

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

761083Orig1s000

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION ¹		
NDA # BLA # 761083	NDA Supplement # BLA Supplement #	If NDA, Efficacy Supplement Type: <i>(an action package is not required for SE8 or SE9 supplements)</i>
Proprietary Name: HEMLIBRA® Established/Proper Name: emicizumab-kxwh Dosage Form: injection		Applicant: Genentech, Inc. Agent for Applicant (if applicable):
RPM: Laura Wall		Division: Division of Hematology Products
NDA Application Type: <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) Efficacy Supplement: <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) BLA Application Type: <input type="checkbox"/> 351(k) <input checked="" type="checkbox"/> 351(a) Efficacy Supplement: <input type="checkbox"/> 351(k) <input type="checkbox"/> 351(a)		<p><u>For ALL 505(b)(2) applications, two months prior to EVERY action:</u></p> <ul style="list-style-type: none"> Review the information in the 505(b)(2) Assessment and submit the draft² to CDER OND IO for clearance. Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity) <ul style="list-style-type: none"> <input type="checkbox"/> No changes <input type="checkbox"/> New patent/exclusivity (<i>notify CDER OND IO</i>) <p>Date of check: _____</p> <p><i>Note: If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.</i></p>
❖ Actions		
<ul style="list-style-type: none"> Proposed action User Fee Goal Date is <u>February 23, 2018</u> 		<input checked="" type="checkbox"/> AP <input type="checkbox"/> TA <input type="checkbox"/> CR
<ul style="list-style-type: none"> Previous actions (<i>specify type and date for each action taken</i>) 		<input checked="" type="checkbox"/> None
❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain _____		<input type="checkbox"/> Received
❖ Application Characteristics ³		

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

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

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

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

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

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

NDAs: Subpart H

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

Subpart I

- Approval based on animal studies

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

BLAs: Subpart E

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

Subpart H

- Approval based on animal studies

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

Comments:

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

Action Letters	
❖ Copies of all action letters (<i>including approval letter with final labeling</i>)	Approval; November 16, 2017
Labeling	
❖ Package Insert (<i>write submission/communication date at upper right of first page of PI</i>)	
<ul style="list-style-type: none"> Most recent draft labeling (<i>if it is division-proposed labeling, it should be in track-changes format</i>) 	<input type="checkbox"/> Included
<ul style="list-style-type: none"> Original applicant-proposed labeling 	<input checked="" type="checkbox"/> Included Submitted draft version on 6/23/17
❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling (<i>write submission/communication date at upper right of first page of each piece</i>)	<input checked="" type="checkbox"/> Medication Guide <input type="checkbox"/> Patient Package Insert <input checked="" type="checkbox"/> Instructions for Use <input type="checkbox"/> Device Labeling <input type="checkbox"/> None
<ul style="list-style-type: none"> Most-recent draft labeling (<i>if it is division-proposed labeling, it should be in track-changes format</i>) 	<input type="checkbox"/> Included
<ul style="list-style-type: none"> Original applicant-proposed labeling 	<input checked="" type="checkbox"/> Included Submitted draft version on 6/23/17
❖ Labels (full color carton and immediate-container labels) (<i>write submission/communication date on upper right of first page of each submission</i>)	
<ul style="list-style-type: none"> Most-recent draft labeling 	<input checked="" type="checkbox"/> Included Submitted on 10/31/17
❖ Proprietary Name <ul style="list-style-type: none"> Acceptability/non-acceptability letter(s) (<i>indicate date(s)</i>) Review(s) (<i>indicate date(s)</i>) 	Letters: 11/3/17 (conditionally acceptable); 8/18/17 (unacceptability) Reviews: 11/1/17 (name review); 9/19/17 (name suffix review); 8/17/17 (name review)
❖ Labeling reviews (<i>indicate dates of reviews</i>)	RPM: 9/27/17 DMEPA: 11/8/17; 10/13/17 DMPP/PLT: 10/23/17 OPDP: 10/24/17 COA: 10/13/17 CSS: <input checked="" type="checkbox"/> None Product Quality: 11/1/17 Other: <input checked="" type="checkbox"/> None
Administrative / Regulatory Documents	
❖ RPM Filing Review ⁴ /Memo of Filing Meeting (<i>indicate date of each review</i>)	8/14/17
❖ All NDA 505(b)(2) Actions: Date each action cleared by 505(b)(2) Clearance Committee	<input checked="" type="checkbox"/> Not a (b)(2)
❖ NDAs/NDA supplements only: Exclusivity Summary (<i>signed by Division Director</i>)	N/A
❖ Application Integrity Policy (AIP) Status and Related Documents http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	

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

<ul style="list-style-type: none"> Applicant is on the AIP 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
<ul style="list-style-type: none"> This application is on the AIP <ul style="list-style-type: none"> If yes, Center Director's Exception for Review memo (<i>indicate date</i>) If yes, OC clearance for approval (<i>indicate date of clearance communication</i>) 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
<ul style="list-style-type: none"> ❖ Pediatrics (<i>approvals only</i>) <ul style="list-style-type: none"> Date reviewed by PeRC <u>N/A</u> If PeRC review not necessary, explain: <u>Orphan Designation for indication</u> 	
<ul style="list-style-type: none"> ❖ Breakthrough Therapy Designation 	<input type="checkbox"/> N/A
<ul style="list-style-type: none"> Breakthrough Therapy Designation Letter(s) (granted, denied, an/or rescinded) 	Granted letter 9/2/15 (IND 122954)
<ul style="list-style-type: none"> CDER Medical Policy Council Breakthrough Therapy Designation Determination Review Template(s) (<i>include only the completed template(s) and not the meeting minutes</i>) 	9/1/15
<ul style="list-style-type: none"> CDER Medical Policy Council Brief – Evaluating a Breakthrough Therapy Designation for Rescission Template(s) (<i>include only the completed template(s) and not the meeting minutes</i>) <p>(<i>completed CDER MPC templates can be found in DARRTS as clinical reviews or on the <u>MPC SharePoint Site</u></i>)</p>	
<ul style="list-style-type: none"> ❖ Outgoing communications: letters, emails, and faxes considered important to include in the action package by the reviewing office/division (e.g., clinical SPA letters, RTF letter, Formal Dispute Resolution Request decisional letters, etc.) (<i>do not include OPDP letters regarding pre-launch promotional materials as these are non-disclosable; do not include Master File letters; do not include previous action letters, as these are located elsewhere in package</i>) 	11/15/17; 11/13/17; 11/8/17 (2); 11/7/17; 11/6/17; 11/1/17 (3); 10/27/17; 10/24/17; 10/19/17 (2); 10/18/17; 10/13/17; 10/10/17 (2); 10/6/17 (4); 9/26/17 (2); 9/22/17; 9/21/17; 9/19/17; 9/13/17; 9/12/17; 9/1/17; 8/29/17; 8/25/17; 8/22/17; 8/18/17; 8/10/17; 8/9/17; 8/1/17; 7/10/17; 7/5/17
<ul style="list-style-type: none"> ❖ Internal documents: memoranda, telecons, emails, and other documents considered important to include in the action package by the reviewing office/division (e.g., Regulatory Briefing minutes, Medical Policy Council meeting minutes) 	Email 11/9/17 SGE/patient advocate Review 11/8/17 SGE/patient advocate; Tcon 10/31/17 with SGE/patient advocate
<ul style="list-style-type: none"> ❖ Minutes of Meetings 	
<ul style="list-style-type: none"> If not the first review cycle, any end-of-review meeting (<i>indicate date of mtg</i>) 	<input checked="" type="checkbox"/> N/A
<ul style="list-style-type: none"> Pre-NDA/BLA meeting (<i>indicate date of mtg</i>) 	3/21/17
<ul style="list-style-type: none"> EOP2 meeting (<i>indicate date of mtg</i>) 	<input checked="" type="checkbox"/> No mtg
<ul style="list-style-type: none"> Mid-cycle Communication (<i>indicate date of mtg</i>) 	9/28/17
<ul style="list-style-type: none"> Late-cycle Meeting (<i>indicate date of mtg</i>) 	10/24/17
<ul style="list-style-type: none"> Other milestone meetings (e.g., EOP2a, CMC focused milestone meetings) (<i>indicate dates of mtgs</i>) 	CMC pre-BLA 4/25/17

❖ Advisory Committee Meeting(s)	<input checked="" type="checkbox"/> No AC meeting
• Date(s) of Meeting(s)	
Decisional and Summary Memos	
❖ Office Director Decisional Memo (<i>indicate date for each review</i>)	See 11/16/17 Multidisciplinary Review Section 18
Division Director Summary Review (<i>indicate date for each review</i>)	See 11/16/17 Multidisciplinary Review Section 17
Cross-Discipline Team Leader Review (<i>indicate date for each review</i>)	See 11/16/17 Multidisciplinary Review Section 1
PMR/PMC Development Templates (<i>indicate total number</i>)	2
Clinical	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) (<i>indicate date for each review</i>)	See 11/16/17 Multidisciplinary Review sections 2, 3, 4, and 7
• Clinical review(s) (<i>indicate date for each review</i>)	See 11/16/17 Multidisciplinary Review sections 2, 3, 4, and 7
• Social scientist review(s) (if OTC drug) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here <input type="checkbox"/> and include a review/memo explaining why not (<i>indicate date of review/memo</i>)	Page 63 of 11/16/17 Multidisciplinary Review
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers (<i>indicate date of each review</i>) ⁵	<input checked="" type="checkbox"/> None
❖ Controlled Substance Staff review(s) and Scheduling Recommendation (<i>indicate date of each review</i>)	<input checked="" type="checkbox"/> N/A
❖ Risk Management <ul style="list-style-type: none"> REMS Documents and REMS Supporting Document (<i>indicate date(s) of submission(s)</i>) REMS Memo(s) and letter(s) (<i>indicate date(s)</i>) Risk management review(s) and recommendations (including those by OSE and CSS) (<i>indicate date of each review and indicate location/date if incorporated into another review</i>) 	DRISK Review: 10/10/17
❖ OSI Clinical Inspection Review Summary(ies) (<i>include copies of OSI letters to investigators</i>)	8/23/17
Clinical Microbiology <input checked="" type="checkbox"/> None	
❖ Clinical Microbiology Team Leader Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> No separate review
Clinical Microbiology Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None
Biostatistics <input type="checkbox"/> None	
❖ Statistical Division Director Review(s) (<i>indicate date for each review</i>)	See 11/16/17 Multidisciplinary Review Section 16
Statistical Team Leader Review(s) (<i>indicate date for each review</i>)	See 11/16/17 Multidisciplinary Review Section 8
Statistical Review(s) (<i>indicate date for each review</i>)	See 11/16/17 Multidisciplinary Review Section 8

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

Clinical Pharmacology <input type="checkbox"/> None	
❖ Clinical Pharmacology Division Director Review(s) <i>(indicate date for each review)</i>	See 11/16/17 Multidisciplinary Review Section 15
Clinical Pharmacology Team Leader Review(s) <i>(indicate date for each review)</i>	See 11/16/17 Multidisciplinary Review Section 6
Clinical Pharmacology review(s) <i>(indicate date for each review)</i>	See 11/16/17 Multidisciplinary Review Section 6
❖ OSI Clinical Pharmacology Inspection Review Summary <i>(include copies of OSI letters)</i>	<input checked="" type="checkbox"/> None requested
Nonclinical <input type="checkbox"/> None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) <i>(indicate date for each review)</i>	See 11/16/17 Multidisciplinary Review Section 14
• Supervisory Review(s) <i>(indicate date for each review)</i>	See 11/16/17 Multidisciplinary Review Section 5
• Pharm/tox review(s), including referenced IND reviews <i>(indicate date for each review)</i>	See 11/16/17 Multidisciplinary Review Section 5
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> None
❖ Statistical review(s) of carcinogenicity studies <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> No carc
❖ ECAC/CAC report/memo of meeting	11/13/17 Supervisory Review
❖ OSI Nonclinical Inspection Review Summary <i>(include copies of OSI letters)</i>	<input checked="" type="checkbox"/> None requested
Product Quality <input type="checkbox"/> None	
❖ Product Quality Discipline Reviews ⁶	
• Tertiary review <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> None
• Secondary review (e.g., Branch Chief) <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> None
• Integrated Quality Assessment (contains the Executive Summary and the primary reviews from each product quality review discipline) <i>(indicate date for each review)</i>	Executive Summary 11/14/17 Drug Substance and Quality 10/21/17 Drug Product 10/17/17 Drug Product Micro 11/15/17 Drug Substance Micro 11/14/17; 10/13/17 Immunogenicity 10/16/17 Facility 11/9/17
❖ Reviews by other disciplines/divisions/Centers requested by product quality review team <i>(indicate date of each review)</i>	<input checked="" type="checkbox"/> None

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

❖ Environmental Assessment (check one) (original and supplemental applications)	
<input checked="" type="checkbox"/> Categorical Exclusion (<i>indicate review date</i>) (<i>all original applications and all efficacy supplements that could increase the patient population</i>)	Page 8 of CMC review dated 10/21/17
<input type="checkbox"/> Review & FONSI (<i>indicate date of review</i>)	
<input type="checkbox"/> Review & Environmental Impact Statement (<i>indicate date of each review</i>)	
❖ Facilities Review/Inspection	
<input type="checkbox"/> Facilities inspections (<i>indicate date of recommendation; within one week of taking an approval action, confirm that there is an acceptable recommendation before issuing approval letter</i>) (<i>only original applications and efficacy supplements that require a manufacturing facility inspection (e.g., new strength, manufacturing process, or manufacturing site change)</i>)	<input checked="" type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation <input type="checkbox"/> Not applicable

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

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

/s/

LAURA C WALL
11/16/2017

From: [Wall, Laura](#)
To: [Robyn Harrington](#)
Cc: schmidt.matthew@gene.com; [Wall, Laura](#)
Subject: BLA 761083 - FDA Labeling Revisions - Please respond ASAP
Date: Monday, November 13, 2017 3:19:46 PM
Attachments: [BLA 761083 USPI 11.13.17.docx](#)

Hi Robyn,

Please refer to the attached labeling revisions to the USPI for BLA 761083.

I wanted to remind you to review the revised labeling with your team by:

- Accepting changes that you agree with
- Making any edits that you do not agree with using track-changes only (***do not reject any changes that the FDA proposed and do not delete any of the FDA's comments***).

If you agree with the edits, you can send a clean version which we can consider as final agreed-upon labeling.

Please send your response via e-mail and officially to your BLA **as soon as possible**.

Kindly confirm receipt.

Thanks,

Laura

14 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/

LAURA C WALL
11/13/2017

Wall, Laura

From: Wall, Laura
Sent: Thursday, November 09, 2017 10:25 AM
To: Christopher Templin
Subject: RE: Templin Christopher M USFDA BLA761083

Hello Christopher,
Thank you very much for your prompt response, I appreciate it.
Kind regards,
Laura

From: Christopher Templin [mailto:christophermtemplin1975@gmail.com]
Sent: Thursday, November 09, 2017 10:22 AM
To: Wall, Laura <Laura.Wall@fda.hhs.gov>
Subject: Re: Templin Christopher M USFDA BLA761083

Hello Laura,

Thank you for this update,

I sort of figured something might have been switches because when I read it it didn't jive with the other things I read.

My recommendation wouldn't change at all and I figured it out because if the person was on the product prophylaxis it would only make sense the bleeding rate was better then if the person was only an on demand user.

No worries and thanks again for your diligence and commitment to your work.

Best Regards, Christopher M Templin

Sent from my BlackBerry 10 smartphone on the Verizon Wireless 4G LTE network.

From: Wall, Laura
Sent: Thursday, November 9, 2017 10:15 AM
To: Christopher Templin
Cc: Wall, Laura
Subject: RE: Templin Christopher M USFDA BLA761083

Hello Christopher,

I was informed that there was an error noted in the briefing document, specifically, the data presented in Table 1. Please note the results that were supposed to be under Arm A were supposed to be under Arm B and vice versa.

Can you please confirm if this error changes your recommendation as soon as possible?

Thank you,

Laura

From: Wall, Laura
Sent: Friday, November 03, 2017 4:11 PM
To: Christopher Templin <christophermtemplin1975@gmail.com>
Subject: RE: Templin Christopher M USFDA BLA761083

Hello Christopher,
Thank you, have a wonderful weekend as well.
Kind regards,
Laura

From: Christopher Templin [<mailto:christophermtemplin1975@gmail.com>]
Sent: Friday, November 03, 2017 2:55 PM
To: Wall, Laura <Laura.Wall@fda.hhs.gov>
Subject: Re: Templin Christopher M USFDA BLA761083

Hello Laura, Your Welcome, Sorry if it took a while, I went thru many drafts and wanted to get it right since my name, reputation and legacy was and is on the line. Have a wonderful weekend. Regards Christopher M Templin

Sent from my BlackBerry 10 smartphone on the Verizon Wireless 4G LTE network.

From: Wall, Laura
Sent: Friday, November 3, 2017 2:52 PM
To: Christopher Templin
Subject: RE: Templin Christopher M USFDA BLA761083

Hello Christopher,
Thank you, I am confirming receipt. If we have any questions, I will let you know. Thank you very much for your time and prompt response.
Kind regards,
Laura

From: Christopher Templin [<mailto:christophermtemplin1975@gmail.com>]
Sent: Friday, November 03, 2017 2:07 PM
To: Wall, Laura <Laura.Wall@fda.hhs.gov>
Cc: christophermtemplin1975@gmail.com
Subject: Fw: Templin Christopher M USFDA BLA761083

Hello Laura,

I hope this information is what the FDA is looking for from me.

I have attached a signed PDF of my document and a word file of the document.

Feel free to contact me if you have any issues with what I created.

Best Regards, Christopher M Templin

Sent from my BlackBerry 10 smartphone on the Verizon Wireless 4G LTE network.

From: amystemplin@gmail.com
Sent: Friday, November 3, 2017 1:48 PM
To: C M TEMPLIN

Subject: Templin Christopher M USFDA BLA761083

TO: Christopher M Templin, EYES ONLY

Sent from [Mail](#) for Windows 10

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

/s/

LAURA C WALL

11/13/2017

Clarification comment dated November 9, 2017 from Patient Advocate SGE regarding the error in the FDA briefing document and the SGE's conclusion remains unchanged.

From: [Wall, Laura](#)
To: [Robyn Harrington](#)
Cc: [Wall, Laura](#)
Subject: BLA 761083 - FDA Labeling Revisions - Please respond no later than COB November 9, 2017
Date: Wednesday, November 08, 2017 2:42:26 PM
Attachments: [BLA 761083 USPI 11.8.17.docx](#)

Hi Robyn,

Please refer to the attached labeling revisions to the USPI for BLA 761083.

I wanted to remind you to review the revised labeling with your team by:

- Accepting changes that you agree with
- Making any edits that you do not agree with using track-changes only (***do not reject any changes that the FDA proposed and do not delete any of the FDA's comments***)

Please send your response via e-mail and officially to your BLA **no later than COB (EST) November 9, 2017.**

Kindly confirm receipt.

Thanks,

Laura

14 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/

LAURA C WALL
11/08/2017

From: [Wall, Laura](#)
To: [Robyn Harrington](#)
Cc: [Wall, Laura](#)
Subject: BLA 761083 - MG and IFU Labeling - Please respond as soon as possible
Date: Wednesday, November 08, 2017 11:39:31 AM
Attachments: [BLA 761083 MG.docx](#)
[BLA 761083 IFU.docx](#)

Hi Robyn,

Please refer to the attached labeling for the BLA 761083 MG and IFU. The USPI will be forthcoming. If you are in agreement with the MG and IFU, then they can constitute final labeling.

Please send your response via e-mail and officially to your BLA **as soon as possible**. I realize that you will have to attach the MG to the USPI; hence, you will need to receive the USPI prior to formally submitting the final-agreed upon labeling for the MG.

Kindly confirm receipt.

Thanks,

Laura

18 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/

LAURA C WALL
11/08/2017

From: [Wall, Laura](#)
To: [Robyn Harrington](#)
Cc: [Wall, Laura](#)
Subject: BLA 761083 - Clinical Pharmacology PMCs - Please respond by 3 PM (EST) November 8, 2017
Date: Tuesday, November 07, 2017 3:08:07 PM
Attachments: [Clinical Pharmacology PMCs BLA 761083.docx](#)

Hi Robyn,

Please find the attached clinical pharmacology PMCs. Please provide your response **by 3 PM (EST) Wednesday, November 8, 2017** via e-mail and officially to your BLA 761083.

Kindly confirm receipt.

Thank you,

Laura

Clinical Pharmacology PMCs for BLA 761083

Conduct an assessment of binding anti-product antibody (APA) responses with a validated assay capable of sensitively detecting APA responses in the presence of emicizumab levels that are expected to be present in the serum at the time of patient sampling. The APA response will be evaluated in at least 50 emicizumab-treated patients. The final report will include information on the level of emicizumab in each patient's test sample at each sampling point.

Final Report Submission: 01/2019

Conduct an assessment of neutralizing anti-product antibody (APA) responses with a validated assay capable of sensitively detecting neutralizing APA responses in the presence of emicizumab levels that are expected to be present in the serum at the time of patient sampling. The neutralizing APA response will be evaluated in at least 50 emicizumab-treated patients. The final report will include information on the level of emicizumab in each patient's test sample at each sampling point.

Final Report Submission: 12/2019

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

/s/

LAURA C WALL
11/07/2017



BLA 761083

**PROPRIETARY NAME REQUEST
WITHDRAWN**

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

ATTENTION: Robyn Harrington
 Regulatory Program Management

Dear Ms. Harrington:

Please refer to your Biologics License Application (BLA) dated and received June 23, 2017, submitted under section 351(a) of the Public Health Service Act for Emicizumab-kxwh, 150 mg/mL, 105 mg/0.7 mL, 60 mg/0.4 mL and 30 mg/mL.

We also refer to:

- Your correspondence, dated and received October 10, 2017, requesting review of your proposed proprietary name, (b) (4)
- Your correspondence, dated and received on October 13, 2017, notifying us that you are withdrawing your request for a review of the proposed proprietary name (b) (4)

This proprietary name request is considered withdrawn as of October 13, 2017.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact me at (240) 402-4156. For any other information regarding this application, contact Laura Wall, Regulatory Project Manager in the Office of New Drugs, at (301) 796-2237.

Sincerely,

{See appended electronic signature page}

Wana Manitsitkul, PharmD, BCPS
Safety Regulatory Project Manager
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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

/s/

WANA MANITPISITKUL
11/06/2017



BLA 761083

**PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE**

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

ATTENTION: Robyn Harrington
Regulatory Program Management

Dear Ms. Harrington:

Please refer to your Biologics License Application (BLA) dated and received June 23, 2017, submitted under section 351(a) of the Public Health Service Act for Emicizumab-kxwh, 150 mg/mL, 105 mg/0.7 mL, 60 mg/0.4 mL and 30 mg/mL.

We also refer to your correspondence, dated and received October 13, 2017, requesting review of your proposed proprietary name, Hemlibra.

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

If any of the proposed product characteristics as stated in your October 13, 2017, submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review. Additionally, if your application receives a complete response, a new request for name review for your proposed name should be submitted when you respond to the application deficiencies.

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

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

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Wana Manitpisitkul, Safety Regulatory Project

Manager in the Office of Surveillance and Epidemiology, at (240) 402-4156. For any other information regarding this application, contact Laura Wall, Regulatory Project Manager in the Office of New Drugs, at (301) 796-2237.

Sincerely,

{See appended electronic signature page}

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

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

/s/

DANIELLE M HARRIS on behalf of TODD D BRIDGES
11/03/2017

Wall, Laura

From: Wall, Laura
Sent: Wednesday, November 01, 2017 4:32 PM
To: 'Robyn Harrington'
Cc: Shiber, Andrew J; Wall, Laura
Subject: BLA 761083 - FDA Information Request CMC PMC 1 and 2 - Please respond by COB, Friday, November 3, 2017
Attachments: CMC PMC 1 and 2 BLA761083 .docx

Hi Robyn,

The team requests that you please respond to the attached CMC PMCs. Please also note that it is merely tracked as a PMC for archival purposes, and the FDA was trying to provide background as to which discipline requested the PMC.

Please send the requested information via e-mail to myself and the CMC RBPM, Andrew Shiber (copied above) and officially to your BLA **by COB, Friday, November 3, 2017**.

Thank you,

Laura

CMC Postmarketing Commitment 1

Develop and validate a sensitive and precise assay for the detection of anti-emicizumab antibodies (ADA). The assay should be capable of sensitively detect ADA responses in the presence of emicizumab levels that are expected to be present in serum at the time of patient sampling. The final report should include screening, confirmation, and titer assay validation reports and assay standard operating procedures.

Sponsor will develop and validate the assay according to the following schedule:

Final Report Submission: January 2019

FDA comment: FDA acknowledges the Roche's commitment to develop an ADA assay with adequate drug tolerance.

You state the new assay drug tolerance will be confirmed in the presence of emicizumab levels of ~ (b) (4) $\mu\text{g/mL}$. The target drug tolerance level of (b) (4) $\mu\text{g/mL}$ is low. The new assay should be capable to detect the ADA in the presence of emicizumab levels that are expected in the majority of patient samples at time of sampling (the determined emicizumab trough plasma concentration is $57.2 \pm 13.5 \mu\text{g/mL}$ for the recommended dose of 1.5 mg/kg/week).

CMC Postmarketing Commitment 2

Develop and validate an assay to evaluate the neutralizing capacity of ADA detected in the patient samples. The assay should be capable of sensitively detect neutralizing ADA in the presence of emicizumab levels that are expected to be present in serum at the time of patient sampling. The final report should include assay validation report and assay standard operating procedure.

Sponsor will develop and validate the assay according to the following schedule:

Final Report Submission: March 2019

FDA comment: FDA does not agree with your proposal (b) (4)

(b) (4)
to evaluate the neutralizing ability of the ADAs.

(b) (4)
Therefore, it is premature to discuss the feasibility of your proposal at this time.

Due to the reasons listed above, a specific assay to evaluate the neutralizing capacity of ADA detected in the patient samples should be pursued.

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

/s/

LAURA C WALL
11/01/2017

From: [Wall, Laura](#)
To: ["Robyn Harrington"](#)
Cc: [Wall, Laura](#)
Subject: BLA 761083 - FDA IFU Labeling Revisions - Please respond by the morning of November 3, 2017
Date: Wednesday, November 01, 2017 10:26:43 AM
Attachments: [BLA 761083 IFU to Applicant 11.1.17.docx](#)

Hi Robyn,

Please refer to the attached labeling revisions to the IFU for BLA 761083.

I wanted to remind you to review the revised labeling with your team by:

- Accepting changes that you agree with
- Making any edits that you do not agree with using track-changes only (***do not reject any changes that the FDA proposed and do not delete any of the FDA's comments***)

Please send your response via e-mail and officially to your BLA **by the morning of Friday, November 3, 2017.**

Kindly confirm receipt.

Thanks,

Laura

16 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/

LAURA C WALL
11/01/2017

From: [Wall, Laura](#)
To: ["Robyn Harrington"](#)
Cc: [Wall, Laura](#)
Subject: BLA 761083 - FDA Labeling Revisions - Please respond by the morning of November 3, 2017
Date: Wednesday, November 01, 2017 8:28:58 AM
Attachments: [BLA 761083 PI to Applicant 11.1.17.docx](#)
[BLA 761083 Med Guide to Applicant 11.1.17.docx](#)

Hi Robyn,

Please refer to the attached labeling revisions to the USPI and Med Guide for BLA 761083.

I wanted to remind you to review the revised labeling with your team by:

- Accepting changes that you agree with
- Making any edits that you do not agree with using track-changes only (***do not reject any changes that the FDA proposed and do not delete any of the FDA's comments***)

Please send your response via e-mail and officially to your BLA **by the morning of Friday, November 3, 2017.**

Kindly confirm receipt.

Thanks,

Laura

18 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

MEMORANDUM OF TELECONFERENCE

Teleconference Date: October 31, 2017

Application Number: BLA 761083

Product Name: emicizumab

Sponsor/Applicant Name: Genentech, Inc.

Subject: The Agency consulted a patient advocate SGE.

FDA Participants

R. Angelo de Claro, MD, Clinical Team Leader

Lori Ehrlich, MD, PhD, Clinical Reviewer

Laura Wall, MS, Regulatory Project Manager

Patient Advocate SGE

Mr. Christopher Templin

1.0 BACKGROUND: The Agency consulted a patient advocate SGE for BLA 761083 emicizumab. The patient advocate SGE reviewed the Agency's briefing document in advance of this teleconference.

2.0 DISCUSSION: The patient advocate's response to the Agency's briefing document was discussed. The Agency acknowledged the patient advocate's response and requested that he send us written responses within one week after the teleconference.

3.0 ACTION ITEMS: The patient advocate SGE acknowledged the Agency's request and noted that he will submit responses to the Agency within one week after the teleconference.

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

/s/

LAURA C WALL
11/03/2017

Kolibab, Kristopher

From: Kolibab, Kristopher
Sent: Friday, October 27, 2017 10:10 AM
To: robynh@gene.com
Subject: BLA 761083/Carton Information Request/Due October 31

Hello Robyn,

Please refer to BLA 761083. Per the request of the review team please provide a response to the following information request by email to me and Laura Wall and officially submit to the BLA **by 2PM (EDT) October 31, 2017.**

Information Request:

1. Ensure the Medication Guide statement (“ATTENTION: Dispense the enclosed Medication Guide to each patient”) appears on the carton labeling per 21 CFR 208.24(d).

Please confirm receipt of this message via e-mail.

Regards,

Kris Kolibab, PhD
Senior Regulatory Health Project Manager
Center for Drug Evaluation and Research
Office of Hematology and Oncology Products
Division of Hematology Products
U.S. Food and Drug Administration

Tel: 240-402-0277



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

/s/

KRISTOPHER KOLIBAB
10/27/2017

From: [Wall, Laura](#)
To: [Robyn Harrington](#)
Cc: [Wall, Laura](#)
Subject: BLA 761083 - FDA Labeling Revisions to MG - Please send MG back with revised USPI and IFU by 3 PM (EST) October 26, 2017
Date: Tuesday, October 24, 2017 9:46:29 AM
Attachments: [BLA 761083 MG 10.24.17.docx](#)

Hi Robyn,

Please refer to the attached labeling revisions to the Med Guide (MG).

I wanted to remind you to review the revised labeling with your team by:

- Accepting changes that you agree with
- Making any edits that you do not agree with using track-changes only (***do not reject any changes that the FDA proposed and do not delete any of the FDA's comments***)

Please send your response **by 3 PM (EST) October 26, 2017 along with the revised USPI and IFU.**

Kindly confirm receipt.

Thanks,

Laura

3 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/

LAURA C WALL
10/24/2017

From: [Wall, Laura](#)
To: [Robyn Harrington](#)
Cc: [Wall, Laura](#)
Subject: BLA 761083 - FDA Labeling Revisions - Please respond by 11 AM (EST) October 24, 2017
Date: Thursday, October 19, 2017 4:07:10 PM
Attachments: [BLA 761083 USPI 10.19.17.docx](#)
[BLA 761083 IFU 10.19.17.docx](#)

Hi Robyn,

Please refer to the attached labeling revisions to the prescribing information (PI) and instructions for use (IFU) for BLA 761083. Revisions will be forthcoming to the Patient Information.

I wanted to remind you to review the revised labeling with your team by:

- Accepting changes that you agree with
- Making any edits that you do not agree with using track-changes only (***do not reject any changes that the FDA proposed and do not delete any of the FDA's comments***)

Please send your response **by 11 AM (EST) October 24, 2017 or sooner if possible as we would like to discuss during the Late Cycle teleconference.**

Kindly confirm receipt.

Thanks,

Laura

32 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/

LAURA C WALL
10/19/2017

From: [Wall, Laura](#)
To: [Robyn Harrington](#)
Cc: [Wall, Laura](#)
Subject: BLA 761083 - FDA Carton and Container Comments - Please respond by 11 AM, October 23, 2017
Date: Wednesday, October 18, 2017 11:18:05 AM
Attachments: [BLA 761083 emicizumab Container Carton Comments 17Oct17.docx](#)

Hi Robyn,

The team requests that you please respond to the attached Information Request regarding FDA's comments to the carton and container labeling for BLA 761083.

Please send me the requested information via e-mail and officially to your application **by 11 AM, October 23, 2017** or sooner if you are able.

Kindly confirm receipt.

Thanks,

Laura

BLA 761083
Hemlibra (emicizumab)
Container Labels and Carton Labeling Comments

We have the following comments regarding your email response submitted on October 10, 2017 to the Agency container labels and carton labeling comments. Submit revised container label and carton labeling with the recommended revisions.

A. General Comments

1. Your proposed nonproprietary name suffix 'kxwh' was found conditionally acceptable. Therefore, revise the proper name to read 'emicizumab-kxwh' on the container labels, carton labeling and throughout all labeling.

B. Carton Labeling

1. We acknowledge the Applicant's concern and agree to not to include the statement "Write the date removed from the refrigerator ___/___/___".

To clarify that the storage statement is referring to an unopened vial, we recommend that the statement read "**Storage:** Refrigerate at 2°C to 8°C (36°F to 46°F) in the original carton to protect from light. Do Not Freeze. Do Not Shake. If the unopened vial is stored out of and then returned to refrigeration, the total combined time out of refrigeration should not exceed 7 days or temperatures above 30°C (86°F)."

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

/s/

LAURA C WALL
10/18/2017

From: Wall, Laura
To: ["Robyn Harrington"](#)
Subject: RE: BLA 761083 - FDA Labeling Revisions for PI and IFU - Please respond by 4 PM (EST) October 12, 2017
Date: Friday, October 13, 2017 11:23:39 AM

Hi Robyn,

I was informed that we can use the scheduled teleconference on Oct 24th (the late-cycle meeting) to discuss questions related to labeling. Please provide a prioritized list of questions that you would like to discuss a few days prior to the teleconference on October 24, 2017 at 3 PM (EST) to facilitate our discussion.

Kindly confirm receipt.

Thanks,

Laura

From: Robyn Harrington [mailto:robynh@gene.com]
Sent: Thursday, October 12, 2017 4:01 PM
To: Wall, Laura
Subject: Re: BLA 761083 - FDA Labeling Revisions for PI and IFU - Please respond by 4 PM (EST) October 12, 2017

Hi Laura-

Attached please find the emicizumab USPI and IFU with the Sponsor responses to FDA comments. Please note that I have also included a response document for a few of the USPI comments. These will be formally submitted to the BLA with both clean, redlined and pdf versions shortly.

With respect to FDA's comments on the Health Related Quality of Life sections, I would like to ask if FDA would be amenable to a short teleconference to discuss. We have not provided our responses in this document. We can be available almost anytime except October 18th from 11:30 am - 1:00 pm EST.

Many thanks in advance-

Robyn

On Fri, Oct 6, 2017 at 9:25 AM, Wall, Laura <Laura.Wall@fda.hhs.gov> wrote:

Hi Robyn,

Please refer to the attached labeling revisions to the prescribing information (PI) and instructions for use (IFU) for BLA 761083. Please note that patient information was omitted, as revisions to that will be forthcoming.

I wanted to remind you to review the revised labeling with your team by:

- Accepting changes that you agree with
- Making any edits that you do not agree with using track-changes only (***do not reject any changes that the FDA proposed and do not delete any of the FDA's comments***)

Please send your response **by 4 PM (EST) October 12, 2017.**

Kindly confirm receipt.
Thanks,

Laura

--

Robyn Harrington
Product Development Regulatory - Program Management
Genentech, Inc.
1 DNA Way, MS 241b
South San Francisco, CA 94080
Ph: [650.467.5133](tel:650.467.5133)
Mobile: (b) (6)

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

/s/

LAURA C WALL
10/13/2017



BLA 761083

INFORMATION REQUEST

Genentech, Inc.
Attn: Robyn Harrington
Regulatory Program Management
1 DNA Way
South San Francisco, California 94080

Dear Ms. Harrington:

Please refer to your Biologics License Application 761083 received June 23, 2017, submitted under section 351(a) of the Public Health Service Act for emicizumab.

We are reviewing your submission and have the following comment. We request a prompt written response in order to continue our evaluation of your application. Please submit your response prior to COB: **October 12, 2017**.



If you have any questions, please contact me at 301-796-4798.

Sincerely,

Andrew Shiber
-S

Digitally signed by Andrew Shiber S
DN: c US, o U.S. Government, ou HHS
ou FDA, ou People, cn Andrew Shiber S
0.9.2342.19200300.100.1.1.0014262141
Date: 2017.10.10 15:24:33 -0400

CDR Andrew Shiber, Pharm.D.
United States Public Health Service
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research



Andrew
Shiber

Digitally signed by Andrew Shiber

Date: 10/10/2017 03:26:41PM

GUID: 508da6dc000266f39bb039bf6ed30638

From: Wall, Laura
To: ["Robyn Harrington"](#)
Subject: RE: BLA 761083 - FDA Labeling Revisions for PI and IFU - Please respond by 4 PM (EST) October 12, 2017
Date: Tuesday, October 10, 2017 11:52:56 AM

Hi Robyn,

I was informed that given the timelines, we will not be able to review your proposed suffixes and that emicizumab-kxwh will be the proper name designated in the license, and you should revise the proposed labels and labeling accordingly.

Kindly confirm receipt.

Thank you,

Laura

From: Robyn Harrington [mailto:robynh@gene.com]
Sent: Friday, October 06, 2017 5:23 PM
To: Wall, Laura
Subject: Re: BLA 761083 - FDA Labeling Revisions for PI and IFU - Please respond by 4 PM (EST) October 12, 2017

Hi Laura-

Great, many thanks for the update.

Robyn

On Fri, Oct 6, 2017 at 12:19 PM, Wall, Laura <Laura.Wall@fda.hhs.gov> wrote:
Hi Robyn,
I followed-up with the team, and I was informed that we will be updating you next week.
Thanks for checking,
Laura

From: Robyn Harrington [mailto:robynh@gene.com]
Sent: Friday, October 06, 2017 1:33 PM
To: Wall, Laura
Subject: Re: BLA 761083 - FDA Labeling Revisions for PI and IFU - Please respond by 4 PM (EST) October 12, 2017

Hi Laura-

Many thanks for the comment. Should I assume that the Agency is not going to review the suffixes we submitted this week and include kxwh? Or should I include a placeholder (e.g. xxxx)?

Thanks again!

Robyn

On Fri, Oct 6, 2017 at 9:52 AM, Wall, Laura <Laura.Wall@fda.hhs.gov> wrote:
Hi Robyn,

Thank you for confirming receipt. Also, please find the below additional comment that the team would like addressed in the labeling:

Revise the non-proprietary name to incorporate the four-letter suffix throughout the product labeling. Per the “FDA Guidance for Industry: Nonproprietary Naming of Biological Products”, “biological products licensed under the PHS Act” should bear “a nonproprietary name that includes an FDA-designated suffix”.

Kindly confirm receipt.

Thanks,

Laura

From: Robyn Harrington [mailto:robynh@gene.com]
Sent: Friday, October 06, 2017 12:46 PM
To: Wall, Laura
Subject: Re: BLA 761083 - FDA Labeling Revisions for PI and IFU - Please respond by 4 PM (EST) October 12, 2017

Hi Laura-

Many thanks, I am confirming receipt.

Robyn

On Fri, Oct 6, 2017 at 9:25 AM, Wall, Laura <Laura.Wall@fda.hhs.gov> wrote:
Hi Robyn,
Please refer to the attached labeling revisions to the prescribing information (PI) and instructions for use (IFU) for BLA 761083. Please note that patient information was omitted, as revisions to that will be forthcoming.
I wanted to remind you to review the revised labeling with your team by:
·Accepting changes that you agree with
·Making any edits that you do not agree with using track-changes only (***do not reject any changes that the FDA proposed and do not delete any of the FDA’s comments***)
Please send your response **by 4 PM (EST) October 12, 2017**.
Kindly confirm receipt.

Thanks,

Laura

--

Robyn Harrington
Product Development Regulatory - Program Management
Genentech, Inc.
[1 DNA Way](#), MS 241b
South San Francisco, CA 94080
Ph: [650.467.5133](#)
Mobile: [REDACTED] (b) (6)

--

Robyn Harrington
Product Development Regulatory - Program Management
Genentech, Inc.
[1 DNA Way](#), MS 241b
South San Francisco, CA 94080
Ph: [650.467.5133](#)
Mobile: [REDACTED] (b) (6)

--

Robyn Harrington
Product Development Regulatory - Program Management
Genentech, Inc.
1 DNA Way, MS 241b
South San Francisco, CA 94080
Ph: 650.467.5133
Mobile: [REDACTED] (b) (6)

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

/s/

LAURA C WALL
10/10/2017



BLA 761083

INFORMATION REQUEST

Genentech, Inc.
Attn: Robyn Harrington
Regulatory Program Management
1 DNA Way
South San Francisco, California 94080

Dear Ms. Harrington:

Please refer to your Biologics License Application 761083 received June 23, 2017, submitted under section 351(a) of the Public Health Service Act for emicizumab.

We are reviewing your submission and have the following comments. We request a prompt written response in order to continue our evaluation of your application. Please submit your response prior to noon Eastern Standard Time, **Wednesday October 11, 2017.**

(b) (4)



If you have any questions, please contact me at 301-796-4798 or email me at Andrew.Shiber@fda.hhs.gov.

Sincerely,

CDR Andrew Shiber, Pharm.D.
United States Public Health Service
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research
For Andrew Shiber

Oumou K Barry -A

D: digitally signed by Oumou K. Barry, A
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, ou=Oumou K. Barry, A
0.9.2342.19200300.100.1.1=200
0330021
Date: 2017.10.06 17:41:12
04:00

From: [Wall, Laura](#)
To: [Robyn Harrington](#)
Cc: [Wall, Laura](#)
Subject: RE: BLA 761083 - FDA Labeling Revisions for PI and IFU - Please respond by 4 PM (EST) October 12, 2017
Date: Friday, October 06, 2017 12:52:42 PM

Hi Robyn,

Thank you for confirming receipt. Also, please find the below additional comment that the team would like addressed in the labeling:

Revise the non-proprietary name to incorporate the four-letter suffix throughout the product labeling. Per the “FDA Guidance for Industry: Nonproprietary Naming of Biological Products”, “biological products licensed under the PHS Act” should bear “a nonproprietary name that includes an FDA-designated suffix”.

Kindly confirm receipt.

Thanks,

Laura

From: Robyn Harrington [mailto:robynh@gene.com]
Sent: Friday, October 06, 2017 12:46 PM
To: Wall, Laura
Subject: Re: BLA 761083 - FDA Labeling Revisions for PI and IFU - Please respond by 4 PM (EST) October 12, 2017

Hi Laura-

Many thanks, I am confirming receipt.

Robyn

On Fri, Oct 6, 2017 at 9:25 AM, Wall, Laura <Laura.Wall@fda.hhs.gov> wrote:

Hi Robyn,

Please refer to the attached labeling revisions to the prescribing information (PI) and instructions for use (IFU) for BLA 761083. Please note that patient information was omitted, as revisions to that will be forthcoming.

I wanted to remind you to review the revised labeling with your team by:

- Accepting changes that you agree with
- Making any edits that you do not agree with using track-changes only (***do not reject any changes that the FDA proposed and do not delete any of the FDA’s comments***)

Please send your response **by 4 PM (EST) October 12, 2017.**

Kindly confirm receipt.

Thanks,

Laura

--

Robyn Harrington
Product Development Regulatory - Program Management
Genentech, Inc.
1 DNA Way, MS 241b
South San Francisco, CA 94080
Ph: 650.467.5133
Mobile: [REDACTED] (b) (6)

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

/s/

LAURA C WALL
10/06/2017

From: [Wall, Laura](#)
To: [Robyn Harrington](#)
Cc: [Wall, Laura](#)
Subject: BLA 761083 - FDA Labeling Revisions for PI and IFU - Please respond by 4 PM (EST) October 12, 2017
Date: Friday, October 06, 2017 12:25:44 PM
Attachments: [BLA 761083 IFU to GNT 10.6.17.docx](#)
[BLA 761083 PI to GNT 10.6.17.docx](#)

Hi Robyn,

Please refer to the attached labeling revisions to the prescribing information (PI) and instructions for use (IFU) for BLA 761083. Please note that patient information was omitted, as revisions to that will be forthcoming.

I wanted to remind you to review the revised labeling with your team by:

- Accepting changes that you agree with
- Making any edits that you do not agree with using track-changes only (***do not reject any changes that the FDA proposed and do not delete any of the FDA's comments***)

Please send your response **by 4 PM (EST) October 12, 2017**.

Kindly confirm receipt.

Thanks,

Laura

34 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/

LAURA C WALL
10/06/2017

From: [Wall, Laura](#)
To: [Robyn Harrington](#)
Cc: [Wall, Laura](#)
Subject: BLA 761083 - FDA Labeling Information Request - Carton/Container - Please respond by October 10, 2017
Date: Friday, October 06, 2017 10:45:47 AM
Attachments: [BLA 761083 emicizumab Container Carton Comments.docx](#)

Hi Robyn,

The team requests that you please respond to the attached carton/container labeling comments for BLA 761083 emicizumab **by October 10, 2017**. Please note that the comments for the PI/PPI/IFU will be forthcoming.

Kindly confirm receipt.

Thanks,

Laura

3 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/

LAURA C WALL
10/06/2017



BLA 761083

MID-CYCLE COMMUNICATION

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

Dear Ms. Harrington:

Please refer to your Biologic License Application (BLA) submitted under section 351(a) of the Public Health Service Act for emicizumab injection, 150 mg/mL (1.0, 0.7, 0.4 mL); 30 mg/1.0 mL.

We also refer to the teleconference between representatives of your firm and the FDA on September 28, 2017. The purpose of the teleconference was to provide you an update on the status of the review of your application.

A record of the teleconference is enclosed for your information.

If you have any questions, call Laura Wall, Regulatory Project Manager at (301) 796-2237.

Sincerely,

{See appended electronic signature page}

R. Angelo de Claro, MD
Clinical Team Leader
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

Enclosure:
Mid-Cycle Communication



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MID-CYCLE COMMUNICATION

Meeting Date and Time: September 28, 2017 at 10:00 AM (EST)
Application Number: BLA 761083
Product Name: emicizumab
Proposed Indication: For routine prophylaxis to prevent bleeding or reduce the frequency of bleeding episodes in patients with hemophilia A (congenital factor VIII deficiency) with factor VIII inhibitors
Applicant Name: Genentech, Inc.
Meeting Chair: R. Angelo de Claro, MD, Clinical Team Leader
Meeting Recorder: Laura Wall, MS, Regulatory Project Manager

FDA ATTENDEES

Office of Hematology and Oncology Products (OHOP), Division of Hematology Products (DHP)

Ann Farrell, MD, Director
Paul Kluetz, MD, Associate Director for Clinical Science
R. Angelo de Claro, MD, Clinical Team Leader
Lori Ehrlich, MD, PhD, Clinical Reviewer
Theresa Carioti, MPH, Chief, Project Management Staff
Diane Leaman, BS, Safety Regulatory Project Manager
Laura Wall, MS, Regulatory Project Manager

OHOP, Division of Hematology Oncology Toxicology (DHOT)

Christopher Sheth, PhD, Supervisory Pharmacologist/Toxicologist
Shwu-Luan Lee, PhD, Pharmacologist Reviewer

Office of Clinical Pharmacology, Division of Clinical Pharmacology V

Stacy Shord, PharmD, Clinical Pharmacology Team Leader
Yuhong Chen, MD, PhD, Clinical Pharmacology Reviewer
Jiang Liu, PhD, Pharmacometrics Team Leader

Office of Biostatistics, Division of Biometrics V

Yuan Li Shen, DrPH, Biometrics Team Leader
Xin Gao, PhD, Biometrics Reviewer

Office of Biotechnology Products, Division of Biotechnology Review and Research IV

Bazarragchaa Damdinsuren, MD, PhD, RAC, Product Quality Team Leader
Aimee Cunningham, PhD, Product Quality Staff Fellow
Marion Michaelis, PhD, Facility Reviewer

Office of Surveillance and Epidemiology

Page Crew, PharmD, MPH, BCPS, Pharmacist, Division of Pharmacovigilance II
Mei-Yean Chen, PharmD, Risk Management Analyst, Division of Risk Management

Office of Prescription Drug Promotion (OPDP)

Robert Nguyen, PharmD, RPh, Regulatory Review Officer

Patient Labeling

Morgan Walker, PharmD, Patient Labeling Reviewer

Clinical Outcomes Assessment

Selena Daniels, PharmD, Clinical Outcomes Assessment Team Leader
Nikunj Patel, PharmD, Clinical Outcomes Assessment Reviewer

APPLICANT ATTENDEES

Elina Asikanius – Senior Statistical Scientist
Jacques Bourquin, PhD – Technical Development Leader
Olivier Catalani - Statistician
Tiffany Chang, MD – Associate Medical Director
Stefan Gottschalk, PhD – Technical Regulatory Leader
Robyn Harrington – Senior Regulatory Program Director
Cristin Hubbard – Lifecycle Leader
Gallia Levy, MD, PhD – Global Development Team Leader
Bruce McCall, MD - Senior Safety Science Leader
Dorothy Nguyen, MD – Safety Science Leader
Bao Phan, PharmD – Global Regulatory Leader
Matt Schmidt – Regulatory Program Manager
Christophe Schmitt, PharmD - Clinical Pharmacologist
Cami Sima MD, MS – Real World Data Scientist
Markus Stephan-Gueldner, PhD – Nonclinical Toxicology
Marianne Uguen - Statistician
Michael Winter, DVM, PhD – Nonclinical Pharmacologist
Jin Xu, PhD – Clinical Scientist

1.0 INTRODUCTION

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

2.0 SIGNIFICANT ISSUES

The Agency noted that the proposed response timeline of November 2017 to FDA Form 483 Observation 1 issued on the DP facility Pre-license Inspection may affect the Agency's ability to take an early action.

Meeting Discussion: The Applicant proposed to submit the response (i.e., related to smoke study) by October 20, 2017. The Agency acknowledged the Applicant's proposal.

3.0 INFORMATION REQUESTS

Your responses to the CMC Information Requests dated September 19, 2017 are expected on September 28, 2017 and October 4, 2017.

Your response to the September 26, 2017 Clinical Pharmacology Information Request should be submitted by October 4, 2017.

Meeting Discussion: The Agency acknowledged the Applicant's response to the CMC Information Requests (attached slide below). The Agency agreed with the proposed date of October 17, 2017 for the submission of the regulatory binding sections; however, an earlier submission date would be appreciated. Regarding bullet number 4 on the slide, the Agency requested clarification as to whether these would affect established conditions and timelines for the submission. The Applicant stated they will provide a response after the meeting.

The Agency provided clarification regarding the clinical pharmacology Information Request. The Applicant acknowledged the clarification and requested an extension to the October 4, 2017 deadline. The Agency noted the extension request and stated that the extension request date should be submitted to the Agency for consideration.

4.0 MAJOR SAFETY CONCERNS/RISK MANAGEMENT

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

We would also like to inform you of our intention to include the following reporting requirement in the action letter for this product, if approved:

For a period of 5 years, submit all cases of thrombotic microangiopathy and thromboembolic events reported with emicizumab as 15-day Alert reports (as described under 21 CFR (b) (4), and provide detailed analyses of events of thrombotic microangiopathy and thromboembolic events reported from clinical study and post-marketing reports in your periodic safety report. These analyses should show cumulative data relative to the date of approval of emicizumab as well as relative to prior periodic safety reports. Medical literature reviews for case reports/case series of thrombotic microangiopathy and thromboembolic events reported with emicizumab should also be provided in the periodic safety report.

Meeting Discussion: The Agency discussed the above Reporting Requirements. The Applicant acknowledged the Reporting Requirements.

5.0 ADVISORY COMMITTEE MEETING

An Advisory Committee meeting is not planned.

Meeting Discussion: The Applicant acknowledged that there will be no Advisory Committee Meeting.

6.0 LATE-CYCLE MEETING /OTHER PROJECTED MILESTONES

As we indicated during the Mid-Cycle Communication, we plan to act early on this application under an expedited review. The Late-Cycle Meeting between you and the review team is currently scheduled for October 24, 2017. 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.

Immunogenicity PMCs:

1. Develop and validate a sensitive and precise assay for the detection of anti-emicizumab antibodies (ADA). The assay should be capable of sensitively detect ADA responses in the presence of emicizumab levels that are expected to be present in serum at the time of patient sampling. Submit screening, confirmation and titer assay validation reports and assay SOPs to the FDA.
2. Develop and validate an assay to evaluate the neutralizing capacity of ADA detected in the patient samples. The assay should be capable of sensitively detect neutralizing ADA in the presence of emicizumab levels that are expected to be present in serum at the time of patient sampling. Submit assay validation report and assay SOP to the FDA.

Clinical Pharmacology:

The development of antiproduct antibodies appears to affect the pharmacokinetics, safety and activity of emicizumab. The following study will likely be requested as a post marketing commitment.

1. Conduct an assessment of binding and neutralizing anti-product antibody (APA) responses with a validated assay capable of sensitively detecting APA responses in the presence of emicizumab levels that are expected to be present in the serum at the time of patient sampling. The APA response will be evaluated in at least 50 emicizumab-treated patients. The final report will include information on the level of emicizumab in each patient's test sample at each sampling point.

Meeting Discussion: The Agency discussed the aforementioned proposed post marketing commitments (PMCs) and stated that the PMCs will be communicated to the Applicant for their review. The Applicant acknowledged this request.

The Applicant provided a brief update on the status of their proposed proprietary name, suffixes, and contingency plan dependent on approvability of the proposed proprietary name. The Agency acknowledged the Applicant's proposed proprietary name and suffixes.

2 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

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

/s/

ROMEO A DE CLARO
10/02/2017

From: [Wall, Laura](#)
To: [Robyn Harrington](#)
Cc: [Wall, Laura](#)
Subject: BLA 761083 - FDA Midcycle Communication Agenda
Date: Tuesday, September 26, 2017 10:54:43 AM
Attachments: [BLA 761083 Midcycle communication agenda.docx](#)

Hi Robyn,

I attached the BLA 761083 mid-cycle communication agenda in preparation for our teleconference scheduled on September 28, 2017 at 10 AM (EST). Please also send me your call-in information.

Kindly confirm receipt.

Thanks,

Laura

BLA 761083 emicizumab PDUFA V Program Mid-Cycle Communication Agenda

Introductory Comments

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

1. Significant Review Issues

The Agency notes that the proposed response timeline of November 2017 to FDA Form 483 Observation 1 issued on the DP facility Pre-license Inspection may affect the Agency's ability to take an early action for your application.

2. Information Requests

Your responses to CMC Information Requests dated September 19, 2017 are expected on September 28, 2017 and October 4, 2017.

3. Major Safety Concerns

There are no major safety concerns at this time.

4. Risk Management Update

There is currently no need for a REMS.

5. Advisory Committee Meeting Plans

An Advisory Committee meeting is not planned.

6. Proposed Date and Format for Late-Cycle Meeting (LCM)

This application has been identified for early action under an expedited review. We intend to send you the LCM background package no less than two business days in advance of the scheduled LCM Teleconference on October 24, 2017.

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

/s/

LAURA C WALL
09/26/2017

From: [Wall, Laura](#)
To: [Robyn Harrington](#)
Cc: [Wall, Laura](#)
Subject: BLA 761083 - Clinical Pharmacology Information Request - Please respond by 3 PM (EST) October 4, 2017
Date: Tuesday, September 26, 2017 4:21:49 PM

Hi Robyn,

The clinical pharmacology team requests that you respond to the following Information Request for BLA 761083:

Although the weight-based dosing regimen of emicizumab is well supported by the correlation between CL/F and body weight, we think a body weight band dosing might be more practical in clinical practice. Propose a body weight band dosing regimen for patients (e.g., 6 months and above) based on the PK, efficacy, and safety of emicizumab. Include justification for the proposed weight bands, including modeling and simulation reports, control streams, outputs and codes.

Please send me the requested information via e-mail and officially to your application **by 3 PM (EST) October 4, 2017**.

Kindly confirm receipt.

Thank you,

Laura

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

/s/

LAURA C WALL
09/26/2017



BLA 761083

INFORMATION REQUEST

Genentech, Inc.
Attn: Robyn Harrington
Regulatory Program Management
1 DNA Way
South San Francisco, California 94080

Dear Ms. Harrington:

Please refer to your Biologics License Application 761083 received June 23, 2017, submitted under section 351(a) of the Public Health Service Act for emicizumab.

We are reviewing your submission and have the following comment. We request a prompt written response in order to continue our evaluation of your application. Please submit your response prior to COB **October 6, 2017**.

Please submit the following information in support of BLA 761083/0 for emicizumab, and update the BLA accordingly.

Drug Substance

[Redacted content] (b) (4)

Drug Product

[Redacted content] (b) (4)

(b) (4)

Regional Section: Comparability Protocol

Refer to “Drug Product Secondary Manufacturing Site – Comparability Protocol (Emicizumab)” submitted in the 3.2.R Regional section of the BLA, for an additional drug product manufacturing facility, (b) (4).

There is not enough information in the package to assess the adequacy of the comparability protocol. The comparability protocol lacks sterility assurance criteria, (b) (4) validation plan with predetermined action limits, and validation plan fo (b) (4).

Additionally, the proposal for reporting the data associated with this CP as a CBE-30 may not be acceptable because (b) (4) may require a pre-license inspection, therefore the data associated with this CP may have to be submitted as a PAS.

For the comparability protocol, please address the following:

21. Submit proposed in-process control limits for drug product and (b) (4) (b) (4)

22. Regarding (b) (4) validation:

(b) (4)

23. Submit validation plan and acceptance criteria to demonstrate microbial control (b) (4).

24. Submit validation plan and acceptance criteria for (b) (4) Submit re-validation program and explain how re-validation constitutes worst-case scenarios. The

- PAS should also contain sterility assurance information for all (b) (4) product contact equipment.
25. Submit the validation plan and acceptance criteria for process simulation media fills and the re-validation program. The following information should be included in the PAS:
- a. The container-closure system.
 - b. The medium and the fill volume.
 - c. The date of the fill, total time for the fill, and the number of units filled.
 - d. The (b) (4) conditions for the filled vials (b) (4) should be described.
 - e. The growth promotion test procedures and the growth promotion test results for the media.
 - f. Compare the media fill conditions to those used for routine production ((b) (4) number of personnel and shift changes, duration of fill, number of containers filled, interventions, etc.) and explain how media fills are designed to provide a worst-case challenge for (b) (4) operations.
 - g. Describe the environmental monitoring program. Summarize the environmental monitoring results from each media fill. Indicate the number of samples taken and identify excursions. For viable monitoring excursions, describe any microorganisms that were identified.
 - h. The acceptance criteria for media fills and the actions taken when media fills fail. Briefly describe how positive units are investigated.
 - i. Indicate how often media fills are performed and describe the requalification strategy, such as matrix approach for different container-closure systems, etc.
26. Indicate the container closure integrity test (CCIT) used in (b) (4) If there are changes in the CCIT, submit in the CP the validation plan with acceptance criteria and submit the data in the PAS.

If you have any questions, please contact me at 301-796-4798.

Sincerely,

Andrew Shiber

-S

Digitally signed by Andrew Shiber S
DN: c=US, ou=U.S. Government, ou=HHS,
ou=FDA, ou=People, cn=Andrew Shiber S
0923421920030010011-0014262141
Date: 2017.09.22 15:31:22 -0400

CDR Andrew Shiber, Pharm.D.
United States Public Health Service
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research



Andrew
Shiber

Digitally signed by Andrew Shiber
Date: 9/22/2017 03:35:52PM
GUID: 508da6dc00266f39bb039bf6ed30638





BLA 761083

GENERAL ADVICE

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

ATTENTION: Robyn Harrington
Regulatory Program Management

Dear Ms. Harrington:

Please refer to your Biologics License Application (BLA) dated and received June 23, 2017, submitted under section 351(a) of the Public Health Service Act for Emicizumab, 150 mg/mL, 105 mg/0.7 mL, 60 mg/0.4 mL and 30 mg/mL.

We also refer to our August 1, 2017, correspondence, notifying of the Agency's intention to designate a proper name that includes a four-letter distinguishing suffix that is devoid of meaning for your product.

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

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Wana Manitpisitkul, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (240) 402-4156. For any other information regarding this application, contact Laura Wall, Regulatory Project Manager in the Office of New Drugs, at (301) 796-2237.

Sincerely,

{See appended electronic signature page}

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

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

/s/

LUBNA A MERCHANT
09/21/2017



BLA 761083

INFORMATION REQUEST

Genentech, Inc.
Attn: Robyn Harrington
Regulatory Program Management
1 DNA Way
South San Francisco, California 94080

Dear Ms. Harrington:

Please refer to your Biologics License Application 761083 received June 23, 2017, submitted under section 351(a) of the Public Health Service Act for emicizumab.

We are reviewing your submission and have the following comments. We request a prompt written response in order to continue our evaluation of your application. Please submit your response prior to noon Eastern Standard Time, **September 28, 2017**.

(b) (4)



If you have any questions, please contact me at 301-796-4798.

Sincerely,

CDR Andrew Shiber, Pharm.D.
United States Public Health Service
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research



Andrew
Shiber

Digitally signed by Andrew Shiber
Date: 9/19/2017 01:02:50PM
GUID: 508da6dc00266f39bb039bf6ed30638



From: [Wall, Laura](#)
To: [Robyn Harrington](#)
Cc: [Wall, Laura](#)
Subject: BLA 761083 - FDA Information Request - Please respond by 1pm EST, Wednesday, September 20, 2017
Date: Wednesday, September 13, 2017 2:52:07 PM
Attachments: [recurrent event analysis SUGI.PDF](#)

Hi Robyn,

The clinical and statistical teams request that you please respond to the following Information Request for BLA 761083 (please also see attached reference):

(1) Conduct time-to-first event and time-to-recurrent event analyses for all treated bleeds and all bleeds for patients in the HAVEN-1 trial comparing Arm A (N=35) and Arm B (N=18).

(2) Repeat the analyses in (1) comparing Arm C previous prophylaxis and Arm C emicizumab prophylaxis including only patients who participated in NIS BH29768 (N = 24).

In both analyses, Please structure your data similar to those described in the SUGI paper (i.e. [Start End] structure for each bleeding event plus the first and last brackets, see attached). For patients who do not have a bleeding event, censor the patient at the last follow-up date. Include analyses based on first 24 weeks and repeat analyses for all available data. For time to recurrent event analyses, the Mean Cumulative Function (MCF) with 95% CI of bleeding counts for each treatment arm in analysis (1) or for each efficacy period in analysis (2) should be included. Please also include analyses by The Anderson-Gill method to estimate the rate ratio along with a robust variance estimator.

Please e-mail me and submit officially a summary report, SAS codes, and analysis datasets to your application, by 1pm EST, Wednesday, September 20, 2017.

Kindly confirm receipt.

Thanks,

Laura

8 Page(s) of Copyright Material has been Withheld in Full 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/

LAURA C WALL
09/13/2017



BLA 761083

**PROPRIETARY NAME
TRANSMITTING NON PUBLIC INFORMATION**

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

ATTENTION: Robyn Harrington
Regulatory Program Management

RE: FDA sharing of non-public information concerning **BLA 761083** and regarding proposed proprietary name, Hemlibra.

Dear Ms. Harrington:

Please refer to your Biologics License Application (BLA) dated and received June 23, 2017, submitted under section 351(a) of the Public Health Service Act for Emicizumab, 150 mg/mL, 105 mg/0.7 mL, 60 mg/0.4 mL and 30 mg/mL.

We also refer to:

- Your correspondence, dated received June 28, 2017, requesting review of your proposed proprietary name, Hemlibra.
- Our August 18, 2017, correspondence informing you that your proposed proprietary name, Hemlibra, is unacceptable due to potential medication errors due to confusion with another product's proposed proprietary name that was also under review.
- Our August 18, 2017, correspondence requesting proprietary name disclosure authorization.
- Your correspondence, dated and received August 23, 2017, authorizing disclosure of non-public information concerning BLA 761083 and regarding proposed proprietary name, Hemlibra.

The United States Food and Drug Administration (FDA) and its staff have been authorized to disclose to you the information included below. This disclosure is for the purpose of facilitating discussions between you and the authorized representative [REDACTED] ^{(b) (4)}

[REDACTED] All parties have provided their written consent to this disclosure and agree to hold FDA harmless for any injury caused by this disclosure of their contact information.

The contact information of the other authorized representative has consented to share is as follows:



If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Wana Manitsitkul, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (240) 402-4156. For any other information regarding this application, contact Laura Wall, Regulatory Project Manager in the Office of New Drugs, at (301) 796-2237.

Sincerely,

{See appended electronic signature page}

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

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

/s/

DANIELLE M HARRIS on behalf of TODD D BRIDGES
09/12/2017

From: [Wall, Laura](#)
To: [Robyn Harrington](#)
Cc: [Wall, Laura](#); [Kolibab, Kristopher](#)
Subject: BLA 761083 - FDA Information Request - Please respond by COB Thursday, September 7, 2017
Date: Friday, September 01, 2017 10:26:04 AM
Attachments: [BLA 761083 PRO Data Information Request final copy.pdf](#)

Hi Robyn,

The team requests that you respond to the attached Information Request for BLA 761083 for the PRO findings in BH29884.

Please send me the requested information via e-mail and officially to your application **by COB Thursday, September 7, 2017**. Please note that I am on leave, so you can send the response to me and my colleague, Kristopher Kolibab (copied above).

Kindly confirm receipt.

Thanks,

Laura

BLA 761083 PRO Data Information Request (IR)

Please provide the following to facilitate review of the PRO findings in the pivotal Study BH29884:

1. Any qualitative evidence, if available, to support the relevance of the content of the Haem-A-QoL and EQ-5D-5L instruments for this target patient population. Additionally, provide any relevant user manuals or training materials.
2. Haem-A-QoL and EQ-5D-5L scoring algorithms (including algorithms for transformation for domains and total scores) and procedures used to handle missing data (also see comments on #10. Present percent of missing QoL assessments over time for each score of interest (Haem-A-QoL [total score, physical health subscale] and EQ-5D-5L[VAS and Index Utility Score]), types of missing at 24 weeks (e.g. missing item component data, missing item data, early drop-out) and reasons for drop out if available.
3. Descriptive statistics (N, mean, standard deviation, minimum, maximum, and % missing) for the Haem-A-QoL items using both the transformed and raw scores (e.g., 1=never; 2=rarely; 3=sometimes; 4=often; 5=all the time; not applicable by treatment arm and each study visit (adults only).
4. Line Plots of the mean (\pm 95 % CI) or median (25 & 75% quartiles) of the raw scores and or standardized scores for Haem-A-QoL (total score, physical health subscale) and EQ-5D-5L (VAS and Index Utility Score) over time.
5. Baseline Haem-A-QoL item scores, domain scores, and total score along with item distributions by response categories, and floor and ceiling effects for each Haem-A-QoL item.
6. The data tables provided in the BH29884 CSR for the EQ-5D 5L presents incorrect response options for EQ-5D 5L pain/discomfort and anxiety/depression items. Clarify whether this is in error and provide the updated tables. For Example:
 - EQ-5D-5L Instrument Copy, Pain & Anxiety Domains (BH 29884 CSR, Page 2432):

PAIN / DISCOMFORT

- I have no pain or discomfort
- I have slight pain or discomfort
- I have moderate pain or discomfort
- I have severe pain or discomfort
- I have extreme pain or discomfort

ANXIETY / DEPRESSION

- I am not anxious or depressed
- I am slightly anxious or depressed
- I am moderately anxious or depressed
- I am severely anxious or depressed
- I am extremely anxious or depressed

• **Data Table, Pain & Anxiety Domains (BH 29884 CSR, pp443-444):**

t_prot03_eq5d_il04_ip21_ip11_pain_ITT APPROVED Distribution of EQ-5D-5L Responses by Visit, Pain/Discomfort, ITT
Protocol: BH29884 Snapshot: k29884a Snapshot Date: 16DEC2016 Cutoff Date: 25OCT2016
Arm B: no prophylaxis; Before up-titration

Visit	B: no prophylaxis (N=18)	A: 1.5mg/kg emicizumab QW (N=35)
Baseline		
n	18	33
No problems	8 (44.4%)	9 (27.3%)
Slight problems	6 (33.3%)	13 (39.4%)
Moderate problems	3 (16.7%)	9 (27.3%)
Severe problems	1 (5.6%)	1 (3.0%)
Extreme problems	0	1 (3.0%)

t_prot03_eq5d_il04_ip21_ip11_anx_ITT APPROVED Distribution of EQ-5D-5L Responses by Visit, Anxiety/Depression, ITT
Protocol: BH29884 Snapshot: k29884a Snapshot Date: 16DEC2016 Cutoff Date: 25OCT2016
Arm B: no prophylaxis; Before up-titration

Visit	B: no prophylaxis (N=18)	A: 1.5mg/kg emicizumab QW (N=35)
Baseline		
n	18	33
No problems	12 (66.7%)	25 (75.8%)
Slight problems	4 (22.2%)	3 (9.1%)
Moderate problems	2 (11.1%)	2 (6.1%)
Severe problems	0	3 (9.1%)
Extreme problems	0	0

7. The sample sizes reported in Table 17 in the BH29884 CSR (Page 115) does not match up with the data tables in the CSR nor the label. Please clarify or provide rationale for this discrepancy.

- 8. Supportive data for the pre-specified clinically meaningful change thresholds for the EQ-5D-5L instrument (VAS and index utility score) in the target patient population. Responder definitions should not be based on minimal important difference (MID) estimates. We are interested in thresholds that represent meaningful change versus the minimal amount of change.**
- 9. Thresholds for meaningful within-patient change using anchor-based methods supplemented with both cumulative distribution function (CDF) and probability density function (PDF) curves.**
 - a. Anchor-based methods– examine thresholds separately for the Haem-A-QoL Physical health domain score and total score (adults only) using EQ-5D 5L mobility, usual activities, and pain/discomfort items. [REDACTED] (b) (4) [REDACTED] the proposed responder thresholds are preliminary, and should be examined and confirmed using Haem-A-QoL data from other hemophilia study populations.**
 - b. Provide the following CDF and PDF plots, including sample sizes for each CDF and PDF curve in each plot’s legend, and median scores for each CDF and PDF curve. Adjacent anchor response categories can be collapsed if the sample size within a particular anchor response category is small (with justification provided); however, you should submit both the non-collapsed and collapsed plots. Examples of CDF and PDF are provided at the end of the document:**
 - i. CDF and PDF plots of the Haem-A-QoL total score change scores from baseline to week 24 for all patients by the different anchor response categories of the EQ-5D 5L mobility item at week 24. Similar CDF and PDF plots should be created for each Haem-A-QoL domain separately.**
 - ii. CDF and PDF plots of the Haem-A-QoL total score change scores from baseline to week 24 for all patients by the different anchor response categories of the EQ-5D 5L usual activities item at week 24. Similar CDF and PDF plots should be created for each Haem-A-QoL domain separately.**
 - iii. CDF and PDF plots of the Haem-A-QoL total score change scores from baseline to week 24 for all patients by the different anchor response categories of the EQ-5D 5L pain/discomfort item at week 24. Similar CDF and PDF plots should be created for each Haem-A-QoL domain separately.**
 - iv. CDF and PDF plots of the Haem-A-QoL Physical Health domain change scores from baseline to week 24 by treatment arms (i.e.**

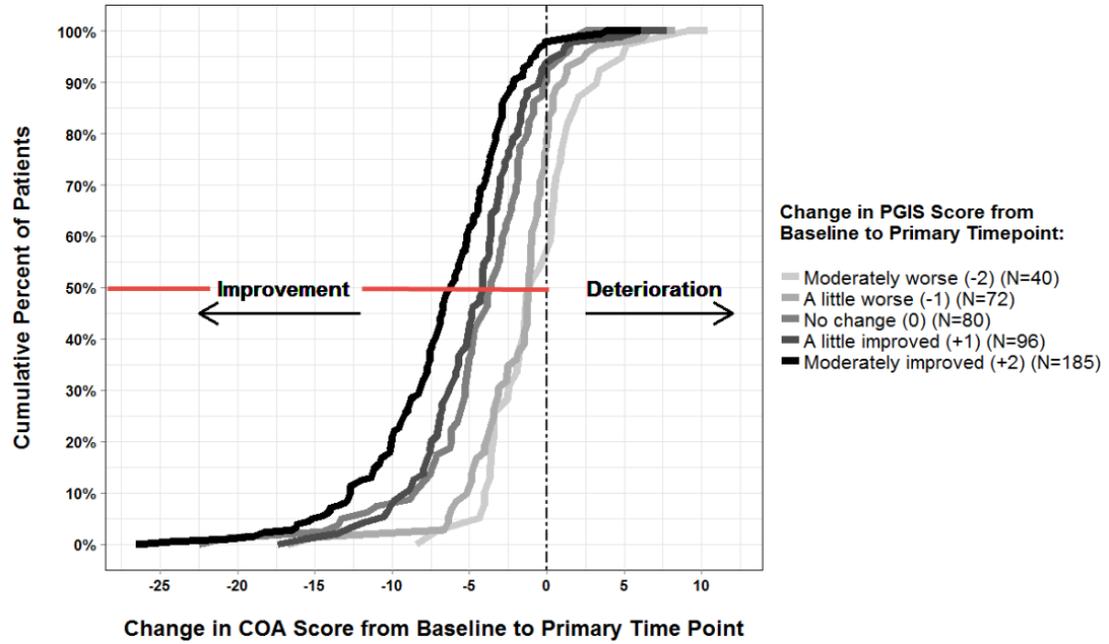
treatment vs. no prophylaxis). Similar CDF and PDF plots should be created for the Haem-A-QoL total score.

- 10. Based on the description of the ANOVA model in the SAP (i.e. model will include, in addition to treatment group, baseline score, time, and treatment by baseline interaction term as covariates). It appears that this analysis may be generated from MMRM (Mixed Effect Model Repeated Measurement) and the missing data imputation for 24 week assessments may be based on the MMRM approach which may require missing at random assumption. We have not been able to locate the SAS programs (either programs used to derived the variables or perform the actual analyses) to confirm. Please clarify the location of the SAS programs and confirm the missing data imputation strategies. Explain why missing at random assumption is appropriate for the corresponding analyses if the MMRM has been used for the analyses considering the small sample sizes and normal assumption may not be met.**
- 11. Explore the normal assumptions for the ANCOA model in the analyses of Haem-A-QoL (total score, physical health subscale) and EQ-5D-5L (VAS and Index Utility Score) at 24 weeks. If the normal assumption is violated, please clarify what additional analyses have been performed to assure robustness of the results.**
- 12. We are not able to identify the variables used for the analyses based on AQS dataset for Haem-A-QoL (total score, physical health subscale) and EQ-5D-5L (VAS and Index Utility Score) at 24 weeks. Please clarify.**

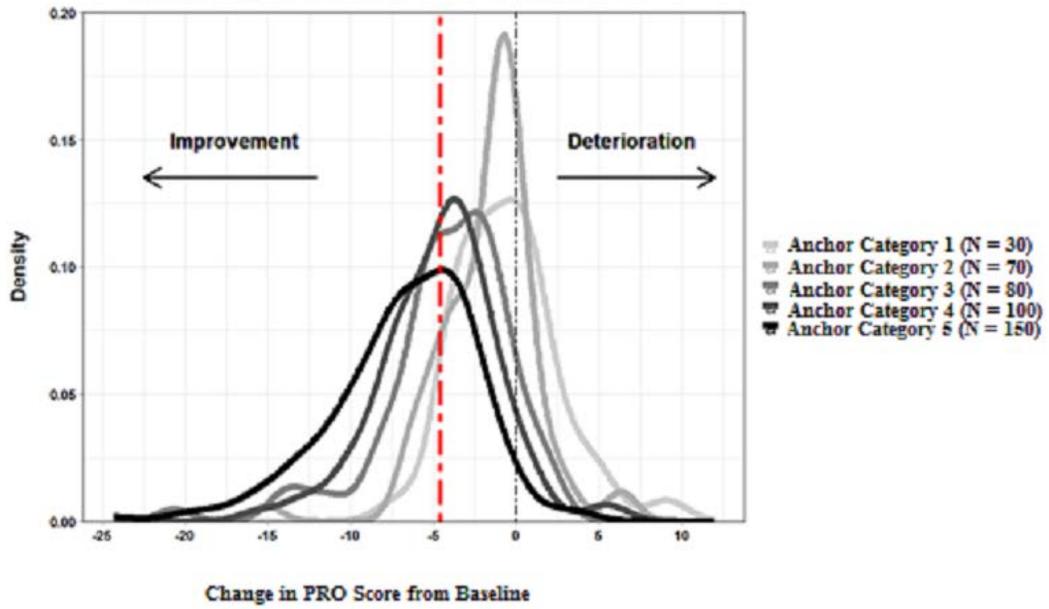
Examples of CDF and PDF curves

EXAMPLE Empirical Cumulative Distribution of Change in COA Score from Baseline to Primary Time Point, by Change in PGIS Score from Baseline to Primary Time Point

Where Change in Score from Baseline to Primary Timepoint = [Score at Primary Time Point] - [Baseline Score]



Example Kernel Density Plot



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

/s/

LAURA C WALL
09/01/2017

From: [Yesmin, Suria](#)
To: robynh@gene.com; schmidt.matthew@gene.com
Cc: [Yesmin, Suria](#); [Baird, Amy](#)
Subject: BLA 761083 Hemlibra/IR/Response Due 09.11.17
Date: Tuesday, August 29, 2017 9:55:52 AM

Dear Robyn and Matt,

With reference to BLA 761083, we have the following request for information. Please respond to the request below via e-mail by **Monday, September 11, 2017** followed by an official submission to the BLA.

Information Request

-
During the course of our review the Agency has noted that your proposed mechanism of action (MOA) for emicizumab is “bridging FIXa and FX”. However, we have not yet located any data indicating that emicizumab specifically binds to FIXa and not to the non-active FXI. The KD values of emicizumab to FIXa and FIX are comparable, i.e., 1.5-1.6 µM, indicating your product binds to both FIXa and FIX with similar affinity. Please provide data and study numbers that point to the evidence that supports your current MOA. Alternatively, modify your MOA statement based on the available data.

Please ***confirm*** receipt.

Thank you,
Suria (on behalf of Laura Wall)

Suria Yesmin

Regulatory Project Manager
Division of Hematology Products (DHP)
FDA/CDER/OHOP
WO22, Room 3224
10903 New Hampshire Avenue
Silver Spring, MD 20993
Phone: 301-348-1725
E-Mail: Suria.Yesmin@fda.hhs.gov

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

/s/

SURIA YESMIN
08/29/2017



BLA 761083

INFORMATION REQUEST

Genentech, Inc.
Attn: Robyn Harrington
Regulatory Program Management
1 DNA Way
South San Francisco, California 94080

Dear Ms. Harrington:

Please refer to your Biologics License Application 761083 received June 23, 2017, submitted under section 351(a) of the Public Health Service Act for emicizumab.

We are reviewing your submission and have the following comments. We request a prompt written response in order to continue our evaluation of your application. Please submit your response prior to noon Eastern Standard Time, **September 1, 2017**.



(b) (4)



(b) (4)

If you have any questions, please contact me at 301-796-4798.

Sincerely,

Andrew Shiber
-S

Digitally signed by Andrew Shiber -S
DN: c=US, o=U.S. Government, ou=HHS,
ou=FDA, ou=People, cn=Andrew Shiber -S,
0.9.2342.19200300.100.1.1=0014262141
Date: 2017.08.25 15:52:38 -0400

CDR Andrew Shiber, Pharm.D.
United States Public Health Service
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research



Andrew
Shiber

Digitally signed by Andrew Shiber
Date: 8/25/2017 03:54:11 PM
GUID: 508da6dc00266f39bb039bf6ed30638





BLA 761083

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

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

Dear Ms. Harrington:

Please refer to your Biologics License Application (BLA) dated June 23, 2017, received June 23, 2017, submitted under section 351(a) of the Public Health Service Act for emicizumab injection, 150 mg/mL (1.0, 0.7, 0.4 mL); 30 mg/1.0 mL.

We also refer to your amendment dated May 31, 2017.

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

However, we plan to act early on this application under an expedited review, provided that no significant application deficiencies or unexpected shifts in work priorities or team staffing prevent an early action.

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

November 23, 2017. This date conforms to the 21st Century Review timeline for your application. If our review continues on an expedited timeline, we may communicate revised dates for labeling and postmarketing requirement/commitment requests. In addition, the planned date for our internal mid-cycle review meeting is September 13, 2017, and the currently scheduled mid-cycle teleconference meeting is September 28, 2017. We are not currently planning to hold an advisory committee meeting to discuss this application.

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

PRESCRIBING INFORMATION

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

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

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

PROMOTIONAL MATERIAL

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

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

Alternatively, you may submit a request for advisory comments electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft Guidance for Industry (available at: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM443702.pdf>).

Do not submit launch materials until you have received our proposed revisions to the package insert (PI), patient PI, and Instructions for Use, and you believe the labeling is close to the final version.

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

REQUIRED PEDIATRIC ASSESSMENTS

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

Because the biological product for this indication has orphan drug designation, you are exempt from this requirement.

If you have any questions, call Laura Wall, Regulatory Project Manager, at (301) 796-2237.

Sincerely,

{See appended electronic signature page}

Ann T. Farrell, MD
Director
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

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

/s/

ANN T FARRELL
08/22/2017



BLA 761083

INFORMATION REQUEST

Genentech, Inc.
Attn: Robyn Harrington
Regulatory Program Management 1 DNA Way
South San Francisco, California 94080

Dear Ms. Harrington:

Please refer to your Biologics License Application 761083 received June 23, 2017, submitted under section 351(a) of the Public Health Service Act for emicizumab.

We are reviewing your submission and have the following comments. We request a prompt written response in order to continue our evaluation of your application. Please submit your response prior to noon Eastern Standard Time, **August 28, 2017**.

1. As agreed during the CMC pre-BLA meeting (April 25, 2017), please submit the following by September 6, 2017:
 - a. Additional stability data available to support the proposed shelf lives for drug substance (DS) and drug product (DP) (FDA Response to Questions 1a and 1b in the meeting minutes).
 - b. DS performance shipping qualification data and DP shipping validation data (Response to Questions 5a and 5b in the meeting minutes).

(b) (4)



If you have any questions, please contact me at 301-796-4798.

Sincerely,

Andrew Shiber -S

Digital y signed by Andrew Shiber S
DN: c=US, o=U S Government, ou=RHS, ou=FDA
ou=People, cn=Andrew Shiber S
0923421920030010011=0014262141
Date: 2017.08.18 16:14:21 -04:00

CDR Andrew Shiber, Pharm.D.
United States Public Health Service
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research



Andrew
Shiber

Digitally signed by Andrew Shiber
Date: 8/18/2017 04:19:54PM
GUID: 508da6dc00266f39bb039bf6ed30638





BLA 761083

**PROPRIETARY NAME REQUEST
UNACCEPTABLE**

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

ATTENTION: Robyn Harrington
 Regulatory Program Management

Dear Ms. Harrington:

Please refer to your Biologics License Application (BLA) dated and received June 23, 2017, submitted under section 351(a) of the Public Health Service Act for Elicizumab, 150 mg/mL, 105 mg/0.7 mL, 60 mg/0.4 mL and 30 mg/mL.

We also refer to your correspondence, dated and received June 28, 2017, requesting review of your proposed proprietary name, Hemlibra.

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

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

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

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

- Draft Guidance for Industry Best Practices in Developing Proprietary Names for Drugs, (<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM398997.pdf>)
- Guidance for Industry Contents of a Complete Submission for the Evaluation of Proprietary Names

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075068.pdf>

- PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2013 through 2017, (<http://www.fda.gov/downloads/ForIndustry/UserFees/PrescriptionDrugUserFee/UCM270412.pdf>)

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Wana Manitpisitkul, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (240) 402-4156. For any other information regarding this application, contact Laura Wall, Regulatory Project Manager in the Office of New Drugs, at (301) 796-2237.

Sincerely,

{See appended electronic signature page}

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

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

/s/

DANIELLE M HARRIS on behalf of TODD D BRIDGES
08/18/2017

From: [Wall, Laura](#)
To: [Robyn Harrington](#); schmidt.matthew@gene.com
Cc: [Wall, Laura](#)
Subject: BLA 761083 - FDA Information Request - Please respond by COB August 18, 2017
Date: Thursday, August 10, 2017 2:33:12 PM

Hi Robyn and Matt,

The clinical pharmacology team requests that you respond to the following Information Request for BLA 761083:

1. In 90-day safety update, provide a summary of the PK data for pediatrics younger than 2 years.
2. Provide a summary of the available information describing the levels of FIX and FX for pediatrics and adults, because some data suggests that the levels of FIX and FX may be less in pediatrics younger than 1 year compared to other pediatrics and adults. The information may be summarized from the literature.

Please send me the requested information via e-mail and officially to your application **by COB, Friday, August 18, 2017**.

Kindly confirm receipt.

Thank you,

Laura

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

/s/

LAURA C WALL
08/10/2017

From: [Wall, Laura](#)
To: [Robyn Harrington](#); schmidt.matthew@gene.com
Cc: [Wall, Laura](#)
Subject: BLA 761083 - FDA Information Request - Please respond by August 14, 2017
Date: Wednesday, August 09, 2017 12:25:27 PM

Hi Robyn and Matt,

The Pharmacometrics team requests that you respond to the following Information Request for BLA 761083:

- 1) Reference is made to the Population PK and PK/PD report entitled “Population Pharmacokinetic Analysis, Exposure-Efficacy and Exposure-Safety Analyses of Emicizumab of Phase III Studies BH29884 and BH29992 and Phase I/II Studies ACE001JP Part C / ACE002JP in Hemophilia A Patients with Factor VIII Inhibitors”. Please submit the analysis datasets, analysis dataset definition, and analysis programs for the exposure-efficacy analyses.
- 2) Reference is made to the population PK report 1078023 entitled “Population Pharmacokinetic and Repeated Time-to-Event Modeling and Simulation of Emicizumab to Support the Dose Selection for Phase III Studies BH29884 and BH29992 Using Data from Phase I-III Studies ACE001JP and ACE002JP”. Please submit the analysis datasets, analysis dataset definition, and analysis programs (in .txt format) with a program table of contents for the population PK and repeated time-to-event modeling and the Figure 9-4 and Figure 9-5 simulations.

Please send me the requested information via e-mail and officially to your application **by Monday, August 14, 2017**.

Kindly confirm receipt.

Thank you,

Laura

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

/s/

LAURA C WALL
08/09/2017



BLA 761083

GENERAL ADVICE

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

ATTENTION: Robyn Harrington
Regulatory Program Management

Dear Ms. Harrington:

Please refer to your Biologics License Application (BLA), dated and received June 23, 2017, submitted under section 351(a) of the Public Health Service Act for Emicizumab, 150 mg/mL, 1 (b)(4) mg/0.7 mL, (b)(4) mg/0.4 mL and 30 mg/mL.

On January 13, 2017, FDA issued final guidance entitled Nonproprietary Naming of Biological Products stating that, for certain biological products, the Agency intends to designate a proper name that includes a four-letter distinguishing suffix that is devoid of meaning.¹

Please note that certain provisions of this guidance describe a collection of information and are under review by the Office of Management and Budget under the Paperwork Reduction Act of 1995 (“PRA”). These provisions of the guidance describe the submission of proposed suffixes to the FDA, and a sponsor’s related analysis of proposed suffixes, which are considered a “collection of information” under the PRA. FDA is not currently implementing provisions of the guidance that describe this collection of information.

However, provisions of the final guidance that do not describe the collection of information should be considered final and represent FDA’s current thinking on the nonproprietary naming of biological products. These include, generally, the description of the naming convention (including its format for originator, related, and biosimilar biological products) and the considerations that support the convention.

Your 351(a) BLA is within the scope of this guidance. As such, we are sending this letter to inform you that FDA intends to assign a four-letter suffix for inclusion in the proper name designated in the license at such time as FDA approves the BLA.

If you have any questions regarding the contents of this letter or any other aspects of the proper name review process, contact Lubna Merchant at (301) 796-5162 or Jill Bourdage at (301) 796-5164.

¹<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM459987.pdf>

For any other information regarding this application, contact Laura Wall, Regulatory Project Manager in the Office of New Drugs, at (301) 796-2237.

Sincerely,

{See appended electronic signature page}

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

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

/s/

LUBNA A MERCHANT
08/01/2017



BLA 761083

**PROPRIETARY NAME
ACKNOWLEDGEMENT**

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

ATTENTION: Robyn Harrington
Regulatory Program Management

Dear Ms. Harrington:

Please refer to your Biologics License Application (BLA) dated and received June 23, 2017, submitted under section 351(a) of the Public Health Service Act for Emicizumab, 150 mg/mL, 1^(b)₍₄₎ mg/0.7 mL, ^(b)₍₄₎ mg/0.4 mL and 30 mg/mL.

We acknowledge receipt of your correspondence, dated and received June 28, 2017, requesting a review of your proposed proprietary name, Hemlibra.

If the application is filed, the user fee goal date will be September 26, 2017.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Wana Manitpisitkul, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (240) 402-4156. For any other information regarding this application, contact Laura Wall, Regulatory Project Manager, in the Office of New Drugs at (301) 796-2237.

Sincerely,

{See appended electronic signature page}

Wana Manitpisitkul, PharmD
Safety Regulatory Project Manager
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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

/s/

WANA MANITPISITKUL
07/10/2017



BLA 761083

BLA ACKNOWLEDGMENT

Hoffmann-La Roche Inc.
c/o Genentech, Inc.
Attention: Robyn Harrington
Regulatory Program Management
1 DNA Way
South San Francisco, CA 94080-4990

Dear Ms. Harrington:

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

Name of Biological Product: emicizumab

Date of Application: June 23, 2017

Date of Receipt: June 23, 2017

Our Reference Number: BLA 761083

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on August 22, 2017, in accordance with 21 CFR 601.2(a).

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

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

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

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

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

If you have any questions, call me at (301) 796-2237.

Sincerely,

{See appended electronic signature page}

Laura Wall, MS, APHN
Regulatory Health Project Manager
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

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

/s/

LAURA C WALL
07/05/2017



IND 122954

MEETING MINUTES

Hoffmann-La Roche Inc.
c/o Genentech, Inc.
Attention: Robyn Harrington
Regulatory Program Management
1 DNA Way
South San Francisco, CA 94080-4990

Dear Ms. Harrington,

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

We also refer to the meeting between representatives of your firm and the FDA on April 25, 2017. The purpose of the meeting was to obtain feedback on certain administrative/regulatory elements of the BLA submission, as well as Chemistry, Manufacturing, and Controls contents of the BLA.

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}

Bazarragchaa Damdinsuren, M.D., Ph.D.
Team Leader
Division of Biotechnology Review and Research IV
Office of Biotechnology Products
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research

Enclosure: Meeting Minutes

MEMORANDUM OF MEETING MINUTES

Meeting Type: Type B
Meeting Category: CMC Only

Meeting Date and Time: April 25, 2017 at 12 P.M. Eastern Standard Time
Meeting Format: Face to face

Application Number: 122954
Product Name: emicizumab
Sponsor/Applicant Name: Hoffmann-La Roche Inc./Genentech, Inc.

Meeting Chair: Gibbes Johnson
Meeting Recorders: Andrew Shiber

FDA ATTENDEES:

Center for Drug Evaluation and Research

Office of Pharmaceutical Quality (OPQ)

Office of Biotechnology Products (OBP)

Gibbes Johnson, Ph.D. Division Director
Bazarragchaa Damdinsuren, M.D., Ph.D. Team Leader
LCDR Leslie Rivera-Rosado, Ph.D. Product Quality Reviewer

Office of Process and Facilities (OPF)

Division of Microbiology Assessment (DMA)

Patricia Hughes, Ph.D. Branch Chief
Maxwell Van Tassell, Ph.D. Microbiology Reviewer
Maria J Lopez-Barragan, Ph.D. Microbiology Reviewer

Division of Inspectional Assessment (DIA)

Michael Shanks Facility Reviewer

SPONSOR ATTENDEES:

Jacques Bourquin, Ph.D. Technical Development Team Leader
Niklas Engler, Ph.D. Head Technical Development Biologics Europe
Stefan Gottschalk, Ph.D. Technical Regulatory Leader
Suguru Kemmoku, Ph.D. Pharmaceutical Technology Leader
Ines Krämer, Ph.D. Head Technical Regulatory Biologics Development Europe
Monika Meier, Ph.D. Manager, Development Analytics
Amy Mutere Head of Global Quality Inspection Management

1. BACKGROUND

Name of drug: emicizumab

Objectives: To obtain feedback on certain administrative/regulatory elements of the BLA submission, as well as Chemistry, Manufacturing, and Controls contents of the BLA.

2. DISCUSSION

Question 1:

With respect to Drug Substance and Drug Product stability, does the Agency agree to:

- a) the Applicant's strategy for the shelf life claim of Drug Substance and submission of additional stability data during the review period?
- b) the Applicant's strategy for the shelf life claim of Drug Product and submission of additional data during the review period?

FDA Response to Questions 1a and 1b:

Yes, your proposed strategies for the shelf-life claims for (a) the drug substance and (b) drug products appear to be acceptable.

If necessary, additional stability data, to support the proposed product shelf-lives, will be requested by the FDA during the review cycle (by September 2017).

- c) the Applicant's strategy for the shelf-life setting of a to-be-developed 150 mg/mL Drug Product at ^(b)₍₄₎mL fill volume?

FDA Response to Question 1c:

We agree that you can leverage the stability data for 60 mg, 105 mg, and 150 mg per vial drug product presentations (150 mg/mL) to support the proposed shelf life of the ^(b)₍₄₎ mg/vial presentation (150 mg/mL), provided that the manufacturing processes for all presentations are the same ^(b)₍₄₎ do not negatively impact the stability of the drug product (5°C and 25°C) and that the ^(b)₍₄₎ mg/vial presentation has comparable stability under stressed condition to the other 150 mg/mL drug product presentations.

- d) the anticipated reporting category of post-licensure shelf-life extensions?

FDA Response to Question 1d:

Yes, we agree with the proposed reporting category (i.e., annual reportable) for drug substance and drug product shelf life extensions per agreed post-approval stability protocols and commitments. The acceptability of the post-approval stability protocols/commitments will be a review issue.

Meeting Discussion:

No discussion for questions for number one.

Question 2

The Applicant intends to submit a comparability protocol along with the BLA, to include an analytical comparability study, in order to facilitate the introduction of a second Drug Product manufacturing site post-licensure. Does the Agency agree that the proposed analytical comparability study will be sufficient to demonstrate comparability of the pre- and post-site change Drug Product with respect to:

- a) the number of batches selected and the bracketing approach?
- b) the analytical tests applied?
- c) the proposed acceptance criteria?

FDA Response to Questions 2a, 2b, and 2c:

Your proposed number of lots and bracketing approach described in the Meeting package appear acceptable. Although the intended strategy for the proposed analytical tests and acceptance criteria appears reasonable, the acceptability of this strategy will require that the full characterization of the molecule and assay capabilities are evaluated, and will need to reflect final agreement on the commercial specifications (test methods and acceptance limits). We remind you that post-approval manufacturing site changes even with an approved comparability protocol may require a facility evaluation and generally do not justify a reporting category other than a PAS or CBE-30. If FDA determines that a pre-license inspection is needed within the 30 days after receipt of a CBE-30 submission for a site change, a PAS will be necessary to gain approval for the new site and any associated process changes.

Meeting Discussion:

No discussion for questions for number two.

Question 3:

Does the Agency agree that the measures implemented by the Applicant are adequate and sufficient to ensure the correct identity of the finished product?

FDA Response to Question 3:

No, we do not agree. The proposed identity measures (b) (4), are not acceptable. In order to comply with 21 CFR 610.14, identity testing should be performed in finished drug product after all labeling operations have been completed.

Applicant's Response:

For emicizumab, the Applicant commits to establish a (b) (4) at Roche Kaiseraugst (packaging and labelling site) to perform identity testing in finished drug product after all labeling operations have been completed. For confirmation of the emicizumab strength, the following physical characteristics of the products are tested: (b) (4)

(b) (4) These tests are executed by the Quality Unit and are part of the packaging batch record, documented in the manufacturing documentation system, and requiring Quality Assurance (QA) approval. The Applicant considers to report these tests in Sections P.3.3 and P.3.4 of the BLA (the test procedure itself will be (b) (4) described in the respective sections of the BLA), and wishes to reach agreement with the FDA that Roche

Kaiseraugst does not need to be specifically mentioned in Section P.3.1 for this ID test performed on the finished product.

In addition, the Applicant wishes to use the opportunity of this F2F meeting to gain a better understanding of the Agency's concern with the initially proposed testing approach for subsequent products, in particular, if a (b) (4) test is a general requirement, or if identity can be confirmed by alternative approaches, e.g.:

(b) (4)

Meeting Discussion:

The Agency reiterated that per CFR 610.14 the identity testing should be performed for each finished drug product lot after all labeling operations have been completed.

Regarding the Sponsor's proposal of not specifically mentioning Roche Kaiseraugst in Section 3.2.P.3.1 as an identity testing site, the Agency clarified that if identity testing is to be performed at Roche Kaiseraugst, the facility has to be included in section 3.2.P.3.1 and the (b) (4) method transfer data package should be provided in the BLA. The Sponsor inquired the possibility of providing the method transfer data for the identity test at the time of the BLA submission (by the end of June 2017). The Agency agreed to the timeline for the identity test transfer data submission.

The Agency noted that discussion on identity testing for subsequent products is outside of the scope of this pre-BLA meeting. The Sponsor agreed.

Question 4

With respect to the Applicant's microbiological control strategies for Drug Substance and Drug Product:

- a) I) Does the Agency agree to the proposed submission of additional data related to Product Quality Microbiology end June 2017?

FDA Response to Question 4aI:

If necessary, methods suitability information will be requested by the FDA during the review cycle (by July 2017).

- II) Does the Agency have any further comment on the Drug Substance hold time validation and in-process control (IPC) strategy, specifically, does the Agency agree that hold time validation is not required (b) (4) and bioburden is monitored routinely (b) (4)?

FDA Response to Question 4aII:

Yes, we agree that (b) (4) hold time validation studies are not required from a microbiology quality perspective (b) (4)

- III) Does the Agency agree to the Applicant's plan to update the license via annual report (b) (4)?

FDA Response to Question 4aIII:

We agree with your plan to update the license via annual report [REDACTED] (b) (4) as described in the BLA.

- b) Does the Agency have any further comment on the Drug Substance [REDACTED] (b) (4)

FDA Response to Question 4b:

The proposed strategy [REDACTED] (b) (4) appear adequate; however, final determination will be made during the BLA review process.

- c) Does the Agency agree to the Drug Product microbiological hold time validation?

FDA Response to Question 4c:

Yes, we agree with the proposed plan.

Meeting Discussion:

No discussion for questions for number four.

Question 5

- a) The Applicant intends to file [REDACTED] (b) (4) as additional storage site for the Drug Substance. While operational shipping qualification (OQ) for the air transportation is completed and will be reported in the BLA, the performance shipping qualification (PQ) data would be available for submission in July. Does the Agency agree to a submission of these particular results by end July 2017, i.e., two months later than the submission of Module 3?
- b) To complement other shipping qualification studies that will be presented in the BLA, a Drug Product shipping validation study is currently ongoing, to evaluate the impact of commercial shipping conditions through representative shipping routes on the quality attributes of Drug Product. Completion of the latter study is foreseen for July 2017. Does the Agency agree to a submission of results from this particular study by end July 2017, i.e. two months later than the submission of Module 3?

FDA Response to Questions 5a and 5b:

If necessary, additional drug substance performance shipping qualification (PQ) data and drug product shipping validation data will be requested by the Agency during the review cycle (by August 2017).

Meeting Discussion:

No discussion for question 5a.

Applicant's Response regarding Question 5b:

To complement simulated shipping qualification studies (e.g. according to ASTM) that will be presented in the BLA, a Drug Product shipping validation study is currently ongoing to evaluate the impact of commercial shipping conditions through representative shipping routes on the quality attributes of Drug Product. For upcoming filings of other products, the Applicant wishes to use the opportunity of the F2F meeting to further inquire about FDA's expectations for DP

shipping validation in terms of real-time shipments of representative DP, followed by assessment of shipment impact on DP quality attributes, and the requirement to use (b) (4) material.

Meeting Discussion:

The Agency noted that discussion on drug product shipping validation for upcoming filings is outside of the scope of this pre-BLA meeting.

Question 6

The Applicant provides updates to the CMC development. Does the Agency have any comments at this stage

- a. to the specification ranges for potency determination?

FDA Response to Question 6a:

We do not have any additional comment regarding the potency specification ranges. Final assessment of adequacy of the proposed acceptance criterion for potency can only be done as part of the BLA review, considering the capabilities of the analytical method, and manufacturing and clinical data.

- b. to the strategy to define and apply multivariate acceptable ranges (MARs) without claiming design space?

FDA Response to Question 6b:

In principle, your approach to defining and establishing MARs without claiming design space appears acceptable. Your application should provide sufficient detail to explain how the MARs were established, how they will be controlled during routine manufacture, and how any potential changes to the MARs will be managed post approval.

- c. to the strategy for (b) (4)

FDA Response to Question 6c:

(b) (4)

Meeting Discussion:

No discussion for questions 6 a, b and c.

Question 6d:

The Applicant provides updates to the CMC development. Does the Agency have any comments at this stage to the establishment of an additional testing site for Drug Substance and Drug Product?

FDA Response to Question 6d:

As stated in our March 1, 2017 communication granting this meeting, under PDUFA V, you and FDA may 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. The addition of a new testing site, and data supporting method transfer activities would not be considered such a minor component. We recommend submitting the additional testing site for drug substance and drug product release and stability testing as a post-approval supplement.

Applicant's Response to 6d and 7a:

We acknowledge FDA's comments. The Applicant reassessed the strategy and we agree to submit (b) (4) for DS and DP release testing as a post-approval submission, assuming a CBE-30 submission. However, for stability testing, in order to ensure execution of the stability commitments, we would like to discuss with the Agency the option to still file (b) (4) as DS and DP stability testing site within the initial BLA and update BLA sections accordingly during review.

The Applicant would also like to comment on the extent of dossier updates that is expected for the establishment of (b) (4) as stability testing site for DS and DP:



- In summary, for this transfer, the Applicant assumes that in order to satisfy the Agencies' requirements, it is adequate to summarize the type of performed studies and to generally confirm the successful transfer. Based on a current estimate, the Applicant assumes that this type of transfer description could be addressed in the updated dossier within 1-2 additional pages in Sections S.4.3 and P.5.3, respectively.
- As outlined in the briefing package, the transfer is planned to be completed end August 2017, hence updated BLA documents could be provided to FDA in September 2017.

Meeting Discussion:

The Agency stated that the reporting category of a post-approval supplement to support the addition of a new testing site will be determined per FDA Guidance for Industry.

The Agency reiterated that the submission of data supporting the method transfer activities during the BLA review cycle would not be considered as a minor update to the BLA. Addition of a new testing site for stability testing or for release and stability testing should be supported by a complete data package including method transfer reports with the BLA submission.

Question 7

The Applicant plans to submit the BLA for emicizumab by the end of June 2017. General agreement on rolling submission of components of the BLA was reached in the frame of a Type B (preBLA) face-to-face meeting with clinical focus (refer to Serial No. 0076, and FDA Preliminary Meeting Comments Ref ID 4070676). In addition, the Agency stated that the emicizumab BLA could meet the criteria for Priority Review.

- a) Does the Agency agree to a target submission date for complete Modules 2.3 and 3.2 as end of May 2017, with few exceptions as outlined?

FDA Response to Question 7a:

Yes, we agree with the target submission date for complete Modules 2.3 and 3.2 as end of May 2017. As noted in the response to Question 6d, we do not agree with your proposal of submission of documents for an additional testing site as an update to the BLA.

See Applicant's Response to 6d and 7a and Meeting Discussion above.

Question 7b:

The Applicant plans to submit the BLA for emicizumab by the end of June 2017. General agreement on rolling submission of components of the BLA was reached in the frame of a Type B (preBLA) face-to-face meeting with clinical focus (refer to Serial No. 0076, and FDA Preliminary Meeting Comments Ref ID 4070676). In addition, the Agency stated that the emicizumab BLA could meet the criteria for Priority Review. Does the Agency agree to the proposed PLI timeframe from July to September 2017 for the Drug Substance and Drug Product manufacturing sites?

FDA Response to Question 7b:

Yes, we agree with your proposed dates for the pre-license inspection(s).

Applicant's Response:

The Applicant acknowledges FDA's feedback and if possible, would like to further confirm the inspection timing, and likelihood of inspection of the Drug Product site, Chugai Utsunomiya (FEI 3006942691):

- For the DS site, we are expecting an inspection as emicizumab Drug Substance manufacturing facilities have not been inspected by FDA. Given that both DS and DP sites are located in close proximity in the greater Tokyo area, Japan, the Applicant respectfully inquires if the Agency would foresee DS and DP site inspections happening in the same time frame, and if inspection of the DP site is considered mandatory.
- As indicated in the Applicants' position, for the Drug Product site, the manufacturer has foreseen a routine maintenance phase (b) (4) and,

therefore, plans to manufacture Drug Product [REDACTED] (b) (4). Drug Product filling will [REDACTED] (b) (4) (refer to Figure 4 of the briefing package). However, as previously outlined, it is still possible at the time of this Type B meeting to switch this maintenance phase [REDACTED] (b) (4) and manufacture Drug Product [REDACTED] (w) (4) should the Agency consider an inspection in this timeframe. For internal planning purposes, in light of potentially accelerated review and approval timelines under breakthrough, the Applicant wishes to use the opportunity of the F2F meeting to provide details of the site and inspection history to understand the likelihood of inspection of the DP site. In addition, if a DP site inspection is likely, we would like to confirm the maintenance phase [REDACTED] (b) (4).

Meeting Discussion:

The FDA requested a delay of the maintenance phase of the Drug Product manufacturing site [REDACTED] (b) (4) in order to facilitate the pre-license inspection planning, considering the potential priority review of the marketing application.

The Agency also stated that the inspections of the Drug Substance and Drug Product manufacturing sites may be performed by two independent inspection teams within a similar time frame. The Agency requested that updated manufacturing schedules be included in Module 1 within the first portion of the rolling BLA submission.

Additional meeting discussion regarding the Pre-Launch Activities Importation Requests (PLAIR):

The Sponsor inquired whether they should inform the CMC project manager (PM) and the reviewers about the submission of the PLAIR. The Agency reiterated that the PLAIR should be submitted to the Office of Compliance and that the CMC PM could be copied in the notification.

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

/s/

BAZARRAGCHAA DAMDINSUREN
05/03/2017



IND 122954

MEETING MINUTES

Hoffmann-La Roche Inc.
c/o Genentech, Inc.
Attention: Robyn Harrington
Regulatory Program Management
1 DNA Way
South San Francisco, CA 94080-4990

Dear Ms. Harrington:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for emicizumab (RO5534262).

We also refer to the teleconference between representatives of your firm and the FDA on March 21, 2017. The purpose of the meeting was to discuss the acceptability of the clinical trial results from pivotal Phase III studies BH29884 and BH29992 and supportive studies to form the basis of a BLA for emicizumab for routine prophylaxis to prevent bleeding or reduce the frequency of bleeding episodes in adults and children with hemophilia A (congenital factor VIII deficiency) with factor VIII inhibitors.

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

If you have any questions, call Laura Wall, Regulatory Project Manager, at (301) 796-2237.

Sincerely,

{See appended electronic signature page}

R. Angelo de Claro, MD
Clinical Team Leader
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type: Type B
Meeting Category: Pre-BLA

Meeting Date and Time: March 21, 2017 from 10:00 AM to 11:00 AM (ET)
Meeting Location: White Oak Building 22, Conference Room: 1311

Application Number: IND 122954
Product Name: emicizumab (RO5534262)
Indication: For routine prophylaxis to prevent bleeding or reduce the frequency of bleeding episodes in adults and children with hemophilia A (congenital factor VIII deficiency) with factor VIII inhibitors

Sponsor/Applicant Name: Hoffmann-La Roche Inc. c/o Genentech, Inc.

Meeting Chair: R. Angelo de Claro, MD, Clinical Team Leader
Meeting Recorder: Laura Wall, MS, Regulatory Project Manager

FDA ATTENDEES

Office of Hematology and Oncology Products (OHOP), Division of Hematology Products (DHP)

Ann Farrell, MD, Director
R. Angelo de Claro, MD, Clinical Team Leader
Lori Ehrlich, MD, PhD, Clinical Reviewer
Andrea Baines, MD, PhD, Clinical Reviewer
Theresa Carioti, MPH, Chief, Project Management Staff
Diane Leaman, BS, Safety Regulatory Project Manager
Laura Wall, MS, Regulatory Project Manager

OHOP, Division of Hematology Oncology Toxicology (DHOT)

Christopher Sheth, PhD, Supervisory Pharmacologist/Toxicologist
Shwu-Luan Lee, PhD, Pharmacologist Reviewer

Office of Clinical Pharmacology, Division of Clinical Pharmacology V

Stacy Shord, PharmD, Clinical Pharmacology Team Leader

Office of Biostatistics, Division of Biometrics V

Yuan Li Shen, DrPH, Biometrics Team Leader
Xin Gao, PhD, Biometrics Reviewer

Office of Biotechnology Products, Division of Biotechnology Review and Research IV
Bazarragchaa Damdinsuren, MD, PhD, RAC, Product Quality Team Leader

Office of Surveillance and Epidemiology, Division of Risk Management
Elizabeth Everhart, MSN, RN, ACNP, Risk Management Analyst
Wana Manitpisitkul, OSE Regulatory Project Manager

SPONSOR ATTENDEES

Elina Asikanius, Senior Statistical Scientist
Tiffany Chang, MD, Associate Medical Director
Shaun Comfort, MD, MBA Senior Safety Science Leader
Robyn Harrington, Regulatory Program Director
Benjamin Kim, MD, Associate Medical Director
Bea Lavery, Regulatory Hematology Franchise Head
Gallia Levy, MD, Global Development Team Leader
Bao Phan, PharmD, Senior Global Regulatory Leader
Christophe Schmitt, PharmD Clinical Pharmacologist
Marianne Uguen, Statistical Scientist
Nancy Valente, MD, Vice President, Global Hematology Development
Lilyan Wright, PhD, Senior Safety Scientist

1.0 BACKGROUND

Emicizumab is a recombinant humanized immunoglobulin IgG4 anti-Factor IXa and anti-Factor X bispecific monoclonal antibody. The proposed indication is for the routine prophylaxis to prevent or reduce the frequency of bleeding episodes in adults and children with hemophilia A with factor VIII inhibitors.

FDA granted breakthrough therapy designation for emicizumab for the above proposed indication on September 2, 2015.

The objectives and expected outcomes of the pre-BLA meeting are to obtain the Agency's concurrence on acceptability of the following:

- Clinical trial results from pivotal Phase III studies BH29884 and BH29992 and supportive studies to form the basis of a BLA
- The regulatory path and timelines.

2.0 DISCUSSION

2.1. Clinical/Statistical

Question 1a: *The Sponsor intends to submit a single BLA supported by efficacy and safety data from two pivotal studies; Study BH29884 in adults and adolescents ≥ 12 years with hemophilia A with factor VIII (FVIII) inhibitors and interim data from Study BH29992 in*

children < 12 years of age with hemophilia A with FVIII inhibitors to enable the following indication:

Emicizumab is indicated for routine prophylaxis to prevent bleeding or reduce the frequency of bleeding episodes in adults and children with hemophilia A (congenital factor VIII deficiency) with FVIII inhibitors

- a) *Does the Agency agree that the efficacy (including all secondary endpoints, in particular results from the intra-patient comparisons, HRQoL, and health status) and safety results from pivotal Phase III Study BH29884 and data from the supporting studies to be included in the BLA provide sufficient and clinically meaningful evidence to characterize the benefits and risks of emicizumab in adults and adolescents (≥ 12 years) with hemophilia A with FVIII inhibitors and support the review of the BLA filing?*

FDA Response to Question 1a:

Yes, the information submitted appears to be sufficiently robust to support the filing and review of the BLA. Final determination on filing of the BLA will be made after submission of the application. Inclusion of secondary endpoints in the prescribing information will be a review issue.

Discussion:

No discussion occurred.

Question 1b: *Does the Agency agree that the efficacy and safety results from the interim analysis of pivotal Phase III Study BH29992, in conjunction with data from pivotal Phase III Study BH29884, as well as data from the supporting studies to be included in the BLA, provide sufficient clinical evidence to characterize the benefits and risks of emicizumab in children < 12 years with hemophilia A with FVIII inhibitors and support the review of the BLA filing?*

FDA Response to Question 1b:

Yes, the information submitted appears to be sufficiently robust to support the filing and review of the BLA including for the treatment of children. The ability of the interim analysis of BH29992 to support an indication for the treatment of children will be a review issue.

Discussion:

The Sponsor provided an update on risk mitigation and minimization. The Agency stated that the risk mitigation and minimization approach will be assessed during the review of the application.

Question 1c: *Does the Agency agree with the above proposed indication statement supported by data from Studies BH29884 and BH29992?*

FDA Response to Question 1c:

The proposed indication statement appears appropriate. See also response to Question 1b.

Discussion:

No discussion occurred.

Question 2: *Does the Agency agree with the proposed detailed format and structure of the raw and derived datasets?*

FDA Response to Question 2:

Yes. The proposed detailed format and structure of the raw and derived datasets appears reasonable. Please use ADaM-compliant dataset names and variables for the derived datasets.

Please address the comments provided as part of the Type C Meeting on August 29, 2016, regarding the Summary of Clinical Pharmacology and submission of the clinical pharmacology sections of the BLA submission.

Sponsor Response (received on March 20, 2017):

The Sponsor will be unable to provide ADaM-compliant dataset names and variables for the derived datasets. As described in the briefing package supporting the Type C Content and Format Meeting held on August 29, 2016, the pivotal and supportive studies planned for inclusion in the emicizumab BLA commenced in the 2016 calendar year or earlier, prior to the CDISC mandate, and, therefore, follow a legacy data format.

The format of our submission does not allow us to name our datasets and variables in order to be ADaM compliant as the structure of our datasets is not fully ADaM compliant. However, please note that part of our derived datasets are close to the CDISC format.

Discussion:

The Agency agreed that the Sponsor's proposal is acceptable:

Question 3: *Does the Agency agree with the proposed list of endpoints supported by the readable SAS code?*

FDA Response to Question 3:

The proposed list of SAS codes appears acceptable. In addition, the SAS programs that are used to create the derived datasets for the efficacy endpoints should be included in the BLA submission.

Discussion:

No discussion occurred.

2.2. Administrative/Regulatory

Question 4: *Does the Agency agree, given the unmet medical need for hemophilia A patients with inhibitors, that the results presented from Studies BH29884 and BH29992, demonstrate*

a substantial improvement over other available therapies, thus qualifying the proposed BLA for Priority Review?

FDA Response to Question 4:

Yes, the submitted topline data could meet the criteria for Priority Review; however, this will not be determined until the application is filed.

Discussion:

No discussion occurred.

Question 5: *Based on the review of the safety data, the Sponsor believes that the information included in the US prescribing information (USPI), Patient Package Insert (to support routine home use) and patient and prescriber educational materials will be sufficient to convey the risks of emicizumab. Does the Agency agree that the proposed risk mitigation measures are adequate and that additional REMS measures are not deemed necessary?*

FDA Response to Question 5:

At this time, the Office of New Drugs and the Office of Surveillance and Epidemiology have insufficient information to determine whether a risk evaluation and mitigation strategy (REMS) will be necessary to ensure that the benefits of the drug outweigh the risks, and if it is necessary, what the required elements will be. We will determine the need for a REMS during the review of your application.

Discussion:

The Agency stated that the need for a REMS will be determined during the review of the application.

Question 6: *Does the Agency foresee that the proposed BLA will be reviewed by an Advisory Committee?*

FDA Response to Question 6:

Decisions regarding the need for an Advisory Committee meeting will not be made until the completion of the initial review of the application.

Discussion:

No discussion occurred.

Question 7: *Would the Agency like to have an applicant orientation meeting/technical walkthrough with the Sponsor after submission to outline the major components of the BLA?*

FDA Response to Question 7:

Yes. We will not be able to contact you with potential dates until the application is submitted with a goal of holding the application orientation meeting within 4-6 weeks.

Discussion:

No discussion occurred.

Question 8: *Would the Agency accept a rolling review with earlier submission of components of Module 1, completed Module 4 and Bioresearch Monitoring (BIMO) information (Module 5) for the planned submission of the BLA in June 2017?*

FDA Response to Question 8:

Yes, rolling review under Breakthrough Therapy Designation would be appropriate. The review clock begins at the time of the final submission.

Please provide your projected timeline of the planned rolling BLA submission, broken down by module(s) and expected submission dates. Also, refer to the *Discussion Of The Content Of A Complete Application* under Other Important Meeting Information below.

Discussion:

The Sponsor acknowledged the Agency recommendation and will submit a proposal for rolling review submission that includes timelines for each eCTD module submission.

Question 9: *At the Type C meeting held with FDA on 29 August 2016, to discuss the proposed contents and format of the initial BLA for emicizumab, FDA agreed with the proposed plan for the 90 day safety update. Given the current benefit-risk profile of emicizumab, does the Agency find the initial proposed plan acceptable?*

FDA Response to Question 9:

Yes, the proposed 90-day safety update appears acceptable.

Discussion:

No discussion occurred.

3.0 OTHER IMPORTANT MEETING INFORMATION

DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

The content of a complete application was discussed. The Agency was able to reach agreement with the Sponsor regarding the content of the non-CMC components of the application. The Agency notes that the Sponsor has a separate meeting to discuss the CMC component of the application.

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

- A preliminary discussion on the need for a REMS was held, and it was concluded that the need for a REMS will be determined during the review of the application.
- Major components of the application are expected to be submitted with the original application and are not subject to agreement for late submission. The Sponsor stated that at this time, there are no planned late submission components for the non-CMC

portion of the submission. Final determination of late components for CMC data should be discussed and agreed upon at the pre-BLA CMC-only meeting.

In addition, we note that a chemistry pre-submission meeting is scheduled for April 25, 2017. A summary of agreements reached at that meeting will be documented in the respective meeting minutes.

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.

Because this biologic product for this indication has an orphan drug designation, you are exempt from these requirements. Please include a statement that confirms this finding, along with a reference to this communication, as part of the pediatric section (1.9 for eCTD submissions) of your application. If there are any changes to your development plans that would cause your application to trigger PREA, your exempt status would change.

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.

OFFICE OF SCIENTIFIC INVESTIGATIONS (OSI) REQUESTS

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

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

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

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

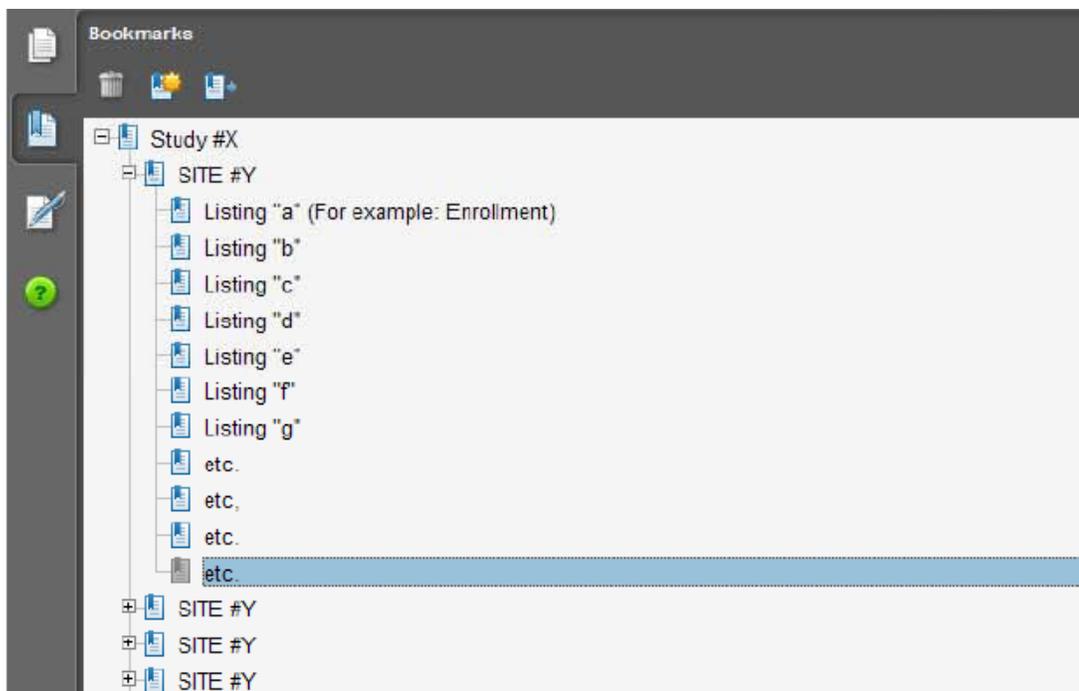
1. Please include the following information in a tabular format in the original NDA for each of the completed pivotal clinical trials:
 - a. Site number
 - b. Principal investigator
 - c. Site Location: Address (e.g., Street, City, State, Country) and contact information (i.e., phone, fax, email)
 - d. Location of Principal Investigator: Address (e.g., Street, City, State, and Country) and contact information (i.e., phone, fax, email). If the Applicant is aware of changes to a clinical investigator's site address or contact information since the time of the clinical investigator's participation in the study, we request that this updated information also be provided.

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

II. Request for Subject Level Data Listings by Site

1. For each pivotal trial: Site-specific individual subject data listings (hereafter referred to as “line listings”). For each site, provide line listings for:
 - a. Listing for each subject consented/enrolled; for subjects who were not randomized to treatment and/or treated with study therapy, include reason not randomized and/or treated
 - b. Subject listing for treatment assignment (randomization)
 - c. Listing of subjects that discontinued from study treatment and subjects that discontinued from the study completely (i.e., withdrew consent) with date and reason discontinued
 - d. Listing of per protocol subjects/ non-per protocol subjects and reason not per protocol
 - e. By subject listing of eligibility determination (i.e., inclusion and exclusion criteria)
 - f. By subject listing of AEs, SAEs, deaths and dates
 - g. By subject listing of protocol violations and/or deviations reported in the NDA, including a description of the deviation/violation

- h. By subject listing of the primary and secondary endpoint efficacy parameters or events. For derived or calculated endpoints, provide the raw data listings used to generate the derived/calculated endpoint.
 - i. By subject listing of concomitant medications (as appropriate to the pivotal clinical trials)
 - j. By subject listing, of testing (e.g., laboratory, ECG) performed for safety monitoring
2. We request that one PDF file be created for each pivotal Phase 2 and Phase 3 study using the following format:



III. Request for Site Level Dataset:

OSI is piloting a risk based model for site selection. Voluntary electronic submission of site level datasets is intended to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process. If you wish to voluntarily provide a dataset, please refer to the draft “Guidance for Industry *Providing Submissions in Electronic Format – Summary Level Clinical Site Data for CDER’s Inspection Planning*” (available at the following link <http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/UCM332468.pdf>) for the structure and format of this data set.

Attachment 1

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

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

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

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



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

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

References:

eCTD Backbone Specification for Study Tagging Files v. 2.6.1
(<http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM163560.pdf>)

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

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

4.0 ISSUES REQUIRING FURTHER DISCUSSION

None

5.0 ACTION ITEMS

None

6.0 ATTACHMENTS AND HANDOUTS

The Sponsor sent the attached supplemental information via e-mail on March 20, 2017.

1 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

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

/s/

ROMEO A DE CLARO
03/27/2017



IND 122954

**GRANT –
BREAKTHROUGH THERAPY DESIGNATION**

Hoffmann-La Roche Inc.
c/o Genentech Inc.
Attention: Robyn Harrington
Regulatory Program Management
1 DNA Way
South San Francisco, CA 94080-4990

Dear Ms. Harrington:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for RO5534262.

We also refer to your July 9, 2015, request for Breakthrough Therapy designation. We have reviewed your request and have determined that RO5534262 for routine prophylaxis to prevent or reduce the frequency of bleeding episodes in adults and adolescents ≥ 12 years old with hemophilia A with FVIII inhibitors 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 RO5534262 for routine prophylaxis to prevent or reduce the frequency of bleeding episodes in adults and adolescents ≥ 12 years old with hemophilia A with FVIII inhibitors 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

In terms of next steps, please submit a Type B meeting request. This meeting will be for a multidisciplinary comprehensive discussion of your drug development program, including planned clinical trials and plans for expediting the manufacturing development strategy. Please refer to MAPP 6025.6 - *Good Review Practice: Management of Breakthrough Therapy-Designated Drugs and Biologics*, Attachment 1, for potential topics for discussion at this initial

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

breakthrough therapy meeting². Please refer to the *Guidance for Industry: Formal Meetings between FDA or Sponsors and Applicants*³ for procedures on requesting a meeting. If you feel that submitting a meeting request for such a meeting at this point is pre-mature or if you have recently held a major milestone meeting, please contact the Regulatory Health Project manager noted below to discuss the timing of this meeting.

If the breakthrough therapy designation for RO5534262 for routine prophylaxis to prevent or reduce the frequency of bleeding episodes in adults and adolescents ≥ 12 years old with hemophilia A with FVIII inhibitors 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 Laura Wall, Regulatory Project Manager, at (301) 796-2237.

Sincerely,

{See appended electronic signature page}

Ann T. Farrell, MD
Director
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

²

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

³ <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM153222.pdf>

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

/s/

ANN T FARRELL
09/02/2015

CDER Breakthrough Therapy Designation Determination Review Template

IND/NDA/BLA #	122954
Request Receipt Date	July 9, 2015
Product	RO5534262
Indication	Routine prophylaxis to prevent or reduce the frequency of bleeding episodes in adults and adolescents \geq 12 years old with hemophilia A with FVIII inhibitors.
Drug Class/Mechanism of Action	Bi-specific monoclonal antibody, binds both factor IX and X
Sponsor	Genentech
ODE/Division	OHOP/DHP
Breakthrough Therapy Request Goal Date (within <u>60</u> days of receipt)	September 7, 2015

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):

RO5534262 is indicated for routine prophylaxis to prevent or reduce the frequency of bleeding episodes in adults and adolescents \geq 12 years old with hemophilia A with FVIII inhibitors.

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.

- *Information regarding the disease and intended population for the proposed indication.*
- *Disease mechanism (if known) and natural history (if the disease is uncommon).*

Hemophilia A is an X-linked bleeding disorder characterized by the congenital deficiency or absence of factor VIII (FVIII). The absence of functional FVIII interrupts the coagulation cascade and the ability to form a stable clot in response to trauma. The resulting bleeding complications can be severe and life-threatening and can lead to long-term morbidity from joint damage due to recurrent bleeds. The standard of care in patients with hemophilia A is treatment with recombinant or plasma-derived FVIII concentrates. Treatment can either be in response to a bleeding event (episodic or “on demand” treatment) or scheduled treatment to prevent bleeds (prophylactic treatment). In resource-rich countries,

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>

prophylactic treatment initiated prior to any joint bleeds is preferred. In a 30-35% of patients with Hemophilia A, a neutralizing antibody, known as a FVIII inhibitor, forms which renders exogenous and endogenous FVIII nonfunctional. Patients with FVIII inhibitors are more difficult to treat in response to bleeding events leading to a much higher rate of progressive joint disease from frequent joint bleeds and an increased risk of death from uncontrolled bleeding.

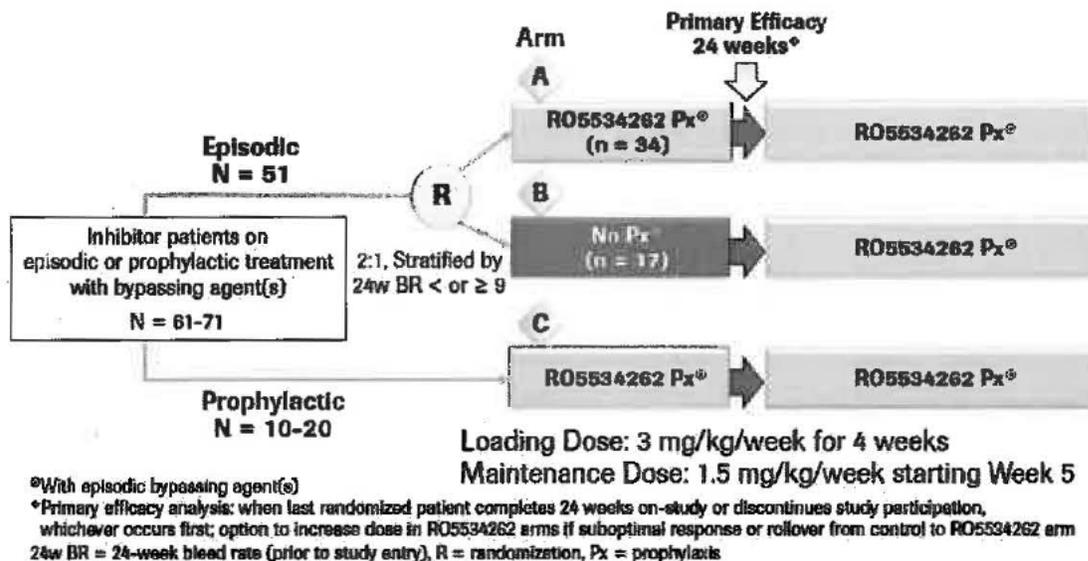
In response to an injury, the coagulation cascade is activated. When FVIII is activated, it functions to bring together activated factor IX (FIX) with factor X (FX). Similarly, RO5534262 is a bispecific antibody where one arm binds to both inactive and active FIX and the other arm binds to both inactive and active FX, bringing together activated factor IX to factor X in the same manner as endogenous or infused FVIII. Importantly, this mechanism does not require the presence of FVIII, and would be active in patients with no endogenous FVIII or inhibitors to FVIII. RO5534262 is administered subcutaneously with a proposed dosing interval of weekly which are less burdensome on the patient compared to available bypassing agents (See question 8 below).

RO5534262 was formerly referred to as ACE910 by Chugai Pharma. In July 2013, Chugai Pharma had a pIND meeting with CBER regarding the clinical development of RO5534262. Chugai has out-licensed the development of RO5534262 for some regions including the United States to Roche in 2014. In October 2013, jurisdiction for RO5534262 was granted to OHOP/DHP in CDER. Two additional pIND meetings were held with DHP, July 2014 and May 2015. The July 2014 was held to discuss a proposed phase 1b study in patients with hemophilia A. Due to manufacturing changes, this study was delayed in the US, and the dosing recommendations rely on studies completed in Japan. The May 2015 meeting was to discuss the proposed phase 3 study included in this BTDR request. Orphan drug designation for RO5534262 was granted for the treatment of hemophilia A in January 2014.

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.

Repeated bleeding, especially into joints, is the hallmark of hemophilia A and analysis of bleeding frequencies is required to evaluate clinical efficacy. Number of bleeds overtime will be used as primary efficacy endpoint throughout the clinical development of RO5534262. The phase 3 trial (BH29884) to be initiated under this IND is a randomized, multicenter, open-label, Phase III clinical trial that will enroll patients aged 12 years or older with hemophilia A who have inhibitors against FVIII comparing prophylaxis with RO5534262 to no prophylaxis. Both arms will receive episodic bypassing agents in response to bleeds (NovoSeven or FEIBA, see question 8). The primary endpoint will be the number of bleeds over 6 months' time. The comparison of the number of bleeds over time between the group randomized to receive RO5534262 prophylaxis versus no prophylaxis will be performed using a negative binomial regression model, which accounts for different follow-up times, with the patient's number of bleeds as a function of randomization and the time that each patient stays on the study included as an offset in the model. The secondary endpoints in this trial include bleeding rates in each patient in the 6 months prior to starting the study drug compared to 6 months on the study drug. They will also collect joint bleeding rates and target joint bleeding rates. The trial also includes health-related quality of life measurements. The trial also includes a treatment arm for patients currently receiving prophylactic treatment with a bypassing agent. All patients in this arm will receive RO5534262 with descriptive analyses of bleeding rate before and after starting study drug. A summary of the design of the phase 3 trial is included below.



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:

- A clinical endpoint that directly measures the clinical benefit of a drug (supporting traditional approval).
- A surrogate/established endpoint that is known to predict clinical benefit of a drug (i.e., a validated surrogate endpoint that can be used to support traditional approval).
- An endpoint that is reasonably likely to predict clinical benefit of a drug (supporting accelerated approval), and the endpoint used in a confirmatory trial or trials to verify the predicted clinical benefit.

The approval of FEIBA for the same indication being sought here was based on a phase 3 randomized, multi-center, open-label, parallel clinical study in hemophilia A or B subjects with persistent high-titer inhibitors or low-titer inhibitors refractory to factor VIII (FVIII) or factor IX (FIX) treatment. The primary efficacy outcome measure in that trial was the annualized bleeding rate (ABR) of all types of bleeds. The ABR is the rate of bleeds corrected for one year. ABR is also the standard reporting measure in other clinical trials in the literature. ABR can be used to compare between treatment arms as well as inpatient comparisons before and after treatment interventions.

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.

N/A

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:

- If the available therapies were approved under accelerated approval, provide the information for the endpoint used to support accelerated approval and the endpoint used to verify the predicted clinical benefit.
- In addition to drugs that have been approved by FDA for the indication, also identify those treatments that may be used off-label for that indication.

The current standard of care available for Hemophilia A is FVIII replacement with recombinant or plasma-derived factor products. Patients with inhibitors cannot be treated with FVIII replacement as the inhibitor would clear the exogenous FVIII and likely increase the inhibitor titer. To clear the FVIII inhibitor, patients may undergo immune tolerance induction (ITI). ITI involves frequent administrations of high dose FVIII to eliminate the antibody overtime and allow patients to resume their prophylactic treatment with FVIII. While this is successful in some patients, there is a failure rate of 20-40%, and those patients who have a resurgence of their antibody after ITI tend to be even more refractory to treatment. It is also a heavy burden for patients both in effort and cost from daily high dose factor VIII infusions.

The available treatments in patients with FVIII inhibitors are episodic treatment with a bypassing agent which bypasses FVIII in the coagulation cascade, usually during ITI. Unfortunately, the efficacies of these agents are unstable compared to FVIII infusions. There are two bypassing agents available (see Table below), NovoSeven® and FEIBA®, and both available agents have limitations of use. NovoSeven is a recombinant activated factor VII product which has a short half-life and requires IV treatment every 2-3 hours. FEIBA, or Factor Eight Inhibitor Bypassing Activity, is a plasma-derived activated prothrombin complex concentrate which is predominately prothrombin and Factor X. This product requires a long infusion time which can be limiting for its use. It also contains small amounts of FVIII, so could augment inhibitor formation in patients not currently undergoing ITI.

Patients with FVIII inhibitors can also receive prophylactic treatment with a bypassing agent. FEIBA was recently approved for this indication. The primary efficacy outcome for the registration trial was annualized bleeding rate (ABR) which is the rate of bleeds normalized to one year. Patients on FEIBA prophylaxis had a median ABR of 8 compared to 27 for patients receiving episodic treatment with FEIBA. Prophylactic treatment is quite costly and burdensome given the need for every other day IV infusions of FEIBA. NovoSeven is not approved for this indication and therefore the dosing regimens used are not standardized and with variable rates of efficacy.

Drug	Recombinant or Plasma-derived	Approved indications	Administration for prophylaxis	Median ABR (prophylaxis)
NovoSeven (rFVIIa)	Recombinant	<ul style="list-style-type: none"> • Episodic treatment • Perioperative management 	IV No standard dosing (Daily to weekly)	(2.2-3 bleeds/month)*
FEIBA (aPCC)	Plasma-derived	<ul style="list-style-type: none"> • Episodic treatment • Prophylactic treatment • Perioperative management 	IV Every other day 20-50 min infusion	7.9

*Not approved for this indication. Rates are based on literature reports

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

None

10. Information related to the preliminary clinical evidence:

- 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.

Preliminary clinical evidence of efficacy and safety is based on the ACE001JP and ACE002JP trials summarized in the following Table.

Study	Design	Number of patients	Dosing regimen/route	Objectives
ACE001JP Phase 1 (conducted in Japan) ongoing; all patients have completed treatment	<i>Part A and B:</i> Placebo-controlled, single-ascending dose study in healthy Japanese (Part A) and Caucasian (Part B) adult male volunteers <i>Part C:</i> Open-label, inter-individual, SC multiple-ascending dose study for 12 weeks in Japanese patients with hemophilia A	Part A+B: N=64 (cohorts of n=8 were randomized 3:1 to receive RO5534262 or placebo) Part C: N=18 (escalating cohorts of n=6)	All SC injections Part A+B: 0.001 mg/kg, 0.01 mg/kg, 0.1 mg/kg, 0.3 mg/kg, 1 mg/kg or placebo Part C: C-1: 1 mg/kg loading dose then 0.3 mg/kg weekly C-2: 3 mg/kg loading dose then mg/kg weekly C-3: 3 mg/kg weekly	1) Tolerability, safety, PK, and PD (2) Part A+B: To evaluate racial differences in the PK and PD responses (3) Part C: To investigate the relationship between RO5534262 dose and the number of bleeding episodes; time to first bleed will be analyzed on an exploratory basis.
ACE002JP Phase I/II (conducted in Japan) ongoing	Open-label extension of Part C (C-1, C-2, and C-3) of Study ACE001JP with possible dose-escalation among treatment groups Treatment for each subject will continue until marketing approval, development discontinuation, or the date a withdrawal criterion is met, whichever is sooner	N=16 patients from Part C of Study ACE001JP	All SC injections Group 1: 0.3 mg/kg weekly (after loading dose) Group 2: 1 mg/kg weekly (after loading dose) Group 3: 3 mg/kg weekly	To investigate the safety and, in an exploratory manner, the inhibitory effect of RO5534262 on bleeding during long-term treatment in patients with hemophilia A who have participated in Study ACE001JP.

Table provided by the Sponsor with modifications

Efficacy results for the 18 patients with hemophilia A who were treated with RO5534262 is summarized in the following Table. The reduction in ABR of each patient was a comparison between the 6 months prior to starting the study drug and the duration on the study drug. At all dose levels, there was a reduction in ABR, and at the higher two dose levels, the median ABR reached 0.

Cohort (N=6)	Median ABR reduction (range)	Median ABR (range)	Mean ABR	Number of patients with “zero” bleeds
C1 (0.3 mg/kg)	89.6% (22.8-100%)	1.70 (0-59.5)	13.7	1
C2 (1 mg/kg)	100% (79.6-100%)	0 (0-5.0)	1.32	4
C3 (3 mg/kg)	100% (77.8-100%)*	0 (0-1.8)	0.58	4

* One non-inhibitor patient had zero bleeds at baseline on FVIII prophylaxis and maintained zero bleeds during treatment with ACE910

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

- *Explain whether the data provided should be considered preliminary clinical evidence of a substantial improvement over available therapies. In all cases, actual results, in addition to reported significance levels, should be shown. Describe any identified deficiencies in the trial that decrease its persuasiveness.*
- *Identify any other factors regarding the clinical development program that were taken into consideration when evaluating the preliminary clinical evidence, such as trial conduct, troublesome and advantageous aspects of the design, missing data, any relevant nonclinical data, etc.*
- *Safety data: Provide a brief explanation of the drug’s safety profile, elaborating if it affects the Division’s recommendation.*

The efficacy data provided shows preliminary evidence of a substantial improvement over the available therapies for prophylaxis in patients with hemophilia A with FVIII inhibitors. The median ABR across all dose cohorts of RO5534262 was 0-1.7, compared to a median ABR of 7.9 for patients receiving prophylaxis with FEIBA. The subcutaneous route of administration and once weekly dosing of RO5534262 is an improvement in the burden to patients and caregivers.

In the 18 patients with hemophilia A, a total of 93 AEs were observed. Every patient experienced at least one AE. All AEs were of mild intensity, except for 4 moderate AEs (upper respiratory tract infection, bipolar I disorder, hemophilia [left hip joint bleeding due to hemophilia], and headache). Local injection site reactions were observed in 6 patients (33.3%), all of mild intensity. One AE (injection site erythema) in the 1 mg/kg/week group resulted in discontinuation of treatment on Treatment Day 29; the event was mild in intensity and resolved. Only one serious adverse event (hemophilia [left hip joint bleeding due to hemophilia]) was reported and this was in the 1 mg/kg/week group. This event was not considered related to RO5534262. There were no thromboembolic events, systemic hypersensitivity reactions, or development of neutralizing antibodies. Three patients who developed treatment-emergent anti-drug antibodies, but none were neutralizing. One healthy volunteer developed a neutralizing antibody to RO5534262.

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

GRANT:

Provide brief summary of rationale for granting:

Note, if the substantial improvement is not obvious, or is based on surrogate/pharmacodynamic endpoint data rather than clinical data, explain further.

Hemophilia A with FVIII inhibitors is a serious and life-threatening disorder. Preliminary clinical evidence indicates that the drug may demonstrate substantial improvement over existing therapies (FEIBA and NovoSeven) for prophylaxis to

reduce the number of bleeding events. The median ABR across all dose cohorts of RO5534262 was 0-1.7, compared to a median ABR of 7.9 for patients receiving prophylaxis with FEIBA. The subcutaneous route of administration and weekly dosing is an improvement in burden of treatment for these patients compared to other bypassing agents. Importantly, RO5534262 has no structural relationship to FVIII and no potential to induce or enhance the development of direct inhibitors to FVIII or other coagulation factors. The design of the registrational phase 3 trial was agreed upon at the pIND meeting in May 2015.

DENY:

Provide brief summary of rationale for denial:

Note that not looking as promising as other IND drugs is not a reason for denial; the relevant comparison is with available (generally FDA-approved) therapy. If the Division does not accept the biomarker/endpoint used as a basis for traditional approval or accelerated approval or as a basis for providing early clinical evidence of a substantial improvement over available therapy, explain why:

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

- a. If recommendation is to grant the request, explain next steps and how the Division would advise the sponsor (for example, plans for phase 3, considerations for manufacturing and companion diagnostics, considerations for accelerated approval, recommending expanded access program):

The phase 3 trial (Study A) to be initiated under this IND will be the registrational trial for regular approval for prophylactic treatment of patients with hemophilia A and FVIII inhibitors. They are also planning a Phase 1b PK study to evaluate extended dosing regimens beyond once weekly (Study B). They will complete a phase 3 trial in patients with hemophilia A without inhibitors (Study C). They are also planning a phase 3, non-randomized trial in pediatric patients with hemophilia A with FVIII inhibitors (Study D). The anticipated launch date for the later 3 trials (Studies B, C, and D) is in 2016.

The Division intends to work with the Sponsor to address Sponsor-identified issues that would be rate limiting with regards to completion of an expedited review. These issues include (a) manufacturing issues and (b) completion of human factors assessment. At the May 2015 pIND meeting, the Division discussed processes for acceleration of the development plan for RO5534262. The current anticipated timeline for completion of at least 6 months on trial for approximately 50 patients will be early 2017. At the meeting, the Sponsor stated that submission of the BLA will be limited by the proposed timeline to complete their human factors studies for home administration of their drug. They are also in the process of implementing a drug substance process change. Process G1 was used in their Japanese trials, and they are currently producing process G2.1 to be used in their phase 3 trial. The processes appear to be highly similar except for the presence of a point mutation in about 1% of the product of unknown significance. They will complete a bioequivalence study in patients in Japan, and our ability to combine safety and efficacy data between trials will depend on the BE study.

The Division discussed an expanded access program with the Sponsor, however, the Sponsor does not intend to open an expanded access program, citing the need to complete all the planned clinical trials (Studies A to D).

- b. If recommendation is to deny the request and the treatment looks promising, explain how the Division would advise the sponsor regarding subsequent development, including what would be needed for the Division to reconsider a breakthrough therapy designation:

13. List references, if any:

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/

LORI A EHRLICH
09/01/2015

ROMEO A DE CLARO
09/01/2015

ANN T FARRELL
09/01/2015

LATE-CYCLE COMMUNICATION
DOCUMENTS



BLA 761083

LATE-CYCLE MEETING MINUTES

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

Dear Ms. Harrington:

Please refer to your Biologic License Application (BLA) submitted under section 351 of the Public Health Service Act for emicizumab injection, 150 mg/mL (1.0, 0.7, 0.4 mL); 30 mg/1.0 mL.

We also refer to the Late-Cycle Meeting (LCM) between representatives of your firm and the FDA on October 24, 2017.

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

If you have any questions, call Laura Wall, Regulatory Project Manager at (301) 796-2237.

Sincerely,

{See appended electronic signature page}

R. Angelo de Claro, MD
Clinical Team Leader
Division of Hematology Products
Office of Hematology and Oncology Products
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 24, 2017 from 2:00 PM to 3:00 PM (EST)
Meeting Location: Teleconference

Application Number: BLA 761083
Product Name: emicizumab
Applicant Name: Genentech, Inc.

Meeting Chair: R. Angelo de Claro, MD, Clinical Team Leader
Meeting Recorder: Laura Wall, MS, Regulatory Project Manager

FDA ATTENDEES

Office of Hematology and Oncology Products (OHOP), Division of Hematology Products (DHP)

Ann Farrell, MD, Director
Albert Deisseroth, MD, PhD, Supervisory Associate Division Director
Paul Kluetz, MD, Associate Director for Clinical Science
R. Angelo de Claro, MD, Clinical Team Leader
Lori Ehrlich, MD, PhD, Clinical Reviewer
Virginia Kwitkowski, MS, ACNP-BC, Associate Director for Labeling
Theresa Carioti, MPH, Chief, Project Management Staff
Diane Leaman, BS, Safety Regulatory Project Manager
Laura Wall, MS, Regulatory Project Manager

OHOP, Division of Hematology Oncology Toxicology (DHOT)

Christopher Sheth, PhD, Supervisory Pharmacologist/Toxicologist
Shwu-Luan Lee, PhD, Pharmacologist Reviewer

Office of Clinical Pharmacology, Division of Clinical Pharmacology V

Olanrewaju Okusanya, PharmD, Clinical Pharmacology Team Leader
Jiang Liu, PhD, Pharmacometrics Team Leader

Office of Biostatistics, Division of Biometrics V

Yuan Li Shen, DrPH, Biometrics Team Leader
Xin Gao, PhD, Biometrics Reviewer

Office of Biotechnology Products, Division of Biotechnology Review and Research IV

Bazarraghaa Damdinsuren, MD, PhD, Product Quality Team Leader
Leslie A. Rivera Rosado, Ph.D., Product Quality Reviewer
Nina Brahme, Ph.D., Product Quality Reviewer
Marion Michaelis, PhD, Facility Reviewer

Office of Surveillance and Epidemiology

Page Crew, PharmD, MPH, BCPS, Pharmacist, Division of Pharmacovigilance II
Mei-Yean Chen, PharmD, Risk Management Analyst, Division of Risk Management
Emeri Potter, PharmD, BCPS, BCACP, Safety Evaluator, Division of Pharmacovigilance II
Wana Manitpisitkul, PharmD, BCPS, Safety Regulatory Project Manager

Office of Prescription Drug Promotion (OPDP)

Robert Nguyen, PharmD, RPh, Regulatory Review Officer

Patient Labeling

Morgan Walker, PharmD, Patient Labeling Reviewer
Ruth Lidoshore, PharmD, Patient Labeling Reviewer, Division of Medical Policy Programs

Clinical Outcomes Assessment

Selena Daniels, PharmD, Clinical Outcomes Assessment Team Leader
Nikunj Patel, PharmD, Clinical Outcomes Assessment Reviewer

APPLICANT ATTENDEES

Elina Asikanius, Senior Statistical Scientist
Jacques Bourquin, PhD, Technical Development Leader
Alicyn Campbell, Global Head of Patient Centers Outcomes Research
Olivier Catalani, Statistician
Tiffany Chang, MD, Associate Medical Director
Wei Dong, MD, PhD, Senior Group Director, Safety Science Oncology
Thomas Emrich, PhD, Large Molecule Bioanalytical Sciences
Stefan Gottschalk, PhD, Technical Regulatory Leader
Robyn Harrington, Senior Regulatory Program Director
Bea Lavery, Global Oncology Regulatory Head
Gallia Levy, MD, PhD, Global Development Team Leader
Amy Mutere, Head Global Quality Inspection Management
Dorothy Nguyen, MD, Safety Science Leader
Matt Schmidt, PharmD, Regulatory Program Manager
Christophe Schmitt, PharmD, Clinical Pharmacologist
Cami Sima MD, MS, Real World Data Scientist
Marianne Uguen, Statistician
Jin Xu, PhD, Clinical Scientist

1.0 BACKGROUND

BLA 761083/0 was submitted on June 23, 2017 for emicizumab.

Proposed indication: For routine prophylaxis to prevent bleeding or reduce the frequency of bleeding episodes in patients with hemophilia A (congenital factor VIII deficiency) with factor VIII inhibitors

PDUFA goal date: February 23, 2018

FDA issued a Background Package in preparation for this meeting on October 19, 2017.

2.0 DISCUSSION

1. Introductory Comments – 5 minutes (RPM/CDTL)

Welcome, Introductions, Ground rules, Objectives of the meeting

The purpose of a Late-Cycle Meeting (LCM) is to share information and to discuss any substantive review issues that we have identified to date, Advisory Committee (AC) meeting plans (if scheduled), and our objectives for the remainder of the review. The application has not yet been fully reviewed by the signatory authority, division director, and Cross-Discipline Team Leader (CDTL) and therefore, the meeting will not address the final regulatory decision for the application. We are sharing this material to promote a collaborative and successful discussion at the meeting.

During the meeting, we may discuss additional information that may be needed to address the identified issues and whether it would be expected to trigger an extension of the PDUFA goal date if the review team should decide, upon receipt of the information, to review it during the current review cycle. If you submit any new information in response to the issues identified in this background package prior to this LCM or the AC meeting, if an AC is planned, we may not be prepared to discuss that new information at this meeting.

2. Discussion of Substantive Review Issues – 5 minutes

The Applicant has committed to submit study data the week of October 20, 2017 in response to FDA Form 483 Observation 1 issued during drug product facility Pre-license Inspection.

Applicant's response to FDA Form 483 issued during drug substance facility Pre-license Inspection is under review.

Discussion: The Agency confirms receipt of the outstanding study reports related to the FDA Form 483 Observation 1 issued during drug product facility Pre-license Inspection.

3. Postmarketing Requirements/Postmarketing Commitments – 10 minutes

Clinical Pharmacology PMC

- 3.1. Conduct an assessment of binding and neutralizing anti-product antibody (APA) responses with a validated assay capable of sensitively detecting APA responses in the presence of emicizumab levels that are expected to be present in the serum at the time of patient sampling. The APA response will be evaluated in at least 50 emicizumab-treated patients. The final report will include information on the level of emicizumab in each patient's test sample at each sampling point.

Chemistry Manufacturing and Controls (CMC) PMCs

- 3.2. Develop and validate a sensitive and precise assay for the detection of anti-emicizumab antibodies (ADA). The assay should be capable of sensitively detect ADA responses in the presence of emicizumab levels that are expected to be present in serum at the time of patient sampling. The final report should include screening, confirmation, and titer assay validation reports and assay standard operating procedures.
- 3.3. Develop and validate an assay to evaluate the neutralizing capacity of ADA detected in the patient samples. The assay should be capable of sensitively detect neutralizing ADA in the presence of emicizumab levels that are expected to be present in serum at the time of patient sampling. The final report should include assay validation report and assay standard operating procedure.
- 3.4. Re-evaluate the action limit and acceptance criterion for [REDACTED] (b) (4) testing by validated [REDACTED] (b) (4) method after data from 30 drug substance batches are available. The final report should include the corresponding data, the analysis, and statistical plan used to evaluate the results, action limit and acceptance criterion, and any proposed changes to the approved limit or criterion.
- 3.5. Re-evaluate the drug substance stability acceptance criteria for stability samples held at the (b) (4)C condition after data from 5 drug substance lots stored at (b) (4)C for (b) (4) months are available. The final report should include the corresponding data, the analysis, and statistical plan used to evaluate the results and acceptance criteria and any proposed changes to the approved criteria.

Discussion: The Agency had a general discussion with the Applicant regarding the proposed PMCs. The Applicant proposes to submit a response to 3.1, 3.2, and 3.3 by October 26, 2017.

4. Major labeling issues – 20 minutes

The Agency requests discussion of the following items:

- 4.1 Inclusion of health-related quality of life information in patient labeling. The Agency requests the Applicant to provide specific items for discussion due to limited information provided by the Applicant in the revised labeling received on October 12, 2017.

On October 19, 2017, the Applicant sent an e-mail including the following items for discussion with regards to the labeling agenda items to discuss the Agency's comments and edits to the HRQoL data in Section 14 (Clinical Studies) of the prescribing information:

- The deletion of the p-value for the Physical Health Score given the pre-specified nature of this analysis as well as the robustness of the results.
- [REDACTED] (b) (4)

- The relevance of this information to patients and prescribers given the considerations noted above.

4.2 Information in labeling (full prescribing information and patient labeling) to convey the risks of thrombotic microangiopathy (TMA) and thromboembolism (TE).

Discussion 4.1: The Applicant requested clarification (b) (4)

[Redacted]

The Applicant requested clarification (b) (4)

[Redacted]

The Agency will consider the Applicant's responses with the labeling negotiations.

The Applicant will include justification for inclusion of the p-value for Physical Health Score.

Discussion 4.2: The Agency had a general discussion with the Applicant regarding TMA and TE. The applicant provided a slide (appended to these meeting minutes) to facilitate discussion. The Agency confirmed that the Applicant can submit proposals for labeling.

5. Review Plans – 5 minutes

The Agency plans to complete the review within the PDUFA timeline. The timeline for review completion would depend on resolution of substantive review issues and agreement with labeling and postmarketing commitments.

6. Wrap-up and Action Items – 5 minutes

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.

Proposed text and table for characterization of aPCC use in emicizumab clinical studies

Section 6.1



(b) (4)

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

/s/

ROMEO A DE CLARO
11/01/2017



BLA 761083

**LATE CYCLE MEETING
BACKGROUND PACKAGE**

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

Dear Ms. Harrington:

Please refer to your Biologic License Application (BLA) submitted under the Public Health Service Act for emicizumab injection, 150 mg/mL (1.0, 0.7, 0.4 mL); 30 mg/1.0 mL.

We also refer to the Late-Cycle Meeting (LCM) scheduled for October 24, 2017. Attached is our background package, including our agenda, for this meeting.

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

If you have any questions, call Laura Wall, Regulatory Project Manager, at (301) 796-2237.

Sincerely,

{See appended electronic signature page}

Ann T. Farrell, MD
Director
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

ENCLOSURE:
Late-Cycle Meeting Background Package

LATE-CYCLE MEETING BACKGROUND PACKAGE

Meeting Date and Time: October 24, 2017 from 3:00 PM to 4:00 PM (EST)

Meeting Location: Teleconference

Application Number: BLA 761083

Product Name: emicizumab

Indication: For routine prophylaxis to prevent bleeding or reduce the frequency of bleeding episodes in patients with hemophilia A (congenital factor VIII deficiency) with factor VIII inhibitors

Applicant Name: Genentech, Inc.

FDA ATTENDEES (tentative)

Office of Hematology and Oncology Products (OHOP), Division of Hematology Products (DHP)

Ann Farrell, MD, Director

Paul Kluetz, MD, Associate Director for Clinical Science

R. Angelo de Claro, MD, Clinical Team Leader

Lori Ehrlich, MD, PhD, Clinical Reviewer

Theresa Carioti, MPH, Chief, Project Management Staff

Diane Leaman, BS, Safety Regulatory Project Manager

Laura Wall, MS, Regulatory Project Manager

OHOP, Division of Hematology Oncology Toxicology (DHOT)

Christopher Sheth, PhD, Supervisory Pharmacologist/Toxicologist

Shwu-Luan Lee, PhD, Pharmacologist Reviewer

Office of Clinical Pharmacology, Division of Clinical Pharmacology V

Olanrewaju Okusanya, PharmD, Clinical Pharmacology Team Leader

Yuhong Chen, MD, PhD, Clinical Pharmacology Reviewer

Jiang Liu, PhD, Pharmacometrics Team Leader

Office of Biostatistics, Division of Biometrics V

Yuan Li Shen, DrPH, Biometrics Team Leader

Xin Gao, PhD, Biometrics Reviewer

Office of Biotechnology Products, Division of Biotechnology Review and Research IV

Bazarraghaa Damdinsuren, MD, PhD, Product Quality Team Leader

Leslie A. Rivera Rosado, Ph.D., Product Quality Reviewer

Nina Brahme, Ph.D., Product Quality Reviewer

Aimee Cunningham, PhD, Product Quality Reviewer

Marion Michaelis, PhD, Facility Reviewer

Office of Surveillance and Epidemiology

Page Crew, PharmD, MPH, BCPS, Pharmacist, Division of Pharmacovigilance II
Mei-Yean Chen, PharmD, Risk Management Analyst, Division of Risk Management

Office of Prescription Drug Promotion (OPDP)

Robert Nguyen, PharmD, RPh, Regulatory Review Officer

Patient Labeling

Morgan Walker, PharmD, Patient Labeling Reviewer

Clinical Outcomes Assessment

Selena Daniels, PharmD, Clinical Outcomes Assessment Team Leader

Nikunj Patel, PharmD, Clinical Outcomes Assessment Reviewer

APPLICANT ATTENDEES

Genentech/Roche Attendees

Elina Asikanius, Senior Statistical Scientist

Jacques Bourquin, PhD, Technical Development Leader

Olivier Catalani, Statistician

Tiffany Chang, MD, Associate Medical Director

Thomas Emrich, PhD, Large Molecule Bioanalytical Sciences

Stefan Gottschalk, PhD, Technical Regulatory Leader

Robyn Harrington, Senior Regulatory Program Director

Bea Lavery, Global Oncology Regulatory Head

Gallia Levy, MD, PhD, Global Development Team Leader

Bruce McCall, MD, Senior Safety Science Leader

Dorothy Nguyen, MD, Safety Science Leader

Kathleen Paatz, PhD, Technical Product Leader

Bao Phan, PharmD, Global Regulatory Leader

Matt Schmidt, PharmD, Regulatory Program Manager

Christophe Schmitt, PharmD, Clinical Pharmacologist

Cami Sima MD, MS, Real World Data Scientist

Marianne Uguen, Statistician

Jin Xu, PhD, Clinical Scientist

INTRODUCTION

The purpose of a Late-Cycle Meeting (LCM) is to share information and to discuss any substantive review issues that we have identified to date, Advisory Committee (AC) meeting plans (if scheduled), and our objectives for the remainder of the review. The application has not yet been fully reviewed by the signatory authority, division director, and Cross-Discipline Team Leader (CDTL) and therefore, the meeting will not address the final regulatory decision for the application. We are sharing this material to promote a collaborative and successful discussion at the meeting.

During the meeting, we may discuss additional information that may be needed to address the identified issues and whether it would be expected to trigger an extension of the PDUFA goal date if the review team should decide, upon receipt of the information, to review it during the current review cycle. If you submit any new information in response to the issues identified in this background package prior to this LCM or the AC meeting, if an AC is planned, we may not be prepared to discuss that new information at this meeting.

BRIEF MEMORANDUM OF SUBSTANTIVE REVIEW ISSUES IDENTIFIED TO DATE

DISCIPLINE REVIEW LETTERS

No Discipline Review letters have been issued to date.

SUBSTANTIVE REVIEW ISSUES

The Applicant has committed to submit study data the week of October 20, 2017 in response to FDA Form 483 Observation 1 issued during drug product facility Pre-license Inspection.

Applicant's response to FDA Form 483 issued during drug substance facility Pre-license Inspection is under review.

ADVISORY COMMITTEE MEETING

An Advisory Committee meeting is not planned.

REMS OR OTHER RISK MANAGEMENT ACTIONS

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

LCM AGENDA

1. Introductory Comments – 5 minutes (RPM/CDTL)

Welcome, Introductions, Ground rules, Objectives of the meeting

2. Discussion of Substantive Review Issues – 5 minutes

Refer to above.

3. Postmarketing Requirements/Postmarketing Commitments – 10 minutes

Clinical Pharmacology PMC

- 3.1. Conduct an assessment of binding and neutralizing anti-product antibody (APA) responses with a validated assay capable of sensitively detecting APA responses in the presence of emicizumab levels that are expected to be present in the serum at the time of patient sampling. The APA response will be evaluated in at least 50 emicizumab-treated patients. The final report will include information on the level of emicizumab in each patient's test sample at each sampling point.

Chemistry Manufacturing and Controls (CMC) PMCs

- 3.2. Develop and validate a sensitive and precise assay for the detection of anti-emicizumab antibodies (ADA). The assay should be capable of sensitively detect ADA responses in the presence of emicizumab levels that are expected to be present in serum at the time of patient sampling. The final report should include screening, confirmation, and titer assay validation reports and assay standard operating procedures.
- 3.3. Develop and validate an assay to evaluate the neutralizing capacity of ADA detected in the patient samples. The assay should be capable of sensitively detect neutralizing ADA in the presence of emicizumab levels that are expected to be present in serum at the time of patient sampling. The final report should include assay validation report and assay standard operating procedure.
- 3.4. Re-evaluate the action limit and acceptance criterion for (b) (4) testing by validated (b) (4) method after data from 30 drug substance batches are available. The final report should include the corresponding data, the analysis, and statistical plan used to evaluate the results, action limit and acceptance criterion, and any proposed changes to the approved limit or criterion.
- 3.5. Re-evaluate the drug substance stability acceptance criteria for stability samples held at the (b) (4) condition after data from 5 drug substance lots stored at (b) (4)C for (b) (4) months are available. The final report should include the corresponding data, the analysis, and statistical plan used to evaluate the results and acceptance criteria and any proposed changes to the approved criteria.

4. Major labeling issues – 20 minutes

The Agency requests discussion of the following items:

- 4.1 Inclusion of health-related quality of life information in patient labeling. The Agency requests the Applicant to provide specific items for discussion due to limited information provided by the Applicant in the revised labeling received on October 12, 2017.
- 4.2 Information in labeling (full prescribing information and patient labeling) to convey the risks of thrombotic microangiopathy and thromboembolism

5. Review Plans – 5 minutes

The Agency plans to complete the review within the PDUFA timeline. The timeline for review completion would depend on resolution of substantive review issues and agreement with labeling and postmarketing commitments.

6. Wrap-up and Action Items – 5 minutes

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

/s/

LAURA C WALL

10/19/2017

Signing on behalf of Ann T. Farrell