

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

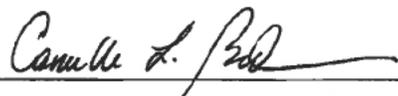
APPLICATION NUMBER:

125513Orig1s000

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**

3. DEBARMENT CERTIFICATION

Alexion Pharma International Srl hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.



Camille L Bedrosian, M.D.

Senior Vice President, Chief Medical Officer



Date

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION ¹		
NDA # BLA # 125513	NDA Supplement # BLA Supplement #	If NDA, Efficacy Supplement Type: <i>(an action package is not required for SE8 or SE9 supplements)</i>
Proprietary Name: Strensiq Established/Proper Name: asfotase alfa Dosage Form: Injection		Applicant: Alexion Pharmaceuticals, Inc. Agent for Applicant (if applicable): N/A
RPM: Lisa Pitt		Division: Gastroenterology and Inborn Errors
NDA Application Type: <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) Efficacy Supplement: <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) BLA Application Type: <input type="checkbox"/> 351(k) <input checked="" type="checkbox"/> 351(a) Efficacy Supplement: <input type="checkbox"/> 351(k) <input type="checkbox"/> 351(a)		<p><u>For ALL 505(b)(2) applications, two months prior to EVERY action:</u></p> <ul style="list-style-type: none"> Review the information in the 505(b)(2) Assessment and submit the draft² to CDER OND IO for clearance. Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity) <p><input type="checkbox"/> No changes <input type="checkbox"/> New patent/exclusivity <i>(notify CDER OND IO)</i> Date of check:</p> <p><i>Note: If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.</i></p>
❖ Actions		
<ul style="list-style-type: none"> Proposed action User Fee Goal Date is <u>October 23, 2015</u> 		<input checked="" type="checkbox"/> AP <input type="checkbox"/> TA <input type="checkbox"/> CR
<ul style="list-style-type: none"> Previous actions <i>(specify type and date for each action taken)</i> 		<input checked="" type="checkbox"/> None
❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain <u>N/A</u>		<input type="checkbox"/> Received
❖ Application Characteristics ³		

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

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

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

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

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

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

NDAs: Subpart H

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

Subpart I

- Approval based on animal studies

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

BLAs: Subpart E

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

Subpart H

- Approval based on animal studies

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

Comments:

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

Action Letters	
❖ Copies of all action letters <i>(including approval letter with final labeling)</i>	Action(s) and date(s) Approval 10/23/15
Labeling	
❖ Package Insert <i>(write submission/communication date at upper right of first page of PI)</i>	
<ul style="list-style-type: none"> Most recent draft labeling <i>(if it is division-proposed labeling, it should be in track-changes format)</i> 	<input checked="" type="checkbox"/> Included 10/23/15
<ul style="list-style-type: none"> Original applicant-proposed labeling 	<input checked="" type="checkbox"/> Included 12/23/2014
❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling <i>(write submission/communication date at upper right of first page of each piece)</i>	<input type="checkbox"/> Medication Guide <input checked="" type="checkbox"/> Patient Package Insert <input checked="" type="checkbox"/> Instructions for Use <input type="checkbox"/> Device Labeling <input type="checkbox"/> None
<ul style="list-style-type: none"> Most-recent draft labeling <i>(if it is division-proposed labeling, it should be in track-changes format)</i> 	<input checked="" type="checkbox"/> Included 10/06/15
<ul style="list-style-type: none"> Original applicant-proposed labeling 	<input checked="" type="checkbox"/> Included 12/23/2014
❖ Labels (full color carton and immediate-container labels) <i>(write submission/communication date on upper right of first page of each submission)</i>	
<ul style="list-style-type: none"> Most-recent draft labeling 	<input checked="" type="checkbox"/> Included Vial: 09/21/15 Carton: 10/02/15
❖ Proprietary Name <ul style="list-style-type: none"> Acceptability/non-acceptability letter(s) <i>(indicate date(s))</i> Review(s) <i>(indicate date(s))</i> 	Acceptable Letter: 4/13/15 Review: 4/10/15
❖ Labeling reviews <i>(indicate dates of reviews)</i>	RPM: <input type="checkbox"/> None 2/27/15 DMEPA: <input type="checkbox"/> None 8/3/15 DMPP/PLT (DRISK): <input type="checkbox"/> None 9/11/15 OPDP: <input type="checkbox"/> None 8/3/15 SEALD: <input checked="" type="checkbox"/> None CSS: <input checked="" type="checkbox"/> None Product Quality <input type="checkbox"/> None 10/8/15 Other: <input type="checkbox"/> None DMPH 8/6/15
Administrative / Regulatory Documents	
❖ RPM Filing Review ⁴ /Memo of Filing Meeting <i>(indicate date of each review)</i>	2/27/15
❖ All NDA 505(b)(2) Actions: Date each action cleared by 505(b)(2) Clearance Committee	<input checked="" type="checkbox"/> Not a (b)(2)
❖ NDAs only: Exclusivity Summary <i>(signed by Division Director)</i>	<input type="checkbox"/> Included
❖ Application Integrity Policy (AIP) Status and Related Documents http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	
<ul style="list-style-type: none"> Applicant is on the AIP 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No

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

<ul style="list-style-type: none"> • This application is on the AIP <ul style="list-style-type: none"> ○ If yes, Center Director's Exception for Review memo (<i>indicate date</i>) ○ If yes, OC clearance for approval (<i>indicate date of clearance communication</i>) 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> Not an AP action
❖ Pediatrics (<i>approvals only</i>) <ul style="list-style-type: none"> • Date reviewed by PeRC _____ If PeRC review not necessary, explain: <u>Product has orphan designation; exempt from PREA.</u> 	
❖ Breakthrough Therapy Designation	<input type="checkbox"/> N/A
<ul style="list-style-type: none"> • Breakthrough Therapy Designation Letter(s) (granted, denied, an/or rescinded) 	Granted: 5/21/2013
<ul style="list-style-type: none"> • CDER Medical Policy Council Breakthrough Therapy Designation Determination Review Template(s) (<i>include only the completed template(s) and not the meeting minutes</i>) 	5/15/2013
<ul style="list-style-type: none"> • CDER Medical Policy Council Brief – Evaluating a Breakthrough Therapy Designation for Rescission Template(s) (<i>include only the completed template(s) and not the meeting minutes</i>) <p>(<i>completed CDER MPC templates can be found in DARRTS as clinical reviews or on the MPC SharePoint Site</i>)</p>	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.) (<i>do not include previous action letters, as these are located elsewhere in package</i>)	4/10/15 Review Extension-PDUFA Clock
❖ Internal documents: memoranda, telecons, emails, and other documents considered important to include in the action package by the reviewing office/division (e.g., Regulatory Briefing minutes, Medical Policy Council meeting minutes)	N/A
❖ Minutes of Meetings	
<ul style="list-style-type: none"> • If not the first review cycle, any end-of-review meeting (<i>indicate date of mtg</i>) 	<input checked="" type="checkbox"/> N/A or no mtg
<ul style="list-style-type: none"> • Pre-NDA/BLA meeting (<i>indicate date of mtg</i>) 	<input type="checkbox"/> No mtg 7/8/14
<ul style="list-style-type: none"> • EOP2 meeting (<i>indicate date of mtg</i>) 	<input type="checkbox"/> No mtg 5/31/11
<ul style="list-style-type: none"> • Mid-cycle Communication (<i>indicate date of mtg</i>) 	<input type="checkbox"/> N/A 7/14/15
<ul style="list-style-type: none"> • Late-cycle Meeting (<i>indicate date of mtg</i>) 	<input type="checkbox"/> N/A 9/2/15
<ul style="list-style-type: none"> • Other milestone meetings (e.g., EOP2a, CMC focused milestone meetings) (<i>indicate dates of mtgs</i>) 	
❖ Advisory Committee Meeting(s)	<input checked="" type="checkbox"/> No AC meeting
<ul style="list-style-type: none"> • Date(s) of Meeting(s) 	
Decisional and Summary Memos	
❖ Office Director Decisional Memo (<i>indicate date for each review</i>)	<input type="checkbox"/> None 10/23/15
Division Director Summary Review (<i>indicate date for each review</i>)	<input type="checkbox"/> None 10/23/15
Cross-Discipline Team Leader Review (<i>indicate date for each review</i>)	<input type="checkbox"/> None 10/23/15
PMR/PMC Development Templates (<i>indicate total number</i>)	<input type="checkbox"/> None 5
Clinical	
❖ Clinical Reviews	

<ul style="list-style-type: none"> Clinical Team Leader Review(s) (<i>indicate date for each review</i>) 	<input checked="" type="checkbox"/> No separate review
<ul style="list-style-type: none"> Clinical review(s) (<i>indicate date for each review</i>) 	10/21/15
<ul style="list-style-type: none"> Social scientist review(s) (if OTC drug) (<i>indicate date for each review</i>) 	<input checked="" type="checkbox"/> None
<ul style="list-style-type: none"> ❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here <input type="checkbox"/> and include a review/memo explaining why not (<i>indicate date of review/memo</i>) 	10/21/15
<ul style="list-style-type: none"> ❖ Clinical reviews from immunology and other clinical areas/divisions/Centers (<i>indicate date of each review</i>) 	<input type="checkbox"/> None DBRUP 04/16/15; DNP 6/24/15; OSE 10/2/15
<ul style="list-style-type: none"> ❖ Controlled Substance Staff review(s) and Scheduling Recommendation (<i>indicate date of each review</i>) 	<input checked="" type="checkbox"/> N/A
<ul style="list-style-type: none"> ❖ Risk Management <ul style="list-style-type: none"> REMS Documents and REMS Supporting Document (<i>indicate date(s) of submission(s)</i>) REMS Memo(s) and letter(s) (<i>indicate date(s)</i>) Risk management review(s) and recommendations (including those by OSE and CSS) (<i>indicate date of each review and indicate location/date if incorporated into another review</i>) 	<input type="checkbox"/> None 10/21/15
<ul style="list-style-type: none"> ❖ OSI Clinical Inspection Review Summary(ies) (<i>include copies of OSI letters to investigators</i>) 	<input type="checkbox"/> None requested Review Summary: 07/30/15; Letters 08/14/15; 08/06/15; 05/27/15
Clinical Microbiology <input checked="" type="checkbox"/> None	
<ul style="list-style-type: none"> ❖ Clinical Microbiology Team Leader Review(s) (<i>indicate date for each review</i>) 	<input type="checkbox"/> No separate review
<ul style="list-style-type: none"> Clinical Microbiology Review(s) (<i>indicate date for each review</i>) 	<input type="checkbox"/> None
Biostatistics <input type="checkbox"/> None	
<ul style="list-style-type: none"> ❖ Statistical Division Director Review(s) (<i>indicate date for each review</i>) 	<input checked="" type="checkbox"/> No separate review
<ul style="list-style-type: none"> Statistical Team Leader Review(s) (<i>indicate date for each review</i>) 	<input checked="" type="checkbox"/> No separate review
<ul style="list-style-type: none"> Statistical Review(s) (<i>indicate date for each review</i>) 	<input type="checkbox"/> None 09/19/15
Clinical Pharmacology <input type="checkbox"/> None	
<ul style="list-style-type: none"> ❖ Clinical Pharmacology Division Director Review(s) (<i>indicate date for each review</i>) 	<input checked="" type="checkbox"/> No separate review
<ul style="list-style-type: none"> Clinical Pharmacology Team Leader Review(s) (<i>indicate date for each review</i>) 	<input checked="" type="checkbox"/> No separate review
<ul style="list-style-type: none"> Clinical Pharmacology review(s) (<i>indicate date for each review</i>) 	<input type="checkbox"/> None 08/09/15; 10/23/15 Addenda
<ul style="list-style-type: none"> ❖ OSI Clinical Pharmacology Inspection Review Summary (<i>include copies of OSI letters</i>) 	<input checked="" type="checkbox"/> None requested

Nonclinical <input type="checkbox"/> None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> No separate review 9/11/2015
• Supervisory Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> No separate review
• Pharm/tox review(s), including referenced IND reviews (<i>indicate date for each review</i>)	<input type="checkbox"/> None 8/27/15
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer (<i>indicate date for each review</i>)	<input type="checkbox"/> None
❖ Statistical review(s) of carcinogenicity studies (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> No carc
❖ ECAC/CAC report/memo of meeting	<input checked="" type="checkbox"/> None Included in P/T review, page
❖ OSI Nonclinical Inspection Review Summary (<i>include copies of OSI letters</i>)	<input checked="" type="checkbox"/> None requested
Product Quality <input type="checkbox"/> None	
❖ Product Quality Discipline Reviews	
• Tertiary review (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
• Secondary review (e.g., Branch Chief) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
• Integrated Quality Assessment (contains the Executive Summary and the primary reviews from each product quality review discipline) (<i>indicate date for each review</i>)	<input type="checkbox"/> None 8/7/15 (DP); 8/6/15(DS); 9/3/15 Addendum
❖ Reviews by other disciplines/divisions/Centers requested by product quality review team (<i>indicate date of each review</i>)	<input type="checkbox"/> None IM 7/10/15
❖ Environmental Assessment (check one) (original and supplemental applications)	
<input checked="" type="checkbox"/> Categorical Exclusion (<i>indicate review date</i>)(<i>all original applications and all efficacy supplements that could increase the patient population</i>)	10/23/15
<input type="checkbox"/> Review & FONSI (<i>indicate date of review</i>)	
<input type="checkbox"/> Review & Environmental Impact Statement (<i>indicate date of each review</i>)	
❖ Facilities Review/Inspection	
<input checked="" type="checkbox"/> Facilities inspections (<i>action must be taken prior to the re-evaluation date</i>) (<i>only original applications and efficacy supplements that require a manufacturing facility inspection(e.g., new strength, manufacturing process, or manufacturing site change)</i>)	<input checked="" type="checkbox"/> Acceptable Re-evaluation date: <input type="checkbox"/> Withhold recommendation <input type="checkbox"/> Not applicable

Day of Approval Activities	
❖ For all 505(b)(2) applications: <ul style="list-style-type: none"> • Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity) 	<input type="checkbox"/> No changes <input type="checkbox"/> New patent/exclusivity (<i>Notify CDER OND IO</i>)
<ul style="list-style-type: none"> • Finalize 505(b)(2) assessment 	<input type="checkbox"/> Done
❖ For Breakthrough Therapy (BT) Designated drugs: <ul style="list-style-type: none"> • Notify the CDER BT Program Manager 	<input checked="" type="checkbox"/> Done 10/23/15 (<i>Send email to CDER OND IO</i>)
❖ For products that need to be added to the flush list (generally opioids): Flush List <ul style="list-style-type: none"> • Notify the Division of Online Communications, Office of Communications 	<input type="checkbox"/> Done
❖ Send a courtesy copy of approval letter and all attachments to applicant by fax or secure email	<input checked="" type="checkbox"/> Done 10/23/15
❖ If an FDA communication will issue, notify Press Office of approval action after confirming that applicant received courtesy copy of approval letter	<input checked="" type="checkbox"/> Done 10/23/15
❖ Ensure that proprietary name, if any, and established name are listed in the <i>Application Product Names</i> section of DARRTS, and that the proprietary name is identified as the “preferred” name	<input checked="" type="checkbox"/> Done 10/23/15
❖ Ensure Pediatric Record is accurate	<input checked="" type="checkbox"/> Done 10/23/15
❖ Send approval email within one business day to CDER-APPROVALS	<input checked="" type="checkbox"/> Done 10/23/15

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

/s/

LISA N PITT
10/27/2015



BLA 125513

MID-CYCLE COMMUNICATION

Alexion Pharmaceuticals, Inc
Attention: Brett Richardson
Senior Manager, Regulatory Affairs
55 Cambridge Parkway
Suite 800
Cambridge, MA 02142

Dear Mr. Richardson:

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

We also refer to the teleconference between representatives of your firm and the FDA on July 14, 2015. The purpose of the teleconference was to provide you an update on the status of the review of your application.

A record of the teleconference is enclosed for your information.

If you have any questions, call me at (240) 402-9651.

Sincerely,

{See appended electronic signature page}

Lisa N. Pitt, PharmD, MSJ
Senior Regulatory Health Project Manager
Division of Gastrointestinal and Inborn Errors Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure:
Mid-Cycle Communication



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MID-CYCLE COMMUNICATION

Meeting Date and Time: July 14, 2015

Application Number: BLA 125513

Product Name: Strensiq (asfotase alfa)

Indication: [REDACTED] ^{(b) (4)} in patients with infantile- and juvenile-onset hypophosphatasia

Applicant Name: Alexion Pharmaceuticals, Inc

Meeting Chair: Anil Rajpal

Meeting Recorder: Lisa Pitt

FDA Center for Drug Evaluation Research (CDER) ATTENDEES

Julie Beitz, MD, Office of Drug Evaluation III (ODE III)
Amy Egan, MD, ODE III
Maria Walsh, RN, MSN, ODE III
Donna Griebel, MD, ODE III, Division of Gastroenterology and Inborn Errors Products (DGIEP)
Andrew Mulberg, MD, FAAP, CPI, ODEIII, DGIEP
Dragos Roman, MD, ODEIII, DGIEP
Joyce Korvick, MD, MPH, ODEIII, DGIEP
Anil Rajpal, MD, ODEIII, DGIEP
Carla Epps, MD, MPH, ODEIII, DGIEP
Joette Meyer, PharmD, ODEIII, DGIEP
Sushanta Chakder, PhD, ODEIII, DGIEP
Dinesh Gautam, PhD, ODEIII, DGIEP
Kevin Bugin, MS, RAC, ODEIII, DGIEP
Lisa Pitt, PharmD, MSJ, ODEIII, DGIEP
Yeh-Fong Chen, PhD, ODEIII, DGIEP
Benjamin Vali, PhD, ODEIII, DGIEP
Yow-Ming Wang, PhD, Office of Clinical Pharmacology (OCP)
Christine Hon, PhD, OCP
Nitin Mehrotra, PhD, OCP
Justin Earp, PhD, OCP
Stephen Voss, MD, ODE III, Division of Bone, Reproductive and Urologic Products (DBRUP)
Teresa Buracchio, MD, ODE I, Division of Neurology Products (DNP)
Ronald Farkas, MD, ODE I, DNP
Larry Bauer, Office of New Drugs (OND)
Jonathan Goldsmith, OND
Kathryn O'Connell, OND

Kimberly Taylor, Office of Strategic Programs
Cristina Ausin, PhD, Office of Biotechnology Products (OBP)
Joslyn Brunelle, PhD, OBP
Gunther Boehhoudt, PhD, OBP
Frederick Mills, OBP
Gerald Feldman, OBP
Jibril Abdus-Samad, OBP
Anita Brown, OBP
Candace Gomez-Broughton, Office of Process and Facilities, Division of Microbiology
Assessment (DMA)
Patricia Hughes, PhD, OPF, DMA
Christina Capacci-Daniel, Office of Process and Facilities, Division of Inspectional Assessment
(DIA)
Carrie Ceresa, Division of Pediatric and Maternal Health (DMPH)
Ethan Hausman, DMPH
Denise Pica-Branco, DMPH
Susan Thompson, Office of Scientific Investigations, Division of Clinical Compliance
Evaluation
Adewale Adeleye, PharmD, Office of Prescription Drug Promotion (OPDP)
Aleksander Winiarski, Office of Safety and Epidemiology (OSE)
Kendra Worthy, OSE, Division of Medication Error Prevention and Analysis (DMEPA)
Matthew Barlow, OSE, DMEPA
Marc Goldstein, Eastern Research Group
Erin Hachey, OSE, DRISK

APPLICANT ATTENDEES

Agustin Melian, MD, Global Medical Sciences
Alfred Boyle, PhD, Global Technical Services
Brett Richardson, Regulatory Affairs
Clare Elkins, MS, Biostatistics
David Thompson, PhD, Global Project Leader
Jill Hillier, PhD, Regulatory Affairs
Kenji Fujita, MD, Clinical Development
Suresh Mahabhashyam, MD, Pharmacovigilance
Lori Martel, PhD, Medical Writing
Mallory Bissett, Clinical Operations
Martine Zimmermann, PharmD, Regulatory Affairs
Pamela Williamson, Senior Vice President, Global Regulatory Affairs and Patient Safety
Rajendra Pradhan, BPharm, MPharm, PhD, Clinical Pharmacokinetics and Pharmacodynamics
Steven Ryder, MD, Senior Vice President and Chief Development Officer
Yas Saotome, PhD, Process Development and Analytical Sciences

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

Clinical: Consider incorporating recommendation for dose escalation in the infantile-onset population.

3.0 INFORMATION REQUESTS

The following information request is outstanding:

CMC:

1. Product Quality Information Request issued on April 17, 2015. Pending responses to Question 4 and Question 10c.

New Information Request(s):

Nonclinical:

1. In the toxicology study reports, e.g. for study Nos, 670315 (6-month IV toxicity study in rats), 670388 (6-month SC toxicity study in monkeys), 902238 (IV Pre- and post- natal development study in rats), and 902237 (IV developmental toxicity in rabbits), the Cmax and AUC values were expressed as mg/L and mg.h/L, respectively. Please confirm that these values are in mg and not in mcg or ng.

Clinical Pharmacology:

1. The Agency is currently discussing the (b) (4) asfotase alfa concentrations and its implications for treatment with asfotase alfa at the 6 mg/kg/week dose. As indicated from your population PK analysis, there is a three-fold change in exposure when comparing the exposure across the (b) (4) (b) (4) (b) (4) in your proposed product specification. We will follow-up with an Information Request(s), if necessary, at the conclusion of our internal discussions.

Clinical:

1. For Study ENB-006-08/ENB-008-10, we note that the 6 Minute Walk Test (6MWT) distances were re-calculated for some but not all patients. Please provide information on

the rationale for re-calculating these distances for these particular patients. Include the methodology used, and provide the two sets of results (i.e., results for distances and percent predicted values for both calculation methods), including point estimates and the 2-sided 95% confidence intervals, side by side in a table. Please also provide the graphs (e.g., scatter plots) to display individual patients' changes.

2. Describe the methodology for collecting growth data for the clinical trials.
3. Please describe the methodology regarding how data was collected for the infantile-onset HPP natural history study, ENB-011-10. If this information is already presented in the BLA, please provide the location.

4.0 MAJOR SAFETY CONCERNS/RISK MANAGEMENT

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

5.0 ADVISORY COMMITTEE MEETING

There are no plans at this time to convene an advisory committee meeting.

6.0 LATE-CYCLE MEETING /OTHER PROJECTED MILESTONES

The proposed date for the late cycle meeting (LCM) is September 2, 2015. In addition, please note the following projected milestone dates:

Labeling, PMR/PMC comments to Applicant:	August 7, 2015
LCM Background Package:	August 22, 2015
PDUFA Goal Date:	November 23, 2015

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/s/

LISA N PITT
07/30/2015



BLA 125513

**PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE**

Alexion Pharmaceuticals, Inc.
352 Knotter Drive
Cheshire, CT 06410

ATTENTION: Pamela M. Williamson
Senior Vice President, Global Regulatory Affairs and Patient Safety

Dear Ms. Williamson:

Please refer to your Biologics License Application (BLA) dated and received December 23, 2014, submitted under section 351(a) of the Public Health Service Act for Asfotase Alfa, Injection 40 mg/mL and 100 mg/mL.

We also refer to your correspondence, dated and received January 15, 2015, requesting review of your proposed proprietary name, Strensiq.

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

If any of the proposed product characteristics as stated in your January 15, 2015, submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

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

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

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Aleksander Winiarski, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-5295. For any other information regarding this application, contact Kevin Bugin, Regulatory Project Manager in the Office of New Drugs, at (301) 796-2302.

Sincerely,

{See appended electronic signature page}

Todd Bridges, RPh
Deputy 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
04/13/2015

TODD D BRIDGES
04/13/2015



BLA 125513

**REVIEW EXTENSION –
MAJOR AMENDMENT**

Alexion Pharmaceuticals, Inc.
Attention: Pamela M. Williamson
Senior Vice President,
Global Regulatory Affairs and Patient Safety
352 Knoter Drive
Cheshire, CT 06410

Dear Ms. Williamson:

Please refer to your Biologics License Application (BLA) dated December 23, 2014, submitted under section 351(a) of the Public Health Service Act for Strensiq (asfotase alfa).

On March 20, 2015, we received your 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 November 23, 2015.

In addition, we are establishing a new timeline for communicating labeling changes and/or postmarketing requirements/commitments in accordance with “PDUFA REAUTHORIZATION PERFORMANCE GOALS AND PROCEDURES – FISCAL YEARS 2013 THROUGH 2017.” If major deficiencies are not identified during our review, we plan to communicate proposed labeling and, if necessary, any postmarketing requirement/commitment requests by August 07, 2015. Furthermore, the new planned date for our internal mid-cycle review meeting is June 24, 2015.

If you have any questions, call Kevin Bugin, Regulatory Project Manager, at (301) 796-2302.

Sincerely,

{See appended electronic signature page}

Richard W. Ishihara
Chief, Project Management Staff
Division of Gastroenterology and Inborn Errors Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

KEVIN B BUGIN

04/10/2015

Signing on behalf of Richard Ishihara.

BLA 125513 STRENSIQ (asfotase alfa) – March 05, 2015 Teleconference (Clinical/Statistics)

Attendees:

Office of Drug Evaluation III (ODEIII)

Julie Beitz
Amy Egan
Maria Walsh

ODEIII/Division of Gastroenterology and Inborn Errors Products

Donna Griebel
Andrew Mulberg
Dragos Roman
Anil Rajpal
Carla Epps
Sushanta Chakder
Dinesh Gautam
Kevin Bugin

Office of Clinical Pharmacology/Division of Clinical Pharmacology III

Christine Hon
Justin Earp

Office of Biostatistics/Division of Biostatistics III

Yeh-Fong Chen
Benjamin Vali

Office of Biotechnology Products/Division of Therapeutic Proteins

Cristina Ausin
Joslyn Brunelle
Gunther Boekhoudt
Anita Brown

BLA 125513 STRENSIQ (asfotase alfa) – March 05, 2015 Teleconference (Clinical/Statistics)

1. Provide updated efficacy data for the following studies along with updated CSRs:
 - ENB-002-08/ENB-003-08 and ENB-010-10- overall survival/ventilator free survival; growth (length/height and weight); PPI/PLP; Radiographic Global impression of change (RGIC)
 - ENB-006-09/ENB-008-10 and ENB-009-10- gait (MPOMA-G), 6 Minute Walk Test, growth (height and weight), PPI/PLP, RGIC

2. Provide updated data on patient immunogenicity status for the following studies:
 - ENB-002-08/ENB-003-08
 - ENB-010-10
 - ENB-006-09/ENB-008-10
 - ENB-009-10

Discussion:

Regarding requests 1 and 2, above, the Agency confirmed that it is reasonable to submit the Tables, Listings, and Figures (TLFs) the week of March 23, 2015, with the final CSRs to be submitted at a later date in the first part of May. The Applicant will also submit the updated datasets along with the TLFs.

3. Please submit a graphical patient profile for each of the patients enrolled in ENB-002-08/ENB-003-08 (10 patients) and ENB-010-10 (28 patients). For each graphical patient profile, please include the following variables by Study Week from randomization up to the currently last available assessment from the ongoing open-label extension period:
 - overall survival/ventilator free survival
 - growth (length/height and weight)
 - PPI/ PLP
 - RGIC

4. Please submit a graphical patient profile for each of the 13 patients enrolled in ENB-006-09/ENB-008-10. For each graphical patient profile, please include the following variables by Study Week from randomization up to the currently last available assessment from the ongoing open-label extension period:
 - Gait (MPOMA-G)
 - 6 Minute Walk Test
 - growth (height and weight)
 - PPI/PLP
 - RGIC

BLA 125513 STRENSIQ (asfotase alfa) – March 05, 2015 Teleconference (Clinical/Statistics)

Discussion:

Regarding requests 3 and 4, above, the Applicant indicated that it would be able to submit the requested patient profiles, the week of April 13, 2015, and this was acceptable to the Agency.

5. Provide a summary table of the change of MPOMA-G by item for all subjects and for each individual subject for the 8 patients in ENB-006-09/ENB-008-10 and the 6 patients in ALX-HPP-502s who have gait assessment data.

Discussion:

Regarding the requested summary table of change in MPOMA-G, the Applicant indicated that this was submitted in the Appendices of the original BLA, and will provide instructions to the Agency to the reference sections where this information is available. The Agency will discuss with its Neurology colleagues and get back to the Applicant if more information is needed.

6. Please provide an analysis of the correlation between MPOMA-G scores and 6 Minute Walk Test scores for juvenile-onset HPP patients.

Discussion:

The Applicant indicated that March 23, 2015, is the earliest that it will be able to provide the additional analysis on MPOMA-G and 6 Minute Walk Test scores as requested in 6, above. This was acceptable to the Agency.

7. Please provide a regional subgroup analysis, specifically USA/Canada vs. Other, for the overall survival and ventilator-free survival analyses in perinatal/infantile patients, i.e., the integrated patients from studies ENB-002-08/ENB-003-08 and ENB-010-10 vs. the subjects from natural history study ENB-011-10.

Discussion:

The Applicant asked for clarification if the Agency wanted the regional subgroup analysis to include the up to date information on the original 28 patients included in the BLA and the additional 31 patients that have been enrolled in the 010-10 study. The Agency confirmed that updated information on both groups of patients was requested and that this information should be integrated. The Applicant will provide this data the week of March 23, 2015.

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/s/

KEVIN B BUGIN
03/16/2015



BLA 125513

**FILING COMMUNICATION -
NO FILING REVIEW ISSUES IDENTIFIED**

Alexion Pharmaceuticals, Inc.
Attention: Pamela M. Williamson
Senior Vice President,
Global Regulatory Affairs and Patient Safety
352 Knotter Drive
Cheshire, CT 06410

Dear Ms. Williamson:

Please refer to your Biologics License Application (BLA) dated December 23, 2014, received December 23, 2014, submitted under section 351(a) of the Public Health Service Act for STRENSIQ (asfotase alfa).

We also refer to your amendments dated March 31, May 20, June 02 and 30, August 01, and December 19, 2014, January 15, and February 06, 09, 10, 12, and 13, 2015.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 601.2(a), this application is considered filed 60 days after the date we received your application. The review classification for this application is **Priority**. 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> . Therefore, the user fee goal date is August 23, 2015.

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

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

labeling and, if necessary, any postmarketing requirement/commitment requests by May 08, 2015. This date conforms to the 21st Century Review timeline for your application. If our review continues on an expedited timeline, we may communicate revised dates for labeling and postmarketing requirement/commitment requests. In addition, the planned date for our internal mid-cycle review meeting is March 27, 2015. We are not currently planning to hold an advisory committee meeting to discuss this application.

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

We request that you submit the following information:

1. In Table 1 of the BLA Presubmission/Cover letter (dated March 31, 2014), it was stated that the data from the Container Closure Integrity method validation studies would be submitted with Wave 3. However, the data has not been submitted. Provide the Container Closure Integrity method validation study data or provide a time line for submitting the data.
2. Provide the study report for the Rabbit Pyrogen Test.

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](#). We encourage you to review the labeling review resources on the [PLR Requirements for Prescribing Information](#) website including:

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

During our preliminary review of your submitted labeling, we have identified labeling issues and are communicating these issues in the attached draft labeling.

(b) (4)

(b) (4) Given that asfotase alpha has no boxed warning and a limited number of Warnings and Precautions, we do not feel that a Medication Guide is appropriate for this product. However, the PI does contain detailed information on how to safely administer the product. Therefore, we recommend (b) (4) (b) (4) a Patient Package Insert (PPI) and separate Instructions for Use (IFU).

Below you will find additional information on how to create a PPI and IFU.

General Patient Labeling Comments:

1. For clarity and to increase readability, separate the PPI from the IFU. For examples of PPIs and IFUs please reference the Insulin products such as Humulin N or other examples which can be found at Drugs@FDA.
2. Use the standard headings and subheadings found in other examples of PPIs.
3. Include all the information described in 21 CFR 208.20. While this citation describes what is necessary in a Medication Guide, we recommend including the information in all patient labeling, including voluntary documents such as a PPI.
4. To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level.
5. Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss.
6. Use a minimum of a 10-point font [required by 21 CFR 208.20 (a)(4)] serif type font for the body of the text. For our reviews, Arial 11-point is the font of choice.
7. Assure that the document is organized according to the format and style described in this document, in the CMI Guidance document (<http://www.fda.gov/cder/guidance/7139fnl.htm>), and in 21 CFR 208.20 (a).
8. Patient labeling materials should utilize simple wording and clear concepts and should be consistent with the Prescribing Information (PI).
9. Left justifying margins with ragged right margins, using a .5 inch margin all around
10. Use spaces between headings, sections, and paragraphs to separate concepts and to indicate changes
11. Rather than highlighting or underlining, use a bold-face type or box to call attention to important information
12. Do not use ALL CAPITAL letters in headings or text. Capital-only words are more difficult to read than mixed upper and lower case words.
13. Use bold print or larger font size to emphasize important words or concepts

Specific High Level Patient Labeling Comments for Content and Formatting of the Instructions for Use (IFU):

- IFU are generally organized as follows:
 1. Standard header

2. Bulleted list of all the supplies needed to complete the task, including an illustration of all supplies needed.
3. Patient instructions that are not sequential should be bulleted.
4. Patient instructions that are sequential should be noted as “Step 1, Step 2” etc.
5. If instructions should be repeated more than once, do not repeat steps. Refer patient back to listed steps. For example “Repeat steps 3 to 5”.
6. Figures should accompany all numbered steps as appropriate and should be placed immediately adjacent to the related step. The figures should be labeled as “Figure A, Figure B” etc.
7. Within the figures, there should be detailed labeling for each part of the device that the patient is expected to become familiar with.
8. For the figures following throughout the rest of the IFU (Figure B, Figure C, etc.), only the parts of the device mentioned in each related step should be labeled within those figures. Refer to each figure at the end of each numbered step. For example, at the end of Step 1, say (See Figure A).
9. When instructions are given to turn or unscrew a part of the device, include the direction the patient should turn. For example, say “unscrew the cap in a clockwise direction”.
10. Storage information as stated in the Prescribing Information (PI) should appear at the end of the IFU if the IFU is a separate document.
11. Disposal information. If needles, syringes or injectable pens are used to prepare or deliver the drug, disposal language should be consistent with the FDA “Safe Sharps Disposal” website language. See <http://www.fda.gov/safesharpsdisposal>.

We request that you resubmit labeling (in Microsoft Word format) that addresses these issues by March 13, 2015. The resubmitted labeling will be used for further labeling discussions. Use the SRPI checklist to correct any formatting errors to ensure conformance with the format items in regulations and guidances.

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

Please respond only to the above requests for information. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

PROMOTIONAL MATERIAL

You may request advisory comments on proposed introductory advertising and promotional labeling. Please submit, in triplicate, a detailed cover letter requesting advisory comments (list each proposed promotional piece in the cover letter along with the material type and material identification code, if applicable), the proposed promotional materials in draft or mock-up form

with annotated references, and the proposed package insert (PI). Submit consumer-directed, professional-directed, and television advertisement materials separately and send each submission to:

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

Do not submit launch materials until you have received our proposed revisions to the package insert (PI), 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 your application holds orphan designation, you are exempt from this requirement.

If you have any questions, call Kevin Bugin, Regulatory Project Manager, at (301) 796-2302.

Sincerely,

{See appended electronic signature page}

Donna Griebel, M.D.
Director
Division of Gastroenterology and Inborn Errors Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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

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/s/

RICHARD W ISHIHARA
02/27/2015
Signing for Donna Griebel.



BLA 125513

BLA ACKNOWLEDGMENT

Alexion Pharmaceuticals, Inc.
Attention: Pamela M. Williamson
Senior Vice President,
Global Regulatory Affairs and Patient Safety
352 Knoter Drive
Cheshire, CT 06410

Dear Ms. Williamson:

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: Strensiq (asfotase alfa) 40 mg/ml and 100 mg/ml solution for subcutaneous injection

Date of Application: December 23, 2014

Date of Receipt: December 23, 2014

Our Reference Number: BLA 125513

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 February 20, 2015, in accordance with 21 CFR 601.2(a).

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

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

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

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

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

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

If you have any questions, call me, Regulatory Project Manager, at (301) 796-2302.

Sincerely,

{See appended electronic signature page}

Kevin B Bugin, MS, RAC
Senior Regulatory Project Manager
Division of Gastroenterology and Inborn Errors Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

KEVIN B BUGIN
01/02/2015



IND 100619

MEETING MINUTES

Alexion Pharmaceuticals
Attention: Brett Richardson
Senior Manager, Regulatory Affairs
55 Cambridge Parkway, Suite 800
Cambridge, MA 021142

Dear Mr. Richardson:

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

We also refer to the meeting between representatives of your firm and the FDA on July 08, 2014. The purpose of the meeting was to discuss the content and structure of the BLA submission for registration of asfotase alfa in the treatment of hypophosphatasia.

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 me at (301) 796-2302.

Sincerely,

{See appended electronic signature page}

Kevin B. Bugin, M.S., R.A.C.
Senior Regulatory Health Project Manager
Division of Gastroenterology and Inborn Errors Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type: B
Meeting Category: Pre-BLA

Meeting Date and Time: July 08, 2014, from 3:00 to 4:00 PM, ET
Meeting Location: 10903 New Hampshire Avenue
White Oak Building 22, Conference Room: 1309
Silver Spring, Maryland 20903

Application Number: IND 100619
Product Name: asfotase alfa
Indication: Hypophosphatasia (HPP)
Sponsor/Applicant Name: Alexion Pharmaceuticals

Attendees:

Office of Drug Evaluation III

Julie Beitz, MD, Director
Amy Egan, MD, Deputy
Maria Walsh, RN, MS, Associate Director for Regulatory Affairs

Division of Gastroenterology and Inborn Errors Products

Andrew E Mulberg, MD, FAAP, CPI, Deputy
Anil Rajpal, MD, MPH, Clinical Team Leader
Carla Epps, MD, Clinical Reviewer
Richard Ishihara, Chief, Project Management Staff
Sushanta Chakder, PhD, Nonclinical Team Leader
Kevin B Bugin, MS, RAC, Senior Regulatory Health Project Manager

Office of Biotechnology Products/Division of Therapeutic Proteins

Joslyn Brunelle, PhD, Quality Team Leader
Fredrick Mills, PhD, Quality Reviewer

Office of Biostatistics/Division of Biostatistics III

Steve Wilson, PhD, Director
Freda Cooner, PhD, Statistics Team Leader

Office of Clinical Pharmacology

Yow-Ming Wang, PhD, Clinical Pharmacology Team Leader

Nitin Mehrotra

Christine Hon, PhD, Clinical Pharmacology Reviewer

Office of Scientific Investigations

Susan Leibenhaut, MD, Team Leader

Office of Safety and Epidemiology/Division of Medication Error Prevention

Matthew Barlow, Reviewer

Office of Safety and Epidemiology/Division of Risk Management

Felicia Duffy, Reviewer

Eastern Research Group (PDUFA V Assessment)

So Hyun (Chelsea) Kim

Sponsor Attendees:

Clare Elkins, Sr. Director Biostatistics

Kenji Fujita, Sr. Director, Clinical Development

Suresh Mahabhashyam, Medical Director, Pharmacovigilance

Agustin Melian, VP, Global Medical Sciences

Rajendra Pradhan, Sr. Director, Clinical PK/PD

Brett Richardson, Sr. Manager, Regulatory Affairs, US

Steve Ryder, SVP and Chief Development Officer

David Thompson, VP Global Team Leader

Pamela Williamson, SVP Global Regulatory Affairs and Patient Safety

Martine Zimmermann, VP Global Regulatory Affairs

1.0 BACKGROUND

Asfotase alfa is a human recombinant tissue-nonspecific alkaline phosphatase (TNSALP) fusion protein being developed for the (b) (4) patients with perinatal, infantile (b) (4) onset Hypophosphatasia. Hypophosphatasia is a rare, inborn error of bone metabolism caused by inactivating mutations in the gene encoding the TNSALP isoenzyme, which inhibits bone mineralization of bone matrix, leading to rickets in infants and children and osteomalacia in patients of all ages.

On April 16, 2013, Alexion and FDA met to discuss the clinical development program, and the Agency's advice provided during the End of Phase 2 meeting with Enobia Pharma on May 31, 2011. In follow up to the April 16, 2013, meeting, FDA provided additional clarification, in the form of written responses, regarding the clinical pharmacology and bioanalytical questions from the meeting.

On May 21, 2013, asfotase alfa received Breakthrough Therapy Designation for treatment of hypophosphatasia in perinatal-, infantile-, and juvenile-onset phenotypes. However, Breakthrough Therapy Designation was not granted for adult-onset HPP (b) (4). In follow up to the Breakthrough Therapy Designation, Alexion submitted a type B meeting request to discuss their development plan, which occurred on September 3, 2013.

Chemistry, Manufacturing and Controls aspects of the BLA were discussed at the Type B Pre-BLA CMC meeting on November 26, 2013, and Alexion.

Following the September 3, 2013 meeting with FDA, Alexion requested a Clinical Pharmacology-focused meeting to discuss and reach agreement on the overall immunogenicity assessment plan for asfotase alfa. The meeting took place on January 14, 2014.

On 21 March 2014, the Agency granted Alexion's rolling submission request that was made on 10 February 2014 (IND 100619; SN0160). Alexion initiated the rolling submission process with the submission of Wave 1 (Modules 3 and 2.3) on 31 March 2014. Following the teleconference on 27 March 2014 with the Agency, Alexion has further refined the rolling submission plans for Waves 2 and 3 and will provide the associated updates in the Briefing Document.

On April 16, 2014, Alexion requested a Pre-BLA Meeting to discuss the content and structure of the BLA submission for registration of asfotase alfa in the treatment of hypophosphatasia (HPP) focused on the Clinical and technical aspects of the application. The meeting was granted and took place on July 08, 2014.

2.0 DISCUSSION

QUESTION 1

Does the Agency agree that the data presentation as outlined in this Briefing Document is adequate to support the demonstration of efficacy of the BLA for asfotase alfa in the treatment of pediatric-onset HPP, including infantile-and juvenile-onset HPP subgroups?

FDA Response:

The Division will determine the adequacy of efficacy data during the submission review.

In your meeting briefing document, you mention the following efficacy endpoints: change in RGI-C, change in a composite endpoint (RGI-C combined with height z-score), and gait assessment. Please clarify what will be the primary efficacy endpoint(s) for an efficacy claim for the juvenile-onset HPP population.

As discussed during the Type B meeting on January 14, 2014, approval based on a surrogate endpoint (i.e., RGI-C, or composite endpoint of RGI-C combined with increase from baseline in height Z-score) requires that a confirmatory trial using clinically meaningful endpoints be underway at the time of your BLA submission.

We continue to recommend that you seek approval via the regular approval pathway (approval based on a clinical endpoint). Please provide your rationale for selecting gait assessment as a clinical endpoint and specify what degree of change in gait measurement you consider to be clinically meaningful for this population. Also, please provide information regarding validation of the Tinetti gait assessment in the juvenile-onset HPP population.

Discussion:

The Sponsor's proposal for the primary endpoint for regular approval was presented in the Sponsor's presentation (see Appendix III). The Sponsor is proposing a modified POMA-G (mPOMA-G) endpoint and proposed the Minimal Clinically Important Difference (MCID) based on statistical/correlational analyses. The FDA and Sponsor agree that the proposal appears reasonable and is an appropriate endpoint to move forward with. However, the FDA noted that the acceptability of this endpoint will be a review issue and recommends the Sponsor provide additional rationale and additional information on methodology for scoring the mPOMA-G with the BLA submission.

QUESTION 2

Does the Agency agree with the proposal for the safety update?

FDA Response:

No, we do not agree. In addition to a summary of serious adverse events, you should provide a summary of deaths and adverse events of interest (injection-related reactions, lipohypertrophy, etc.) reported after the analysis cutoff.

Discussion:

The Sponsor agrees with the FDA's comments. No further discussion.

QUESTION 3

Does the Agency agree with the proposed integrated analyses detailed in the Statistical Analysis Plans?

FDA Response:

We cannot agree with the proposed integrated analyses because you have not specified which endpoint will be the primary efficacy endpoint for the juvenile-onset HPP population (see response to Question 1 above). Moreover, it is unclear which analyses would be based on the pooled data of both infantile-onset and juvenile-onset HPP populations, and which analyses would be based on each subpopulation separately (see Additional Comments below). You should revise your integrated analyses to clarify.

QUESTION 4

Does the Agency agree with the content and format of the application?

FDA Response:

Regarding application content, you will need to provide additional safety data (see response to Question 2).

From a technical standpoint (not content related), yes, the proposed format for the planned BLA is acceptable. However, please see additional comments below.

We have the following general comments:

- **For archival purposes, please submit a pdf version of any labeling document submitted in word and make sure the leaf title of the word document includes "word", so reviewers could quickly identify the word version from the pdf version.**
- **The tabular listing in module 5.2 and synopsis of individual studies in m2.7.6 should be provided in tabular format and linked to the referenced studies in m5.**

We have the following comments regarding the rolling submission status of your application:

- **Code the initial US Regional.xml file as "original application" however,**
- **Cover letter and form should state "presubmission to rolling submission – e.g., part 1 of 3 (depending on how many parts before the final submission)**
- **All subsequent sequences prior to the final sequence, should be coded as "amendment" in the us-regional.xml file, relating to the original application sequence number**
- **The cover letter and form of the final submission should state "original application", Part 3 of 3. That way, reviewers would know that this is the final part to the rolling submission.**

We have the following Clinical Pharmacology comments:

- We noted that you performed a population pharmacokinetic (Pop-PK) model analysis to identify several covariates on the PK of asfotase alfa, which included body weight, (b) (4) batch size, and immunogenicity. We also noted that you performed exposure-response analyses to establish the relationship between average steady state asfotase alfa concentration (C_{avg,ss}) with several pharmacodynamics (PD) endpoints such as the change in 6MWT and BOT-2 score, etc. Simulations from the Pop-PK model showed that a wide range of C_{avg,ss} would result (b) (4). We recommend that you assess the impact (b) (4) on efficacy, safety, as well as dosing or product specification (if there is any).
- We understand that (b) (4) varies from batch to batch during product manufacturing. This suggests that enzyme concentrations in terms of activity (U/L) may not be an appropriate metric for Pop-PK analysis to illustrate the PK characteristics. Instead, concentrations in mass units (e.g., ng/mL) may be more appropriate for PK assessment without the influence (b) (4). Typically, we recommend inclusion of PK characteristics in mass units in labeling of enzyme replacement therapy (ERT) products. As such, we request that you perform additional Pop-PK modeling using concentrations in mass units to assess asfotase alfa Pop-PK characteristics and confirm the significance of the covariates. Furthermore, you should justify the adequacy of the proposed dosing regimen based on this additional analysis. We also recommend that you provide a summary of all the product lots that were used in each patient in the clinical trials, the specific activity in each manufacturing lot, and the conversion factor between enzyme activity in U/L and concentration in ng/mL for each specific manufacturing lot.

Discussion:

The FDA clarified that PK labeling is to be done for the to-be-marketed product with mass by volume units. The FDA clarified that the exposure response analysis using activity U/L is appropriate. The acceptability of the Sponsor's additional proposals would be a review issue and depends on the adequacy of the model. The Sponsor clarified that 25% of the PK data was obtained using the to-be-marketed product. The FDA requested the Sponsor to present the model validation results stratified by to-be-marketed formulation vs. other lots.

The Sponsor acknowledges the FDA's comments and will look at ways to provide concentration in mass/volume units.

- In your evaluation of the relationship between PK exposure and overall survival in infantile-onset HPP patients, you showed that hazard for overall survival was scaled proportionally with asfotase alfa PK activity. We recommend that you assess whether there is/are a subpopulation(s) of patients who did not respond and may benefit from further dose modification or optimization.
- With regard to the exposure-response relationship for adverse events, we recommend that you provide information on dose modifications or interruptions and assess whether these dose changes have any impact on your exposure-response analysis for adverse events.

- We recommend that you provide justification for using $C_{avg,ss}$ as an exposure metric in all of your exposure-response analyses.
- In addition to the Pop-PK modeling analysis, we request that you also provide PK results analyzed by non-compartmental analysis and any PK/PD analysis results associated with this PK information. Submit all datasets including the original PK and PD data, PK/PD analysis datasets, and PK/PD parameter datasets for our review.

Discussion:

The Sponsor clarified the content of the PK data to be provided in the BLA. FDA indicates that the proposed reporting for the data is acceptable.

The FDA requested additional information on immunogenicity analyses and expressed its concerns about the potential limitations of pop-PK analysis methodology in assessing immunogenicity impact. The Sponsor clarified that they will present immunogenicity data at the individual subject level.

- We note that you plan to provide genotype information (gene mutation class, amino acid change, and nucleotide change) along with immunogenicity data in your submission. We recommend that you also conduct exploratory analyses to assess the impact of genotype on PK, PD, immunogenicity, safety, and efficacy.
- In addition to Summary of Clinical Pharmacology Findings in the eCTD submission, we request that you provide a Clinical Pharmacology Summary as a review aid according to the format provided in the appendix. The review aid will allow us to perform the regulatory review more efficiently and in a timely manner. It can be submitted under eCTD section 1.11.4.
- For general expectations of submitting pharmacometric data and models, please refer to <http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm180482.htm>.
- Simulations for various endpoints were conducted to justify the proposed dosing regimen. The methodology of these simulations should be clearly articulated in the report. The datasets and codes for key simulations (e.g., the projected clinical response over time in Figure 5 as shown in p.48 of the briefing package) should be provided.
- Regarding the Pop-PK datasets,
 - Provide the unique subject identification number (e.g., USUBJID) for each subject.
 - Include all observations for asfotase alfa concentration including concentrations that were below the limit of quantitation.
 - Identify in a separate column the analytical method (i.e., CBRG or WIL) that was used to determine concentrations of asfotase alfa.
 - Include PK sampling time points that have missing data.
- Regarding the biomarkers inorganic pyrophosphate (PPi) and pyridoxal-L-phosphate (PLP),

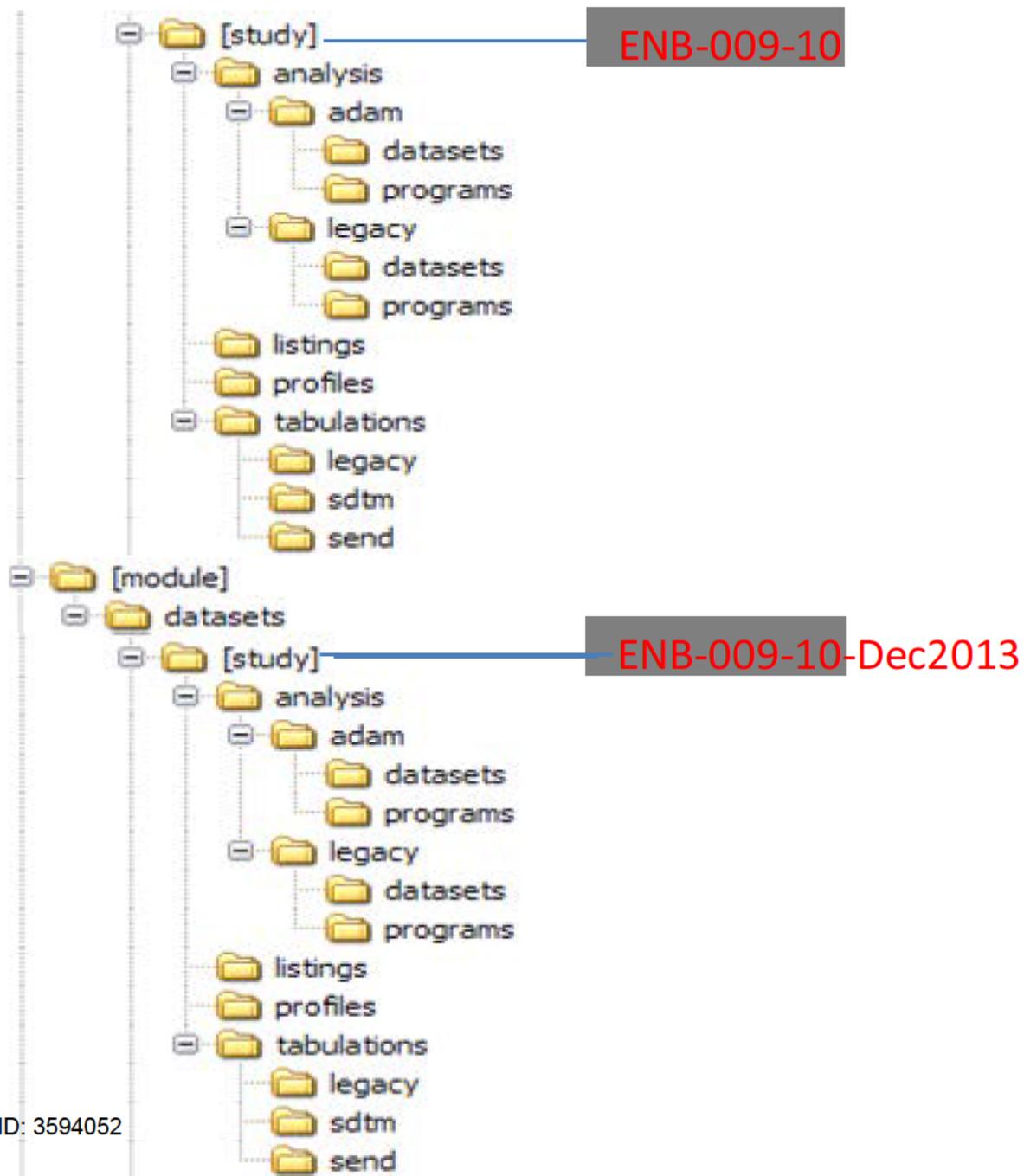
- **Include all observations for these biomarker concentrations including concentrations that were below the limit of quantitation and those that were not included in data analysis.**
- **Provide in a separate document the information on the regression analyses that established the mathematical relationships for conversion of biomarker concentrations between different analytical methods.**

QUESTION 5

Does the Agency agree with the proposed folder structure for the data?

FDA Response:

We prefer you use two different study names ENB-009-10 and ENB-009-10-Dec2013 for study ENB-009-10 since there are two data cutoff. It will be more clear this way.



QUESTION 6

Does the Agency concur with the plan to present the eCTD as described in a meeting to be held approximately 30 days following submission of the final Wave 3 of the Rolling Review?

FDA Response:

We acknowledge and appreciate your offer to provide an opportunity to demonstrate the eCTD submission of your BLA application. The Division has been working with electronic submissions in the eCTD format for several years and feels confident it can navigate the eCTD and does not feel an additional meeting is required to review the application. However, in the past we have found it extremely helpful for the applicant to provide a Reviewer's Reference Guide which discusses the general structure and content locations of the application, with specific emphasis on deviations from major eCTD specifications or guidance. In addition, an annotated prescribing information with navigable hyperlinks to the appropriate reference information to support labeling text is a highly effective tool for the review teams.

FDA ADDITIONAL COMMENTS:

We do not agree with your proposal for an indication for a (b) (4) Based on our review of the literature for hypophosphatasia, this term is not used by the clinical community. Therefore, our preference would be to specify the populations your drug would be indicated for (i.e., patients with infantile-onset HPP and juvenile-onset HPP).

3.0 DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

- The content of a complete application was discussed. The application will be complete at the time of submission of the final unit of the rolling review. There was no agreement or discussion of late submission components.
- All applications are expected to include a comprehensive and readily located list of all clinical sites and manufacturing facilities included or referenced in the application.
- A preliminary discussion on the need for REMS was not held.
- Major components of the application are expected to be submitted with the original application and are not subject to agreement for late submission. You stated you intend to submit a complete application and therefore, there are no agreements for late submission of application components.

4.0 PREA REQUIREMENTS

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

Because this drug product for this indication has an orphan drug designation, you are exempt from these requirements. 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](#). As you develop your proposed PI, we encourage you to review the labeling review resources on the [PLR Requirements for Prescribing Information](#) website including:

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

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

6.0 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.				

7.0 APPENDIX I – Clinical Pharmacology QBR Template

CLINICAL PHARMACOLOGY SUMMARY

1. Goal

In addition to summarizing the relevant findings the goal of the Clinical Pharmacology Summary is to focus sponsor and reviewer on the critical review issues of a submission. To guide sponsors in creating the Clinical Pharmacology Summary in NDA and BLA submissions a generic questionnaire is provided that covers the entire Clinical Pharmacology realm. The aggregate answers provided by sponsors generate the desired Clinical Pharmacology Summary in NDA and BLA submissions. Where needed instructions are added to the questions to clarify what the answers should address. The questions and instructions included in this guide are not intended to be either inclusive of all or exclusive of any questions that specific reviews will address.

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

2. Question Based Review

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

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

2.2 General Attributes of the Drug

1. 2.2.1 What are the highlights of the chemistry and physical-chemical properties of the drug substance and the formulation of the drug product?

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

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

2.

3. 2.2.3 What are the proposed dosages and routes of administration?

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

B.

C. 2.3 GENERAL CLINICAL PHARMACOLOGY

1.

2. 2.3.1 What are the design features of the clinical pharmacology and biopharmaceutics studies and the clinical studies used to support dosing or claims?

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

3. 2.3.2 What is the basis for selecting the response endpoints and how are they measured in clinical pharmacology studies?

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

4. 2.3.3 Are the active moieties in plasma and clinically relevant tissues appropriately identified and measured to assess pharmacokinetic parameters and exposure response relationships?

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

5. 2.4 Exposure-Response

a) 2.4.1 What are the characteristics of the exposure-response relationship for effectiveness?

Describe briefly the method(s) used to determine the exposure-effectiveness relationship. Indicate whether the selected effectiveness endpoints are continuous, categorical or event driven variables. Indicate the number of pooled subjects studied and identify the trials they were enrolled in. Provide the results of the analysis of the dose- and/or concentration-effectiveness relationship. Indicate major covariates (e.g. age, body weight, sex, race/ethnicity, creatinine clearance, disease severity, genetic factors, hormonal status) impacting the exposure-effectiveness relationship. Provide point estimate as well as a measure of the inter-subject variability for continuous and categorical endpoints. Indicate proportion of responders, if applicable. Indicate minimum and maximum effective dose- and concentration levels (major active moieties). Provide evidence that with the proposed regimens clinically meaningful effectiveness is maintained throughout the entire dose interval or alternatively provide evidence that maintenance of effectiveness during the entire dose interval is not important. Indicate the magnitude of the effect at peak and trough concentrations with the tested dose regimens. Indicate steady-state trough and peak plasma concentrations of the major active moieties with the proposed dose regimens. Indicate whether AUC,

C_{max} or C_{min} is more correlated with effectiveness. Show the distribution of the effect size for each dose/concentration level tested.

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

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

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

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

c) **2.4.3 Does this drug prolong QT/QTc Interval?**

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

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

Indicate the therapeutic dose and/or concentration range for the drug and provide evidence that the proposed dose regimens are optimal given the exposure-response relationship for both efficacy and safety of the drug.

6. 2.5 What are the PK characteristics of the drug?

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

Briefly describe methods (two-stage and/or population approaches, compartment model dependent or-independent methods) in healthy subjects and in patients with the target disease used to determine the pharmacokinetic parameters of parent drug and relevant metabolites (pharmacologically active or impacting the exposure to parent drug or co-administered drugs). Provide mean, median (SD, CV%) pharmacokinetic parameters of parent drug and relevant metabolites after single doses and multiple doses at steady-state [C_{max}, t_{max}, AUC, C_{max,ss}, C_{min,ss}, C_{max,ss}/C_{min,ss}, t_{max,ss}, AUC_{0-τ}, CL/F, V/F and t_{1/2} (half-life determining accumulation factor), accumulation factor, fluctuation, time to steady-state]. Indicate how attainment of steady-state is determined. Provide evidence for attainment of steady-state.

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

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

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

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

c) **2.5.4 What are the characteristics of drug absorption?**

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

d) **2.5.5 What are the characteristics of drug distribution?**

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

e) **2.5.6 What are the characteristics of drug metabolism?**

f) **2.5.7 What are the characteristics of drug elimination in urine?**

g) **2.5.8 Based on PK parameters, what is the degree of the proportionality of the dose-concentration relationship?**

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

h) **2.5.9 How do the PK parameters change with time following chronic dosing?**

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

D. 2.6 INTRINSIC FACTORS

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

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

Provide mean (SD) parameters for AUC, C_{max}, clearance, volume of distribution and t_{1/2} for pairs studied: elderly vs. young, male vs female, normal body weight vs. obese, race/ethnicity x vs. race/ethnicity y, mild vs. severe target disease

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

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

2.6.2.1 Severity of Disease State

2.6.2.2 Body Weight

a) 2.6.2.3 Elderly

b) 2.6.2.4 Pediatric Patients

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

2.6.2.5 Race/Ethnicity

c) 2.6.2.6 Renal Impairment

2.6.2.7 Hepatic Impairment

2. 2.6.2.8 What pregnancy and lactation use information is available?

2.6.3 Does genetic variation impact exposure and/or response?

Describe the studies in which DNA samples have been collected. If no DNA samples were collected state so. Include a table with links to the studies in which DNA was analyzed and genomic/genetic information is reported. In the description of these studies include demographics, purpose of DNA analysis (effectiveness, safety, drug metabolism, rule in-out of patients, etc.), rationale for the analysis, procedures for bio-specimen sample collection and DNA isolation, genotyping methods, genotyping results in individual subjects, statistical procedures, genotype-phenotype association analysis and results, interpretation of results, conclusions. If genomic polymorphism impacts either exposure and/or response indicate the measures to be taken to safeguard efficacy and safety of the drug in subjects with varying genotypes. Indicate the contribution of genetic factors to inter-subject variability.

2.6.4 Immunogenicity

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

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

2.6.4.3 Do the anti-product antibodies have neutralizing activity?

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

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

E. 2.7 EXTRINSIC FACTORS

a)

2. 2.7.1 What extrinsic factors influence exposure and/or response, and what is the impact of any differences in exposure on effectiveness or safety responses?

Indicate extrinsic factors that impact significantly exposure and/or effectiveness and safety of the drug. Indicate extent of increase or decrease in exposure and/or response caused by extrinsic factors. State whether an adjustment of the dose is or is not required and provide supporting evidence for either case.

3. 2.7.2 What are the drug-drug interactions?

Provide a list of the drug-drug interaction studies (PK or PD based mechanism) performed and give a rationale for conducting the listed studies. Indicate the suspected mechanism responsible for the interaction. For each of the *in vivo* studies performed provide a rationale for the design selected (single or multiple dose regimens, randomized/non-randomized cross-over or parallel design for perpetrator and/or victim).

a) Drug of interest is impacted by co-administered other drugs

For each method and analyte provide concentration range of calibration curve and indicate respective concentration range for relevant moieties with therapeutic regimens. Indicate fit type of the calibration curves.

a) 2.9.1.2 What are the lower and upper limits of quantitation?

For each method and analyte indicate LLOD, LLOQ and ULOQ for undiluted and diluted samples.

b) 2.9.1.3 What are the accuracy, precision, and selectivity at these limits?

For each method and analyte indicate inter-day and intra-day precision (CV%) and inter-day and intra-day accuracy (RE%).

2.9.1.4 What is the sample stability under conditions used in the study?

For all studies in which concentrations of the drug of interest and relevant metabolites were measured provide information on initiation date of study, date of last sample analyzed and total sample storage time. For each method and matrix provide information on the stability of the analytes, i.e. number of freeze-thaw cycles, benchtop stability at room temperature and stability during long term storage at $\leq -20^{\circ}\text{C}$.

c) 2.9.1.5 What is the plan for the QC samples and for the reanalysis of the incurred samples?

For each study, method and analyte indicate precision (CV%) and accuracy (%RE) using the QC samples measured alongside samples with unknown concentrations. Indicate the concentrations of the QC and incurred samples used.

2.9.2 What bioanalytical methods are used to assess the pharmacodynamic markers?

Briefly describe the methods and summarize the assay performance.

2.9.3 What bioanalytical methods are used to assess the immunogenicity? Briefly describe the methods and assay performance including sensitivity, specificity, precision, cut point, interference (including drug interference) and matrix, etc.

2.9.3.1 What is the performance of the binding anti-product antibody assay(s)?

2.9.3.2 What is the performance of the neutralizing assay(s)?

8.0 APPENDIX II – OSI

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).

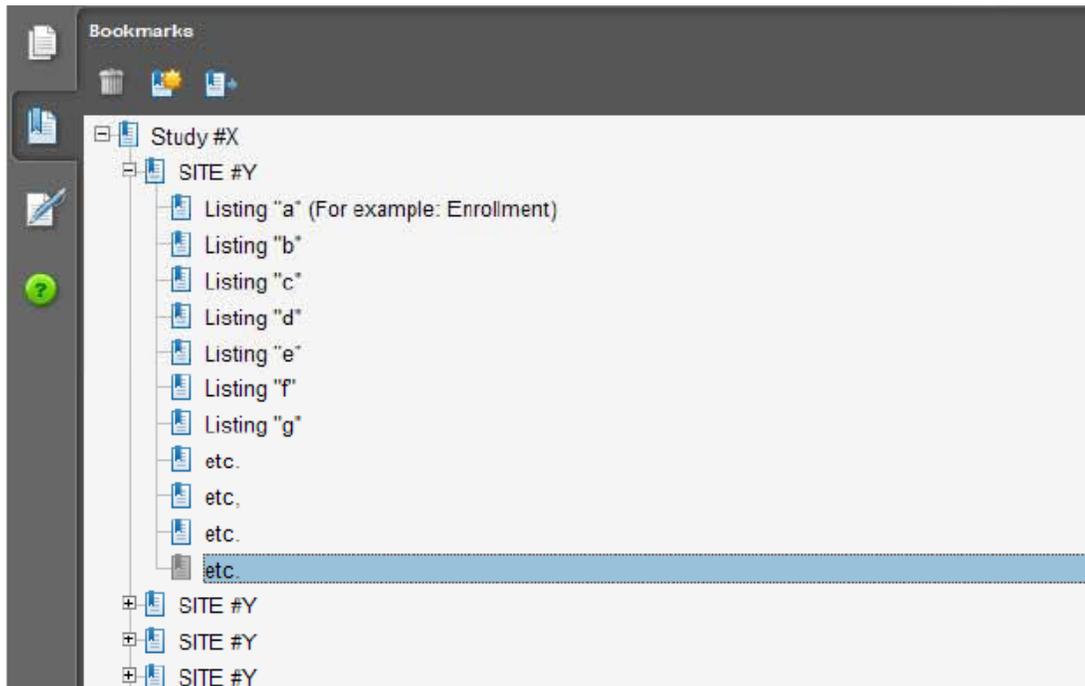
I. Request for general study related information and comprehensive clinical investigator information (if items are provided elsewhere in submission, describe location or provide link to requested information).

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 APPENDIX III – SPONSOR PRESENTATION

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/s/

KEVIN B BUGIN
07/22/2014



IND 100619

MEETING MINUTES

Alexion Pharma International Sarl
c/o Alexion Pharmaceuticals
Attention: Brett Richardson
Senior Manager, Regulatory Affairs
55 Cambridge Parkway, Suite 800
Cambridge, MA 02142

Dear Mr. Richardson:

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

We also refer to the meeting between representatives of your firm and the FDA on January 14, 2014. The purpose of the meeting was to discuss the clinical development program in patients with juvenile-onset hypophosphatasia (HPP).

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 me at (301) 796-0193.

Sincerely,

{See appended electronic signature page}

Elizabeth A. S. Ford, R.N.
Senior Regulatory Health Project Manager
Division of Gastroenterology and Inborn Errors
Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type: B
Meeting Category: Post Breakthrough Therapy, Clinical Meeting

Meeting Date and Time: January 14, 2014, 11:30-12:30
Meeting Location: FDA White Oak Building 22, Room 1419

Application Number: IND 100619
Product Name: asfotase alfa
Indication: (b) (4) (b) (4) for patients with perinatal, infantile or juvenile onset hypophosphatasia (HPP).
Sponsor/Applicant Name: Alexion Pharma International Sarl (Alexion)

Meeting Chair: Lara Dimick, M.D.
Meeting Recorder: Elizabeth Ford, R.N.

FDA ATTENDEES (tentative)

Division of Gastroenterology and Inborn Errors Products (DGIEP)

Donna Griebel, M.D., Director
Andrew E. Mulberg, M.D., Deputy Director
Lara Dimick, M.D., Acting Clinical Team Leader
Carla Epps, M.D., Medical Officer
Brian K. Strongin, R.Ph., M.B.A., Chief, Project Management Staff
Elizabeth A.S. Ford, R.N., Senior Regulatory Health Project Manager

Division of Bone, Reproductive and Urologic Products

Marcea Whitaker, M.D., Medical Officer
Theresa Kehoe, M.D., Clinical Team Leader

Division of Metabolism and Endocrinology Products

Marina Zemskova, M.D., Clinical Reviewer

Office of Orphan Products Development

Jeff Fritsch, Regulatory Review Officer

Office of Translational Sciences

Office of Biostatistics, Division of Biostatistics III

Behrang Vali, M.S., Biostatistics Reviewer

Office of Translational Sciences

Office of Clinical Pharmacology/Division of Clinical Pharmacology 3

Jie Wang, Ph.D., Biologics Team Leader, Acting
Christine Hon, Pharm.D., Clinical Pharmacology Reviewer

Office of Biotechnology Products

Division of Therapeutic Proteins

Joslyn Brunelle, Ph.D., Product Quality Reviewer
Frederick Mills, Ph.D., Biologist
Susan Kirshner, Ph.D., Review Chief

Office of New Drugs/Immediate Office

Rare Diseases Program

Kathryn O'Connell, M.D., Medical Officer

SPONSOR ATTENDEES

Clare Elkins, MS, Senior Director, Biostatistics
Suresh Mahabhashyam, MD, Medical Director, Pharmacovigilance
Agustin Melian, MD, Vice President, Clinical Development Excellence
Brett Richardson, Senior Manager, Regulatory Affairs, US
Steven Ryder, MD, Senior Vice President and Chief Development Officer
David Thompson, PhD, Vice President, Global Project Leader
Martine Zimmermann, Vice President, Global Regulatory Affairs
Rajendra Pradhan, Senior Director, Clinical PK/PD
Lan Li, Director, Bioanalytical Development
Chetan Lathia, Executive Director, Clinical Pharmacology

1.0 BACKGROUND

Asfotase alfa is a human recombinant tissue-nonspecific alkaline phosphatase (TNSALP) fusion protein being developed for the [REDACTED] ^{(b) (4)} for patients with perinatal, infantile or childhood onset Hypophosphatasia. Hypophosphatasia is a rare, inborn error of bone metabolism caused by inactivating mutations in the gene encoding the TNSALP isoenzyme, which inhibits bone mineralization of bone matrix, leading to rickets in infants and children and osteomalacia in patients of all ages.

On April 16, 2013, Alexion and FDA met to discuss the clinical development program, and the Agency's advice provided during the End of Phase 2 meeting with Enobia Pharma on May 31, 2011. In follow up to the April 16, 2013, meeting, FDA provided additional clarification, in the form of written responses, regarding the clinical pharmacology and bioanalytical questions from the meeting.

On May 21, 2013, asfotase alfa received Breakthrough Therapy Designation for treatment of hypophosphatasia in perinatal-, infantile-, and juvenile-onset phenotypes. However,

Breakthrough Therapy Designation was not granted for adult-onset HPP [REDACTED] (b) (4)

[REDACTED] In follow up to the Breakthrough Therapy Designation, Alexion submitted a type B meeting request to discuss their development plan. The meeting was granted, and scheduled for September 3, 2013.

Following the September 3, 2013 meeting with FDA, Alexion requested an additional clinical meeting, received September 20, 2013, to discuss the clinical development program in patients with juvenile-onset hypophosphatasia (HPP).

2.0 DISCUSSION

2.1. Introductory Comments

The Division is committed to working closely with you towards the goal of expeditiously developing a successful BLA package that will contain all the necessary information for approval. Accelerated approval requires the submission of data from a controlled clinical trial. You are proposing to use a historical control but not submit the data from your natural history study with the marketing application (BLA). You must submit your control data (either historical or controlled trial) with your marketing application for either regular or accelerated approval pathways.

The regular approval pathway involves the use of clinical benefit endpoints, which generally describe how the person feels, functions or survives.

We remind you that the accelerated approval pathway involves the use of surrogate endpoints for initial marketing approval. Validity of that surrogate to predict clinically meaningful benefit for that population must then be proven by a controlled clinical trial utilizing a clinical benefit endpoint. The surrogate must be accepted to be reasonably likely to predict clinical benefit in the population, and must be based on epidemiologic, therapeutic, pathophysiologic, or other scientific evidence.

The Division has concerns about your proposal to seek approval for the juvenile-onset population using the co-primary surrogate of an increase from baseline in height z-score, and an RGI-C of ≥ 1.5 at Week 24, in the treated group compared to the untreated natural history data group.

While growth is typically considered a clinical endpoint, we are concerned that it might not be the best choice for the juvenile onset population. See details of this discussion in the answer to question #4 below.

The RGI-C could be considered as a surrogate endpoint. One of the problems is that there are no established surrogate endpoints for this population. It is unclear how potential surrogate measures (such as radiographic measures, biochemical parameters, etc) correlate to clinical outcomes in the natural history population.

Another concern is the feasibility of collecting natural history data on clinically meaningful endpoints that are of sufficient quality to evaluate for a clinically relevant treatment effect in patients treated with asfotase alfa. For example, the interpretability of growth assessments depends upon consistent and accurate methodology for measuring growth, i.e. use of stadiometer.

Finally, approval based on the use of a surrogate endpoint via the accelerated approval pathway requires a confirmatory trial with clinically meaningful endpoints be underway at the time of the submission of the BLA. We are concerned about the feasibility of completing a confirmatory clinical trial post-approval.

If you wish to pursue approval with the data from your natural history study providing the basis for a historical control, we strongly suggest that you submit the data from the natural history study to us for review prior to submission of your BLA. Review of this data will allow us to determine if this data is acceptable as a historical control and best advise you on choice of endpoints.

We continue to recommend you seek approval via the regular pathway with a clinical endpoint by conducting a randomized, double-blind, placebo-controlled trial. During discussions in the April 16, 2013 Type C meeting, we had requested that you provided adequate justification for use of the Distance (6MWD) as the primary endpoint for your proposed trial. Based on the 6MWD data that you provided with your request for Breakthrough Designation, we consider the 6MWD to be an acceptable functional clinical endpoint for the trial. We would suggest that you perform a responder analysis (e.g., percent of children whose 6MWD performance for age is below a pre-specified threshold at baseline that achieve normal 6 MWD performance for age) and the trial be designed to include an interim analysis of efficacy, so that early determination of efficacy be made by an appropriately empowered DSMB. Therefore, patients on placebo could be transferred to treatment if early results show a clinically significant treatment effect.

2.2. Questions and Responses

Question 1: Would the Agency consider the package, including all infantile-onset data (clinical trial and natural history), completed juvenile-onset data (clinical trial plus added growth data to current radiological historical control), and an ongoing natural history study in juvenile-onset HPP, as supportive of [REDACTED]^{(b) (4)} for the juvenile-onset indication?

FDA Response to Question 1:

No we do not agree, see introductory comments.

We agree that all data collected in this population (i.e., clinical, radiographic, and biochemical data), and survival and ventilator-free survival data for the infantile-onset population can be used as supportive evidence for an indication for the juvenile-onset population. See further discussion of possible endpoint designs in the response to Question #4.

Additional Discussion: None

Question 2: Does the Agency agree that Alexion's proposed natural history study is adequately designed to establish a historical control group that can serve as a nonconcurrent comparator for the group of juvenile-onset HPP patients that have already been treated in clinical trials of asfotase alfa for HPP?

FDA Response to Question 2:

Yes, we agree with the proposed eligibility criteria for ALX-HPP-502. However, we do not agree with the proposed (b) (4) (see response to Question 4).

Additional Discussion: None

Question 3: Does the Agency agree that the proposed matching criteria for the historical control and treatment group are appropriate to establish a nonconcurrent comparison to define treatment effect in the juvenile-onset HPP population?

FDA Response to Question 3:

Yes, we agree with the population matching criteria listed in Table 6 of the meeting briefing package, with the exception of the radiograph matching criterion. Because the time intervals between paired radiographs are different for the control and treatment groups (allowed time interval is between 6 weeks and up to 5 years apart for historical controls compared to a 6-month interval for treated patients), we are concerned about the ability to evaluate for differences in outcomes between the two groups. Justify the difference in time intervals between x-rays performed in the treated group vs. the historical control. In addition, we do not agree with the criteria for the primary comparative analysis (see responses to Questions 2 and 4).

Additional Discussion: None

Question 4: Does the Agency agree with Alexion's proposed analysis for demonstrating the benefit in patients with juvenile-onset HPP treated with asfotase alfa to the matched untreated patients from the natural history study?

FDA Response to Question 4:

As stated earlier, there are no established surrogate endpoints for the juvenile-onset HPP population. Therefore, we are unable to recommend any specific surrogate endpoints prior to a review of the natural history data for this population.

Growth may potentially be a clinically meaningful endpoint for the juvenile-onset population. However, in the absence of natural history data, it is unclear how growth is

impacted in this population. We note that the majority of juvenile-onset patients in clinical trials had baseline and end-of-study height z-scores that were within the normal limits of height based on age (i.e., z-scores that correspond to age-based height percentiles >10%). Therefore, we are unable to agree with your proposed (b) (4)

You will need to provide adequate justification for the criterion used to identify patients to be included in the growth analysis (height z-score < 0; age-based height percentile 50%) or for the degree of change in growth that represents a clinically significant change (change in z-score of 0.3). In addition, you will need to provide information on methodology, frequency, and quality of growth assessments (see below).

Other information that may be helpful to you in developing your endpoint analysis includes:

Bone information

1. Justify the use of percent of healthy mean, as opposed to actual or percent change, for the osteoid thickness correlations. In addition, present correlation analyses using actual and percent change in osteoid thickness.

Growth Information

1. Present information on how the height data are collected in Study ENB-006-09/ENB -008010; specifically, the methodology of height measurements, whether there was a consistent protocol/procedure that was followed, who was allowed to collect the data at the site (assigned or random health care provider), whether there was a single measurement or multiple measurements; if multiple measurements were done, how many were used and if any were thrown out. Similar information should be provided for the retrospective natural history study ALX-HPP-502.
2. Consider conducting an analysis of the variability of the height measurements (assuming that more than one height measurement was collected at any given visit) and how this variability in measurements relates to the size of the proposed treatment effect.
3. A relatively simple analysis of data quality is to check if for each individual patient there were reductions in height over time. Linear growth in children can be stunted, but unlike weight it should not regress unless there are events that affect the integrity of the skeleton. Even children with growth hormone deficiency have some small degrees of linear growth over time. Loss of height over time is evidence of poor height data collection.
4. Indicate if they have pretreatment height data for the 8 patients enrolled in Study ENB-006-09/ENB -008010. Such data can be used to calculate a pretreatment height velocity (generally data > 6 months are desirable, ideally within one year and collected at similar intervals for all patients).
5. Indicate the frequency of height measurements in Study ENB-006-09/ENB -008010, whether they were done according to a consistent schedule and if so how frequently.

- 6. Indicate whether bone age radiographs were collected in the juvenile HPP program, particularly in Study ENB-006-09/ENB -008010, and if so at what intervals.**
- 7. Present final height SDS in any patient in which it may be available. It is possible that some patients were enrolled close to puberty, in which case 3 years of treatment may bring them to an age close to that at which final height would be collected.**
- 8. Because development of neutralizing antibodies may inhibit the treatment effect in general and on height in particular. Please provide any immunogenicity data collected and analysis of the data on any endpoint studied. Has the validity of the immunoassays been established by the agency?**
- 9. A descriptive analysis of individual height SDS in patients enrolled in Study ENB-006-09/ENB -008010 accompanied by a graphic display of the height trajectory may be informative in assessing the treatment effect. Given the small size of the treatment arm a graph integrating all these profile may also be of help.**

Additional Discussion: None

3.0 PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable. Because this drug product for this indication has an orphan drug designation, you are exempt from these requirements. If there are any changes to your development plans that would cause your application to trigger PREA, your exempt status would change.

4.0 ISSUES REQUIRING FURTHER DISCUSSION

See introductory comments. FDA expanded on concerns regarding the quality of growth measurements, the potential for improvement at puberty, and possibility that the magnitude of difference may not be highly persuasive. FDA reiterated that if Alexion uses growth for a primary clinical endpoint that it be supported with other clinical endpoints such as other functional endpoints.

5.0 ACTION ITEMS

Action Item/Description	Owner	Due Date
Follow-up meeting between FDA and Alexion Pharma	Alexion Pharma	Pending revised clinical development proposal and subsequent meeting request.

6.0 ATTACHMENTS AND HANDOUTS

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/s/

ELIZABETH A FORD
02/11/2014



IND 100619

MEETING MINUTES

Alexion Pharma International Sarl
c/o Alexion Pharmaceuticals
Attention: Brett Richardson
Senior Manager, Regulatory Affairs
55 Cambridge Parkway, Suite 800
Cambridge, MA 02142

Dear Mr. Richardson:

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

We also refer to the meeting between representatives of your firm and the FDA on January 14, 2014. The purpose of the meeting was to discuss and reach agreement on the overall immunogenicity assessment plan for asfotase alfa.

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 me at (301) 796-0193.

Sincerely,

{See appended electronic signature page}

Elizabeth A.S. Ford, R.N.
Senior Regulatory Health Project Manager
Division of Gastroenterology and Inborn Errors
Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type: B
Meeting Category: Other/Breakthrough Therapy, Immunology Focus

Meeting Date and Time: January 14, 2014, 10:30-11:30
Meeting Location: White Oak Building 22, Room 1419

Application Number: IND 100619
Product Name: asfotase alfa
Indication: Asfotase alfa is indicated for [REDACTED] (b) (4)
[REDACTED] (b) (4) for patients with perinatal-, infantile- or juvenile-onset hypophosphatasia.

Sponsor/Applicant Name: Alexion Pharma International Sarl

Meeting Chair: Lara Dimick, M.D.
Meeting Recorder: Elizabeth Ford, R.N.

FDA ATTENDEES

Division of Gastroenterology and Inborn Errors Products (DGIEP)

Donna Griebel, M.D., Director

Andrew E. Mulberg, M.D., Deputy Director

Lara Dimick, M.D., Acting Clinical Team Leader

Carla Epps, M.D., Medical Officer

Brian K. Strongin, R.Ph., M.B.A., Chief, Project Management Staff

Elizabeth A.S. Ford, R.N., Senior Regulatory Health Project Manager

Office of Translational Sciences

Office of Clinical Pharmacology/Division of Clinical Pharmacology 3

Jie Wang, Ph.D., Biologics Team Leader, Acting

Christine Hon, Pharm.D., Clinical Pharmacology Reviewer

Office of Biotechnology Products

Division of Therapeutic Proteins

Joslyn Brunelle, Ph.D., Product Quality Reviewer

Frederick Mills, Ph.D., Biologist

Susan Kirshner, Ph.D., Review Chief

SPONSOR ATTENDEES

Clare Elkins, MS, Senior Director, Biostatistics
Suresh Mahabhashyam, MD, Medical Director, Pharmacovigilance
Agustin Melian, MD, Vice President, Clinical Development Excellence
Brett Richardson, Senior Manager, Regulatory Affairs, US
Steven Ryder, MD, Senior Vice President and Chief Development Officer
David Thompson, PhD, Vice President, Global Project Leader
Martine Zimmermann, Vice President, Global Regulatory Affairs
Rajendra Pradhan, Senior Director, Clinical PK/PD
Lan Li, Director, Bioanalytical Development
Chetan Lathia, Executive Director, Clinical Pharmacology

1.0 BACKGROUND

Asfotase alfa is a human recombinant tissue-nonspecific alkaline phosphatase (TNSALP) fusion protein being developed for the [REDACTED] (b) (4) for patients with perinatal, infantile or childhood onset Hypophosphatasia. Hypophosphatasia is a rare, inborn error of bone metabolism caused by inactivating mutations in the gene encoding the TNSALP isoenzyme, which inhibits bone mineralization of bone matrix, leading to rickets in infants and children and osteomalacia in patients of all ages.

On April 16, 2013, Alexion and FDA met to discuss the clinical development program, and the Agency's advice provided during the End of Phase 2 meeting with Enobia Pharma on May 31, 2011. In follow up to the April 16, 2013, meeting, FDA provided additional clarification, in the form of written responses, regarding the clinical pharmacology and bioanalytical questions from the meeting.

On May 21, 2013, asfotase alfa received Breakthrough Therapy Designation for treatment of hypophosphatasia in perinatal-, infantile-, and juvenile-onset phenotypes. However, Breakthrough Therapy Designation was not granted for adult-onset HPP [REDACTED] (b) (4)

[REDACTED] In follow up to the Breakthrough Therapy Designation, Alexion submitted a type B meeting request to discuss their development plan. The meeting was granted, and scheduled for September 3, 2013.

Following the September 3, 2013 meeting with FDA, Alexion requested an immunology-focused meeting to discuss and reach agreement on the overall immunogenicity assessment plan for asfotase alfa. The meeting was granted, and scheduled for December 10, 2013. Following a weather-related closure, the meeting was rescheduled for January 14, 2014.

2.0 DISCUSSION

2.1. Questions and Responses

Question 1: Based on this assessment Alexion would like to reach an agreement with the FDA on the acceptability of the immunogenicity assessment for asfotase alfa. Is this plan acceptable to the FDA?

FDA Response: The immunogenicity assessment plan as currently described does not provide enough information for us to fully evaluate its adequacy.

We acknowledge that you have a refined population pharmacokinetic (PPK) model that showed a small neutralizing antibody (NAb) effect on asfotase alfa clearance, and you will present these results together with findings from a population PK-PD meta-analysis in an upcoming Clinical Pharmacology focused Type C meeting. We will comment on this PPK model and the population PK-PD meta-analysis at the requested Clinical Pharmacology focused meeting.

We also note that you will adopt a two-step process of immunogenicity impact assessment strategy to address the issue about the time-varying nature of the immunogenicity data: data visualizations of the immunogenicity impact on PK/efficacy/safety at both the patient- and population-level, followed by modeling of the PK/efficacy/safety data that demonstrate clear correlations with immunogenicity. We request that you provide details of the modeling approach/techniques that you plan to use to account for the time-varying nature of immunogenicity and the analysis results for our review.

In addition to the model-based analysis for immunogenicity impact assessment, we recommend that you perform the following comparisons to assess the impact of immunogenicity on PK:

1. Antidrug antibody (ADA) positive vs. ADA negative
2. NAb positive vs. NAb negative
3. High ADA titers vs. low ADA titers
4. Before and after the development of ADA/NAb in ADA and/or NAb positive subjects

As part of the statistical plan (SAP) for the ISS and ISE, you plan to assess the impact of immunogenicity by comparing safety and efficacy in ADA positive vs. ADA negative and NAb positive vs. NAb negative subjects. We recommend that you also compare high ADA titer vs. low ADA titer subjects. In addition, consider explore the occurrence of adverse events before and after the development of ADA and/or NAb.

Furthermore, correlation analyses can also be performed between PK/efficacy/safety data and ADA titers or % inhibition of asfotase alfa activity in NAb+ subjects.

For other therapeutic proteins, immune-mediated alteration of efficacy may require prolonged administration (Kappos et al,2005, Neurology 65, pp 40-47). This indicates a need for long-term monitoring of immunogenicity and PK, PD, safety, and efficacy.

Additional Discussion: Alexion will analyze the data from the low and high titer ADA positive patients to characterize the relationship between the presence/absence of neutralizing antibodies and ADA titer. Alexion will need to provide a clinically meaningful justification for the low and high titer classifications.

Question 2: Does the FDA agree that Alexion's assessment and strategy will adequately address the FDA's request of tolerizing regimens to manage the potential immunogenicity associated with the administration of asfotase alfa?

FDA Response: As also noted for Question 1, immune-mediated changes in efficacy may occur after prolonged administration, and thus long term evaluation of risk is important for assessing the need for immune tolerization.

Additional Discussion: None

Question 3: Does the FDA agree with Alexion's proposed approach for characterizing anti-asfotase alfa antibodies specific to the D10 moiety?

FDA Response: Your approach is generally acceptable. The Agency notes that evaluating purity of a D10 peptide is critical to ensure that non-specific competition does not arise in their proposed competition-based assay. In the alternate strategy involving

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

Regarding your proposed assessment of the current ADA assay positive control (PC) for anti-D10 activity, the FDA notes that D10 affinity purification may be used to enhance anti-D10 binding.

Additional Discussion: None

Question 4: Does the FDA agree that Alexion's CRIM assay development and implementation plan is sufficient?

FDA Response: Your approach is generally acceptable. If sufficient sensitivity can be demonstrated, your alternative LC/MS strategy may be a relatively quick pathway for development of a CRIM assay.

Regarding the extent of genetic screening:

Clarify whether all patients will be screened to identify all non-missense patients. This is an important first step because true CRIM negative patients may be rare, and the chances of identifying these individuals will be improved by performing CRIM assays on the largest possible number of non-missense samples.

Additional Discussion: None

Question 5: Does the FDA agree with Alexion's proposed approach for a revised titration cut point to be used for evaluating patient titers for anti-asfotase alfa antibodies?

FDA Response: Your approach is acceptable.

Additional Discussion: None

3.0 PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable. Because this drug product for this indication has an orphan drug designation, you are exempt from these requirements. If there are any changes to your development plans that would cause your application to trigger PREA, your exempt status would change.

4.0 ISSUES REQUIRING FURTHER DISCUSSION

None

5.0 ACTION ITEMS

None

6.0 ATTACHMENTS AND HANDOUTS

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/s/

ELIZABETH A FORD
02/10/2014



IND 100619

**GRANT –
BREAKTHROUGH THERAPY DESIGNATION**

Alexion Pharma International Sarl
c/o Alexion Pharmaceuticals
Attention: Brett Richardson
Senior Manager, Regulatory Affairs
55 Cambridge Parkway
Suite 800
Cambridge, MA 02142

Dear Mr. Richardson:

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

We also refer to your March 19, 2013 request for Breakthrough Therapy designation for the treatment of hypophosphatasia (HPP), which has been investigated in ^{(b) (4)} HPP phenotypes: perinatal-, infantile-, juvenile-^{(b) (4)}-onset. We have reviewed your request and have determined that asfotase alfa for treatment of hypophosphatasia in perinatal-, infantile-, and juvenile-onset phenotypes meets the criteria for Breakthrough Therapy designation. Therefore, we are granting your request for Breakthrough Therapy designation in those phenotypes. 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 asfotase alfa for treatment of hypophosphatasia, including providing advice on generating evidence needed to support approval of the drug in an efficient manner. 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). A guidance document is currently under development.

In terms of next steps, please submit a Type B meeting request. This meeting will be for a multidisciplinary comprehensive discussion of your development program, including planned clinical trials and plans for expediting the manufacturing development strategy. Please refer to the *Guidance for Industry: Formal Meetings between FDA or Sponsors and Applicants*¹ for procedures on requesting a meeting.

¹ <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM153222.pdf>

If you have any questions, contact Elizabeth Ford, Regulatory Project Manager, at (301) 796-0193.

Sincerely,

{See appended electronic signature page}

Donna Griebel, M.D.
Director
Division of Gastroenterology and Inborn Errors
Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

DONNA J GRIEBEL
05/21/2013



IND 100619

MEETING MINUTES

Enobia Pharma Inc.
Attention: James A. Taylor, Ph.D.
Regulatory Advisor for Enobia Pharma
539 Tori Court
New Hope, PA 18938

Dear Dr. Taylor:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for ENB-0040 (sALP-Fc-D10).

We also refer to the meeting between representatives of your firm and the FDA on May 31, 2011. The purpose of the meeting was to discuss clinical and nonclinical studies to support the ENB-0040 development program.

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 me, at (301) 796-0193.

Sincerely,

{See appended electronic signature page}

Elizabeth A.S. Ford, R.N.
Senior Regulatory Health Project Manager
Division of Gastroenterology and Inborn Errors
Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

ENCLOSURE:
Meeting Minutes



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type: B
Meeting Category: End-of-Phase 2

Meeting Date and Time: May 31, 2011, 12:00 PM
Meeting Location: White Oak Building 22, Conference Room 1417

Application Number: IND 100619
Product Name: ENB-0040
Indication: Treatment of hypophosphatasia
Sponsor/Applicant Name: Enobia Pharma

Meeting Chair: Lynne Yao, M.D.
Meeting Recorder: Elizabeth A.S. Ford, R.N.

FDA ATTENDEES

Office of Drug Evaluation III
Julie Beitz, M.D., Director

Division of Gastroenterology and Inborn Error Products (DGIEP)
Donna Griebel, M.D., Director
Lynne Yao, M.D., Clinical Team Leader
Carla Epps, M.D., Clinical Reviewer
Sushanta Chakder, Ph.D., Nonclinical Team Leader
Charles Wu, Ph.D., Nonclinical Reviewer
Elizabeth A.S. Ford, R.N., Senior Regulatory Health Project Manager

Office of Translational Sciences
Office of Clinical Pharmacology
Gilbert Burckart, PharmD, Associate Director

Office of Translational Sciences
Office of Clinical Pharmacology/Division of Clinical Pharmacology 3
Yeruk Mulugeta, Ph.D., Clinical Pharmacology Reviewer

Office of Biotechnology Products
Division of Therapeutic Proteins
Emanuela Lacana, Ph.D., Associate Lab Chief
Joslyn Brunelle, Ph.D., Product Quality Reviewer

Office of Biostatistics/Division of Biometrics III

Behrang Vali, M.S., Statistical Reviewer

Office of New Drugs/Immediate Office

Anne Pariser, M.D., Acting Associate Director for Rare Diseases

Larry Bauer, R.N., M.A., Regulatory Health Project Manager

Dan Slack, Rare Disease Program

SPONSOR ATTENDEES

Enobia Pharma

Deborah Ramsdell V.P., Regulatory Affairs & Clinical Operations

Hal Landy, M.D. V.P., Medical Affairs & Chief Medical Officer

James Taylor, Ph.D., Consultant, Regulatory Affairs

Janet Wittes, Ph.D., Consultant, Statistics

Matthew Downs, M.P.H., Consultant, Statistics

Michael Whyte, MD, Ph.D., Medical Consultant and HPP Investigator

Robert Heft, Ph.D., President and Chief Executive Officer

Horacio Plotkin, M.D., Senior Medical Director

Alison Skrinar, M.A., M.Ph., Sr. Director, Clinical Research and Regulatory Affairs

1.0 BACKGROUND

On March 23, 2011, Enobia Pharma (Enobia) requested two End of Phase 2 meetings for ENB-0040, contained in one supporting document (SDN 68). Enobia proposed a clinical and nonclinical meeting, separated (by at least two weeks) from a CMC-only meeting. The sponsor was advised to submit a separate meeting request for the CMC-only meeting. The CMC-only meeting was scheduled for June 15, 2011, but was cancelled on May 27, 2011 due to changes in the drug substance manufacturing process proposed in an IND amendment (outlined in the May 27, 2011 FDA meeting cancellation letter).

The clinical and nonclinical meeting was granted on April 13, 2011, and scheduled for May 31, 2011. The sponsor planned to discuss the status of the clinical development program, including ongoing and completed studies, and plans for submission of a BLA under accelerated approval. However, as discussed in the preliminary comments issued on May 27, 2011, the FDA provided detailed discussion points reflecting back on the December 16, 2009 meeting between FDA and Enobia.

2. DISCUSSION

Will the completed and ongoing clinical studies and available and planned natural history data presented in this dossier support submission of a BLA under accelerated approval in patients with hypophosphatasia?

FDA Response:

Clinical Comments:

As discussed during the end-of-Phase 1 meeting on December 16, 2009, in order to obtain labeling indications that include treatment for infant, juvenile, (b) (4) onset HPP, your clinical trials must demonstrate a clinically meaningful benefit of treatment with ENB-0040 in each of these populations. We have concerns regarding the interpretability of the data you have collected to date to support a BLA submission for these three distinct patient populations. These concerns include the following:

- 1. Infant HPP: The preliminary clinical data presented in your meeting package appear to demonstrate improvements in bone radiographs in infants with HPP who were treated with your product. However, it is unclear whether these patients represent a similar phenotype and whether you have selected a clearly defined control group from natural history studies that will provide an adequate and interpretable comparison. If you plan to use data from natural history studies to define a nonconcurrent control group to support the effectiveness of your product, we strongly recommend that you carefully define the historical control group *a priori* and that the control group is defined based on clinically relevant baseline patient characteristics (i.e., expected survival, presence of seizures, etc.). Additionally, you should plan to enroll patients that are carefully matched to the**

historical control group based on these baseline characteristics. If such a study is performed, it is possible that based on improvements in radiographic findings, submission of a BLA under accelerated approval regulations may be possible for this population. As stated in 21 CFR 601 Subpart E, approval based on a surrogate endpoint must be “...reasonably likely, based on epidemiologic, therapeutic, pathophysiologic, or other evidence, to predict clinical benefit.” You will need to provide justification that the changes in bone radiographs of these patients would be reasonably likely to predict a clinical outcome (e.g., time to walking, ventilator-free survival, etc.). However, approval under 21 CFR 601 Subpart E will be subject to the requirement that you study the drug further to verify and describe its clinical benefit and such studies “would usually be studies already underway.”

2. Juvenile (b) (4) HPP: To support an indication in juvenile (b) (4) patients with HPP, we continue to recommend adequate and well-controlled (i.e., randomized, double-blind, placebo-controlled) trials evaluating clinically meaningful endpoints you have identified based on the natural history of the disease in these populations. We remain concerned that data obtained from open-label trials using an unestablished surrogate endpoint may not be interpretable and therefore may not support an indication for treatment of these populations.

Additional Discussion:

FDA confirmed that demonstration of benefit in survival in infantile onset HPP could support regular approval for this population. FDA also noted that for this, and other populations, (b) (4) using a surrogate marker could be acceptable, but verification studies would usually be studies already underway. FDA agrees to review the Natural History protocol (SN0070, submitted April 28, 2011), and provide comments; however, FDA cannot guarantee a specific timeline for the completion of this review. FDA clarified that in choosing a natural history cohort to be used in an historical controlled study, a patient enrolled in the study would not be matched directly to a control patient (i.e., enrolled patients would not be matched 1:1 with the non-concurrent control group). However, in order to obtain interpretable data from a non-concurrently controlled study, the patients enrolled in the study should be appropriately matched for important baseline characteristics to the historical control group and the endpoints to be evaluated should be prospectively defined.

The sponsor would like the FDA to consider study 006 as the potential pivotal study in juvenile onset HPP and will submit a complete data package for review. FDA remains concerned about the interpretability of the data in such a study. If a durable and clinically meaningful treatment effect is demonstrated compared to a minimal effect, or no change in natural history controls, that could support a BLA submission.

Clinical Pharmacology Comments:

1. The pharmacokinetics of ENB0040 should be presented in the BLA to support labeling including any unique elimination pathway that may apply to this molecule.

- 2. Appropriate evaluations (physiochemical, non-clinical, and clinical) must be conducted to demonstrate comparability between the two products used in preclinical and clinical studies. Comparative pharmacokinetics may be necessary to establish equivalence between two products.**
- 3. Please provide a scientific rationale for exclusive use of ENB0040 activity. The assay validation and in-study performance data should be included in the submission to support your efficacy data. Please refer to the Guidance for Industry: Bioanalytical Method Validation (<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm070107.pdf>).**
- 4. The provided information for ENB-001-08, ENB-002-08, and ENB-006-09 is not sufficient to determine whether the studies are acceptable from a clinical pharmacology perspective and will therefore be a review issue.**
- 5. We recommend evaluation of the relationship between ENB0040 serum concentration/activity and pharmacodynamic response (PK/PD) for efficacy and safety to support the proposed doses.**
- 6. We recommend evaluation of the relationship of ENB0040 activity levels, allergic responses, functional assessments, and pharmacodynamic measurements (PLP and PPI) with the development of antibodies in all clinical studies including extension studies.**

Nonclinical Comments:

- 1. In addition to the nonclinical studies listed in Table 4-1 of the briefing package, you need to conduct a pre- and post- natal developmental toxicity study in rats with ENB 0040.**

CMC Comments:

- 1. We refer you to a separate CMC correspondence sent to you prior to this scheduled meeting. We encourage you to follow the advice as outlined in the letter regarding your product development plans.**
- 2. ENB-0040 contains an intact IgG1 Fc region and can potentially bind to Fc-receptors and activate the complement system. In addition, because ENB-0040 exists as a tetramer, there is a potential that it crosslinks Fc-receptors which provides an apoptotic signal to B cells. Interaction of ENB-0040 with Fc-receptors or complement could also enhance immunogenicity. We strongly recommend testing the capacity of ENB-0040 to bind to Fc-receptors and activate the complement system. If the results are positive, further tests and monitoring may be necessary.**

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

None

5.0 ACTION ITEMS

None

6.0 ATTACHMENTS AND HANDOUTS

Enobia End of Phase 2 Meeting Handout (attached)

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/s/

ELIZABETH A FORD
06/29/2011

LATE-CYCLE COMMUNICATION
DOCUMENTS



BLA 125513

LATE-CYCLE MEETING MINUTES

Alexion Pharmaceuticals, Inc.
Attention: Brett Richardson
Senior Manager, Regulatory Affairs
55 Cambridge Parkway, Suite 800
Cambridge, MA 02142

Dear Mr. Richardson:

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

We also refer to the Late-Cycle Meeting (LCM) teleconference between representatives of your company and the FDA on September 2, 2015.

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 Lisa Pitt, Regulatory Project Manager at (240) 402-9651.

Sincerely,

{See appended electronic signature page}

Anil Rajpal, MD
Medical Officer Team Leader
Division of Gastroenterology and Inborn Errors Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure:
Late Cycle Meeting Minutes



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF LATE-CYCLE MEETING MINUTES

Meeting Date and Time: September 2, 2015
Meeting Location: White Oak Building 22, Conference Room 1421

Application Number: 125513
Product Name: Strensiq (asfotase alfa)
Applicant Name: Alexion Pharmaceuticals Inc.

Meeting Chair: Anil Rajpal
Meeting Recorder: Lisa Pitt

FDA ATTENDEES

Julie Beitz, MD, Office of Drug Evaluation III (ODE III)
Amy Egan, MD, MPH, ODE III
Maria Walsh, RN, MSN, ODE III
Donna Griebel, MD, ODE III, Division of Gastroenterology and Inborn Errors Products (DGIEP)
Dragos Roman, MD, ODEIII, DGIEP
Joyce Korvick, MD, MPH, ODEIII, DGIEP
Anil Rajpal, MD, ODEIII, DGIEP
Carla Epps, MD, MPH, ODEIII, DGIEP
Sushanta Chakder, PhD, ODEIII, DGIEP
Dinesh Gautam, PhD, ODEIII, DGIEP
Kevin Bugin, MS, RAC, ODEIII, DGIEP
Lisa Pitt, PharmD, MSJ, ODEIII, DGIEP
Yeh-Fong Chen, PhD, ODEIII, DGIEP
Benjamin Vali, PhD, ODEIII, DGIEP
Vicki Moyer, MS, ODEIII, DGIEP
Yow-Ming Wang, PhD, Office of Clinical Pharmacology (OCP)
Christine Hon, PhD, OCP
Nitin Mehrotra, PhD, OCP
Justin Earp, PhD, OCP
Kathryn O'Connell, Rare Diseases Program (RDP)
Jonathan Goldsmith, RDP
Kimberly Taylor, Office of Strategic Programs
Cristina Ausin, PhD, Office of Biotechnology Products (OBP)
Joslyn Brunelle, PhD, OBP
Gunther Boekhoudt, PhD, OBP
Frederick Mills, OBP
Gerald Feldman, OBP
Jibril Abdus-Samad, PharmD, OBP

Candace Gomez-Broughton, Office of Process and Facilities (OPF), Division of Microbiology Assessment (DMA)
Patricia Hughes, PhD, OPF, DMA
Steven Fong, MS, PhD, OPF, Division of Inspectional Assessment (DIA), Branch 1
Christina Capacci-Daniel, OPF, DIA
Carrie Ceresa, Division of Pediatric and Maternal Health (DPMH)
Ethan Hausman, DPMH
Denise Pica-Branco, DPMH
Adewale Adeleye, PharmD, Office of Prescription Drug Promotion (OPDP)
David Shih, Office of Surveillance and Epidemiology (OSE), Division of Epidemiology I (DEPI I)
Sukhminder Sandhu, OSE, DEPI I
Joel Weissfeld, OSE, DEPI I
Kendra Worthy, OSE, Division of Medication Error Prevention and Analysis (DMEPA)
Matthew Barlow, OSE, DMEPA
Jasminder Kumar, PharmD, OSE, Division of Risk Management

EASTERN RESEARCH GROUP ATTENDEES

Marc Goldstein, Independent Assessor
Peggha Khorrami, Independent Assessor

APPLICANT ATTENDEES

Agustin Melian, MD, Global Medical Sciences
Alexander Cole, DSc, Epidemiology
Alfred Boyle, PhD, Global Technical Services
Brett Richardson, Regulatory Affairs
Clare Elkins, MS, Biostatistics
Coleen Glessner, R&D Quality and Compliance
David Thompson, PhD, Global Project Leader
Declan Kelly, MS, Chief Quality Officer
Jill Hillier, PhD, Regulatory Affairs
Kenji Fujita, MD, Clinical Development
Suresh Mahabhashyam, MD, Pharmacovigilance
Lori Martel, PhD, Medical Writing
Mallory Bissett, Clinical Operations
Martine Zimmermann, PharmD, Regulatory Affairs
Rachel Alford, Biochemical Process Development
Rajendra Pradhan, BPharm, MPharm, PhD, Clinical Pharmacokinetics and Pharmacodynamics
Scott Nickerson, MS, Quality Assurance and Quality Control
Scott Moseley, MS, Biostatistics

1.0 BACKGROUND

BLA 125513 was submitted on December 23, 2014 for Strensiq (asfotase alfa).

Proposed indication(s): [REDACTED] (b) (4) [REDACTED] (b) (4) in patients with infantile- and juvenile-onset hypophosphatasia (HPP)

PDUFA goal date: November 23, 2015

FDA issued a Background Package in preparation for this meeting on August 19, 2015. The meeting was held as a teleconference per the Applicant's request.

2.0 DISCUSSION

1. Introductory Comments

Welcome, Introductions, Ground rules, Objectives of the meeting

2. Discussion of Substantive Review Issues

Discussion:

As communicated in the late-cycle meeting package one facility, the [REDACTED] (b) (4) secondary testing site, has received a Form FDA 483 for pre-license inspection observations. Alexion has decided to remove this site from the BLA. A formal submission, including updates to all impacted sections of the BLA, will be made by Friday, September 4, 2015.

3. Information Requests

Discussion:

All outstanding Information Requests communicated in the background package have been addressed.

4. Postmarketing Requirements/Postmarketing Commitments

Discussion:

We refer to the Postmarketing Requirements/Commitments (PMR/PMC) sent to the Applicant on August 7, 2015, and PMR clarification comments sent on September 1, 2015. Alexion stated that they are already preparing a global registry protocol based on the recent European Medicines Agency (EMA) Strensiq marketing authorization application (MAA) approval and it is their intent that this protocol will also address the Agency's PMR

provided on August 7, 2015. Alexion provided a summary of the planned registry that includes asfotase alfa-treated and untreated patients, evaluating efficacy and key safety events of interest such as ectopic calcifications, injection site reactions including systemic anaphylaxis and severe allergic reactions. Enrollment of untreated patients has already begun under the current registry study, entitled “An Observational, Longitudinal, Prospective, Long-Term Registry of Patients with Hypophosphatasia (HPP)”, NCT Number NCT02306720. Alexion agreed to submit copies of both protocols for review. Dr. Korvick commented that the information from both of these protocols will be useful for finalizing the PMRs for inclusion in the action letter.

5. Review Plans

Discussion:

We will review remaining labeling items (PI comments and revised carton/container) received from Alexion and will follow-up with our responses as necessary after an internal meeting on September 9, 2015. It remains our intent to complete the review in advance of the current PDUFA goal date.

6. Wrap-up and Action Items

- a. Alexion to submit copies of the current ongoing registry protocol for untreated patients (NCT 02306720) and the draft planned global registry protocol.
- b. FDA to provide labeling comments following internal team meeting(s) to review Applicant labeling comments. Initial team meeting to be held September 9, 2015.

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

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/s/

ANIL K RAJPAL
09/14/2015