CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761065Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION[1]		
BLA # 761065	BLA Supplement # N/A (Original BLA)	If NDA, Efficacy Supplement Type: N/A *(an action package is not required for SE8 or SE9 supplements)*
Proprietary Name: TROGARZO Established/Proper Name: ibalizumab-uiyk Dosage Form: injection		Applicant: TaiMed Biologics Inc. Agent for Applicant (if applicable):
RPM: Christian Yoder/Elizabeth Thompson		Division: DAVP

NDA Application Type: ☐ 505(b)(1) ☐ 505(b)(2) Efficacy Supplement: ☐ 505(b)(1) ☐ 505(b)(2) BLA Application Type: ☐ 351(k) ☒ 351(a) Efficacy Supplement: ☐ 351(k) ☐ 351(a)	**For ALL 505(b)(2) applications, two months prior to EVERY action:** • **Review the information in the 505(b)(2) Assessment and submit the draft[2] to CDER OND IO for clearance.** • **Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity)** ☐ No changes ☐ New patent/exclusivity *(notify CDER OND IO)* Date of check: ***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.***

❖ Actions	
• Proposed action • User Fee Goal Date is April 3, 2018	☒ AP ☐ TA ☐ CR
• Previous actions *(specify type and date for each action taken)*	☒ Major Amendment – 11/9/17
❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain _____	☐ Received
❖ Application Characteristics [3]	

[1] The **Application Information** Section is (only) a checklist. The **Contents of Action Package** Section (beginning on page 2) lists the documents to be included in the Action Package.
[2] For resubmissions, 505(b)(2) applications must be cleared before the action, but it is not necessary to resubmit the draft 505(b)(2) Assessment to CDER OND IO unless the Assessment has been substantively revised (e.g., new listed drug, patent certification revised).
[3] Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA.

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

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

(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

BLAs: Subpart E
☐ Accelerated approval (21 CFR 601.41)
☐ Restricted distribution (21 CFR 601.42)
Subpart H
☐ 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

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

Comments:

❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 *(approvals only)*	☐ Yes ☒ No This product is exempted from lot release because it is a specified product per 21 CFR 601.2(a)
❖ Public communications *(approvals only)*	
• Office of Executive Programs (OEP) liaison has been notified of action	☒ Yes ☐ No
• Indicate what types (if any) of information were issued	☐ None ☒ FDA Press Release ☐ FDA Talk Paper ☐ CDER Q&As ☐ Other
❖ Exclusivity	
• Is approval of this application blocked by any type of exclusivity (orphan, 5-year NCE, 3-year, pediatric exclusivity)? • If so, specify the type	☒ No ☐ Yes
❖ Patent Information (NDAs only)	N/A
• Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought.	☐ Verified ☐ Not applicable because drug is an old antibiotic.

CONTENTS OF ACTION PACKAGE

Officer/Employee List

❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list *(approvals only)* (link)	☒ Included
Documentation of consent/non-consent by officers/employees (link)	☒ Included

Action Letters	
❖ Copies of all action letters *(including approval letter with final labeling)*	Action(s) and date(s) Approval; March 6, 2018
Labeling	
❖ Package Insert *(write submission/communication date at upper right of first page of PI)*	
• Most recent draft labeling *(if it is division-proposed labeling, it should be in track-changes format)*	☒ Included (2-26-18)
• Original applicant-proposed labeling	☒ Included (5-3-2017)
❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling *(write submission/communication date at upper right of first page of each piece)*	☐ Medication Guide ☒ Patient Package Insert ☐ Instructions for Use ☐ Device Labeling ☐ None
• Most-recent draft labeling *(if it is division-proposed labeling, it should be in track-changes format)*	☒ Included (2-15-18)
• Original applicant-proposed labeling	☒ Included (5-3-2017)
❖ Labels (**full color** carton and immediate-container labels) *(write submission/communication date on upper right of first page of each submission)*	
• Most-recent draft labeling	☒ Included (10-12-17)
❖ Proprietary Name • Acceptability/non-acceptability letter(s) *(indicate date(s))* • Review *(indicate date(s)* • General Advice letter (nonproprietary name suffix) • Review memo (nonproprietary name suffix) • General Advice letter (nonproprietary name suffix)	☒ 11/17/16 ☒ 11/10/16 ☒ 9/22/17 ☒ 9/20/17 ☒ 7/10/17
❖ Labeling reviews *(indicate dates of reviews)*	RPM: ☒ 5-31-2017 (PLR format) DMEPA: ☒ 8/24/17 & 11/3/17 DMPP/PLT (DRISK): ☒ 12/1/17 OPDP: ☒ 12/1/17 Product Quality ☒ 2-14-2018
Administrative / Regulatory Documents	
❖ RPM Filing Review[4]/Memo of Filing Meeting *(indicate date of each review)* ❖ All NDA 505(b)(2) Actions: Date each action cleared by 505(b)(2) Clearance Committee	☒ 6/27/17 ☒ Not a (b)(2)
❖ NDAs/NDA supplements only: Exclusivity Summary *(signed by Division Director)*	☐ Completed (Do not include)
❖ Application Integrity Policy (AIP) Status and Related Documents http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default htm	
• Applicant is on the AIP	☐ Yes ☒ No

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

• This application is on the AIP o If yes, Center Director's Exception for Review memo *(indicate date)* o If yes, OC clearance for approval *(indicate date of clearance communication)*	☐ Yes ☒ No ☐ Not an AP action
❖ Pediatrics *(approvals only)* • Date reviewed by PeRC If PeRC review not necessary, explain:	N/A Product has orphan drug status
❖ Breakthrough Therapy Designation	☒
• Breakthrough Therapy Designation Letter(s) (granted, denied, an/or rescinded)	Granted 2/23/15 (IND 9776)
• CDER Medical Policy Council Breakthrough Therapy Designation Determination Review Template(s) *(include only the completed template(s) and not the meeting minutes)*	1/30/15
• CDER Medical Policy Council Brief – Evaluating a Breakthrough Therapy Designation for Rescission Template(s) *(include only the completed template(s) and not the meeting minutes)* *(completed CDER MPC templates can be found in DARRTS as clinical reviews or on the MPC SharePoint Site)*	N/A
❖ Outgoing communications: letters, emails, and faxes considered important to include in the action package by the reviewing office/division (e.g., clinical SPA letters, RTF letter, Formal Dispute Resolution Request decisional letters, etc.) *(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)*	Included
❖ Internal documents: memoranda, telecons, emails, and other documents considered important to include in the action package by the reviewing office/division (e.g., Regulatory Briefing minutes, Medical Policy Council meeting minutes)	N/A (no meeting held; council agreed with division and product was removed from mtg discussion)
❖ Minutes of Meetings	
• If not the first review cycle, any end-of-review meeting *(indicate date of mtg)*	N/A
• Pre-BLA or BPD Type 4 meeting *(indicate date of mtg)*	☒ 9/26/16
• EOP2 meeting *(indicate date of mtg)*	☒ 6/14/11
• Mid-cycle Communication *(indicate date of mtg)*	☒ 8/18/17
• Late-cycle Meeting *(indicate date of mtg)*	☒ 10/31/17
• Other milestone meetings (e.g., EOP2a, BPD Type 3, CMC focused milestone meetings) *(indicate dates of mtgs)*	2/3/16 CMC Pre-BLA 11/20/15 BT-Initial Comprehensive 9/4/2015: CMC EOP2

❖ Advisory Committee Meeting(s)	☒ No AC meeting
• Date(s) of Meeting(s)	N/A
Decisional and Summary Memos	
❖ Office Director Decisional Memo *(indicate date for each review)*	☒ 3-6-18 (combined Office Director, Division Director and CDTL review)
Division Director Summary Review *(indicate date for each review)*	☒ 3-6-18 (combined Office Director, Division Director and CDTL review)
Cross-Discipline Team Leader Review *(indicate date for each review)*	☒ 11/5/17 (memo) and 3-6-18 (combined Office Director, Division Director and CDTL review)
PMR/PMC Development Templates *(indicate total number)*	☒ 8
Clinical	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) *(indicate date for each review)*	No separate review
• Clinical review(s) *(indicate date for each review)*	☒ 10/3/17 ☒ 11/6/17 Addendum
• Social scientist review(s) (if OTC drug) *(indicate date for each review)*	None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here ☐ and include a review/memo explaining why not *(indicate date of review/memo)*	Refer to Clinical Review, Section 13.2, pp. 114-115
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers *(indicate date of each review)*[5]	None
❖ Controlled Substance Staff review(s) and Scheduling Recommendation *(indicate date of each review)*	N/A
❖ Risk Management • REMS Documents and REMS Supporting Document *(indicate date(s) of submission(s))* • REMS Memo(s) and letter(s) *(indicate date(s))* • Risk management review(s) and recommendations (including those by OSE and CSS) *(indicate date of each review and indicate location/date if incorporated into another review)*	 N/A N/A ☒ 9/22/17
❖ OSI Clinical Inspection Review Summary(ies) *(include copies of OSI letters to investigators)*	☒ Summary 10/10/17 ☒ Letters 8/3/17, 10/17/17, 10/26/17, 11/29/17

[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 Microbiology ☐ None	
❖ Clinical Microbiology Team Leader Review(s) *(indicate date for each review)*	No separate review
Clinical Microbiology Review(s) *(indicate date for each review)*	☒ 10/3/17 ☒ 1/22/18 Addendum
Biostatistics ☐ None	
❖ Statistical Division Director Review(s) *(indicate date for each review)*	No separate review
Statistical Team Leader Review(s) *(indicate date for each review)*	No separate review
Statistical Review(s) *(indicate date for each review)*	☒ 10/3/17
Clinical Pharmacology ☐ None	
❖ Clinical Pharmacology Division Director Review(s) *(indicate date for each review)*	No separate review
Clinical Pharmacology Team Leader Review(s) *(indicate date for each review)*	No separate review
Clinical Pharmacology review(s) *(indicate date for each review)*	☒ 10/2/17
❖ OSI Clinical Pharmacology Inspection Review Summary *(include copies of OSI letters)*	None requested
Nonclinical ☐ None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) *(indicate date for each review)*	☒ 3/6/18
• Supervisory Review(s) *(indicate date for each review)*	No separate review
• Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	☒ 9/29/17
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer *(indicate date for each review)*	None
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	No carc
❖ ECAC/CAC report/memo of meeting	None
❖ OSI Nonclinical Inspection Review Summary *(include copies of OSI letters)*	None requested

Product Quality ☐ None	
❖ Product Quality Discipline Reviews[6]	
• Tertiary review (*indicate date for each review*)	None
• Secondary review (e.g., Branch Chief) *(indicate date for each review)*	None
• Integrated Quality Assessment (contains the Executive Summary and the primary reviews from each product quality review discipline) *(indicate date for each review)*	☒ Executive Summary: 10-20-2017; 3-2-2018 (addendum) Product Quality: 10-3-2017; 2-20-2018 (addendum) Immunogenicity Review: 2-28-2018 Product Quality Micro (DS): 10-3-2017; 1-25-2018 (addendum) Product Quality Micro (DP): 10-3-2017; 1-22-2018 (addendum 1); 2-14-2018 (addendum 2) Facilities: 10-3-2017 ;1-30-2018 (addendum)
❖ Reviews by other disciplines/divisions/Centers requested by product quality review team *(indicate date of each review)*	None
❖ Environmental Assessment (check one) (original and supplemental applications)	
☒ Categorical Exclusion *(indicate review date) (all original applications and all efficacy supplements that could increase the patient population)*	10/3/17 Refer to page 5 of Product Quality Review
☐ Review & FONSI *(indicate date of review)*	
☐ Review & Environmental Impact Statement *(indicate date of each review)*	
❖ Facilities Review/Inspection	
☒ Facilities inspections (indicate date of recommendation; within one week of taking an approval action, confirm that there is an acceptable recommendation before issuing approval letter) *(only original applications and efficacy supplements that require a manufacturing facility inspection(e.g., new strength, manufacturing process, or manufacturing site change)*	☒ Acceptable; 1-30-2018 ☐ Withhold recommendation ☐ Not applicable

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

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

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/s/

ELIZABETH G THOMPSON
03/06/2018

From: Helen Shu
To: Thompson, Elizabeth
Subject: Re: FW: BLA 761065: labeling comments
Date: Thursday, March 01, 2018 10:28:04 AM
Attachments: image001.png

Yes, thank you. Ok to make change.

On Thu, Mar 1, 2018 at 7:25 AM, Thompson, Elizabeth <Elizabeth.Thompson@fda.hhs.gov> wrote:

> Helen-
>
> Trying to send again. Is it appearing in the email below?
>
> ---
>
> **From:** Thompson, Elizabeth
> **Sent:** Thursday, March 01, 2018 10:25 AM
> **To:** Thompson, Elizabeth <Elizabeth.Thompson@fda.hhs.gov>
> **Subject:** RE: BLA 761065: labeling comments
>
> **6.2 Immunogenicity**
>
> As with all therapeutic proteins, there is potential for immunogenicity. The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to ibalizumab-uiyk in the studies described below with the incidence of antibodies in other studies or to other products may be misleading.
>
> All subjects enrolled in clinical trial TMB-301 and trial TMB-202 (a Phase 2b clinical trial that studied TROGARZO administered intravenously as 2,000 mg every 4 weeks or 800 mg every 2 weeks; the safety and effectiveness of this dosing regimen has not been established), were tested for the presence of anti (b) (4) ibalizumab (b) (4) antibodies throughout their participation. One sample tested positive with low titer anti-ibalizumab antibodies. No adverse reaction or reduced efficacy was attributed to the positive sample reported in this subject.
>
> > **From:** Helen Shu [mailto:hshu@taimedbio.com]
> > **Sent:** Thursday, March 01, 2018 10:18 AM
> > **To:** Thompson, Elizabeth <Elizabeth.Thompson@fda.hhs.gov>
> > **Subject:** Re: BLA 761065: labeling comments

Dear Beth

Please make the correction. BTW, there was no attachment with your email.

Thanks

Helen

On Thu, Mar 1, 2018 at 3:51 AM, Thompson, Elizabeth <Elizabeth.Thompson@fda.hhs.gov> wrote:

> Helen-
>
> We found another labeling item (minor) that needs to be revised. Section 6.2 (see below). If TaiMed agrees with this change, I will make it and add to the final version of the label. Just need agreement by email and no need to submit official label at this time.
>
> Beth
>
> Chief, Project Management Staff
>
> FDA/CDER/OAP/DAVP
>
> 301-796-0824

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/s/

ELIZABETH G THOMPSON
03/02/2018

From: Helen Shu
To: Thompson, Elizabeth
Subject: Re: BLA 761065 information
Date: Wednesday, February 28, 2018 11:40:30 AM

Yes, pls do as needed. Thank you, appreciate it.

On Wed, Feb 28, 2018 at 6:50 AM, Thompson, Elizabeth <Elizabeth.Thompson@fda.hhs.gov> wrote:

> Helen-
>
> We are working on finalizing the action. For your label (PI), I noted at the end of the FPI there was a placeholder for the license number, as well as a "Date". Dates are only included in Highlights and at the end of the Patient Information, so I will remove this placeholder. Also, I will add the license number to your label so that when it is loaded on Drugs@FDA it will be filled in.
>
> If you are ok with me making these changes I will do so with NO ACTION REQUIRED on your part.
>
> Regards,
>
> Beth
> Chief, Project Management Staff
> FDA/CDER/OAP/DAVP
> 301-796-0824

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/s/

ELIZABETH G THOMPSON
02/28/2018

From:	Thompson, Elizabeth
To:	"Helen Shu"
Cc:	Thompson, Elizabeth
Subject:	BLA 761065: labeling comments
Date:	Monday, February 26, 2018 10:46:40 AM
Attachments:	022618 ibalizumab final.docx
Importance:	High

Helen-

This should be our final round for labeling. Attached please find a revised label with re-formatting and movement of temperature in Section 2.2. Please let me know if you have any questions. If you agree, please submit final word version officially to the BLA.

Regards,

Beth

Chief, Project Management Staff

FDA/CDER/OAP/DAVP

301-796-0824

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/s/

ELIZABETH G THOMPSON
02/26/2018

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

BLA 761065

INFORMATION REQUEST

TaiMed Biologics USA Corp.
Attention: Helen P. Shu, Ph.D.
VP Regulatory Affairs and Quality
425 San Lucas Drive
Solano Beach, CA 92075

Dear Dr. Shu:

Please refer to your Biologics License Application (BLA) dated May 3, 2017, received May 3, 2017, submitted under section 351(a) of the Public Health Service Act for ibalizumab injectable.

We are reviewing the CMC section of your submission and have the following comments and information requests. We request a prompt written response by February 26, 2018 in order to continue our evaluation of your BLA.

1. Your current ibalizumab bulk drug substance (BDS) container closure system is a [redacted] (b) (4) (b) (4) Laboratory grade materials are not appropriate for use as the BDS container closure because the materials may not be sufficiently controlled to ensure consistent performance throughout the lifecycle of the product. Therefore a new BDS container closure system should be developed, validated, and implemented using appropriate pharmaceutical grade materials. The new container closure system should be validated to ensure compatibility with ibalizumab BDS, stability of BDS stored in the container, and should pose no risk of extractable and leachable material to the quality of product. Prior to implementation of the new container closure system for ibalizumab BDS, the BLA license should be updated through the submission of a prior approval supplement (PAS). Please agree to the following post-marketing commitment:

   To develop, validate, and implement an appropriate pharmaceutical grade container closure system for ibalizumab bulk drug substance.
   The final study report(s) will be reported according to 21 CFR 601.12 by {propose month}, 2019.

2. Your shipping qualification study did not include an assessment of product quality after the shipment of ibalizumab drug product from Wuxi, China to the United States. Analytical testing should be performed on the product to assess product quality before

and after shipping to evaluate the impact of the shipping conditions on ibalizumab drug product. The testing parameters used to evaluate product quality should include the critical quality attributes of the product including, but not limited to, size heterogeneity, charge heterogeneity, aggregation, particulates, appearance, and potency. Your real-time shipping study should capture the worst-case scenario of your proposed shipping conditions (temperature, containers, and mode of transportation) that will be used for commercial product shipping. These studies should be performed using commercial shipping lane(s) that adequately represent the product's distribution network and modes of transport. To assess the effect of real-time shipping conditions on product quality, products should be tested both pre- and post-shipment against adequate pre-determined acceptance criteria. Please agree to the following post-marketing commitment:

To perform a drug product shipping study using the approved commercial shipping lane to evaluate the impact of shipment on product quality.
The final study report(s) will be reported by {propose month}, 2018.

If you have any questions, please contact Anita Brown, Regulatory Business Process Manager, at (301)796-2066 or Anita.Brown@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Anita N. Brown
Regulatory Business Process Manager
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research

Anita Brown

Digitally signed by Anita Brown
Date: 2/22/2018 02:43:43PM
GUID: 508da6dc000266ff1f7013ac7142cacd

From:	Thompson, Elizabeth
To:	"Helen Shu"
Cc:	Thompson, Elizabeth
Subject:	BLA 761065: PI comments
Date:	Wednesday, February 21, 2018 3:15:35 PM
Attachments:	PI FDA edits 2-21-18.docx

Helen-

We reviewed your last submission and have some additional edits. If you agree, please submit clean copies to the BLA. If you need to propose additional text, please submit tracked and clean versions to the BLA.

Regards,

Beth

Chief, Project Management Staff

FDA/CDER/OAP/DAVP

301-796-0824

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/s/

ELIZABETH G THOMPSON
02/21/2018

From:	Thompson, Elizabeth
To:	"Helen Shu"
Cc:	Thompson, Elizabeth
Subject:	BLA 761065: PI labeling comments
Date:	Thursday, February 15, 2018 2:47:14 PM
Attachments:	DAVP PI comments 2-15-18.pdf
Importance:	High

Helen-

We reviewed your response to labeling comments submitted today, and have 2 further comments/proposed edits. Please provide a response to the BLA with both tracked changes and clean word versions. Please also confirm receipt of this correspondence.

Beth

Chief, Project Management Staff

FDA/CDER/OAP/DAVP

301-796-0824

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/s/

ELIZABETH G THOMPSON
02/15/2018

From:	Thompson, Elizabeth
To:	"Helen Shu"
Cc:	Thompson, Elizabeth
Subject:	BLA 761065: FDA comments on PI and PPI
Date:	Wednesday, February 14, 2018 3:17:11 PM
Attachments:	BLA 761065 PI FDA revisions 2-14-18.docx PPI FDA revisions 2-14-18.doc.docx
Importance:	High

Helen-

We've completed our review of all labeling, including CMC. Attached please find FDA comments on the PI and PPI. If you are in agreement with the changes, please accept and submit clean labeling (in word) officially to the BLA. If you have further revisions/proposals/responses, please provide by email first in tracked changes. We will review and work with you by email to finalize and then you can provide a clean version officially to the BLA once agreed upon.

Please confirm receipt of this information request.

Beth

Chief, Project Management Staff

FDA/CDER/OAP/DAVP

301-796-0824

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/s/

ELIZABETH G THOMPSON
02/14/2018

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

BLA 761065

INFORMATION REQUEST

TaiMed Biologics USA Corp.
Attention: Helen P. Shu, Ph.D.
VP Regulatory Affairs and Quality
425 San Lucas Drive
Solano Beach, CA 92075

Dear Dr. Shu:

Please refer to your Biologics License Application (BLA) dated May 3, 2017, received May 3, 2017, submitted under section 351(a) of the Public Health Service Act for ibalizumab injectable.

We are reviewing the CMC section of your submission and have the following comments and information requests. We request a prompt written response by February 15, 2018 in order to continue our evaluation of your BLA.

Please update your FDA FORM 356h, and all other relevant sections of the submitted application, regarding the FEI number for the WuXi Apptec Biopharmaceuticals Drug Substance and Drug Product Manufacturing Site to reflect the appropriate number (FEI 3010606982).

If you have any questions, please contact Anita Brown, Regulatory Business Process Manager, at (301)796-2066 or Anita.Brown@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Anita N. Brown
Regulatory Business Process Manager
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research

Anita Brown

Digitally signed by Anita Brown
Date: 2/12/2018 12:22:47PM
GUID: 508da6dc000266ff1f7013ac7142cacd

From: Helen Shu
To: Thompson, Elizabeth
Subject: Re: BLA 761065: Virology PMR clarification
Date: Wednesday, February 07, 2018 3:25:58 PM

Hello Beth

Yes, that's fine. Thanks

Helen

On Wed, Feb 7, 2018 at 12:08 PM, Thompson, Elizabeth <Elizabeth.Thompson@fda.hhs.gov> wrote:

> Helen-
>
> We revised one of the virology PMRs only to add the titles of the trials, as they needed to be included. Please let me know if you agree.
>
> PMR Description:
> Provide the fastq envelope sequences from the next generation sequencing of samples collected from subjects who failed treatment in clinical trials TMB-202, entitled *"A Phase 2b, Randomized, Double-Blinded, 48-Week, Multicenter, Dose-Response Study of Ibalizumab plus an Optimized Background Regimen in Treatment-Experienced Patients Infected with HIV-1" (Amended to 24 Week Study)* and TMB-301, *entitled "A Phase 3, Single Arm, 24-Week, Multicenter Study of Ibalizumab plus an Optimized Background Regimen (OBR) in Treatment-Experienced Patients Infected with Multi-Drug Resistant HIV-1"* to better characterize the HIV-1 gp120 sequence at the time of failure.
>
> PMR Schedule Mileston:
> Final Report Submission: 04/2018
>
> Regards,
>
> Beth
> Chief, Project Management Staff
> FDA/CDER/OAP/DAVP
> 301-796-0824

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/s/

ELIZABETH G THOMPSON
02/08/2018

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

BLA 761065

INFORMATION REQUEST

TaiMed Biologics USA Corp.
Attention: Helen P. Shu, Ph.D.
VP Regulatory Affairs and Quality
425 San Lucas Drive
Solano Beach, CA 92075

Dear Dr. Shu:

Please refer to your Biologics License Application (BLA) dated May 3, 2017, received May 3, 2017, submitted under section 351(a) of the Public Health Service Act for ibalizumab injectable.

We are reviewing the CMC section of your submission and have the following comments and information requests. We request a prompt written response by 12:00 EST February 12, 2018 in order to continue our evaluation of your BLA.

In your response to FDA comment #3 submitted on 10/12/2017, you proposed in-process testing [redacted] (b) (4) The in-process testing strategy should specify alert limits or rejection limits and justification for those limits based on criticality. Because ibalizumab is an important drug that addresses an unmet medical need, an appropriate in-process control strategy would help ensure each ibalizumab batch will likely meet its release and stability requirements, thereby preventing or minimizing the risk of drug shortage for ibalizumab. The Agency has the following comments regarding your in-process testing strategy:

a. [redacted] (b) (4)

Update the acceptance criteria to include appropriate numerical ranges for the [redacted] (b) (4) [redacted] (b) (4) peaks that are consistent with your manufacturing experience.

b. [redacted] (b) (4)

manufacturing process. Update your in-process control strategy to include an analysis of

[redacted] (b) (4) with appropriate numerical acceptance criteria consistent with your manufacturing experience.

c. Provide a commitment that you will re-evaluate the in-process control strategy for the ibalizumab manufacturing process after you have gained additional manufacturing experience. Please propose the number of ibalizumab batches you intend to manufacture prior to your re-evaluation of in-process control strategy.

If you have any questions, please contact Anita Brown, Regulatory Business Process Manager, at (301)796-2066 or Anita.Brown@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Anita N. Brown
Regulatory Business Process Manager
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research

Anita Brown

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Date: 2/08/2018 02:40:20PM
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DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

BLA 761065

INFORMATION REQUEST

TaiMed Biologics USA Corp.
Attention: Helen P. Shu, Ph.D.
VP Regulatory Affairs and Quality
425 San Lucas Drive
Solano Beach, CA 92075

Dear Dr. Shu:

Please refer to your Biologics License Application (BLA) dated May 3, 2017, received May 3, 2017, submitted under section 351(a) of the Public Health Service Act for ibalizumab injectable.

We are reviewing the CMC section of your submission and have the following comments and information requests. We request a prompt written response by February 1, 2018 in order to continue our evaluation of your BLA.

Section 3.2.S.5 Reference Standards and Materials part 2: Wuxi Ibalizumab Reference Standard describes the preparation and qualification protocol for the new ibalizumab reference material [redacted] (b) (4) at WuXi Biologics. However, it is unclear from the language used in this section, particularly in parts 2.2, 2.3, 2.4 and 2.5, that the information is applicable only to reference material [redacted] (b) (4) and is not a protocol applicable to future preparations of ibalizumab primary or working reference material. For example, [redacted] (b) (4) This is inappropriate given the deficiencies described in previous FDA communications (refer to 9/22/2017 FDA information request comments 5 and 6 and 10/3/2017 FDA information request comment 1) and your previous commitment to remove the reference standard qualification protocol from the BLA. Section 3.2.S.5 should be revised as follows:

1. When describing the procedure that was used to prepare and qualify the existing reference material [redacted] (b) (4), it should be clearly indicated that the information is specific for [redacted] (b) (4), and is not a protocol applicable to future reference material preparations. It may be beneficial to remove or revise the language written in the present tense [redacted] (b) (4) because it is unclear that this has already been performed.

2. Wherever you refer to reference material, explicitly state which reference material you are referring to, including the identification number and whether it is the primary or working reference material.

3. Include a summary of the analytical qualification results for [redacted] (b) (4).

4. You propose to [redacted] (b) (4) [redacted] (b) (4) working and primary reference standards. In the event that a new working reference standard is qualified, you propose [redacted] (b) (4) [redacted] (b) (4) This is acceptable. Any information that is no longer relevant to the currently proposed 2-tiered system for reference material [redacted] (b) (4) should be removed from the application.

If you have any questions, please contact Anita Brown, Regulatory Business Process Manager, at (301)796-2066 or Anita.Brown@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Anita N. Brown
Regulatory Business Process Manager
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research

Anita Brown

Digitally signed by Anita Brown
Date: 1/30/2018 09:46:58AM
GUID: 508da6dc000266ff1f7013ac7142cacd

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Antimicrobial Products
Division of Antiviral Drug Products

FACSIMILE TRANSMITTAL SHEET

DATE: January 29, 2018

To: Dr. Helen Shu	**From: Christian Yoder, MPH**
Company: TaiMed Biologics	**Title: Regulatory Project Manager**
Fax number: 858 724-1844	**Fax number: 301-796-9883**
Phone number: 858 481-6863	**Phone number: (240) 402-9990**

Subject: BLA 761065

Total number of pages including cover:

Comments:

Helen – Can you email me to confirm receipt? Thanks.

Document to be mailed: ☐ YES ☑ NO

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Division of Antiviral Drug Products
Food and Drug Administration
Silver Spring, MD 20993

MEMORANDUM OF FACSIMILE CORRESPONDENCE

BLA: **761065**

Drug: **Ibalizumab**

Date: **January 29, 2018**

To: **Helen Shu, Ph.D., Vice President, Regulatory Affairs and Quality**

From: **Christian Yoder, MPH, Regulatory Project Manager**

Subject: **BLA 761065 Information Request: proposed Postmarketing Requirements**

Please refer to your BLA 761065 that was submitted May 3, 2017 for TROGARZO (ibalizumab). We have the following additional proposed postmarketing requirements (PMRs). Please provide confirmation of your agreement with these PMRs and populate the milestone dates no later than February 5, 2018.

1. PMR Description

Conduct a phenotypic study to determine the impact of the following gp120 amino acid substitutions on ibalizumab susceptibility: S143P, K171E, N186K/S/R, Q308H/P, G352K/E, and V547A/G.

PMR Schedule Milestones:
Study/Trial Completion: MM/YYYY
Final Report Submission: MM/YYYY

2. PMR Description

Provide integrated virology datasets for clinical trials TMB-202, entitled "*A Phase 2b, Randomized, Double-Blinded, 48-Week, Multicenter, Dose-Response Study of Ibalizumab plus an Optimized Background Regimen in Treatment-Experienced Patients Infected with HIV-1*" (Amended to 24 Week Study) and TMB-301, entitled "*A Phase 3, Single Arm, 24-Week, Multicenter Study of Ibalizumab plus an Optimized Background Regimen (OBR) in Treatment-Experienced Patients Infected with Multi-Drug Resistant HIV-1*". This should include one database for each clinical trial with baseline data for all subjects who were enrolled, and time of virologic failure data for all subjects who failed treatment and were assessed for resistance.

PMR Schedule Milestones:
Study/Trial Completion: MM/YYYY
Final Report Submission: MM/YYYY

PLEASE REPLY BY EMAIL (christian.yoder@fda.hhs.gov) to confirm receipt. We are providing this above information via telephone facsimile for your convenience. Please feel free to contact me at 240-402-9990 if you have any questions regarding this transmission.

Christian P. Yoder, MPH
Regulatory Project Manager
Division of Antiviral Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

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/s/

CHRISTIAN P YODER
01/29/2018

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

BLA 761065

INFORMATION REQUEST

TaiMed Biologics USA Corp.
Attention: Helen P. Shu, Ph.D.
VP Regulatory Affairs and Quality
425 San Lucas Drive
Solano Beach, CA 92075

Dear Dr. Shu:

Please refer to your Biologics License Application (BLA) dated May 3, 2017, received May 3, 2017, submitted under section 351(a) of the Public Health Service Act for ibalizumab injectable.

We are reviewing the CMC section of your submission and have the following comments and information requests. We request a prompt written response by January 19, 2018 in order to continue our evaluation of your BLA.

1. It appears that qualification data of the DS sample for the bioburden test using 30 mL test volume has not been provided. Provide the summary qualification data and report.

2. Update Section 3.2.S.2.4 "Controls of critical steps and intermediates" or 3.2.S.2.2 "Description of manufacturing process and process controls" with the proposed [redacted] (b) (4) provided in your response to Question 6 in the amendment dated August 11, 2017.

3. Update Section 3.2.S.4.2, "Analytical procedure" for the culture purity (sterility) test of the [redacted] (b) (4) sample to indicate [redacted] (b) (4)

4. Critical in-process controls and process parameters have been removed from section 3.2.P.3.4. Update section 3.2.P.3.4 with the IPCs and process parameters as described in Table 3.2.P.3.4.1 in response to item 7 in the amendment dated October 27, 2017 (sequence 0058).

5. Section 3.2.P.3.1 of the BLA includes [redacted] (b) (4) as the site of secondary packaging and labeling of ibalizumab drug product, and [redacted] (b) (4) as the site of identity testing of labeled drug product. However, these sites are not included on the Form FDA 356h submitted with your application. Update the Form FDA 356h to include all sites involved in the production, packaging, and testing of ibalizumab. Clearly define the roles and responsibilities of each site included in your BLA application.

6. The proposed stability acceptance criteria for drug product protein concentration and potency are wider than the release acceptance criteria. The wider stability acceptance criteria are not justified by previous ibalizumab manufacturing experience. Update the stability acceptance criteria for protein concentration and potency to be consistent with the release acceptance criteria for ibalizumab drug product.

7. In your response to the FDA information request comment #3 submitted on October 12, 2017, you proposed in-process testing of [redacted] (b) (4) However, this testing has not been included in section 3.2.S.2.4 Control of Critical Steps and Intermediates. Update section 3.2.S.2.4 to include the proposed in-process [redacted] (b) (4) testing.

8. In your response to the FDA information request comment #1 submitted on October 12, 2017, you proposed to remove [redacted] (b) (4) from the BLA. However, [redacted] (b) (4) is still found under section 3.2.P.6 of the BLA. Remove [redacted] (b) (4) and any other outdated or irrelevant information from the BLA.

If you have any questions, please contact Anita Brown, Regulatory Business Process Manager, at (301)796-2066 or Anita.Brown@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Anita N. Brown
Regulatory Business Process Manager
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research

Anita Brown

Digitally signed by Anita Brown
Date: 1/12/2018 01:45:53PM
GUID: 508da6dc000266ff1f7013ac7142cacd

From:	Yoder, Christian
To:	Helen Shu
Subject:	Ibalizumab label
Date:	Friday, December 22, 2017 7:14:00 AM
Attachments:	image001.png BLA 761065 PPI draft text 12-22-17.pdf BLA 761065 PI draft labeling text 12-22-17.pdf

---

Hello Helen,

Please refer to the PI and PPI of the ibalizumab labels attached. Kindly accept all the changes in the labels that you agree with, and include any additional revisions in track changes, and resubmit them no later than January 5, 2018. I acknowledge there are some pending revisions so we will finalize those at a later date. Also, please note that the dates in the labels will be inserted at the time of approval.

Please let me know if you have any questions.

Christian

Christian P. Yoder, BSN, MPH
Regulatory Project Manager

Division of Antiviral Products (DAVP)
CDER/OND/OAP
U.S. Food and Drug Administration
White Oak Complex, Bldg. 22 Rm. 6334
10903 New Hampshire Avenue
Silver Spring, MD 20993
Tel: (240) 402-9990
christian.yoder@fda.hhs.gov

U.S. FOOD & DRUG ADMINISTRATION

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

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/s/

CHRISTIAN P YODER
12/22/2017

From:	Yoder, Christian
To:	Helen Shu
Subject:	Draft labeling
Date:	Friday, December 08, 2017 9:24:00 AM
Attachments:	image001.png BLA 761065 PI draft-labeling-text 12-8-17.docx BLA 761065 PPI draft text 12-8-17.docx

---

Hello Helen,

Please see attached draft labels for ibalizumab. The prescribing information (PI) has been separated from the patient prescribing information (PPI) for now and we will reconnect these later.

Please accept all the changes that you agree with and delete comments that are no longer applicable. If you have additional changes and/or comments please include them in tracked changes and submit the labels (Word versions) to the BLA no later than Friday, December 15.

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

Regards,

Christian

Christian P. Yoder, BSN, MPH
Regulatory Project Manager

Division of Antiviral Products (DAVP)
CDER/OND/OAP
U.S. Food and Drug Administration
White Oak Complex, Bldg. 22 Rm. 6334
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CHRISTIAN P YODER
12/08/2017

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

BLA 761065

INFORMATION REQUEST

TaiMed Biologics USA Corp.
Attention: Helen P. Shu, Ph.D.
VP Regulatory Affairs and Quality
425 San Lucas Drive
Solano Beach, CA 92075

Dear Dr. Shu:

Please refer to your Biologics License Application (BLA) dated May 3, 2017, received May 3, 2017, submitted under section 351(a) of the Public Health Service Act for ibalizumab injectable.

We are reviewing the CMC section of your submission and have the following comments and information requests. We request a prompt written response by December 15, 2017 in order to continue our evaluation of your BLA.

1. In your response to the FDA information request provided on September 18, 2017 you described a scaled-down stability study of ibalizumab drug product [redacted] (b) (4) [redacted] The product was tested periodically using CEX-HPLC, CE-SDS, and SEC-HPLC. The FDA has the following comments regarding this approach:

    a. The test methods used in your study do not sufficiently monitor the potential impact of your preparation conditions on ibalizumab stability. Specifically, you did not provide data for appearance, protein concentration, subvisible particulates, or product potency after storage. This data should be provided.

    b. The volume used in your scaled-down study is [redacted] (b) (4) below the 250 mL volume recommended for the preparation of ibalizumab drug product prior to administration. Therefore the conditions used in your study may not be truly representative of the conditions of use. Provide evidence that your scaled down conditions are representative of full scale conditions including the protein concentration, type of infusion bag, product contact area with the infusion bag, and all other product contact materials used under actual conditions of use. Alternatively, perform the study at the full 250 mL scale recommended for the clinical preparation of ibalizumab.

2. In your General Correspondence letter dated November 2, 2017 you refer to (b) (4) cell culture media information. You also refer to (b) (4) as "authorized suppliers" of the media. It is unclear from your description what the roles of (b) (4) are regarding the supply of cell culture media for the ibalizumab manufacturing process. Explain the roles of each company including where the (b) (4) cell culture media used in the production of ibalizumab at WuXi AppTec to date has been manufactured and from which vendors it has been purchased. Information regarding the composition, manufacturing process, control strategy, batch analyses, and representative certificates of analysis for each of the (b) (4) should be provided to the Agency. This information can be submitted directly to the BLA or alternatively can be provided as DMFs submitted by the manufacturers of the (b) (4) media.

3. The proposed drug product stability acceptance criteria for the SEC-HPLC, CEX-HPLC, SDS-PAGE (non-reduced), CE-SDS (non-reduced), and CE-SDS (reduced) methods are wider than the release acceptance criteria. The data provided in your response to the FDA information request on September 18, 2017 do not adequately justify the widening of these stability acceptance criteria as compared to the acceptance criteria used for release. Update your drug product stability specification acceptance criteria to be consistent with the drug product release specification acceptance criteria.

4. The release acceptance criteria for the Cell-Cell Fusion Inhibition bioassay listed in Table 1 of section 3.2.P.5.6 is (b) (4)% of Ref Std" which is inconsistent with the acceptance criteria of (b) (4)% of Ref Std" listed in Table 1 of section 3.2.P.5.1. Update all specifications within the BLA to be current and accurate.

5. Section 3.2.P.3.1 of the BLA refers to (b) (4) as the site of identity testing for the labeled commercial drug product. However, the data supporting the identity method transfer to the new site was not provided. Provide the method transfer report for the transfer of the identity test method from the current testing lab to (b) (4).

6. Your application contains several documents that are not relevant to your currently proposed process and should therefore be removed. For example (b) (4) in section 3.2.S.2.4 are not relevant to the application because you are not proposing (b) (4) for drug substance. Update the BLA to remove all information that is no longer relevant to your currently proposed process.

If you have any questions, please contact Anita Brown, Regulatory Business Process Manager, at (301)796-2066 or Anita.Brown@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Anita N. Brown
Regulatory Business Process Manager
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research

Anita Brown

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Date: 12/08/2017 10:46:33AM
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Food and Drug Administration
Center for Drug Evaluation and Research
Office of Antimicrobial Products
Division of Antiviral Drug Products

FACSIMILE TRANSMITTAL SHEET

DATE: December 6, 2017

To: Dr. Helen Shu	**From: Christian Yoder, MPH**
Company: TaiMed Biologics	**Title: Regulatory Project Manager**
Fax number: 858 724-1844	**Fax number: 301-796-9883**
Phone number: 858 481-6863	**Phone number: (240) 402-9990**

Subject: BLA 761065

Total number of pages including cover:

Comments:

Helen – Can you email me to confirm receipt? Thanks.

Document to be mailed: ☐ YES ☑ NO

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Division of Antiviral Drug Products
Food and Drug Administration
Silver Spring, MD 20993

MEMORANDUM OF FACSIMILE CORRESPONDENCE

BLA: **761065**

Drug: **Ibalizumab**

Date: **December 6, 2017**

To: **Helen Shu, Ph.D., Vice President, Regulatory Affairs and Quality**

From: **Christian Yoder, MPH, Regulatory Project Manager**

Subject: **BLA 761065 Information Request: proposed Postmarketing Requirements**

Please refer to your BLA 761065 that was submitted May 3, 2017 for TROGARZO (ibalizumab). We have the following proposed postmarketing requirements (PMRs). Please provide confirmation of your agreement with these PMRs and populate the milestone dates no later than December 15, 2017.

1. PMR Description

Conduct a phenotypic study to determine the impact of the following gp120 amino acid substitutions on ibalizumab susceptibility: P236E, K303R, P367L, I369V, R474K, K615R/N, N649I/R, L774S, and L831V. In addition, determine the phenotypes of the substitutions observed in the various coding sequences noted: C1cons_V75I; gp41cons_E229G/Q229P/R and gp41cons_L274V/A274T; V1V2_N12K and V1V2_N14D/V14M/deletion; V4_T23N/deletion.

PMR Schedule Milestones:
Final Report Submission: MM/YYYY

2. PMR Description

Provide the fastq envelope sequences from the next generation sequencing of samples collected from subjects who failed treatment in clinical trials TMB-202 and TMB-301 to better characterize the HIV-1 gp120 sequence at the time of failure.

PMR Schedule Milestones:
Final Report Submission: MM/YYYY

3. PMR Description

Submit the final study report for the enhanced pre/postnatal development study in cynomolgus monkeys.

PMR Schedule Milestones:
Final Protocol Submission: N/A
Study/Trial Completion: N/A
Final Report Submission: MM/YYYY

4. PMR Description

Complete and provide a risk assessment of the carcinogenic potential of ibalizumab.

PMR Schedule Milestones:
Final Protocol Submission: N/A
Study/Trial Completion: N/A
Final Report Submission: MM/YYYY

PLEASE REPLY BY EMAIL (christian.yoder@fda.hhs.gov) to confirm receipt. We are providing this above information via telephone facsimile for your convenience. Please feel free to contact me at 240-402-9990 if you have any questions regarding this transmission.

Christian P. Yoder, MPH
Regulatory Project Manager
Division of Antiviral Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

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/s/

CHRISTIAN P YODER
12/06/2017

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

BLA 761065

INFORMATION REQUEST

TaiMed Biologics USA Corp.
Attention: Helen P. Shu, Ph.D.
VP Regulatory Affairs and Quality
425 San Lucas Drive
Solano Beach, CA 92075

Dear Dr. Shu:

Please refer to your Biologics License Application (BLA) dated May 3, 2017, received May 3, 2017, submitted under section 351(a) of the Public Health Service Act for ibalizumab injectable.

We are reviewing the CMC section of your submission and have the following comments and information requests. We request a prompt written response by December 15, 2017 in order to continue our evaluation of your BLA.

The Agency acknowledges receipt of your email correspondence dated November 9, 2017. Your proposal to add an additional errata table in Module 1 to summarize the most recent changes to the BLA is acceptable. Please submit all updates to the BLA by December 15, 2017. These updates should include the new errata table in Module 1, a complete and accurate version of Module 3, as well as any applicable updates to Module 2. The Agency strongly recommends contacting the CDER Electronic Submission Support (eSUB) group prior to submitting the updates to the BLA to ensure that the documentation is added to the appropriate sections of the eCTD.

If you have any questions, please contact Anita Brown, Regulatory Business Process Manager, at (301)796-2066 or Anita.Brown@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Anita N. Brown
Regulatory Business Process Manager
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research

Anita Brown

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Date: 11/20/2017 05:14:42PM
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DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

BLA 761065

PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE

TaiMed Biologics USA Corp.
425 San Lucas Drive
Solana Beach, CA 92075

ATTENTION: Helen P. Shu, Ph.D.
Vice President, Regulatory Affairs & Quality

Dear Dr. Shu:

Please refer to your first section of the Biologics License Application (BLA) under the program for step-wise submission, dated and received July 19, 2016, submitted under section 351(a) of the Public Health Service Act for Ibalizumab, 150 mg/mL.

We also refer to your correspondence, dated and received September 6, 2016, requesting review of your proposed proprietary name, Trogarzo.

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

If any of the proposed product characteristics as stated in your September 6, 2016, 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 Danyal Chaudhry, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at 301-796-3813. For any other information regarding this application, contact Christian Yoder, Regulatory Project Manager in the Office of New Drugs, at 240-402-9990.

Sincerely,

{See appended electronic signature page}

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

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/s/

AZEEM D CHAUDHRY
11/17/2016

LUBNA A MERCHANT on behalf of TODD D BRIDGES
11/17/2016

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Antimicrobial Products
Division of Antiviral Drug Products

FACSIMILE TRANSMITTAL SHEET

DATE: November 16, 2017

To: Dr. Helen Shu	**From: Christian Yoder, MPH**
Company: TaiMed Biologics	**Title: Regulatory Project Manager**
Fax number: 858 724-1844	**Fax number: 301-796-9883**
Phone number: 858 481-6863	**Phone number: (240) 402-9990**

Subject: BLA 761065

Total number of pages including cover:

Comments:

Helen – Can you email me to confirm receipt? Thanks.

Document to be mailed: ☐ YES ☑ NO

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Division of Antiviral Drug Products
Food and Drug Administration
Silver Spring, MD 20993

MEMORANDUM OF FACSIMILE CORRESPONDENCE

BLA: **761065**

Drug: **ibalizumab**

Date: **November 16, 2017**

To: **Helen Shu, Ph.D., Vice President, Regulatory Affairs and Quality**

From: **Christian Yoder, MPH, Regulatory Project Manager**

Subject: **BLA 761065 Information Request**

Please refer to your BLA 761065 that was submitted May 3, 2017, and to comments in the label that were submitted on November 14, 2017. Please see the following Division response:

> As previously stated, the pharmacological drug class should be succinct and describe medically relevant information, i.e., the target and mechanism of action of the drug. We have had a multidisciplinary discussion of your proposed class description: (b) (4) and have the following comments:
>
> - From our perspective, the most important descriptors of ibalizumab activity are:
> - It specifically inhibits HIV-1 infection
> - It binds to CD4 but does not prevent HIV-1 attachment to CD4, does not interfere with normal CD4 function, and exerts its antiviral activity post-attachment
> - It may not compete with other drugs that directly block CD4-gp120 interactions
>
> None of these points are captured in the proposed pharmacologic class description provided.
>
> - As described in the Guidance entitled ***Labeling for Human Prescription Drug and Biological Products — Determining Established Pharmacologic Class for Use in the Highlights of Prescribing Information***, the pharmacologic class is a group of drugs that share scientifically documented properties. Therefore, the pharmacologic class is not designed to specifically describe the drug being labeled, but instead

should capture the pharmacologic activity that may be used to describe other drugs with similar properties.

- The significance of the [redacted] (b) (4) descriptor is not likely to be appreciated by most clinicians; it is more appropriate to describe this under the mechanism of action section of the label, as is currently the case. [redacted] (b) (4)

- Mentioning CD4 without describing the post-attachment mechanism would imply to many that ibalizumab is an HIV-1 attachment inhibitor, and, mentioning it without mentioning HIV-1 might imply that it targets normal CD4 activity.

- In general, we do not disagree with using [redacted] (b) (4); however, adding that to the proposed class description would increase the length to the point that it would no longer be succinct. Using the descriptor 'inhibitor' captures that it inhibits HIV-1 infection, whereas [redacted] (b) (4) speaks more to [redacted] (b) (4) of the drug.

Therefore, given that ibalizumab exerts its antiviral activity at an undefined step after attaching to CD4 domain 2 to block HIV-1 infection, "CD4 directed post-attachment HIV-1 inhibitor" will be the class used.

PLEASE REPLY BY EMAIL (christian.yoder@fda.hhs.gov) to confirm receipt. We are providing this above information via telephone facsimile for your convenience. Please feel free to contact me at 240-402-9990 if you have any questions regarding this transmission.

Christian P. Yoder, MPH
Regulatory Project Manager
Division of Antiviral Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

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/s/

CHRISTIAN P YODER
11/16/2017

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

BLA 761065

**REVIEW EXTENSION –
MAJOR AMENDMENT**

TaiMed Biologics USA Corp.
Attention: Helen P. Shu, Ph.D.
VP Regulatory Affairs and Quality
2 Executive Circle, Suite 280
Irvine, CA 92614

Dear Dr. Shu:

Please refer to your Biologics License Application (BLA) dated and received May 3, 2017, submitted under section 351 of the Public Health Service Act for TROGARZO (ibalizumab-uiyk) injection.

We received your October 25, 2017 major amendment to this application. Therefore, we are extending the goal date by three months to provide time for a full review of the submission. The extended user fee goal date is April 3, 2018.

If you have any questions, call Christian Yoder, MPH, Regulatory Project Manager at (240) 402-9990 or (301) 796-1500.

Sincerely,

{See appended electronic signature page}

Debra Birnkrant, MD
Director
Division of Antiviral Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

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/s/

DEBRA B BIRNKRANT
11/09/2017

From:	Thompson, Elizabeth
To:	"Helen Shu"
Cc:	Yoder, Christian; Thompson, Elizabeth
Subject:	BLA 761065: labeling comments
Date:	Wednesday, November 08, 2017 4:01:19 PM
Attachments:	BLA 761065 draft-labeling-text 11-5-17.docx CD4.pdf
Importance:	High

Dr. Shu-

Attached please find the Agency's labeling comments. We request that you provide a response in 7 days (Wednesday, November 15th). When providing a response, please submit both clean and tracked changes versions and:

1. Please accept all edits in the document with which you agree.
2. Please remove all comments associated with edits with which you agree.
3. Please make any new edits in track changes directly in the label.
4. Please include comments in support of any substantive changes you propose.

Also attached please find a pdf which contains the codes for CD4 results (see comment in Section 14).

If you have any questions, please do not hesitate to contact myself or Christian.

Regards,

Beth

Chief, Project Management Staff

FDA/CDER/OAP/DAVP

301-796-0824

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/s/

ELIZABETH G THOMPSON
11/08/2017

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

BLA 761065

INFORMATION REQUEST

TaiMed Biologics USA Corp.
Attention: Helen P. Shu, Ph.D.
VP Regulatory Affairs and Quality
425 San Lucas Drive
Solano Beach, CA 92075

Dear Dr. Shu:

Please refer to your Biologics License Application (BLA) dated May 3, 2017, received May 3, 2017, submitted under section 351(a) of the Public Health Service Act for ibalizumab injectable.

We are reviewing the CMC section of your submission and have the following comments and information requests. We request a prompt written response by November 20, 2017 in order to continue our evaluation of your BLA.

1. There are two sets of sterilization validation data for [redacted] (b) (4)
   Within section 3.2.P.3.5, provide subheadings and a brief explanation for the two sets of validation studies at the beginning of the sterilization validation section to clarify which validation studies support the PPQ runs or the routine production runs.
2. Acceptance criteria for [redacted] (b) (4) were updated in section 3.2.P.3.5 on October 25, 2017 (sequence 0056). Provide a timeline for submission of results for the next [redacted] (b) (4) using the new acceptance criteria.
3. Section 3.2.P.3.5 contains redundant and outdated information for the validation of the manufacturing process for ibalizumab. Provide a revised 3.2.P.3.5 with the following changes:
   a. Remove the redundant Tables 3.2.P.3.5.2.4, 3.2.P.3.5.2.5, and 3.2.P.3.5.2.6 pertaining [redacted] (b) (4). The data is summarized in Table 3.2.P.3.5.2.8.

b. Remove the redundant Tables 3.2.P.3.5.2.16 and 3.2.P.3.5.2.17 pertaining to (b) (4) [redacted]. They contain the same information as Tables 3.2.P.3.5.18 and 3.2.P.3.5.19.
c. Remove Table 3.2.P.3.5.3.1 and associated narrative summary (b) (4) [redacted] In addition to the type of information in Table 3.2.P.3.5.3.1, include the DP lot used and test parameters.
d. Remove the redundant Table 3.2.P.3.5.4.1 concerning 2014-2015 media fills. Incorporate all media fills through November 2017 into one table to replace Tables 3.2.P.3.5.4.2 and 3.2.P.3.5.4.7. Clearly indicate which media fills used product-dedicated equipment.
e. Remove the redundant Table 3.2.P.3.5.4.5. Summarize all growth promotion testing results for media fills 2014-2017 into one table to replace Tables 3.2.P.3.5.13 and 3.2.P.3.5.4.19.
f. Remove [redacted] (b) (4), including Tables 3.2.P.3.5.5.6 through Tables 3.2.P.3.5.5.14. The results are adequately summarized in Table 3.2.P.3.5.5.5.

4. For the bacterial endotoxin method validation, Table 3.2.P.5.3.26 reports (b) (4) [redacted] Remove the inaccurate endotoxin recovery data from section 3.2.P.5.3.
5. Update section 3.2.P.5.6 [redacted] (b) (4) (sequence 0025).

If you have any questions, please contact Anita Brown, Regulatory Business Process Manager, at (301)796-2066 or Anita.Brown@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Anita N. Brown
Regulatory Business Process Manager
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research

Anita Brown

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DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

BLA 761065

INFORMATION REQUEST

TaiMed Biologics USA Corp.
Attention: Helen P. Shu, Ph.D.
VP Regulatory Affairs and Quality
425 San Lucas Drive
Solano Beach, CA 92075

Dear Dr. Shu:

Please refer to your Biologics License Application (BLA) dated May 3, 2017, received May 3, 2017, submitted under section 351(a) of the Public Health Service Act for ibalizumab injectable.

We are reviewing the CMC section of your submission and have the following comments and information requests. We request a prompt written response by November 1, 2017 in order to continue our evaluation of your BLA.

(b) (4)

[redacted]

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If you have any questions, please contact Anita Brown, Regulatory Business Process Manager, at (301)796-2066 or Anita.Brown@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Anita N. Brown
Regulatory Business Process Manager
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research

Anita Brown

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Food and Drug Administration
Center for Drug Evaluation and Research
Office of Antimicrobial Products
Division of Antiviral Drug Products

FACSIMILE TRANSMITTAL SHEET

DATE: October 23, 2017

To: Dr. Helen Shu	**From: Christian Yoder, MPH**
Company: TaiMed Biologics	**Title: Regulatory Project Manager**
Fax number: 858 724-1844	**Fax number: 301-796-9883**
Phone number: 858 481-6863	**Phone number: (240) 402-9990**

Subject: BLA 761065

Total number of pages including cover:

Comments:

Helen – Can you email me to confirm receipt? Thanks.

Document to be mailed: ☐ YES ☑ NO

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Division of Antiviral Drug Products
Food and Drug Administration
Silver Spring, MD 20993

MEMORANDUM OF FACSIMILE CORRESPONDENCE

BLA: **761065**

Drug: **ibalizumab**

Date: **October 23, 2017**

To: **Helen Shu, Ph.D., Vice President, Regulatory Affairs and Quality**

From: **Christian Yoder, MPH, Regulatory Project Manager**

Subject: **BLA 761065 Information Request**

Please refer to your BLA 761065 that was submitted May 3, 2017, and to the labeling comments you submitted on October 12, 2017. Please see the following comments and respond by November 2, 2017:

Thank you for providing an explanation for the high proportion of subjects with Grade 3 and 4 hypophosphatemia seen in the TMB-202 study. We had noted that this laboratory abnormality was much more frequent in TMB-202 compared to TMB-301. Please note that this explanation should have been provided in the BLA's Summary of Clinical Safety (Section 3.2.2.1, Table 46).

1) Please elaborate on the changes you made to standardize the TMB-202 serum phosphate results. Did you simply convert from mg/dL to mmol/L or did you calculate different values based on changes between the two different assays' normal ranges?

2) If you standardized the results based on the two different serum phosphate assay's normal ranges, please provide the normal range for the original TMB-202 assay and the normal range for the TMB-301 assay.

3) You noted that when you compared the original results to the DAIDS toxicity table, only two TMB-202 participants experienced grade 3 or 4 abnormalities of phosphate.
    a. Did you use the 2004 DAIDS toxicity table or the 2014 DAIDS toxicity table for this comparison?

b. In this analysis, did you compare mg/dL results to the mg/dl criteria in the toxicity table or mmol/L to the mmol/L results to the mmol/L criteria? We ask this because it appears to us that the grading could be different in the 2014 toxicity table based on the units used. For example, although 1.8 mg/dL is equal to 0.58 mmol/L, the 1.8 mg/dL value would be considered Grade 2 whereas the 0.58 mmol/L value would be considered Grade 3.

4) Please provide a side-by-side comparison of the TMB-202 serum phosphate maximum toxicity results using the original results and the standardized results. For example:

Maximum Toxicity Grade	**GRADE 1**	**GRADE 2**	**GRADE 3**	**GRADE 4**
Original results	# subjects (%)	# subjects (%)	# subjects (%)	# subjects (%)
Standardized results	# subjects (%)	# subjects (%)	# subjects (%)	# subjects (%)

5) You seem to be suggesting that we should use the original results rather than the standardized results to determine the frequency of graded serum phosphate abnormalities seen in TMB-202. If this is correct, please provide us a rationale for doing so.

PLEASE REPLY BY EMAIL (christian.yoder@fda.hhs.gov) to confirm receipt. We are providing this above information via telephone facsimile for your convenience. Please feel free to contact me at 240-402-9990 if you have any questions regarding this transmission.

Christian P. Yoder, MPH
Regulatory Project Manager
Division of Antiviral Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

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/s/

CHRISTIAN P YODER
10/23/2017

From: CDER Electronic Document Room Staff
Center for Drug Evaluation and Research
U.S. Food and Drug Administration

REJECTION NOTIFICATION

As per section 745A(a) of the Federal Food, Drug, and Cosmetic Act (FD&C Act), effective **May 5, 2017**, all NDA, ANDA, and BLA submissions must be in an electronic format specified by the FDA. The Electronic Common Technical Document (eCTD) format is the required standard electronic format. Non-standard electronic formats or paper submissions will no longer be accepted by CDER.

In addition, CDER will not accept submissions on physical media (e.g., CD/DVD/USB drive) if the submission size is less than 10 Gigabytes (GB). For submissions less than 10 GB, sponsors and applicants must use the FDA Electronic Submissions Gateway (see www.fda.gov/esg).

Submissions that do not meet the requirements will not be filed or received, and are subject to rejection upon receipt.

While processing your submission, we encountered the issue(s) stated below. Please review and take the appropriate corrective action.

Application Number:	BLA 761065
Letter Date:	October 17, 2017

☐ Your submission was received in paper format

☒ Your physical electronic submissions was less than 10 GB

☐ Your submission was received in Non-eCTD format

If you have any questions regarding this communication or electronic submissions in general: Email CDER's Electronic Submissions Support Team at ESUB@FDA.HHS.GOV

For information about submitting electronically to CDER, please see our website: www.fda.gov/ectd

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/s/

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10/23/2017

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Division of Antiviral Drug Products
Food and Drug Administration
Silver Spring, MD 20903

MEMORANDUM OF ELECTRONIC MAIL CORRESPONDENCE

BLA: **761065**

Drug: **TROGARZO (ibalizumab)**

Date: **October 11, 2017**

To: **Dr. James Chang, Chief Executive Officer (CEO)**

Sponsor: **TaiMed Biologics**

Subject: **Information request**

Please refer to your BLA 761065 that we received on May 3, 2017 and to the following comment:

> At this time we have significant concerns with BLA 761065 that may impact the approvability of the application. (b) (4) In order to ensure that our concerns are appropriately communicated, we would like to meet directly with you (Dr. James Chang, CEO), and the other key members of TaiMed Biologics that you deem appropriate, as soon as possible. We strongly prefer to meet in person at the FDA campus, however if that is not possible a teleconference can be arranged. Please provide by Friday, October 13, 2017, a list of dates and times during the month of October 2017 when this meeting can be scheduled.

PLEASE REPLY BY EMAIL (christian.yoder@fda.hhs.gov) to confirm receipt. We are providing this above information via email for your convenience. Please feel free to contact me at (240) 402-9990 if you have any questions regarding the contents of this transmission.

{See appended electronic signature page}

Christian P. Yoder, BSN, MPH
Regulatory Project Manager
Division of Antiviral Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

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/s/

CHRISTIAN P YODER
10/11/2017

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

BLA 761065

INFORMATION REQUEST

TaiMed Biologics USA Corp.
Attention: Helen P. Shu, Ph.D.
VP Regulatory Affairs and Quality
425 San Lucas Drive
Solano Beach, CA 92075

Dear Dr. Shu:

Please refer to your Biologics License Application (BLA) dated May 3, 2017, received May 3, 2017, submitted under section 351(a) of the Public Health Service Act for ibalizumab injectable.

We are reviewing the CMC section of your submission and have the following comments and information requests. We request a prompt written response by October 13, 2017 in order to continue our evaluation of your BLA.

Microbiology:
Provide a brief description of the [redacted] (b) (4) including total test volume. Update Section 3.2.S.4.2 accordingly.

Product Quality:

1. We acknowledge your Information Request response dated September 28, 2017, where you proposed to establish a two-tier reference standard system [redacted] (b) (4). Your proposal appears reasonable.

   [redacted] (b) (4)

   sufficient to serve as primary reference material throughout the ibalizumab product lifecycle, provided that this primary reference material is appropriately stored to ensure

its stability. Please be aware that a primary reference standard qualification protocol is not required for approval of a BLA application. Therefore, please withdraw the new reference material qualification protocol from the BLA. The protocol (b) (4) can be provided as a Prior Approval Supplement (PAS) at a later time, if the ibalizumab BLA is approved.

2. Your proposed release specifications for drug substance (DS) and drug product (DP) are not supported by your clinical and manufacturing experience. Therefore, you should revise the DS and DP acceptance criteria for the following test methods to align with your clinical experience from pivotal studies:

(b) (4)

3. (b) (4) . Update the in-process control strategy of your drug substance manufacturing process by including appropriate (b) (4) to offer a better control on overall process performance and improve the long term robustness of the process.

4. Your shipping validation study (VD1037-PVR) did not include an assessment of the biochemical stability of the product post-shipment. Therefore, it is unclear whether the

shipping process negatively impacts the quality attributes of the ibalizumab drug product. Provide data using stability-indicating methods demonstrating that the ibalizumab drug product remains stable after shipment from WuXi AppTec (Wuxi, China) to (b) (4)

5. (b) (4) . Indicate whether a deviation was initiated to investigate the root cause of the particulates and, if so, provide a summary of the investigation and associated corrective and preventative actions. In addition, provide a copy of Standard Operating Procedure for Visual Inspection of ibalizumab DP and clearly describe the AQL and rejection limits for visible particles in ibalizumab DP batches.

6. You did not describe your stability program for the master cell bank (MCB) and working cell bank (WCB). The stability of MCB and WCB should be periodically monitored to ensure their continued suitability for ibalizumab manufacturing. Describe the stability programs for MCB and WCB, including the test parameters (for example: cell viability, cell count, plasmid retention, and restriction analysis), associated acceptance criteria, re-testing requirements and stability time points. In addition, provide all available stability data for MCB (b) (4) and WCB (b) (4).

7. Section 3.2.S.2.1 includes the Tanox Inc. (Houston, TX) and Tanox West (San Diego, CA) as manufacturing facilities for ibalizumab drug substance. Since these sites were used during product development but are not proposed commercial manufacturers of ibalizumab DS they should be removed from section 3.2.S.2.1 and should instead be included in section 3.2.S.2.6 Manufacturing Process Development.

8. Please provide your sampling plans for Drug Substance and Drug Product lot release. In addition, please describe and justify any hold times allowed prior to release testing the samples taken from a lot.

9. Your submission refers to an ongoing study of leachables from the drug product container closure system (study protocol 7700631), however there is no commitment in the BLA to report the results of this study to the Agency as they become available. Provide a commitment to provide the results of leachable study 7700631 in an Annual Report to the Agency should the BLA be approved.

If you have any questions, please contact Anita Brown, Regulatory Business Process Manager, at (301)796-2066 or Anita.Brown@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Anita N. Brown
Regulatory Business Process Manager
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research

Anita Brown

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DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

BLA 761065

INFORMATION REQUEST

TaiMed Biologics USA Corp.
Attention: Helen P. Shu, Ph.D.
VP Regulatory Affairs and Quality
425 San Lucas Drive
Solano Beach, CA 92075

Dear Dr. Shu:

Please refer to your Biologics License Application (BLA) dated May 3, 2017, received May 3, 2017, submitted under section 351(a) of the Public Health Service Act for ibalizumab injectable.

We are reviewing the CMC section of your submission and have the following comments and information requests. We request a prompt written response by October 9, 2017 in order to continue our evaluation of your BLA.

(b) (4)

[redacted]

If you have any questions, please contact Anita Brown, Regulatory Business Process Manager, at (301)796-2066 or Anita.Brown@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Anita N. Brown
Regulatory Business Process Manager
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research

Anita Brown

Digitally signed by Anita Brown
Date: 10/02/2017 04:12:35PM
GUID: 508da6dc000266ff1f7013ac7142cacd

From:	Yoder, Christian
To:	"Helen Shu"
Subject:	BLA label
Date:	Thursday, September 28, 2017 1:04:54 PM
Attachments:	BLA 761065 draft-labeling-text 9-28-17.docx image001.png

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Hello Helen,

Please see attached the label for ibalizumab with the Division's comments and proposed changes. Please review and accept all the changes with which you agree, and include any proposed additional changes in tracked changes and then submit the Word document to the BLA no later than October 13, 2017.

Please let me know if you have any additional questions.

Regards,

Christian

Christian P. Yoder, BSN, MPH
Regulatory Project Manager

Division of Antiviral Products (DAVP)
CDER/OND/OAP
U.S. Food and Drug Administration
White Oak Complex, Bldg. 22 Rm. 6334
10903 New Hampshire Avenue
Silver Spring, MD 20993
Tel: (240) 402-9990
christian.yoder@fda.hhs.gov

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/s/

CHRISTIAN P YODER
09/28/2017

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

BLA 761065

INFORMATION REQUEST

TaiMed Biologics USA Corp.
Attention: Helen P. Shu, Ph.D.
VP Regulatory Affairs and Quality
425 San Lucas Drive
Solano Beach, CA 92075

Dear Dr. Shu:

Please refer to your Biologics License Application (BLA) dated May 3, 2017, received May 3, 2017, submitted under section 351(a) of the Public Health Service Act for ibalizumab injectable.

We are reviewing the CMC section of your submission and have the following comments and information requests. We request a prompt written response by September 29, 2017 in order to continue our evaluation of your BLA.

1. Your SOP for the A280 protein concentration method (QC –LAB-082) indicates that the extinction coefficient of ibalizumab is (b) (4) It is unclear how the extinction coefficient for ibalizumab was determined. Provide a summary description of the approach used to establish the extinction coefficient of ibalizumab as well as any relevant supporting data. Update section 3.2.S.1.3 to include the extinction coefficient of ibalizumab.

2. Your response to FDA information request #21 received on August 11, 2017 refers to the (b) (4): Leachables & Extractables Risk Assessment of WBP236 Manufacturing Process" which was not provided in the submission. Submit the leachables and extractables risk assessment to section 3.2.R of the BLA.

3. Appearance testing is performed for ibalizumab drug substance (DS) and drug product (DP) at release and on stability. Particulate matter testing is performed at DP release. The method verification reports for the appearance and particulate matter tests were not provided in the submission. Provide the method verification reports to the section 3.2.R of the BLA.

4. The method validation report VD0581-MVR for the cell-cell fusion inhibition method does not include an evaluation of method robustness. Indicate whether the method robustness (e.g. incubation times, incubation temperatures) was evaluated for critical steps of the procedure and provide a summary of the supporting data.

5. You have provided qualification data for a new primary reference material [redacted] (b) (4) However, your reference standard program currently does not include a working or secondary reference material. The Agency recommends a 2-tiered system consisting of a primary reference material and a working reference material. As described in ICH Q6B, an appropriately characterized primary reference material that is representative of production and clinical materials can be used to qualify a working reference material to minimize the risk of drift in quality attributes over time. Use of a working or secondary reference material qualified against a single primary reference material for routine release and stability testing of commercial lots provides additional assurance that commercially manufactured product is representative of the clinical trial material.

6. [redacted] (b) (4)

7. Your proposed stability program includes testing at 0, 6 and 12 months for DS and 0, 12, 24, and 36 months for DP. For products with proposed shelf-lives of greater than 1 year, ICH Q5C recommends that stability studies should be conducted every 3 months during the first year of storage, every 6 months during the second year, and annually thereafter. Update your proposed post-approval stability protocols for ibalizumab DS and DP to be consistent with ICH Q5C: *Quality of Biotechnological Products: Stability Testing of Biotechnological/Biological Products.*

8. The number and frequency of DS and DP batches to be monitored on the post-approval stability protocol is not clear. Indicate in sections 3.2.S.7.2 and 3.2.P.8.2 of the BLA how the batches to be tested in the stability protocol will be determined.

9. Sections 3.2.S.7.2 and 3.2.P.8.2 of your BLA currently do not include a commitment to provide annual stability data to the BLA. Update sections 3.2.S.7.2 and 3.2.P.8.2 of your BLA to include a statement that annual stability data for ibalizumab DS and DP will be reported to the BLA in an annual report.

10. Section 3.2.P.8.2 of the BLA states "the Drug Product lot release testing data will be used as time zero. Time zero and stability timepoints are defined as [redacted] (b) (4) " It is unclear from this statement how the time zero and subsequent stability timepoints are defined. Clarify how

the stability timepoints are defined for DS and DP and indicate the allowable testing timeframe around each stability time point.

11. In the summary document of section 3.2.S.2.4: Control of Critical Steps and Intermediates, you have removed information regarding the in-process controls and in-process tests for the ibalizumab DS manufacturing process. Update the summary document of section 3.2.S.2.4 appropriately to include all in-process controls and tests with acceptance criteria for all steps of the ibalizumab DS manufacturing process.

12. Letters of authorization for the drug master files (DMFs) related to your drug substance and drug product container closure system were not provided in the BLA. Provide letters of authorization from the DMF holders for the Agency to review the DMFs for the packaging components of the container closure system.

13. In your response to Agency comment #21 submitted on August 11, 2017 you refer to an ongoing leachable study for ibalizumab DP in contact with the container closure system. Provide a description of the leachable study including a rationale for the leachable species being monitored, the batches of ibalizumab tested, storage conditions, analytical methods, and a summary of the available data.

If you have any questions, please contact Anita Brown, Regulatory Business Process Manager, at (301)796-2066 or Anita.Brown@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Anita N. Brown
Regulatory Business Process Manager
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research

Anita
Brown

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DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

BLA 761065

INFORMATION REQUEST

TaiMed Biologics USA Corp.
Attention: Helen P. Shu, Ph.D.
VP Regulatory Affairs and Quality
425 San Lucas Drive
Solano Beach, CA 92075

Dear Dr. Shu:

Please refer to your Biologics License Application (BLA) dated May 3, 2017, received May 3, 2017, submitted under section 351(a) of the Public Health Service Act for ibalizumab injectable.

We are reviewing the CMC section of your submission and have the following comments and information requests. We request a prompt written response by September 29, 2017 in order to continue our evaluation of your BLA.

(b) (4)

[redacted]

Provide the bioburden qualification data of the DS sample using 30 mL test volume by October 31, 2017

If you have any questions, please contact Anita Brown, Regulatory Business Process Manager, at (301)796-2066 or Anita.Brown@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Anita N. Brown
Regulatory Business Process Manager
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research

Anita
Brown

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DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

BLA 761065

GENERAL ADVICE

TaiMed Biologics USA Corp.
Attention: Helen P. Shu, Ph.D.
Vice President, Regulatory Affairs & Quality
425 San Lucas Drive
Solana Beach, CA 92075

Dear Dr. Shu:

Please refer to your Biologics License Application (BLA) submitted under section 351(a) of the Public Health Service Act for Ibalizumab, 150 mg/mL.

We also refer to our July 10, 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, ibalizumab-uiyk, conditionally acceptable for your proposed product. Should your 351(a) BLA be approved during this review cycle, ibalizumab-uiyk 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 Danyal Chaudhry, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at 301-796-3813. For any other information regarding this application, contact Christian Yoder, Regulatory Project Manager in the Office of New Drugs, at 240-402-9990.

Sincerely,

{See appended electronic signature page}

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

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/s/

AZEEM D CHAUDHRY
09/22/2017

LUBNA A MERCHANT
09/22/2017

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Antimicrobial Products
Division of Antiviral Drug Products

FACSIMILE TRANSMITTAL SHEET

DATE: September 21, 2017

To: Dr. Helen Shu	**From: Christian Yoder, MPH**
Company: TaiMed Biologics	**Title: Regulatory Project Manager**
Fax number: 858 724-1844	**Fax number: 301-796-9883**
Phone number: 858 481-6863	**Phone number: (240) 402-9990**

Subject: BLA 761065

Total number of pages including cover:

Comments:

Helen – Can you email me to confirm receipt? Thanks.

Document to be mailed: ☐ YES ☑ NO

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Division of Antiviral Drug Products
Food and Drug Administration
Silver Spring, MD 20993

MEMORANDUM OF FACSIMILE CORRESPONDENCE

BLA: **761065**

Drug: **ibalizumab**

Date: **September 21, 2017**

To: **Helen Shu, Ph.D., Vice President, Regulatory Affairs and Quality**

From: **Christian Yoder, MPH, Regulatory Project Manager**

Subject: **BLA 761065 Information Request**

Please refer to your BLA 761065 that was submitted May 3, 2017. Please see the following comments and respond by September 27, 2017:

The TMB-301 protocol states the following regarding laboratory testing:

> Collection of blood and urine samples for clinical laboratory assessments will be part of a normal safety profile assessment for the study patients. Patients need not fast before blood sampling. Samples will be processed using standard procedures as described in the laboratory procedures manual and will be analyzed by a central laboratory unless otherwise noted.
>
> The samples will be analyzed for the following:
>
> - **Hematology:** complete white blood cell count with differential, hemoglobin, hematocrit, and platelets.
> - **Serum chemistry profile:** albumin, alkaline phosphatase, alanine aminotransferase (ALT), amylase, aspartate aminotransferase (AST), blood urea nitrogen, calcium, chloride, creatine phosphokinase, creatinine, direct bilirubin, gamma glutamyl transferase, glucose, lactate dehydrogenase, lipase, lipid profile (total cholesterol, high-density lipoprotein, low-density lipoprotein, and triglycerides), magnesium, phosphorus, potassium, sodium, total bilirubin, total protein, and uric acid.
> - **Urinalysis:** visual inspection for appearance and dipstick assessment for color, pH, specific gravity, ketones, protein, glucose, bilirubin, nitrite, urobilinogen, and leukocyte esterase.

The language in the TMB-202 protocol specifies testing for the same parameters.

Laboratory-related datasets (STDM LB, ADAM ADLB, and ADAM ADLBTOX) for both protocols are missing several parameters, including three important parameters that are included in the DAIDS toxicity table. These include: creatinine, urine protein, and urine glucose. Please provide updated datasets with these data, including grading. Please also include tabular summaries of these graded events for trials TMB-202 and TMB-301. Please respond with tabular summarizes and updated datasets by Wednesday, September 27, 2017.

PLEASE REPLY BY EMAIL (christian.yoder@fda.hhs.gov) to confirm receipt. We are providing this above information via telephone facsimile for your convenience. Please feel free to contact me at 240-402-9990 if you have any questions regarding this transmission.

Christian P. Yoder, MPH
Regulatory Project Manager
Division of Antiviral Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

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/s/

CHRISTIAN P YODER
09/21/2017

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

BLA 761065

INFORMATION REQUEST

TaiMed Biologics USA Corp.
Attention: Helen P. Shu, Ph.D.
VP Regulatory Affairs and Quality
425 San Lucas Drive
Solano Beach, CA 92075

Dear Dr. Shu:

Please refer to your Biologics License Application (BLA) dated May 3, 2017, received May 3, 2017, submitted under section 351(a) of the Public Health Service Act for ibalizumab injectable.

We are reviewing the CMC section of your submission and have the following comments and information requests. We request a prompt written response by September 18, 2017 in order to continue our evaluation of your BLA.

(b) (4)

(b) (4)

[redacted]

If you have any questions, please contact Anita Brown, Regulatory Business Process Manager, at (301)796-2066 or Anita.Brown@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Anita N. Brown
Regulatory Business Process Manager
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research

Anita
Brown

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DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

BLA 761065

INFORMATION REQUEST

TaiMed Biologics USA Corp.
Attention: Helen P. Shu, Ph.D.
VP Regulatory Affairs and Quality
425 San Lucas Drive
Solano Beach, CA 92075

Dear Dr. Shu:

Please refer to your Biologics License Application (BLA) dated May 3, 2017, received May 3, 2017, submitted under section 351(a) of the Public Health Service Act for ibalizumab injectable.

We are reviewing the CMC section of your submission and have the following comments and information requests. We request a prompt written response by September 18, 2017 in order to continue our evaluation of your BLA.

1. In Section 2.2 of your proposed label, you state that "If not administered immediately, store the diluted TROGARZO solution at room temperature for no more than 4 hours". However, data supporting the stability of the diluted ibalizumab drug product throughout the conditions of use were not provided in the BLA submission. Provide data supporting the in-use stability of ibalizumab drug product under the recommended conditions of preparation, handling, and administration.

2. The proposed drug product stability acceptance criteria for the SEC-HPLC, CEX-HPLC, SDS-PAGE (non-reduced), CE-SDS (non-reduced), and CE-SDS (reduced) methods are wider than the release acceptance criteria. You did not provide a justification for using wider acceptance criteria for the drug product stability specifications than for the drug product release specifications. Provide a justification for the proposed ibalizumab drug product stability specifications.

3. [redacted] (b) (4) are critical components of [redacted] (b) (4) manufacturing of ibalizumab drug substance. The compositions of the [redacted] (b) (4) raw materials were not provided with the BLA submission.

    a. Provide a list of components in the [redacted] (b) (4) raw materials.

b. If the composition of the [redacted] (b) (4) is proprietary information, provide a letter of cross-reference from the drug master file (DMF) holder to the BLA for the Agency to review relevant DMFs for the [redacted] (b) (4) raw materials.

c. Provide one representative certificate of analysis for each of the [redacted] (b) (4) [redacted] raw materials.

If you have any questions, please contact Anita Brown, Regulatory Business Process Manager, at (301)796-2066 or Anita.Brown@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Anita N. Brown
Regulatory Business Process Manager
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research

Anita
Brown

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Food and Drug Administration
Center for Drug Evaluation and Research
Office of Antimicrobial Products
Division of Antiviral Drug Products

FACSIMILE TRANSMITTAL SHEET

DATE: August 29, 2017

To: Dr. Helen Shu	**From: Christian Yoder, MPH**
Company: TaiMed Biologics	**Title: Regulatory Project Manager**
Fax number: 858 724-1844	**Fax number: 301-796-9883**
Phone number: 858 481-6863	**Phone number: (240) 402-9990**

Subject: BLA 761065

Total number of pages including cover:

Comments:

Helen – Can you email me to confirm receipt? Thanks.

Document to be mailed: ☐ YES ☑ NO

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Division of Antiviral Drug Products
Food and Drug Administration
Silver Spring, MD 20993

MEMORANDUM OF FACSIMILE CORRESPONDENCE

BLA: **761065**

Drug: **ibalizumab**

Date: **August 29, 2017**

To: **Helen Shu, Ph.D., Vice President, Regulatory Affairs and Quality**

From: **Christian Yoder, MPH, Regulatory Project Manager**

Subject: **BLA 761065 Information Request**

Please refer to your BLA 761065 that was submitted May 3, 2017. Please see the following comments and respond by September 8, 2017:

1. The confirmatory anti-drug antibody (ADA) assay used to test samples from study TMB-301 uses a cut point based on a (b) (4) false positive rate. The Agency recommends using a confirmatory assay cut point based on a 1% false positive rate in order to minimize the risk of false negative sample results. Re-calculate the confirmatory assay cut point using a 1% false positive rate and re-evaluate the confirmatory assay results from study TMB-301 using the modified cut point. Provide information for any samples that are confirmed ADA positive using the modified cut point including the Patient ID, sampling time point, and levels of on-board drug (if available). For guidance refer to *Assay Development and Validation for Immunogenicity Testing for Therapeutic Protein Products: FDA Draft Guidance for Industry, April 2016.*

2. Your submission indicates that samples collected during study TMB-202 were tested for ADA using screening and confirmatory assays at (b) (4) However, the confirmatory ADA assay cut point used to test samples from study TMB-202 is not clear. Provide the confirmatory cut point used to evaluate samples from study TMB-202 as well as a summary of the statistical methodology used to establish the cut point.

3. The sample analysis data from the screening and confirmatory assays for study TMB 202 and the confirmatory assay for study TMB-301 were not provided in your submission. For each study provide a table with the following information:

    a. Patient ID

b. Sample ID

c. Sample time point

d. Concentration of on-board ibalizumab

e. Screening assay cut point

f. Screening assay result

g. Confirmatory assay cut point

h. Confirmatory assay results

i. Titer

j. Neutralizing assay cut point

k. Neutralizing assay result

4. Your screening, confirmatory, and neutralizing ADA assays for studies TMB-202 and TMB-301 used an anti-ibalizumab positive control antibody for system suitability. Qualification information for the positive control antibody was not provided. Provide a summary of how the positive control antibody was developed as well as qualification data demonstrating that the antibody is suitable for its intended use.

PLEASE REPLY BY EMAIL (christian.yoder@fda.hhs.gov) to confirm receipt. We are providing this above information via telephone facsimile for your convenience. Please feel free to contact me at 240-402-9990 if you have any questions regarding this transmission.

Christian P. Yoder, MPH
Regulatory Project Manager
Division of Antiviral Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

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/s/

CHRISTIAN P YODER
08/29/2017

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

BLA 761065

INFORMATION REQUEST

TaiMed Biologics USA Corp.
Attention: Helen P. Shu, Ph.D.
VP Regulatory Affairs and Quality
425 San Lucas Drive
Solano Beach, CA 92075

Dear Dr. Shu:

Please refer to your Biologics License Application (BLA) dated May 3, 2017, received May 3, 2017, submitted under section 351(a) of the Public Health Service Act for ibalizumab injectable.

We are reviewing the CMC section of your submission and have the following comments and information requests. We request a prompt written response by August 31, 2017 in order to continue our evaluation of your BLA.

The release specifications for ibalizumab drug substance include testing for (b) (4) [redacted]. The validation report for the (b) (4) [redacted] was not provided in the BLA submission. Please provide this validation report.

If you have any questions, please contact Anita Brown, Regulatory Business Process Manager, at (301)796-2066 or Anita.Brown@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Anita N. Brown
Regulatory Business Process Manager
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research

Anita
Brown

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DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

BLA 761065

INFORMATION REQUEST

TaiMed Biologics USA Corp.
Attention: Helen P. Shu, Ph.D.
VP Regulatory Affairs and Quality
425 San Lucas Drive
Solano Beach, CA 92075

Dear Dr. Shu:

Please refer to your Biologics License Application (BLA) dated May 3, 2017, received May 3, 2017, submitted under section 351(a) of the Public Health Service Act for ibalizumab injectable.

We are reviewing the CMC section of your submission and have the following comments and information requests. We request a prompt written response by September 6, 2017 in order to continue our evaluation of your BLA.

Drug substance

(b) (4)

[redacted]

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(b) (4)

Drug Product

11. Update section 3.2.P.3.4, "Controls of critical steps and intermediates" with a limit for (b) (4)

12. Clarify for (b) (4) which filter is the sterilizing filter.

If you have any questions, please contact Anita Brown, Regulatory Business Process Manager, at (301)796-2066 or Anita.Brown@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Anita N. Brown
Regulatory Business Process Manager
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research

Anita
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Food and Drug Administration
Center for Drug Evaluation and Research
Office of Antimicrobial Products
Division of Antiviral Drug Products

FACSIMILE TRANSMITTAL SHEET

DATE: August 28, 2017

To: Dr. Helen Shu	**From: Christian Yoder, MPH**
Company: TaiMed Biologics	**Title: Regulatory Project Manager**
Fax number: 858 724-1844	**Fax number: 301-796-9883**
Phone number: 858 481-6863	**Phone number: (240) 402-9990**

Subject: BLA 761065

Total number of pages including cover:

Comments:

Helen – Can you email me to confirm receipt? Thanks.

Document to be mailed: ☐ YES ☑ NO

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Division of Antiviral Drug Products
Food and Drug Administration
Silver Spring, MD 20993

MEMORANDUM OF FACSIMILE CORRESPONDENCE

BLA: **761065**

Drug: **ibalizumab**

Date: **August 28, 2017**

To: **Helen Shu, Ph.D., Vice President, Regulatory Affairs and Quality**

From: **Christian Yoder, MPH, Regulatory Project Manager**

Subject: **BLA 761065 Information Request**

Please refer to your BLA 761065 that was submitted May 3, 2017. Please see the following comments and respond by September 11, 2017:

Container Labels and Carton Labeling Comments

A. General Comments

1. Confirm there is no text on the ferrule and cap overseal of the vials to comply with a revised United States Pharmacopeia (USP), General Chapters: <1> Injections, Packaging, Labeling on Ferrules and Cap Overseals.

2. Confirm there is sufficient area on the container to allow for visual inspection when the label is affixed to the vial and indicate where the visual area of inspection is located per 21 CFR 610.60(e).

B. Vial Container Label

1. Reduce the prominence of the "Rx only" statement and relocate to appear in the upper right corner of the Principal display panel to permit space for the revised storage temperature statement.

2. Per 21 CFR 610.60 (c), Remove the distributor information and add the licensed manufacturer (the Applicant listed on the submitted Form FDA 356h) as follows:

TaiMed Biologics USA Corp
US License No. xxxx

3. Revise from [redacted] (b) (4) to read "For Intravenous Infusion Only".

4. Revise to the appropriate package type term, from [redacted] (b) (4) to read "single-dose" (see Draft Guidance: Selection of the Appropriate Package Type Terms and Recommendations for Labeling Injectable Medical Products Packaged in Multiple-Dose, Single-Dose, and Single-Patient-Use Containers for Human Use Guidance for Industry.

5. Revise the strength presentation to be expressed as strength per total volume followed by strength/mL in parenthesis "200 mg/1.33 mL (150 mg/mL)" (see USP General Chapters <7> Labeling (Strength per total volume for single dose and multiple dose injectable drug products).

6. Revise the dosage form from [redacted] (b) (4) to the appropriate dosage form for this drug product "Injection" and relocate to appear underneath the proper name (placed in parenthesis) followed by the revised strength presentation as follows:

   Trogarzo
   (ibalizumab)
   Injection
   200 mg/1.33 mL (150 mg/mL)
   For Intravenous Infusion Only
   Single-dose vial. Discard unused portion. (include this line if space permits)

7. Revise the storage requirements to read "2º to 8ºC (36º-46 ºF)" per USP definitions (see USP chapter <659> Packaging and Storage Requirements).

8. This is considered to be a partial label and the usual dose statement is not required information and can be deleted to permit space for required information. However, if space permits once revisions have been made to include the required information, revise usual dosage statement from [redacted] (b) (4) to read "Dosage: See prescribing information" and relocate to the side panel to allow for critical information to appear on the principal display panel (PDP).

C. Carton Labeling

1. Revise the dosage form from [redacted] (b) (4) to the appropriate dosage for this drug product "Injection" and relocate to appear underneath the proper name (placed in parenthesis) followed by the revised strength presentation as follows:

   Trogarzo
   (ibalizumab)
   Injection
   200 mg/1.33 mL (150 mg/mL)
   For Intravenous Infusion only
   Single-dose vial. Discard unused portion.

2. Per 21 CFR 610.61(b) revise the licensed manufacturer and address to appear as the Applicant listed on the submitted Form FDA 356h as follows:

   Manufactured by: TaiMed Biologics USA Corp
   Irvine, California 92614
   US License No. xxxx

3. Remove the statement (b) (4) since they are not the applicant listed on Form FDA 356h.

4. Per 21 CFR 610.64 if your intent is to include the distributor's name (Theratechnologies Inc) then it should be listed as follows: "Distributed by: Name and address."

5. If no preservative, ensure "No preservative" appears on the carton labeling per 21 CFR 610.61 (e).

6. Revise the strength presentation to be expressed as strength per total volume followed by strength/mL in parenthesis "200 mg/1.33 mL (150 mg/mL)" (see USP General Chapters <7> Labeling (Strength per total volume for single dose and multiple dose injectable drug products).

7. Remove statemen (b) (4) since this is not the appropriate strength presentation for this dosage form.

8. Revise from (b) (4) to read "For Intravenous Infusion Only".

9. Revise the list of ingredients based on how much is deliverable in 1.33 mL of solution and by placing the active ingredient first with its quantitative amount followed by the list of all inactive ingredients in alphabetical order (see USP Chapter <1091>) with their quantitative information using the metric system of weight in parenthesis (x mg) except for those inactive ingredients added to adjust pH or tonicity or water for injection as follows:

   "Each 1.33 mL single dose vial contains 200 mg ibalizumab, L-histidine (xx mg), Polysorbate 80 (xx mg), Sodium Chloride (xx mg), and Sucrose (xx mg)".

10. Add the words "No U.S. standard of potency" per 21CFR 610.61 (r).

11. Unbold "Rx Only" to reduce the prominence and to allow for prominence of other critical information on the PDP.

12. Unbold the NDC number to reduce the prominence and to allow for prominence of other critical information on the PDP.

13. Revise to the appropriate package type term, from (b) (4) to read "single-dose" (see Draft Guidance: Selection of the Appropriate Package Type Terms and Recommendations for Labeling Injectable Medical Products Packaged in Multiple-Dose, Single-Dose, and Single-Patient-Use Containers for Human Use Guidance for Industry).

14. Remove the duplicative usual dose statement [redacted] (b) (4) from the principal display panel to permit space for other important information including package type term and discard unused portion statement.

15. Revise the usual dose statement from [redacted] (b) (4) to read "See prescribing information for dosage, preparation, administration, and storage".

PLEASE REPLY BY EMAIL (christian.yoder@fda.hhs.gov) to confirm receipt. We are providing this above information via telephone facsimile for your convenience. Please feel free to contact me at 240-402-9990 if you have any questions regarding this transmission.

Christian P. Yoder, MPH
Regulatory Project Manager
Division of Antiviral Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

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/s/

CHRISTIAN P YODER
08/28/2017

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Antimicrobial Products
Division of Antiviral Drug Products

FACSIMILE TRANSMITTAL SHEET

DATE: August 22, 2017

To: Dr. Helen Shu	**From: Christian Yoder, MPH**
Company: TaiMed Biologics	**Title: Regulatory Project Manager**
Fax number: 858 724-1844	**Fax number: 301-796-9883**
Phone number: 858 481-6863	**Phone number: (240) 402-9990**

Subject: BLA 761065

Total number of pages including cover:

Comments:

Helen – Can you email me to confirm receipt? Thanks.

Document to be mailed: ☐ YES ☑ NO

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Division of Antiviral Drug Products
Food and Drug Administration
Silver Spring, MD 20993

MEMORANDUM OF FACSIMILE CORRESPONDENCE

BLA: **761065**

Drug: **ibalizumab**

Date: **August 22, 2017**

To: **Helen Shu, Ph.D., Vice President, Regulatory Affairs and Quality**

From: **Christian Yoder, MPH, Regulatory Project Manager**

Subject: **BLA 761065 Information Request**

Please refer to your BLA 761065. Please see the following comments and respond by August 25, 2017:

Clinical Pharmacology

1. In method validation report UNS2 TMB-202, for the measurement of ibalizumab serum concentrations in the TMB-202 study, the dilution linearity was only established up to 10, 000 ng/mL. However, the observed concentrations in TMB-202 were up to 990, 000 ng/mL. Please provide your strategy to address this issue to ensure the accuracy of concentrations above 10, 000 ng/mL in the TMB-202 study.

PLEASE REPLY BY EMAIL (christian.yoder@fda.hhs.gov) to confirm receipt. We are providing this above information via telephone facsimile for your convenience. Please feel free to contact me at 240-402-9990 if you have any questions regarding this transmission.

Christian P. Yoder, MPH
Regulatory Project Manager
Division of Antiviral Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

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/s/

CHRISTIAN P YODER
08/22/2017

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

BLA 761065

MID-CYCLE COMMUNICATION

TaiMed Biologics USA Corp.
Attention: Helen P. Shu, Ph.D.
VP Regulatory Affairs and Quality
2 Executive Circle, Suite 280
Irvine, CA 92614

Dear Dr. Shu:

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

We also refer to the teleconference between representatives of your firm and the FDA on August 18, 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 Christian Yoder, Regulatory Project Manager at (240) 402-9990 or (301) 796-1500.

Sincerely,

{See appended electronic signature page}

Adam Sherwat, MD
Medical Team Leader
Division of Antiviral Products
Office of Antimicrobial 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: August 18, 2017

Application Number: BLA 761065
Product Name: TROGARZO (ibalizumab) injection, 200 mg/vial.
Indication: For the treatment of HIV-infected adults with multi-resistant virus
Applicant Name: TaiMed Biologics USA Corp.

Meeting Chair: Adam Sherwat, Medical Team Leader, Division of Antiviral Products (DAVP)
Meeting Recorder: Christian Yoder, Regulatory Project Manager, Division of Antiviral Products (DAVP)

FDA ATTENDEES

OND/Office of Antimicrobial Products (OAP)
Edward M. Cox, MD, MPH, Director
John Farley, MD, Deputy Director

OND/OAP/Division of Antiviral Products (DAVP)
Debra Birnkrant, MD, Director
Jeffrey S. Murray, MD, MPH, Deputy Director
Adam Sherwat, MD, Medical Team Leader
Virginia Sheikh, MD, Medical Officer
Julian O'Rear, PhD, Virology Team Leader
Eric Donaldson, PhD, Virology Reviewer
David McMillian, PhD, Pharm/Tox Reviewer

OTS/OCP/Division of Clinical Pharmacology IV (DCP4)
Shirley Seo, PhD, Clinical Pharmacology Team Leader
Qin (Cheen) Sun, PhD, Clinical Pharmacology Reviewer
Jeffry Florian, PhD, Clinical Pharmacology Reviewer

OTS/OB/Division of Biometrics IV (DBIV)
Thamban Valappil, PhD, Acting Statistical Team Leader

Office of Surveillance and Epidemiology (OSE)
Elizabeth Everhart, MSN, RN, ACNP, Risk Management Analyst
Chih-Ying (Natasha) Pratt, PhD, Epidemiologist

Office of Pharmaceutical Quality (OPQ), Office of Biotechnology Products (OBP)
Steven Bowen, PhD, Product Reviewer
Ramesh Potla, PhD, Team Leader

Office of Pharmaceutical Quality (OPQ), Office of Process and Facilities (OPF)
Marion Michaelis, Inspection Lead
Bo Chi, PhD, CMC Microbiology Reviewer
Virginia Carroll, PhD, CMC Microbiology Reviewer
Patricia Hughes, PhD, Acting Branch Chief

APPLICANT ATTENDEES

TaiMed Biologics
Brian Bell, BS, Manager, Clinical Services
Jon Ho, BS, Director, Business Development & Alliance Management
Stanley Lewis, MD, MPH, VP, Clinical and Chief Medical Officer
Helen Shu, PhD, VP, Regulatory Affairs and Quality
Steve Weinheimer, PhD, VP, Biological Sciences
Kuei-Ling Kuo, PhD, Principal Scientist
YingAn Lai, MS, Manager of Clinical Operations
Jason Mao, PhD, Director of R&D
Chen-Yu Wang, PhD, Senior Pharmaceutical Analysis Manager

Theratechnologies
Christian Marsolais, PhD, Sr. Vice President, Chief Medical Officer

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 following issues were conveyed to the sponsor.

Clinical and Clinical Pharmacology

We have identified several sections of the ibalizumab label where we intend to make significant changes. An overview of those changes is provided below. Detailed labeling

changes will be provided by October 3, 2017, and will include these revisions plus additional revisions as generated by all of the review disciplines.

- Indications and Usage. The Phase 3 ibalizumab clinical trial was designed for heavily-treatment experienced, HIV-infected patients with multi-drug (and often multi-class) resistance, a rare population with limited treatment options. Important aspects of this trial, such as its small sample size, early virologic primary endpoint, and the absence of a control group, were acceptable only in the context of this rare patient population at high risk for progression to AIDS and death absent viable treatment options. Notably, ibalizumab's orphan disease designation was granted specifically for this population, i.e., the treatment of HIV-1 infection in treatment experienced adult patients with documented multi-antiretroviral class resistance and evidence of HIV-1 replication despite ongoing antiretroviral therapy. For these reasons, we intend to narrow ibalizumab's indication to be consistent with the patient population studied and ibalizumab's orphan designation.

- Section 6.1 Adverse Reactions. Clinical Trials Experience. Because TMB-301 was the only trial that used the ibalizumab dose proposed in the label, we will primarily focus on the safety results in TMB-301. Furthermore, as detailed in the FDA guidance for adverse reactions section of labeling (https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075057.pdf), the listing of adverse events should be concise and focused on events for which this is a basis to believe that there is a causal relationship with the drug. Therefore, we will likely include only one table in this section; a table of adverse reactions (related AEs) listed by specific term in order of event frequency.

- Section 6.2 Adverse Reactions. Laboratory Evaluations. We intend to include a table of Grade 3 and 4 laboratory abnormalities that occurred in trial TMB-301.

- Section 14. Efficacy. As is described in the FDA guidance for Clinical Studies Section of Labeling (https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075059.pdf), this section should not include information from clinical studies with results that imply effectiveness for an unapproved dosing regimen. Therefore, this section will include results from TMB-301 only.

- Section 12.3 Pharmacokinetics. Due to the lack of study reports (b) (4) we plan to remove these data from the label.

Product Quality

1. The BLA submission does not contain information regarding identity testing of labeled ibalizumab drug product vials. 21 CFR 610.14 requires that identity testing be performed on each filled DP lot after all labeling operations have been completed. The identity test

method for the labeled drug product should be appropriately validated for its intended use. Update your BLA with the following information:

- a description of the identity test method for the labelled drug product
- appropriate method validation, or if applicable, method transfer data
- revise FDA-356h form to include testing facility information
- revise Section 3.2.P.3.1 of Module 3 to include the testing facility information.
- We also note that Section 3.2.P.3.1 currently lists Wuxi AppTec facility to perform the following operations for ibalizumab drug product – (b) (4) Please update Section 3.2.P.3.1 and FDA-356h form to list all appropriate facilities involved in the manufacturing, labeling, packaging, testing, and storage of ibalizumab drug product.

2. We observed a number of discrepancies between the information submitted in the BLA and manufacturing and testing operations conducted at Wuxi facility. The Agency communicated several examples of these discrepancies with TaiMed and Wuxi AppTec during the pre-license inspection of Wuxi facility for ibalizumab. In order for the Agency to make a meaningful assessment of the application, it is critical that the information provided in the BLA be accurate and complete. Update your BLA to ensure that the information provided in the BLA aligns completely with the manufacturing and testing operations conducted at Wuxi AppTec facility for ibalizumab drug substance and drug product.

3. Ibalizumab drug product vials have an excess volume of (b) (4) Excess volume in filled ibalizumab drug product vials should comply with excess volume prescribed by USP per 21 CFR 201.51(g). Provide a justification and supporting extractable content testing data for the excess volume in ibalizumab drug product vials in accordance with the labeling instructions.

4. Your proposed shelf-life for ibalizumab drug substance is (b) (4) at (b) (4) °C. A (b) (4) shelf-life for ibalizumab drug substance may not be commercially viable because unforeseen delays in drug product manufacturing may result in shortage of drug supply for ibalizumab. Considering that drug substance stability data at (b) (4) °C is available for up to (b) (4) months, you may request an appropriate shelf-life for your drug substance stored at (b) (4) °C in order to prevent drug shortage and to ensure continued market supply. In addition, provide a commitment to place ibalizumab drug product lots made using DS lots older than the (b) (4) shelf-life on real-time and accelerated stability.

5. We noticed that, while submitting your responses to the Agency's Information Requests (IRs), you are updating Module 3 with duplicate or triplicate files under each section.

Replace the pertinent section with one updated version of the file. Provide your IR responses in an information amendment in Module 1 and clearly include active hyperlinks in your IR response that will direct the FDA review team to the replaced version of the pertinent file in Module 3.

6. Rabbit pyrogen test results were requested by August 15, 2017 in the filing letter. The rabbit pyrogen test is a requirement per 21 CFR 610.13(b).

7. (b) (4)

8. Satisfactory evaluation of the manufacturing facilities is required for BLA approval. Review of the pre-license inspection is currently pending.

3.0 INFORMATION REQUESTS

- We acknowledge receipt of your IR response dated August 11, 2017. The information submitted in your response is currently under review.
- We sent an IR on August 16, 2017. We request you to submit your response by August 28, 2017.

4.0 MAJOR SAFETY CONCERNS/RISK MANAGEMENT

Since no major safety concerns have been identified at this time, there is currently no plan for a REMS.

5.0 ADVISORY COMMITTEE MEETING

Currently there are no plans for an Advisory Committee meeting.

6.0 LATE-CYCLE MEETING /OTHER PROJECTED MILESTONES

The Late Cycle Meeting (LCM) is scheduled for October 31, 2017. The purpose of the LCM is to share information and discuss any review issues identified to date, as well as objectives for the remainder of the review cycle. The Division will send the meeting backgrounder package for the LCM by October 19, 2017. We will send you our proposed labeling changes and post-marketing commitments/requirements by October 3, 2017.

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/s/

ADAM I SHERWAT
08/21/2017

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Antimicrobial Products
Division of Antiviral Drug Products

FACSIMILE TRANSMITTAL SHEET

DATE: August 16, 2017

To: Dr. Helen Shu	**From: Christian Yoder, MPH**
Company: TaiMed Biologics	**Title: Regulatory Project Manager**
Fax number: 858 724-1844	**Fax number: 301-796-9883**
Phone number: 858 481-6863	**Phone number: (240) 402-9990**

Subject: BLA 761065

Total number of pages including cover:

Comments:

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Document to be mailed: ☐ YES ☑ NO

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Division of Antiviral Drug Products
Food and Drug Administration
Silver Spring, MD 20993

MEMORANDUM OF FACSIMILE CORRESPONDENCE

BLA: **761065**

Drug: **ibalizumab**

Date: **August 16, 2017**

To: **Helen Shu, Ph.D., Vice President, Regulatory Affairs and Quality**

From: **Christian Yoder, MPH, Regulatory Project Manager**

Subject: **BLA 761065 Information Request**

Please refer to your BLA 761065. Please see the following comments and respond by August 23, 2017:

In bioanalytical report TNJS15-051 for measure of ibalizumab serum concentrations in TMB-301 study, it is indicated that long-term matrix stability to support the sample storage time and conditions in this study has been established for 214 days. You stated that additional stability to support the storage time for the samples reported in this report is ongoing and will be reported in conjunction with the validation study, since maximum time from collection to analysis for TMB-301 study is 683 days as stated in the bioanalytical report.

1. Please submit all available updated long-term stability results.

2. Please summarize and submit information for all the samples (include Subject ID, Sample Time, Ibalizumab Conc.), which have been analyzed beyond the established long-term stability range of up to 214 days.

3. Please submit long-term stability results for TNX-355.01, TNX-355.02, TNX-355.03, TMB-202, and please summarize and submit information for all the samples (please include Dose, Subject ID, Sample Time, Ibalizumab Conc.), which have been analyzed beyond the established long-term stability range for those studies, if applicable.

4. Please submit the bioanalytical report for measurement of ibalizumab serum concentrations in TNX-355.03 study, and bioanalytical report for measurement of ADA

in TMX-355.02, which are indicated as missing at the time of last submission, if available.

PLEASE REPLY BY EMAIL (christian.yoder@fda.hhs.gov) to confirm receipt. We are providing this above information via telephone facsimile for your convenience. Please feel free to contact me at 240-402-9990 if you have any questions regarding this transmission.

Christian P. Yoder, MPH
Regulatory Project Manager
Division of Antiviral Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

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/s/

CHRISTIAN P YODER
08/16/2017

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

BLA 761065

INFORMATION REQUEST

TaiMed Biologics USA Corp.
Attention: Helen P. Shu, Ph.D.
VP Regulatory Affairs and Quality
425 San Lucas Drive
Solano Beach, CA 92075

Dear Dr. Shu:

Please refer to your Biologics License Application (BLA) dated May 3, 2017, received May 3, 2017, submitted under section 351(a) of the Public Health Service Act for ibalizumab injectable.

We are reviewing the CMC section of your submission and have the following comments and information requests. We request a prompt written response by August 28, 2017 in order to continue our evaluation of your BLA.

(b) (4)

[redacted]

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

(b) (4)

If you have any questions, please contact Anita Brown, Regulatory Business Process Manager, at (301)796-2066 or Anita.Brown@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Anita N. Brown
Regulatory Business Process Manager
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research

Anita Brown

Digitally signed by Anita Brown
Date: 8/16/2017 12:08:11PM
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Food and Drug Administration
Center for Drug Evaluation and Research
Office of Antimicrobial Products
Division of Antiviral Drug Products

FACSIMILE TRANSMITTAL SHEET

DATE: August 8, 2017

To: Dr. Helen Shu	**From: Christian P. Yoder, MPH**
Company: TaiMed Biologics	**Title: Regulatory Project Manager**
Fax number: 858 724-1844	**Fax number: 301-796-9883**
Phone number: 858 481-6863	**Phone number: 240-402-9990**

Subject: BLA 761065

Total number of pages including cover:

Comments:

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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Division of Antiviral Drug Products
Food and Drug Administration
Silver Spring, MD 20993

MEMORANDUM OF FACSIMILE CORRESPONDENCE

BLA: **761065**

Drug: **ibalizumab**

Date: **August 8, 2017**

To: **Helen Shu, Ph.D., Vice President, Regulatory Affairs and Quality**

From: **Christian P. Yoder, MPH, Regulatory Project Manager**

Subject: **BLA 761065 Information Request**

Please refer to your BLA 761065 and the following comment and request from the Statistical Team. Please see the following comment and respond by August 22, 2017:

1. While using data in ADEFFOUT.XPT for ISS-ISE, we came across some discrepancies in age, baseline viral load and CD4 counts as presented in Tables 8 and 9 in the study report for TMB-202. The following table summarizes the results in Tables 8 and 9 and those generated based on ADEFFOUT.XPT. Please clarify.

	Ibalizumab 800 mg Q2W (N=59)	Ibalizumab 2000 mg Q4W (N=54)	Total (N=113)
Age			
Clinical study report (Table 8)			
Mean (SD)	48.3 (8.1)	47.9 (6.6)	48.1 (7.4)
Median	48.7	47.3	47.5
Min, Max	29.6, 69.5	32.6, 62.3	29.6, 69.5
Based on ADEFFOUT.XPT (variable AGE)			
Mean (SD)	47.9 (8.2)	47.5 (6.6)	47.7 (7.4)
Median	48.0	47.0	47.0
Min, Max	29.0, 69.0	32.0, 62.0	29.0, 69.0
Baseline viral load (copies/mL)			
Clinical study report (Table 9)			
Mean (SD)	114,675.3 (202,894.6)	136,197.2 (251,282.3)	124,859.8 (226,290.1)
Median	43,850.0	48,766.7	46,633.3
Min, Max	58.0, 1,087,333.3	15,933.3, 161,333.3	13,661.7, 132,720.8
Based on ADEFFOUT.XPT (variable VLOADBLN)			
Mean (SD)	130,190.9 (244,098.5)	169,380.48 (411,269.3)	148,918.7 (333,591.5)

Median	39,500.0	52,300.0	51,300.0
Min, Max	71.4, 1,500,000	145, 2,920,000	71.4, 2,920,000
Baseline viral load (log10 copies/mL)			
Clinical study report (Table 9)			
Mean (SD)	4.6 (0.8)	4.7 (0.7)	4.6 (0.7)
Median	4.6	4.7	4.6
Min, Max	1.8, 6.0	3.3, 6.2	1.8, 6.2
Based on ADEFFOUT.XPT (variable VLOADBLN)			
Mean (SD)	4.5 (0.9)	4.7 (0.8)	4.6 (0.8)
Median	4.6	4.7	4.7
Min, Max	1.9, 6.2	2.2, 6.5	1.9, 6.5
Baseline CD4 cell counts (cells/mm^3)			
Clinical study report (Table 9)			
Mean (SD)	106.4 (91.3)	112.4 (118.5)	109.3 (104.7)
Median	80.5	54.0	69.5
Min, Max	19.0, 375.0	10.0, 476.5	10.0, 476.5
Based on ADEFFOUT.XPT (variable CD4BLN)			
Mean (SD)	102.3 (91.7)	110.5 (126.4)	106.2 (109.2)
Median	76.0	47.5	68.0
Min, Max	19.0, 368.0	6.0, 518.0	6.0, 518.0

2. A variable for the duration of diagnosis of HIV was not available in the submitted datasets. Please clarify how you have calculated the duration.

	Ibalizumab 800 mg Q2W (N=59)	Ibalizumab 2000 mg Q4W (N=54)	Total (N=113)
Years since HIV diagnosis			
Clinical study report (Table 9)			
n	23	29	52
Mean (SD)	17.0 (4.4)	16.9 (6.2)	17.0 (5.4)
Median	16.3	17.1	17.0
Min, Max	8.1, 24.8	0.3, 26	0.3, 26.3

3. The differences in HIV viral load in $\log_{10}$ scale for Subjects 202-32-004, 202-45-004 and 202-61-006 were greater than 0.5 log reduction based on the data of HIV RNA at baseline (i.e., variable VLOADBLN) and at end of study (i.e., variable DSVL_S) in ADEFFOUT.XPT. However, the flag variable EOS_S5 indicated they did not achieve 0.5 log reduction (i.e., variable EOS_S5 = N). Please find the details below and clarify.

Obs	USUBJID	VLOADBLN	Log10 of VLOADBLN	DSVL_S	log10 of DSVL_S	difference in log	EOS_S5
1	202-32-004	126000	5.10037	16600	4.22011	-0.88026	N
2	202-45-004	219000	5.34044	44800	4.65128	-0.68917	N
3	202-61-006	4540	3.65706	49	1.69020	-1.96686	N

4. Similar to Comment 3, the differences in HIV viral load in $\log_{10}$ scale for Subjects 202-51-004 and 202-61-006 were greater than 1 $\log_{10}$ reduction based on the data of HIV RNA at baseline and at end of study data in ADEFFOUT.XPT, but the flag variable EOS_S1 indicated that they did not achieve 1 log reduction. Please find the details below and clarify.

Obs	USUBJID	VLOADBLN	Log10 of VLOADBLN	DSVL_S	log10 of DSVL_S	difference in log	EOS_S1
1	202-51-004	14000	4.14613	1370	3.13672	1.00941	N
2	202-61-006	4540	3.65706	49	1.69020	1.96686	N

5. Based on DS.XPT and LB.XPT, the last study day for Subject 202-12-001 was Day 169 and the subject's CD4 cell count on that day was 169 cells/mm^3. However, ADEFFOUT.XPT showed it was 278 cells/mm^3 (i.e., variable DSCD4_S) which was on Day 141. Similar discrepancy was found for Subject 202-42-017. The last CD4 cell count at end of study for the subject was 376 cells/mm^3 on Day 175 based on DS.XPT and LB.XPT, but ADEFFOUT.XPT showed it was 280 on Day 164. Please clarify.

PLEASE REPLY BY EMAIL (christian.yoder@fda.hhs.gov) to confirm receipt. We are providing this above information via telephone facsimile for your convenience. Please feel free to contact me at 301-796-1500 if you have any questions regarding the contents of this transmission.

Christian P. Yoder, MPH
Regulatory Project Manager
Division of Antiviral Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

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/s/

CHRISTIAN P YODER
08/08/2017

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Antimicrobial Products
Division of Antiviral Drug Products

FACSIMILE TRANSMITTAL SHEET

DATE: July 26, 2017

To: Dr. Helen Shu	**From: Christian Yoder, MPH**
Company: TaiMed Biologics	**Title: Regulatory Project Manager**
Fax number: 858 724-1844	**Fax number: 301-796-9883**
Phone number: 858 481-6863	**Phone number: (240) 402-9990**

Subject: BLA 761065

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Division of Antiviral Drug Products
Food and Drug Administration
Silver Spring, MD 20993

MEMORANDUM OF FACSIMILE CORRESPONDENCE

BLA: **761065**

Drug: **ibalizumab**

Date: **July 26, 2017**

To: **Helen Shu, Ph.D., Vice President, Regulatory Affairs and Quality**

From: **Christian Yoder, MPH, Regulatory Project Manager**

Subject: **BLA 761065 Information Request**

Please refer to your BLA 761065. Please see the following comments and respond by August 2, 2017:

1. In your July 24th response to our July 20th IR, you noted that the protocol deviations were typed out into the OSI listing program. With the BLA submission on May 3rd, you included a document titled "TMB-202 OSI Listings 20170419". This document is 4153 pages long and is categorized by site. We have reviewed the TMB-202 protocol deviations summary in the "TMB-202 Study Report Body" and the lists of Major Protocol Deviations found in Listing 16.2.3 and Table 14.1.3.1. In these three locations, you have summarized only "major" protocol deviations. Please provide a line listing of all TMB-202 protocol deviations.

2. In the TMB-202 Clinical Study Report Narratives for Other Significant Adverse Events (Section 12.3.2.3 page 128), you describe subject 13-003/MJR's hypersensitivity event. The narrative explains that this subject was enrolled in the study in violation of the inclusion criteria because her baseline HIV RNA, drawn on Day 1, was >1000 c/ml. The narrative implies that the site was instructed to remove the subject before Day 2, when the subject developed cough, chills, and myalgia. The narrative then states that on study day 21, the subject was reported to have "hypersensitivity" (allergic reaction) and study drug was discontinued. The SDTM dataset "ex" includes two doses of Ibalizumab for the subject, one entire dose on study day 1 and one partial dose on study day 22.

a. Please provide a full narrative that describes the subject's clinical symptoms and the clinical course of those symptoms as they relate to Ibalizumab administration and the diagnosis of hypersensitivity.

b. Please clarify when the site was notified that the subject should be discontinued due to ineligibility. If the site was notified before Day 2, please explain why the participant received a second dose of Ibalizumab on Day 22.

c. The TMB-202 "Study Report Body" (page 59, Table 7), states "patient 13-003 discontinued study due to an AE of hypersensivity. Did the subject discontinue Ibalizumab because of hypersensitivity or ineligibility?

d. Did the subject experience symptoms of hypersensitivity during the Ibalizumab infusion on Day 22 and, therefore, receive only a partial infusion?

PLEASE REPLY BY EMAIL (christian.yoder@fda.hhs.gov) to confirm receipt. We are providing this above information via telephone facsimile for your convenience. Please feel free to contact me at 240-402-9990 if you have any questions regarding this transmission.

Christian P. Yoder, MPH
Regulatory Project Manager
Division of Antiviral Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

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/s/

CHRISTIAN P YODER
07/26/2017

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Antimicrobial Products
Division of Antiviral Drug Products

FACSIMILE TRANSMITTAL SHEET

DATE: July 21, 2017

To: Dr. Helen Shu	**From: Christian Yoder, MPH**
Company: TaiMed Biologics	**Title: Regulatory Project Manager**
Fax number: 858 724-1844	**Fax number: 301-796-9883**
Phone number: 858 481-6863	**Phone number: (240) 402-9990**

Subject: BLA 761065

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Public Health Service

Division of Antiviral Drug Products
Food and Drug Administration
Silver Spring, MD 20993

MEMORANDUM OF FACSIMILE CORRESPONDENCE

BLA: **761065**

Drug: **ibalizumab**

Date: **July 21, 2017**

To: **Helen Shu, Ph.D., Vice President, Regulatory Affairs and Quality**

From: **Christian Yoder, MPH, Regulatory Project Manager**

Subject: **BLA 761065 Information Request**

Please refer to your BLA 761065 and to the submission we received on May 3, 2017. Please see the following comment and respond by July 28, 2017:

1. Many ibalizumab samples with concentrations less than 1 ug/mL were not included in the updated NONMEM dataset (m101906.xpt). Please provide another NONMEM dataset including these samples. Also include another column in the dataset denoting whether the sample was below the limit of quantification. Please provide viral load and CD4+ count information if the data were collected. If possible, please provide the SAS or R code you used to generate the updated NONMEM dataset, including which datasets from Study 355.01, 355. 02 and 355.03 were used. Finally, provide an updated define file for this dataset. The define file should completely describe abbreviations, calculations, and derived variables used in the dataset.

2. Please re-submit receptor occupancy and receptor density datasets for TMB-202 to include all raw data without censoring (data were censored in submitted dataset cd4r-202.xpt).

PLEASE REPLY BY EMAIL (christian.yoder@fda.hhs.gov) to confirm receipt. We are providing this above information via telephone facsimile for your convenience. Please feel free to contact me at 240-402-9990 or 301-796-1500 if you have any questions regarding the contents of this transmission.

Christian P. Yoder, MPH
Regulatory Project Manager
Division of Antiviral Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

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CHRISTIAN P YODER
07/21/2017

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Antimicrobial Products
Division of Antiviral Drug Products

FACSIMILE TRANSMITTAL SHEET

DATE: July 20, 2017

To: Dr. Helen Shu	**From: Christian Yoder, MPH**
Company: TaiMed Biologics	**Title: Regulatory Project Manager**
Fax number: 858 724-1844	**Fax number: 301-796-9883**
Phone number: 858 481-6863	**Phone number: (240) 402-9990**

Subject: BLA 761065

Total number of pages including cover:

Comments:

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Document to be mailed: ☐ YES ☑ NO

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Division of Antiviral Drug Products
Food and Drug Administration
Silver Spring, MD 20993

MEMORANDUM OF FACSIMILE CORRESPONDENCE

BLA: **761065**

Drug: **ibalizumab**

Date: **July 20, 2017**

To: **Helen Shu, Ph.D., Vice President, Regulatory Affairs and Quality**

From: **Christian Yoder, MPH, Regulatory Project Manager**

Subject: **BLA 761065 Information Request**

Please refer to your BLA 761065. Please see the following comments and respond by July 27, 2017:

Clinical

1. For trial TMB-202, please provide an SDTM dataset for protocol deviations or provide the specific location of that data within the submitted files.

Virology

2. We note that you submitted a study entitled, "CD4 polymorphisms in ethnic groups that could potentially impact ibalizumab efficacy" to IND 009776 on 9/29/15. Please submit this file to BLA 761065 or identify where this information can be found in the BLA if it has already been submitted.

PLEASE REPLY BY EMAIL (christian.yoder@fda.hhs.gov) to confirm receipt. We are providing this above information via telephone facsimile for your convenience. Please feel free to contact me at 240-402-9990 if you have any questions regarding this transmission.

Christian P. Yoder, MPH
Regulatory Project Manager
Division of Antiviral Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

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CHRISTIAN P YODER
07/20/2017

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Antimicrobial Products
Division of Antiviral Drug Products

FACSIMILE TRANSMITTAL SHEET

DATE: July 12, 2017

To: Dr. Helen Shu	**From: Nina Mani, PhD, MPH**
Company: TaiMed Biologics	**Title: Senior Regulatory Project Manager**
Fax number: 858 724-1844	**Fax number: 301-796-9883**
Phone number: 858 481-6863	**Phone number:**

Subject: BLA 761065

Total number of pages including cover:

Comments:

Helen – Can you email me to confirm receipt? Thanks.

Document to be mailed: ☐ YES ☑ NO

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Division of Antiviral Drug Products
Food and Drug Administration
Silver Spring, MD 20993

MEMORANDUM OF FACSIMILE CORRESPONDENCE

BLA: **761065**

Drug: **ibalizumab**

Date: **July 12, 2017**

To: **Helen Shu, Ph.D., Vice President, Regulatory Affairs and Quality**

From: **Nina Mani, Senior Regulatory Project Manager**

Subject: **BLA 761065 Information Request**

Please refer to your BLA 761065 and the following comment and request from the Statistical Team. Please see the following comment and respond by **Monday, July 17, 2017**:

> In your ADEFFOUT.XPT, we note that subject 301-04-001 had baseline HIV RNA of 5660 copies/mL (i.e., VLOADBLN = 5660; $\log_{10} = 3.75$) and HIV RNA at Week 25 of 535 (i.e., DSVL_S = 535; $\log_{10} = 2.73$). However, the variable for change from baseline at Week 25 in the same dataset indicated no change (i.e., EOS_CB = 0). Based on the viral load data, change from baseline at Week 25 should be around -1.02 $\log_{10}$ (=2.73-3.75) instead of 0. Please provide your rationale for this change.

PLEASE REPLY BY EMAIL (nina.mani@fda.hhs.gov) to confirm receipt. We are providing this above information via telephone facsimile for your convenience. Please feel free to contact me at 301-796-1500 if you have any questions regarding the contents of this transmission.

Nina Mani, PhD, MPH
Senior Regulatory Project Manager
Division of Antiviral Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

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/s/

NINA MANI
07/12/2017

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

BLA 761065

GENERAL ADVICE

TaiMed Biologics USA Corp.
Attention: Helen P. Shu, Ph.D.
Vice President, Regulatory Affairs & Quality
425 San Lucas Drive
Solana Beach, CA 92075

Dear Dr. Shu:

Please refer to your Biologics License Application (BLA) submitted under section 351(a) of the Public Health Service Act for Ibalizumab, 150 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 this guidance contains information collection provisions that are subject to review by the Office of Management and Budget (OMB) under the Paperwork Reduction Act (PRA) of 1995. These provisions of the guidance describe the submission of proposed suffixes to FDA and a sponsor's related analysis of proposed suffixes, which are considered, under the PRA, as information collection. FDA is not currently implementing information collection provisions of the guidance.

However, provisions of the final guidance that do not describe the information collection provisions 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, MS, PharmD at (301) 796-5162 or Jill Bourdage, RPh, PMP at (301) 796-5164.

[1] http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM459987.pdf

For any other information regarding this application, contact Christian Yoder, MPH, Regulatory Project Manager in the Office of New Drugs, at (240) 402-9990.

Sincerely,

{See appended electronic signature page}

Lubna Merchant, MS, PharmD
Acting Deputy Director
Office of Medication Error Prevention and Risk Management
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

AZEEM D CHAUDHRY
07/10/2017

LUBNA A MERCHANT
07/10/2017

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Antimicrobial Products
Division of Antiviral Drug Products

FACSIMILE TRANSMITTAL SHEET

DATE: July 5, 2017

To: Dr. Helen Shu	**From: Christian Yoder, MPH**
Company: TaiMed Biologics	**Title: Regulatory Project Manager**
Fax number: 858 724-1844	**Fax number: 301-796-9883**
Phone number: 858 481-6863	**Phone number: (240) 402-9990**

Subject: BLA 761065

Total number of pages including cover:

Comments:

Helen – Can you email me to confirm receipt? Thanks.

Document to be mailed: ☐ YES ☑ NO

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Division of Antiviral Drug Products
Food and Drug Administration
Silver Spring, MD 20993

MEMORANDUM OF FACSIMILE CORRESPONDENCE

BLA: **761065**

Drug: **ibalizumab**

Date: **July 5, 2017**

To: **Helen Shu, Ph.D., Vice President, Regulatory Affairs and Quality**

From: **Christian Yoder, MPH, Regulatory Project Manager**

Subject: **BLA 761065 Information Request**

Please refer to your BLA 761065 and to the submission we received on May 3, 2017. Please see the following comment and respond by July 7, 2017:

1. We note that in submission BLA761065 SN 21 (SDN 023, June 29, 2017) that you submitted revised Clinical Virology Report Appendices for studies TMB-202 and TMB-301 stating that "the replacement Appendices correct errors in those documents submitted earlier". It was reported that TMB-301 Appendix A was revised and replaced, whereas TMB-202 Appendix I and TMB-301 Appendices C and F were only modified in format (expanding to provide tables for individual subjects). Please confirm that no changes were made to any data entries in any other appendix besides TMB-301 Appendix A and provide a detailed description of each change made to TMB-301 Appendix A and the reason for it. This information is required as soon as possible to prevent a potential delay in the review process; we encourage you to provide this information by 7/7/17 at 5 p.m

PLEASE REPLY BY EMAIL (christian.yoder@fda.hhs.gov) to confirm receipt. We are providing this above information via telephone facsimile for your convenience. Please feel free to contact me at 240-402-9990 or 301-796-1500 if you have any questions regarding the contents of this transmission.

Christian P. Yoder, MPH
Regulatory Project Manager
Division of Antiviral Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

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/s/

CHRISTIAN P YODER
07/05/2017

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Antimicrobial Products
Division of Antiviral Drug Products

FACSIMILE TRANSMITTAL SHEET

DATE: June 30, 2017 (Fax #2)

To: Dr. Helen Shu	**From: Christian Yoder, MPH**
Company: TaiMed Biologics	**Title: Regulatory Project Manager**
Fax number: 858 724-1844	**Fax number: 301-796-9883**
Phone number: 858 481-6863	**Phone number: (240) 402-9990**

Subject: BLA 761065

Total number of pages including cover:

Comments:

Helen – Can you email me to confirm receipt? Thanks.

Document to be mailed: ☐ YES ☑ NO

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Division of Antiviral Drug Products
Food and Drug Administration
Silver Spring, MD 20993

MEMORANDUM OF FACSIMILE CORRESPONDENCE

BLA: **761065**

Drug: **ibalizumab**

Date: **June 30, 2017**

To: **Helen Shu, Ph.D., Vice President, Regulatory Affairs and Quality**

From: **Christian Yoder, MPH, Regulatory Project Manager**

Subject: **BLA 761065 Information Request**

Please refer to your BLA 761065 and to the submission we received on May 3, 2017. Please see the following comments and respond no later than close of business Friday, July 7, 2017:

Virology

1. We have received and reviewed the define files that you submitted for TMB-202 and TMB-301 on June 30, 2017, and unfortunately, these files do not provide sufficient detail to explain many of the variables used in Appendices A-F for studies TMB-301 and TMB-202. For example, variables in Appendix A include "EXTRTHIV", "HIVHIST", and "PRVARV", but no definitions are provided for these terms. Please provide a define file that defines all of the variables that were used in the data tables provided in the appendices (A-F for TMB-301 and 1-17 for TMB-202). Please provide this information as soon as possible but no later than July 7, 2017 by the end of the day.

Clinical

2. Thank you for providing clarifying information for subject 301-04-002 in your June 15th submission. This subject started part of the OBR on Day 13 (May 10, 2016). Please provide the names of the OBR medication(s) and dose(s) that the subject took on May 10th, 2016.

3. The TMB-301 protocol states that in order to be included in the trial, subjects must have documented resistance to at least one medication for each of three classes of

antiretroviral medications as measured by resistance testing. Subject 301-25-001 appears to have no Genotypic/Phenotypic evidence of resistance to NNRTI, NRTI, or PI. Please clarify how this subject met inclusion criteria for the trial.

4. In your ADAM lab dataset, we note that for subject 301-14-001, you used the Day 0 CD4 T cell count value, rather than the Day 7 value, as the Day 7 (baseline) value. Please provide your rationale for this change. We acknowledge that the actual Day 7 value included in the SDTM lab dataset (341 cells/mcl) is unexpected given the values at Day 0 (63 cells/mcl) and Day 14 (75 cells/mcl).

5. Thank you for providing the clinical narrative for subject 301-01-001, who died of Kaposi's Sarcoma. With regards to this subject's changes in OBR, please clarify the following:
    a. The narrative states that the subject's OBR included cabotegravir. This implies that cabotegravir was included in the initial OBR, however the SDTM dataset includes a cabotegravir start study day of Day 156. Please clarify when cabotegravir was started and stopped.
    b. The narrative states that BMS663068 (fostemsavir), darunavir, and ritonavir were stopped while the subject was in the ICU in septic shock on December 17th or 18th (Study day 100 or 101).
        i. Please provide the reason why these OBR drugs were stopped.
        ii. Please also provide the start date for fostemsavir, which is not included in the CM dataset.
    c. The SDTM dataset (but not the narrative), includes atazanavir with a study start day 102 and end day of 110. Please provide the reason why this drug was added and subsequently removed from the OBR.
    d. The SDTM dataset (but not the narrative) includes enfuvirtide with study start day 129 and study end day 169. Please provide the reason why this drug was added to the OBR.

6. In Tables 10 and 12 of the Summary of Clinical Safety, you have listed the time since HIV-diagnosis in years for participants in trials TMB-301 and TMB-202. Please provide the location and name of the dataset file that includes these data.

7. Please inform us as to whether or not Ibalizumab is undergoing regulatory evaluation overseas.

PLEASE REPLY BY EMAIL (christian.yoder@fda.hhs.gov) to confirm receipt. We are providing this above information via telephone facsimile for your convenience. Please feel free to contact me at 240-402-9990 or 301-796-1500 if you have any questions regarding the contents of this transmission.

Christian P. Yoder, MPH
Regulatory Project Manager
Division of Antiviral Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

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/s/

CHRISTIAN P YODER
06/30/2017

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

BLA 761065

FILING COMMUNICATION –
FILING REVIEW ISSUES IDENTIFIED

TaiMed Biologics USA Corp.
Attention: Helen P. Shu, Ph.D.
VP Regulatory Affairs and Quality
2 Executive Circle, Suite 280
Irvine, CA 92614

Dear Dr. Shu:

Please refer to your Biologics License Application (BLA) dated and received May 3, 2017, submitted under section 351(a) of the Public Health Service Act for ibalizumab injection, 200mg/vial.

We also refer to your amendment dated June 13, 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 January 3, 2018. This application is also subject to the provisions of "the Program" under the Prescription Drug User Fee Act (PDUFA) V (refer to: http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm272170.htm.

We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, mid-cycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing requirement/commitment requests by October 3, 2017. In addition, the planned date for our internal mid-cycle review meeting is August 11, 2017. We are not currently planning to hold an advisory committee meeting to discuss this application.

During our filing review of your application, we identified the following potential review issues (please note these review issues have been previously communicated to you by information requests as listed below):

1. OPQ/Micro – sent June 23, 2017, due July 10, 2017

2. OPQ/Micro – The Rabbit Pyrogen Test should be conducted on three lots of drug product in accordance with 21 CFR610.13(b). Clarification of the protocol was provided by the Agency in an information request dated June 23, 2017 (item 21). Please submit the Rabbit Pyrogen Test summary report and results to section 3.2.P.5.3 by August 15, 2017.

We are providing the above comments to give you preliminary notice of potential review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review. Issues may be added, deleted, expanded upon, or modified as we review the application. If you respond to these issues during this review cycle, we may not consider your response before we take an action on your application.

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.

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

1. Please add horizontal line between the Table of Contents and the Full Prescribing Information.

2. The revision date at the end of the Highlights section should be right justified.

3. The heading "Full Prescribing Information" should all be on one line.

4. Subsection 6.2 contains lab abnormalities. Please remove this information and add it under Subsection 6.1, as Subsection 6.2 is reserved for either immunogenicity or postmarketing data.

5. Section 15 is improperly formatted and contains references that should not be included. Please delete this Section.

6. Section 16 should not include subsections. Please revise.

7. The Patient Counseling Information Statement in Highlights should not be underlined.

We request that you resubmit labeling (in Microsoft Word format) that addresses these issues by July 21, 2017. The resubmitted labeling will be used for further labeling discussions. Use the SRPI checklist to correct any formatting errors to ensure conformance with the format items in regulations and guidances. The checklist is available at the following link: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/UCM373025.pdf

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 and patient package insert. 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 and patient package insert, 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 Christian Yoder, Regulatory Project Manager, at (240) 402-9990 or (301) 796-1500.

Sincerely,

{See appended electronic signature page}

Debra Birnkrant, MD
Director
Division of Antiviral Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

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/s/

DEBRA B BIRNKRANT
06/30/2017

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Antimicrobial Products
Division of Antiviral Drug Products

FACSIMILE TRANSMITTAL SHEET

DATE: June 30, 2017

To: Dr. Helen Shu	**From: Christian Yoder, MPH**
Company: TaiMed Biologics	**Title: Regulatory Project Manager**
Fax number: 858 724-1844	**Fax number: 301-796-9883**
Phone number: 858 481-6863	**Phone number: (240) 402-9990**

Subject: BLA 761065

Total number of pages including cover:

Comments:

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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Division of Antiviral Drug Products
Food and Drug Administration
Silver Spring, MD 20993

MEMORANDUM OF FACSIMILE CORRESPONDENCE

BLA: **761065**

Drug: **ibalizumab**

Date: **June 30, 2017**

To: **Helen Shu, Ph.D., Vice President, Regulatory Affairs and Quality**

From: **Christian Yoder, MPH, Regulatory Project Manager**

Subject: **BLA 761065 Information Request**

Please refer to your BLA 761065 and to the submission we received on May 3, 2017. Please see the following comments and respond by July 12, 2017:

1. Please submit receptor occupancy and receptor density datasets for TMB-202 similar to what was submitted for TMB-301.
2. Please provide rationale for the different ibalizumab concentrations required for complete receptor occupancy (e.g., > 5 µg/mL, > 300 ng/mL, > 130 ng/mL) in TNX-355.01, TNX-355.02, TNX-355.03, TMB-202, and TMB-301 studies.
3. For ADA detection in TMB-202 and TMB-301 studies, please submit detailed information for all ADA tested samples, including: subject #, sample relative study day or week, ADA result, and ibalizumab concentration. If ibalizumab concentration has not been measured, please specify them as not determined.

PLEASE REPLY BY EMAIL (christian.yoder@fda.hhs.gov) to confirm receipt. We are providing this above information via telephone facsimile for your convenience. Please feel free to contact me at 240-402-9990 or 301-796-1500 if you have any questions regarding the contents of this transmission.

Christian P. Yoder, MPH
Regulatory Project Manager
Division of Antiviral Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

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/s/

CHRISTIAN P YODER
06/30/2017

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

BLA 761065

INFORMATION REQUEST

TaiMed Biologics USA Corp.
Attention: Helen P. Shu, Ph.D.
VP Regulatory Affairs and Quality
425 San Lucas Drive
Solano Beach, CA 92075

Dear Dr. Shu:

Please refer to your Biologics License Application (BLA) dated May 3, 2017, received May 3, 2017, submitted under section 351(a) of the Public Health Service Act for ibalizumab injectable.

We are reviewing the CMC section of your submission and have the following comments and information requests. We request a prompt written response as specified below in order to continue our evaluation of your BLA.

Provide your response to the Agency's comments 1 and 2 by COB July 10, 2017:

1. Please provide a diagram showing all the bioburden and endotoxin sampling points, locations of the [redacted] (b) (4) processes of the commercial ibalizumab manufacturing process. Indicate on the diagram if the bioburden and endotoxin samples are taken [redacted] (b) (4) and if the samples are taken [redacted] (b) (4).

2. Table 3.2.S.2.4.2.10 provided in Section 3.2.S.2.4 lists the final stability data of [redacted] (b) (4). Provide a table in Section 3.2.S.2.4 to include all the proposed [redacted] (b) (4) for the commercial ibalizumab process [redacted] (b) (4).

Provide your response to the Agency's comments below by COB August 08, 2017:

3. The cell culture is [redacted] (b) (4) [redacted] Alternatively, justify the current practice.

4. Move the data obtained from the PPQ runs in Section 3.2.S.2.4 to Section 3.2.S.2.5, "Process Validation and/or evaluation", if the data are not already there. Include in Section 3.2.S.2.4 only the acceptance criteria or limits for in-process controls for the commercial ibalizumab manufacturing process.

5. Provide a table in Section 3.2.S.2.2, "description of manufacturing process and process controls" listing all [redacted] (b) (4) In addition, provide endotoxin limits [redacted] (b) (4). Clarify if [redacted] (b) (4) are tested for endotoxin prior to use.

6. Clarify if the expiry time provided in Table 3.2.S.2.4.2.2.11 is the proposed [redacted] (b) (4) for the ibalizumab commercial manufacturing process. Clarify if all [redacted] (b) (4).

7. Clarify if [redacted] (b) (4). If so, update Sections 3.2.S.2.2 and 3.2.S.2.4, accordingly.

8. Include [redacted] (b) (4) in the lifetime study at commercial scale. Provide the study protocols and include the bioburden and endotoxin limits. In addition, conduct studies at scale to verify the effectiveness of [redacted] (b) (4). Provide the study protocols and include the bioburden and endotoxin limits.

9. The bioburden specification for ibalizumab drug substance is ≤ [redacted] (b) (4). The bioburden specification should be [redacted] (b) (4) mL for ibalizumab DS stored at [redacted] (b) (4) °C, as any bioburden in the DS may proliferate during the shelf life at [redacted] (b) (4) °C. Update the bioburden specification in the BLA.

10. The [redacted] (b) (4) in Section 3.2.S.2.4 are expressed as [redacted] (b) (4). The limits should be expressed as ">"CFU/10 mL or ">"EU/mL instead. Update Section 3.2.S.2.4 accordingly.

11. The [redacted] (b) (4) in Section 3.2.S.2.4 appear to be high and may not allow for adequate microbial control. Please tighten the [redacted] (b) (4) to reflect process capabilities. Update Section 3.2.S.2.4 accordingly.

12. With regard to the endotoxin test, provide the [redacted] (b) (4) endotoxin samples. In addition, provide the routine dilution for the [redacted] (b) (4) DP endotoxin release samples.

13. Your FMEA risk assessment and Design of Experiment (DoE) studies identified process parameters that you classified as critical process parameters (CPPs), key process parameters (KPPs) and non-key process parameters. It is unclear from your submission how you define "critical" versus "key" process parameters, and whether these parameters are monitored differently. Please define the terms "critical" and "key" as used in your

control strategy. Indicate how the Quality System responds to out-of-range values for CPPs, KPPs, and non-key process parameters.

14. Your submission indicates that the process parameters used in the (b) (4) L WuXi AppTec process were adopted from the (b) (4) L manufacturing process at Tanox. Provide a summary of how the process parameter ranges were established at Tanox including the number of batches and the statistical methods used.

15. The flow diagram shown in Figure 3.2.S.2.2.2.1 for the downstream process indicates (b) (4) Provide in a table (b) (4) controls with acceptance criteria that will be used during the proposed commercial upstream and downstream TMB-355 manufacturing process.

16. Your manufacturing process includes a (b) (4) Describe whether there is a potential for (b) (4) and provide an assessment (b) (4)

17. You did not provide an upper limit for (b) (4) manufacturing process. Update your process parameters for the production (b) (4) that is supported by process validation studies demonstrating clearance of this impurity. Also, provide a table with amounts of (b) (4) for all drug substance batches manufactured to date.

18. It is unclear how TMB-355 drug substance and drug product batch numbers are assigned. Provide a description of the batch numbering system used to track lots of TMB-355 drug substance and drug product manufactured at the WuXi AppTec facility. Indicate whether batch numbers are assigned for each (b) (4).

19. The description of the manufacturing process provided in section 3.2.S.2.2 does not provide sufficient detail regarding the transfer and storage of the product (b) (4). Provide a description of how the product is moved (b) (4) throughout the drug substance manufacturing process including equipment, transfer conditions, storage conditions, and maximum allowable hold times between steps.

20. The operating parameters for [redacted] (b) (4) were provided in section 3.2.R of your application. Changes to these parameters could potentially impact process performance and product quality. Update the BLA to include the [redacted] (b) (4) within the appropriate subsections of 3.2.S.

21. Provide a risk assessment on the potential leachables from the materials used in the manufacture of ibalizumab drug substance and drug product. You may consider the extractable data conducted by the manufacturers of product contact equipment and storage containers used [redacted] (b) (4)) in the manufacture of your product to conduct an initial risk assessment of potential extractables and leachables.

22. You established normal operating ranges (NOR) and maximum operating ranges (MOR) for [redacted] (b) (4). It is unclear how the NOR and MOR are used to control the ibalizumab manufacturing process and how events that are out-of-range are dealt with for each range. Summarize how the NOR and MOR are used to control the ibalizumab manufacturing process, including how out-of-range values are investigated.

23. The production [redacted] (b) (4) . The NOR provided in table 3.2.S.2.2.4.1 indicates a NOR of [redacted] (b) (4) (b) (4). Provide an explanation for the discrepancy between these ranges and a justification for the (b) (4) limits used during the proposed commercial ibalizumab manufacturing process.

24. Your analytical comparability study report RRT15035-WBP236-01 indicates that a side-by-side stability comparability study was initiated to compare ibalizumab DP manufactured at Tanox to ibalizumab DP manufactured WuXi AppTec, but that no data was available at the time of the report. Provide updated side-by-side stability comparability data under normal and accelerated conditions for the Tanox and WuXi AppTec ibalizumab DP.

25. You refer to several documents regarding the characterization of your manufacturing process that were not provided in the application. Please provide the following documents for the Agency to review:

[redacted] (b) (4)

(b) (4)

26.

27. Your proposed DS shelf life is unclear. You refer to a maximum DS storage time (b) (4) . Clarify the proposed DS shelf life and update the BLA with the correct information where appropriate.

28. Forced Degradation Study Report TMB-RD-R2015001 indicates that TMB-355 is highly sensitive to visible light exposure, resulting in changes to appearance, aggregation, charge heterogeneity, size heterogeneity, and potency. Since visible light can negatively impact product quality, controls should be in place to minimize the exposure of the DS and DP material to visible light. Describe how the exposure of the product to visible light is controlled throughout the manufacturing process to prevent light-induced degradation.

29. You did not provide data characterizing the Fc-mediated effector functions of ibalizumab. Fc-mediated effector functions including antibody dependent cellular cytotoxicity (ADCC), complement-dependent cytotoxicity (CDC) and antibody-dependent cellular phagocytosis (ADCP) can influence the biological activity of the drug and should therefore be characterized. Please submit data evaluating the Fc-mediated potencies of ibalizumab including complement fixation and Fc-receptor binding affinity.

30. Your submission does not contain a comprehensive list of TMB-355 batches manufactured throughout the development of the product. Provide a table containing a complete list of all TMB-355 drug substance and drug product batches that have been manufactured at the Tanox and WuXi AppTec facilities to date. The table should include batch numbers, manufacturing dates, manufacturing scale, and a description of how the material was used (e.g. clinical studies, comparability studies, characterization studies,

forced degradation studies, reference standard material, proposed commercial material). For all clinical lots indicate the phase and clinical study number for which the material was used. Clearly indicate which Drug Product batches correspond to which Drug Substance batches.

31. We note that the DS stability specifications have been updated in some sections of the BLA (e.g. 3.2.S.7.2) but not others (e.g. 3.2.S.4.1, 2.3.S). Please update the BLA to ensure that all information is current and consistent between sections.

32. The data from your Forced Degradation Study Report indicates that under stressed conditions ibalizumab forms acidic and basic charge variants [redacted] (b) (4) [redacted]. Your release and stability acceptance criteria [redacted] (b) (4) which are inadequate because they do not provide sufficient control over the levels of acidic and basic variants in ibalizumab drug substance and drug product. Update your release and stability specifications with numerical acceptance criteria for the acidic and basic charge variants of ibalizumab.

33. The numerical reporting of data for the Cell-Fusion Inhibition assay are inconsistent throughout the application. The data is expressed as a proportion of the reference standard in some sections of the application (e.g. 3.2.S.4.1) and as a percentage of the reference standard in other sections (e.g. 3.2.S.4.4) Update the acceptance criteria and data to be consistently reported as either a proportion of the reference standard or a percentage of the reference standard throughout the application.

34. For all drug substance lots manufactured to date using the [redacted] (b) (4) L scale manufacturing process, provide the following information:
    (a) control charts with trend analyses of upstream [redacted] (b) (4) [redacted] phases
    (b) control charts with trend analyses of downstream [redacted] (b) (4) data [redacted] (b) (4)

If you have questions, please contact Anita Brown, Regulatory Business Process Manager, at (301) 796-2066 or Anita.Brown@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Anita N. Brown
Regulatory Business Process Manager
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research

Kelly
Ballard

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Date: 6/30/2017 04:33:16PM
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Food and Drug Administration
Center for Drug Evaluation and Research
Office of Antimicrobial Products
Division of Antiviral Drug Products

FACSIMILE TRANSMITTAL SHEET

DATE: June 23, 2017

To: Dr. Helen Shu	**From: Christian Yoder, MPH**
Company: TaiMed Biologics	**Title: Regulatory Project Manager**
Fax number: 858 724-1844	**Fax number: 301-796-9883**
Phone number: 858 481-6863	**Phone number: (240) 402-9990**

Subject: BLA 761065

Total number of pages including cover:

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Helen – Can you email me to confirm receipt? Thanks.

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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Division of Antiviral Drug Products
Food and Drug Administration
Silver Spring, MD 20993

MEMORANDUM OF FACSIMILE CORRESPONDENCE

BLA: **761065**

Drug: **ibalizumab**

Date: **June 23, 2017**

To: **Helen Shu, Ph.D., Vice President, Regulatory Affairs and Quality**

From: **Christian Yoder, MPH, Regulatory Project Manager**

Subject: **BLA 761065 Information Request**

Please refer to your BLA 761065 and to the submission we received on May 3, 2017. Please see the following comment:

1. Please submit a data definition table for all files (AppxA through AppxG) in the Data Analysis Data/Analysis Dataset Legacy directories for studies TMB-202 and TMB-301. The data definition table should describe all of the variables used in the .xpt files and provide a short description about how the results were derived. Please provide this information as soon as possible but no later than 6/30/2017 at 5 p.m. EDT.

PLEASE REPLY BY EMAIL (christian.yoder@fda.hhs.gov) to confirm receipt. We are providing this above information via telephone facsimile for your convenience. Please feel free to contact me at 240-402-9990 or 301-796-1500 if you have any questions regarding the contents of this transmission.

Christian P. Yoder, MPH
Regulatory Project Manager
Division of Antiviral Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

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/s/

CHRISTIAN P YODER
06/23/2017

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

BLA 761065

INFORMATION REQUEST

TaiMed Biologics USA Corp.
Attention: Helen P. Shu, Ph.D.
VP Regulatory Affairs and Quality
425 San Lucas Drive
Solano Beach, CA 92075

Dear Dr. Shu:

Please refer to your Biologics License Application (BLA) dated May 3, 2017, received May 3, 2017, submitted under section 351(a) of the Public Health Service Act for ibalizumab injectable.

We are reviewing the CMC section of your submission and have the following comments and information requests. We request a prompt written response by July 10, 2017 in order to continue our evaluation of your BLA.

(b) (4)

[redacted]

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(b) (4)

[redacted]

If you have questions, please contact Anita Brown, Regulatory Business Process Manager, at (301) 796-2066 or Anita.Brown@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Anita N. Brown
Regulatory Business Process Manager
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research

Kelly
Ballard

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Food and Drug Administration
Center for Drug Evaluation and Research
Office of Antimicrobial Products
Division of Antiviral Drug Products

FACSIMILE TRANSMITTAL SHEET

DATE: June 20, 2017

To: Dr. Helen Shu	**From: Christian Yoder, MPH**
Company: TaiMed Biologics	**Title: Regulatory Project Manager**
Fax number: 858 724-1844	**Fax number: 301-796-9883**
Phone number: 858 481-6863	**Phone number: (240) 402-9990**

Subject: BLA 761065

Total number of pages including cover:

Comments:

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Document to be mailed: ☐ YES ☑ NO

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Division of Antiviral Drug Products
Food and Drug Administration
Silver Spring, MD 20993

MEMORANDUM OF FACSIMILE CORRESPONDENCE

BLA: **761065**

Drug: **ibalizumab**

Date: **June 20, 2017**

To: **Helen Shu, Ph.D., Vice President, Regulatory Affairs and Quality**

From: **Christian Yoder, MPH, Regulatory Project Manager**

Subject: **BLA 761065 Information Request**

Please refer to your BLA 761065 and to the submission we received on May 3, 2017. Please see the following comments:

> Different PK related assays were performed in Phase 1 to 3 studies, including: 1) serum concentration, 2) anti-drug antibody, 3) neutralizing antibody, 4) receptor occupancy or T-cell coating, 5) receptor density.
>
> Although validation reports were submitted for those assays, the bioanalytical reports for the clinical samples have not been submitted.
>
> Please submit the bioanalytical reports for all PK related assays for Phase 1 to 3 clinical studies no later than July 10, 2017.

PLEASE REPLY BY EMAIL (christian.yoder@fda.hhs.gov) to confirm receipt. We are providing this above information via telephone facsimile for your convenience. Please feel free to contact me at 240-402-9990 or 301-796-1500 if you have any questions regarding the contents of this transmission.

Christian P. Yoder, MPH
Regulatory Project Manager
Division of Antiviral Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

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/s/

CHRISTIAN P YODER
06/20/2017

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

BLA 761065

INFORMATION REQUEST

TaiMed Biologics USA Corp.
Attention: Helen P. Shu, Ph.D.
VP Regulatory Affairs and Quality
425 San Lucas Drive
Solano Beach, CA 92075

Dear Dr. Shu:

Please refer to your Biologics License Application (BLA) dated May 3, 2017, received May 3, 2017, submitted under section 351(a) of the Public Health Service Act for ibalizumab injectable.

We are reviewing the CMC section of your submission and have the following comments and information requests. We request a prompt written response by June 27, 2017 in order to continue our evaluation of your BLA.

Your submission does not include standard operating procedures (SOPs) for the analytical methods used for in-process, release, and stability testing of ibalizumab. The SOPs for the analytical methods are critical for us to understand how the method validation exercise was executed and how routine testing of ibalizumab will be performed. Please provide the SOPs for all analytical methods used for in-process, release, and stability testing of ibalizumab.

If you have any questions, please contact Anita Brown, Regulatory Business Process Manager, at (301)796-2066 or Anita.Brown@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Anita N. Brown
Regulatory Business Process Manager
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research

Anita Brown

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Date: 6/20/2017 11:08:19AM
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Food and Drug Administration
Center for Drug Evaluation and Research
Office of Antimicrobial Products
Division of Antiviral Drug Products

FACSIMILE TRANSMITTAL SHEET

DATE: June 8, 2017

To: Dr. Helen Shu	**From: Christian Yoder, MPH**
Company: TaiMed Biologics	**Title: Regulatory Project Manager**
Fax number: 858 724-1844	**Fax number: 301-796-9883**
Phone number: 858 481-6863	**Phone number: (240) 402-9990**

Subject: BLA 761065

Total number of pages including cover:

Comments:

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Document to be mailed: ☐ YES ☑ NO

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Division of Antiviral Drug Products
Food and Drug Administration
Silver Spring, MD 20993

MEMORANDUM OF FACSIMILE CORRESPONDENCE

BLA: **761065**

Drug: **ibalizumab**

Date: **June 8, 2017**

To: **Helen Shu, Ph.D., Vice President, Regulatory Affairs and Quality**

From: **Christian Yoder, MPH, Regulatory Project Manager**

Subject: **BLA 761065 Information Request**

Please refer to your BLA 761065 and to the submission we received on May 3, 2017. Please see the following comments and respond no later than Friday, June 16, 2017:

1. We cannot locate the coding dictionary used for mapping investigator verbatim terms to preferred terms. Please submit your coding dictionary or provide the location for the coding dictionary within the submitted documents.

2. Please provide your rationale for assuming the applicability of foreign data to the U.S. population/practice of medicine. Please note the following manuscripts that describe differences in viral kinetics and epidemiology of HIV subtypes circulating in Taiwan (Huang SW et al. PLoS One. 2014 Dec 11; 9(12):ee114441. doi: 10.1371/journal.pone.0114441. eCollection 2014 and Chen Y et al. J Acquir Immune Defic Syndr. 2012 Apr 15;59(5):438-46. doi: 10.1097/QAI.0b013e3182454ea3).

3. Thank you for providing a clear explanation for how the Overall Susceptibility Scores (OSS) were calculated using GSS/PSS scores and other parameters (16.7 TMB-301 Clinical Virology Report, Appendix A). Please provide a similar detailed summary and references for the algorithms used to calculate the GSS and PSS scores.

4. We have reviewed the list of protocol deviations submitted for TMB-301 and need clarification regarding one deviation that has the potential to affect the primary efficacy endpoint of the trial. In SDTM dataset DV under subject 301-04-002, there is a protocol deviation "OBR Started 1 day early" (DVSEQ 3). The CM datasets, however, list the starting dates for the new components of the OBR as May 11, 2016 (Day 14) on the same day as the Day 14 HIV RNA sample was collected. Unless the starting dates in the CM datasets are incorrect or the OBR was started the same day *prior* to the collection of the sample (11:35AM), this does not appear to be a deviation from the protocol because the OBR is supposed to start on Day 14. Please provide clarification regarding this reported protocol deviation.

PLEASE REPLY BY EMAIL (christian.yoder@fda.hhs.gov) to confirm receipt. We are providing this above information via telephone facsimile for your convenience. Please feel free to contact me at 240-402-9990 or 301-796-1500 if you have any questions regarding the contents of this transmission.

Christian P. Yoder, MPH
Regulatory Project Manager
Division of Antiviral Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

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/s/

CHRISTIAN P YODER
06/08/2017

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Antimicrobial Products
Division of Antiviral Drug Products

FACSIMILE TRANSMITTAL SHEET

DATE: May 31, 2017

To: Dr. Helen Shu	**From: Christian Yoder, MPH**
Company: TaiMed Biologics	**Title: Regulatory Project Manager**
Fax number: 858 724-1844	**Fax number: 301-796-9883**
Phone number: 858 481-6863	**Phone number: (240) 402-9990**

Subject: BLA 761065

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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Division of Antiviral Drug Products
Food and Drug Administration
Silver Spring, MD 20993

MEMORANDUM OF FACSIMILE CORRESPONDENCE

BLA: **761065**

Drug: **ibalizumab**

Date: **May 31, 2017**

To: **Helen Shu, Ph.D., Vice President, Regulatory Affairs and Quality**

From: **Christian Yoder, MPH, Regulatory Project Manager**

Subject: **BLA 761065 Information Request**

Please refer to your BLA 761065 and to the submission we received on May 3, 2017. Please see the following comments from the Clinical Pharmacology reviewers and respond no later than Friday, June 16, 2017:

1. Submit PK datasets for Study TMB-301 (Phase 3) and Study TMB-202 (Phase 2b). Submit those datasets in CDISC SDTM and ADaM format, if available.

2. Submit PK datasets for Study Hu5A8.01 (Phase 1a), TNX-355.02 (Phase 1b), and TNX-355.03 (Phase 2a) in CDISC SDTM and ADaM format, if available.

3. In 2.7.2 (Summary of Clinical Pharmacology Studies), you mentioned different formulations were used for Phase 1/2 and Phase 3 (the commercial formulation) studies. Provide details for all the formulations and summarize the difference.

4. Population PK analysis:

   a) Reference is made to section 5.3.3.5, study report "Population Pharmacokinetic Modeling of TNX-355". Submit datasets, NONMEM control streams and output listings for population PK model of ibalizumab. Also, submit parameter estimates and diagnostic plots. Finally, please confirm whether the population PK analysis is being used to inform on relevant covariate effects on ibalizumab exposure. If such analyses have not been provided but have been performed, please provide these analyses.

- Datasets should be submitted as a SAS transport files (*.xpt). A description of each data item should be provided in a define.pdf file. Any data point and/or subjects that have been excluded from the analysis should be flagged and maintained in the datasets. The flag of exclusion should be clearly explained in the define.pdf file.
- NONMEM control streams and output listings should be submitted as ASCII text files with *.txt extension (e.g.: myfile_ctl.txt, myfile_out.txt).

b) The population PK analysis provided in the submission was based only on data from Study 355. Please confirm whether any additional population PK analyses have been performed that included data from TMB-202 and TMB-301. If such analyses have been conducted, provide the datasets, control streams, and output listings as described above.

c) Reference is made to section 5.3.3.5, study report "Population PK Study Reports". For those studies where NCA analyses were performed, please provide the input dataset and output population PK parameters.

d) No exposure-response analyses for efficacy or safety were provided with the submission. Can you please confirm whether such analyses are available? If so, we request you submit these analyses as described above the population PK analysis.

PLEASE REPLY BY EMAIL (christian.yoder@fda.hhs.gov) to confirm receipt. We are providing this above information via telephone facsimile for your convenience. Please feel free to contact me at 240-402-9990 or 301-796-1500 if you have any questions regarding the contents of this transmission.

Christian P. Yoder, MPH
Regulatory Project Manager
Division of Antiviral Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

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/s/

CHRISTIAN P YODER
05/31/2017

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

BLA 761065

INFORMATION REQUEST

TaiMed Biologics USA Corp.
Attention: Helen P. Shu, Ph.D.
VP Regulatory Affairs and Quality
425 San Lucas Drive
Solano Beach, CA 92075

Dear Dr. Shu:

Please refer to your Biologics License Application (BLA) dated May 3, 2017, received May 3, 2017, submitted under section 351(a) of the Public Health Service Act for ibalizumab injectable.

We are reviewing the CMC section of your submission and have the following comments and information requests. We request a prompt written response by June 16, 2017 in order to continue our evaluation of your BLA.

Your 351(a) BLA appears to be incomplete and does not contain all of the information necessary to support a substantive review of ibalizumab from a sterility assurance perspective. Refer to the FDA responses that were provided in the meeting minutes from the CMC Type B Teleconferences on September 4, 2015 and February 3, 2016 and to the 1994 Guidance for Industry for the Submission Documentation for Sterilization Process Validation in Applications for Human and Veterinary Drug Products. All translations of documents should be certified.

1. Section 3.2.P of the BLA does not contain validation data summaries and information, as requested, to support the manufacture of sterile ibalizumab. Update section 3.2.P.3.3 to include the following:

(b) (4)

[redacted]

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

(b) (4)

[redacted]

If you have any questions, please contact Anita Brown, Regulatory Business Process Manager, at (301)796-2066 or Anita.Brown@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Anita N. Brown
Regulatory Business Process Manager
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research

Anita
Brown

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Food and Drug Administration
Center for Drug Evaluation and Research
Office of Antimicrobial Products
Division of Antiviral Drug Products

FACSIMILE TRANSMITTAL SHEET

DATE: May 17, 2017

To: Dr. Helen Shu	**From: Christian Yoder, MPH**
Company: TaiMed Biologics	**Title: Regulatory Project Manager**
Fax number: 858 724-1844	**Fax number: 301-796-9883**
Phone number: 858 481-6863	**Phone number: (240) 402-9990**

Subject: BLA 761065

Total number of pages including cover:

Comments:

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Document to be mailed: ☐ YES ☑ NO

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Division of Antiviral Drug Products
Food and Drug Administration
Silver Spring, MD 20993

MEMORANDUM OF FACSIMILE CORRESPONDENCE

BLA: **761065**

Drug: **ibalizumab**

Date: **May 17, 2017**

To: **Helen Shu, Ph.D., Vice President, Regulatory Affairs and Quality**

From: **Christian Yoder, MPH, Regulatory Project Manager**

Subject: **BLA 761065 Information Request**

Please refer to your BLA 761065 and to the submission we received on May 3, 2017. Please see the following comment from the review team and respond no later than Friday, May 19, 2017:

1. For both TMB-301 and TMB-202, please let us know if any of the principal investigators listed in the enrolling sites are no longer at those sites and, if so, please provide contact information (address, phone number, and email) for the individuals who are now responsible for the study documents.

2. Please provide a complete list of TMB-301 enrolling sites that includes the site number, principal investigator name, the institution, the address, phone number, and email address. The document titled "TMB-301 Enrolling sites (n=19)" found in Module 5.3.5.4 under "TMB-301" then "List Description" is missing sites 3, 17, and 20.

PLEASE REPLY BY EMAIL (christian.yoder@fda.hhs.gov) to confirm receipt. We are providing this above information via telephone facsimile for your convenience. Please feel free to contact me at 240-402-9990 or 301-796-1500 if you have any questions regarding the contents of this transmission.

Christian P. Yoder, MPH
Regulatory Project Manager
Division of Antiviral Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

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/s/

CHRISTIAN P YODER
05/17/2017

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Antimicrobial Products
Division of Antiviral Drug Products

FACSIMILE TRANSMITTAL SHEET

DATE: May 5, 2017

To: Dr. Helen Shu	**From: Christian Yoder, MPH**
Company: TaiMed Biologics	**Title: Regulatory Project Manager**
Fax number: 858 724-1844	**Fax number: 301-796-9883**
Phone number: 858 481-6863	**Phone number: (240) 402-9990**

Subject: BLA 761065

Total number of pages including cover:

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Document to be mailed: ☐ YES ☑ NO

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Division of Antiviral Drug Products
Food and Drug Administration
Silver Spring, MD 20993

MEMORANDUM OF FACSIMILE CORRESPONDENCE

BLA: **761065**

Drug: **ibalizumab**

Date: **May 5, 2017**

To: **Helen Shu, Ph.D., Vice President, Regulatory Affairs and Quality**

From: **Christian Yoder, MPH, Regulatory Project Manager**

Subject: **BLA 761065 Information Request**

Please refer to your BLA 761065 and to the submission we received on May 3, 2017. Please see the following comment from the review team:

1. We have received your BLA submission and are in the process of our preliminary review. We have found that although you have submitted both SDTM and ADaM datasets for the TMB-202 trial, the data for your Phase 3 registration trial TMB-301 is in legacy format. As we discussed in the pre-BLA communications, legacy datasets will not be compatible with many of our review tools. Please note that during the pre-BLA meeting (see Meeting Minutes "Question 11" October 11, 2016), you agreed to submit CDISC-compliant data for TMB-301 and TMB-202 both as part of ISS and ISE as well as for the individual trials (later determined to be TMB-301 and TMB-202). In addition, in your communication dated January 23, 2017 related to the mock data sets which were SDTM compliant, you confirmed that you would be sending ADaM datasets with your BLA submission. In order to facilitate our review, please provide SDTM and ADaM datasets for TMB-301. Please confirm that you will be able to submit these datasets and provide a timeline by Tuesday, May 9, 2017, for doing so.

PLEASE REPLY BY EMAIL (christian.yoder@fda.hhs.gov) to confirm receipt. We are providing this above information via telephone facsimile for your convenience. Please feel free to contact me at 240-402-9990 or 301-796-1500 if you have any questions regarding the contents of this transmission.

Christian P. Yoder, MPH
Regulatory Project Manager
Division of Antiviral Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

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/s/

CHRISTIAN P YODER
05/05/2017

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

BLA 761065

BLA ACKNOWLEDGMENT

TaiMed Biologics USA Corp.
Attention: Helen P. Shu, Ph.D.
VP Regulatory Affairs and Quality
2 Executive Circle, Suite 280
Irvine, CA 92614

Dear Dr. Shu:

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: ibalizumab, injection, 200 mg/vial

Date of Application: May 3, 2017

Date of Receipt: May 3, 2017

Our Reference Number: BLA 761065

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 July 2, 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. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action. The content of labeling must conform to the content and format requirements of revised 21 CFR 201.56-57.

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

Title VIII of FDAAA amended the PHS Act by adding new section 402(j) [42 USC § 282(j)], which expanded the current database known as ClinicalTrials.gov to include mandatory registration and reporting of results for applicable clinical trials of human drugs (including biological products) and devices.

In addition to the registration and reporting requirements described above, FDAAA requires that, at the time of submission of an application under section 351 of the PHS Act, the application must be accompanied by a certification that all applicable requirements of 42 USC § 282(j) have been met. Where available, the certification must include the appropriate National Clinical Trial (NCT) numbers [42 USC § 282(j)(5)(B)].

You did not include such certification when you submitted this application. You may use Form FDA 3674, "Certification of Compliance, under 42 U.S.C. § 282(j)(5)(B), with Requirements of ClinicalTrials.gov Data Bank," [42 U.S.C. § 282(j)] to comply with the certification requirement. The form may be found at http://www.fda.gov/opacom/morechoices/fdaforms/default.html.

In completing Form FDA 3674, you should review 42 USC § 282(j) to determine whether the requirements of FDAAA apply to any clinical trial(s) referenced in this application. Please note that FDA published a guidance in January 2009, "Certifications To Accompany Drug, Biological Product, and Device Applications/Submissions: Compliance with Section 402(j) of The Public Health Service Act, Added By Title VIII of the Food and Drug Administration Amendments Act of 2007," that describes the Agency's current thinking regarding the types of applications and submissions that sponsors, industry, researchers, and investigators submit to the Agency and accompanying certifications. Additional information regarding the certification form is available at:
http://www.fda.gov/RegulatoryInformation/Legislation/FederalFoodDrugandCosmeticActFDCAct/SignificantAmendmentstotheFDCAct/FoodandDrugAdministrationAmendmentsActof2007/ucm095442.htm. Additional information regarding Title VIII of FDAAA is available at:
http://grants.nih.gov/grants/guide/notice-files/NOT-OD-08-014.html. Additional information for registering your clinical trials is available at the Protocol Registration System website
http://prsinfo.clinicaltrials.gov/.

When submitting the certification for this application, **do not** include the certification with other submissions to the application. Submit the certification within 30 days of the date of this letter. In the cover letter of the certification submission clearly identify that it pertains to **BLA 761065** submitted on May 3, 2017, and that it contains the FDA Form 3674 that was to accompany that application.

If you have already submitted the certification for this application, please disregard the above.

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 Antiviral 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 Christian Yoder, Regulatory Project Manager, at (240) 402-9990 or (301) 796-1500.

Sincerely,

{See appended electronic signature page}

Christian P. Yoder, MPH
Regulatory Project Manager
Division of Antiviral Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

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/s/

CHRISTIAN P YODER
05/04/2017

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

BLA 761065

INFORMATION REQUEST

TaiMed Biologics USA Corp.
Attention: Helen P. Shu, Ph.D.
VP Regulatory Affairs and Quality
425 San Lucas Drive
Solano Beach, CA 92075

Dear Dr. Shu:

Please refer to your Biologics License Application (BLA) dated July 15, 2016, received July 19, 2016, submitted under section 351(a) of the Public Health Service Act for ibalizumab injectable.

We are reviewing the CMC section of your submission and have the following comments and information requests. We request a prompt written response by March 9, 2017 in order to continue our evaluation of your BLA.

Please provide manufacturing schedule for activities representative of the ibalizumab drug product manufacturing process during the revised Lot6-Lot8 DS manufacturing dates.

If you have any questions, please contact Anita Brown, Regulatory Business Process Manager, at (301)796-2066 or Anita.Brown@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Anita N. Brown
Regulatory Business Process Manager
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research

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/s/

ANITA N BROWN
02/23/2017

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 9776

MEETING MINUTES

TaiMed Biologics USA
Attention: Helen P. Shu, Ph.D.
VP Regulatory Affairs and Quality
2 Executive Circle, Suite 280
Irvine, CA 92614

Dear Dr. Shu:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for IV ibalizumab, TNX, Hu5A8.

We also refer to the teleconference between representatives of your firm and the FDA on September 26, 2016. The purpose of the meeting was to discuss the clinical, clinical virology and toxicology content and format requirements for the BLA submission.

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 Christian Yoder, Regulatory Project Manager at (240) 402-9990 or (301) 796-1500.

Sincerely,

{See appended electronic signature page}

Christian P. Yoder, BSN, MPH
Regulatory Project Manager
Division of Antiviral Products
Office of Antimicrobial 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: September 26, 2016
Meeting Location: Teleconference

Application Number: IND 9776
Product Name: IV ibalizumab, TNX 355; Hu5A8
Indication: Treatment of HIV-1 infection
Sponsor/Applicant Name: TaiMed Biologics, Inc.
Meeting Chair: Adam Sherwat, MD
Meeting Recorder: Christian Yoder, BSN, MPH

FDA ATTENDEES:

OND/OAP
Edward Cox, MD, MPH, Director

OND/OAP/DAVP
Debra Birnkrant, MD, Director, Division of Antiviral Products
Jeffrey Murray, MD, MPH, Deputy Director
Adam Sherwat, MD, Medical Officer Team Lead
Regina Alivisatos, MD, Medical Officer
Virginia Sheikh, MD, Medical Officer
Patrick Harrington, PhD, Acting Clinical Microbiology Team Lead
Eric Donaldson, PhD, Clinical Microbiology Reviewer
Christopher Ellis, PhD, Pharmacology/Toxicology Team Lead
David McMillan, PhD, Pharmacology/Toxicology Reviewer
Karen Winestock, Chief, Project Management Staff
Christian P. Yoder, BSN, MPH, Regulatory Project Manager

OTS/OCP/DCP4
Mario Sampson, PhD, Acting Clinical Pharmacology Team Lead
Amal Ayyoub, PhD, Clinical Pharmacology Reviewer

DBRRIII/OBP/OPQ
Steven Bowen, PhD, Product Quality Reviewer
Ramesh Potla, PhD, Product Quality Team Lead

OTS/OB/DBIV
Thamban Valappil, PhD, Statistical Team Lead
Karen Qi, PhD, Statistician

OSE/OMEPRM
Valerie Wilson, PharmD, Safety Evaluator
Jamie Wilkins Parker, PharmD, Team Lead

SPONSOR ATTENDEES:

TAIMED
Jon Ho, BS, Director, Project Management
Stanley Lewis, MD, VP Clinical and Chief Medical Officer
Helen Shu, PhD, VP Regulatory Affairs and Quality
Steve Weinheimer, PhD, VP Biological Sciences

WESTAT
Christine Anderson, PhD, Project Director
Stephen Black, MS, Biostatistics Manager
Ken Gerald, PhD, Biostatistics Director
Jennifer Fulton, MS, Statistician
Tracy Wolbach, BA, Project Manager

TAIMED OBSERVERS
Brian Bell, BS, Manager, Clinical Services
Meng-Hsin Chen, PhD, VP Research and Development
Chen-Yu Wang, PhD, QC Senior Manager
Stacy Chan, MS, Scientist

THERATECHNOLOGIES OBSERVERS
Zvi Cohen, PhD, Senior Medical Advisor
Maria Perrotta, MA, Director, Regulatory Affairs, Quality and Compliance
Christian Marsolais, PhD, Senior Vice President and Chief Medical Officer

1.0 BACKGROUND

Ibalizumab is a humanized immunoglobulin (IgG) isotype 4 monoclonal antibody (MAb). It binds to a conformational epitope on domain 2 of CD4, inhibiting HIV entry into cells. TaiMed Biologics (TaiMed) has developed an intravenous formulation of ibalizumab to be administered in combination with other antiretroviral agents, for the treatment of HIV-1 infection in highly treatment-experienced adult patients with documented drug resistance to at least one agent from each of three approved classes of antiretroviral agents and evidence of HIV-1 replication despite ongoing antiretroviral therapy. A request for Breakthrough Therapy designation was granted February 23, 2015. A pre-BLA CMC meeting was held February 3, 2016 and a request for Rolling Review was granted July 19, 2016, and on the same date TaiMed submitted Module 3 to new BLA 761065. The main purpose of this Pre-BLA meeting is to discuss the remaining

components of the BLA application, with the final component currently proposed for submission in early 2017.

FDA sent Preliminary Comments to TaiMed Biologics on September 21, 2016.

2.0 DISCUSSION

Your meeting questions from your August 26, 2016 meeting package are in standard font, followed by our response in **bold** font. Meeting discussion comments are included in *italic font*.

2.1. Clinical/Biostatistics

Question 1: **2.1 Overall clinical format and contents of the BLA.** The annotated Table of Contents for the BLA Summaries (Module 2) and Clinical sections (Module 5) are provided in **ATTACHMENTS A** and **B**, respectively. The format follows the ICH guideline. The annotations describe the specific information for ibalizumab i.v. that would be provided. Is this acceptable for

a. Module 2?
b. Module 5?

FDA Response to Question 1a and 1b:

Yes, this is acceptable.

There was no meeting discussion.

Question 2: **2.2.1. ISE location.** The ISE will be provided in Module 5. The ISE in Module 5 would consist of the text, in-text Tables and Figures, and Appendices with supporting Tables and Figures. The text and in-text Tables and Figures from Module 5 would also be provided in the Module 2 Clinical Summary. Is this acceptable?

FDA Response to Question 2:

Yes, this is acceptable.

There was no meeting discussion.

Question 3a**: 2.2.2. ISE studies.** The description of all ibalizumab i.v. clinical studies is summarized in **Table 1**. The description of clinical studies for the ISE is shown in **Table 2**. TMB-301 is the registrational trial in HIV+ subjects with multidrug resistance where the single 2000 mg loading dose (monotherapy) is followed by 800 mg q 2 wks maintenance doses in combination with the optimized background antiretroviral regimens to Week 25. The primary efficacy endpoint is assessed after 7 days in the monotherapy phase (study Day 14). The durability of efficacy is assessed at Week 25 as a secondary endpoint.

TMB-202 is a supportive trial conducted in a similar patient population as TMB-301. TMB-202 patients are treated with either 800 mg q 2 wk or 2000 mg q 4 wk while on optimized background antiretroviral drug regimens for 24 weeks.

The proposed ISE statistical analysis would treat TMB-301 as the registrational trial with additional analysis of TMB-202 data as a supportive trial. The ISE for the 2000 mg loading dose would consist of the TMB-301 trial data (day 14 compared with baseline). The ISE for the 800 mg q 2 wk maintenance dose would consist of both the TMB-301 and TMB-202 data after 24 weeks on study drug. The statistical analysis plan to be submitted after the teleconference will describe the analyses in more detail. Is this acceptable?

FDA Response to Question 3a:

Yes, this is acceptable.

There was no meeting discussion.

Question 3b: The Snapshot Table on patient viral outcome for TMB-202 and the proposed Snapshot Table for TMB-301 are presented below (Tables 3 & 4). The Snapshot Table for TMB-301 has been adapted to the trial design for TMB-301. Is this acceptable?

FDA Response to Question 3b:

Yes, this is acceptable.

There was no meeting discussion.

Question 4: **2.2.3 ISE Tables, Listings and Graphs for TMB-301 and TMB-202.** The list of proposed ISE tables, listings and graphs is provided for TMB-301 and TMB-202 (Table 5). The final versions will be provided in the statistical analysis plan to be submitted after the teleconference. Is this acceptable?

FDA Response to Question 4:

Yes, this is acceptable.

There was no meeting discussion.

Question 5: **ISS Location.** The ISS will be provided in Module 5. The ISS in Module 5 would consist of the text, in-text Tables and Figures, and Appendices with supporting Tables and Figures. The text and in-text Tables and Figures would also be provided in Module 2 Clinical Summary. Is this acceptable?

FDA Response to Question 5:

Yes, this is acceptable.

There was no meeting discussion.

Question 6: **ISS Studies**. **Table 6** identifies the primary safety data sources used in the proposed integrated safety summary and enumerates the number of patients by clinical trial type (controlled vs uncontrolled), dose (single vs multiple), phase, and length of study participation (short vs long term).

The safety population (SAF) is defined as all patients who receive at least one partial dose of study drug. Patients will be analyzed according to the treatment they actually received. The SAF Population will be used for the integrated safety analyses.

The proposed grouping of studies for the ISS is presented in Table 6. Group 1, SAF, consists of all subjects who received at least a partial dose of ibalizumab i.v. Group 2 is the TMB-301 fixed dose groups for 2000 mg loading and 800 mg q 2 wk dose. Group 3 and 4 are the TMB-202 fixed dose groups for 2000 mg q 4 wk and 800 mg q 2 wk, respectively. Group 5 consists of TNX 355.03 patients administered long term doses by body weight at 15 mg/kg or 10 mg/kg. Group 6 consists of TNX 355.02 patients administered short term doses by body weight at 10 mg/kg, 6 mg/kg and 25 mg/kg. Group 7 consists of Hu5A8.011 patients administered single doses of 0.3, 1.0, 3.0, 10, 25 mg/kg. Group 8 consists of TMB-202 patients who continued to receive study drug for up to 7 years in an extension study under investigator sponsored INDs.

Safety analysis of patients in Groups 1 to 7 are described below. Safety analysis of Group 8 patients is discussed in **Section 2.4**.

Overall Safety Summary of Group 1

The clinical study reports (CSR) will be reviewed for Group 1 studies, consisting of the SAF patient population, defined as all patients who received a partial dose of i.v. ibalizumab. An overall safety summary of Group 1, the SAF patients, will be written as a narrative with reference to the appropriate clinical study reports (CSR). This summary is a comprehensive discussion of safety findings prioritized to cover the major safety issues and critical concerns. This summary will address the following topics:

- A discussion of the adequacy of exposure with regard to the size of the safety database and the duration of exposure.
- A safety issue problem list. This problem list will convey the key data about any safety issues. Each safety issue on the problem list will have the key adverse event and measurement data summarized, including references to the relevant CSR subsections.
- Safety concerns suggested by the safety database will be assessed for benefit to the patient vs. risk.
- A discussion of any information excluded from the safety review and reasons for exclusion.
- Overall conclusions about the safety of the drug:
    - Overall assessment of the adequacy of the available safety information;
    - The limitations of the available data, including analyses that would be important if the data existed;

- Comparison, to the extent possible, of the safety of the drug under review to the safety of other available drugs, and the basis for that comparison (direct comparative data versus inference);
- Whether a risk evaluation and mitigation strategy (REMS) is needed and why.

The overall incidence of Treatment Emergent Adverse Events (TEAEs) will be summarized for all patients in the SAF Population. The number and percentage of patients having the following will be tabulated:

- TEAE
- Serious TEAE
- TEAE leading to discontinuation
- TEAE with outcome of death
- TEAE related to study drug (definitely, probably, or possibly)
- Severe TEAE
- Class C TEAE per the Centers for Disease Control and Prevention (CDC) Classification System for HIV Infection

The overall incidence of TEAEs will also be summarized by System Organ Class (SOC), and by SOC and Preferred Term (PT) for each individual study and also pooled over the studies. The number and percentage of patients reporting an event, as well as the number of events reported by the patients will be tabulated. The incidence of serious TEAEs and TEAEs leading to study discontinuation (if any) will be summarized in the same manner. If there are multiple occurrences of the same TEAE within any SOC or PT for the same patient, only the first occurrence will be counted.

The incidence of TEAEs by severity/grade (mild, moderate, severe, or potentially life-threatening) and by relationship to study drug (unrelated, possibly related, probably related, and definitely related), and the incidence of SAEs by relationship to study drug, will also be summarized.

A summary (listing) of all AEs that resulted in death whether the death occurred during the studies or is known to have occurred subsequent to study completion will be provided. Narratives of patient deaths, serious adverse events, and other significant adverse events deemed to be of special interest will be summarized.

If the incidence for a specific adverse event differs substantially between the individual studies, this difference will be noted with any explanations that can be determined from individual patient reports or noted differences such as variation study populations or investigative sites.

All other AEs will be classified as non-TEAEs and identified in listings only. Serious TEAEs, TEAEs leading to study discontinuation, and TEAEs with an outcome of death will be presented in separate listings, as needed.

Summary statistics will be presented for laboratory measurements (hematology and chemistry) overall for all patients in the SAF Population.

Summary statistics for vital signs and weight will be presented overall for all patients in the SAF Population for all scheduled visits.

Physical examination abnormal findings at each scheduled visit will be summarized overall for all patients in the SAF Population. Is this acceptable?

FDA Response to Question 6:

a. **For the written ISS, in addition to the planned pooled analyses, please provide safety summaries for each of the individual trials (Phase 1 through Phase 3) with a focus on TMB-202 and TMB-301.**

Meeting Discussion: *TaiMed confirmed that the written ISS will include individual safety summaries for each of the trials.*

b. **Please provide safety narratives for all of the following events, regardless of causality that occurred in any clinical study under IND 9776: Deaths, SAEs, and Discontinuations due to AEs. We recommend that you use the narrative template which we have attached to this response or a similar template capturing the requested data.**

Meeting Discussion: *TaiMed agreed to provide the safety narratives in the requested populations and agreed to the use of a narrative format consistent with the example provided by the FDA.*

c. **Please provide mock ISS datasets in order for us to assure that the format will be compatible with our data review tools (e.g., JReview and JMP).**

Meeting Discussion: *TaiMed agreed to provide mock ISS datasets.*

d. **Please confirm that the ISS dataset will have flags for each trial to enable us to assess data from each trial separately.**

Meeting Discussion: *TaiMed confirmed that the ISS dataset will have flags for each trial.*

e. **Please confirm that the ISS dataset will have a treatment-emergent flag and please provide your rationale for defining treatment-emergent events taking into account the long half-life of the drug.**

Meeting Discussion: *TaiMed confirmed that the ISS dataset will include a treatment-emergent flag.*

Question 7a: **Safety Analysis of Groups 2-4**. Patients in Groups 2-4, comprised of TMB-301 and TMB-202 studies, share many similarities and will be analyzed together. The patient profiles, drug doses, dosing frequency, dosing duration and OBR are similar. The studies collected AE, vital sign, and medication data at 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, and 24 weeks after the Baseline visit and laboratory data at 2, 4, 8, 12, 16, 20, and 24 weeks after the Baseline visit.

Descriptive statistical analysis will be performed for demographics and physical characteristics, patient disposition, and study drug exposure. Safety and tolerability will be assessed by both clinical and laboratory examinations. Summary statistics will be presented for adverse events (AEs); hematology and chemistry; vital signs, changes from Baseline, and clinically significant findings; electrocardiograms (ECGs), changes from screening, and abnormal findings; abnormal physical examination findings; antibody results; and concomitant medications in the SAF Population. Clinical laboratory values outside the normal ranges will be flagged in patient data listings and by shift from Baseline plots. Non-numeric data will be presented in patient data listings, but will not be tabulated.

All prescriptions or over-the-counter medications continued at the start of the trial or started during the trial, and different from the study drug will be recorded. All of these medications will be coded, using WHO Drug Dictionary (March 2014). Both the coded terms and verbatim terms will be presented in data listings for:

- Concomitant procedures
- Previous and Concomitant medications
- OBR medications (antiretroviral drugs taken during the clinical study)
- ART medications (any antiretroviral drug ever taken)

FDA Response to Question 7a:

The Sponsor's proposal to provide exploratory pooled safety analyses of TMB 202 and TMB 301 in the ISS written summary is acceptable. However, due to differences in dosing in TMB 301 and the two arms of TMB 202, the primary safety analyses for TMC301 and TMB 202 should be performed and presented separately in the ISS written summary (i.e., the focus of the written ISS should be the assessment of safety in the individual clinical trials, not the pooled assessment).

Meeting Discussion: *TaiMed agreed to present the safety analyses separately for each study as well as in the planned pooled analysis.*

Question 7b. Summary statistics for the development of anti-drug antibodies (ADAs) will be performed. Is this acceptable?

FDA Response to Question 7b: The proposal to include summary statistics for the development of anti-drug antibodies in patients from studies TMB-301 and TMB-202 is acceptable. Due to the differences in ibalizumab dose and treatment schedule, the data from TMB-301 (group 2) and each arm of TMB 202 (groups 3 and 4) should be analyzed and presented separately in the integrated safety summary.

Meeting Discussion: *TaiMed agreed that this is acceptable.*

Question 7c. Assay validation reports for TMB-202 and TMB-301 assays for Pharmacokinetics, will be summarized and provided. Is this acceptable?

FDA Response to Question 7c:

Yes, this is acceptable.

There was no meeting discussion.

Question 7d. Assay validation reports for TMB-202 and TMB-301 assays for immunogenicity and antidrug antibodies will be summarized and provided. Is this acceptable?

FDA Response to Question 7d:

Your proposal to summarize and provide the validation reports for the anti-drug antibody (ADA) assays used to test clinical samples from TMB 202 and TMB 301 is acceptable. In the BLA submission include full validation reports for the ADA assays in section 5.3.1.4 of the eCTD Module 5. In addition, provide in the BLA an integrated immunogenicity summary report in Section 5.3.5.3 Reports of Analyses of Data from More than One Study.

This report should:

a. **Describe your multi-disciplinary immunogenicity risk assessment process and your immunogenicity testing strategy.**
b. **Summarize your bioanalytical methods for measuring anti-ibalizumab binding and neutralizing antibodies.**
c. **Summarize the immunogenicity results for each clinical study, and include information on lots of drug product used.**
d. **Evaluate the impact of anti-drug antibodies on PK, efficacy, and safety.**
e. **Provide a post-marketing plan to link adverse events to immunogenicity, if appropriate.**
f. **Provide the immunogenicity dataset for each study as a SAS transport file.**

Meeting Discussion: *TaiMed agreed to submit the Integrated Immunogenicity Summary as described in the Agency response. TaiMed requested clarification of part e. of the FDA written response to Question 7d.: "Provide a post-marketing plan to link adverse events to immunogenicity, if appropriate". The Agency stated that the Integrated Immunogenicity Summary should include an analysis of any correlation between ADA and adverse events, PK, or efficacy (as noted in part d. of the FDA written response). Regarding part e., if the presence of ADA is linked to any adverse events the Sponsor should also provide in the Integrated Immunogenicity Summary a post-marketing plan to monitor the connection between immunogenicity and adverse events in patients receiving ibalizumab.*

Question 7e: **Safety Analysis of Groups 2-4**. The incidence of ibalizumab immunogenicity is low (~5%) and has not been associated with any adverse events or negative effects on efficacy (i.e., outcomes, viral load response, PK). A more drug-tolerant assay for detecting ADA was developed and validated and submitted to the agency for review (S-297) for use in TMB-301.

TMB is also developing an assay to delineate neutralizing ADAs in TMB-301 samples; this work is still on-going. TMB-301 samples would be tested only if they have a confirmed, drug-specific positive signal in the ADA assay – this number should be very small, possibly zero.

The anticipated timeline for final validation of this assay and testing of the TMB-301 samples is close to the time of the BLA submission. Is this acceptable?

FDA Response to Question 7e:

The FDA does not object to your proposal to submit the neutralizing antibody assay validation report and the results of clinical testing with the original BLA submission. However, we strongly recommend that you submit the complete validation report for the neutralizing antibody assay for our review prior to the testing of clinical samples from TMB-202 and TMB-301.

Meeting Discussion*: TaiMed asked if it would be acceptable to submit data for neutralizing antibodies within the 30 day window of submitting the BLA. The Agency strongly recommended that TaiMed submit the assay validation report before the clinical samples are tested and that the results of clinical testing be included at the time of BLA submission. TaiMed was not sure if it would be possible to provide the validation report ahead of the BLA submission or before the testing of clinical samples. TaiMed will provide a response after consulting with the CRO responsible for the immunogenicity assay development and testing. The Agency clarified that results of binding and neutralizing antibody testing should be submitted for study TMB-202 as well as study TMB-301. TaiMed indicated that this was acceptable.*

Question 8: **Safety Analysis of Groups 5, 6, and 7.** Any safety effect of dosing by body weight in Group 5 and 6 will be compared with Groups 2-4 that received fixed doses. Any safety effect of long term dosing by body weight in Group 5 vs. short term dosing in Group 6 will be assessed. Any safety effect of single doses in Group 7 will be compared with multi-doses in Group 6. Is this acceptable?

FDA Response to Question 8:

Yes, this is acceptable.

There was no meeting discussion.

Question 9: **2.3.3 ISS Tables, Listings and Graphs for TMB-301 and TMB-202.** The list of proposed ISS tables, listings and graphs is provided for TMB-301 and 202 (Table 7). Is this acceptable?

FDA Response to Question 9:

Yes, this is acceptable.

There was no meeting discussion.

Question 10(a and b): **2.4. Proposal for Extension Studies (Group 8) As Supplemental Long Term ISS Data.** U.S. patients from TMB-301 and 202 continued to receive study drug, if they met eligibility requirements, in uncontrolled extension studies. TMB-202 patients who continued to receive drug have accumulated about 7 years of drug experience data from 2009 to 2015

beyond the original 24 week study. For TMB-202 patients, the extension period occurred under physician sponsored INDS. In early 2016, for both the TMB-202 and TMB-301 patients, the patients started to roll over into TMB-311 Cohort 1 and this is on-going. TMB-311 Cohort 2 accepted eligible patients who were not previously enrolled in TMB-301 or TMB-202. The data from the TMB-202 and TMB-301 patients under TMB-311 are relatively sparse, as TMB-311 duration is still short and relatively few patients have enrolled in TMB-311. For the ISS, we propose to apply a data cut off of at the end of 2015 for analysis of the long term safety data from the TMB- 02 uncontrolled study under physician sponsored INDs. We propose to analyze the available data, between 2009 and 2015 on former TMB-202 patients, to supplement the ISS data in Module 5. For patients enrolled in TMB-311, we propose to continue to track these patients under the IND until the time of drug approval. The safety data from TMB-311 would be provided 120 days after the BLA submission date. The proposal is described in greater detail below.

Question 10a: **2.4.1 TMB-311 extension data**. For patients enrolled in TMB-311, a date for data cut off would be established. The safety data from the TMB-311 patients will be summarized as is typically done for an IND Annual Report and submitted 120 days after the BLA submission. Is this acceptable?

FDA Response to Question 10a:

No, this is not acceptable. All available safety data from TMB-311 should be submitted at the time of the BLA submission. Updates to the safety data from TMB-311 should be submitted as a component of the Safety Update Report.

Because a priority review may be granted, please plan to provide the Safety Update Report two months after the final component of your BLA submission with an appropriate data cut-date to meet this request.

Meeting Discussion: *With regard to study TMB-311, TaiMed asked if it would be acceptable to submit only SAEs rather than a complete safety analysis at the time of application in March, and then submit a full analysis within 2 months after submission. The Division stated that submission of safety data limited to SAEs would not be acceptable. The Division further stated that TaiMed should designate an appropriate data cut date so that a full safety summary could be submitted with the application with any final updates made 2 months later in the Safety Update Report. TaiMed noted there are few subjects enrolled and wondered if all grades of AEs need to be included. The Division responded that there could be a focus on high level safety events (SAEs, discontinuations due to AEs, deaths, other Grade 3-4 events) but that an overall safety summary including the frequency of common events, etc. irrespective of grade should also be provided. The Division stressed the importance of TaiMed providing an electronic dataset for TMB-311 for our review in the original submission as this would allow us to perform a full safety analysis of the trial.*

The Sponsor agreed to provide the Safety Update Report two months after the last component of the original BLA is submitted.

Question 10b: **2.4.2 TMB-202 extension safety data**. Patients who completed week 24 in TMB-202, provided they met entry criteria, were permitted to continue on ibalizumab i.v. treatment under investigator sponsored INDs from 2009 to early 2016. Annually since 2009, the Investigators provided viral load and safety data for the patients to TaiMed for inclusion in the TaiMed IND Annual Reports. Although these data are unmonitored by TaiMed and self-reported by the sites, they represent the long term use of ibalizumab i.v. under real life conditions. We propose to provide such data from 2009 to the end of 2015 in a separate section of BLA Module 5 as supplemental uncontrolled long term ISS data.

Table 8 summarizes the TMB-202 patients who received drug in an extension setting starting in 2009 and tracks their enrollment status through 2015. The numbers enrolled in 2009 in the 800 mg q 2 wk and 2000 mg q 4 wk are defined as baseline. The Table also summarizes the numbers (%) of patients with SAEs the sites reported to TaiMed each year for the Annual Report.

Descriptive statistical safety analysis would be performed for the patients in the TMB-202 uncontrolled extension study and compared with the data in the controlled TMB-202 study. Is this acceptable?

FDA Response to Question 10b:

Yes, this is acceptable.

There was no meeting discussion.

Question 11: **2.5.1 CDISC compliance.** The TMB-301 clinical study report will be CDISC compliant. TMB-301 and TMB-202 datasets will be CDISC compliant for the ISS and ISE. Is this acceptable?

FDA Response to Question 11:

We appreciate that the datasets for study TMB-301 and TMB-202 will be CDISC compliant for ISS and ISE.

a. **Please provide mock ISS datasets in order for us to assure that the format will be compatible with our data review tools (e.g., JReview and JMP).**
b. **Please confirm that the ISS dataset will have flags for each trial to enable us to assess data from each trial separately.**
c. **Please confirm that the ISS dataset will have a treatment-emergent flag and please provide your rationale for defining treatment-emergent events taking into account the long half-life of the drug.**
d. **In addition to the ISS dataset, please provide individual datasets for all other clinical trials (we understand that only the datasets for TMB-301 and TMB-202 will be CDISC compliant).**

Meeting Discussion: *TaiMed asked if incomplete data for TMB-301 would be acceptable for use as a mock ISS dataset and the Division agreed that this would be acceptable. TaiMed further confirmed that they would provide this mock dataset as SAS Transport Files. Taimed asked if they should submit a Define file and the Division confirmed that they should.*

TaiMed clarified that they were not planning on providing electronic datasets from studies other than TMB-202 and TMB-301. They explained that Genentech bought Tanox and Genentech still has the raw data for the early nonclinical and phase 1-2a studies. The sponsor has not yet determined what data, likely in paper format, exists and can be obtained for conversion to electronic format for the submission. The Division strongly emphasized the importance of submitting complete clinical study reports and electronic datasets for all clinical trials including TMB-311, TMB-301, TMB-202, TNX-355.03, TNX-355.02, and Hu5A8.011 with the original BLA submission. TaiMed agreed to actively pursue obtaining the data from Genentech for the non-clinical studies and clinical trials and will provide an update to the Division on their progress in the next few weeks.

Question 12: **2.5.2 Bookmarking and hyperlinks.** For non-clinical study reports, discussions that refer to the studies will be hyperlinked to the reports. For clinical studies, other than TMB-301 and TMB-202, where data are discussed, they will be hyperlinked to the pdf of the relevant clinical study report. Is this acceptable?

FDA Response to Question 12:

Yes, this is acceptable.

There was no meeting discussion.

Question 13: **2.5.3 ADEFFOUT.** Per Agency request of June 6, 2016, mock efficacy datasets in the ADEFFOUT format are provided. Samples of a TMB-301 and TMB-202 dataset for efficacy and related covariates in the ADEFFOUT format are presented in **ATTACHMENT E**. The format has been adapted to the TMB-301 and 202 study designs. Is this acceptable?

FDA Response to Question 13:

The proposed ADEFFOUT.XPT for integrated Studies TMB-202 and TMB-301 is acceptable. Please submit ADEFFOUT.XPT for the individual study TMB-301 as well. TMB-301 is a single arm study with subjects serving as their own controls. Your SAP submitted in SDN264 on September 29, 2015 proposed that "McNemar's statistical test will be used to make a paired comparison between the proportion of patients achieving a ≥ 0.5 $\log_{10}$ decrease from Day 0 in viral load at Day 7 and the proportion of patients achieving a ≥ 0.5 $\log_{10}$ decrease from Day 7 in viral load at Day 14" in the primary efficacy analysis. Therefore, please include a variable to indicate whether a subject achieved a ≥ 0.5 $\log_{10}$ decrease from Day 0 in viral load at Day 7 in ADEFFOUT.XPT for TMB-301 in order to perform the proposed analysis.

Meeting Discussion*: The Division reiterated that in addition to ADEFFOUT.XPT for the integrated Studies TMB-202 and TMB-301, ADEFFOUT.XPT should also be provided for the individual Study TMB-301 and it should include a variable to indicate whether a subject achieve a ≥ 0.5 log10 decrease from Day 0 in viral load at Day 7 in order to perform the proposed analysis.*

Question 14: **2.6** (b) (4)

The proposed indication for the ibalizumab i.v. program is currently:

(b) (4)

Is this acceptable?

FDA Response to Question 14:

The specific indication language in product labeling will be a review issue. However, the Division does not agree that (b) (4)

Meeting Discussion: *TaiMed restated their proposal to revise the indication to include* (b) (4)

As previously elaborated in our initial response, the Division responded that the specific labeling language will be a review issue but that we do not agree that (b) (4)

(b) (4)

Question 15: (submitted as an attachment to update the pre-BLA backgrounder). Request to modify the definition of the transition period from TMB 301 to TMB 311.

The current TMB 301 protocol includes a Week 25/End of Study (EOS) visit and a Week 29 Follow-Up visit. Study patients may elect to transition into the expanded access protocol, TMB 311. If patients elect to continue ibalizumab treatment in TMB 311, the transition occurs at Week 25 to avoid interruption of study drug. We are requesting permission to declare Week 25 as the end of TMB 301. Any patient completing the Week 25/End of Study visit would be considered a 'completer'. Apart from routine safety assessments, the Anti-Drug Antibody (ADA) sample due for collection at Week 29 would be obtained at Week 25/EOS along with other EOS laboratory assessments.

The rationale for this modification to the protocol is practical. TaiMed has now determined that all patients currently enrolled in TMB 301 plan to transition to the TMB 311 expanded access protocol. The Week 29 Follow-Up visit was included in the TMB 301 protocol to obtain post treatment follow-up safety assessments including any new or ongoing adverse events after the final administration of study drug at Week 23 for patients choosing to discontinue. Additionally, Week 29 procedures included a single laboratory assessment for immunogenicity testing. This immunogenicity testing was to be conducted in the absence of study drug (i.e. drug-free washout period).

However, since remaining patients have elected to continue into the TMB-311 protocol, patients will not have an interruption in study drug. Therefore, there will not be a drug-free washout period. The safety assessments per TMB 311 are identical to those performed in TMB-301 with the exception of the aforementioned ADA assessment. With no patients planning to discontinue study drug at the conclusion of TMB 301, the Week 29 visit is unnecessary as it will not provide any information not otherwise obtainable at Week 25/EOS. TaiMed considers this modification an administrative change as it does not affect patient dosing, patient care or the analysis of safety or efficacy data. Is this acceptable?

FDA Response to Question 15:

It is acceptable to use the Week 25 visit as the EOS visit for TMB-301 and forego the Week 29 follow-up visit for subjects who have elected to enroll in TMB-311. However, if a subject misses the Week 25 visit, they should be re-scheduled to be seen as soon as possible in order to complete their EOS visit under TMB- 301 (not TMB -311). Any subjects who will not be enrolled in TMB-311 should return for the Week 29 follow-up visit.

Meeting Discussion: *TaiMed confirmed that this change would be made as outlined.*

2.2 Clinical Virology

Question 16: **3.1 Proposal for the integrated analysis of clinical virology data.** Clinical virology data will be presented in the individual study reports. In addition, the integrated clinical virology data from TMB-202 and TMB-301 will be summarized in Module 5.

The Bristol Myers Squibb investigational drug (068) is permitted per TMB-301 protocol as an OBR. TaiMed has no data concerning the safety or effectiveness of this drug. The BLA will not include any discussion of this drug. Is this acceptable?

FDA Response to Question 16:

Clinical Virology: Any additional resistance data generated for BMS-068 should be described in detail. Please include in the virology summary a detailed description of how gp120 substitutions and/or other changes (insertions/deletions) were linked to BMS-068 versus ibalizumab.

Providing clinical virology data in individual study reports and an integrated report on TMB-202 and TMB-301 in Module 5 (5.3.5.4 Other Study Reports) is acceptable. In addition, a virology summary should be provided in Module 2 (2.7.2.4 Special Studies).

Meeting Discussion: *The sponsor stated that they will do some analyses with the genotypic resistance data to determine if BMS-068 resistance-associated substitutions can be identified.*

Clinical: Please conduct additional safety analyses for Study TMB-301 to compare the safety of the population of patients receiving BMS-068 (as part of optimized therapy) versus the population of patients who did not receive BMS-068 and summarize the results of these analyses in the CSR for Study TMB-301 and in the written ISS.

In the dataset for Study TMB-301 and in the ISS dataset, please include an individual flag for each investigational drug used in the study, including BMS-068. This will allow the Agency to conduct similar, confirmatory analyses as those requested above.

Meeting Discussion: *The Sponsor agreed to include the requested flags and to perform the additional safety analyses as requested.*

Question 17: **3.1.1 Location.** The integrated data in Module 5 would consist of the text, in-text Tables and Figures, and Appendices with supporting Tables and Figures. The text and in-text Tables and Figures would also be provided in Module 2 Clinical Summary. Is this acceptable?

FDA Response to Question 17:

Yes, the integrated data set in Module 5 and the summaries of figures and tables in Module 2 would be acceptable.

There was no meeting discussion.

Question 18: **3.1.2 Studies.** The TMB-301 Clinical Virology Report will have the same format and subject content as the TMB-202 Clinical Virology Report (submitted as S-277). The integrated clinical virology data from TMB-202 and TMB-301 will be discussed.

The TMB-301 Clinical Virology Report will comport with FDA instructions for the submission of resistance data sets and sequence data. Samples from all patients in TMB-301 who experienced virologic failure or viral load rebound will be analyzed. Paired samples from N=11 patients who fit this description are currently being analyzed. It is possible that an additional 1-4 patients could rebound or experience virologic failure before the completion of TMB-301.

Phenotypic and genotypic analyses to date, including analysis of paired patient samples from TMB-202 and paired envelope clones from the Phase 1b study, have revealed no evidence or reason to suspect that ibalizumab resistance has any cross resistance implications for other approved anti-HIV drugs, including the approved entry inhibitors enfuvirtide and maraviroc. Unlike the situation that is commonly observed for drugs that bind to conserved targets in HIV for which consistent trends with common amino acid substitutions can be identified (i.e. RT, protease, integrase, and gp41), the gp120 primary amino acid sequence contains several hypervariable regions, including the V5 loop. The results for paired baseline and virologic failure samples from 17 patients on TMB-202 revealed no consistent amino acid substitutions associated with reduced ibalizumab susceptibility, similar to findings from the analysis of 96 cloned envelopes from Phase 1b. A consistent theme has been that changes in the hypervariable regions of HIV gp120, and particularly in the V5 loop, affect the number and location of potential N-linked glycosylation sites (PNGSs). A PNGS is identified by the presence of a canonical, three amino acid sequence element: Asn-Xxx-Ser/Thr (where Asn = asparagine, Xxx = any amino acid other than proline, and Ser = serine /Thr = threonine). Amino acid changes that result in the loss of a PNGS include the replacement of asparagine at the position 1 with any amino acid, the insertion of proline at position 2, the substitution of any amino acid that is not serine or threonine at position 3, and any insertion or deletion that disrupts the three amino acid PNGS sequence element. Because changes associated with ibalizumab treatment failure occur primarily in hypervariable regions of gp120, particularly in V5, and because a wide variety of amino acid substitutions at multiple amino acid positions can be associated with the loss of PNGSs, mutational patterns in these regions are not consistent and no common amino acid substitutions have been identified or would be expected.

The testing for 11 or more patients from TMB-301 along with the previously reported results from TMB-202 will create a data set for 28 or more patients with extensive ARV resistance and MDR. If the results from TMB-301 are consistent with previous results showing that a wide variety of substitutions in gp120 hypervariable regions, and particularly in V5, are associated with ibalizumab resistance and that common amino acid substitution are not identified, then TMB suggests that additional testing of samples from TMB-202 is very unlikely to produce different results. If the results from TMB-301 unexpectedly demonstrate a consistent genotypic trend in ibalizumab resistant HIV and point to the identification of common amino acid substitutions, then this would suggest that the current cohort of TMB-301 patients may be different. In this case, TMB proposes to discuss the data with the Agency on next steps. Is this acceptable?

FDA Response to Question 18:

We note that ibalizumab resistance testing to date has not identified any cross resistance implications for other approved anti-HIV-1 drugs, including the approved gp41 fusion inhibitor enfuvirtide and the CCR5 co-receptor antagonist maraviroc, as resistance to ibalizumab results in a wide variety of substitutions in the gp120 hypervariable regions, and particularly in V5. We agree that if the results from TMB-301 unexpectedly demonstrate a consistent genotypic trend in ibalizumab-resistant HIV and point to the identification of common amino acid substitutions that the FDA and the sponsor should discuss the data on next steps.

There was no meeting discussion.

Question 19: **3.1.3 Format.** The TMB-301 Clinical Virology Report will have the same format and subject content as the clinical virology report written for TMB-202. TaiMed will work with (b) (4) to resolve the formatting issues with NGS that occurred with TMB-202 results presented in Appendices E and F in S 277.

In addition to data Tables, the data format would also consist of individual patient viral load plots for patients who received monotherapy in TMB-301 2000 mg loading dose and 800 mg q 2wk maintenance dose. Is this acceptable?

FDA Response to Question 19:

Yes, this approach is acceptable. We have received and reviewed the modified Appendices E and F (received as SN 320) and these now contain the appropriate level of detail describing the NGS protocol and NGS analysis pipeline (Appendix E) and the correct information for the NGS frequency table (Appendix F) for review of NGS data.

There was no meeting discussion.

Question 20: **3.3.1 Question on Monogram's testing methods, Appendix E and F submitted in S 277.** *For the TMB-202 Clinical Virology Report, supporting documentation for NGS submission (Appendix E: Next generation sequencing (NGS) experimental methods and Appendix F: TMB-202 V5 NGS data table) were insufficient for review purposes.*

The CRO that conducted this work, (b) (4), is well informed of the expectations specified in the NGS template for review purposes and TaiMed Biologics has a standing request with them to correct these deficiencies. The response time has been slow but the CRO has expressed an interest in meeting the FDA requirements. TaiMed Biologics anticipates resubmitting the two appendices for the TMB-202 data with corrective revisions in the near term, hopefully before the pre-BLA teleconference scheduled for September 26, 2016. Is this acceptable?

FDA Response to Question 20:

Yes, we have received the revised *Appendix E: Next generation sequencing (NGS) experimental methods and Appendix F: TMB-202 V5 NGS data table*. These formats are acceptable for review (see the answer to the previous question). We note that the sponsor has previously agreed to submit NGS sequences in fastq format in addition to the frequency tables and NGS protocol information for each study. In addition, it is not clear how the PNGSs associated with resistance to ibalizumab will be defined or at what cutoff by NGS analysis a motif would be considered to be lost. Detailed information regarding the frequency cutoffs used for defining important motifs or amino acid changes will be necessary for review of NGS data submitted in the NDA.

Meeting Discussion: *TaiMed acknowledged receipt of additional NGS data from* (b) (4) *that could potentially address which sequences are present pre- and post-treatment. They asked the Agency to provide a frequency cut-off. The FDA requested that Taimed submit raw next generation sequencing datasets with no cut-off and summary NGS data using a 15% cut-off. The FDA confirmed receipt of the previous NGS data from* (b) (4) *that contained the raw fastq files, a frequency table, and a comprehensive outline of their sequencing protocol and NGS analysis pipeline and noted that it looked acceptable. Taimed agreed to provide the NGS data from 301 and 311 using the fastq format.*

Question 21: **3.3.2 Polymorphism.** *Please determine the frequency of polymorphisms occurring at positions L96, P121, P122 and Q163 in domain 2 E77 and S79 in domain 1 using a comprehensive database of HIV envelope protein sequences (sic).*

The FDA comment refers to CD4 amino acid positions previously identified as contact sites for ibalizumab, i.e. the ibalizumab epitope. Polymorphisms at these positions using comprehensive databases of CD4 sequences (not HIV envelope protein sequences) has been reported previously (S-269, Attachment B). The relevant information from S-269 is reproduced in **ATTACHMENT G**. Is the information provided acceptable?

FDA Response to Question 21:

We note that this information was received and reviewed under SN 269. The sponsor used public database searches to identify the presence of genetic polymorphisms within the coding region of the CD4 molecule, and reported several low frequency polymorphisms that were proximal to or occurred within one of the three major binding contact sites in domain 2 of CD4. Of particular interest are substitutions Q165R and K166E, which are proximal to or within the FG loop and are present in the African American population at 0.045% and 1.9%, respectively; and G123D, which alters a charge in the BC loop and is present in the African American population at 0.038%.This item has been adequately addressed by the sponsor.

In addition, we note that a database survey was conducted by the sponsor (submitted under SN 269) to determine the frequency and location of potential N-linked glycosylation sites (PNGS) in the V5 loop of HIV-1 envelope sequences for predominant circulating HIV-1 clades, or subtypes. The predominant HIV-1 subtype in the US is subtype B (>96% in 2011)

followed by subtype C (1.12% in 2011) and then subtype A (0.61% in 2011) (Pyne et al., 2013). Based upon the sponsor's analyses, 18.4% of circulating HIV-1 subtype B would potentially be less susceptible to ibalizumab, 31.1% for HIV-1 subtype C, and 6.8% for HIV-1 subtype A based on V5 sequences associated with high ibalizumab MPI, including loss or alteration of PNGS.

***Meeting Discussion*:** *Taimed stated that the clade by clade analysis of susceptibility to ibalizumab was incorrectly stated. For example, they noted that the prevalence of circulating HIV-1 subtype B viruses that would potentially be less susceptible to ibalizumab would range from 2-16% instead of the 18.4% that was noted in the response, and was calculated using their data table. Taimed also stated that the clade by clade analysis was performed using a public database that may have viruses that have been adapted in cell culture and they believe the results do not reflect the true prevalence of viruses that are less susceptible to ibalizumab. They stated that clinical isolates and information from the clinical trials should be used to determine a more accurate picture. In response, the FDA agreed that clinical isolates and information from their development program would be more appropriate for determining the prevalence of HIV-1 viruses that are not susceptible to ibalizumab, and agreed that the public database was not likely to be a highly accurate predictor of strains that would be less susceptible to ibalizumab.*

Question 22: **3.3.3 Viral resistance data from Phase 1a, 1b and 2a studies.** TaiMed responses to reviewer comments from the Type B meeting dated Dec. 3 2015 is presented in A**TTACHMENT H** and the accompanying **Appendices A**, **B**, **C** and **D**. Is the information provided acceptable?

FDA Response to Question 22:

Attachment H was reviewed and the data submitted in the appendices was sufficient for review purposes. However, an assessment of the data provided in the four appendices will be conducted and a review written and archived at a future date, as this will take more time than is permitted for the review of a meeting background package.

There was no meeting discussion.

2.4 Pharmacology/Toxicology

Question 23: The annotated Tables of Contents for the Summaries (Module 2) and non-clinical section (Module 4) are provided in **ATTACHMENTS B** and **C** respectively. The format follows the ICH guideline. The annotations show the specific information for ibalizumab i.v. that would be provided. Is this acceptable?

FDA Response to Question 23:

The proposed content and formatting generally appears acceptable. Please submit all available nonclinical data referenced in your Investigator's Brochure, including the in vitro/ex vivo studies in T cells and PBMCs. Please also confirm your intent to submit this data and indicate where and in what form these studies will be included in your application.

Meeting Discussion: *TaiMed stated they have in vitro/ex vivo study data in T cells and PMBCs and that they will put these data into report form before submission.*

Additional FDA Comments

Regulatory

1. **We note that you have revised your rolling review schedule and it now appears that your final BLA submission will arrive in March 2017. Please confirm that Modules 1, 2, 4, 5 and Module 3's stability updates for lots 2, 3, 4 and 5 will be submitted in a single submission.**

   Meeting Discussion: *TaiMed asked if it is acceptable to submit a stability update with the application in March and then all the stability data within 30 days of the application. The Division informed TaiMed that all of the stability data up to the shelf life of the product must be included in the final BLA submission and that only minor changes can be made after the BLA is submitted. Taimed will need to determine how much stability data will be available when the final BLA component is submitted to the Agency.*

2. **We have reviewed your table of contents (TOC) for module 1 and it is incomplete. The following documents are missing from your TOC and need to be included in your final submission:**
   a. **FDA Form 356h**
   b. **FDA Form 3674**
   c. **Labeling in structured product labeling (SPL) format as described at** ***http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm*****. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action. The content of labeling must conform to the content and format requirements of revised 21 CFR 201.56-57.**

   In addition, the content and format of the TOC for module 1 submitted in the briefing package does not match the the TOC for an eCTD submission. Please refer to ***http://www.fda.gov/downloads/drugs/developmentapprovalprocess/formssubmissionrequirements/electronicsubmissions/ucm163175.pdf*** **for additional information.**

   Meeting Discussion: *TaiMed agreed to include the forms and labeling in the application.*

Clinical

3. **Please submit financial disclosure information consistent with the February 2013 Financial Disclosure Guidance. We request that you specifically provide the following information:**
   a. **Total number of investigators (primary and sub-investigators) for TMB-202 and TMB-301**

b. **For the investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study:**
   i. **Significant payments of other sorts**
   ii. **Proprietary interest in the product tested held by investigator**
   iii. **Significant equity interest held by investigator in sponsor of covered study**
   iv. **If applicable, please provide a description of the steps taken to minimize potential bias.**

Meeting Discussion: *TaiMed agreed to include all financial disclosure information.*

4. **Please submit the following information for each clinical site used in TMB-202 and TMB-301:**
   a. **Number of patients screened**
   b. **Number of patients enrolled**
   c. **Number of protocol violations**
   d. **Brief description of each protocol violation.**

Meeting Discussion: *TaiMed agreed to provide the clinical site information*

Clinical Virology

5. **To help facilitate labeling discussions, please include complete study reports in electronic file format for the following items in the BLA submission:**
   a. **Mechanism of action studies**
   b. **Antiviral activity studies**

Meeting Discussion: *TaiMed acknowledged that the early data are not in report format but that they will make a focused effort to retrieve the data and put it into report format.*

Product Quality

6. **The table of proposed BLA amendments in your cover letter dated July 15, 2016 includes the following items that have not yet been received:**
   a. **Cell bank genetic stability-Southern blot analysis, estimated for August, 2016.**
   b. **Forced Degradation study-Addendum with additional characterization data, estimated for August, 2016.**
   c. **Reduced and non-reduced CE SDS Method Validation Report, estimated for September, 2016.**

   Please indicate the current status and projected submission dates for the above amendments.

Meeting Discussion: *TaiMed stated that all these studies are delayed by approximately 1 month and that the Southern Blot analysis and Forced Degradation study would be submitted soon. The CE-SDS Method Validation Report is now estimated for October of 2016.*

7. **During the Type B pre-BLA meeting held on February 3, 2016 you committed to provide the following items that have not yet been received:**
    a. **Cell line clonality control assessment, estimated for 2Q 2016.**

Meeting Discussion: *TaiMed clarified that the cell line clonality assessment was provided in Module 3 of the rolling BLA submission.*

    b. **Stability data for 3 PPQ lots of bulk drug substance stored (b) (4) , estimated for October 2016.**

Please indicate the current status and projected submission dates for the above amendments.

Meeting Discussion*: TaiMed provided a status update on the bulk drug substance stability studies performed at (b) (4) °C. TaiMed explained that stability data from 3 PPQ lots of bulk DS at (b) (4) °C will not be available because these PPQ lots were not tested on stability at (b) (4) °C. All three DS PPQ lots were used in the manufacture of ibalizumab drug product (DP) lots. TaiMed described (b) (4) TaiMed also noted that the next lot of ibalizumab DS to be manufactured in March/April of 2017 will be monitored for stability at (b) (4) °C, but the pertinent data will not be available during the BLA review cycle. The FDA told the Sponsor that they would discuss the issue internally and provide feedback.*

Post-meeting Comment: *The FDA determined that (b) (4) stability study using one lot of ibalizumab DP (study protocol S16014-DS-O1) is not sufficiently representative of ibalizumab drug substance to allow approval of this storage condition for DS. Therefore, the FDA recommends removing this storage condition from the current BLA submission until real-time stability data from at least three commercial-scale lots of ibalizumab DS are available. In order to support the proposed shelf-life of DS (b) (4) it should be demonstrated in at least three commercial-scale lots that the DS remains stable at (b) (4) °C throughout the proposed shelf-life. Furthermore, appropriate validation data should be provided to demonstrate that use of ibalizumab DS stored (b) (4) °C does not negatively impact the process consistency and the product quality of ibalizumab drug product.*

3.0 DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

The content of a complete application was discussed. TaiMed expressed a desire to request a late submission for stability data, the OSI component, and the neutralizing antibody

report. The Division emphasized that an application must be complete at the time of submission, and that only minor updates could be made during a 30 day window.

- 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. TaiMed stated that no serious safety risk has been seen in development and the product will be administered by IV under medical supervision. The Division agreed that the safety data available thus far suggests that a REMS will not be required but that the final determination will be a review issue.

- TaiMed stated that final reproductive toxicity studies would not be complete until November 2017. The Division recommended that the labeling be submitted according to the Pregnancy and Lactation Labeling Rule and a PMR would be issued until the final reports could be submitted.

- TaiMed inquired if OSI site inspection information could be submitted within 30 days after the application. The Division stated that since the review would likely be managed as priority, there would not be enough time to complete the inspections. The Division also confirmed that OSI requests for General Study Related Information and Comprehensive Clinical Investigator information, as well as Subject Level Data Listings by Site is mandatory, whereas the Request for Site Level Dataset is voluntary.

- Major components of the application are expected to be submitted with the original application and are not subject to agreement for late submission. You stated you intend to submit a complete application and therefore there are no agreements for late submission of application components.

In addition, we note that a chemistry pre-submission meeting was held on February 3, 2016. We refer you to the minutes of that meeting for any additional agreements that may have been reached.

4.0 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 drug 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.

5.0 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.

6.0 SUBMISSION FORMAT REQUIREMENTS

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

7.0 SECURE EMAIL COMMUNICATIONS

Secure email is required for all email communications from FDA to applicants when confidential information (e.g., trade secrets, manufacturing, or patient information) is included in the message. To receive email communications from FDA that include confidential information (e.g., information requests, labeling revisions, courtesy copies of letters), applicants must establish secure email. To establish secure email with FDA, send an email request to SecureEmail@fda.hhs.gov. Please note that secure email may not be used for formal regulatory submissions to applications (except for 7-day safety reports for INDs not in eCTD format).

8.0 MANUFACTURING FACILITIES

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

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

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

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

Corresponding names and titles of onsite contact:

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

9.0 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.

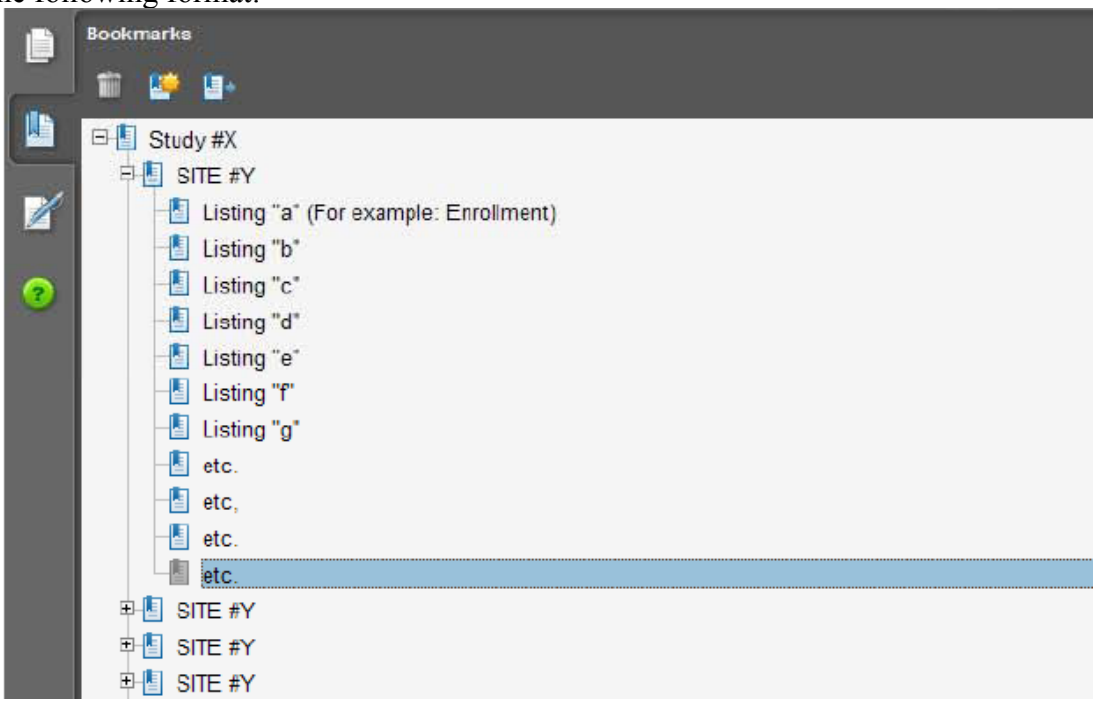
4. For each pivotal trial, provide a sample annotated Case Report Form (or identify the location and/or provide a link if provided elsewhere in the submission).
5. For each pivotal trial provide original protocol and all amendments ((or identify the location and/or provide a link if provided elsewhere 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

9.0 ACTION ITEMS

Action Item/Description	Owner	Due Date
TaiMed will actively pursue obtaining study data from Genentech and give an update to the Division.	TaiMed	2 weeks

10.0 ATTACHMENTS AND HANDOUTS

There are no attachments or handouts for the meeting minutes.

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/s/

CHRISTIAN P YODER
10/11/2016

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Antimicrobial Products
Division of Antiviral Drug Products

FACSIMILE TRANSMITTAL SHEET

DATE: August 25, 2016

To: Dr. Helen Shu	**From: Christian Yoder, MPH**
Company: TaiMed Biologics	**Title: Regulatory Project Manager**
Fax number: 858 724-1844	**Fax number: 301-796-9883**
Phone number: 858 481-6863	**Phone number: (240) 402-9990**

Subject: BLA 761065

Total number of pages including cover:

Comments:

Helen – Can you email me to confirm receipt? Thanks.

Document to be mailed: ☐ YES ☑ NO

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Division of Antiviral Drug Products
Food and Drug Administration
Silver Spring, MD 20993

MEMORANDUM OF FACSIMILE CORRESPONDENCE

BLA: **761065**

Drug: **ibalizumab, TNX, Hu5A8**

Date: **August 25, 2016**

To: **Helen Shu, Ph.D., Vice President, Regulatory Affairs and Quality**

From: **Christian Yoder, MPH, Regulatory Project Manager**

Subject: **BLA 761065 Information Request**

Please refer to your BLA 761065 and to the Pre-submission we received on July 19, 2016. Please see the following comment from the review team and respond no later than August 31, 2016:

1. Provide a current detailed 2016/2017 manufacturing schedule for Ibalizumab Drug Substance and Drug Product manufactured at WuXi AppTec Biopharmaceuticals Co., Ltd, Wuxi, China.

We are providing this above information via telephone facsimile for your convenience. Please feel free to contact me at 240-402-9990 or 301-796-1500 if you have any questions regarding the contents of this transmission.

Christian P. Yoder, MPH
Regulatory Project Manager
Division of Antiviral Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

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/s/

CHRISTIAN P YODER
08/25/2016

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

BLA 761065

ACKNOWLEDGE PRESUBMISSION

TaiMed Biologics USA
Attention: Helen P. Shu, Ph.D.
VP Regulatory Affairs and Quality
2 Executive Circle, Suite 280
Irvine, CA 92614

Dear Dr. Shu:

We have received the first section of your Biologics License Application (BLA) under the program for step-wise submission of sections of a marketing application under 351 of the Public Health Service Act) for the following:

Name of Drug Product: ibalizumab, for intravenous use

Date of Submission: July 19, 2016

Date of Receipt: July 19, 2016

Our Reference Number: BLA 761065

We will review this presubmission as resources permit. Presubmissions are not subject to a review clock or to a filing decision by FDA until the application is complete.

Please cite the application listed above at the top of the first page of any communications concerning this supplemental application. Unless you are using the FDA Electronic Submissions Gateway (ESG), send all submissions by overnight mail or courier to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Antiviral 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 Christian Yoder, Regulatory Project Manager, at (240) 402-9990 or (301) 796-1500.

Sincerely,

{See appended electronic signature page}

Christian P. Yoder, MPH
Regulatory Project Manager
Division of Antiviral Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

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/s/

CHRISTIAN P YODER
07/21/2016

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 9776

MEETING MINUTES

TaiMed Biologics USA
Attention: Helen P. Shu, Ph.D.
VP Regulatory Affairs and Quality
2 Executive Circle, Suite 280
Irvine, CA 92614

Dear Dr. Shu:

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

We also refer to the telecon between representatives of your firm and the FDA on February 3, 2016. The purpose of the meeting was to discuss the organization of the CMC section of the BLA, timing for the BLA and pre-approval inspection for the intravenous ibalizumab product.

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

If you have any questions, call Maryam Changi, Regulatory Business Process Manager at (240) 402-2725.

Sincerely,

{See appended electronic signature page}

Howard Anderson, PhD
Product Quality Team Leader
Division of Biologics Review and Research III
Office of Biotechnology 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: February 3, 2016 from 11:00 AM to 12:00 PM Est.

Application Number: 9776
Product Name: Ibalizumab Intravenous
Indication: Treatment of HIV-1 infection in treatment-experienced adult patients with documented multi-antiretroviral class resistance and evidence of HIV-1 replication despite ongoing antiretroviral therapy

Sponsor/Applicant Name: TaiMed Biologics USA

Meeting Chair: Howard Anderson, Ph.D.
Meeting Recorder: Maryam Changi, PharmD. RBPM, OPRO

FDA ATTENDEES
Steven Bowen, PhD, Product Quality Reviewer, DBRRIII/OBP/OPQ
Howard Anderson PhD, Product Quality Team Lead, DBRRIII/OBP/OPQ
Natalia Pripuzova, PhD, Microbiology Reviewer, DMA/OPF/OPQ
Bo Chi, PhD, Microbiology Reviewer, DMA/OPF/OPQ
Thomas Colleen, PhD, Acting Quality Assessment Lead, DMA/OPF/OPQ
Steven Fong, Facility Reviewer Team Lead, DIA/OPF/OPQ
Michael Shanks, Facility Reviewer, DIA/OPF/OPQ
Maryam Changi, Pharm.D., RBPM,OPRO,OPQ
Christian Yoder, BSN, MPH, OND/OAP/DAVP

SPONSOR ATTENDEES
From the mfg CRO, WuXi Biologics (A Wholly-owned subsidiary of WuXi AppTec):
Chris Chen, PhD, Chief Executive Officer of WuXi Biologics
Gang Huang, PhD, V.P., Analytical & Formulation Dev. & Regulatory Affairs
Ken Chen, MBA, Director, Regulatory Affairs
Jimmy Li, PhD, Executive Director, Cell Culture Process Development
Jerry Xu, PhD, Vice President, Quality Assurance
Matt Luo, MBA, Senior Director, Quality Assurance
Debbie Lou, MS, Senior Director, Quality Assurance

From TaiMed:
Jon Ho, Director, Business Development & Alliance Management
Chen Yu Wang, Ph.D., Pharmaceutical Analysis Manager
Helen Shu, Ph.D., V.P., Regulatory Affairs and Quality

1.0 BACKGROUND

The purpose of this meeting is to discuss the organization of the CMC section of the BLA, timing for the BLA and pre-approval inspection for the intravenous ibalizumab product.

FDA sent Preliminary Comments to TaiMed Biologics USA on January 21, 2016.

2. DISCUSSION

Question 1:

The BLA Table of Contents follows ICH CTD format. Selected study reports are generally embedded in their sections unless the ICH guidance specify that they belong in the Appendix or Regional sections.

• Assay validation packages for DS and DP are presented in the Module for Regional documents, 3.2.R. Assay summaries are presented in 3.2.S and 3.2.P and cross referenced to 3.2.R for details.

• Viral clearance validation reports are presented in the Modules for Appendices in 3.2.A. Are there other examples where the Reviewers prefer study reports not be embedded in the CMC sections, but in the Appendices or Regional sections?

FDA Response to Question 1:

Your proposal to place the QA approved assay validation reports in the Regional Module is acceptable. In sections 3.2.S and 3.2.P method summaries should be provided that include summary tables for validation parameters and representative primary results (data) for chromatograms, electropherograms, SDS-PAGE gels, etc.

Discussion:

The Sponsor agreed with the Agency's feedback. There was no further discussion.

Question 2:
To avoid duplication, we propose to cross reference the assay validation sections for DS 3.2.S and DP 3.2.P to 3.2.R and not provide the validation reports again. Is this acceptable?

FDA Response to Question 2:

Yes, cross referencing the assay validation reports in section 3.2.R in sections 3.2.S and 3.2.P is acceptable.

Discussion:

The Sponsor agreed with the Agency's feedback. There was no further discussion.

Question 3:

For the HCP assay, where assay modifications were made during the testing of the 5 GMP lots to get greater coverage, we will summarize the assay modifications and which assays have been used to test different WuXi AppTec GMP lots in 3.2.S.4.3. The validation report of the HCP assay will be presented in 3.2.R. Is this acceptable?

FDA Response to Question 3:

Yes, summarizing in section 3.2.S.4.3 the modifications made to the HCP assay and providing the validation reports in 3.2.R is acceptable. In addition provide summaries of all changes to the HCP assay during development in section 3.2.S.4.3. Provide two-dimensional results for total HCP stained with a sensitive dye and anti-HCP antiserum immunoblot results. HCP antiserum coverage should be quantified and the numerical results provided in section 3.2.S.4.3.

Discussion:

The Sponsor agreed with the Agency's feedback. There was no further discussion.

Question 4:

Some information has been submitted previously to the IND by Tanox. For continuity and completeness of the BLA, we propose to submit these previously submitted reports in the relevant sections of the BLA:

• Tanox reports on viral testing of the MCB and WC B in 3.2.S.2.3
• Tanox viral clearance reports in 3.2.S.2.3

Additional viral testing of the MCB and WCB performed by WX will be submitted in the same BLA section.
• WX reports on additional MCB and WCB testing in 3.2.S.2.3
• WX process viral characterization report in scale down models in 3.2.S.2.3
• WX viral process validation reports are presented in 3.2.A.
Is this acceptable?

FDA Response to Question 4:

Yes, submission of these study reports to the indicated sections of the BLA is acceptable.

Discussion:

The Sponsor agreed with the Agency's feedback. There was no further discussion.

Question 5:

Summaries of the process validation for cell culture and purification for 3 PPQ lots are presented in 3.2.S.2.5. A summary of the process validation for fill finish for 3 PPQ lots is presented in 3.2.P.3.5. The complete process validation reports are presented after the summaries in the respective Sections. Is this acceptable?

FDA Response to Question 5:

Yes, it is acceptable to submit a summary of the process validation for cell culture and purification in section 3.2.S.2.5 and a summary of the process validation for fill finish in section 3.2.P.3.5 with the full process validation reports included in the respective sections.

Discussion:

The Sponsor agreed with the Agency's feedback. There was no further discussion.

Question 6:

We propose to present summaries of the development history for the DS manufacturing process, Section 3.2.S.2.6, of the Tanox process at (b) (4) scale. Summaries of the technology transfer from Tanox to WX through small scale process runs will be described. We propose to present the Comparability Study Report comparing the Tanox (b) (4) and WX (b) (4) process. Is this acceptable?

FDA Response to Question 6:

Yes, the information you propose to include in section 3.2.S.2.6 is acceptable.

Discussion:

The Sponsor agreed with the Agency's feedback. There was no further discussion.

Question 7:

Information to address unique questions in this BLA that are forward looking ,e.g., new reference standard and request to remove certain assays, are embedded in their respective sections in the ICH CTD format. Is this acceptable or does the Agency have other

preferences?
• Example 1, Section 3.2.S.4.1: we propose to present the request and rationale (b) (4) from the DS specifications.
• Example 2, Section 3.2.S.4.1: we propose to present a Report summarizing the bridging data to support replacing the SDS PAGE assay with the CE-SDS assay. The CE-SDS validation is on-going.
• Example 3, Section 3.2.S.5.1: we propose to present the Qualification Report for the Tanox Reference Standard and the Qualification Protocol for the WX Reference Standard.
Is this acceptable?

FDA Response to Question 7:

Yes, any proposed modifications pertaining to product quality should be included in the relevant sections of Module 3. Indicate in the request when the BLA will be amended prior to the PDUFA action date. If it is anticipated that the change will be made post approval indicate what type of supplement will be submitted to the FDA.

Discussion:

The Sponsor agreed with Agency's feedback. The Sponsor clarified examples 1 and 2 above will be in the BLA and example 3 data for new reference standard will be submitted post-BLA submission and the Agency will provide an information request if there are deficiencies with the qualification report or qualification protocol for reference standard.

Question 8:

The Force Degradation Study Report is presented in 3.2.S.3.1 and 3.2.P.2.2.3.
The standard QC assays are crossed referenced to 3.2.R. Characterization assays are described in the force degradation study report.
Is this acceptable?

FDA Response to Question 8:

Yes, however please indicate in the Stability Section of the BLA that the forced degradation studies are located in the Characterization Section.

Discussion:

The Sponsor agreed with the Agency's feedback. There was no further discussion.

Question 9:

Section 3.2.P.3.5 will address the microbiology/endotoxin measurements made during the manufacturing process. This section will also have Reports on filter validation, extractables and leachables. The DP Container Closure Integrity Test will be implemented for mo 12, 24 and 36, and the Rabbit Pyrogen Test will be done as soon as the protocol is

finalized.
Is this acceptable?

FDA Response to Question 9:

In general, this is acceptable. We have an additional comment regarding the microbial control and sterility assurance. The letter to the Agency dated December 2, 2015, stated that (b) (4)

Discussion:

The sponsor agreed with Agency's feedback. The sponsor explained that the bulk drug substance data (b) (4) will be provided in BLA. The sponsor also explained that bulk drug substance for 3 PPQ lots stored (b) (4). The Sponsor will provide the data after the BLA submission, expected in October 2016.

Question 10:

Section 3.2.R has Executed Batch Records to fulfill the US requirement. WuXi AppTec manufactured five GMP lots, including 3 PPQ lots. How many Batch Records should be provided in this section?

FDA Response to Question 10:

Provide in English the Master Batch Record and one executed PPQ batch record for the Drug Substance and Drug Product.

Discussion:

The Sponsor agreed with the Agency's feedback. There was no further discussion.

Question 11:

Information on equipment qualification, routine environmental program and three successful consecutive media fill runs, including summary environmental monitoring data obtained during the runs will be provided in 3.2.A.
Is this acceptable?

FDA Response to Question 11:

No, this is not acceptable. The information listed in Question 11 should be submitted in Section 3.2.P.3.5 of the BLA (Process Validation and/or Evaluation) and not in the Appendix.

The Appendix (3.2.A) should include a description of the facilities and equipment proposed for Ibalizumab DS and DP manufacture. This description should include (but not be limited to): air handling systems, water systems; plant steam; cross contamination control procedures; product changeover procedures; a list of the major rooms (including classification) used for manufacture, a list (including location) of the major manufacturing equipment; equipment cleaning procedures; and facility cleaning procedures. In addition, please provide design plans for the DS and DP sites, including schematics, room classifications, and flow diagrams for personnel, materials, waste, product, and equipment.

Discussion:

The Sponsor agreed with the Agency's feedback. There was no further discussion.

Question 12:

During the manufacture of the third PPQ lot (the fifth GMP lot) at WuXi Apptec, there was an excursion in the environmental monitoring data where mold and bacteria were detected on environmental and personnel samples taken during (b) (4) steps in the (b) (4) area. A detailed investigation is underway. This lot will not be used in humans either in clinical trials or post-approval. The A summary of the investigation will be provided in 3.2.A .1 Facilities and Equipment.
Is this acceptable?

FDA Response to Question 12:

Please provide a summary of the investigation together with (b) (4) data (Section 3.2.P.3.5 of the BLA). In addition, the third PPQ lot may need to be repeated depending on the results of the investigation

Discussion:

The Sponsor agreed with the Agency's feedback. The Sponsor will provide the summary in Section 3.2.P.3.5 of the BLA.

Question 13:

We propose to provide the BLA as a paper submission:
Is this acceptable?
How many official paper copies are required?
How many Reviewer desk copies are needed?
For the desk copies, is there a preference for paper vs. copies on CD?

FDA Response to Question 13:

As previously discussed, electronic BLA submissions are **strongly** *recommended. Although*

electronic BLA submissions are not yet mandatory, they have already become the industry standard. The Agency's ability to expedite review of a product with Breakthrough Therapy designation depends on both the quality of the information in the application and on the ease of use of the application format. Compared to electronic applications, paper applications take longer for the Agency to review due to the inefficient format and the additional time required for communication.

In addition, please note that electronic BLA submissions will become mandatory in May 2017. After the electronic submission requirement has been implemented, any BLA amendments, reports, supplements, etc. must be submitted in electronic format even if the original BLA was submitted to the Agency prior to implementation of this requirement. Please refer to the FDA Guidance for Industry titled "Providing Regulatory Submissions in Electronic Format - Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications" available at http://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugsgen/ documents/document/ucm333969.pdf.

Discussion:

The Sponsor agreed with the Agency's feedback. The Sponsor is speaking with potential vendors who can provide the infrastructure for this service.

Question 14:

We propose the BLA as a rolling submission. Module 3 is the first Section to be submitted. We propose to submit Modules 1 and Module 2 (Quality Overall Summary) at a later time when the other Modules of the BLA are submitted, estimated for 3Q 2016. Is this acceptable?

FDA Response to Question 14:

Yes it is acceptable to submit Module 3 first, and Module 1 and Module 2 at a later date.

Discussion:

The Sponsor agreed with the Agency's feedback. There was no further discussion.

Question 15:

The current status on the timing for Module 3 is summarized below. We seek Agency feedback on the proposal to submit the core Module 3 first, with subsequent updates, as described below:
A. Module 3 core: estimated in 1Q 2016
The date of submission to be finalized after review of the current drafts of sections, what still remains to be written, data verification against source documents and time for the formatting and production of the Module.

B. The following items are proposed to be submitted as updates to the core Module 3 submission with their estimated submission dates:

- Stability updates: determined by stability protocol pull dates (b) (4)
- Cell line stability assessment: 2Q 2016
- Clonality control assessment: 2Q 2016
- Report of the Rabbit Pyrogen Test: 2Q 2016
- DP Contain Closure Integrity Test and specifications implemented in the stability protocol for mo 12, 24 and 36 for the 3 PPQ lots and 2 clinical lots: starting mid 2016
- Additional characterization of CEX and SDS PAGE bands: 3Q 2016
- CE SDS assay validation report: 3Q 2016
- Bulk drug substance for 3 PPQ lots (b) (4) will be monitored for stability and leachables. Data expected in October 2016.

Is the acceptable?

FDA Response to Question 15:

Module 3 may be submitted in a rolling manner, but the review clock will not begin until the BLA submission is complete. Indicate in the original submission which sections will be updated. Inspections may not be conducted until the BLA submission is complete and is fileable by the Agency.

Discussion:

The Sponsor will monitor the timing for Module 3 and subsequent updates closely and will communicate any revisions.

The sponsors indicated that the original submission will indicate which sections will be updated.

To finalize the rabbit pyrogen protocol, The Sponsor will submit to the IND for Agency review the question on the appropriate dose as defined in the USP 151 vs. 21 CFR 310.13 (previously submitted as S 275, Oct. 28, 2015).

The decision date to file the BLA is 60 days from the submission date. When the BLA is determined to be fileable a cGMP inspection will be schedule. The inspection will occur when the company is producing the product.

Question 16:

Depending on the schedule for the PAI by the Agency, a 6th GMP lot may be scheduled in late 3Q or early 4Q 2016. Is this acceptable?

FDA Response to Question 16:

This may be acceptable depending on the timing of the complete BLA submission.

Discussion:

The Sponsor agreed with the Agency's feedback. The Sponsor will be scheduling a product run at WuXi AppTec depending on when the BLA is filed.

Question 17:

Are there any foreseeable refuse-to-file issues?

FDA Response to Question 17:

We do not see anything in the meeting package that we would consider a refuse-to-file issue. Please refer to the additional comments below.

Additional Comments:

Product Quality Microbiology comments:

Additional product quality microbiology comments were previously communicated to you on September 4, 2015. The following information is still missing in the proposal you have submitted to the Agency:

1) ***Section 3.2.S.2.5,*** *Process Validation and Evaluation, should include the following:*

- *Microbial data from three successful product intermediate hold time validation runs at manufacturing scale.*

Discussion:

The manufacturing process is (b) (4) The Agency clarified that (b) (4) . However, the (b) (4) bioburden and endotoxin test results should still be provided in section 3.2.S.2.5 of the BLA.

(b) (4)

Discussion:

Please see the previous comment.

- *Information and summary results from the shipping validation studies*

Discussion:

The drug substance is not shipped because the drug product is produced at the same facility. The drug product vials for clinical trials have been shipped from WuXi, China to (b) (4) US by (b) (4) in their validated shippers at 2-8°C. Temptales in the shipments monitored the vial temperatures while in transit. The drug product validation report will present data on the validated shipper and the vial temperatures in transit. TaiMed has the option to submit this to the IND initially prior to the BLA.

2) ***Section 3.2.S.4.3*** *should include the summary reports and results from bioburden and endotoxin test methods qualification performed for* (b) (4) *the drug substance.*

Discussion:

The Sponsor agreed with the Agency's feedback. There was no further discussion.

3) ***Section 3.2.P.2.5****, Microbiological Attributes*
In the event you propose the storage of the product post-dilution before injection for more than 4 hours at 2-8°C or at room temperature, you should conduct a microbial challenge study data to support the proposed storage conditions. The test should be run at the label's recommended storage conditions, be conducted for twice the recommended storage period, and use the label-recommended diluent. Periodic intermediate sample times are recommended. Challenge organisms may include strains described in USP <51> plus typical skin flora or species associated with hospital-borne infections.

Discussion:

The Sponsor agreed with the Agency's feedback. The product label would permit the use of the diluted drug product up to 4 hours after dilution in (b) (4). The registration trial currently allows product use up to 6 hours post-dilution, but the site will be told to limit the post-dilution storage time to not more than 4 hours. Other ongoing trials will also revise the instructions to indicate that the post-dilution storage time should be limited to not more than 4 hours.

(b) (4)

(b) (4)

Discussion:

Section 3.2.P.3.3 (Description of Manufacturing Process and Process Controls) is a narrative about the process and its controls. Section 3.2.P.3.4 (Controls of Critical Steps and Intermediates) identifies the key steps for control and includes quantitative parameters that are set for these key steps. Some information may be appropriate for both Sections. The Sponsor has the option to submit questions to the IND for clarification prior to the BLA.

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

/s/

HOWARD A ANDERSON
03/03/2016

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 9776

MEETING MINUTES

TaiMed Biologics
Attention: Helen P. Shu, Ph.D.
VP Regulatory Affairs and Quality
18201 Von Karman Ave., Ste. 470
Irvine, CA 92612

Dear Dr. Shu:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for ibalizumab, TNX; Hu5A8.

We also refer to the teleconference between representatives of your firm and the FDA on November 20, 2015. The purpose of the meeting was to discuss the clinical, virology, and toxicology plans for IV ibalizumab.

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 Christian Yoder, Regulatory Project Manager at (240) 402-9990.

Sincerely,

{See appended electronic signature page}

Debra Birnkrant, MD
Director
Division of Antiviral Products
Office of Antimicrobial 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: Breakthrough Therapy-Initial Comprehensive

Meeting Date and Time: November 20, 2015 11:00 a.m. to 12:00 noon
Meeting Location: Teleconference

Application Number: IND 9776
Product Name: ibalizumab, TNX 355; Hu5A8
Indication: Treatment of HIV-1 infection
Sponsor/Applicant Name: TaiMed Biologics (TaiMed)

Meeting Chair: Adam Sherwat, MD, Medical Team Lead
Meeting Recorder: Christian Yoder, BSN, MPH, Regulatory Project Manager

FDA ATTENDEES

1. Debra Birnkrant, MD, Director, Division of Antiviral Products (DAVP)
2. Jeffrey Murray, MD, MPH, Deputy Director, DAVP
3. Adam Sherwat, MD, Medical Team Lead, DAVP
4. Regina Alivisatos, MD, Clinical Reviewer, DAVP
5. Eric Donaldson, PhD, Virology Reviewer, DAVP
6. Julian O'Rear, PhD, Virology Team Lead, DAVP
7. Vikram Arya, PhD, Clinical Pharmacology Reviewer, OCP, DCPIV
8. Islam Younis, PhD, Clinical Pharmacology Team Lead, OCP, DCPIV
9. Christopher Ellis, PhD, Pharmacology/Toxicology Reviewer, DAVP
10. Hanan Ghantous, PhD, Pharmacology/Toxicology Team Lead, DAVP
11. Karen Qi, Biometrics Reviewer, OB, DBIV
12. Thamban Valappil, Biometrics Team Lead, OB, DBIV
13. Steven Bowen, PhD, Product Quality Team Lead, DBRR, Division 1
14. Danyal Chaudhry, MS, OSE Project Manager
15. Karen Winestock, Chief, Project Management Staff, DAVP
16. Christian Yoder, Regulatory Project Manager, DAVP

SPONSOR ATTENDEES

18. Jon Ho, Director, Project Manager
19. Stanley Lewis, MD, VP clinical and Chief Medical Officer
20. Helen Shu, PhD, VP Regulatory Affairs and Quality
21. Steve Weinheimer, PhD, VP Biological Sciences

1.0 BACKGROUND

Ibalizumab is a humanized immunoglobulin (IgG) isotype 4 monoclonal antibody that binds to a conformational epitope on domain 2 of CD4, inhibiting HIV entry into cells. TaiMed Biologics (TaiMed) has developed an intravenous formulation of ibalizumab to be administered in combination with other antiretroviral agents, for the treatment of HIV-1 infection in highly treatment-experienced adult patients with documented drug resistance and evidence of HIV-1 replication despite ongoing antiretroviral therapy. A request for Breakthrough Therapy designation was granted February 23, 2015, and this meeting will be considered as the initial comprehensive multidisciplinary breakthrough meeting. The main purpose of this meeting is to discuss the ongoing phase 3 study, TMB-301, and reach agreement on the timing for the submission of the primary endpoint data and the reproductive toxicology and carcinogenicity study data.

FDA sent Preliminary Comments to TaiMed Biologics on November 17, 2015.

2. DISCUSSION

Questions from the meeting background package and the Agency's responses, as well as additional comments from the meeting background package are provided below.

2.1. Clinical

Question 1: **TMB 301 primary endpoint data/timing discussion – are the proposed plans acceptable? Can the primary endpoint data be submitted early while the study is on-going?**

FDA Response to Question 1: *The early submission of the primary efficacy data is not encouraged.*

A substantive review of this data can only be performed after the complete study report and corresponding data sets are received.

Question 2: **Is the proposal for TMB 311, the expanded access protocol, acceptable?**

FDA Response to Question 2: *Your intent to start the expanded access protocol in time to enroll the first patients who complete study TMB 301 is reasonable. In the absence of a draft protocol or protocol schema for review no further comment can be provided.*

Meeting Discussion: TaiMed reported on the progress of their Phase 3 registrational trial. They have identified 50 sites; however, 15 sites informed them that they do not have patients who meet the enrollment criterion. They currently have 19 sites in the United States (U.S) and two sites in Taiwan and a total of ten subjects have been enrolled, one in Taiwan and nine in the U.S. They have not seen any unexpected adverse events that would cause safety concerns and subjects are responding as expected. TaiMed referenced the Agency's request that the clinical trial include a diverse patient population that should

include women and blacks, but they noted that they have been enrolling more white gay males in the clinical trial. TaiMed pointed out that despite increasing the number of sites, recruitment is challenging and they asked if there would be flexibility in the Agency's requested minimum number of 30 U.S. subjects. The Division responded that 30 U.S. subjects is the minimum number of subjects needed to demonstrate relevance of the data to the U.S. population. The use of data from Taiwanese subjects is of concern because there may be host or viral factors that result in differences in efficacy between the U.S. and Taiwanese populations. TaiMed agreed to continue to try to enroll 30 subjects in the U.S. In addition, TaiMed agreed to submit quarterly updates on the status of enrollment of subjects in TMB 301.

TaiMed is preparing the TMB 311 expanded access protocol and plans to submit it soon. It will be similar to TMB 301, but the plan for monitoring patients will be revised. The current plan is to enroll patients who complete the TMB 301 study and patients currently being treated under single patient investigator sponsored INDs.

Additional FDA Comments:

1. *You have indicated your intention to request an Accelerated Approval pathway for your BLA. However, an option for Accelerated Approval is no longer available for HIV drug approval as the impact of treatment on VL is considered a validated endpoint. Therefore a traditional route of approval must be sought.*
2. *You have indicated an intention to request an exemption for all pediatric drug development because of orphan drug status. The Pediatric Research Equity Act states, "This section does not apply to any drug for an indication for which orphan designation has been granted under section 526" (21 U.S.C. 360bb). FDA has not issued regulations applying PREA to orphan-designated indications, thus, submission of a pediatric assessment is not required for an application to market a product for an orphan-designation indication, and waivers are not needed at this time.*
3. *TaiMed was recently reminded that the 30 subjects who will be included in the primary analysis in Study 301 should all be from the U.S.*

2.2. Clinical Virology

Question 3: **With the exception of the pending submission on the TMB 202 genotypic and phenotypic data, do the submitted documents address the Reviewers' questions?**

FDA Response to Question 3: *In general the sponsor's responses have adequately addressed the recommendations communicated by clinical virology. We note, however, that the study report addressing the genotypic/phenotypic resistance analysis is to be submitted in November 2015. The FDA appreciates the thoroughness of your comprehensive analyses of public databases to identify CD4 polymorphisms. Please see the additional Clinical Virology recommendations for this submission.*

Meeting discussion: TaiMed acknowledged that the TMB 202 genotypic and phenotypic data are still outstanding and they plan to submit them next month. They also plan to submit additional requested data including the study report on maraviroc resistance.

TaiMed agreed to sequence the HIV-1 Env gene for subjects who failed treatment with ibalizumab, but has had difficulty finding the draft NGS template. The Division agreed to provide the template.

TaiMed is hopeful that new resistance data will be available to determine if resistance to ibalizumab confers cross-resistance to HIV-1 attachment inhibitor [redacted] (b) (4), but since they do not have access to the compound there may be a delay in responding.

Additional FDA Comments:

4. *Please submit the phase 1b clinical trial (TNX-355.02) resistance data in the template format for review. Please include the paired baseline and on-treatment virus sequences for all subjects who failed treatment. If these data have been previously submitted, please identify the submission in which these were provided.*
5. *Please provide viral load plots for each individual who has received ibalizumab monotherapy (or functional monotherapy) or identify when these items were submitted to the IND.*
6. *Please provide a study report detailing the assessment of the susceptibility of ibalizumab resistant virus to maraviroc. If this report has been submitted, please identify the submission in which these data were provided.*
7. *Please evaluate published maraviroc resistance substitutions for susceptibility to ibalizumab with emphasis on those closest to ibalizumab resistance residues. Note that the Agency defines maraviroc resistance in the context of virus using CCR5 only as a co-receptor as opposed to a tropism switch.*
8. *We recommend sequencing the entire HIV-1 Env gene for subjects who failed treatment with ibalizumab. A complete study report should be submitted with all NGS data detailing all of the steps used to prepare and amplify the sample, to perform the sequencing of samples, to clean up and filter sequence reads for analysis, to analyze the sequences, and to interpret the results. In addition, the fastq sequences should also be submitted on a portable hard drive or DVD (depending upon the size of the dataset) along with the fasta sequences for all reference sequences used in the analysis. Please see the DRAFT NGS Template entitled, Submitting Next Generation Sequencing Data to the Division of Antiviral Products Experimental Design and Data Submission.*
9. *Please determine if resistance to ibalizumab confers cross-resistance to HIV-1 attachment inhibitor* [redacted] (b) (4) *and vice versa. Does resistance to one confer cross resistance to the other?*

2.3. Pharmacology/Toxicology

Question 4: **Is the proposed ePPND study and dose for the reproduction toxicity study acceptable?**

FDA Response to Question 4: *Based on the estimated monkey to human exposure ratios provided in Table 2 (refer to submission #0261, letter dated August 31, 2015), the 110 mg/kg qwk dose level selected for the proposed ePPND study appears to be acceptable. However, we cannot comment on the acceptability of the ePPND study design until after Agency review of your draft protocol.*

Question 5: **Is the proposed timing for the ePPND study acceptable?**

FDA Response to Question 5: *Our understanding is that you intend to submit a draft ePPND study protocol for Agency review, prior to initiating the ePPND study and following review of PK data collected from cohorts 1E and 1F in your ongoing trial (TMB 121), which you expect to be available in early 2016. However, the expected timing of draft protocol submission and study initiation were not specified. Please note that utilizing clinical PK data obtained from cohorts 1E and 1F to calculate the estimated monkey to human exposure ratios is not considered essential for finalizing the dose level selected for the ePPND study. In addition, the ePPND study must be ongoing at the time of BLA submission (i.e. 3Q of 2016) and so we recommend submitting the draft protocol no later than in the 1Q of 2016, with the study initiated in the 2Q of 2016. Please provide the anticipated timeframe for draft protocol submission and ePPND study initiation.*

Meeting discussion: TaiMed confirmed that the dose of 110 mg/kg/wk for the ePPND study will be used, since they assume that AUC values obtained following IM dosing in their ongoing trial will be as predicted. They plan to submit a draft ePPND study protocol in the first quarter of 2016, with the study initiated in the second quarter of 2016. The Division expressed agreement with this time frame.

Question 6: **Is the proposal to assess the carcinogenic potential as a post-BLA activity acceptable?**

FDA Response to Question 6: *We agree that it is acceptable to submit your assessment of the carcinogenic potential of ibalizumab as a post-approval requirement. However, you may wish to consider providing your risk assessment prior to BLA submission. Please note that this assessment is typically based on a weight of evidence approach utilizing all relevant data from a variety of sources (refer to the ICH S6 Addendum). At this point, it appears that the currently available data for ibalizumab may be sufficient for this assessment, and so the need for additional in-vitro or in-vivo data with ibalizumab seems unlikely. However, final determination of the need for additional studies to address the carcinogenic potential of ibalizumab can only be made following Agency review of your assessment. We anticipate that the primary focus of your risk assessment will be to provide a detailed review and description of the known (or potential) effects of ibalizumab on the immune system, with emphasis on those effects that could alter or disrupt the immune system's role in tumor prevention (e.g. role in tumor immune surveillance, preventing virus-induced tumors).*

Meeting discussion: TaiMed confirmed that they plan to submit their assessment of the carcinogenic potential of ibalizumab post-approval.

2.4. Division of Medication Error Prevention and Analysis

Additional FDA Comments:

10. *We acknowledge your plans for submission of a proprietary name request in the background information submitted for the Type B teleconference. Reference is made to your Investigational New Drug Application submitted to the Agency for "Ibalizumab." Reference is also made to your Granted Breakthrough Therapy Designation received February 23, 2015. The Division of Medication Error Prevention and Analysis (DMEPA) encourages you to submit your Request for Proprietary Name Review as soon as possible in order to allow ample time to work with you in finding an acceptable name for your proposed product, preferably prior to your BLA submission. The content requirements for such a submission can be found in the draft guidance for industry, Contents of a Complete Submission for the Evaluation of Proprietary Names, available at*
    http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075068.pdf

Meeting discussion: There was no meeting discussion on this point.

3.0 ISSUES REQUIRING FURTHER DISCUSSION

TaiMed informed the Division that they would like to submit the upcoming BLA application in paper format. The Division strongly urged TaiMed to consider an electronic submission in order to facilitate the review but if this is not feasible, the Division suggested that TaiMed submit a written proposal that will identify the components of the NDA submission that TaiMed intends to submit in paper versus electronic format.

4.0 ACTION ITEMS

Action Item/Description	Owner	Due Date
Clinical Virology to send NGS database format	FDA	Sent November 20, 2015
Submit a written proposal for the paper BLA.	TaiMed	

6.0 ATTACHMENTS AND HANDOUTS

There were no attachments/handouts used during the discussion at the meeting.

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/s/

DEBRA B BIRNKRANT
12/03/2015

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 9776

MEETING MINUTES

TaiMed Biologics
Attention: Helen Shu, Ph.D.
Vice President, Regulatory Affairs and Quality
18201 Von Karman Avenue, Suite 470
Irvine, CA 92612

Dear Dr. Shu:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Ibalizumab, TNX-355, Hu5A8.

We also refer to the meeting between representatives of your firm and the FDA on September 4, 2015. The purpose of the meeting was to follow-up on previous submissions and to clarify other items prior to a pre-BLA meeting.

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

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

Sincerely,

{See appended electronic signature page}

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

Enclosure:
Meeting Minutes

MEMORANDUM OF MEETING MINUTES

Meeting Type: B
Meeting Category: CMC

Meeting Date and Time: September 4, 2015 at 8:00 AM
Meeting Location: Teleconference

Application Number: IND 9776

Product Name: Ibalizumab, TNX-355, Hu5A8
Indication: Treatment of HIV-1 Infection

Sponsor/Applicant Name: TaiMed Biologics

Meeting Chair: Marjorie Shapiro, Ph.D.
Meeting Recorder: Melinda Bauerlien, M.S.

FDA ATTENDEES
Tzanko Stantchev, M.D., Product Reviewer, Division of Biotechnology Review and Research I
Steven Bowen, Ph.D., Product Reviewer, Division of Biotechnology Review and Research III
Marjorie Shapiro, Ph.D., Team Leader, Division of Biotechnology Review and Research I
Peter Qui, Ph.D., Acting Branch Chief, OPQ/OPF/DIA/IABI
Steven Fong, Ph.D., Facility Reviewer, OPQ/OPF/DIA/IABI
Michael Shanks, Ph.D., Facility Reviewer, OPQ/OPF/DIA/IABI
Patricia Hughes, Ph.D., Acting Branch Chief, Division of Microbiology Assessment/Branch IV
Christian Yoder, Project Manager, OND/OAP/DAVP
Melinda Bauerlien, M.S., Senior Regulatory Business Process Manager, OPRO

SPONSOR ATTENDEES
Peter Shen, WuXi AppTec, Executive Director, purification process development
Chris Chen, WuXi AppTec, Senior VP, CTO of Biologics
Gang Huang, WuXi AppTec, VP, Analytical Development & Regulatory Affairs
Jimmy Li, WuXi AppTec , Executive Director, Cell Culture Process Development
Ken Chen, WuXi AppTec , Director II, Regulatory Affairs
Chen-Yu Wang, TaiMed Pharmaceutical Analysis Manager
Jon Ho, TaiMed, Director, Business Development & Alliance Management
Helen Shu, TaiMed, VP, Regulatory Affairs and Quality

1.0 BACKGROUND

To follow-up on previous submissions and to clarify other items prior to a pre-BLA meeting.

2.0 DISCUSSION

Question 1:
Does the Agency have comments on the CMC program submitted by TaiMed (S 248, May 21, 2015)?

2.1 Proposal for HCP assay?

(b) (4)

[redacted]

WuXi AppTec will continue to attempt to generate new HCP reagent and raise anti-HCP polyclonal antibody to achieve better coverage and ELISA assay performance.
Is this acceptable?

FDA Response:
In general, your approach to develop a more sensitive assay for residual HCP appears adequate. Please note that (b) (4) [redacted]. *The adequacy of the HCP coverage of either anti-HCP reagent will be a BLA review issue. If necessary, the development of an improved assay for HCP will be managed as a post-marketing commitment.*

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1.4 Other reviewer comments?

FDA Response:
CMC comments:

(b) (4)

Regarding stability data to be submitted with the BLA, both DS and DP are produced at WuXi Apptec and are very similar in composition (b) (4) ***For DS at*** (b) (4) ***°C, TaiMed will submit 1 lot with 6 month data and 2 lots with 3 month data. For DP at 2-8°C they will submit 1 lot with12 month data and 2 lots with 3 month data. Currently the DS is*** (b) (4) ***. The Agency responded that typically we expect at***

least 6 month stability data for 3 lots each DS and DP, but for DS that is stored for short periods, the amount of data that will be provided is acceptable.

The Agency recommended submitting updated stability data when the remaining modules of the BLA are submitted in 2016. The sponsor stated that by mid-2016 they will have DP stability out to 24 months for 1 lot and 12 and 9 months for the other 2 lots. When the product was acquired from Tanox, they had approximately 10 lots that were 5 years old. Some of these lots showed some new minor bands on SDS-PAGE, but they were unable to find any trends or consistency. They will have accelerated data at 25 and 40°C. The Agency responded that this is supportive data and we will not extrapolate for expiry.

The Agency also recommended that for future product development, the sponsor may want to consider DS stability studies for up to 3 years under frozen storage conditions that would support a longer DS expiration dating period and could provide TaiMed with flexibility for manufacturing DP lots.

Question 2:
Does the Agency have comments on the Process Validation Plans submitted by TaiMed (S 243, March 31, 2015)?

<u>FDA Response:</u>
The following information is missing or deficient in the package provided by the TaiMed:

1. *<u>Drug Substance and Drug Product:</u> Possible LER (low endotoxin recovery) issue should be addressed in the BLA submission, because the formulation of the product includes polysorbate 80. Provide evidence in the BLA that the endotoxin recovery is not affected by the presence of polysorbate* (b) (4) *Consider conducting small-scale studies to determine the effect of holding on endotoxin recovery* (b) (4) *and drug product with known amount of endotoxin. These studies should be conducted in the containers in which the product and samples are held prior to endotoxin testing.*

2. *<u>Drug Product:</u> No Container Closure Integrity Test (CCIT) is proposed as a release test in the package provided in S 243. CCIT should be implemented as a release specification. Container closure integrity methods validation should demonstrate that the assay is sensitive enough to detect breaches that could allow microbial ingress. Container closure integrity testing should be performed in lieu of sterility testing for stability samples every 12 months (annually) and at expiry.*

3. *<u>Drug Product:</u> Rabbit Pyrogen Test should be conducted on three batches of drug product in accordance with 21 CFR 610.13(b).*

4. *<u>Drug Product:</u> Sterilizing filter validation studies are proposed in the package but not described in details. Please refer to PDA Technical Report #26 for guidance.*

Question 3:
Does the Agency have comments on the Viral Clearance Validation Plan submitted by TaiMed (S 247, May 20, 2015)?

FDA Response:
In general, your Virus Clearance Validation Plan appears acceptable. Clarify the following:

- *In the document WBP236 Virus Clearance Study for Phase III and BLA, in Section 6.2 you state* (b) (4) *Clarify how these conditions represent the worst-case scenario.*
- *You indicate that at least three GMP and/or PPQ lots will be tested to establish the range of retrovirus-like particles concentration* (b) (4)*. Please note that the highest concentration of retrovirus-like particles established in these* (b) (4) *lots should be used to calculate the virus safety factor.*
- *You state in the cover letter that the intent of the virus clearance studies is to demonstrate a virus safety factor of* (b) (4)*, based on a feedback provided by the Agency in May 2006. We note that our comment to Tanox was* (b) (4) *which also has served as a base for the development of current WuXi Apptec manufacturing process. Note that the calculation of the estimated particles per dose should be performed according to Appendix 5 in ICH Q5A(R1) Viral Safety Evaluation of Biotechnology Products Derived from Cell Lines or Human or Animal Origin. Based on the manufacturing steps used for your proposed commercial process, we expect that you would easily achieve these higher levels of retrovirus clearance.*

Meeting Discussion:
The sponsor provided the rationale that the conditions tested represent the worst case scenario. The Agency responded that the sponsor should provide justification in the BLA submission and it will be a review issue. (b) (4)

Question 4:
Cell Bank -- TaiMed will propose additional studies to characterize the cell bank for Agency review.

FDA comment from Feb. 19, 2015
You have indicated in some of your previous amendments that the ibalizumab expressing cell line (b) (4). *Please describe your plan to confirm and/or control MCB clonality.*

FDA comment from July 2011 at TaiMed EOP2 mtg:
Cell bank characterization should conform to existing guidance documents [ICH Topic Q5D "Derivation and Characterization of Cell Substrates Used for Production of Biotechnological / Biological Products" and "Points to Consider in the Manufacture and Testing of Monoclonal Antibody Products for Human Use (1997)"]. Master Cell Bank characterization should include assays for sterility, mycoplasma, virus (adventitious, species-specific, and retrovirus), authenticity, the number of integrated of expression plasmid/genome, and a confirmation that the DNA sequence of the gene transcript cDNAs encodes the expected antibody amino acid sequence. Working Cell Bank characterization should include assays for sterility, mycoplasma, and authenticity.

The original IND submitted by Tanox in 2001 described the production cell line development, cell banking, and cell bank testing (b) (4)

TaiMed is proposing to characterize the cell line further for the following:
1. Genetic analysis of the MCB for copy number, integration sites, absence of insertions or deletions, cDNA sequencing

2. Testing of cells (b) (4)

(b) (4) Results will be reported in the BLA.
3. Demonstration of cell line clone stability (b) (4)

Clone stability data will be provided in the BLA that demonstrate the stability of the WCB (b) (4) (b) (4) In addition, (b) (4). The available historical data demonstrate good process consistency and thus also support MCB clonality.

FDA Response:
In general, your plan to further characterize the ibalizumab MCB and end of production (EOP) cells appears adequate. However, historical data demonstrating process consistency are not sufficient to support MCB clonality. (b) (4) *he clonality of the MCB will be a BLA review issue.*

Question 5:
Process development--the sampling plan for the validation lots is not statistically based. We propose to generate additional data over time post-approval to demonstrate inter and intra batch consistency. Is this acceptable?

The commercial DP (b) (4) Bioburden, endotoxin and protein concentration are determined a (b) (4) DP critical quality attributes (protein concentration, aggregates, oxidation and deamidation) to gain understanding of impact of process parameters on drug product critical quality attributes. Data will be accumulated over time to demonstrate that the production is consistent in a controlled manner. Considering the predicted small batch size and supply demand, we are proposing that three consecutive batches will be produced without statistical sampling to support process validation. The process characterization sampling will be performed for each batch post approval over time to demonstrate inter and intra batch variability. Is this acceptable?

FDA Response:
Your approach may be acceptable; however this will be a BLA review issue. We recommend that you implement a continued process verification (CPV) plan for the ibalizumab drug product (and for drug substance) manufacturing process to help you understand drug product manufacturing and batch variability. See the BioPhorum Operation Group CPV case study as an industry example of a drug substance CPV plan.
http://www.biophorum.com/article/103/cpv-continued-process-verification-case-study.

Question 6:
Specifications
For post approval, we request that the specification (b) (4) be removed from the drug substance specification. This request will be supported by data from 5 GMP lots made at WuXi AppTec in the BLA. Is this acceptable?

FDA Response:
Your request to remove the release testing (b) (4) may be acceptable, but will be a BLA review issue. The approach should be similar to removing (b) (4) assay from release testing.

Question 7:
Forced degradation study--we will provide a summary on the scope of the study.

The forced degradation study will assess 3 GMP lots (Lots 1 and 2 of the drug product and Lot 3 of the drug substance) summarized in Forced Degradation Protocol (not included in the Meeting Minutes). The data will be compared with concurrent runs of the Tanox reference standard.
Is this acceptable?

FDA Response:
Your plan to study the forced degradation of ibalizumab DS and/or DP under different conditions appears adequate. However, typically, forced degradation studies are performed separately for drug substance and drug product and data are not combined.

Meeting Discussion:
The sponsor stated that (b) (4) they do not feel the need to do degradation studies on both DS and DP. The Agency responded that DS and DP have different container closure systems so they degradation studies are needed for both. However, the sponsor replied that both DS and DP are stored (b) (4), with the DS stored (b) (4) The Agency recommended focusing on the DP forced degradation study since DS is not held for very long, but this would be a review issue. They should also provide a justification that the DP container closure is representative of the DS container closure if they want to apply the DP studies to the DS. The adequacy of the forced degradation studies will be a review issue.

Additional FDA Comments:

Facility and Inspection comments:
We refer to the email exchanges between you and the Agency from June 4 through June 8, 2015, when you 1) informed the Agency that the 3rd validation lot (5th GMP lot) manufactured by your CMO, WuXi Apptec, was scheduled to be manufactured starting June 19, 2015 and; 2) that due to the small orphan disease population for ibalizumab, there are currently no manufacturing plans after the manufacture of the 3rd validation lot.

At the time the Agency replied that in rare circumstances, such as manufacturing lots for an orphan indication where the validation campaign would produce a sufficient number of lots to treat patients for several years, it may be possible for the FDA to perform a meaningful inspection, if a similar product was being manufactured at the time of the pre-license inspection (PLI) in the same suites, using the same equipment.

However, we also stated that this should be discussed during the pre-BLA meeting and agreement was needed by the entire CMC review team, which includes reviewers from the Office of Pharmaceutical Quality/Office of Process and Facilities/Division of Microbiology Assessment and Division of Inspectional Assessment, in addition to reviewers from the Office of Biotechnology Products. Below is our standard comment to sponsors regarding facilities and readiness for inspection.

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

Based on the 5 GMP lots manufactured to date, provide an estimate of the number of doses currently available to treat patients and how soon you would need to manufacture additional lots to replenish supplies.

You also stated that you plan to submit a Rolling BLA, starting with Module 3 at the end of 2015. Provide an updated timeline of your plans for submission of each module for the Rolling BLA, particularly CMC Module 3 and when you expect the final Module to be submitted. The BLA review clock will not begin until the BLA submission is complete. We are unlikely to schedule a PLI prior to the BLA being filed.

Meeting Discussion:
The sponsor stated that GMP lots 4 and 5 are intended for launch and should last 6 to 12 months. They anticipate the next manufacturing run will be mid to late 2017. The Agency recommended that since it might be a year between the submission of module 3 and the BLA submission, the sponsor should reconsider their manufacturing schedule. It is possible that the Agency could inspect the facility while a different product is being manufactured.

In this situation, the sponsor should provide their manufacturing schedule along with a comparison of the other product being manufactured. The sponsor stated that it is highly unlikely the other client will allow the Agency to inspect their process. The Agency stated that if we can't inspect the facility and see an active DS manufacturing process, we won't be able to approve the BLA. The Sponsor and WuXiApptec stated they would reconsider the ibalizumab manufacturing schedule to coincide with a time frame for an inspection.

The Agency stated that they will most likely not inspect the manufacturing facilities before the BLA is filed. Since both DS and DP are manufactured at the same location, we would inspect both facilities at the same time. Therefore, the sponsor should plan manufacturing runs to occur shortly after the BLA filing to allow for a meaningful inspection of the manufacturing facilities in operation. The Agency also stated that unlike the case with DS, the drug product facility could be inspected while in operation (b) (4) processing either drug product, media fills or another product. The Agency stated they they will be at the facility for at least 2-3 weeks. The sponsor stated that they anticipate submitting module 3 in December 2015, with the full BLA being submitted in 3rd quarter of 2016. Given that ibalizumab has breakthrough designation, the early submission of Module 3 will enable the reviewers to have a thorough knowledge of the manufacturing process prior to the inspection and this will allow for planning the inspection shortly after the BLA is filed. TaiMed should provide the manufacturing schedule for ibalizumab DS and DP activities prior to submission of the final Module as it takes at least 2 months for the Agency to arrange foreign travel.

<u>Microbiology Comments:</u>
We are providing additional product quality microbiology comments for you to consider during development of your commercial manufacturing process and preparation of your BLA submission.

The CMC Drug Substance section of the BLA (Section 3.2.S) should contain information and data summaries for microbial and endotoxin control. The provided information should include, but not be limited to the following:

- *Bioburden and endotoxin levels at critical manufacturing steps should be monitored using qualified bioburden and endotoxin tests. The pre-established bioburden and endotoxin limits should be provided (3.2.S.2.4).*
- *Three successful consecutive product* [redacted] (b) (4) *validation runs at manufacturing scale. Bioburden and endotoxin levels before and after the maximum allowed* [redacted] (b) (4) *should be monitored and bioburden and endotoxin limits provided (3.2.S.2.5).*
- *Information and summary results data demonstrating microbial control* [redacted] (b) (4) *(3.2.S.2.5).*
- *Bioburden and endotoxin data obtained during manufacture of at least three conformance lots (3.2.S.2.5).*
- *Information and summary results from the shipping validation studies (3.2.S.2.5).*
- *Drug substance bioburden and endotoxin release specifications (3.2.S.4). Please note that DS specification for bioburden is* (b) (4) *CFU/* (b) (4) *mL for bulk materials stored at* [redacted] (b) (4).
- *Summary report and results from bioburden and endotoxin test methods qualification performed for* [redacted] (b) (4) *the drug substance (3.2.S.4).*

The CMC Drug Product section of the BLA (Section 3.2.P) should contain validation data summaries to support the [redacted] (b) (4) *and sterility assurance. For guidance on the type of data and information that should be submitted, refer to the 1994 "FDA Guidance for Industry, Submission Documentation for Sterilization Process Validation in Applications for Human and Veterinary Drug Products" at http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm072171.pdf*

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

- *Bacterial filter retention study for the sterilizing filter.*
- *Sterilization and depyrogenation of equipment and components that contact the sterile drug product. Provide summary data for the three most recent requalification studies and describe the equipment requalification program.*
- *In-process microbial controls and hold times. Three successful consecutive product* [redacted] (b) (4) *validation runs at manufacturing scale. Bioburden and endotoxin levels before and after the maximum allowed* [redacted] (b) (4) *should be monitored and bioburden and endotoxin limits provided.*
- [redacted] (b) (4)
- *Isolator decontamination, if applicable.*
- *Three successful consecutive media fill runs, including summary environmental monitoring data obtained during the runs.*

- *A description of the routine environmental monitoring program.*
- *Shipping validation studies, including container closure integrity data.*

Meeting Discussion:
The sponsor asked if the sample volume could be 10mL for the (b) (4) sample. The Agency responded that in cases where the batch volume is very small, the Agency will allow for 10 ml test volumes instead of 100 mL with an adequate justification in the BLA. The justification should include consideration of batch size and microbial controls (b) (4).

The following method validation information should be provided:

- *Container closure integrity testing (3.2.P.2.5). System integrity (including maintenance of the microbial barrier) should be demonstrated initially and during stability. Container closure integrity methods validation should demonstrate that the assay is sensitive enough to detect breaches that could allow microbial ingress. We recommend that container closure integrity testing be performed in lieu of sterility testing for stability samples at the initial time point and every 12 months (annually) until expiry (3.2.P.8.2).*
- *Summary report and results for qualification of the bioburden, sterility and endotoxin test methods performed for (b) (4) the drug product, as appropriate.*
- *Summary report and results of the Rabbit Pyrogen Test conducted on three batches of drug product in accordance with 21CFR610.13(b).*
- *Formulations with certain excipient and polysorbate combinations have been reported to interfere with endotoxin recoverability in the USP LAL test methods over time. The effect of (b) (4) on endotoxin recovery should be assessed (b) (4) and the drug product and then testing for recoverable endotoxin over time.*

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

/s/

MARJORIE A SHAPIRO
09/08/2015

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 9776

GRANT –
BREAKTHROUGH THERAPY DESIGNATION

TaiMed Biologics
Attention: Helen P. Shu, PhD
VP Regulatory Affairs and Quality
18201 Von Karman Ave., Ste. 470
Irvine, CA 92612

Dear Dr. Shu:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for IV ibalizumab, TNX 355; Hu5A8, for intravenous injection (IV).

We also refer to your December 31, 2014, request for Breakthrough Therapy designation. We have reviewed your request and have determined that IV ibalizumab for the treatment of HIV-1 infection in treatment-experienced adult patients with documented multi-antiretroviral class resistance and evidence of HIV replication despite antiretroviral therapy 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 IV ibalizumab for the treatment of HIV-1 infection in treatment-experienced adult patients with documented multi-antiretroviral class resistance and evidence of HIV replication despite antiretroviral therapy 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]

Please refer to the January 22, 2015, teleconference with the FDA to discuss issues related to the chemistry, manufacturing and control (CMC) programs for your product development. We also note your pending March 02, 2015, teleconference with the FDA to discuss the clinical requirements for the registration package for ibalizumab administered via the intravenous route in HIV positive heavily treated patients with multidrug resistant virus infection. The results of the March 02, 2015 teleconference with the FDA will likely determine the clinical issues that should be addressed during your initial Breakthrough Therapy meeting.

[1] http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM358301.pdf

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, as well as a continuing discussion of the recently addressed CMC and clinical plans. 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 breakthrough therapy meeting[2]. 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 IV ibalizumab for the treatment of HIV-1 infection in treatment-experienced adult patients with documented multi antiretroviral class resistance and evidence of HIV replication despite antiretroviral therapy 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, call Sohail Mosaddegh, PharmD, Regulatory Project Manager, at (301) 796-4876 or (301) 796-1500.

Sincerely yours,

{See appended electronic signature page}

Debra Birnkrant, MD
Director
Division of Antiviral Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

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[2] http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ManualofPoliciesProcedures/default.htm.

[3] http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM153222.pdf

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/s/

JEFFREY S MURRAY
02/23/2015

Benton, Sandra J

From: Benton, Sandra J
Sent: Wednesday, January 28, 2015 7:38 AM
To: Temple, Robert; Moscicki, Richard; Jenkins, John K; Woodcock, Janet; Dal Pan, Gerald; Griebel, Donna; Mahoney, Karen M (Deputy DD, DNDP); Hinton, Denise; Sacks, Leonard V
Cc: Raggio, Miranda; Brounstein, Daniel; Cox, Edward M; Unger, Ellis; Beitz, Julie G; Ganley, Charles J; Pazdur, Richard; Rosebraugh, Curtis; Throckmorton, Douglas C; Mosaddegh, Sohail; Yoder, Christian; Alivisatos, M R; Sherwat, Adam; Birnkrant, Debra B; Murray, Jeffrey S
Subject: RE: February 17, 2015 - Medical Policy Council – Breakthrough Therapy Designation - IND 9776

As the Council agrees with DAVP's recommendation to grant TaiMed's breakthrough therapy designation request and does not believe a Council discussion is needed, this request will be cancelled from the February 17 meeting agenda.

The Council has commented on the needed size of the safety database as requested in DAVP's review (please see other emails as well). If DAVP needs any further discussion or questions, I will be happy to schedule a follow-up discussion.

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

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

From: Temple, Robert
Sent: Wednesday, January 21, 2015 6:15 PM
To: Moscicki, Richard; Benton, Sandra J; Jenkins, John K; Woodcock, Janet; Dal Pan, Gerald; Griebel, Donna; Mahoney, Karen M (Deputy DD, DNDP); Hinton, Denise; Sacks, Leonard V
Cc: Raggio, Miranda; Brounstein, Daniel; Cox, Edward M; Unger, Ellis; Beitz, Julie G; Ganley, Charles J; Pazdur, Richard; Rosebraugh, Curtis; Throckmorton, Douglas C; Mosaddegh, Sohail; Yoder, Christian; Alivisatos, M R; Sherwat, Adam; Birnkrant, Debra B; Murray, Jeffrey S
Subject: RE: February 17, 2015 - Medical Policy Council – Breakthrough Therapy Designation - IND 9776

I also concur. The Division asked the MPC to comment on the needed size of the safety data base, which they had specified several years ago as at least (b) (4) patients on the highest proposed dose. (b) (4) the sponsor now has, according to the division, about 150 patients with such exposure. The size of the planned phase 3 trial is not specified (unless I missed it) but would seem likely to have at least another (b) (4) patients for at least 24 weeks, which seems pretty close to the expected exposure. Given the urgent treatment needs for the target population (patients with documented multi-antiretroviral class resistance), a total population of (b) (4) patients 9i.e., somewhat fewer than the specified (b) (4)) seems adequate for approval. I also note, however, that if these patients are really 8% of the HIV-positive population in the U.S. (page 2), it seems pretty unlikely that there will be any scarcity of patients for entry into the phase 3 trial.

From: Moscicki, Richard
Sent: Wednesday, January 21, 2015 2:55 PM
To: Benton, Sandra J; Temple, Robert; Jenkins, John K; Woodcock, Janet; Dal Pan, Gerald; Griebel, Donna; Mahoney,

Karen M (Deputy DD, DNDP); Hinton, Denise; Sacks, Leonard V
Cc: Raggio, Miranda; Brounstein, Daniel; Cox, Edward M; Unger, Ellis; Beitz, Julie G; Ganley, Charles J; Pazdur, Richard; Rosebraugh, Curtis; Throckmorton, Douglas C; Mosaddegh, Sohail; Yoder, Christian; Alivisatos, M R; Sherwat, Adam; Birnkrant, Debra B; Murray, Jeffrey S
Subject: RE: February 17, 2015 - Medical Policy Council – Breakthrough Therapy Designation - IND 9776

I concur with the division. Rich.

From: Benton, Sandra J
Sent: Friday, January 16, 2015 2:02 PM
To: Temple, Robert; Jenkins, John K; Woodcock, Janet; Dal Pan, Gerald; Griebel, Donna; Mahoney, Karen M (Deputy DD, DNDP); Hinton, Denise; Sacks, Leonard V
Cc: Raggio, Miranda; Brounstein, Daniel; Cox, Edward M; Unger, Ellis; Beitz, Julie G; Ganley, Charles J; Pazdur, Richard; Rosebraugh, Curtis; Moscicki, Richard; Throckmorton, Douglas C; Mosaddegh, Sohail; Yoder, Christian; Alivisatos, M R; Sherwat, Adam; Birnkrant, Debra B; Murray, Jeffrey S
Subject: February 17, 2015 - Medical Policy Council – Breakthrough Therapy Designation - IND 9776

Hi! OMP has scheduled a Medical Policy Council discussion on February 17, 2015 regarding the breakthrough therapy designation request from TaiMed for its IND 9776, TNX-355, Hu5A8 for the treatment of HIV-1 infection in treatment-experienced adult patients with documented multi antiretroviral class resistance and evidence of HIV replication despite antiretroviral therapy.

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

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

Would you please review DAVP's recommendation and let me know by COB Friday, January 23 if –

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

If the Council agrees with bullet 1, I will cancel the discussion for IND 9776.

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

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

<< File: BTDR-MPC-BG-9776-01-2015.doc >> << File: S-0239.pdf >>

Benton, Sandra J

From: Woodcock, Janet
Sent: Friday, January 16, 2015 3:46 PM
To: Benton, Sandra J; Temple, Robert; Jenkins, John K; Dal Pan, Gerald; Griebel, Donna; Mahoney, Karen M (Deputy DD, DNDP); Hinton, Denise; Sacks, Leonard V
Cc: Raggio, Miranda; Brounstein, Daniel; Cox, Edward M; Unger, Ellis; Beitz, Julie G; Ganley, Charles J; Pazdur, Richard; Rosebraugh, Curtis; Moscicki, Richard; Throckmorton, Douglas C; Mosaddegh, Sohail; Yoder, Christian; Alivisatos, M R; Sherwat, Adam; Birnkrant, Debra B; Murray, Jeffrey S
Subject: RE: February 17, 2015 - Medical Policy Council – Breakthrough Therapy Designation - IND 9776

I concur with the division.

As I have noted before, I believe the size of the safety database surely can be adjusted based on the size of the anticipated population. (b) (4) patients out of an anticipated (b) (4) target population is more representative than (b) (4) patients out of a million or more target population. jw

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From: Benton, Sandra J
Sent: Friday, January 16, 2015 2:02 PM
To: Temple, Robert; Jenkins, John K; Woodcock, Janet; Dal Pan, Gerald; Griebel, Donna; Mahoney, Karen M (Deputy DD, DNDP); Hinton, Denise; Sacks, Leonard V
Cc: Raggio, Miranda; Brounstein, Daniel; Cox, Edward M; Unger, Ellis; Beitz, Julie G; Ganley, Charles J; Pazdur, Richard; Rosebraugh, Curtis; Moscicki, Richard; Throckmorton, Douglas C; Mosaddegh, Sohail; Yoder, Christian; Alivisatos, M R; Sherwat, Adam; Birnkrant, Debra B; Murray, Jeffrey S
Subject: February 17, 2015 - Medical Policy Council – Breakthrough Therapy Designation - IND 9776

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

If the Council agrees with bullet 1, I will cancel the discussion for IND 9776.

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

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

<< File: BTDR-MPC-BG-9776-01-2015.doc >> << File: S-0239.pdf >>

CDER Medical Policy Council Brief
Breakthrough Therapy Designation
Division of Antiviral Products
29 January 2015

Summary Box

1. IND: 9776
2. Company: TaiMed
3. Products: Ibalizumab, TNX-355, Hu5A8
4. Indication: treatment of HIV-1 infection in treatment-experienced adult patients with documented multi antiretroviral class resistance and evidence of HIV replication despite antiretroviral therapy
5. These drugs are intended to treat a serious or life-threatening disease or condition.
6. The preliminary clinical evidence indicates that this drug in combination with other approved antiretrovirals may demonstrate substantial improvement over existing therapies on 1 or more clinically significant endpoints (efficacy and safety).

1. Brief description of the drug

Ibalizumab is a humanized immunoglobulin (IgG) isotype 4 MAb. It binds to a conformational epitope on domain 2 of CD4, inhibiting HIV entry into cells.

2. Brief description of the disease, intended population, and currently available therapies

The United States Centers for Disease Control (CDC) reported the first clinical evidence of Acquired Immunodeficiency Syndrome (AIDS) in June 1981. Shortly thereafter the link between HIV-1 infection and AIDS was discovered. Since that time HIV/AIDS has been recognized as a global epidemic with an estimated 65 million people being infected and over 25 million deaths from the disease. In 2012, over 35 million people worldwide were living with HIV infection and 1.6 million people died from HIV/AIDS. The CDC's most recent estimate of the US prevalence for HIV infection in 2011, both diagnosed and undiagnosed, is >1.1 million adults and adolescents (447.8 per 100,000) (CDC 2013).

Infection with HIV-1 results in chronic, progressive depletion of T-lymphocytes (CD4+ or helper T-cells) and also affects macrophages and other cells important for immune surveillance, HIV infection, if left untreated or suboptimally treated, is characterized by deterioration in immune function with subsequent occurrence of opportunistic infections and malignancies, ultimately resulting in death.

The primary objective of anti-HIV treatment is to suppress viral replication to undetectable levels through the use of a combination of highly active antiretroviral drugs (HAART). Persons with ongoing viral replication are at risk for disease progression and death. The principle reasons for treatment failure include the development of viral resistance, non-adherence, and intolerance to the available medications.

A subset of the HIV-1 infected population consists of individuals previously treated with HIV drugs who have developed documented drug resistance to at least one agent from each of the most widely used classes of antiretroviral agents, nucleos(t)ide reverse transcriptase inhibitors (NRTI), non-nucleoside reverse transcriptase inhibitors (NNRTI), protease inhibitors (PI) and integrase inhibitors, and have evidence of HIV-1 replication despite ongoing antiretroviral therapy. The size of this subset of the HIV-positive population has been estimated by two sources as 8% of the HIV-positive population in the US. This is the population for which ibalizumab is being developed.

Ibalizumab prevents HIV from infecting the host cells by inhibiting HIV entry. To date there are two FDA approved agents that treat HIV infection by inhibiting HIV-1 entry, Fuzeon® (enfuvirtide; T 20) and Selzentry® (maraviroc). Both of these compounds have been shown to be efficacious in clinical trials with treatment-experienced patients when combined with an optimized background regimen (OBR). The safety and efficacy data from these clinical trials support the rationale for studying agents that intervene in the process of HIV-1 pathogenesis at the point of entry into host cells.

3. Endpoints used in the available clinical data, endpoints planned for later studies, and endpoints currently accepted by the review division in the therapeutic area

Initally decreases in HIV RNA levels below the level of detection were utilized in clinical trials as endpoints to support both accelerated and traditional approvals of antiretrovirals because they were predictive of meaningful clinical benefit. These trials assessed efficacy at 24 (accelerated approval) or 48 weeks (traditional approval) where the drug's contribution toward the durability of the effect on HIV RNA levels was assessed. HIV RNA is now considered a validated surrogate for predicting the efficacy of antiretrovirals and the paradigm of accelerated approvals based on HIV RNA levels at 24 weeks followed by traditional approvals based on levels at 48 weeks is no longer necessary. At this point approval is more dependent on the timing of HIV RNA assessments in the population under study. In the population of highly treatment experienced subjects the Division is now assessing virologic response (proportion of patients with HIV-RNA decreases from baseline exceeding 0.5 log) at 2 weeks plus virologic follow-up at 24 weeks.

The Sponsor is relying on this paradigm as the efficacy endpoint to support their request for a breakthrough therapy designation, and this endpoint will also be used in the Sponsor's pivotal trials of this drug combination. This endpoint which assesses early virologic changes in heavily treatment experienced subjects is accepted by the Division as a clinically significant endpoint for HIV-1 treatment trials in such highly treatment experienced subjects. This is a surrogate endpoint known to predict clinical benefit, as achievement of HIV-1 viral suppression has been associated with reduced morbidity and all-cause mortality,

4. Brief description of any drugs being studied for the same indication that received breakthrough therapy designation

There are no similar drugs being studied for the same indication that have received breakthrough therapy designation.

5. Description of preliminary clinical evidence

Ibalizumab administered intravenously has been studied in Phase 1 single and multiple dose trials as well as in a Phase 2a Dose-finding trial: Multiple-Dose Safety, Efficacy, And Pharmacokinetic Study with IV Ibalizumab (Protocol TNX-355.03) and a Phase 2b Multiple-Dose Safety, Efficacy, And Pharmacokinetic Study (Protocol TMB-202) in HAART experienced subjects. In addition 31 subjects who did not experience virologic failure during the double-blind (Week 24) portion of TMB 202 were permitted to continue receiving open-label ibalizumab at the same study dose under principal investigator sponsored INDs (PI-IND) for a number of years. (b) (4)

(b) (4)

Safety Background of Ibalizumab

The available safety data for Ibalizumab at the proposed doses reveal it to be relatively safe and well tolerated. There were few associated toxicities and none were dose limiting. The most frequently reported adverse events were rash, fatigue, headache, and diarrhea. The rash events often appeared to be treatment related and in some cases led to treatment discontinuation. Hypersensitivity reactions, judged related to study drug per investigator and leading to study drug discontinuation, have also been reported in clinical trials. Safety assessments for injection site reactions, intradermal antigen reactivity, and immunogenicity were also performed.

Few primary AEs related to the immune system, other than rashes during and post infusion occurred. Increased immunogenicity has not been a significant issue to date with few subjects developing transient anti-TNX355 antibodies during the studies. The clinical implications of the transient development of anti-ibalizumab antibodies are unknown. There is also a theoretical possibility that ibalizumab may cause a decrease in the number and/or effectiveness of CD4 cells given its mechanism of action; however this phenomenon has not been reported in clinical trials to date

<u>Efficacy of Ibalizumab:</u>

An overview of the efficacy of ibalizumab is presented in the Table below. Generally, Ibalizumab has demonstrated clinically meaningful viral load reductions as monotherapy and durable viral suppression with an optimized background regimen (OBR). Across the studies the primary efficacy endpoints were met and ibalizumab was effective in reducing viral load in a dose dependent manner.

This could be seen in the Phase 1a SD, dose escalation study (355.01) where mean reductions of more than 1 log10 in viral load were observed for 1-2 weeks after administration of a single dose of 10 and 25 mg/kg of

ibalizumab, and a mean reduction of more than 0.6 log10 was observed after administration of 3 mg/kg. Lower doses (0.3 mg/kg and 1 mg/kg) were not associated with clinically significant viral load reductions.

TABLE 1a. IV Ibalizumab Completed Clinical Studies in HIV-Infected Subjects: Drug Efficacy Summary

Protocol Number	Dose Arms	Ibalizumab Dose Per Protocol		Study Duration Per Protocol	No. of Subjects Per Protocol	Efficacy Viral Load Reduction	
Hu5A8.01 (Phase 1a, open label, N = 30)	Single Dose	0.3 mg/kg		N/A	6	n.s.	
		1.0 mg/kg			6	n.s.	
		3.0 mg/kg			6	>0.6 log	
		10 mg/kg			6	>1.0 log	
		25 mg/kg			6	>1.0 log	
TNX-355.02 (Phase 1b, open label, N = 22)	Multidose Arm A	10 mg/kg q wk for 10 doses		10 wks	9	0.95 log, wk 1	
	Multidose Arm B	10 mg/kg single dose	6 mg/kg q 2 wks for 5 doses	10 wks	10	0.83 log, wk2	
	Multidose Arm C	25 mg/kg q 2 wks for 5 doses		10 wks	3	0.96 wk 1	
TNX-355.03 (Phase 2a, Double blind, placebo controlled, N = 82)*	Multidose Arm A	15 mg/kg q 2 wks for 48 wks		48 wks DB, total up to 216 wks	28	Mean 0.95 log, wk 24	Mean 0.71 log, wk 48
	Multidose Arm B	9 mg/kg q wk for 9 doses, 10 q 2 wks for 39 wks		48 wks DB, total up to 216 wks	27	Mean 1.16 log, wk 24	Mean 0.96 log, wk 48
	Placebo	Placebo (Upon VF, switch to 15mg/kg)		48 wks DB, total up to 216 wks	27 placebo (23 switched to active)	Mean 0.20 log, wk 24	Mean 0.14 log, wk 48
TMB 202 (Phase 2b, Double blind, dose response, ibalizumab and OBR, treatment experienced)	Multidose	800 mg q 2 wks		24 wks	59	Wk 24 ITT MEF [a]: 44% <50 copies/mL; 58% <400 copies/mL; 63% > 1 log drop from baseline;	
	Multidose	2000 mg q 4 wks		24 wks	54	Wk 24 ITT MEF [a] 28% <50 copies/mL; 46% <400 copies/mL; 59% > 1 log drop from baseline;	

Source: Sponsor's Submission in Support of Breakthrough Designation

In the Phase 1b proof-of-concept study (355.02) which compared weekly and biweekly dose regimens of intravenous Ibalizumab (nine subjects in Arm A received 10 mg/kg administered every week for 10 total doses, ten subjects in Arm B received a single loading dose of 10 mg/kg, followed 1 week later by 6 mg/kg every 14 days for a total of five maintenance doses and three subjects in Arm C received 25 mg/kg of intravenous ibalizumab every 14 days for five total doses) clinically significant viral load reductions (≥0.5 log10) were observed with all three dose regimens. Mean maximal viral load reductions were 0.95 log10 and 0.83 log10 for Arm A and Arm B, respectively. A 0.96 log10 mean maximal viral load reduction was seen in Arm C. Viral load nadirs were observed during Week 1 for Arms A and C, and Week 2 for Arm B.

In study 355.03 the phase 2a MD trial where Ibalizumab was assessed in combination with an OBR in 82 treatment-experienced HIV-infected patients who received weekly and biweekly dosages of intravenous Ibalizumab (Arm A – 15 mg/kg every 2 weeks, or Arm B – 10 mg/kg every week for nine doses followed by 10 mg/kg every two weeks), the primary endpoint was the mean change in viral load at Week 24 between either of the two active arms of ibalizumab plus OBR and the placebo plus OBR (Arm C). Both active doses

demonstrated statistically significant reductions in the mean viral load compared with placebo. Treatment with the 10 mg/kg regimen (Arm B) resulted in a 1.16 log10 reduction in viral load compared with a 0.20 log10 reduction in the placebo group (P <0.001). Treatment with the 15 mg/kg regimen resulted in a 0.95 log10 reduction in viral load compared with the placebo group (P = 0.003). At Week 48, the 10 mg/kg regimen maintained a 0.96 log10 reduction in viral load (P <0.001) and the 15 mg/kg regimen maintained a 0.71 log10 viral load reduction (P = 0.009) compared with a 0.14 log10 reduction in the placebo group.

In study TMB-202 which assessed biweekly or monthly fixed dose regimens of ibalizumab (Arm A – 800 mg every 2 weeks, or Arm B – 2000 mg/kg every 4 weeks in combination with OBR), the primary endpoint of percentage of subjects with undetectable (<50 copies/mL) HIV-1 RNA at 24 weeks was achieved in 44% of patients in the 800 mg q2wk arm and 28% of patients in the 2000 mg q4wk arm. This study was not designed to observe a statistical difference between the 800 mg q2wk dose and the 2000 mg q4wk dose. Additional viral load results at Week 24, including percent of patients with ≥ 1.0 log10 reduction in HIV-1 RNA from Baseline and mean change in viral load from Baseline, were similar between the 800 mg q2wk and the 2000 mg q4wk dose groups. Treatment with 800 mg q2wk resulted in 63% of patients experiencing a ≥ 1.0 log10 decline in viral load from Baseline and a mean change from Baseline in HIV-1 RNA of -1.6 log10. Treatment with 2000 mg q4wk resulted in 59% with ≥ 1.0 log10 decline from Baseline and a mean change of -1.5 log10 in HIV-1 RNA.

Thirty-one subjects continued to receive IV ibalizumab at the conclusion of this study as long as they maintained an HIV RNA level ≥ 0.7 log10 decrease from baseline. Of 15 subjects receiving 800mg ibalizumab, 100% maintained a >1 log10 reduction from baseline in HIV-1 RNA, 87% had <400 copies/mL HIV-1 RNA, and 60% had undetectable HIV-1 RNA (<50 copies/mL), with a mean change from baseline of -2.7log10 HIV RNA copies/mL. Of the 16 subjects receiving 2000mg ibalizumab, 88% maintained a >1 log10 reduction from baseline in HIV-1 RNA, 88% had <400 copies/mL HIV-1 RNA, and 63% had undetectable HIV-1 RNA (<50 copies/mL), with a mean change from baseline of -2.5 log10 HIV RNA copies/mL.

6. Division's recommendation and rationale

The breakthrough therapy designation for Ibalizumab is supported by the following:

1. Ibalizumab is a humanized monoclonal antibody that prevents HIV from infecting host cells by inhibiting HIV entry in a novel way by inhibiting binding to the conformational epitope on domain 2 of CD4 cells. Binding to domain 2 avoids the immunosuppressive issues that can occur with other monoclonals that bind to domain 1 and thus interfere with major histocompatibility complex class II-mediated immune functions, which also require access to CD4 domain 1.

2. Because Ibalizumab binds to domain 2 it inhibits infection by a wide variety of clinical isolates spanning all HIV subtypes. Unlike the approved maraviroc and other CCR5 entry inhibitors in development, ibalizumab is active against both CCR5 and CXCR4 tropic viruses.

3. Ibalizumab's unique mechanism of action allows for potent blockade of HIV entry, and is effective against HIV strains resistant to other antiretroviral agents. Conversely, HIV that becomes resistant

to ibalizumab remains sensitive to other antiretrovirals. This lack of cross-resistance with other agents greatly enhances ibalizumab's utility in the treatment for HIV.

4. Ibalizumab is dosed infrequently (every 2 or 4 weeks) which may lead to improved adherence.

5. Ibalizumab is reasonably well tolerated to date. Because it is administered intravenously or parenterally there are few GI side effects. The most common events of rash, fatigue, and headache have not appeared to be dose-limiting.

6. The population for which Ibalizumab is being developed, those subjects who are highly treatment experienced with multi-class drug resistance and few therapeutic options, have a great need for new innovative treatments.

Based on the data presented, DAVP believes that Ibalizumab meets the definition of a breakthrough therapy for the treatment of HIV-1 infection in treatment-experienced adult patients with documented multi antiretroviral class resistance and evidence of HIV replication despite antiretroviral therapy as outlined in Section 903 of the Food and Drug Administration Safety and innovation Act and recommends that Ibalizumab be given a breakthrough therapy designation.

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

The Division plans to work closely with the Sponsor to advance their development program. Specifically, the Division intends to work with the Sponsor to develop their Phase 3 registrational trial in a timely manner which will allow for NDA submission within the next two years.

8. **Questions for the MPC**

The DAVP requests the MPC's comment on the size of the proposed safety database necessary to support a BLA submission if breakthrough designation is granted. Of note, this product has also recently been granted an Orphan Drug designation.

To date, the Sponsor has treated approximately 70 subjects with the 2000 mg dose (administered every 4 weeks for at least 24 weeks) and approximately 60 subjects with the 800 mg dose (administered every 2 weeks). In addition, there is available safety data from the longer term use of ibalizumab in approximately 20 – 30 subjects enrolled under investigator INDs.

Several years ago, the Sponsor was told that a minimum of (b) (4) subjects would be necessary at the highest proposed dose. However, both the Sponsor and the Division agree that finding and enrolling the intended patient population for this product (i.e. the HIV "salvage" population) for the pivotal Phase 3 trial may be challenging. The Division is working with the Sponsor to help facilitate collaborations that may help in this regard, for example with NIH's Division of AIDS. Regardless, the DAVP would like to inquire of the MPC whether there is potential flexibility around the size of the required safety database (i.e. whether a safety database of less than (b) (4) subjects at the proposed dose might be deemed satisfactory under these

circumstances). If this is acceptable, the size of the future pivotal Phase 3 trial could be scaled down, thus potentially expediting the completion of the trial and approval of the product.

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/s/

SANDRA J BENTON
01/29/2015

DEBRA B BIRNKRANT
01/30/2015

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 9776

MEETING MINUTES

TaiMed Biologics USA
Attention: Helen Shu, Ph.D.
Vice President, Regulatory Affairs and Quality
5251 California Avenue, Ste. 230
Irvine, CA 92617

Dear Dr. Shu:

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

We also refer to the face to face meeting between representatives of your firm and the FDA on June 14, 2011. The purpose of the meeting was to discuss the results from Phase 2b trial, TMB202 and reach agreement on the Phase 3 trial design and chemistry, manufacturing, and controls (CMC) plan.

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

If you have any questions, call Sherly Abraham, R.Ph., Regulatory Project Manager at (301) 796-3198.

Sincerely,

{See appended electronic signature page}

Debra Birnkrant, M.D.
Director
Division of Antiviral Products
Office of Antimicrobial 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: B
Meeting Category: End of Phase 2

Meeting Date and Time: June 14, 2011, 12:15 PM

Meeting Location: Food and Drug Administration (FDA)
White Oak, Building 22, Room 1313
10903 New Hampshire Ave
Silver Spring, MD 20993

Application Number: IND 9776
Product Name: IV Ibalizumab
Indication: Treatment of HIV infection
Sponsor/Applicant Name: TaiMed Biologics

Meeting Chair: Kim Struble, Pharm.D.
Meeting Recorder: Sherly Abraham, R.Ph.

FDA ATTENDEES

1. Kendall Marcus, M.D., Safety Deputy Director, Division of Antiviral Products (DAVP)
2. Kimberly Struble, Pharm.D., Clinical Team Leader, DAVP
3. Regina Alivisatos, M.D., Medical Officer, DAVP
4. Yodit Belew, M.D., Medical Officer, DAVP
5. Jules O'Rear, Ph.D., Clinical Virology Team Leader, DAVP
6. Damon Deming, Ph.D., Clinical Virology Reviewer, DAVP
7. Sarah Robertson, Pharm.D., Clinical PharmacologyTeam Leader, Division of Clinical Pharmacology 4, (OTS/OCP/DCP4)
8. Vikram Arya, Ph.D., Clinical Pharmacology Reviewer, Division of Clinical Pharmacology 4, (OTS/OCP/DCP4)
9. Greg Soon, Ph.D., Acting Biometrics Team Leader, Division of Biometrics IV (OTS/OB/DVIV)
10. Thomas Hammerstrom, Ph.D., Statistician, Division of Biometrics IV (OTS/OB/DVIV)
11. David Frucht, M.D., Chief, Laboratory of Cell Biology, Division of Monoclonal Antibodies (DMA)

12. Mark Paciga, Ph.D., Product Quality Reviewer, DMA
13. Karen Winestock, Chief, Project Management Staff, DAVP
14. Sherly Abraham, RPh, Regulatory Project Manager, DAVP

SPONSOR ATTENDEES

1. (b) (4) Pharmacokinetics Consultant
2. Stanley Lewis, M.D., VP Clinical and Chief Medical Officer
3. Helen Shu, Ph.D., VP Regulatory Affairs and Quality
4. Steve Weinheimer, Ph.D., Sr. Dir. Biological Sciences

1.0 BACKGROUND

TaiMed Biologics (TaiMed) has developed an intravenous formulation of ibalizumab to be administered in combination with other antiretroviral agents, for the treatment of HIV-1 infection in highly treatment-experienced adult patients with documented drug resistance to at least one agent from each of three approved classes of antiretroviral agents and evidence of HIV-1 replication despite ongoing antiretroviral therapy. TaiMed had a Type C teleconference with FDA on October 20, 2010, to discuss the adequacy and qualification of the available and projected clinical data for registration of ibalizumab intravenous formulation in a subset of the HIV treatment-experienced patient population who are multi-drug resistant. The purpose of this end of Phase 2 meeting was to review the new data from the Phase 2b (TMB 202) trial, to discuss the proposed Phase 3 trial (TMB-301), to discuss the manufacturing plans for the Phase 3 clinical trial material, and to finalize requirements that could enable the submission of a Biologics License Application (BLA).

The proposed Phase 3 study, TMB-301, is a randomized, double blind, 48 week, multicenter study of two dosing regimens of ibalizumab plus an optimized background regimen in treatment experienced patients infected with HIV-1. TaiMed plans to enroll approximately (b) (4) patients from approximately 50 sites. TaiMed proposes to initiate the study with the remaining drug product (DP) manufactured by the Tanox, then subsequently transition to DP manufactured by TaiMed's contract manufacturer.

On April 13, 2011, TaiMed requested a face-to-face end of Phase 2 meeting. After reviewing the request, the FDA requested that TaiMed submit a separate end of Phase 2 CMC meeting request. Preliminary comments for both meetings were provided to TaiMed on Friday, June 10, 2011. The meeting discussion focused on clinical questions one through ten regarding the proposed Phase 3 trial and CMC general discussion. TaiMed's questions are in regular font, and the preliminary comments and discussion are in italics.

2. DISCUSSION

The Division of Antiviral Products (DAVP) stated that the preliminary comments on TaiMed's proposed trial design and primary endpoint evaluation were based on discussions at the Forum for HIV Collaborative Research meeting. DAVP stated, although we support the comments provided to TaiMed with respect to the two-part hybrid trial design, concurrence from CDER's senior management on the 2-week primary endpoint assessment is needed. Additionally, a final decision by senior management has not been made regarding the elimination of accelerated approval for HIV products because HIV RNA is now a validated endpoint and the BLA application could be submitted for traditional approval review. Once TaiMed submits the revised protocol incorporating DAVP's comments, additional feedback will be provided.

DAVP cited 21 CFR 312.42, which states having insufficient quantities of clinical trial material, whether the trial is well designed or not, is a clinical hold issue. Prior to initiating Phase 3 clinical trials, TaiMed must demonstrate that they can manufacture sufficient quantities of drug substance (DS) and DP that are comparable to ibalizumab manufactured by Tanox. TaiMed

confirmed that they do not have adequate supply of Tanox's ibalizumab DP to complete the Phase 3 trial. DAVP strongly recommended that TaiMed resolve the manufacturing issues. TaiMed should submit a draft of their Phase 3 protocol for review before submitting a request for a special protocol assessment (SPA). TaiMed agreed to manufacture sufficient quantities of DS and DP, comparable to the Tanox-manufactured DS and DP, prior to submitting the final protocol.

2.1 CLINICAL:

Questions 1-10:
The questions on the proposed Phase 3 protocol as a pivotal trial are addressed below:

1. Is the overall design of the trial acceptable?
2. Are the proposed doses and dose regimens acceptable?
3. Is the size of patient population for enrollment acceptable?
4. Are the inclusion and exclusion criteria acceptable?
5. Are the primary and secondary efficacy and safety endpoints acceptable?
6. Is the absence of a 2 week lead in monotherapy period acceptable?
7. Is the viral load reduction at Week 12 for protocol required discontinuation of ≥ 0.7 $\log_{10}$ reduction from baseline acceptable?
8. Is the viral load reduction at Week 24 for protocol required discontinuation of ≥ 1.0 $\log_{10}$ reduction from baseline acceptable?
9. Assuming a Phase 3 trial enrolls (b) (4) patients and approximately (b) (4) patients reach Week 24, is this acceptable?
10. Assuming a Phase 3 trial enrolls (b) (4) patients and approximately (b) (4) patients reach Week 48, is this acceptable?

FDA Response:
Based on discussions at the Forum for HIV Collaborative Research meeting and prior telecons with you, your proposed trial requires changes to the overall design and primary endpoint evaluation. Please include a short term (7 days-2 week) monotherapy lead-in phase for this phase 3 trial. In this design, patients experiencing ongoing viral replication on their current regimen and who need a new drug to construct a new viable regimen are randomized to either continue their current regimen plus placebo or to receive a new investigational drug in addition to their current regimen (randomization to the investigational drug at two dose levels as proposed is acceptable). Please provide a justification for the short term duration monotherapy period with your revised protocol. The primary efficacy evaluation of investigational drug versus placebo occurs over a short duration. After the placebo comparison, all participants can receive the investigational new drug (at the two dose levels proposed) added to a re-optimized background. In this proposal a second assessment occurs at 24 weeks to assess for a dose response, safety, durability of initial response, and emergence of resistance to the investigational drug and other drugs in the regimen. However, the primary efficacy analysis will be the short duration placebo comparison.

It is envisioned that the above trial design would be statistically overpowered for the primary endpoint, but will provide the minimal safety data base of approximately 300 patients needed for the 24 week assessment. This would allow identification of treatment-related adverse events occurring at a frequency approximating 1 in 100. Alternatively, one could power the trial to rule out potential differences in response between doses at 24 weeks. Another potential design option is to start all subjects on their OBR and then randomize subjects to begin study drug immediately or start study drug after 7 days -2 weeks.

In addition, please include discontinuation criteria and your definition of virologic failure (VF) for each phase of the study (monotherapy phase and OBR phase).

For example you could define VF during the functional monotherapy phase as a less than 0.5 $\log_{10}$ copies/mL decrease in HIV RNA at Day XX (depending on the duration of the monotherapy phase), unless the HIV RNA is < 400 copies/mL. This value does not require confirmatory testing.

During the OBR phase a virologic non response could be defined as a decrease in plasma HIV RNA of < 1 $\log_{10}$ by week 16 unless it is < 400 copies/mL or an HIV RNA level ≥ 400 copies on or after week 24.

Virologic Rebound during the OBR phase can be defined as

• Confirmed rebound in plasma HIV-1 RNA levels to ≥ 400 copies/mL after prior confirmed suppression to < 400 copies/mL.

• Confirmed plasma HIV-1 RNA levels > 1 $\log_{10}$ copies/mL above the nadir value where nadir is ≥ 400 copies/mL.

Values during this phase should be confirmed by a second measurement performed at least one week but not more than four weeks apart from the date of the original sample.
You may choose other criteria; however, please provide a justification in the revised protocol.

The primary efficacy endpoint for hypothesis testing in this study will be the mean change from baseline in plasma HIV-1 RNA ($\log_{10}$ copies/mL) at Day XX depending on the duration of the monotherapy phase using a last observation carried forward (discontinuation equals baseline) dataset.

The study's primary objective should be the characterization of antiviral activity at both Day 8 or 15 and Week 24. The Week 24 assessment is the proportion of subjects with plasma HIV-1 RNA <50 copies/mL at Week 24 using FDA's "snapshot" algorithm.

Clarification and additional rationale is needed for your proposal to (b) (4) *Also, this product is administered by IV and likely in a clinic or home*

healthcare setting (b) (4)

(b) (4)

At this time, there are ongoing discussions with senior management regarding the relevance of accelerated approval for HIV products given that HIV RNA is now a validated endpoint. A final decision regarding this issue has not yet been made but potentially, this BLA application will have to be submitted for traditional approval review. In this case, a postmarketing requirement (PMR) for longer term safety, efficacy and resistance is likely. We are still in discussions about the overall safety database required at Week 48 for the to-be-marketed dose. However, your current proposal for approximately (b) (4) *subjects total appears insufficient. Therefore, you need to reconsider the proposed number of patients to be enrolled in the Phase 3 trial and the overall safety database should be increased so you can attain the stated goals of having sufficient number of subjects to support BLA filings at 24 and 48 weeks.*

Discussion:

TaiMed inquired about the possibility of not including a short-term monotherapy lead-in phase since the ibalizumab has demonstrated efficacy in multiple trials. FDA clarified that although ibalizumab has demonstrated preliminary efficacy in previous trials, it is critical to include the short term monotherapy lead-in phase to differentiate the contribution of the investigational drug in the treatment regimen in the pivotal Phase 3 study and for registration. TaiMed had some concerns about development of resistance during the monotherapy phase and inquired if they could propose an unequal randomization. DAVP requested the protocol include their rationale for the randomization scheme along with justification for the monotherapy period. TaiMed inquired if they have to use the DAVP's definition of viral rebound. The Agency clarified that the definitions of viral rebound are given as examples, and that TaiMed can provide their own definition which will be used for their analyses.

DAVP questioned TaiMed's development plan (b) (4) *specifically 800 mg q 2week based on efficacy* (b) (4)*. The Agency clarified that TaiMed has to justify th* (b) (4)

(b) (4)

. However, TaiMed can provide a rationale in their draft protocol for DAVP review. If TaiMed's Phase 3 trial is not blinded, TaiMed needs to provide a rationale.

DAVP stated if upper management agrees the accelerated approval is no longer applicable for HIV drugs, this BLA application would filed for traditional approval review and would likely have a postmarketing requirement (PMR) to submit 48 week safety, efficacy and resistance data. The Agency strongly recommended TaiMed increase their safety database from 300 patients to approximately 500 patients. This will ensure TaiMed will have an adequate number of patients at Week 48.

EFFICACY QUESTIONS:

Question 1:
FDA guidance of October 15, 2010 stated that in addition to the Phase 2b trial,
(b) (4)
We recognize the trial is not powered to detect a dose response. A minimum of (b) (4) additional patients will increase your safety database to the required 300 - 500 patients needed to support an accelerated approval submission. Please note if safety issues arise during this trial additional patients or longer duration may be needed to support a BLA submission. Patients who need IV ibalizumab to construct a viable suppressive antiretroviral regimen should be enrolled and this definition is similar to the enrollment criteria for the ongoing phase 2b trial. The trial should be designed for 48 weeks duration".
At the proposed to be marketed dose and dose regimen of 800 mg q 2 wk (b) (4) from the Phase 1, 2a, 2b and 3 trials, approximately (b) (4) patients in total are estimated to be on drug for 24 weeks and about (b) (4) patients on drug for 48 weeks. Do the estimated total numbers of HIV+ treatment experienced patients at Weeks 24 and 48 meet Agency requirements for a BLA registration package for HIV+ treatment experienced patients?

FDA Response:
Please refer to the response above.

Question 2:
Do the primary and secondary efficacy endpoints in the prior clinical trials meet Agency requirements for the BLA application?

FDA Response:
Please refer to the response above.

Question 3:
Does the duration of drug exposure in the Phase 1, 2a, 2b and 3 studies meet Agency requirements for the registration package?

FDA Response:
Yes, 24 weeks is the minimum number of weeks required in order to submit a BLA package. 48 week data will also be required post approval.

Question 4:
Do the proposed doses and dose regimen meet Agency requirements for a BLA application?

FDA Response:
This is a review issue. At the present time, we agree that based on the Phase 2b data further assessment of both doses is acceptable.

Question 5:
Is the definition of the patient population in the proposed indication acceptable for registration?

FDA Response:
Yes; however, this is contingent on the actual population enrolled and is a review issue.

Question 6:
FDA fax of October 15, 2010 provided guidance for a 48 week (b) (4) patient trial with respect to requirements for accelerated and traditional approvals:
"Specifically, additional efficacy data are needed to support dose selection and additional safety data are needed prior to a BLA submission. Overall, 300 – 500 subjects at the proposed dose (or higher) and duration of treatment is needed to support accelerated approval"…"Therefore, this 48 week trial can serve for both accelerated approval and traditional approval providing sufficient number of patients still remain in the trial at 48 weeks. If sufficient number of patients do not remain in the trial for 48 weeks, a new confirmatory trial would be needed to fulfill the accelerated approval requirements."
.**6a.** Does a BLA package with 24 week data from the Phase 1, 2a, 2b and 3 trials for about (b) (4) patients at 800 mg q 2 wk and (b) (4) meet Agency requirement for patient numbers and duration of treatment for accelerated approval?

FDA Response:
Please refer to the previous responses regarding patient numbers.

Question 6b:
Does a BLA package with 48 week data from the Phase 1, 2a, 2b and 3 trials for about (b) (4) patients meet Agency requirements for patient numbers and duration of treatment for traditional approval?

FDA Response:
Please refer to the previous responses regarding patient numbers.

SAFETY QUESTIONS

Question 1:
From all trials, the BLA registration package is estimated to have 547 patients exposed to one or more dose and 517 exposed to multiple doses of ibalizumab. Do the expected total numbers of subjects for safety at the completion of the Phase 3 trial, combined with the Phase 1, 2a and 2b trials and the TMB 202 patients on investigator sponsored INDs, meet Agency requirements for patient drug exposure numbers for the BLA registration package?

FDA Response:
Please refer to the previous responses regarding patient numbers.

Question 2:
Does the duration of exposure in the Phase 1, 2a, 2b and 3 studies and during the extended treatment periods meet Agency requirements for a BLA application?

FDA Response:
Yes, the proposed 24 and 48 week durations of treatment meet the Agency requirements for a BLA application.

Question 3:
Are the proposed doses and dose regimen for the safety database acceptable for a BLA application?

FDA Response:
Please refer to the previous responses regarding patient numbers.

GENERAL QUESTIONS:

Question 1:
Upon agreement on the general outline of a Phase 3 study design, TaiMed proposes to follow up with the Agency to submit the Phase 3 protocol and request a special protocol assessment. Is this acceptable?

FDA Response:
Yes, you may submit the Phase 3 protocol for a special protocol assessment.

Question 2:
Does the Agency have feedback on other aspects of the clinical trial that have not been asked, but would help TaiMed in its plans for intravenous ibalizumab?

FDA Response:
Not at this time. Further comments will be provided after we receive a complete protocol for review.

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2.2 CHEMISTRY, MANUFACTURING AND CONTROLS (CMC)

Discussion:
TaiMed stated that the Tanox-manufactured product has been used in all clinical trials completed to date, but they will not have sufficient product to complete the Phase 3 clinical trial. They are in the process of identifying a CMO to manufacture DS and DP. TaiMed proposes to initiate Phase 3 studies with the drug product manufactured by Tanox and subsequently transition to drug product manufactured by their CMO. TaiMed will manufacture the development lots first then move to the larger scale manufacturing lots. FDA stated that ideally, the product manufactured at the final commercial scale should be used to show comparability to the Tanox product. However, the Division is accomodating TaiMed's situation by allowing them to use the lots manufactured at the (b) (4) L scale for the initial comparability studies necessary to initiate Phase 3 studies. FDA reiterated that TaiMed must manufacture sufficient product to complete Phase 3 trials and demonstrate comparability, including appropriate clinical bridging studies, before initiating the Phase 3 trials. Ideally, FDA prefers that TaiMed only use product manufactured using their CMO's process for their Phase 3 studies. However, if they use a mixture of TaiMed and Tanox products, then comparability must be demonstrated prior to initiation of Phase 3 studies. FDA cautioned that utilizing a mixture of products is highly risky and introduces an additional variable to the pivotal phase 3 trial. TaiMed will submit a detailed manufacturing plan and protocol, along with a detailed protocol to be used to establish comparability between the Tanox- and TaiMed-manufactured DS and DP, for FDA review before initiating the phase 3 trial.

Question 1:
TaiMed is proposing to make a change in the manufacture of the drug substance and drug product. The proposal is to increase the protein concentration to (b) (4) mg/mL from the currently (b) (4) mg/mL for intravenous ibalizumab, and to modify slightly the formulation matrix to accommodate the higher protein concentration. (b) (4) Is this acceptable?

FDA Response:
The data that you have provided are insufficient to determine whether your approach is acceptable. Most importantly, you must demonstrate that you can manufacture sufficient material comparable to ibalizumab manufactured by Tanox and used in early clinical trials prior to initiating phase 3 trials. The Agency recommends that a detailed comparability study protocol be submitted in advance for review. The protocol should include a description of the assay(s) to be performed and pre-determined acceptance for the new drug substance and drug product. Please also refer to the responses to questions 2-4.

Question 2:
The CMC requirements discussed with Tanox for the (b) (4) L scale will be followed for the new CMO's (b) (4) L lot (1 lot) and adapted as appropriate for the (b) (4) L scale lots (2 lots) for the registration/stability lots and validation/commercial lots (3 lots) at (b) (4) L scale with TaiMed modification for a more concentrated drug. The new lots will be at the (b) (4) mg/mL TBD concentration with minor modification to the formulation. Is this acceptable?

FDA Response:
We note that you proposed to initiate the phase 3 study with the Tanox formulation and subsequently change to the TaiMed/CMO formulation in mid-trial. Later, you plan to scale up from (b) (4) L during the phase 3 trial. However, you have not provided the Agency with detailed information regarding your new manufacturing processes. This information must be submitted for review in order to assess the acceptability of your approach.

Question 3:
The comparability protocol discussed with Tanox for the (b) (4) L scale will be followed for the new CMO (b) (4) L lot and the (b) (4) L scale lots for the registration/stability and validation/commercial lots with minor TaiMed assay modifications. Is this acceptable?

FDA Response:
The rigor with which comparability must be demonstrated following manufacturing changes increase as product development proceeds. That is, requirements for Tanox at earlier clinical phases might not be appropriate for changes made during pivotal phase 3 trials. As stated in the response to question #1, the Agency would need to review the detailed comparability protocols in advance to determine whether the development approach is acceptable.

Question 4:
Are the 3 lots (Tanox (b) (4) L scale and new CMO (b) (4) L and (b) (4) L scale lots) proposed for use in the Phase 3 clinical trial acceptable?

FDA Response:
The proposal to change manufacturing processes during the phase 3 clinical trial carries significant risks. It is not possible to predict in advance whether the changes in manufacturing facilities, product formulation, and/or scale of production will result in changes in product quality. You have not provided data demonstrating an ability to manufacture product that is comparable to the ibalizumab product manufactured by Tanox, introducing a risk that the pivotal trials would be interrupted due to insufficient drug supply. For this reason, phase 3 studies should not be initiated until you have manufactured at least two (b) (4) L lots of ibalizumab that are deemed comparable by the Agency to the Tanox-manufactured product used in earlier clinical studies.

Question 5:
Are the proposed release specifications for the drug substance and drug product at the (b) (4) L and (b) (4) L scale, stability program and data proposed for the BLA registration package acceptable?

FDA Response:
We do not agree with the proposed specifications. In particular, we do not agree with the decision to discontinue the (b) (4) assay, unless it is substituted by another test that detects charge variants. In addition, "PASS" is listed as a release and stability specification for drug substance (b) (4) assessment. This is ill-defined and it should instead be numerical. Moreover, please describe your plans to comply with 21 CFR 610.12 (a) regarding the assessment of bulk drug substance sterility.

Question 6:
Are the proposed approaches to manufacture the validation and commercial lots acceptable?

FDA Response:
Assuming that comparability can be established during the manufacturing process change transitions, this approach is acceptable.

Question 7:
TaiMed will provide a process validation plan after the CMO is identified. Is this acceptable?

FDA Response:
Process validation is a key component of BLA registration; the process validation plan may be provided after the CMO is identified.

Question 8:
Does the Agency concur with the proposed characterizations for the new (b) (4) L lots?

FDA Response:
In general, the proposed tests for characterization of the drug substance are acceptable. However, you have not provided information regarding the drug product stability program that will be conducted to support comparability.

Question 9:
TaiMed does not plan to perform further characterization of the cell banks established and characterized by Tanox. Is this acceptable for the BLA submission?

FDA Response:
Cell bank characterization should conform to existing guidance documents [ICH Topic Q5D "Derivation and Characterization of Cell Substrates Used for Production of Biotechnological / Biological Products" and "Points to Consider in the Manufacture and Testing of Monoclonal Antibody Products for Human Use (1997)"]. Master Cell Bank characterization should include assays for sterility, mycoplasma, virus (adventitious, species-specific, and retrovirus), authenticity, the number of integrated of expression plasmid/genome, and a confirmation that the DNA sequence of the gene transcript cDNAs encodes the expected antibody amino acid sequence. Working Cell Bank characterization should include assays for sterility, mycoplasma, and authenticity.

Question 10:
TaiMed proposes to adopt Tanox's approach to setting in process limits and specifications for both (b) (4) L scale process. Is this acceptable?

FDA Response:
As the (b) (4) L scale process has not yet been established, the Agency cannot make a determination at this point in time.

11. Based on the plan presented for the stability program for the (b) (4) L drug substance and product, does the Agency concur with the proposed stability program for the Phase 3 clinical trials and subsequent BLA?

FDA Response:

In general, we agree with the parameters you propose to assess in the drug substance and drug product stability program. However, we do not agree with expanding/ loosening the numerical specifications for key product quality attributes (e.g., pH, charge variants, osmolality, product

related impurities defined by SDS-PAGE, potency). In addition, you list "PASS" as a release and stability specification for drug substance bioburden assessment. As noted previously, this specification is ill-defined and should instead be numerical

ADDITIONAL COMMENTS:

CMC:

1. Please p*rovide a detailed description of the methodology and plans for validation of the assay(s) that will be used for the detection of anti-drug antibodies (ADA) in patient samples. This information should include data demonstrating that the assay is specific, sensitive and reproducible, as well as data regarding the sensitivity of the assay to product interference. The validated immunogenicity assay should be capable of detecting ADA responses in the presence of drug levels that are expected to be present at the time of patient sampling. In addition, an assay should be developed that is able to delineate neutralizing ADA responses. Information regarding these assays and their validation should be provided as an amendment to the IND prior to the initiation of pivotal clinical trials.*

   Discussion:
   TaiMed provided a brief summary detailing when samples were collected. The assay used to detect ADA had been re-validated, and the data will be submitted to the IND.

VIROLOGY:

1. *Please change inclusion criterion 8 to state that subjects must have virus "fully sensitive/susceptible" to at least one component of OBR.*

2. *Please provide the data and algorithm used to define OSS and NRS for each HIV-1 isolate. Please note that discordant susceptibility results between genotypic and phenotypic assays should always be interpreted as resistance.*

   Discussion:
   TaiMed stated they had only performed phenotypic analayses for Study 202. I (b) (4) *they will try to do genotypic analyses. DAVP recognized the difficulty of genotyping the envelope gene of HIV-1, but noted that the genotypic characterization of ibalizumab-resistant viruses was limited to isolates from four subjects.*

3. *Please provide the GSS and PSS scores for all baseline isolates.*

   Discussion:
   DAVP clarified that TaiMed should provide GSS, PSS, and OSS data for the completed TMB 202 trial as well as for their proposed Phase 3 trial, when available.

4. *Please provide the median and range values for changes in HIV-1 RNA levels of subjects in TMB 202.*

5. *Please submit the study report for the resistance analysis of TMB 202 when completed. The analyses should include a genotypic characterization of the TMB 202 HIV-1 failure isolates to verify the role of gp120 V5 PNGSs in resistance or identify novel genetic pathways to resistance.*

6. *Among the twelve virologic failure isolates tested for susceptibility to ibalizumab, two did not exhibit a marked reduction in MPI values. Please clarify if these samples were characterized by a significant shift in EC_{50} value. If not, please verify their CD4-dependence.*

7. *Please determine if anti-idiotypic antibodies to ibalizumab were present in subject samples that demonstrated high serum ibalizumab concentrations but low CD4 receptor occupancies. If anti-idiotypic antibodies are not present, please evaluate the impact of differences in CD4 expression levels or the presence of CD4 amino acid polymorphisms that may affect ibalizumab binding.*

3.0 DATA STANDARDS FOR STUDIES

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

4.0 ISSUES REQUIRING FURTHER DISCUSSION

1. The design of the Phase 3 pivotal trial.
2. The future of the accelerated approval pathway for HIV drug development.
3. Manufacturing plan

5.0 ACTION ITEMS

- TaiMed will submit a draft clinical protocol for DAVP review and comments prior to submitting a request for special protocol assessment (SPA).
- TaiMed will submit a detailed manufacturing plan for FDA review.
- TaiMed will submit a detailed comparability protocol for FDA review and feedback.
- TaiMed will manufacture DS and DP before initiating their Phase 3 clinical trial

6.0 ATTACHMENTS AND HANDOUTS

There were no attachments or handouts.

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

/s/

KENDALL A MARCUS
07/01/2011

LATE-CYCLE COMMUNICATION DOCUMENTS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

BLA 761065

LATE-CYCLE MEETING MINUTES

TaiMed Biologics USA Corp.
Attention: Helen P. Shu, Ph.D.
VP Regulatory Affairs and Quality
2 Executive Circle, Suite 280
Irvine, CA 92614

Dear Dr. Shu:

Please refer to your Biologic License Application (BLA) submitted under section 351 of the Public Health Service Act for TROGARZO (ibalizumab-uiyk) injection.

We also refer to the Late-Cycle Meeting (LCM) between representatives of your firm and the FDA on October 31, 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 Christian Yoder, MPH, Regulatory Project Manager at (240) 402-9990 or (301) 796-1500.

Sincerely,

{See appended electronic signature page}

Adam Sherwat, MD
Cross Discipline Team Lead
Division of Antiviral Products
Office of Antimicrobial 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 31, 2017, 11:00 am – 12:30 pm
Meeting Location:	10903 New Hampshire Avenue White Oak, Building 22, Conference Room 1415 Silver Spring, MD 20993
Application Number:	BLA 761065
Product Name:	TROGARZO (ibalizumab-uiyk) injection
Applicant Name:	TaiMed Biologics USA Corp
Meeting Chair:	Adam Sherwat, MD
Meeting Recorder:	Christian Yoder, MPH

FDA PARTICIPANTS

OND/Office of Antimicrobial Products (OAP)
John Farley, MD, Deputy Director

OND/OAP/Division of Antiviral Products (DAVP)
Debra Birnkrant, MD, Director
Jeffrey S. Murray, MD, MPH, Deputy Director
Adam Sherwat, MD, Medical Team Leader
Virginia Sheikh, MD, Medical Officer
Poonam Mishra, MD, Deputy Director for Safety
Julian O'Rear, PhD, Clinical Virology Team Leader
Eric Donaldson, PhD, Clinical Virology Reviewer
Annamaris Colberg-Poley, PhD, Clinical Virology Reviewer
Michael Thomson, PhD, Clinical Virology Reviewer
David McMillian, PhD, Pharm/Tox Reviewer
Chris Ellis, PhD, Pharm/Tox Team Leader
Elizabeth Thompson, MS, Chief, Project Management Staff
Christian Yoder, BSN, MPH, Regulatory Project Manager

OTS/OCP/Division of Clinical Pharmacology IV (DCP4)
Qin Sun, PhD, Clinical Pharmacology Reviewer
Su-Young Choi, PhD, Clinical Pharmacology Reviewer
Luning Zhuang, PhD, Clinical Pharmacology Reviewer

Office of Surveillance and Epidemiology (OSE)
Ingrid Chapman, Risk Management Analyst

Office of Pharmaceutical Quality (OPQ), Office of Biotechnology Products (OBP)
Ramesh Potla, PhD, Team Leader
Susan Kirshner, PhD, Review Chief

Office of Pharmaceutical Quality (OPQ), Office of Process and Facilities (OPF)
Marion Michaelis, Inspection Lead
Bo Chi, PhD, CMC Microbiology Reviewer
Virginia Carroll, PhD, CMC Microbiology Reviewer
Patricia Hughes, PhD, Acting Branch Chief

Office of Pharmaceutical Quality (OPQ), Office of Program and Regulatory Operations (OPRO)
Anita Brown, Regulatory Business Process Manager

APPLICANT ATTENDEES

TaiMed Biologics USA
Brian Bell, BS, Manager, Clinical Services
Jonathan Ho, BS, Director, Business Development & Alliance Management
Stanley Lewis, MD, MPH, VP, Clinical and Chief Medical Officer
Helen Shu, PhD, VP, Regulatory Affairs and Quality
Steve Weinheimer, PhD, VP Biological Sciences
James Chang, PhD, Chief Executive Officer

Theratechnologies
Christian Marsolais, PhD, Senior VP and Chief Medical Officer

1.0 BACKGROUND

BLA 761065 was submitted on May 3, 2017, for TROGARZO (ibalizumab-uiyk) injection.

Proposed indication: For the treatment HIV-1 infection in heavily treatment-experienced adults with multidrug resistant HIV-1 infection failing current antiretroviral therapy.

PDUFA goal date: January 3, 2017

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

2.0 DISCUSSION

1. Introductory FDA Comments

FDA thanked TaiMed for taking the time to attend the meeting in person. FDA stated that they are actively reviewing the BLA and feel that ibalizumab has the potential to meet an unmet medical need for heavily treatment experienced HIV patients with multi-drug resistant HIV infection. This is evidenced by the Agency granting Breakthrough and Orphan Drug designation and by our designating this a Priority review. However, FDA has noted numerous product quality-related issues, some of which could preclude approval, during the course of this review.

FDA stated that the primary goal of today's meeting is to discuss the key, outstanding product quality issues with the hope that these issues could be satisfactorily addressed in a timely fashion. FDA noted that if time remains, we can engage in a brief discussion on the current postmarketing requirements/commitments under consideration by the Agency and provide an update on the status of product labeling. The discussion began with a presentation by TaiMed outlining their manufacturing strategy and quality assurance proposals.

2. TaiMed manufacturing strategy/quality assurance presentation (refer to slides attached below).

   a. Slide 4 meeting discussion:

      i. FDA asked clarification on increasing the person-in-plant to cover every manufacturing campaign and what they would be doing differently in the future to ensure better QA. TaiMed responded that (b) (4) [redacted] They also would like to do random audits to ensure consistency. (b) (4) [redacted].

   b. Slide 5 meeting discussion:

      i. TaiMed discussed the challenges of developing the regulatory CMC systems, and has been attempting to update and correct the BLA submissions so that data is appropriately filed. FDA will go through the recent submissions and may send an information request to clarify missing/mislocated data.

   c. Slide 7 meeting discussion:

      i. FDA asked clarification about whether all deviations would be reviewed, or only key deviations. TaiMed stated they would be willing to review all deviations; FDA may send an information request asking TaiMed to define key deviations, and how they plan to ensure that all deviations associated with manufacturing and testing of ibalizumab are appropriately classified, root-cause investigations are carried out with sufficient scientific rigor, and that all deviations are appropriately closed before TaiMed's Quality Unit formally signs off batch release for each ibalizumab product lot.

   d. Slide 8 meeting discussion:

      i. FDA inquired about the role of the people to be hired. TaiMed responded that they plan to use people experienced in managing BLA applications (b) (4) [redacted]

   e. Slide 14 meeting discussion:

      i. FDA, TaiMed, and Theratechnologies discussed the planned BLA (b) (4) [redacted]. TaiMed will continue to oversee

the manufacturing contract with WuXi AppTec. (b) (4)

3. Discussion of Substantive Review Issues

Product Quality

a. In the meeting held on October 16, 2017 between TaiMed Biologics and the FDA, TaiMed CEO James Chang committed to present (b) (4) , and the communication strategy with the WuXi AppTec manufacturing site.

See discussion above

b. The comprehensive list of errata needs to be submitted to the BLA before a substantive review of the application can be completed. The Agency requests that TaiMed commit to a timeline for providing this information to the BLA.

Meeting discussion: This was submitted October 25, 2017 and FDA is still reviewing the submission. TaiMed stated that the new Module 3 update provided to the Agency still has a few sections with mislocated information. TaiMed asked if it is acceptable to the Agency to further revise the affected sections of Module 3 to include hyperlinks to other locations within the BLA where the pertinent information is located. FDA will need to discuss internally and will provide a response separately as a post-meeting comment regarding the need to restructure Module 3 to include the correct information under appropriate eCTD sections. FDA inquired whether TaiMed had an opportunity to contact Electronic Submission Support (ESUB) group within FDA, as advised during a teleconference between the FDA and TaiMed on September 26, 2017. TaiMed informed the Agency that they did not contact the ESUB group yet and will seek ESUB group's help in a timely manner to resolve the document submission issues in the eCTD format.

Post-meeting addendum: FDA would like all parts of the BLA application to be in their correct location. Relying on hyperlinks could result in reviewers missing critical information.

c. All relevant sections of the BLA need to be updated with current information. The Agency requests that TaiMed commit to a timeline for providing this information to the BLA.

There was no meeting discussion

d. All outstanding IR items need to be provided in a timely manner, including letters of authorization to review the drug master files (DMFs) for the cell culture media

(b) (4) and the components of the container closure systems for the drug substance and drug product.

Meeting discussion: FDA advised TaiMed to contact (b) (4) and obtain a Letter of Authorization from (b) (4) (DMF holder) authorizing TaiMed to cross-reference the pertinent DMFs in their ibalizumab BLA.

e. Complete summary data and information for two additional successful media fills, as requested, will be reviewed prior to approval. We acknowledge that the relevant study results were planned to be submitted by October 15, 2017.

Meeting discussion: There remains one Media Fill to be completed and TaiMed expects to be able to submit the results by November 30, 2017.

4. Information Requests

<u>Product Quality</u>

a. The list of pending action items and proposed timelines for completion that was discussed during the teleconference on 9/26/2017 should be provided.
b. Letters of authorization to review the drug master files (DMFs) for the cell culture media (b) (4) and the components of the container closure systems for the drug substance and drug product should be provided.
c. A 9-item CMC microbiology information request was sent on 9/22/2017 with a response due date of 9/29/2017. Response to Items 4-9 is still pending.
d. A 10-item CMC information request was sent on 10/3/2017 with a response requested by COB 10/13/2017.

Meeting discussion: Several product quality submissions were submitted recently and are still under review. TaiMed referenced the two manufacturing lots (b) (4) (b) (4) was found and asked if they could be commercially released pending approval of the BLA; FDA will need to discuss internally and will provide a response later in the review cycle.

5. Postmarketing Requirements/Postmarketing Commitments

<u>Pharmacology/Toxicology</u>

a. Provide a risk assessment of the carcinogenic potential of ibalizumab using a weight-of-evidence based approach, consistent with the ICH S6(R1) guidance.
b. Submit the final study report for the enhanced pre/postnatal development study in cynomolgus monkeys.

Meeting discussion: TaiMed acknowledged that the enhanced pre/postnatal study is in progress and that they plan to hire someone to provide the carcinogenicity risk assessment. FDA indicated that, should TaiMed choose to submit a waiver for carcinogenicity studies, the risk assessment would still be required. TaiMed asked if they should submit a waiver, but the FDA clarified that the decision to submit a

waiver or not lay with the sponsor and that, once the carcinogenicity risk assessment is completed, TaiMed can make that decision based on the weight of evidence.

Clinical Virology

a. Conduct a phenotypic study to determine the impact of the following gp120 amino acid substitutions on ibalizumab susceptibility: P236E, K303R, P367L, I369V, R474K, K615R/N, N649I/R, L774S, and L831V. In addition, determine the phenotypes of the substitutions observed in the various coding sequences noted: C1cons_V75I; gp41cons_E229G/Q229P/R and gp41cons_L274V/A274T; V1V2_N12K and V1V2_N14D/V14M/deletion; V4_T23N/deletion.
b. Provide the fastq envelope sequences from the next generation sequencing of samples collected from subjects who failed treatment to better characterize the HIV-1 gp120 sequence at the time of failure. (We note that the Sanger sequencing data contained a lot of positions that could not be adequately called.)

   Meeting discussion: TaiMed indicated that there would be no problem with the first virology PMR requesting phenotypic data for several potential resistance-associated substitutions that were identified during review. In addition, TaiMed expressed that they are willing to meet the second virology PMR requesting fastq files for entire envelope sequences, provided they can get these data from the company that performed the sequencing (b) (4) FDA confirmed that they received the recent submission of fastq files and datasets for additional subjects who were treated with ibalizumab but failed treatment. FDA will work with TaiMed in the future to ensure smooth processing of NGS data files.

6. Major labeling issues

   The Division received revised labeling from the Sponsor on October 12, 2017, based on the Agency's earlier edits/comments, including revised carton/container labels. These are currently under internal review.

   Meeting discussion: TaiMed questioned the source of the change in the CD4 cell count in the label and requested an explanation. FDA will include a comment to address this in the label which we anticipate returning to them by November 10, 2017. FDA will send the label to OPDP for internal review once the label is substantially complete.

7. Additional topics discussed

   Meeting discussion: TaiMed inquired about asking for a longer shelf life, as it is sometimes difficult to forecast production. FDA informed TaiMed that the shelf life can be extended using stability data and recommended developing a long-term protocol for this purpose.

8. Review Plans

- Continue to work with TaiMed to address product quality and manufacturing issues
- Continue labeling negotiations

9. Wrap-up and Action Items

This application has not yet been fully reviewed by the signatory authority, division director, and Cross-Discipline Team Leader (CDTL) and therefore, this meeting did not address the final regulatory decision for the application. However, the importance of addressing the outstanding product quality concerns was strongly emphasized by the Agency.

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/s/

ADAM I SHERWAT
11/14/2017

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

BLA 761065

LATE CYCLE MEETING
BACKGROUND PACKAGE

TaiMed Biologics USA Corp.
Attention: Helen P. Shu, Ph.D.
VP Regulatory Affairs and Quality
2 Executive Circle, Suite 280
Irvine, CA 92614

Dear Dr. Shu:

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

We also refer to the Late-Cycle Meeting (LCM) scheduled for October 31, 2017. Attached is our background package, including our agenda, for this meeting.

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

If you have any questions, call Christian Yoder, Regulatory Project Manager, at (240) 402-9990 or (301) 796-1500.

Sincerely,

{See appended electronic signature page}

Debra Birnkrant, MD
Director
Division of Antiviral Products
Division of Antimicrobial Products
Center for Drug Evaluation and Research

ENCLOSURE:
Late-Cycle Meeting Background Package

LATE-CYCLE MEETING BACKGROUND PACKAGE

Meeting Date and Time:	October 31, 2017, 11:00 am – 12:30 pm
Meeting Location:	10903 New Hampshire Avenue White Oak, Building 22, Conference Room 1415 Silver Spring, MD 20903
Application Number:	BLA 761065
Product Name:	TROGARZO (ibalizumab)
Indication:	Treatment of adults infected with HIV-1 resistant to at least one other agent in three different classes
Applicant Name:	TaiMed Biologics USA Corp

FDA ATTENDEES (tentative)

OND/Office of Antimicrobial Products (OAP)
Edward M. Cox, MD, MPH, Director
John Farley, MD, Deputy Director

OND/OAP/Division of Antiviral Products (DAVP)
Debra Birnkrant, MD, Director
Jeffrey S. Murray, MD, MPH, Deputy Director
Adam Sherwat, MD, Medical Team Leader
Virginia Sheikh, MD, Medical Officer
Julian O'Rear, PhD, Virology Team Leader
Eric Donaldson, PhD, Virology Reviewer
Christopher Ellis, PhD, Pharm/Tox Team Leader
David McMillan, PhD, Pharm/Tox Reviewer

OTS/OCP/Division of Clinical Pharmacology IV (DCP4)
Shirley Seo, PhD, Clinical Pharmacology Team Leader
Qin Sun, PhD, Clinical Pharmacology Reviewer
Jeffry Florian, PhD, Pharmacometrics Team Leader
Ada Zhuang, PhD, Pharmacometrics Reviewer

OTS/OB/Division of Biometrics IV (DBIV)
Thamban Valappil, PhD, Acting Statistical Team Leader
Karen Qi, PhD, Statistical Reviewer

Office of Surveillance and Epidemiology (OSE)
Elizabeth Everhart, MSN, RN, ACNP, Risk Management Analyst
Chih-Ying (Natasha) Pratt, PhD, Epidemiologist

Office of Pharmaceutical Quality (OPQ), Office of Biotechnology Products (OBP)
Steven Bowen, PhD, Product Reviewer

Ramesh Potla, PhD, Team Leader
Susan Kirshner, PhD, Review Chief

Office of Pharmaceutical Quality (OPQ), Office of Process and Facilities (OPF)
Marion Michaelis, Inspection Lead
Michael Shanks, PhD, Facilities Reviewer
Peter Qiu, PhD, Branch Chief
Bo Chi, PhD, CMC Microbiology Reviewer
Virginia Carroll, PhD, CMC Microbiology Reviewer
Patricia Hughes, PhD, Acting Branch Chief

APPLICANT ATTENDEES

TaiMed Biologics (to be confirmed)
Brian Bell, BS, Manager, Clinical Services
Jon Ho, BS, Director, Business Development & Alliance Management
James Chang, PhD, Chief Executive Officer
Stanley Lewis, MD, MPH, VP, Clinical and Chief Medical Officer
Helen Shu, PhD, VP, Regulatory Affairs and Quality

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 following substantive review issues have been identified to date:

Product Quality

1. The Sponsor has not submitted the errata to address the discrepancies observed between the information submitted in the BLA and manufacturing and testing operations conducted at the Wuxi facility. In the CMC amendment dated 09/15/2017, the Sponsor stated that the errata will be provided as a separate submission, but did not indicate a timeline for this submission. In a subsequent teleconference on 9/26/2017 the Sponsor was unable to clarify when the errata would be submitted. The complete list of all discrepancies between the BLA and the manufacturing and testing operations at the Wuxi facility is necessary before a substantive review can be completed.

2. All sections of the BLA need to be updated with current information. Changes to the application that the Sponsor is proposing in response to Agency comments need to be integrated into all relevant sections of the BLA. All information that is inaccurate or no longer relevant needs to be removed.

3. The Sponsor is not submitting the documentation to electronic common technical document (eCTD) appropriately. This is resulting in multiple versions of the same document appearing within the same section of the eCTD. To correct this, the Sponsor was advised in the teleconference on 9/26/2017 to contact the FDA ESUB group to resolve the electronic submission issues for this BLA.

4. Letters of authorization to review the drug master files (DMFs) for the cell culture media (b) (4) and the components of the container closure systems for the drug substance and drug product were requested and have not yet been provided. These letters of authorization are needed to evaluate whether the components of the cell culture media are adequately controlled and whether the container closure systems are compatible with ibalizumab DS and DP.

5. In the teleconference held on 9/26/2017 the Sponsor committed to provide a list of action items and a proposed timeline to the agency early in the week of October 3rd. This list has yet to be provided.

6. Complete summary data and information for two additional successful media fills, as requested, will be reviewed prior to approval. We acknowledge that the relevant study results were planned to be submitted by October 15, 2017.

7. Currently the review of the PLI at WuXi, DS and DP manufacturer, is under review and pending the firm's response to a RAI. Satisfactory resolution of the FDA-483 items regarding the WuXi PLI is required for BLA 761065 approval.

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 (Christian Yoder, Regulatory Project Manager/Adam Sherwat, Cross-Discipline Team Lead)

   Welcome, Introductions, Ground rules, Objectives of the meeting

2. Discussion of Substantive Review Issues – 50 minutes

   Each issue will be introduced by FDA and followed by a discussion.

   Product Quality

   - In the meeting held on October 16, 2017 between TaiMed Biologics and the FDA, TaiMed CEO James Chang committed to present TaiMed's strategy (b) (4) [redacted].
   - The comprehensive list of errata needs to be submitted to the BLA before a substantive review of the application can be completed. The Agency requests that TaiMed commit to a timeline for providing this information to the BLA.
   - All relevant sections of the BLA need to be updated with current information. The Agency requests that TaiMed commit to a timeline for providing this information to the BLA.
   - All outstanding IR items need to be provided in a timely manner, including letters of authorization to review the drug master files (DMFs) for the cell culture media (b) (4) [redacted] and the components of the container closure systems for the drug substance and drug product.

- Complete summary data and information for two additional successful media fills, as requested, will be reviewed prior to approval. We acknowledge that the relevant study results were planned to be submitted by October 15, 2017.

3. Information Requests – 10 minutes

Product Quality

- The list of pending action items and proposed timelines for completion that was discussed in the teleconference on 9/26/2017 should be provided.
- Letters of authorization to review the drug master files (DMFs) for the cell culture media (b) (4) and the components of the container closure systems for the drug substance and drug product should be provided.
- A 9-item CMC microbiology information request was sent on 9/22/2017 with a response due date of 9/29/2017. Response to Items 4-9 is still pending.
- A 10-item CMC information request was sent on 10/3/2017 with a response requested by COB 10/13/2017.

4. Postmarketing Requirements/Postmarketing Commitments – 10 minutes

Pharmacology/Toxicology

- Provide a risk assessment of the carcinogenic potential of ibalizumab using a weight-of-evidence based approach, consistent with the ICH S6(R1) guidance.
- Submit the final study report for the enhanced pre/postnatal development study in cynomolgus monkeys.

Clinical Virology

- Conduct a phenotypic study to determine the impact of the following gp120 amino acid substitutions on ibalizumab susceptibility: P236E, K303R, P367L, I369V, R474K, K615R/N, N649I/R, L774S, and L831V. In addition, determine the phenotypes of the substitutions observed in the various coding sequences noted: C1cons_V75I; gp41cons_E229G/Q229P/R and gp41cons_L274V/A274T; V1V2_N12K and V1V2_N14D/V14M/deletion; V4_T23N/deletion.
- Provide the fastq envelope sequences from the next generation sequencing of samples collected from subjects who failed treatment to better characterize the HIV-1 gp120 sequence at the time of failure. (We note that the Sanger sequencing data contained a lot of positions that could not be adequately called.)

5. Major labeling issues – 5 minutes

The Division received revised labeling from the Sponsor on October 12, 2017, based on the Agency's earlier edits/comments, including revised carton/container labels. These are currently under internal review.

6. Review Plans – 5 minutes
    - Continue to work with TaiMed to address product quality and manufacturing issues
    - Continue labeling negotiations

7. Wrap-up and Action Items – 5 minutes

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/s/

JEFFREY S MURRAY
10/19/2017