

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**125561Orig1s000**

**ADMINISTRATIVE and CORRESPONDENCE  
DOCUMENTS**

# ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION <sup>1</sup>		
NDA # BLA # 125561/0	NDA Supplement # BLA Supplement #	If NDA, Efficacy Supplement Type: <i>(an action package is not required for SE8 or SE9 supplements)</i>
Proprietary Name: KANUMA Established/Proper Name: sebelipase alfa Dosage Form: injection, for intravenous use		Applicant: Alexion Pharmaceuticals, Inc Agent for Applicant (if applicable):
RPM: Kevin Bugin		Division: DGIEP
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 checked="" type="checkbox"/> 351(k) <input type="checkbox"/> 351(a) Efficacy Supplement: <input type="checkbox"/> 351(k) <input type="checkbox"/> 351(a)		<p><b><u>For ALL 505(b)(2) applications, two months prior to EVERY action:</u></b></p> <ul style="list-style-type: none"> <li>Review the information in the 505(b)(2) Assessment and submit the draft<sup>2</sup> to CDER OND IO for clearance.</li> <li>Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity)</li> </ul> <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"> <li>Proposed action</li> <li>User Fee Goal Date is <u>12/08/2015</u></li> </ul>		<input checked="" type="checkbox"/> AP <input type="checkbox"/> TA <input type="checkbox"/> CR
<ul style="list-style-type: none"> <li>Previous actions (<i>specify type and date for each action taken</i>)</li> </ul>		<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 <a href="http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf">http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf</a> ). If not submitted, explain _____		<input type="checkbox"/> Received
❖ Application Characteristics <sup>3</sup>		

<sup>1</sup> 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.

<sup>2</sup> 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).

<sup>3</sup> 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 |   |

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 checked="" type="checkbox"/> CDER Q&As <input type="checkbox"/> Other
❖ Exclusivity	
• Is approval of this application blocked by any type of exclusivity (orphan, 5-year NCE, 3-year, pediatric exclusivity)? • If so, specify the type	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes
❖ Patent Information (NDAs only)	
• Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought.	<input type="checkbox"/> Verified <input type="checkbox"/> Not applicable because drug is an old antibiotic.
<b>CONTENTS OF ACTION PACKAGE</b>	
<b>Officer/Employee List</b>	
❖ 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 (including approval letter with final labeling)	Approval: 12/08/2015
Labeling	
❖ Package Insert (write submission/communication date at upper right of first page of PI)	
• Most recent draft labeling (if it is division-proposed labeling, it should be in track-changes format)	<input checked="" type="checkbox"/> Included 12/01/2015
• Original applicant-proposed labeling	<input checked="" type="checkbox"/> Included 11/21/2015
❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling (write submission/communication date at upper right of first page of each piece)	<input type="checkbox"/> Medication Guide <input type="checkbox"/> Patient Package Insert <input type="checkbox"/> Instructions for Use <input type="checkbox"/> Device Labeling <input checked="" type="checkbox"/> None
• Most-recent draft labeling (if it is division-proposed labeling, it should be in track-changes format)	<input type="checkbox"/> Included
• Original applicant-proposed labeling	<input type="checkbox"/> Included
❖ Labels (full color carton and immediate-container labels) (write submission/communication date on upper right of first page of each submission)	
• Most-recent draft labeling	<input checked="" type="checkbox"/> Included 09/03/2015
❖ Proprietary Name	12/15/2015 12/09/2015
• Acceptability/non-acceptability letter(s) (indicate date(s))	
• Review(s) (indicate date(s))	
❖ Labeling reviews (indicate dates of reviews)	RPM: <input type="checkbox"/> None 02/13/2015 DMEPA: <input type="checkbox"/> None 04/14/2015; 07/29/2015 DMPP/PLT (DRISK): <input checked="" type="checkbox"/> None OPDP: <input type="checkbox"/> None 06/03/2015 SEALD: <input checked="" type="checkbox"/> None CSS: <input checked="" type="checkbox"/> None Product Quality <input type="checkbox"/> None 08/13/2015 Other: <input checked="" type="checkbox"/> None
Administrative / Regulatory Documents	
❖ RPM Filing Review <sup>4</sup> /Memo of Filing Meeting (indicate date of each review)	02/13/2015
❖ All NDA 505(b)(2) Actions: Date each action cleared by 505(b)(2) Clearance Committee	<input checked="" type="checkbox"/> Not a (b)(2)
❖ NDAs only: Exclusivity Summary (signed by Division Director)	<input type="checkbox"/> Included
❖ Application Integrity Policy (AIP) Status and Related Documents <a href="http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm">http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm</a>	
• Applicant is on the AIP	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No

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

<ul style="list-style-type: none"> <li>This application is on the AIP <ul style="list-style-type: none"> <li>If yes, Center Director's Exception for Review memo (<i>indicate date</i>)</li> <li>If yes, OC clearance for approval (<i>indicate date of clearance communication</i>)</li> </ul> </li> </ul>	<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"> <li>Date reviewed by PeRC _____ If PeRC review not necessary, explain: _____</li> </ul>	N/A
❖ Breakthrough Therapy Designation	<input type="checkbox"/> N/A
<ul style="list-style-type: none"> <li>Breakthrough Therapy Designation Letter(s) (granted, denied, an/or rescinded)</li> </ul>	Granted: 05/13/2014
<ul style="list-style-type: none"> <li>CDER Medical Policy Council Breakthrough Therapy Designation Determination Review Template(s) (<i>include only the completed template(s) and not the meeting minutes</i>)</li> </ul>	05/13/2014
<ul style="list-style-type: none"> <li>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>)</li> </ul> <p>(<i>completed CDER MPC templates can be found in DARRTS as clinical reviews or on the <a href="#">MPC SharePoint Site</a></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> )	N/A
❖ 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"> <li>If not the first review cycle, any end-of-review meeting (<i>indicate date of mtg</i>)</li> </ul>	<input checked="" type="checkbox"/> N/A or no mtg
<ul style="list-style-type: none"> <li>Pre-NDA/BLA meeting (<i>indicate date of mtg</i>)</li> </ul>	<input type="checkbox"/> No mtg    02/12/2014; 08/15/2014
<ul style="list-style-type: none"> <li>EOP2 meeting (<i>indicate date of mtg</i>)</li> </ul>	<input checked="" type="checkbox"/> No mtg
<ul style="list-style-type: none"> <li>Mid-cycle Communication (<i>indicate date of mtg</i>)</li> </ul>	<input type="checkbox"/> N/A    04/24/2015
<ul style="list-style-type: none"> <li>Late-cycle Meeting (<i>indicate date of mtg</i>)</li> </ul>	<input type="checkbox"/> N/A    07/14/2015
<ul style="list-style-type: none"> <li>Other milestone meetings (e.g., EOP2a, CMC focused milestone meetings) (<i>indicate dates of mtgs</i>)</li> </ul>	EoP1: 06/12/2012; PIND: 07/29/2010; BRKTR: 05/13/2014 PreNADA: 04/23/2014
❖ Advisory Committee Meeting(s)	<input checked="" type="checkbox"/> No AC meeting
<ul style="list-style-type: none"> <li>Date(s) of Meeting(s)</li> </ul>	
<b>Decisional and Summary Memos</b>	
❖ Office Director Decisional Memo ( <i>indicate date for each review</i> )	<input type="checkbox"/> None    09/12/2015; 12/08/2015
Division Director Summary Review ( <i>indicate date for each review</i> )	<input type="checkbox"/> None    09/08/2015; 12/07/2015;
Cross-Discipline Team Leader Review ( <i>indicate date for each review</i> )	<input type="checkbox"/> None    09/06/2015
PMR/PMC Development Templates ( <i>indicate total number</i> )	<input type="checkbox"/> None    12/07/2015
<b>Clinical</b>	

❖ Clinical Reviews		
• Clinical Team Leader Review(s) ( <i>indicate date for each review</i> )		<input checked="" type="checkbox"/> No separate review
• Clinical review(s) ( <i>indicate date for each review</i> )		06/08/2015; 03/16/2015
• Social scientist review(s) (if OTC drug) ( <i>indicate date for each review</i> )		<input checked="" type="checkbox"/> None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here <input type="checkbox"/> and include a review/memo explaining why not ( <i>indicate date of review/memo</i> )		See Final Clinical Review: 06/08/2015, page 16.
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers ( <i>indicate date of each review</i> )		<input checked="" type="checkbox"/> None
❖ Controlled Substance Staff review(s) and Scheduling Recommendation ( <i>indicate date of each review</i> )		<input checked="" type="checkbox"/> N/A
❖ Risk Management		
• REMS Documents and REMS Supporting Document ( <i>indicate date(s) of submission(s)</i> )		N/A
• REMS Memo(s) and letter(s) ( <i>indicate date(s)</i> )		N/A
• 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 checked="" type="checkbox"/> None
❖ OSI Clinical Inspection Review Summary(ies) ( <i>include copies of OSI letters to investigators</i> )		<input type="checkbox"/> None requested 06/22/2015; Letters: 08/17/2015; 06/25/2015 (2); 05/29/2105(3); 03/19/2015;
<b>Clinical Microbiology</b>		<input checked="" type="checkbox"/> None
❖ Clinical Microbiology Team Leader Review(s) ( <i>indicate date for each review</i> )		<input type="checkbox"/> No separate review
Clinical Microbiology Review(s) ( <i>indicate date for each review</i> )		<input type="checkbox"/> None
<b>Biostatistics</b>		<input type="checkbox"/> None
❖ Statistical Division Director Review(s) ( <i>indicate date for each review</i> )		<input checked="" type="checkbox"/> No separate review
Statistical Team Leader Review(s) ( <i>indicate date for each review</i> )		<input checked="" type="checkbox"/> No separate review
Statistical Review(s) ( <i>indicate date for each review</i> )		<input type="checkbox"/> None 06/12/2015; 01/20/2015;
<b>Clinical Pharmacology</b>		<input type="checkbox"/> None
❖ Clinical Pharmacology Division Director Review(s) ( <i>indicate date for each review</i> )		<input checked="" type="checkbox"/> No separate review
Clinical Pharmacology Team Leader Review(s) ( <i>indicate date for each review</i> )		<input checked="" type="checkbox"/> No separate review
Clinical Pharmacology review(s) ( <i>indicate date for each review</i> )		<input type="checkbox"/> None 06/10/2015; 06/08/2015; 01/20/2015;
❖ OSI Clinical Pharmacology Inspection Review Summary ( <i>include copies of OSI letters</i> )		<input checked="" type="checkbox"/> None requested

<b>Nonclinical</b> <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 05/14/2015
• 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 06/08/2015; 01/20/2015;
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> None
❖ Statistical review(s) of carcinogenicity studies ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> No carc
❖ ECAC/CAC report/memo of meeting	<input checked="" type="checkbox"/> None Included in P/T review, page
❖ OSI Nonclinical Inspection Review Summary ( <i>include copies of OSI letters</i> )	<input checked="" type="checkbox"/> None requested
<b>Product Quality</b> <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 type="checkbox"/> None 12/07/2015; 06/22/2015
• 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 12/07/2015; 08/24/2015; 08/21/2015; 07/31/2015; 06/22/2015; 06/12/2015; 06/10/2015; 06/09/2015; 06/09/2015; 06/08/2015;
❖ Reviews by other disciplines/divisions/Centers requested by product quality review team ( <i>indicate date of each review</i> )	<input checked="" type="checkbox"/> None
❖ Environmental Assessment (check one) (original and supplemental applications)	
<input checked="" type="checkbox"/> Categorical Exclusion ( <i>indicate review date</i> )( <i>all original applications and all efficacy supplements that could increase the patient population</i> )	Page 11 of 06/09/2015 CMC review.
<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

<b>Day of Approval Activities</b>	
❖ For Breakthrough Therapy (BT) Designated drugs: <ul style="list-style-type: none"><li>• Notify the CDER BT Program Manager</li></ul>	<input checked="" type="checkbox"/> Done <i>(Send email to CDER OND IO)</i>
❖ Send a courtesy copy of approval letter and all attachments to applicant by fax or secure email	<input checked="" type="checkbox"/> Done
❖ If an FDA communication will issue, notify Press Office of approval action after confirming that applicant received courtesy copy of approval letter	<input checked="" type="checkbox"/> Done
❖ Ensure that proprietary name, if any, and established name are listed in the <i>Application Product Names</i> section of DARRTS, and that the proprietary name is identified as the “preferred” name	<input checked="" type="checkbox"/> Done
❖ Send approval email within one business day to CDER-APPROVALS	<input checked="" type="checkbox"/> Done

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

/s/  
-----

KEVIN B BUGIN  
12/08/2015



BLA 125561/0

**MID-CYCLE COMMUNICATION**

Synageva Biopharma Corp.  
Attention: Sara Saltzman  
Director, Regulatory Affairs  
33 Hayden Avenue  
Lexington, MA 02421

Dear Ms. Saltzman:

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

We also refer to the teleconference between representatives of your firm and the FDA on April 23, 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 (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

Enclosure:  
Mid-Cycle Communication



FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH

---

**MID-CYCLE COMMUNICATION**

**Meeting Date and Time:** April 23, 2015, from 3:00 to 4:00 PM, ET

**Application Number:** BLA 125561/0  
**Product Name:** KANUMA (sebelipase alfa)  
**Indication:** Treatment of LAL Deficiency  
**Applicant Name:** Synageva Biopharma Corp.

**Meeting Chair:** Jessica Lee  
**Meeting Recorder:** Kevin Bugin

**FDA ATTENDEES**

Julie Beitz, MD, CDER, Office of Drug Evaluation III (ODE III)  
Amy Egan, MD, CDER, ODE III  
Maria Walsh, RN, MSN, CDER, ODE III  
Andrew Mulberg, MD, FAAP, CPI, CDER, ODEIII, Division of Gastroenterology and Inborn Errors Products (DGIEP)  
Joyce Korvick, MD, MPH, CDER, ODEIII, DGIEP  
Joette Meyer, PharmD, CDER, ODEIII, DGIEP  
Jessica Lee, MD, MMSc, CDER, ODEIII, DGIEP  
Juli Tomaino, MD, MSCR, CDER, ODEIII, DGIEP  
Lauren Weintraub, MD, CDER, ODEIII, DGIEP  
Sushanta Chakder, PhD, CDER, ODEIII, DGIEP  
Tamal Chakraborti, PhD, CDER, ODEIII, DGIEP  
Kevin Bugin, MS, RAC, CDER, ODEIII, DGIEP  
Lisa Pitt, PharmD, CDER, ODEIII, DGIEP  
Yeh-Fong Chen, PhD, CDER, ODEIII, DGIEP  
Benjamin Vali, PhD, CDER, ODEIII, DGIEP  
Yow-Ming Wang, PhD, CDER, Office of Clinical Pharmacology (OCP)  
Jing Fang, PhD, CDER, OCP  
Juhong Liu, PhD, CDER, Office of Biotechnology Products (OBP)  
Christopher Downey, PhD, CDER, OBP  
Joao Pedras-Vasconcelos, PhD, CDER, OBP  
Patricia Hughes, PhD, CDER, OBP  
Colleen Thomas, PhD, CDER, OBP  
Jibril Abdus-Samad, CDER, OBP  
Aleksander Winiarski, CDER, Office of Safety and Epidemiology (OSE)  
Matthew Barlow, CDER, OSE, Division of Medication Error Prevention and Analysis  
Felicia Duffy, RN, BSN, MEd, OSE, Division of Risk Management  
Lori Gorski, CDER, Division of Pediatric and Maternal Health

Julie Golden, MD, CDER, Division of Metabolic and Endocrine Products  
Lalji Mishra, MD, CDER, Division of Antiviral Products  
Brenda Dass, MPH, PhD, ALAT, Center for Veterinary Medicine, Animal Biotechnology  
Interdisciplinary Group  
Prakash Jha, MD, MPH, Center for Devices and Radiological Health, Office of In-Vitro  
Diagnostics, Division of Molecular Genetics and Pathology  
Patrick Zhou, Eastern Research Group

#### **APPLICANT ATTENDEES**

Mark Hayes, PhD, Regulatory Affairs  
Sara Saltzman, Regulatory Affairs  
Lori Whittemore, Regulatory Affairs CMC  
Dee DeOliveira, Regulatory Operations  
Tanya Green, Regulatory Affairs  
Valeria Winslow, PhD, Regulatory Affairs International  
Nina Wolfendale, Pharmacovigilance  
Tony Quinn, MD, PhD FRCP, Chief Medical Officer and Head of Research and Development  
Sandra Rojas-Caros, MD, Clinical Research and Exploratory Development  
Glen Williams, Technical Operations  
Tony Rossomando, PhD, Bioanalytical Development  
Abdul Sankoh, PhD, Biostatistics

### **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**

#### **Product Quality**

We acknowledge receipt of your responses to the product quality review issues communicated in the filing letter, dated February 20, 2015. Review of these responses is ongoing at this time.

#### **Product Quality Microbiology**

The endotoxin limit calculation for the drug product did not include a safety margin. Endotoxin limit calculations should include a minimum 2-fold safety factor to account for the variability of the LAL bacterial endotoxin assay. A larger safety factor should be used for products that are diluted prior to administration (as additional endotoxin is present in the diluent) and for products

that are administered to pediatric patients. Recalculate the endotoxin specification for the drug product based on the maximum dose and include a safety factor in the calculation. Revise the endotoxin specifications for the drug substance and drug product accordingly.

### **Clinical**

As we have conveyed to you in multiple meetings and letters, the primary efficacy endpoint for Study LAL-CL02, normalization of ALT, neither directly measures clinical benefit of treatment (i.e., how a patient feels, functions, or survives) nor represents a surrogate endpoint reasonably likely to predict clinical benefit in children and adults with late-onset LAL deficiency (i.e., cholesteryl ester storage disease [CESD]). Based on our review of the BLA application, we remain concerned that elevation of ALT does not necessarily reflect synthetic dysfunction of the liver and its normalization does not reliably reflect improvement in liver disease related to LAL deficiency. For example, while the inclusion criteria for Study LAL-CL02 required patients to have elevated ALT at baseline, the study population did not have evidence of hepatic synthetic dysfunction as reflected by clinically significant abnormalities in albumin or INR. Furthermore, there does not appear to be a relationship between ALT normalization and changes in liver histology, including fibrosis scores. Therefore, we have determined that ALT normalization cannot serve as the primary endpoint to support efficacy of sebelipase alfa in patients with CESD.

Instead, the Division has reviewed all available clinical and laboratory parameters for which there were pre- and on-treatment data, and has concluded that LDL, the first-ranked key secondary endpoint, is the most suitable endpoint to assess efficacy in patients with CESD. LDL is included in the causal pathway of LAL deficiency, as LDL cholesterol is made up in part by cholesteryl esters and triglycerides that accumulate in the lysosome when LAL is deficient, thereby contributing to disease manifestations seen in patients with CESD. In addition, elevation of LDL is a well-established risk factor for coronary heart disease, and hyperlipidemia and accelerated atherosclerosis are known complications of LAL deficiency. Over half of the patients enrolled in Study LAL-CL02 had a baseline LDL  $\geq$  190 mg/dL, placing them at high risk for coronary heart disease. Hence, our assessment of efficacy will focus on change from baseline in LDL and normalization of LDL on sebelipase alfa treatment in patients with CESD.

If sebelipase alfa is approved for CESD, we anticipate that additional data will be requested as a post-marketing study to demonstrate the long-term treatment benefit of sebelipase alfa on the progression of liver disease and development of adverse cardiovascular events in patients with CESD.

### **3.0 INFORMATION REQUESTS**

#### **The following information requests are outstanding:**

1. Letter issued on April 16, 2015: Included 5 requests for information from Clinical.
2. Letter issued on April 16, 2015: Included 2 requests for information from Clinical Pharmacology.

**New Information Requests:**

• **Product Quality:**

1. The Drug Substance specification limit for the cIEF test is (b) (4) .  
(b) (4)  
The relative levels of charge variants of rhLAL is a critical quality attribute of sebelipase alfa. To provide sufficient control of charge variants for release of the Drug Substance, revise the acceptance criteria for the cIEF test to include limits for relative peak areas for individual major peaks or groups of peaks in the electropherogram.
2. The Drug Substance specification for (b) (4) includes only a limit for (b) (4) .  
(b) (4) . To minimize risk from these process-related impurities and improve control the manufacturing process, implement quantitative specification limits for (b) (4) tested by ELISA in addition to the existing limit for (b) (4) .
3. Drug Substance release testing includes RP-HPLC testing only on the Drug Substance. (b) (4)  
(b) (4) . Therefore, implement a RP-HPLC test (b) (4) to your Drug Substance release testing.
4. Characterization and method validation testing demonstrate that the SEC-HPLC method detects potential impurities (b) (4) . Verify that the standard operating procedure for this method requires measuring to (b) (4) minutes.

We request that you respond to these requests by May 15, 2015.

• **Clinical:**

1. Conduct a responder analysis for patients with abnormal baseline LDL (i.e., LDL  $\geq$  130 mg/dL) who eventually achieved LDL normalization (i.e., LDL < 130 mg/dL) at Week 20 or the last assessment during the double-blind treatment period. For this analysis, indicate the number of patients in whom the last double-blind LDL assessment did not occur at Week 20 and the study week of the last double-blind LDL assessment. Repeat the same analysis except designate patients who did not have a Week 20 LDL assessment as a “non-responder.” Conduct a similar responder analysis by assessing whether patients with abnormal baseline LDL eventually achieved LDL normalization at the latest data cut-off point within the open-label extension period. Point estimates pertaining to response rates and corresponding 95% Confidence Intervals should also be presented for these responder analyses.

We request that you respond to these requests by May 04, 2015.

- **Immunogenicity:**

We have reviewed your immunogenicity method validation reports 8285-711 “Validation of an immunoassay for the detection, confirmation and titration of anti-SBC-102 antibodies in human serum samples”, 8291-329 “Validation of enzymatic activity based neutralization assay for the detection of anti-SBC-102 neutralizing antibodies in human serum”, and 8298-036 “Validation of Cell Based Neutralization Assay for Detection and Titration of Anti-SBC-102 Antibodies in Human Serum” and have the following information requests:

1. You established the cut point of your anti-drug antibody (ADA) assay and your neutralizing antibody (NAb) assay using data from normal donor sera. However, you did not confirm the assay cut points with pre-treatment sera from the target population. While we recognize that the infantile-onset patients are very limited in number, the number of late-onset patients reaches 65 and thus could be used for cut point analysis. Provide data to show that the cut point obtained with sera from late onset patients is not statistically different from the cut point established using normal sera.
2. The assessment of assay robustness for both your ADA assay and your NAb assay is incomplete because you only evaluated the stability of the positive control. See FDA Draft Guidance for Industry: Assay development for immunogenicity testing of therapeutic proteins (2009) for additional robustness parameters that should be assessed. Provide summary information for the robustness parameters evaluated during assay development.
3. You report that in clinical study LAL-CL01 two subjects developed infusion reactions, and one of those subjects was tested for anti-SBC-102 IgE antibodies and anti-egg white antibodies. However, no information on these assays was submitted to the BLA application. Submit validation reports for the assays to detect anti-SBC-102 IgE antibodies and anti-egg white antibodies.

We request that you respond to these requests by May 30, 2015.

#### **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 July 8, 2015. In addition, please note the following projected milestone dates:

Labeling, PMR/PMC comments to Applicant:	June 8, 2015
LCM Background Package:	June 26, 2015
PDUFA Goal Date:	September 8, 2015

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

/s/  
-----

KEVIN B BUGIN  
04/24/2015



BLA125561

**PROPRIETARY NAME REQUEST  
CONDITIONALLY ACCEPTABLE**

Synageva BioPharma Corp.  
33 Hayden Avenue  
Lexington, MA 02421

ATTENTION: Tanya Green  
Senior Manager, Regulatory Affairs

Dear Ms. Green:

Please refer to your Biologics License Application (BLA) dated and received October 21, 2014, submitted under section 351(a) of the Public Health Service Act for Sebelipase Alfa, 2 mg/mL.

We also refer to your correspondence, dated and received October 29, 2014, requesting review of your proposed proprietary name, Kanuma.

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

If any of the proposed product characteristics as stated in your October 29, 2014, submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

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

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

/s/  
-----

TODD D BRIDGES  
12/15/2014



IND 108460

**MEETING PRELIMINARY COMMENTS**

Synageva BioPharma Corp.  
Attention: Tanya Green  
Senior Manager, Regulatory Affairs  
33 Hayden Avenue  
Lexington, MA 02421

Dear Ms. Green:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for sebelipase alfa (SBC-102).

We also refer to your May 27, 2014, correspondence requesting a Pre-BLA meeting to discuss plans for the filing of a BLA for sebelipase alfa.

Our preliminary responses to your meeting questions are enclosed.

You should provide, to the Regulatory Project Manager, a hardcopy or electronic version of any materials (i.e., slides or handouts) to be presented and/or discussed at the meeting.

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:  
Preliminary Meeting Comments



FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH

---

**PRELIMINARY MEETING COMMENTS**

**Meeting Type:** B  
**Meeting Category:** Pre-BLA

**Meeting Date and Time:** August 19, 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 108460  
**Product Name:** sebelipase alfa (SBC-102)  
**Indication:** LAL Deficiency (wolman disease)  
**Sponsor/Applicant Name:** Synageva

**Introduction:**

This material consists of our preliminary responses to your questions and any additional comments in preparation for the discussion at the meeting scheduled for August 19, 2014, between Synageva and the Division of Gastroenterology and Inborn Errors Products. We are sharing this material to promote a collaborative and successful discussion at the meeting. The meeting minutes will reflect agreements, important issues, and any action items discussed during the meeting and may not be identical to these preliminary comments following substantive discussion at the meeting. If you determine that discussion is needed for only some of the original questions, you have the option of reducing the agenda and/or changing the format of the meeting (e.g., from face to face to teleconference). Contact the Regulatory Project Manager (RPM) if there are any major changes to your development plan, the purpose of the meeting, or the questions based on our preliminary responses, as we may not be prepared to discuss or reach agreement on such changes at the meeting.

**1.0 BACKGROUND**

Sebelipase alfa is a recombinant human lysosomal acid lipase (rhLAL) enzyme, purified from egg white of transgenic *Gallus*, being developed by Synageva. LAL has been shown to catalyze the hydrolysis of cholesteryl esters and triglycerides to free cholesterol, glycerol, and free fatty acids. The initial IND application for sebelipase alfa was submitted in December 2010 and intended for the treatment of LAL deficiency. It has subsequently received Orphan Drug designation (July 2010), Fast Track designation (June 2011), and Breakthrough Therapy designation for LAL deficiency presenting in infants (May 2013).

On May 27, 2014, the Sponsor submitted a correspondence requesting a Pre-BLA meeting to discuss plans for the filing of a BLA for sebelipase alfa. The meeting was granted and scheduled to occur on August 19, 2014.

## 2.0 DISCUSSION

### Clinical

1. A summary of key results from the primary analyses for pivotal studies, LAL-CL03 and LAL-CL02, are provided in [Section 6.3](#). Does the Division agree that the proposed clinical trial data to be included in the BLA are sufficient to support the review of sebelipase alfa for long-term ERT for patients with LAL Deficiency?

#### **FDA Response:**

**The content proposed for your upcoming BLA submission seems adequate to support filing of the application for FDA review. However, an assessment of the adequacy of the clinical trial data to support the scope of the proposed treatment indication and/or patient population will be determined during BLA review.**

**As discussed in previous communications, including the Type C meeting held on April 1, 2014, we recommend that efficacy assessments in your BLA focus on data from infantile-onset patients with LAL deficiency, with supportive data from children and adults with LAL deficiency (i.e., CESD). We remain concerned that the proposed clinical trial endpoints for late-onset LAL deficiency neither directly measure clinical benefit of treatment (i.e., how a patient feels, functions or survives) nor represent surrogate endpoints reasonably likely to predict clinical benefit. As communicated previously, it will be important to link the disease manifestations in infants to children and adults with LAL deficiency to facilitate extrapolation of the clinical benefit observed in infants to the broader population.**

2. Does the Agency agree that, based on the currently available benefit/risk profile, inclusion of a Risk Evaluation and Mitigation Strategy (REMS) in the initial sebelipase alfa BLA submission is not warranted?

#### **FDA Response:**

**It is acceptable if you choose at this time not to include a REMS with your initial BLA submission. However, a final determination for the need for a REMS will be made during the review of your BLA application.**

Regulatory

3. Synageva would like to consider the option to file the sebelipase alfa BLA on a rolling basis. The proposed schedule for rolling submission of completed BLA sections is provided below.
  - a. Is this plan acceptable to FDA?

**FDA Response:**

**The proposed plan and schedule for a rolling submission of your BLA appears acceptable. However, you also need to provide a schedule for the submission of all required information to support your NADA application. As per 21 CFR 314.50 (g)(1), you may cross reference the NADA in your BLA.**

- b. Would a rolling BLA submission impact the anticipated timing of key milestones during the BLA review process, including Sponsor meetings and a potential Advisory Committee meeting?

**FDA Response:**

**While a rolling review may permit early identification of issues that could delay or prolong the review process, we remind you that the review clock will not begin until you inform the Agency that a complete BLA has been submitted. A complete BLA includes all requested information from the CVM on your product (i.e., recombinant DNA construct engineered to express recombinant human lysosomal acid lipase) to conduct review of your NADA. After the Agency is notified of the complete application, we will make a filing determination within the usual time. Therefore, the timing of key milestones during the BLA review process (e.g., sponsor meetings, potential Advisory Committee meeting) is unlikely to be impacted by a rolling submission. We also remind you that NADA approval will be required prior to BLA approval.**

4. Synageva intends to request Priority Review at the time of BLA submission. Does the Division agree that sebelipase alfa may meet the requirements for a Priority Review designation?

**FDA Response:**

**Yes, we agree that sebelipase alfa may meet the requirements for a Priority Review designation. However, the eligibility for a priority review designation is determined once the BLA has been submitted. The Agency will inform the applicant in writing of a priority review designation by Day 60 of the review.**

**Additional Comments:**

- 1. You need to provide justification(s) for the proposed dosing regimen for each specific patient population with supporting data and data analyses. Exposure-response analysis is considered useful for this purpose. Include the justification as to why body weight-based dosing is necessary. We remind you that adequate safety information must be obtained at dosage level(s) intended for marketing.**

**In Study LAL-CL03, patients received variable doses and dosing frequencies of sebelipase alfa and were dose-escalated at different times without a pre-specified criterion to guide dose escalation. Therefore, we are concerned that available data will be insufficient to inform dosing for product labeling. Due to the limited number of patients enrolled in Study LAL-CL03 and the variable dosing regimens they received, a careful analysis of the available data would be needed to justify the appropriateness of the proposed dosing regimen in infants. Include the following information to justify your dosing proposal.**

- Dose-response on an individual basis for efficacy**
- The time course of relevant biomarker concentrations (provided separately for each biomarker) and the growth curve over time for each patient. On these time course profiles, indicate the timing of dosing changes.**
- Clinical experience with different dosages and titration schedules**

**For Study LAL-CL02 in which patients  $\geq 4$  years old were enrolled, we recommend that you consider exposure-response analysis to support the proposed dosing regimen as indicated in our previous comments in the Post-Breakthrough Meeting Minutes dated March 21, 2014. Exposure-response should be provided for both efficacy and safety when possible.**

- 2. The Agency no longer considers the terms “infusion reaction” and “allergic reaction” appropriate for use in product labeling. Although the term “infusion reaction” implies a temporal relationship, infusion reactions are not well defined and may encompass a wide range of clinical events, including anaphylaxis. Instead, the term “hypersensitivity reaction” should be used to refer to immune-mediated adverse reactions. In addition, the Sampson diagnostic criteria<sup>1</sup> should be used to identify the subset of hypersensitivity reactions which qualify as “anaphylaxis.” Non-immune-mediated adverse reactions with a temporal relationship to a study drug infusion, previously included in category of “infusion reactions,” should be listed separately according to their preferred terms.**

---

<sup>1</sup> Sampson HA, Muñoz-Furlong A, Campbell RL, Adkinson NF Jr, Bock SA, Branum A, Brown SG, Camargo CA Jr, Cydulka R, Galli SJ, Gidudu J, Gruchalla RS, Harlor AD Jr, Hepner DL, Lewis LM, Lieberman PL, Metcalfe DD, O'Connor R, Muraro A, Rudman A, Schmitt C, Scherrer D, Simons FE, Thomas S, Wood JP, Decker WW. Second symposium on the definition and management of anaphylaxis: summary report--Second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network symposium. *J Allergy Clin Immunol.* 2006 Feb;117(2):391-7.

All safety analyses for the BLA should be performed using this new terminology because these data will be used to support future product labeling. For additional information, please refer to the Draft Guidance for Industry: Immunogenicity Assessment for Therapeutic Protein Products, available at: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM338856.pdf>

3. We request that Adverse Events datasets include information regarding the timing of events with respect to the most recent infusion. Coding of adverse events should be based on time categories, such as “occurring during the infusion or within 2 hours of completion of the infusion”/“occurring between 2 hours and 24 hours after completion of the infusion”/“occurring at least 24 hours after the completion of an infusion”.
4. The meeting background package refers to a “post hoc unblinded evaluation of slides” for liver biopsies. Please note that your BLA should include liver biopsy data and analyses obtained from blinded pathologic interpretations only.
5. In addition to numerical biopsy scoring data, all biopsy reports (in narrative form) should be submitted with your application.
6. Please clarify whether laboratory studies, particularly those used as clinical trial endpoints (i.e., ALT and LDL), were performed by a central laboratory and provide references for the normal values used in your clinical trials.
7. In addition to Summary of Clinical Pharmacology Findings in the eCTD submission, we request that you provide 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.
8. We noted that you have obtained frequent pharmacokinetic (PK) samples in adult patients and planned to conduct non-compartmental analysis (NCA) with these PK data. Submit all datasets used in the NCA analysis and the results in the SAS transport file format (i.e., .xpt file).
9. We recommend that you use the results from the NCA to explore potential correlations between PK and various pharmacodynamic (PD) responses in adult patients. Submit all datasets for the PK/PD analyses, including the original PK and PD data, PK/PD analysis datasets, and PK/PD parameter datasets for our review. All data files should be submitted in the SAS transport file format.
10. You plan to characterize sebelipase alfa PK using all data from clinical trials using a population PK approach. Please refer to the following link for general expectations of submitting pharmacometric data and models: <http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm180482.htm>. Regarding the population PK datasets,
  - Provide the unique subject identification number (e.g., USUBJID) for each subject.

- **Include all observations for sebelipase alfa concentration, including concentrations that were below the limit of quantitation.**
  - **Include PK sampling time points that have missing data.**
- 11. If simulations for various endpoints are conducted to justify the proposed dosing regimen(s) using a population PK/PD approach, you need to describe clearly the methodology of the simulations in the report and provide the datasets and the codes used for the simulations in your BLA submission.**
- 12. We request you assess the immunogenicity impact on PK, PD, efficacy and safety. We refer you to the Meeting Minutes dated March 21, 2014 for our comments regarding immunogenicity impact assessment on PK as well as genotyping data.**

**Additional OSI Comments:**

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

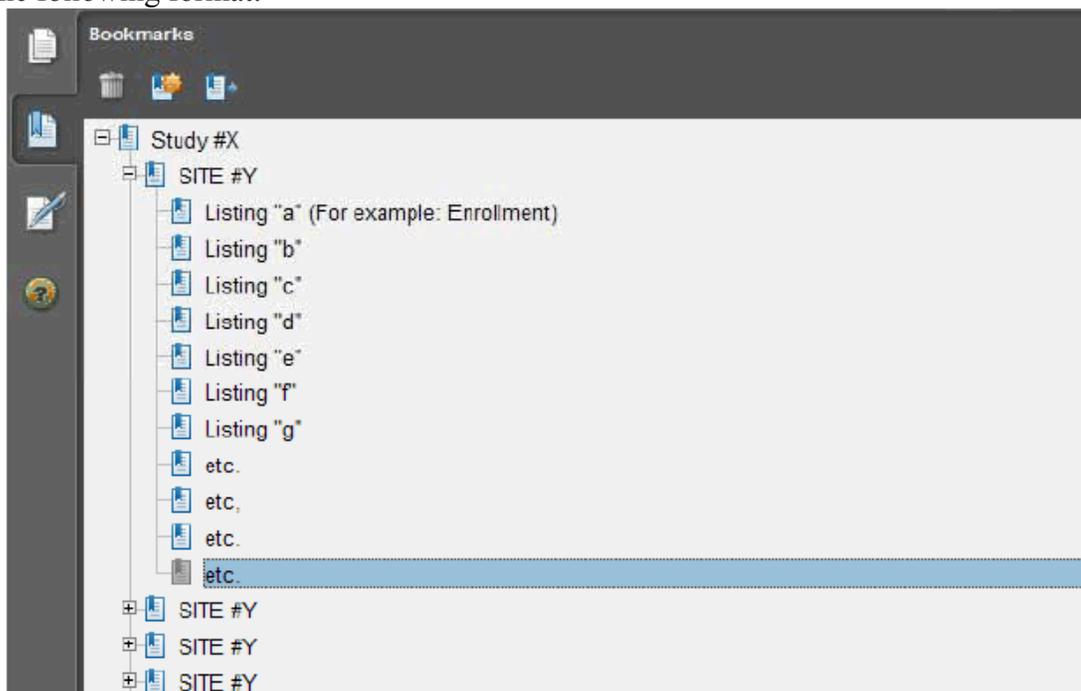
investigator's participation in the study, we request that this updated information also be provided.

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.”

<b>DSI Pre-NDA Request Item<sup>2</sup></b>	<b>STF File Tag</b>	<b>Used For</b>	<b>Allowable File Formats</b>
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.

<sup>2</sup> 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](mailto:ESUB@fda.hhs.gov)

### **3.0 DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION**

As stated in our June 13, 2014 communication granting this meeting, if, at the time of submission, the application that is the subject of this meeting is for a new molecular entity or an original biologic, the application will be subject to “the Program” under PDUFA V. Therefore, at this meeting be prepared to discuss and reach agreement with FDA on the content of a complete application, including preliminary discussions on the need for risk evaluation and mitigation strategies (REMS) or other risk management actions. You and FDA may also reach agreement on submission of a limited number of minor application components to be submitted not later than 30 days after the submission of the original application. These submissions must be of a type that would not be expected to materially impact the ability of the review team to begin its review. All major components of the application are expected to be included in the original application and are not subject to agreement for late submission.

Discussions and agreements will be summarized at the conclusion of the meeting and reflected in FDA’s meeting minutes. If you decide to cancel this meeting and do not have agreement with FDA on the content of a complete application or late submission of any minor application components, your application is expected to be complete at the time of original submission.

In addition, we remind you that the application is expected to include a comprehensive and readily located list of all clinical sites and manufacturing facilities.

Finally, in accordance with the PDUFA V agreement, FDA has contracted with an independent contractor, Eastern Research Group, Inc. (ERG), to conduct an assessment of the Program. ERG will be in attendance at this meeting as silent observers to evaluate the meeting and will not participate in the discussion. Please note that ERG has signed a non-disclosure agreement.

Information on PDUFA V and the Program is available at <http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm272170.htm>.

### **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.				

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

/s/  
-----

KEVIN B BUGIN  
08/15/2014



IND 108460

**GRANT –  
BREAKTHROUGH THERAPY DESIGNATION**

Synageva BioPharma Corp.  
Attention: Mark J. Hites  
Director, Regulatory Affairs  
150 Ben Burton Road  
Bogart, GA 30622

Dear Mr. Hites:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for SBC-102 (sebelipase alfa; recombinant human lysosomal acid lipase).

We also refer to your March 14, 2013, request for Breakthrough Therapy designation for the treatment of lysosomal acid lipase (LAL) deficiency. (b) (4)

We have reviewed your request and have determined that SBC-102 for the treatment of Wolman disease meets the criteria for Breakthrough Therapy designation. Therefore, we are granting your request for Breakthrough Therapy designation. Please note that if the clinical development program does not continue to meet the criteria for Breakthrough Therapy designation, we may rescind the designation.

FDA will work closely with you to provide guidance on subsequent development of SBC-102 for Wolman disease, 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*<sup>1</sup> for procedures on requesting a meeting.

(b) (4)

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

For further information regarding Fast Track, refer to the guidance for industry *Fast Track Drug Development Programs – Designation, Development, and Application Review*.

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

Sincerely,

*{See appended electronic signature page}*

Andrew Mulberg, M.D.  
Deputy Director  
Division of Gastroenterology and Inborn Errors  
Products  
Office of Drug Evaluation III  
Center for Drug Evaluation and Research

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

/s/  
-----

ANDREW E MULBERG  
05/13/2013



IND 108460

**MEETING PRELIMINARY COMMENTS**

Synageva BioPharma Corp.  
Attention: Lorraine Copertino Whittemore  
Director, Regulatory Affairs CMC  
33 Hayden Avenue  
Lexington, MA 02421

Dear Ms. Whittemore:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for sebelipase alfa (SBC-102).

We also refer to your December 2, 2013, correspondence, received December 2, 2013, requesting a meeting to discuss manufacturing and analytical development plans for sebelipase alfa.

Our preliminary responses to your meeting questions are enclosed.

You should provide, to the Regulatory Project Manager, a hardcopy or electronic version of any materials (i.e., slides or handouts) to be presented and/or discussed at the meeting.

If you have any questions, call me at (240) 402-3746.

Sincerely,

*{See appended electronic signature page}*

Lyndsay Hennessey  
Regulatory Project Health Manager  
Office of Biotechnology Products  
Office of Pharmaceutical Science  
Center for Drug Evaluation and Research

ENCLOSURE:  
Preliminary Meeting Comments



FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH

---

**PRELIMINARY MEETING COMMENTS**

**Meeting Type:** B  
**Meeting Category:** Pre-BLA CMC

**Meeting Date and Time:** February 12, 2014 12:30-1:30 P.M. Eastern Standard Time (EST)  
**Meeting Location:** Teleconference

**Application Number:** 108460  
**Product Name:** sebelipase alfa (SBC-102)  
**Indication:** (b) (4) LAL Deficiency  
**Sponsor/Applicant Name:** Synageva BioPharma Corp.

**Introduction:**

This material consists of our preliminary responses to your questions and any additional comments in preparation for the discussion at the meeting scheduled for February 12, 2014 12:30-1:30 P.M. EST between Synageva BioPharma Corp. and the Division of Therapeutic Products. We are sharing this material to promote a collaborative and successful discussion at the meeting. The meeting minutes will reflect agreements, important issues, and any action items discussed during the meeting and may not be identical to these preliminary comments following substantive discussion at the meeting. If you determine that discussion is needed for only some of the original questions, you have the option of reducing the agenda. Contact the Regulatory Project Manager (RPM) if there are any major changes to your development plan, the purpose of the meeting, or the questions based on our preliminary responses, as we may not be prepared to discuss or reach agreement on such changes at the meeting.

## 1.0 BACKGROUND

- (i) **Purpose of meeting:** To discuss manufacturing and analytical development plans for sebelipase alfa
- (ii) **Names of drug:** Sebelipase alfa (recombinant human lysosomal acid lipase; SBC-102)
- (iii) **Context for planned submissions:** Synageva plans to submit drafts of each of the INAD sections describing the transgenic *Gallus gallus* line used to produce sebelipase alfa containing egg white to CVM for a phased review. Following this phased review, Synageva is anticipating the submission of an Administrative NADA in Q3 2014 and the submission of a BLA in December 2014. A limited number of minor components of the BLA may be submitted no more than thirty days following the initial application.
- (iv) **Expected outcome for the meeting:**
  - a. To assure concurrence with the Agency regarding the expectations and requirements for the addition of new facilities, which include new facilities for production of the starting material, egg white (EW) from transgenic *Gallus gallus*, as well as redundant purification capabilities for the production of Drug Substance through the use of a second contract manufacturer, (b) (4)
  - b. To provide a status update on the analytical method development and confirm Agency agreement with plans for control of the product for BLA/NADA submissions.
  - c. To urge the sponsor to continue conversations directly with CVM on the substantive and administrative components of their INAD and NADA submissions.

## 2.0 DISCUSSION

**Question 1:** Does the Agency agree that this approach to cross-referencing is acceptable and that the appropriate point for separation of the information between the NADA and BLA is at the point of (b) (4)?

### **FDA Response to Question 1:**

No. We agree in principle with your approach to cross-referencing, but disagree with your proposed point for NADA and BLA separation. Harvesting the egg whites represents the first step in processing of the animal-derived material into Drug Substance (DS). Control of this step will directly impact the quality of material that enters downstream DS purification and is a potential entry point for adventitious agents. Consequently, the point of separation between the NADA and BLA should be at the point of collection of the contents of the eggs from the transgenic hens (i.e., the egg crack, as the contents of the eggs are the starting material for DS manufacture). Until the point of egg crack, the eggs resemble “food” and if transported outside the egg collection facility, must bear a label that indicates that they may contain an unapproved new animal drug and are not for consumption by humans or other animals, as well as any other labeling that CDER requires. Documentation to support the procedures for egg collection,

cleaning, storage and transportation are suitable for their intended purposes should also be included in your BLA submission.

The egg white harvest process should be conducted in a suitably controlled environment using a process designed to minimize microbial contamination. Incoming egg white materials should have appropriate specifications for bioburden and endotoxin and should be shown to be free of objectionable microorganisms (e.g., Salmonella, Listeria). The BLA should contain the following information regarding the egg white harvest process:



CVM agrees that cross referencing is an important component of the overall evaluation of the review of both the NADA and BLA. It is the agency's intent to work towards decreasing the duplication of sponsor submitted data and information. CVM intends to continue working with CDER and the sponsor with regard to determining the most effective ways to facilitate data sharing. Nonetheless, CVM has a statutory requirement to approve the "first" regulated article, which is the recombinant DNA construct in the GE chicken, including an assessment of the construct, the reliability of its "manufacture", its genotypic and phenotypic stability, the health of the animal, the health of the animal handlers, ensuring that the claim made by the sponsor is indeed met, and ensuring that no edible products from these GE animals enters the food supply. Clearly, there is overlap between some of the data and information that is evaluated under the New Animal Drug provisions of the FD&C Act, and the manufacturing and safety components of the BLA. To the extent that the agency can work with the sponsor to ensure that data that needs to be evaluated by both Centers is submitted in such a way as to meet either and both Center's requirements, we encourage data sharing and cross-referencing.

One key issue of importance is ensuring that edible products from investigational animals do not enter the food supply without prior authorization, or if intended to be kept out of the food supply, that adequate measures have been taken to avoid such eventualities. Chickens and the eggs they produce have traditionally been considered as food and are commonly encountered in the food supply chain. One concern relates to the potential for inadvertent or malicious release of these genetically engineered (GE) eggs and animals into the food supply chain. To this end, the Agency would request information such as but not limited to standard operating procedures related to biosecurity of the animals and the eggs (GE and non-GE), disposal of waste materials such as unused or cracked eggs, labels used on storage and shipping containers, and record keeping such as bio-surveillance, shipment, and disposal logs. At the point of collected and frozen egg white, the probability of the GE material entering the food supply chain or being mistaken as food decreases thereby also decreasing the risk. Hence, we anticipate data and

information provided by the sponsor up to the egg white collection step to be adequate for the phased review of the INAD and subsequent NADA.

**Question 2:** To provide a high degree of assurance of supply continuity, does FDA agree with Synageva's plan to include both HPF and BPF in the referenced NADA to support approval of both facilities as a critical component of the supply chain for the anticipated BLA?

**FDA Response to Question 2:**

No. According to your proposed production and regulatory filing schedules, you will not process any materials produced at your Bogart Production Facility (BPF) until after you have submitted your BLA. You would therefore have no data in the BLA to support qualification of BPF for use in supplying starting material for DS production. If you cannot provide comprehensive data to support use of this or any other facility at the time of your BLA filing, we advise you to request approval of the facility in a post-approval BLA supplement.

Further, information on the BPF is part of the submission required for approval of the sponsor's NADA to ensure appropriate animal husbandry practices to meet both required good manufacturing practices and animal safety determinations. We further reiterate that any production facility or facilities listed in the INAD and subsequent NADA would require an inspection. Information such as location, facility floor plans, materials and personnel flow diagrams, security, containment etc. will be required as part of the phased review process. Any significant changes to the conditions approved in the original NADA may be submitted for evaluation (and possible inspection) via post-approval NADA supplements.

**Question 3:** Does the Agency agree that the current measures in place and proposed for the control of adventitious agents are acceptable?

**FDA Response to Question 3:**

Yes. Based on the available data, your adventitious agent control strategy and biosurveillance schedule is reasonable, provided you address our concerns for PCR testing of influenza A/B and West Nile virus discussed in our response for Question 6.

Additionally, Standard Operating Procedures for methods used as part of flock health and disease surveillance will be requested as part of the phenotypic characterization section of the INAD phased review process. Biosurveillance reports will also be requested on an ongoing basis while the GE line is being maintained for investigational purposes.

**Question 4:** Does the Agency agree that after appropriate process validation, Drug Substance can be sourced from two CMOs for the purposes of commercial supply?

**FDA Response to Question 4:**

No. To support commercial manufacture of DS at the two facilities, you must demonstrate comparability of materials at both sites. You are planning process changes at both facilities after completion of your ongoing comparability study and prior to process validation. Therefore, an additional comparability study for materials produced by the validated manufacturing processes at the two sites will be required for approval of the two DS manufacturing facilities. Both facilities must also be found acceptable in Pre-Approval Inspections. The considerable additional comparability data collection and inspectional activities necessitated by including a second DS purification facility in your original licensing application could potentially delay your submission timeline and would significantly complicate review of the application. Unless inclusion of the (b) (4) site is essential to meet market demand, we recommend that you request approval of your second DS downstream purification site post-licensure in a Prior Approval Supplement.

Be advised that with multiple DS manufacturing sites, DS release and stability must still be tested by the same validated assay at the same laboratory, or you must demonstrate equivalence for any tests that are performed at different laboratories.

You have not described whether you plan to pool DS lots for DP manufacture. To ensure traceability to source material in the event of, for example, an adverse event, you should not pool DS from two facilities until you have demonstrated DS manufactured at the two sites are comparable.

**Question 5:** Does the Agency agree that the minor process changes proposed for implementation prior to PV are acceptable for implementation for the continuing production of clinical trial material and for the proposed commercial process, assuming biochemical comparability can be demonstrated?

**FDA Response to Question 5:**

Yes, to the extent that these drug manufacturing processes apply only to the “second” regulated product (the human drug). Since you plan to conduct your Drug Product (DP) manufacturing process validation using DS produced by your current non-commercial manufacturing process, you will need to manufacture one confirmatory DP batch under your process validation protocol using DS prepared by the validated commercial DS manufacturing process. We note that you cannot commercialize any DP batches produced from DS manufactured by a non-validated process.

**Question 6:** Does FDA agree that the proposed lot release testing plan for Egg White, (b) (4), Drug Substance, and Drug Product is acceptable to support licensure of sebelipase alfa?

**FDA Response to Question 6:**

No. We have the following comments regarding your lot release testing plan:

a) (b) (4)

In any case, you did not provide sufficient information in the meeting briefing materials for us to assess your justifications (b) (4)

b) To maintain the ability to track enzymatic activity throughout the manufacturing process and to trend across production batches, you should use the same activity test throughout in-process testing, DS release, and DP release. (b) (4)

(b) (4)

(b) (4)

c) We recommend you develop as a DS release and stability test one of your characterization assays for cellular uptake of SBC-102.

d) (b) (4)

e)

(b) (4)

f)

(b) (4)

g)

(b) (4)

- h) Incoming egg white materials should have appropriate specifications for bioburden and endotoxin and should be shown to be free of objectionable microorganisms (e.g., *Salmonella*, *Listeria*).

**Question 7:** Does the Agency agree that it is acceptable for Synageva to submit the following information within 30 days of the original BLA submission: Final results from DS PV, batch analysis data from DS PV, and updated DS and DP stability data tables?

**FDA Response to Question 7:**

No. In your pre-BLA Meeting Package submitted on January 23, 2014, you state in Regulatory Question 1 that you intend to submit a single, comprehensive BLA. A complete BLA submission must include complete process validation results, batch analyses, and sufficient stability data to support your proposed expiry. To facilitate our review, you may submit the bulk of your application prior to submitting the final process validation results and batch analysis, but the PDUFA clock for review of the BLA will not start until all data supporting process validation are submitted to complete the application. Your BLA should include all available stability data for both DS and DP at the time of your BLA submission. You may submit updates with stability data as they become available during the review cycle to further support expiry.

**ADDITIONAL AGENCY COMMENTS:**

All facilities should be registered with FDA at the time of the BLA submission and ready for inspection in accordance with 21 CFR 600.21 and 601.20(b)(2). Please include in the BLA submission a complete list of manufacturing and testing sites with their corresponding FEI numbers.

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

- Evidence of monitoring of bioburden and endotoxin levels at critical purification and bulk formulation steps using qualified bioburden and endotoxin tests. Pre-determined bioburden and endotoxin limits should be provided (3.2.S.2.4).
- Three successful product intermediate hold time validation runs at manufacturing scale. Bioburden and endotoxin levels before and after the maximum allowed hold time should be monitored and bioburden and endotoxin limits provided (3.2.S.2.5).
- Column resin and UF/DF membrane sanitization and storage validation data and information (3.2.S.2.5).
- Bioburden and endotoxin data obtained during manufacture of the conformance lots (3.2.S.2.5).
- Data summaries of shipping validation studies (3.2.S.2.5).
- Drug substance bioburden and endotoxin release specifications. The bioburden limit should be < 1 CFU/10 mL for bulk materials allowed to be stored for extended periods of time at refrigerated temperatures (3.2.S.4).
- Qualification data for bioburden and endotoxin test methods performed for in-process intermediates, buffers, and drug substance (3.4.S.4).
- The effect of hold time on endotoxin recovery should be assessed by spiking a known amount of endotoxin into undiluted drug substance and then testing for recoverable endotoxin over time. The studies should be conducted using containers of similar composition as those used for drug substance during hold. Effects of sampling containers on endotoxin recovery should also be evaluated.

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

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

- Bacterial filter retention study for the sterilizing filter.
- Sterilization and depyrogenation of equipment and components that contact the sterile drug product. The equipment requalification program should be described.
- In-process microbial controls and hold times. Hold times should be validated at manufacturing scale.
- Isolator decontamination, if applicable.

- Three successful consecutive media fill runs, including summary environmental monitoring data obtained during the runs. Media fill and environmental monitoring procedures should be described.
- A description of the routine environmental monitoring program.
- Shipping validation studies.

The following method validation information should be provided:

- Container closure integrity testing (3.2.P.2.5). System integrity (including maintenance of the microbial barrier) should be demonstrated for the complete manufacturing process. Container closure integrity methods validation should demonstrate that the assay is sensitive enough to detect breaches that could allow microbial ingress and should include routine manufacturing process defects as controls. We recommend that container closure integrity testing be performed *in lieu* of sterility testing for stability samples at the initial time point and every 12 months (annually) until expiry (3.2.P.8.2).
- Qualification data for bioburden, sterility and endotoxin test methods performed for in-process intermediates and buffers (where applicable) and the drug product, as appropriate (3.2.P.5).
- Perform the Rabbit Pyrogen Test on three batches of drug product in accordance with 21 CFR 610.13(b).
- The effect of hold time on endotoxin recovery should be assessed by spiking a known amount of endotoxin into undiluted drug product and then testing for recoverable endotoxin over time. The studies should be conducted using containers of similar composition as those used for drug product during hold. Effects of sampling containers on endotoxin recovery should also be evaluated.

### **3.0 DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION**

As stated in our December 17, 2013 communication granting this meeting, if, at the time of submission, the application that is the subject of this meeting is for a new molecular entity or an original biologic, the application will be subject to “the Program” under PDUFA V. Therefore, at this meeting be prepared to discuss and reach agreement with FDA on the content of a complete application, including preliminary discussions on the need for risk evaluation and mitigation strategies (REMS) or other risk management actions. You and FDA may also reach agreement on submission of a limited number of minor application components to be submitted not later than 30 days after the submission of the original application. These submissions must be of a type that would not be expected to materially impact the ability of the review team to begin its review. All major components of the application are expected to be included in the original application and are not subject to agreement for late submission.

Discussions and agreements will be summarized at the conclusion of the meeting and reflected in FDA’s meeting minutes. If you decide to cancel this meeting and do not have agreement with FDA on the content of a complete application or late submission of any minor application components, your application is expected to be complete at the time of original submission.

In addition, we remind you that the application is expected to include a comprehensive and readily located list of all clinical sites and manufacturing facilities.

Finally, in accordance with the PDUFA V agreement, FDA has contracted with an independent contractor, Eastern Research Group, Inc. (ERG), to conduct an assessment of the Program. ERG will be in attendance at this meeting as silent observers to evaluate the meeting and will not participate in the discussion. Please note that ERG has signed a non-disclosure agreement.

Information on PDUFA V and the Program is available at <http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm272170.htm>.

### **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.				

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

/s/  
-----

LYNDSAY J HENNESSEY  
02/07/2014



IND 108460

**MEETING MINUTES**

Synageva BioPharma Corp.  
Attention: Mark Hites  
Director, Regulatory Affairs  
111 Riverbend Road  
Athens, GA 30605

Dear Mr. Hites:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Recombinant Human Lysosomal Acid Lipase (SBC-102).

We also refer to the meeting between representatives of your firm and the FDA on June 12, 2012. The purpose of the meeting was to discuss your clinical development plan for SBC-102.

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 1

**Meeting Date and Time:** June 12, 2012, 12:00 – 1:00 PM  
**Meeting Location:** White Oak Building 22, Room 1309

**Application Number:** IND 108460  
**Product Name:** SBC-102  
**Indication:** Treatment of Lysosomal Acid Lipase Deficiency  
**Sponsor/Applicant Name:** Synageva BioPharma Corp.

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

**FDA ATTENDEES**

Division of Gastroenterology and Inborn Error Products (DGIEP)

Andrew Mulberg, M.D., Deputy Director  
Lynne Yao, M.D., Clinical Team Leader  
Nancy Snow, M.D., Clinical Reviewer  
Sushanta Chakder, Ph.D., Supervisory Pharmacologist  
Babatunde Akinshola, Ph.D., Pharmacologist  
Elizabeth A.S. Ford, R.N., Senior Regulatory Health Project Manager

Office of Translational Sciences

Office of Clinical Pharmacology/Division of Clinical Pharmacology 3

Gilbert Burckart, Associate Director, Office of Clinical Pharmacology  
Dionna Green, Clinical Pharmacology Reviewer

Office of Biostatistics/Division of Biometrics III

Mike Welch, Ph.D., Deputy Director  
Behrang Vali, Statistics 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

Office of Orphan Products Development

Christine Mueller, M.D., Medical Officer

**SPONSOR ATTENDEES**

Mark Hayes, Ph.D., Vice President, Regulatory Affairs

Mark Hites, Director, Regulatory Affairs

Anthony Quinn, MB ChB., Ph.D., FRCP, Senior Vice President, Chief Medical Officer  
and Head of Research & Development

Eugene Schnieder, M.D. Senior Medical Director

Mark Goldberg, M.D., Senior Vice President, Product Development

Donna Mackey, Senior Director, Clinical Operations

Tara O'Meara, Director, Clinical Operations

Stephen Eckert, Ph.D., Senior Director, Biostatistics

Christine Maurer, Vice President, Program Management & Operations

[REDACTED] (b) (4)

[REDACTED] (b) (4)

## 1.0 BACKGROUND

SBC-102 is a recombinant human lysosomal acid lipase (rhLAL) purified from the egg whites of rhLAL transgenic gallus, and is indicated for the treatment of Lysosomal acid lipase (LAL) deficiency, a rare lysosomal storage disease. The investigation of SBC-102 for LAL deficiency was granted Fast Track designation on June 14, 2011.

On February 7, 2012, Synageva BioPharma Corp. (Synageva) requested a meeting to discuss the clinical development plan for SBC-102. Synageva seeks to confirm key elements of their clinical development plan intended to provide evidence of safety and efficacy for Recombinant human lysosomal acid lipase (SBC-102) as a treatment for Lysosomal Acid Lipase (LAL) Deficiency. The clinical development plan for SBC-102 was previously discussed at a Pre-IND meeting between Synageva and FDA on July 29, 2010.

## 2. DISCUSSION

### Introductory clinical comments

**In general, we agree with your plans to evaluate patients with both Wolman disease and CESD. We also agree with your plans to study the natural history of patients with Wolman disease and CESD through your two natural history studies (LAL-1-NH01 and LAL-2-NH01). Much of the information regarding appropriate endpoints for study, target population and length of study should be based on a careful review of the data collected from these two studies. You have not provided any data from these studies for review as part of the justification for your target population and endpoint selections. We recommend that you carefully review data from these studies to identify the most appropriate and feasible endpoints and populations for study and include data from these studies as part of your justification for any future study designs.**

**Additionally, you have provided very little information on your completed Phase 1/2 study (LAL-CL01). It is difficult to make any substantive agreements without data from this study.**

1. Does FDA agree that the existing and proposed nonclinical development studies will be sufficient to support a BLA for treatment of patients with Lysosomal Acid Lipase Deficiency? Specifically, does FDA agree 1) with the proposed reproductive toxicology plan and 2) that genotoxicity and carcinogenicity studies are not applicable to SBC-102 based on the nature of this product? (Section 10.2)

### FDA Response:

**Yes, we agree.**

### Additional Discussion:

*None*

2. Regarding LAL-CL02, *A Multicenter, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Safety and Efficacy of SBC-102 in Subjects with Lysosomal Acid Lipase Deficiency*, we have the following questions:
- a. Does FDA agree that the number of subjects planned for enrolment in LAL-CL02 (i.e., [REDACTED]<sup>(b) (4)</sup>) is sufficient to assess the safety and efficacy of SBC-102 in the treatment of patients with late onset LAL Deficiency? (Section 10.3.3.1)

**FDA Response:**

**We cannot agree on the number of subjects planned for enrolment in LAL-CL02 until we reach agreement on endpoints to be evaluated, and the degree of treatment effect expected to be demonstrated, and overall study design.**

**Additional Discussion:**

*None*

- b. Does FDA agree that the patient population to be enrolled as defined by the proposed eligibility criteria, allowances/restrictions for concomitant medications, and limitations on number of patients to be enrolled who may be at high risk for concomitant NAFLD, is acceptable and adequately defines patients with late onset LAL Deficiency who may benefit from therapy with SBC-102? (Section 10.3.3.2)

**FDA Response:**

**We agree with your plan to enroll a broad spectrum of patients with late onset LAL deficiency as an earlier phase study. It does not appear that you have sufficient data collected to clearly identify a target population for study in a confirmatory registration trial. We have the following concerns about your proposed entry criteria:**

- **It is unclear how many patients with CESD are obese (BMI >35). Additional Information regarding the demographics of patients enrolled in your natural history study would be helpful to review.**
- **It is not clear how you plan to identify patients for study less than 18 years of age. [REDACTED]<sup>(b) (4)</sup>, this will have the practical result of functionally excluding patients under the age of 6 or 7 years. We do not agree with limiting these younger patients, since they are at high risk for morbidities associated with disease progression and will likely use the drug if approved.**

**Additional Discussion:**

*None*

- c. Does FDA agree that inclusion of pediatric patients with late onset LAL Deficiency in LAL-CL02, with entry criteria defined by [REDACTED] (b) (4), is appropriate and acceptable? (Section 10.3.3.3)

**FDA Response:**

**No, we do not agree (see response to question 2b). You should also consider additional endpoints that would be feasible for study based on all available data.**

**Additional Discussion:**

***None***

- d. Does FDA agree with the rationale for the dose and regimen proposed to be administered in the LAL-CL02 study? (Section 10.3.3.4)

**FDA Response:**

**You have not provided sufficient data from your phase 1/2 study to agree to a dose and regimen for a registration trial. However, we agree that based upon the summary data obtained from the adult late-onset LALD subjects enrolled in study LAL-CL01, your rationale to include a 1 mg/kg qow dosage regimen as one of the proposed doses to be administered in a phase 2 dose-ranging study is acceptable. This study should evaluate clinically-meaningful endpoints. We must caution that because study LAL-CL02 will be enrolling a more heterogeneous population, including pediatric subjects who may have varying degrees of disease severity, it is unclear at this point if every other week dosing would provide an adequate treatment effect in a more severe subset of patients. Furthermore, you have not provided us any data that correlate exposure with clearance of substrate from the affected target organs.**

**We also have concerns about the initial dosing of patients. It appears that some patients experienced substantial elevations of total cholesterol, LDL cholesterol, and triglycerides. Therefore, alternative initial dosing strategies may be necessary. Additionally, it is not clear what concomitant medications patients in LAL-CL01 were receiving and how these concomitant medications may have affected the pattern of lipid changes.**

**Additional Discussion:**

***None***

- e. Does FDA agree that either [REDACTED] (b) (4), would be appropriate and acceptable as a primary endpoint to demonstrate efficacy in patients with late onset LAL Deficiency? (Section 10.3.3.5)

**FDA Response:**

**No, we do not agree.** [REDACTED] (b) (4)

**Additional Discussion:**

*None*

- f. Does FDA agree with the selection of key secondary efficacy endpoints, including improvements in hepatic transaminases (if not considered as a potential primary endpoint), liver and spleen volume, and serum lipids, and the proposed schedule of clinical assessments to be performed in LAL-CL02, as well as the pharmacokinetic sampling plan? (Section 10.3.3.6)

**FDA Response:**

**Your proposed secondary endpoints appear acceptable. We encourage you to study as many secondary and exploratory endpoints as is feasible. However, you should provide justification for the expected changes in these endpoints based on all available data, including data from natural history studies.**

**Yes, we agree with your proposed PK sampling plan. For your sparse sampling proposal in pediatric subjects, clarify your intended sample size. Please be aware of the sampling volume constraints that will need to be considered for this vulnerable population who may have or be at increased risk for anemia. Clarify the volume that would be required for each sample. In addition, at the time of data analysis, please be attentive to anti-drug antibody status of treated subjects as the anti-drug antibody status may need to be a covariate in your PK model or a level of stratification when interpreting your PK data.**

**Additional Discussion:**

*None*

- g. Does FDA agree [REDACTED] (b) (4) [REDACTED] in the proposed pivotal trial in late onset LAL Deficiency? (Section 10.3.3.7)

**FDA Response:**

**We do not agree at this time (see response to question 2e for further comments). You state in your protocol that up to 2/3 of patients with CESD are pediatric patients. As the article by Hulkova et al. states proper immunohistochemical analysis can facilitate recognition of CESD. You should identify enrollment criteria and endpoint selection that all patients in the study can perform or undergo. If different endpoint and enrollment criteria are used interpretation of results from the study may be difficult or impossible.**

**Additional Discussion (e,f,g):**

*FDA does not agree that change in serum ALT alone can be used as a primary endpoint for a registration trial in CESD patients. FDA recommends Synageva request another meeting to discuss the best path forward before starting clinical trials in patients, and will invite consultants from Division of Metabolism and Endocrinology Products (DMEP) for consultation.*

*FDA is also interested in reviewing data from a single patient with Wolman disease who has received treatment for over 1 year, and is 18 months of age now. If Synageva can provide evidence that treatment with rhLAL provides a survival benefit in infants with Wolman disease then these data could potentially be used to provide substantial evidence of effectiveness of rhLAL in Wolman disease.*

- h. Does FDA agree that the proposed duration of the study [REDACTED] (b) (4), including the acceptability of placebo arm for the duration of the randomized period of the study, after which patients will be allowed to transition to open label active therapy, will allow for an adequate assessment of efficacy and safety of SBC-102 in patients with late onset LAL Deficiency? (Section 10.3.3.8)

**FDA Response:**

**It is premature to agree to this study duration (see responses to 2a, 2b, 2e). We cannot agree to a length of study until we have agreed to an endpoint. You need to provide data to support that a change in endpoint will occur over the length of time proposed for the trial.**

**Additional Discussion:**

*None*

- i. Does FDA agree that the proposed safety and laboratory monitoring, including the utilization of an independent monitoring committee, monitoring for immunogenicity and potential infusion-related reactions, is acceptable and will allow for an adequate assessment of safety in LAL-CL02? (Section 10.3.3.9 and Section 10.3.3.10)

**FDA Response:**

**We agree with the use of an independent monitoring committee and an independent safety physician to assess hyperlipidemia. Because of the risk of pancreatitis associated with elevated triglycerides, and other safety concerns associated with hyperlipidemia, your protocol should be more explicit regarding management of hyperlipidemia and hypertriglyceridemia.**

**You state that you will establish pre-defined criteria for sustained hyperlipidemias requiring possible intervention such as dose modification or treatment interruption. These may include acute triglyceride to >1000 mg/dL, and/or severe hypercholesterolemia >500 mg/dL for >6 months duration. The protocol should state the exact values that will require intervention, and make clear the stopping rules associated with acute and/or sustained hyperlipidemia.**

**In order to provide an adequate assessment of the potential impact of anti-drug antibodies on the PK of your product, your immunogenicity sampling scheme should coincide with your PK sampling scheme during at least two time points. Therefore, we recommend that your immunogenicity sampling scheme include the following time points: Weeks 0, 4, 12, 16, 28, and 52. We also remind you that your immunogenicity assay should be validated and should be capable of sensitively detecting ADA responses in the presence of drug levels that are expected to be present at the time of patient sampling. Please refer to the *Guidance for Industry: Assay Development for Immunogenicity Testing of Therapeutic Proteins* for more information.**

**<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM192750.pdf>**

**Additional Discussion:**

*None*

- j. Does FDA agree that the proposed approach to our analysis plan for LAL-CL02, in particular the fixed sequence hierarchical testing for key secondary endpoints, is acceptable from a statistical perspective, and that if these endpoints are statistically significant according to this testing procedure, [REDACTED] (b) (4) [REDACTED]? (Section 10.3.3.11)

**FDA Response:**

**It is premature to comment on the analysis plan for LAL-CL02 (see responses to questions 2a, 2b and 2e).**

**Additional Discussion:**

*None*

- k. Does FDA agree that the design and endpoints of the proposed randomized placebo controlled trial LAL-CL02, should be able to provide substantial evidence of safety and efficacy based on an adequate assessment of benefit-risk in pediatric and adult patients with late onset Lysosomal Acid Lipase Deficiency that could support an indication for treatment of patients with Lysosomal Acid Lipase Deficiency?

**FDA Response:**

**We do not agree that study LAL-CL02 should be conducted as a registration trial (See response to questions 2b, 2c and 2i).**

**Additional Discussion:**

*None*

Questions Pertaining to Evaluation of the Safety and Efficacy of SBC-102 in Infantile Patients with Early Onset Lysosomal Acid Lipase Deficiency:

3. Does FDA agree that use of a historical control as a comparator to the population enrolled in early onset study LAL-CL03 (or initiated under compassionate use) is acceptable and will allow for interpretation of survival data, given the nature of the population under evaluation, i.e. infants with rapid onset of severe, irreversible, and inevitably fatal disease? (Section 10.3.4)

**FDA Response:**

**We do not agree with the current design of study LAL-CL-03 for use as a phase 3 trial. You have not yet provided sufficient evidence that patients who would be enrolled in this study would be sufficiently similar to the historical control population. You will need to provide data that support the characteristics of the control population that clearly identify them as patients that are likely to progress rapidly without treatment. These characteristics must be used as enrollment criteria for the treatment group and must be identified *a priori*. Patients that do not clearly fit these enrollment criteria cannot be enrolled in the study.**

**You note that there is overlap between Wolman and CESD in some pediatric patients and that it is not clear how some pediatric patients will progress. However, you state that patients with growth failure prior to 6 months of age will define Wolman patients. You have not provided any information to suggest that this finding will clearly identify Wolman patients with severe outcomes. You also state that in patients from your natural history study that median age of death of 2.95 months (in patients who did not receive hematopoietic or liver transplant). Therefore, we do not agree with including patients greater than 6 months of age.**

**Additional Discussion:**

***None***

4. Synageva is making every effort to enroll all early onset patients meeting the entry criteria for LAL-CL03 into this study; however, one patient has transitioned to Synageva's company-sponsored study who initiated treatment under compassionate use in France due to the need for emergent treatment before the LAL-CL03 protocol could be activated there. Does FDA agree that data from this patient, and any other patient who may, under exceptional emergent circumstances, be required to initiate treatment outside of LAL-CL03 due to an inability to immediately access an active trial site, can be included in the analysis of outcomes with patients who originated treatment under protocol LAL-CL03? (Section [10.3.5](#))

**FDA Response:**

**We do not fully understand what you are asking. As noted above, a compassionate use protocol would allow for treatment of these patients and allow for the collection of additional clinical data in patients enrolled in this protocol.**

**Additional Discussion:**

***None***

5. Does FDA agree with the dose escalation strategy and rationale for long-term dosing in patients enrolled onto LAL-CL03? (Section [10.3.6](#))

**FDA Response:**

**We note that you have already opened, and are actively recruiting patients for LAL-CL03. Your proposed dose escalation strategy for this protocol appears acceptable. We noted that study LAL-CL03 will include an option to dose escalate to 3 mg/kg weekly (for those patients with inadequate treatment response from 1.0 mg/kg weekly). This dose level is higher than the proposed dose level (1.0 mg/kg) to be evaluated in study LAL-CL02. While this may be appropriate since the patient population in this study has more severe disease than that for study LAL-CL02, further justification for the selection of this dose level is needed. In addition, close monitoring of the study subjects is warranted and adequate stopping rules should**

**be pre-specified in the protocol given the adverse effects observed in adult patients during study LAL-CL01 (i.e., hyperlipidemia and hypertriglyceridemia which may potentially have been dose-related).**

**Additional Discussion:**

*None*

6. Does FDA agree that a primary endpoint of survival at 12 months in patients treated in LAL-CL03, compared to survival of an untreated historical cohort with similar clinical characteristics, is acceptable to demonstrate efficacy in support of an indication for SBC-102 of treatment of patients with early onset Lysosomal Acid Lipase Deficiency? (Section 10.3.7)

**FDA Response:**

**It is premature to answer this question. (see our response to question 3)**

**Additional Discussion:**

*None*

7. Does FDA agree that safety data from late onset patients can be used to augment safety data in the patients enrolled in LAL-CL03 to provide evidence in support of an indication for SBC-102 for the treatment of patients with early onset Lysosomal Acid Lipase Deficiency given the extreme rarity of the early onset form? (Section 10.3.8)

**FDA Response:**

**Safety data from late onset disease may be relevant, but if the natural history of the diseases is dissimilar you will still need to provide adequate safety data from patients with the early onset form.**

**Additional Discussion:**

*None*

**Additional Comments**

**Electronic Data Submission**

**Please provide the following for each adequate and well-controlled clinical study (per 21 CFR 314.126) you plan to include in your eventual BLA submission:**

1. **All clean/locked clinical data presented in electronic datasets, submitted utilizing SAS Version 5 Transport, along with the annotated case report form (aCRF) and a thorough data definition file. We recommend that the electronic datasets, aCRF, and data definition file fully comply with the latest CDISC/SDTM, CDISC/CDASH, and CDISC/Define.XML standards respectively. Define.PDF also an acceptable format for the data definition file.**

2. All corresponding analysis data presented in electronic datasets, submitted utilizing SAS Version 5 Transport, along with a thorough data definition file. We recommend that these electronic datasets fully incorporate the modeling approaches described by the latest CDISC/ADaM standard along with both the CDER Data Standards Common Issues Document and the Study Data Specifications document (<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm>). We recommend that the data definition file fully comply with the latest CDISC/Define.XML standard, however Define.PDF is also acceptable.
3. A well commented and organized software program written for each analysis dataset and efficacy table created.

### 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

Appropriate endpoints to be used in clinical trials evaluating rhLAL in CESD patients will require additional discussion (see “Additional Comments e,f,g ” in minutes, above).

### 5.0 ACTION ITEMS

Action Item/Description	Owner	Due Date
Meeting Request (regarding additional comments e, f, g)	Synageva	

### 6.0 ATTACHMENTS AND HANDOUTS

SBC-102 Type B Meeting Handouts

9 Page(s) have been Withheld in Full as B4 (CCI/TS) immediately following this page

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

/s/  
-----

ELIZABETH A FORD  
07/10/2012



PIND 108460

**MEETING MINUTES**

Synageva BioPharma  
Attention: Mark J. Hites  
Director, Regulatory Affairs  
111 Riverbend Road  
Athens, GA 30605

Dear Mr. Hites:

Please refer to your Pre-Investigational New Drug Application (PIND) file for SBC-102 (recombinant human lysosomal acid lipase (rhLAL)).

We also refer to the meeting between representatives of your firm and the FDA on July 29, 2010. The purpose of the meeting was to discuss your proposed development program for SBC-102.

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

In addition to the official minutes of the meeting, we have included the following post-meeting comments that may be considered:

1. A full, 6-month, repeat-dose toxicology study in juvenile cynomolgus monkeys of appropriate age could be used to support dosing in human children. Therefore, our recommendation that you begin with phase 1 studies in older affected populations first, may be modified if a full juvenile study in cynomolgus monkeys is completed and included for review at the time of the initial IND submission (see section 2.2.1 of the meeting minutes).
2. We performed literature searches and found two references that address monitoring of protein aggregates in the presence of HSA (Braun, A. and Alsenz, J, Pharmaceutical Research, Vol 14, No. 10, 1997, and Kumarasamy et.al, Pharmaceutical research, Vol 11, No.3, 1994). Methods such as, but not limited to, those described in the reference papers, could be used as sensitive measures of protein aggregation (see section 2.3.2 of the meeting minutes).

If you have any questions, call me at (301) 796-4857.

Sincerely,

*{See appended electronic signature page}*

Todd Phillips, PharmD  
Regulatory Project Manager  
Division of Gastroenterology Products  
Office of Drug Evaluation III  
Center for Drug Evaluation and Research



FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH

---

**MEMORANDUM OF MEETING MINUTES**

**Meeting Type:** Type B  
**Meeting Category:** Pre-IND

**Meeting Date and Time:** July 29, 2010 / 1:00 – 2:00 pm EST  
**Meeting Location:** FDA White Oak Campus, Building 22, Room 1313

**Application Number:** PIND 108460  
**Product Name:** SBC-102 (recombinant human lysosomal acid lipase (rhLAL))  
**Indication:** For use in patients with lysosomal acid lipase deficiency  
**Sponsor/Applicant Name:** Synageva BioPharma

**Meeting Chair:** Lynne Yao, M.D., Medical Officer, Acting Team Leader  
**Meeting Recorder:** Todd Phillips, Pharm.D., Regulatory Project Manager

**FDA ATTENDEES:**

Donna Griebel, M.D., Director, Division of Gastroenterology Products  
Andrew Mulberg, M.D., Deputy Director, Division of Gastroenterology Products  
Lynne Yao, M.D., Medical Officer, Acting Team Leader, Division of Gastroenterology Products  
Tamara Johnson, M.D., Medical Officer, Division of Gastroenterology Products  
Milton Fan, Ph.D., Acting Statistical Team Leader, Division of Biometrics III  
Hae-Young Ahn, Ph.D., Deputy Director, Division of Clinical Pharmacology III  
Jang-Ik Lee, Pharm.D., Ph.D., Clinical Pharmacology Reviewer, Division of Clinical Pharmacology III  
Sushanta Chakder, Ph.D., Supervisory Pharmacologist, Division of Gastroenterology Products  
Emmanuel Akinshola, Ph.D., Pharmacology Reviewer, Division of Gastroenterology Products  
Emanuela Lacana, Ph.D., Supervisory Research Chemist, Division of Therapeutic Proteins  
Akhilesh Nagaich, Ph.D., Research Chemist, Division of Therapeutic Proteins  
Christine Mueller, M.D., Medical Officer, Office of Orphan Products Development  
Todd Phillips, Pharm.D., Regulatory Project Manager, Division of Gastroenterology Products

PIND 108460  
Meeting Minutes  
Type B (Pre-IND)

**SPONSOR ATTENDEES:**

Anthony Quinn, BMSc, MBChB, Ph.D., FRCP, Head of R&D and Chief Medical Officer

Mark Leavitt, Ph.D., Head of Product Development

Brian Conner, General Manager, Head of Quality and Regulatory

Chris Oliver, Director, Facilities and Operations

Christine Maurer, Associate Director, Program and Alliance Management

Mark Hites, Director, Regulatory Affairs

Sanj Patel, President and CEO

<sup>(b) (4)</sup>, Project Consultant, <sup>(b) (4)</sup>

## 1.0 BACKGROUND

On April 1, 2010, Synageva requested a type B / Pre-IND Meeting with the Division of Gastroenterology to discuss their proposed Clinical and Chemistry, Manufacturing and Controls development programs for SBC-102.

Lysosomal acid lipase (LAL) deficiency, also known as Wolman Disease or Cholesteryl Ester Storage Disease (CESD), is a rare lysosomal storage disease that is progressive and often fatal. LAL deficiency is characterized by a failure to breakdown cholesteryl esters and triglycerides in lysosomes due to a deficiency of the enzyme. The clinical effects of LAL deficiency are due to an accumulation of lipid material in the lysosomes in a number of tissues and a disturbance in cholesterol and lipid homeostatic mechanisms, including substantial increases in hepatic cholesterol synthesis. LAL deficiency is a multi-system disease that most commonly manifests with gastrointestinal, liver and cardiovascular complications.

SBC-102 is a recombinant human lysosomal acid lipase (rhLAL) purified from the egg whites of rhLAL transgenic gallus. The sponsor has developed a methodology for the production of rhLAL using transgenic gallus. The sponsor has filed an Investigational New Animal Drug application (INAD) with the Center for Veterinary Medicine describing the construct and establishment of the line, and the procedures and practices for handling and monitoring the transgenic line and the eggs produced.

## 2. DISCUSSION

### 2.1. Clinical

#### **Question 1:**

Does the Agency concur with the proposed conduct of two concurrent Phase 1/2 studies in LAL Deficiency/Wolman phenotype and LAL Deficiency/CESD phenotype, and with the proposed design of these studies?

#### **FDA Response:**

**No, we do not agree. The major concern for first-in-human studies is safety. Therefore, a first-in-human study needs to provide some reasonable safety information to inform future trials, prior to administering the product to special or vulnerable populations, such as young children. Other endpoints, such as pharmacokinetic (PK) parameters, and pharmacodynamic (PD) or preliminary efficacy parameters, should be evaluated in older patients to inform the design and monitoring of clinical trials in younger patients. Therefore, we strongly recommend that you begin with phase 1 studies in older affected populations first.**

**Furthermore, your currently proposed (b) (4) toxicology study will not support your proposed study lengths (b) (4). You also lack the necessary nonclinical data to support human dosing in the age group you propose, young children. You must conduct appropriate repeat-dose toxicology studies of**

**appropriate duration in a rodent and non-rodent species of appropriate age prior to initiating clinical trials (see response to question 2.2.1) in that population.**

**Once you have established sufficient nonclinical safety data to initiate clinical trials, we have the following additional comments and questions regarding your proposed dose and dosing regimen based on your proposed protocol synopses:**

- **Your protocol should begin with the lowest dose to be studied. If the initial dose is found to be safe and tolerable, the next dose level to be studied should be no more than 2- to 3-fold higher than the previous dose evaluated.**
- **You should consider evaluation of additional dose levels in your protocol. An initial evaluation of more than two dose levels allows a better opportunity to evaluate the lowest effective dose. Please refer to the “Guideline for Industry: Dose-Response Information to Support Drug Registration (ICH-E4) November 1994”, <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm073115.pdf>.**
- **You have proposed a weekly infusion schedule for Wolman patients and a twice monthly infusion for CESD patients, however, you have not provided justification for this difference in dosing regimen. Provide the evidentiary basis for this difference in dosing schedule.**
- **You intend to have the same starting dose for infants (LAL-1) and pediatric patients older than 5 years (LAL-2). Provide justification for this dose based on all available nonclinical data.**
- **Your current study synopsis for LAL-1 proposes to increase the dose given in the first cohort (Cohort A) if no improvement in growth is demonstrated at week 4. We recommend that patients remain at the same dose level for the duration of the study.**

**Meeting Discussion:**

***The Sponsor confirmed that they will initiate first-in-human studies in adult CESD patients. Initiation of clinical studies in the pediatric CESD population will begin after an adequate amount of adult CESD safety data has been accumulated and evaluated by the sponsor, the DSMB (Data Safety Monitoring Board), and the Agency.***

***The sponsor agreed to modify their first-in-human protocol to begin with the lowest dose to be studied. The sponsor agreed that, if the initial dose is found to be safe and tolerable, the next dose level to be studied will be 2-to-3- fold higher than the previous dose. The sponsor will also consider evaluating additional dose levels based on recommendations by the Agency. The sponsor confirmed they will include a rationale for the selected starting dose in the initial IND submission.***

**Question 2:**

Does the Agency concur with proposed number of doses and number of patients per cohort and the timing of sequential enrollment?

**FDA Response:**

**No, we do not agree (see response to question 2.1.1). Initiation of dosing in infants should not begin until safety information has been collected in older patients. The proposed number of doses to be used must be based on and supported by all available clinical and nonclinical safety information. Additionally, please provide justification for the currently proposed patient enrollment based on the prevalence of each disease phenotype.**

**Meeting Discussion**

*The Agency stated that data obtained from the LAL deficiency mouse model may be useful in determining an initial dose and dosing schedule in a first-in-human trial.*

**Question 3:**

Does the Agency concur with the timing and frequency of safety evaluations?

**FDA Response:**

**No, we do not agree. For all study protocols, safety should be assessed up to 30 days after the last dose of study drug, and serious adverse events should be followed until resolution. Additionally, you should evaluate the safety of the product related to any potential accumulation in the body over time.**

**We have the following additional comments and questions regarding your proposed safety evaluations based on your proposed protocol synopses:**

- **Patients with allergy to egg should be excluded from the study.**
- **Your protocol should provide a specific clinical definition of anaphylaxis, allergic reactions, and infusion reactions. The CRF should be designed to specifically identify allergic reactions, anaphylaxis, and infusion reactions.**
- **Provide a severity grading system that will be used to classify adverse events (e.g., NCI CTCAE v.4.0).**
- **Provide individual patient and overall study stopping criteria. For example, based on specific potential adverse events (e.g., anaphylaxis) that may occur with use of the study drug in the patient population. For example, the study will be stopped if 2 patients developed the same Grade 3 Adverse Event, or for any patient that develops a Grade 4 Adverse Event based on NCI CTCAE.**
- **Provide specific plans for the monitoring and treatment of hypersensitivity reactions.**

- **A Drug Safety Monitoring Board (DSMB) should be convened to review the safety data.**

**Meeting Discussion:**

*The sponsor agreed to incorporate the Agency's safety evaluation recommendations. The sponsor confirmed that they will convene a DSMB. The sponsor confirmed they will submit the Case Report Form (CRF) and Informed Consent Form (ICF) to the Agency.*

**Question 4:**

LAL Deficiency is a rare, severe, progressive, life-threatening disease. Does the Division concur that demonstration of substantial clinical benefit in the proposed Phase 1/2 studies for LAL Deficiency, including the extension study in the LAL Deficiency/Wolman phenotype, would provide evidence of safety and efficacy sufficient to support a BLA application for SBC-102 as enzyme replacement therapy for patients with lysosomal acid lipase deficiency?

**FDA Response:**

**It is premature to answer this question. However, we have the following recommendations regarding your clinical development program for SBC-102:**

**We note that your clinical development program focuses on two LAL deficiency populations: Wolman Disease and Cholesterol Ester Storage Disease (CESD). Therefore, studies should be designed to adequately evaluate the efficacy and safety of each of these clinical phenotypes. The clinical trials should be designed to demonstrate a clinically meaningful benefit of SBC-102 in each of these populations.**

**We agree with your plans to study the natural history of LAL deficiency Wolman Disease. We additionally recommend that you study the natural history for CESD. Selection of clinical endpoints in future studies should be based on data collected from these natural history studies.**

**In the protocol synopsis for study LAL-1ext, we note that two key endpoints are planned: 1) survival through 12 months of age and 2) a composite endpoint which has not been defined. We agree that evaluation of survival would be clinically meaningful. Please explain how this composite endpoint will be determined. We recommend that any composite endpoint chosen for study be based on data collected from the natural history studies. The composite selected must also represent a clinically meaningful benefit.**

**Question 5:**

Based on agencies previous experience with natural history studies, does the Agency have any specific suggestions about the rationale, objectives, and key questions as outlined in Appendix B?

**FDA Response:**

See response to question 2.1.4. We have the following additional comments regarding the design of the natural history studies:

- The natural history study should be designed to collect both retrospective and prospective data.
- Growth data collection should include weight, length, BMI, and head circumference.
- Consider Including periodic assessments of adrenal function, mevalonic acid levels, liver and spleen volume by MRI.
- Neurocognitive development data should be collected using an age-appropriate, validated test.
- Collect information on other medical interventions, to include TPN, surgery, bone marrow transplant, enzyme replacement therapies, and concomitant medications used.

We encourage you to submit the natural history protocol for FDA review prior to initiation.

**Meeting Discussion:**

*The sponsor concurred with the Agency that a Wolman Disease natural history study would greatly assist with the clinical development program for their product. However, the sponsor stated that a prospective natural history study in Wolman Disease would not be feasible. Therefore, the sponsor would like to conduct a retrospective natural history study for Wolman Disease. Additionally, the sponsor informed the Agency that some of the natural history design characteristics proposed by the Agency could not be implemented due to factors associated with the disease. The Agency recommended the sponsor provide appropriate justification for the design of their proposed natural history study.*

*The sponsor stated that a natural history study in CESD patients may not be necessary in the clinical development program for their product. The sponsor believes adequate data to support the safety and efficacy of their product in CESD can be obtained through placebo-controlled phase 1 and 2 studies. The sponsor acknowledged the utility of information gathered from both retrospective and prospective natural history studies in CESD patients. The sponsor stated they plan to collect retrospective natural history data and a limited amount of prospective data from future clinical trials. The Agency recommended the sponsor prospectively evaluate as many CESD patients as possible for as long as possible.*

*The Agency stated that data from natural history studies could be used to inform decisions associated with selection of appropriate clinical endpoints for both CESD and Wolman Disease. The Agency recommended the sponsor submit any natural*

*history protocol for review prior to initiation; however, the sponsor should start the study prior to receipt of comments from the Agency.*

## 2.2. Preclinical

### **Question 1:**

Does the Agency concur that the designs of the proposed studies are adequate to support the proposed Phase 1/2 use of the drug product in patients with LAL Deficiency/Wolman phenotype and LAL Deficiency/CESD phenotype?

### **FDA Response:**

**No, we do not concur. You need to conduct repeat-dose toxicology studies of appropriate duration in a rodent and non-rodent species of appropriate age. Since the age of the patient population in the proposed clinical trial is 1 month or higher, toxicology studies in juvenile animals will be needed. The high dose used in toxicology studies should provide at least 10-fold multiple over the highest anticipated clinical exposure. The duration of the nonclinical study should mimic the duration the clinical trial. Your proposed (b) (4) toxicology study will support dosing in clinical trials for only up to (b) (4) in adults.**

### **Meeting Discussion:**

*The Agency confirmed that toxicology studies in two species (rodent and non-rodent) of appropriate age are required to support first-in-human trials. The Agency agreed that the rat and cynomolgus monkey are the appropriate species. The Agency stated that the sponsor can conduct a one-month, repeat-dose toxicology study in rats and cynomolgus monkeys. If the results are comparable, a single 6-month, repeat-dose toxicology study in juvenile cynomolgus monkeys of appropriate age will support clinical studies in both juvenile and adult patients. The Agency stated that full histopathological evaluations are required prior to first-in-human dosing and requested this information be included in the initial IND submission.*

*The sponsor proposed a 6-month toxicology study with submission of full toxicological evaluation (including full histopathological evaluation) at interim time points (e.g., submission of data at 1, 3 and 6 months). The Agency confirmed that this would be acceptable; however, administration of SBC-102 to humans would not be allowed to continue beyond the duration of toxicology data that has been reviewed by the Agency.*

### **Post-Meeting Comment:**

*The Agency would like to further clarify with the sponsor that if a full, 6-month, repeat-dose toxicology study in juvenile cynomolgus monkeys of appropriate age is completed; these data could be used to support dosing in human children. Therefore, the Agency's recommendation that you begin with phase 1 studies in older affected populations first (see response to Question 2.1.1), may be modified if a full juvenile*

*study in cynomolgus monkeys is completed and included for review at the time of the initial IND submission.*

**Question 2:**

Based on data from preclinical pharmacology models of LAL Deficiency, we anticipate the clinical dosing schedule will be either weekly or every other week. We believe that once weekly dosing in the proposed toxicology study is sufficient to support either once weekly or every other week dosing in clinical studies. Does the agency concur with our assessment?

**FDA Response:**

**Your approach appears to be acceptable. Once weekly dosing in toxicology studies may support your proposed once weekly or every other week dosing in clinical studies.**

**Question 3:**

Please note that in the design of the toxicology studies (Appendix E), pre-dose administration of diphenhydramine is planned based on known reactions to administration of human proteins in this species, AND duration of infusion has been extended beyond the infusion time planned in the proposed clinical study to accommodate administration of the high dose (50mg/kg), which poses certain technical constraints relative to dose volume and formulation in rats. Synageva believes these modifications are acceptable and will support the proposed dose administration in humans. Does the Agency concur?

**FDA Response:**

**Pre-dose administration of diphenhydramine is acceptable provided the control group also received the same dose of diphenhydramine. However, the duration of infusion in animals should mimic the duration of infusion in humans. The duration of infusion may be related to the toxicity profiles of the drug, since prolonged duration of infusion will lower the Cmax.**

**Question 4:**

The proposed toxicology program includes an additional toxicology study to support a marketing application (BLA). With the addition of a 6-month repeat dose toxicology study in cynos, does the Agency concur that the proposed studies are adequate, or will additional toxicology studies be required to support a successful BLA application?

**FDA Response:**

**As mentioned in the nonclinical response to question 9.2.1, toxicology studies in two species will be needed. In addition to General Toxicology and Safety Pharmacology studies, you will need to conduct reproductive toxicology studies, depending on the**

**patient population. You will also need to address the carcinogenic potential of SBC-102.**

### 2.3. Chemistry, Manufacturing and Controls (CMC)

#### **Question 1:**

Are the proposed procedures for purification, virus reduction and final lot release of the clinical product appropriate and acceptable to the Agency, and what if any specific suggestions does the Agency have on how these could be improved?

#### **FDA Response:**

**Your purification process appears adequate; however, a final determination will be made at the time you submit the IND. We have the following recommendations:**

- 1. Your manufacturing process should include** (b) (4)  
[REDACTED].
- 2. The manufacturing process should be validated to demonstrate viral clearance.** (b) (4)  
[REDACTED]

**For additional information, please refer to ICH Q5A “Viral Safety Evaluation of Biotechnology Products Derived from Cell Lines of Human or Animal Origin”.**

- 3. In your original IND submission, please provide data to support stability of the drug product for the duration of the clinical trial. For future development, please include accelerated and stressed stability conditions in your stability protocol for drug substance and drug product. For additional information on stability, please refer to ICH Q5C “Quality of Biotechnological Products: Stability Testing of Biotechnological/Biological Products”.**

#### **Question 2:**

Given the stage of development, the indication and the target population, are the proposed release specifications for Drug Substance and Drug Product appropriate, and what if any modifications would the Agency want us to consider?

#### **FDA Response:**

- 1)** [REDACTED] (b) (4)

- 2) We recommend that peptide mapping be used to monitor for drug substance purity as well as identity.**

- 3) In regard to your drug product release and stability protocol, (b) (4) is not an adequate method to monitor for protein aggregates. We recommend that you use SEC-HPLC for this purpose.

**Meeting Discussion:**

(b) (4)

**Post-Meeting Comment:**

*After the meeting, the Agency performed literature searches and found two references that address monitoring of protein aggregates in the presence of HSA: (Braun, A. and Alsenz, J, Pharmaceutical Research, Vol 14, No. 10, 1997, and Kumarasamy et.al, Pharmaceutical research, Vol 11, No.3, 1994). Methods such as, but not limited to, those described in the reference papers, could be used as sensitive measures of protein aggregation.*

- 4) The following assays are not required for initiation of studies under the IND; however, we recommend that you develop and implement them in your drug substance and drug product release and stability protocol, as soon as possible:
- A potency assay that measures the kinetic parameters ( $K_M$  and  $K_{cat}$ ) using a physiologically relevant substrate.
  - A potency assay that measures the cellular uptake of SBC-102.
  - Please include in your drug product release and stability protocol, assays that monitor for charge heterogeneity and product degradation.

**Question 3:**

Are the specifications for host cell protein impurities appropriate for this stage of development? If not, does the Agency have any specific suggestions?

**FDA Response:**

No. We recommend that you also quantify (b) (4).

**Question 4:**

Are the procedures and practices established for handling and monitoring of the transgenic line and eggs acceptable as described in INAD 011-919? If not, does the Agency have any specific suggestions?

**FDA Response:**

Our evaluation of the initial submission to your Investigational New Animal Drug (INAD) file is in process. In general, the procedures and practices for handling and

**monitoring of the transgenic line and eggs described in INAD 011-919 are consistent with those previously evaluated for INAD [REDACTED] (b) (4) [REDACTED]. Here too, the procedures and practices are acceptable as described for this stage of the development of this product. Nonetheless, we strongly urge you to schedule a separate meeting with the Center for Veterinary Medicine to discuss preparing and filing New Animal Drug Applications (NADAs) for all four of these products. We remind you that this process is not automatic with your CDER/CBER applications.**

**Question 5:**

Initial clinical supplies for Phase 1/2 program will be manufactured at Synageva's Athens facility in accordance with guidance for production of Phase 1 investigational drugs ("CGMP for Phase 1 Investigational Drugs", DHHS/FDA/CDER/CBER/ORR, July 2008). It is anticipated that during the conduct of Phase 1/2 clinical trials, the manufacture plan for SBC-102 will be transferred to a CMO where processes will be fully validated. Comparability of the test materials will be evaluated on the basis of biochemical and biological characterization (i.e., identity, purity, stability, and potency) in consultation with FDA and in accordance with applicable comparability regulatory guidance. These activities will be staged concurrently during the conduct of the Phase 1/2 trials to ensure completion in time to support a BLA submission, should data from clinical warrant submission at the completion of the Phase 1/2 program. Does the Agency concur that this manufacturing development plan is adequate for the supply of clinical materials and for support of a license application?

**FDA Response:**

**Your approach appears reasonable. We recommend that you contact the Agency as soon as feasible to discuss your comparability study. Please be advised that, depending on the robustness of your comparability testing program, the nature of the changes and the results of your physicochemical comparability studies, additional preclinical and clinical studies may be necessary to ensure that the change in the manufacturing site has no adverse effect on the quality, safety and clinical efficacy of the product.**

**Additional comments:**

- 1) Information on manufacturing process of the non-clinical and clinical lots, highlighting differences in manufacturing if present, should be provided in the original IND submission. If there are differences in the manufacturing process of the non-clinical and clinical lot, the results of direct head-to-head comparisons of lots used in the non-clinical studies and to be used in the proposed clinical studies, with qualitative and quantitative information, must be provided.**
- 2) The drug substance must be extensively characterized. We recommend that a large battery of physicochemical tests be utilized in addition to release tests. For example, orthogonal methods for the detection of aggregates should be**

**used. Process-related impurities and product-related impurities and substances should be characterized and controlled.**

- 3) For future product development, the reference standard should be extensively characterized. We recommend that a large battery of physico-chemical tests be utilized in addition to release tests, including but not limited to, determination of enzyme kinetic parameters, peptide mapping coupled to mass spectrometry, chromatography, capillary electrophoresis and orthogonal methods for the detection of aggregates.**

**Additional Clinical Pharmacology comment:**

**We recommend that some blood samples be drawn for pharmacokinetic analyses in phase 3 studies. Blood sampling scheme can be discussed with the Agency when you submit phase 3 protocols.**

**2.4. Expanded Access**

**Question 1:**

What are the regulatory mechanisms for providing access to SBC-102 for patients like this?

**FDA Response:**

**Sponsors seeking expanded access to investigational drugs for treatment use should consult the final rule published in the *Federal Register* of August 13, 2009 (74 FR 40900 at 40945). Upon receipt, the Agency will evaluate an expanded access submission in accordance with the regulations defined in Part 312, Subpart I of the Code of Federal Regulations. Sponsors who anticipate a significant number of requests for individual patient access to an investigational drug for the same use are encouraged to consider an intermediate-size patient expanded access protocol or IND, as defined in 21 CFR 312.315. However, we strongly recommend that your clinical trials be designed to enroll all available patients. A specific clinical trial could be designed to include patients that do not meet inclusion criteria for your planned study. Furthermore, inclusion criteria for the currently proposed study could include patients with a life expectancy of less than 2 weeks, with a pre-specified plan to analyze efficacy results from these patients separately.**

**Question 2:**

Does the Agency have any specific concerns or suggestions about how we best approach this?

**FDA Response:**

**We strongly recommend that your clinical trials be designed to enroll all available patients (see response to question 9.4.1). We also remind you that expanded access protocols cannot compete with ongoing clinical trials. For this reason, we**

**recommend that you make every effort to design clinical trials with eligibility criteria that will allow the broadest access to drug and, at the same time, capture critical efficacy and safety information on your product.**

## **2.5. Additional Comments**

### **Additional Clinical Pharmacology Comments**

**We recommend you collect pharmacokinetic (PK) blood samples during infusion (e.g., 2 hours after the initiation of infusion) and immediately (i.e., a few minutes) before the end of infusion.**

### **Meeting Discussion:**

*The sponsor agreed to incorporate the PK sampling strategy recommended by the Agency.*

### **Additional Clinical Comments:**

**We have the following additional comments and questions regarding your proposed study design synopses:**

- Please clarify the rationale for the use of plasma mevalonic acid levels as a pharmacodynamic endpoint in your proposed studies.**
- Please submit copies of the Informed Consent Form and the Case Report Forms to be used in the proposed studies.**

## **3.0 ACTION ITEMS**

<b>Action Item/Description</b>	<b>Owner</b>	<b>Delivery Date</b>
Provide a table detailing the age categories in humans and suggested corresponding ages in animal models	FDA	Table sent to sponsor on August 3, 2010

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
IND-108460	GI-1	SYNAGEVA BIOPHARMA CORP	Recombinant human lysosomal acid lipase (rhLAL), transgenic Gallus

---

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

---

/s/

---

TODD D PHILLIPS  
09/01/2010

**LATE-CYCLE COMMUNICATION**  
**DOCUMENTS**



BLA 125561/0

**LATE-CYCLE MEETING MINUTES**

Alexion Pharmaceuticals, Inc  
Attention: Sara Saltzman  
Director, Regulatory Affairs  
33 Hayden Avenue  
Lexington, MA 02421

Dear Ms. Saltzman:

Please refer to your Biologic License Application (BLA) submitted under the Public Health Service Act for KANUMA (sebelipase alfa).

We also refer to the Late-Cycle Meeting (LCM) between representatives of your firm and the FDA on July 08, 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 Kevin Bugin, Regulatory Project Manager at (301) 796-2302.

Sincerely,

*{See appended electronic signature page}*

Jessica J. Lee, M.D., M.M.Sc.  
Medical Officer Team Leader  
Division of Gastroenterology and Inborn Errors 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:** July 08, 2015, from 3:00 to 4:00 PM, ET  
**Meeting Location:** White Oak Building 22, Conference Room 1309  
10903 New Hampshire Ave,  
Silver Spring, MD 20903

**Application Number:** BLA 125561/0  
**Product Name:** KANUMA (sebelipase alfa)  
**Indication:** treatment of lysosomal lipase deficiency  
**Sponsor/Applicant Name:** Alexion Pharmaceuticals, Inc.

**Meeting Chair:** Jessica J. Lee  
**Meeting Recorder:** Kevin B. Bugin

**FDA ATTENDEES**

Center for Drug Evaluation and Research

Julie Beitz, M.D., Director, Office of Drug Evaluation III (ODEIII)  
Amy Egan, M.D., Deputy, ODEIII  
Maria Walsh, R.N., M.S., Associated Director for Regulatory Affairs, ODEIII  
Andrew E. Mulberg, M.D., F.A.A.P., C.P.I., Deputy, Division of Gastroenterology and Inborn Errors Products (DGIEP), ODEIII  
Joette Meyer, Pharm.D., Associate Director for Labeling, DGIEP, ODEIII  
Jessica J. Lee, M.D., M.M.Sc., Medical Team Leader, DGIEP, ODEIII  
Juli Tomaino, M.D., M.S.C.R., Medical Reviewer, DGIEP, ODEIII  
Lauren Weintraub, M.D., Medical Reviewer, DGIEP, ODEIII  
Tamal Chakraborti, Ph.D., Nonclinical Reviewer, DGIEP, ODEIII  
Kevin B. Bugin, M.S., R.A.C., Acting Chief of Project Management Staff, DGIEP, ODEIII  
Lisa Pitt, Pharm.D., M.S.J., Senior Regulatory Project Manager, *via teleconference*  
Yeh-Fong Chen, Ph.D., Biostatistics Team Leader, Office of Biostatistics, Division of Biostatistics III  
Poonam Mishra, M.D., M.P.H., Deputy Director for Safety, Division of Antiviral Products, Office of Antimicrobial Products  
David Frucht, M.D., Acting Director, DBRR II, Office of Biotechnology Products, *via teleconference*  
Juhong Liu, Ph.D., Acting Review Chief, DBRR II, Office of Biotechnology Products (OBP)  
Christopher Downey, Ph.D., Quality Reviewer, DBRR II, OBP  
Jibril Abdus-Samad, Pharm.D., Labeling Reviewer, OBP  
Joao Pedras-Vasconcelos, Ph.D., Immunogenicity Reviewer, OBP, *via teleconference*  
Arulvathani Arudchandran, Ph.D., Product quality reviewer, DBRR II, OBP, *via teleconference*  
Christina Capacci-Daniel, Ph.D., Consumer Safety Officer, Division of Inspectional Assessment, Office of Process and Facilities (OPF)

Colleen Thomas, Ph.D., Quality Micro Reviewer, Division of Microbiology Assessment,  
OPQ/OPF

Matthew Barlow, R.N., B.S.N., Safety Evaluator, Division of Medication Error Prevention and  
Analysis, Office of Safety and Epidemiology (OSE)

Jamie Wilkins Parker, Pharm.D., Risk Management Analyst, Acting Team Leader, Division of  
Risk Management, OSE, *via teleconference*

Kimberly Swank, Pharm.D., Safety Evaluator, Division of Pharmacovigilance I, OSE, *via  
teleconference*

Center for Veterinary Medicine

Brinda Dass, M.P.H., Ph.D., A.L.A.T., Biologist, Animal Biotechnology Interdisciplinary Group,  
*via teleconference*

**EASTERN RESEARCH GROUP ATTENDEES**

Marc Goldstein, Independent Assessor

**APPLICANT ATTENDEES**

Pamela Williamson, Global Regulatory Affairs & Patient Safety

Jill Hillier, PhD, US Regulatory Affairs

Mark Hayes, PhD, Regulatory Affairs

Sara Saltzman, Regulatory Affairs

Tanya Green, Regulatory Affairs

Leslie Wilder, Regulatory Affairs CMC

Lori Whittlemore, Regulatory Affairs CMC, *via teleconference*

Anthony Quinn, MD, PhD FRCP, R&D

Sandra Rojas-Caro, MD, Clinical Research and Exploratory Development

Agustin Melian, MD, Global Medical Operations

Dana Martin, PharmD, Medical Operations

Nina Wolfendale, Pharmacovigilance

Marina Escudero, Clinical Operations

Declan Kelly, Quality, Chief Quality Officer

Mike Bauer, PhD, Quality

Stephen Machatha, PhD, CMC Project Management

**1.0 BACKGROUND**

BLA 125561/0 was received on January 08, 2015, for KANUMA (sebelipase alfa).

Proposed indication(s): treatment of lysosomal lipase deficiency

PDUFA goal date: September 08, 2105

FDA issued a Background Package in preparation for this meeting on June 26, 2015.

## 2.0 DISCUSSION

### 1. Introductory Comments

**Discussion:**

*The Agency conveyed that the purpose of the Late-Cycle Meeting (LCM) is to share information and to discuss any substantive review issues that we have identified to date and our objectives for the remainder of the review. The Agency further indicated that the application has not yet been fully reviewed by the signatory authority, division director, and Cross-Discipline Team Leader (CDTL), and therefore, the meeting will not address the final regulatory decision for the application.*

### 2. Discussion of Substantive Review Issues

- Facilities

**Discussion:**

*The Agency reiterated that satisfactory evaluation of all manufacturing facilities is required for BLA approval and encouraged the Applicant to work closely with the facilities that received 483s to address remaining deficiencies.*

- Quality Micro – Drug Product

**Discussion:**

*The Applicant indicated that the endotoxin test method has been improved such that it is suitable for measuring drug product endotoxin at the current specification. The Applicant also indicated that it may not be possible to further increase the sensitivity of the test method. The Applicant informed the Agency that the requested studies should conclude by the end of July, with anticipated submission to the Agency in early August. The Agency indicated that it will review the submission as soon as it arrives.*

### 3. Information Requests

- Outstanding Quality and Quality Micro Postmarketing Comments – sent June 08, 2015
- Outstanding Quality Micro Comments – sent June 09, 2015
- Outstanding Quality and Quality Micro Comments – sent June 18, 2015

**Discussion:**

*Information requests included in the LCM briefing package were noted as submitted to the Agency. The Applicant acknowledged additional information requests communicated on July 07, 2015, including the revised labeling. The Agency also indicated that an additional Quality Micro information request would be forthcoming.*

4. Postmarketing Requirements/Postmarketing Commitments

**Discussion:**

***Postmarketing Requirements/Commitments Comments sent on June 08, 2015 were noted and acknowledged as responded to.***

5. Major Labeling Issues

- [REDACTED] (b) (4)

**Discussion:**

***The Applicant acknowledged the receipt of the revised labeling sent on July 07, 2015. The Agency reiterated the reasons for excluding [REDACTED] (b) (4) in the labeling as there is currently insufficient information to support that [REDACTED] (b) (4).***

***The Agency, however, is agreeable to including a general statement describing reductions in ALT and liver fat content following sebelipase alfa treatment, as described in the revised labeling sent on July 07, 2015. The Applicant agreed with the Agency's approach and indicated that it would respond to the Agency's revised labeling the week of July 15.***

- Inclusion of in-line filter

**Discussion:**

***A brief discussion took place regarding the Agency's concerns related to the in-line filter and the importance of planning proactively, through labeling and/or education, to ensure safe dosage and administration of the product. The Applicant acknowledged the Agency's July 07, 2015, information request and provided an update on efforts to collect additional information from sites and current providers. [REDACTED] (b) (4)***

***[REDACTED] and proper handling of the product during preparation is very important. [REDACTED] (b) (4)***

***[REDACTED] The Applicant will submit its response to the Agency's in-line filter information request by the requested date of July 14, 2015.***

6. Review Plans

The Agency indicated that it plans to take action on this BLA application by the use fee goal date, September 08, 2015. CVM also indicated that it plans to take action on the New Animal Drug Application by the CDER goal date of September 08, 2015.

7. Wrap-up and Action Items

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

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

/s/  
-----

JESSICA J LEE  
07/14/2015



BLA 125561/0

**LATE CYCLE MEETING  
BACKGROUND PACKAGE**

Synageva Biopharma Corp.  
Attention: Sara Saltzman  
Director, Regulatory Affairs  
33 Hayden Avenue  
Lexington, MA 02421

Dear Ms. Saltzman:

Please refer to your Biologic License Application (BLA) submitted under the Public Health Service Act for KANUMA (sebelipase alfa).

We also refer to the Late-Cycle Meeting (LCM) scheduled for July 08, 2015. Attached is our background package, including our agenda, for this meeting.

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

Sincerely,

*{See appended electronic signature page}*

Andrew E. Mulberg, M.D., F.A.A.P., C.P.I.  
Deputy Director  
Division of Gastroenterology and Inborn Errors Products  
Office of Drug Evaluation III  
Center for Drug Evaluation and Research

ENCLOSURE:  
Late-Cycle Meeting Background Package

## **LATE-CYCLE MEETING BACKGROUND PACKAGE**

**Meeting Date and Time:** July 08, 2015, from 3:00 to 4:30 PM, ET  
**Meeting Location:** White Oak Building 22, Conference Room 1309  
10903 New Hampshire Ave,  
Silver Spring, MD 20903

**Application Number:** BLA 125561/0  
**Product Name:** KANUMA (sebelipase alfa)  
**Indication:** treatment of lysosomal lipase deficiency  
**Sponsor/Applicant Name:** Synageva Biopharma Corp.

### **INTRODUCTION**

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

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

### **BRIEF MEMORANDUM OF SUBSTANTIVE REVIEW ISSUES IDENTIFIED TO DATE**

#### **1. Discipline Review Letters**

No Discipline Review letters have been issued to date.

#### **2. Substantive Review Issues**

The following substantive review issues have been identified to date:

OFFICE OF PROCESS AND FACILITIES, DIVISION OF INSPECTIONAL ASSESSMENT -

Three facilities have received 483s for pre-license inspection observations. These inspectional findings and any facility responses received within 15 days of the inspection will be reviewed.

We will communicate any additional requests directly to these sites. Please ensure that all facilities are ready for commercial CGMP manufacturing activities as described in the BLA. Satisfactory evaluation of all manufacturing facilities is required for BLA approval.

#### QUALITY MICRO – DRUG PRODUCT -

We acknowledge that studies to evaluate or improve the sensitivity of endotoxin test methods for the drug product are in progress as of June 2015, and the release test method for the drug product has not yet been determined. The drug product release test methods must be determined prior to approval.

#### **ADVISORY COMMITTEE MEETING**

An Advisory Committee meeting is not planned.

#### **REMS OR OTHER RISK MANAGEMENT ACTIONS**

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

#### **LCM AGENDA**

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

Welcome, Introductions, Ground rules, Objectives of the meeting

2. Discussion of Substantive Review Issues – 15 minutes

Each issue will be introduced by FDA and followed by a discussion.

- Facilities
- Quality Micro – Drug Product

3. Additional Applicant Data – 20 minutes (Applicant)

4. Information Requests – 5 minutes

- Outstanding Quality and Quality Micro Comments – sent June 08, 2015
- Outstanding Quality Micro Comments – sent June 09, 2015
- Outstanding Quality and Quality Micro Comments – sent June 18, 2015

5. Postmarketing Requirements/Postmarketing Commitments – 15 minutes

We refer to the Postmarketing Requirements/Commitments Comments sent on June 08, 2015.

6. Major labeling issues – 15 minutes

-  (b) (4)
- Inclusion of in-line filter

7. Review Plans

We plan to take action on this application by the use fee goal date, September 08, 2015, as noted in our filing communication dated February 20, 2015.

8. Wrap-up and Action Items – 15 minutes

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

/s/  
-----

DONNA J GRIEBEL  
06/26/2015