effort to identify the lowest effective dose (even if such a dose is less effective than a higher dose, but still effective) to allow for a comprehensive risk/benefit analysis. Most important, you should identify the lowest maximally effective dose.

Sponsor's response:

The Sponsor acknowledges the Agency's comments with respect to doses proposed for Phase III. We believe it is reasonably likely we will establish the lowest maximally effective and the minimally effective dose in our Phase III program with the proposed doses based on the following:

Lowest maximally effective dose

Based on our Phase II MS dose ranging study, we believe that the Phase III MS studies will demonstrate that 2 x 300mg is the lowest maximally effective dose in the proposed patient population.

- The 2 x 300mg dose was shown to be safe and highly effective in the Phase II MS study
- While there is no difference in the per-group analysis, there appears to be a dose response between 2 x 300mg and 2 x 1000mg in highly active MS patients (see Table below)
- The proposed Phase III MS population is more severe than the Phase II MS patient population

Dose-response: OCR MS phase II trial, WA21493, (24 week data)
Total T1 from Weeks 12- 24 by Baseline T1

Baseline	Imputed Analysis		Completer Analysis*	
Total number of Gd+T1	OCR 2x300mg N Mean (SD)	OCR 2x1000mg N Mean (SD)	OCR 2x300mg N Mean (SD)	OCR 2x1000mg N Mean (SD)
0	N = 23 0.0 (0.0)	N = 26 0.12 (0.59)	N = 15 0.0 (0.0)	N = 14 0.21 (0.80)
1-2	N = 12 0.17 (0.58)	N = 16 0.03 (0.13)	N = 11 0.18 (0.60)	N = 13 0.0 (0.0)
3 – 4	N = 7 1.79 (2.06)	N = 2 1.0 (0.0)	N = 4 1.75 (1.71)	N = 1 1.0
> 4	N = 5 3.03 (2.89) Med = 2.0	N = 6 0.83 (1.28) Med = 0.09	N = 4 3.5 (3.1) Med = 3.5	N = 4 0.75 (1.5) Med = 0.0

Minimally effective dose

We considered studying lower doses in MS, however, based on PK/PD, immunogenicity (HAHA), and clinical efficacy endpoints in the RA program, 2 x 200mg appears to be on the ascending portion of the dose response curve and is reasonably likely to be the minimally effective dose for the MS patient population based on the following:

- In a Phase I/II study in RA patients (ACTION), doses <2 x 200 mg (2 x 10 mg and 2 x 50mg) were inferior to 2 x 200mg, 2 x 500mg and 2 x 1000mg
 - Less pronounced improvement in high hurdle clinical endpoints (ACR70, DAS remission, etc.)
 - No effect on CRP reductions compared to placebo
 - Higher rates of immunogenicity (HAHA)
- PK is not linear below 2 x 200mg implying incomplete receptor occupancy
- PD data indicates faster repletion of B cells at doses less than 2 x 200mg
- In a Phase III RA study (SCRIPT), 2 x 200mg provided sub-optimal benefit compared to 2 x 500mg in TNF-IR trial patients based on radiographic endpoints
- In a second Phase III study (FEATURE), a dose of 1 x 400mg was clinically inferior to 2 x 200mg

Further, 2 x 200mg had an acceptable safety profile in Phase III RA studies.

Relevance of RA data for MS dose selection

- PK/PD data to date indicate no major differences across indications
- Immunogenicity was seen at lower doses (<2 x 200 mg) in the RA studies, which may be a safety issues across indications. Furthermore, MS patients have a higher likelihood of developing immunogenicity due to lack of concomitant immunosuppressive therapy

Discussion:

The sponsor considered the issues raised in FDA's response and presented the additional information above

(b) (4)

QUESTION 2

The patient population for the proposed program includes patients who have exhibited prior evidence of neurological disability (i.e., EDSS 1.0-5.5). Patients must demonstrate high disease activity on clinical grounds (either on, or off of currently available DMT), with at least two clinical attacks in the 3 years prior to screening, one of which must have occurred in the year prior to screening. In addition, the Sponsor plans to include a proportion of patients with relapsing SPMS (to comprise no more than 20% of the ITT population), provided they meet the relapse-related (as well as all other) eligibility criteria.

Does the Agency agree that the inclusion/exclusion criteria will yield a patient population that will support the proposed indication?

FDA Response: Yes. The protocol synopsis lists 49 selection criteria. Many of these criteria exclude patients for potential safety concerns that will have to be considered when labeling is written.

Sponsor's response:

We acknowledge the Agency's comment. Are there any specific selection criteria that the Agency would recommend changing or modifying based on our proposed labeled patient population?

Discussion:

FDA emphasized the concern that extensive exclusion criteria may serve to limit the data available to inform product labeling. The exclusions will likely impact the generalizability of the results of the trials to the patient population with the indications for

the drug. Some of the medical and other treatment exclusions could exclude large numbers of patients for reasons that are not unusual among MS patients. For instance, many MS patients with the proposed indication are older than 50. The sponsor acknowledged and understood this concern and will review each exclusion criterion in that context in an effort to determine its necessity and possible eventual impact on study generalizability

QUESTION 3

The Sponsor proposes to use IFN beta-1a (Rebif) as an active comparator.

(b) (4)

Does the Agency agree with the planned methodologies for ensuring data integrity and minimizing bias in these studies?

FDA Response: No, we strongly disagree. Published reports have emphasized the importance of double blinding in MS trials.

(b) (4)

Sponsor's response:

We acknowledge the Agency's significant concern regarding double-blinding the studies and will take this under advisement.

Discussion:

None

QUESTION 4

Because of the sample size required to demonstrate a statistically significant difference in disability progression between ocrelizumab and an active comparator, the Sponsor is planning to pool data from the two Phase III studies for each ocrelizumab dosage arm and compare with Rebif across the two studies. Given that both of the proposed Phase III studies use the same active comparator, have identical inclusion/exclusion criteria, and will be implemented concurrently, does the Agency agree that demonstration of statistically and clinically significant benefit, based on the pooling of data across the two Phase III studies, will support a disability claim for ocrelizumab?

FDA Response: Yes, we agree, but only if the trials are blinded as described in our responses to question 1b and 3.

Discussion:

None

QUESTION 5

Given the safety data on ocrelizumab collected from the RA, LN, and MS studies to date, and assuming that the proposed Phase III studies demonstrate adequate safety and statistically significant efficacy results, does the Agency believe the benefit/risk profile for ocrelizumab would be sufficiently favorable to support the proposed indication in RMS?

FDA response: This will be largely a matter of review. The addition of a brief and reliable global measure of function or disability would help us weigh relative benefits and risks. Examples include the Karnofsky and modified Rankin scales.

Sponsor's response:

We appreciate the Agency's suggestion to include global measures of function in order to establish the benefit of ocrelizumab in MS. We would like to further discuss how the Agency envisions using the Karnofsky and modified Rankin scales or others in the Phase III MS studies?

Discussion:

FDA stated that disability scales were proposed as tertiary outcomes to provide the same type of information provided by the patient reported outcomes that have been proposed. Like the QOL scores, they will help interpret the significance of the EDSS scores according to a more widely understood standard measure. In a disease that affects cognition, disability scales may give a more realistic global assessment of the patient than patient reported outcomes. A global measure of disability will also aid in assessing the significance of adverse events. It is not expected that the disability scales will be as sensitive as the EDSS to change in the neurological status of the participants.

QUESTION 6

Does the Agency agree that the number of patients treated with ocrelizumab and duration of treatment in the proposed RMS clinical development plan will provide an adequate safety database to support a BLA for RMS?

FDA Response: Yes. To improve the quality and usefulness of the safety data, we encourage you to modify the extension study so that patients continue the same drug they received in the trials until the results are known.

Sponsor's response:

We appreciate the Agency's comments and will take this under advisement. We would like to note that should patients remain on the same drug they received in the trial until results are known, this would have an effect on the size of the safety database. There would be approximately 800 fewer patients (2600 vs. 1800) in the safety database resulting in approximately 800 fewer patient years follow up (6000 vs. 5200).

Discussion:

FDA stated that it appeared sufficient safety data would remain in the safety database and that data from a randomized control group would add significantly to the ability to accurately describe the effects of ocrelizumab.

Additional Comment:

With regard to Selection Criterion 37, the period off all approved treatment should be kept to a minimum, particularly if the patient is asked to stop treatment in order to participate in the trial.

Sponsor's response:

We acknowledge the Agency's comments and will review the inclusion criteria accordingly.

Discussion:

None

Additional Sponsor Responses:

The Sponsor notes that the following question was included in the PMP:

The Sponsor's plan is to submit the Phase III protocols with supporting information for the initiation of the studies in the United States.

- Final protocols for two Phase III studies
- Informed consents
- Updated Investigator Brochure
- Interim report for Study WA21493/ACT4422g

An IND amendment will also be submitted supporting the manufacturing site change.

Does the Agency agree with the contents of the proposed submission?

Discussion:

FDA agreed with the contents of the proposed submission. FDA requested that the protocol submission include drafts of the case report forms and a draft charter for a data safety monitoring committee. It is not expected that the DSMB be appointed or meet prior to submission.

Additional FDA Post Meeting Comment: During the meeting, the sponsor mentioned that electronic data capture will likely be used for some of the outcome measures. FDA understands this may offer opportunities to increase both efficiency and data quality but may require changes in the usual procedures for data quality control. FDA wishes to inform the sponsor that the Division of Scientific Investigations, Office of Compliance, CDER (DSI), is willing to work cooperatively with the Division of Neurology Products to review your plans for data quality control early in your clinical development program as it pertains to this issue with the intent that

all will have more confidence in the accuracy of the data at the end of the trials. This is not a requirement and is offered only to inform the sponsor of the opportunity to interact with DSI while planning the trials. FDA encourages the sponsor to contact the Division of Neurology Products if interested in this approach.

APPEARS THIS WAY ON ORIGINAL

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/s/

RUSSELL G KATZ
10/22/2010



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

IND 100,593

Genentech, Inc.
Attention: Todd W. Rich, M.D.
Vice President, Development Regulatory Affairs
1 DNA Way
South San Francisco, CA 94080-4990

Dear Dr. Rich:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for rhuMAb 2H7 (ocrelizumab).

We also refer to the meeting between representatives of your firm and the FDA on December 5, 2008.

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, Regulatory Project Manager, at 301-796-1136.

Sincerely,

{ See appended electronic signature page }

Russell Katz, MD
Director
Division of Neurology Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosure - Meeting Minutes

MEMORANDUM OF MEETING MINUTES

MEETING DATE: December 5, 2008
TIME: 9:00-10:00 AM EST
LOCATION: CDER WO Room 1313
APPLICATION: IND 100,593
DRUG NAME: rhuMAb 2H7 (Ocrelizumab)
TYPE OF MEETING: Type B/End of Phase II

MEETING CHAIR: Russell Katz, M.D.

MEETING RECORDERS: James Reese, Ph.D.
Stephanie N. Keefe

FDA ATTENDEES:

Russell Katz, MD, Division Director, DNP
Billy Dunn, MD, Clinical Team Leader, DNP
Jody Green, MD, Clinical Reviewer, DNP
Lois Freed, PhD, Non-Clinical Team Leader, DNP
Ta-Chen Wu, PhD, Clinical Pharmacology Reviewer, DNP
Sharon Yan, PhD, Biostatistics Reviewer, DNP
James Reese, PhD, Regulatory Project Manager, DNP

GENENTECH, INC. ATTENDEES:

Clinical:

Paul Brunetta, MD
Peter Chin, MD, MS
Craig Smith, MD
Donna Masterman, MD, MS

Non-Clinical:

Anu Vaidyanathan, PhD

Clinical Pharmacology:

Banmeet Anand, PhD

Statistics:

Jiameng Zhang, PhD
David Zhang, MD
Ming Yin

Regulatory Affairs:

Carmen Ladner
Miko Maruoka, M.S.
Joel Selcher, PhD
Nathan Winslow

BIOGEN IDEC, INC. ATTENDEES:

Clinical:

Diego Cadavid, MD
Michael Panzara, MD, MPH

Regulatory Affairs:

Paula Sandler, PhD

F. HOFFMAN-La ROCHE, LTD. ATTENDEES:

Clinical:

Valerie Hiltbrunner, MD

Regulatory Affairs:

Denise Morgan

BACKGROUND:

Genentech, Inc., in partnership with F. Hoffman-La Roche Ltd. and Biogen Idec, Inc., is developing Ocrelizumab (b) (4)

(b) (4). Ocrelizumab is a recombinant humanized monoclonal antibody against the CD20 antigen present on human B cells. The purpose of this meeting is for Genentech to obtain Agency feedback (b) (4)

(b) (4) for the proposed indication.

QUESTIONS:

I. [Questions that were submitted in the November 4, 2008 Briefing Document]

(b) (4)

Linked Applications

Sponsor Name

Drug Name / Subject

IND 100593

GENENTECH INC

Ocrelizumab (PRO70769)

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/s/

RUSSELL G KATZ

02/10/2009

LATE-CYCLE COMMUNICATION
DOCUMENTS



BLA 761053

LATE-CYCLE MEETING MINUTES

Genentech, Inc.
Attention: Sonali Patel, Pharm.D.
Associate Program Director
1 DNA Way
South San Francisco, CA 94080-4990

Dear Dr. Patel:

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

We also refer to the Late-Cycle Meeting (LCM) between representatives of your firm and the FDA on October 18, 2016.

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

If you have any questions, call LCDR Nahleen Lopez, Regulatory Project Manager at (240) 402-2659.

Sincerely,

{See appended electronic signature page}

Eric Bastings, MD
Deputy Director
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: October 18, 2016, 3:00-4:00pm EST

Meeting Location: Teleconference

Application Number: 761053

Product Name: Ocrevus (ocrelizumab)

Applicant Name: Genentech, Inc.

Meeting Chair: Billy Dunn, MD

Meeting Recorder: LCDR Nahleen Lopez, PharmD

FDA ATTENDEES

Division of Neurology Products:

Billy Dunn, MD, Director

Eric Bastings, MD, Deputy Director

John Marler, MD, Clinical Team Leader

Lois Freed, PhD, Nonclinical Team Leader

Sally Jo Yasuda, MS, PharmD, Safety Team Leader

Tracy Peters, PharmD, Associate Director for Labeling

Nahleen Lopez, PharmD, Regulatory Project Manager

Office of Surveillance and Epidemiology:

Charlene Flowers, Acting Team Leader

Elisa Braver, Reviewer

David Croteau, Medical Officer

Laura Zendel, PharmD, Risk Management Analyst

Office of Biotechnology Products:

Sarah Kennett, Review Chief

Linan Ha, Team Leader

Milos Dokmanovic, Product Quality Reviewer

Office of Biostatistics:

Sharon Yan, Biostatistics Reviewer

Eastern Research Group:

Marc Goldstein, Independent Assessor

APPLICANT ATTENDEES

Sonali Patel, Pharm.D., Associate Program Director, US Regulatory

Erica Evans, Ph.D., Senior Global Regulatory Leader

Jennifer Sexton, Regulatory Program Director, Pharma Technical Regulatory

Kathy Francissen, Ph.D., Senior Director, Pharma Technical Regulatory

Damian Cunningham, Ph.D., Technical Development Leader, Pharma Technical Development

Simona Skerjanec, MBA, Lifecycle Leader, Global Product Strategy

Anne-Marie Li-Kwai-Cheung, Global Development Team Leader

Hideki Garren M.D., Group Medical Director, Clinical Science Leader

Fabian Model, Ph.D., Associate Director, CNS Biostatistics

Gaelle Klingelschmitt, Project Lead Statistician

Ann Santen, Global Operations Program Leader
An Song, PhD, Director and Senior Scientist, BioAnalytical Sciences and Pharmacology Subteam Leader
Heidemarie Kletzl, Ph.D, Clinical Pharmacology
Nicole Mairon M.D., Senior Safety Science Leader
David Wormser, Ph.D, Senior Epidemiologist
Karen Rutherford, Ph.D., Scientist, Late Stage Pharmaceutical Development, Pharma Technical Development
Melissa Mun, M.S., Senior Engineer, Late Stage Cell Culture, Pharma Technical Development
John Joly, Ph.D Senior Director, Analytical Development and Quality Control, Pharma Technical Development
Pin Yee Wong, M.S., Director, Biological Technologies, Pharma Technical Development
Pedro Mauri, Quality Product Leader, Pharma Technical Quality
Robert Kiss, Ph.D., Senior Director, Late Stage Cell Culture, Pharma Technical Development
Brian Kelley, Ph.D., Vice President, BioProcess Development, Pharma Technical Development
Dieter Schmalzing, Ph.D., Director, Global Biologics Quality Control, Pharma Technical Quality

1. BACKGROUND

BLA 761053 was submitted on April 28, 2016, for Ocrevus (ocrelizumab).

Proposed indication(s): Relapsing forms of multiple sclerosis (RMS) and Primary Progressive Multiple Sclerosis (PPMS)

PDUFA goal date: December 28, 2016

FDA issued a Background Package in preparation for this meeting on October 11, 2016.

2. DISCUSSION

A. Introductory Comments

Welcome, Introductions, Ground rules and Objectives of the meeting were presented.

Discussion: *FDA welcomed the sponsor and clarified that the safety labeling did not belong in the list of substantive review issues in the meeting background package.*

B. Discussion of Substantive Review Issues

- Potency and drug substance (DS) manufacturing
The current manufacturing process control strategy is not adequate to ensure that the manufacture of ocrelizumab is well controlled and will produce product with consistent CDC and ADCC potency. The following elements of the control strategy should be considered with respect to supporting consistency of the process and the product:
 - a. Process parameters and testing outlined in Sections S.2.2 and S.2.4

- b. Control of raw materials (specifically, cell culture materials with potentially high levels of variability)
 - c. New Working Cell Bank manufacturing and qualification
 - d. DS and drug product (DP) release and stability specifications
 - e. Post-approval lifetime management plan
- Polysorbate 20 degradation and DP stability
 - Degradation of the Polysorbate 20 excipient has led to concerns regarding visible particle formation and potential impact to other aspects of product quality, particularly the aggregation of ocrelizumab, including susceptibility to mechanical stress-induced aggregation. This issue affects the following aspects of the DP control strategy.
 - a. DP expiry period
 - b. DP shipping validation

Discussion: *The details of the substantive review issues and additional deficiencies were conveyed to the sponsor in an information request (IR) on October 13, 2016. During the meeting, the sponsor requested further clarification for the following IR items:*

Question 1c: *The sponsor committed to providing the requested process data by October 20, and stated that an electronic version of the data could also be made available to FDA. FDA indicated that the electronic version would be useful. Information provided by the sponsor in advance of the meeting indicated that a subset of process data (b) (4) was excluded. FDA asked the reason for excluding these data, and the sponsor clarified that this is due to the volume and complexity of these data. FDA acknowledged the response and stated that if the data (b) (4) are determined to be necessary, they will be requested separately.*

Question 1f: *The sponsor committed to implement an ADCC bioassay in the DS release specification as an additional potency assay. They stated that the initial assay characterization indicated that this assay is suitable for release testing. The assay qualification data and the timeline for assay validation and implementation will be provided in the October 20 IR response. FDA agreed that this approach seemed feasible with the establishment of a PMC for confirmation of ADCC assay validation and implementation. However, FDA did not agree with the rationale provided for excluding additional assays from DS testing, because the assays are not redundant to the ADCC and CDC assays. FDA emphasized that uncoupling binding and effector functions could be beneficial in the understanding the full impact of potential manufacturing changes on the function of ocrelizumab, and this cannot be accomplished using the ADCC and CDC assays. In addition, the NK cell based ADCC assay used for ocrelizumab would not be redundant with an ADCP assay. The sponsor acknowledged FDA's concern and clarified that assays capturing additional mechanisms of action of ocrelizumab will be included as part of characterization for the next ocrelizumab manufacturing campaign and to support future manufacturing changes.*

Question 2: *The sponsor agreed to remove the post-approval lifecycle management (PALM) plan from the BLA and committed to implement the testing planned to be performed under the PALM as part of the DS release specifications or in-process testing. The timeline for*

assay validations and implementation will be provided in the October 20 IR response. Assay validation would not be complete during the review cycle. FDA agreed that the assay characterization data could be reconsidered with respect to the proposed purpose and the potential for performing confirmatory validation studies as PMCs

C. Postmarketing Requirements/Postmarketing Commitments

- We are considering the following PMRs if OCREVUS is approved:
 - a. An observational study to evaluate [REDACTED] (b) (4) the risk of malignancies.
 - b. A Pregnancy Registry. We are evaluating your proposal [REDACTED] (b) (4)
- We are considering the following PMCs if OCREVUS is approved:
 - a. A shipping study to confirm validation of the commercial ocrelizumab drug product shipping conditions. The study would include testing of pre- and post-shipping samples for product quality.
 - b. PMCs may also be requested as part of the management of the ocrelizumab product quality control strategy.

Discussion: *The Agency clarified that for the PMRs, the sponsor's proposals for both the observational study and the pregnancy registry would be considered.*

D. Major Labeling Issues

- Safety labeling
 - In addition to Warnings and Precautions for infusion reactions and infections, we anticipate the following Warnings and Precautions:
 - a. Malignancies, particularly breast cancer [REDACTED] (b) (4)

Discussion: *The sponsor questioned why the stated adverse reactions were being considered for inclusion in the Warnings and Precautions section rather than the Adverse Reactions section of labeling. FDA explained that because there is an imbalance of malignancies, particularly in breast cancer, FDA would consider this as a serious adverse reaction for inclusion in the Warnings and Precautions section.* [REDACTED] (b) (4)

E. Review Plans

***Discussion:** FDA stated there is no change to the review schedule for this BLA. The sponsor questioned when they could expect to receive labeling. FDA responded that the first round of labeling could begin the first week of November.*

F. Wrap-up and Action Items

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

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/s/

ERIC P BASTINGS
11/14/2016