CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125561Orig1s000

<u>OTHER REVIEW(S)</u>

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for ***each*** PMR/PMC in the Action Package.

NDA/BLA #	BLA 125561
Product Name:	
PMR/PMC Description: PMC 2920-1	Evaluate the long-term, prospective clinical outcomes of treatment with sebelipase alfa in adult and pediatric patients with LAL deficiency, including but not limited to progression of liver and cardiovascular diseases and changes in anthropometric assessments (i.e., length/height z-scores, and weight z-scores). At a minimum, liver assessments will include results of liver biopsies and imaging studies, changes in liver synthetic function, evidence for clinical progression to end stage liver disease (e.g., assessed by the Model for End-Stage Liver Disease [MELD] score), receipt of liver transplantation, and fatal outcomes. Cardiovascular assessments will include incidence rates of non-fatal stroke, myocardial infarction, and cardiovascular death. Additional evaluations will include dosing regimens administered and reasons for any dose modifications. This trial will also collect data on the occurrence of any serious hypersensitivity reactions, such as anaphylaxis, as well as changes in antibody status (i.e., detection and titers of binding and neutralizing antibodies, and detection of IgE antibodies). Eligible patients will be enrolled over an initial 3-year period and followed for a minimum of 10 years from the time of enrollment or until death, whichever comes first. This trial may be conducted as a separate study or as a sub-study within the Lysosomal Acid Lipase registry.

PMR/PMC Schedule Milestones:	Final Protocol Submission:	03/31/2016
	Trial Completion:	09/30/2029
	Final Report Submission:	04/30/2030
	Other: _____	MM/DD/YYYY

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

   - ☒ Unmet need
   - ☒ Life-threatening condition
   - ☒ Long-term data needed
   - ☐ Only feasible to conduct post-approval
   - ☐ Prior clinical experience indicates safety
   - ☐ Small subpopulation affected
   - ☐ Theoretical concern
   - ☐ Other

Reference ID: 3856695

Upon approval, Kanuma (sebelipase alfa) will be the only available therapy for patients with Lysosomal Acid Lipase Deficiency (LAL-D), which is a rare, serious, life-threatening lysosomal storage disease. While clinical trials included in the BLA provided adequate efficacy and safety data to support approval of sebelipase alfa for the treatment of LAL deficiency, they were not sufficient in duration to assess a clinically meaningful change in the underlying liver disease (e.g., progression to end stage liver disease, receipt of liver transplantation) or the long-term clinical benefit of sebelipase alfa on cardiovascular outcomes, both of which are key contributors to morbidity and mortality in this patient population. Since efficacy and safety data included in the BLA are sufficient to support approval of sebelipase alfa for the treatment of this serious and life-threatening disease, marketing access to this patient population should not be delayed in order to obtain additional long-term clinical outcome data.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

The goal of this PMC study is to assess the long-term clinical outcomes of pediatric and adult patients with LAL deficiency treated with sebelipase alfa.

The Applicant submitted results from two clinical trials, an open-label, single-arm trial (LAL-CL03) in infants with rapidly progressive disease (Wolman disease) and a randomized, double-blind, placebo-controlled trial (LAL-CL02) in pediatric and adult patients with LAL deficiency (CESD), to support the efficacy and safety of sebelipase alfa in patients with LAL deficiency. Of the 9 sebelipase alfa-treated infants in LAL-CL03, 6 patients survived beyond 12 months of age, compared to 0 of 21 patients in the historical cohort, all of whom died by 8 months of age. In LAL-CL02, significant improvements in percent change from baseline in low density lipoprotein cholesterol (LDL-c) and other lipid parameters were observed in the sebelipase alfa-treated group as compared to the placebo group after 20 weeks of treatment. In addition, there were improvements in liver-related pharmacodynamics measures (i.e., ALT values and liver fat content measured by MRI) during this period. However, 20 weeks is an insufficient duration of time to observe a clinically meaningful change in the underlying liver disease (e.g., progression to end stage liver disease, receipt of liver transplantation) or to evaluate the long-term clinical benefit of sebelipase alfa on cardiovascular outcomes, both of which are key contributors to morbidity and mortality in this patient population. Therefore, additional data are being requested to better characterize the long-term clinical benefit of sebelipase treatment on liver- and cardiovascular-related outcomes. In addition, this study will also collect data on the occurrence of any serious hypersensitivity reactions, such as anaphylaxis, as well as changes in antibody status.

This study is not a FDAAA PMR study.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.
If not a PMR, skip to 4.

- **Which regulation?**
  - ☐ Accelerated Approval (subpart H/E)
  - ☐ Animal Efficacy Rule
  - ☐ Pediatric Research Equity Act
  - ☐ FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**
  - ☐ Assess a known serious risk related to the use of the drug?
  - ☐ Assess signals of serious risk related to the use of the drug?
  - ☐ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

Reference ID: 3856695

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

☐ Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

☐ Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

☐ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

☐ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

Evaluate the long-term, prospective clinical outcomes of treatment with sebelipase alfa in adult and pediatric patients with LAL deficiency, including but not limited to progression of liver and cardiovascular diseases and changes in anthropometric assessments (i.e., length/height z-scores, and weight z-scores). At a minimum, liver assessments will include results of liver biopsies and imaging studies, changes in liver synthetic function, evidence for clinical progression to end stage liver disease (e.g., assessed by the Model for End-Stage Liver Disease [MELD] score), receipt of liver transplantation, and fatal outcomes. Cardiovascular assessments will include incidence rates of non-fatal stroke, myocardial infarction, and cardiovascular death. Additional evaluations will include dosing regimens administered and reasons for any dose modifications. This study will also collect data on the occurrence of any serious hypersensitivity reactions, such as anaphylaxis, as well as changes in antibody status (i.e., detection and titers of binding and neutralizing antibodies, and detection of IgE antibodies). Eligible patients will be enrolled over an initial 3-year period and followed for a minimum of 10 years from the time of enrollment or until death, whichever comes first. This study may be conducted as a separate study or as a sub-study within the Lysosomal Acid Lipase registry.

Required

☐ Observational pharmacoepidemiologic study
☐ Registry studies
☐ Primary safety study or clinical trial
☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
☐ Thorough Q-T clinical trial
☐ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
☐ Pharmacokinetic studies or clinical trials
☐ Drug interaction or bioavailability studies or clinical trials
☐ Dosing trials

Reference ID: 3856695

Continuation of Question 4

☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

_____

☐ Meta-analysis or pooled analysis of previous studies/clinical trials
☐ Immunogenicity as a marker of safety
☐ Other (provide explanation)

_____

Agreed upon:

☐ Quality study without a safety endpoint (e.g., manufacturing, stability)
☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
☒ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
☐ Dose-response study or clinical trial performed for effectiveness
☐ Nonclinical study, not safety-related (specify)

_____

☐ Other

_____

5. Is the PMR/PMC clear, feasible, and appropriate?

☒ Does the study/clinical trial meet criteria for PMRs or PMCs?
☒ Are the objectives clear from the description of the PMR/PMC?
☒ Has the applicant adequately justified the choice of schedule milestone dates?
☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

☐ Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

If so, does the clinical trial meet the following criteria?

☐ There is a significant question about the public health risks of an approved drug
☐ There is not enough existing information to assess these risks
☐ Information cannot be gained through a different kind of investigation
☐ The trial will be appropriately designed to answer question about a drug's efficacy and safety, and
☐ The trial will emphasize risk minimization for participants as the protocol is developed

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PMR/PMC Development Coordinator:

☒ *This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

_____

(signature line for BLAs)

Reference ID: 3856695

PMR/PMC Development Template: Product Quality (CMC)

This template should be completed by the review chemist (ONDQA) or biologist (OBP) and included for *each* type of CMC PMR/PMC in the Action Package. See #4 for a list of CMC PMR/PMC types

NDA/BLA # STN125561
Product Name: Kanuma (sebelipase alfa)

PMC 2920-2 Description: Increase the bioburden test volume for [redacted] (b) (4) samples to improve the sensitivity of the bioburden tests. In addition, provide bioburden qualification data for all in-process and drug substance samples from a total of three lots.

PMC Schedule Milestones:		
	Final Protocol Submission:	MM/DD/YYYY
	Study/Trial Completion:	MM/DD/YYYY
	Final Report Submission:	01/31/2016
	Other: _____	MM/DD/YYYY

PMC 2920-3 Description: Provide endotoxin qualification data for the in-process drug substance samples from a total of three lots.

PMC Schedule Milestones:		
	Final Protocol Submission:	MM/DD/YYYY
	Study/Trial Completion:	MM/DD/YYYY
	Final Report Submission:	1/31/2016
	Other: _____	MM/DD/YYYY

PMC 2920-4 Description: Improve the endotoxin method for the [redacted] (b) (4) samples by optimizing the endotoxin test procedures.

PMC Schedule Milestones:		
	Final Protocol Submission:	MM/DD/YYYY
	Study/Trial Completion:	MM/DD/YYYY
	Final Report Submission:	01/31/2016
	Other: _____	MM/DD/YYYY

- **ADD MORE AS NEEDED USING THE SAME TABULAR FORMAT FOR EACH PMC.**
- **INCLUDE DESCRIPTIONS AND MILESTONES IN THE TABLE ABOVE FOR ALL CMC/OBP NON-REPORTABLE PMCS *FOR WHICH THE FOLLOWING ANSWERS WILL BE IDENTICAL.*USE A SEPARATE TEMPLATE FOR EACH PMR/PMC FOR WHICH THE ANSWERS TO THE FOLLOWING QUESTIONS DIFFER.**
- ***DO NOT USE THIS FORM* IF ANY STUDIES WILL BE REQUIRED UNDER FDAAA OR WILL BE PUBLICALY REPORTABLE**

1. During application review, explain why this issue is appropriate for a PMC instead of a pre-approval requirement. Check reason below and describe.

   ☐ Need for drug (unmet need/life-threatening condition)
   ☒ Long-term data needed (e.g., stability data)
   ☐ Only feasible to conduct post-approval

Reference ID: 3856695

☒ Improvements to methods
☐ Theoretical concern
☐ Manufacturing process analysis
☐ Other

The qualification studies of the bioburden and endotoxin tests and feasibility study for increased bioburden test volumes need to use product samples generated at the next product campaign. In addition, the sponsor needs time to optimize the endotoxin test procedures for the (b) (4) samples. These are appropriate as PMCs because they do not affect the safety of the product. The risk of microbial contamination is mitigated by other microbial controls in place during manufacturing.

2. Describe the particular review issue and the goal of the study.

The bioburden test volumes for (b) (4) samples are small. The sponsor needs to conduct feasibility studies to increase the test volume and increase the sensitivity of the bioburden tests (PMC #1). In addition, the in-process and drug substance bioburden samples (PMC #1) and in-process endotoxin samples (PMC #2) have been qualified with samples from only one lot. The sponsor needs to provide qualification data using samples from two additional lots. The endotoxin method for the (b) (4) samples needs to be optimized to obtain consistent results (PMC #3).

3. [OMIT – for PMRs only]

4. What type of study is agreed upon (describe and check type below)?

Select only one. Fill out a new sheet for each type of PMR/PMC study.

☐ Dissolution testing
☒ Assay
☐ Sterility
☐ Potency
☐ Product delivery
☐ Drug substance characterization
☐ Intermediates characterization
☐ Impurity characterization
☐ Reformulation
☐ Manufacturing process issues
☐ Other

Describe the agreed-upon study:

PMC 2920-2
Increase the bioburden test volume for (b) (4) samples to improve the sensitivity of the bioburden tests. In addition, provide bioburden qualification data for all in-process and drug substance samples from a total of three lots.
PMC 2920-3
Provide endotoxin qualification data for the in-process drug substance samples from a total of three lots.
PMC 2920-4
Improve the endotoxin method for the (b) (4) samples by optimizing the endotoxin test procedures.

Reference ID: 3856695

5. To be completed by ONDQA/OBP Manager:

☒ Does the study meet criteria for PMCs?
☒ Are the objectives clear from the description of the PMC?
☒ Has the applicant adequately justified the choice of schedule milestone dates?
☒ Has the applicant had sufficient time to review the PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

☒ *This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

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(signature line for BLAs only)

Reference ID: 3856695

PMR/PMC Development Template: Product Quality (CMC)

This template should be completed by the review chemist (ONDQA) or biologist (OBP) and included for *each* type of CMC PMR/PMC in the Action Package. See #4 for a list of CMC PMR/PMC types

NDA/BLA #	STN125561
Product Name:	Kanuma (sebelipase alfa)
PMC 2920-5 Description:	Develop and validate a reliable endotoxin test for the unformulated drug substance sample. In addition, validate the (b) (4) and drug substance endotoxin test using the modified endotoxin method involving the use of (b) (4) sample preparation system. Provide the validation information and data.

PMC Schedule Milestones:		
	Final Protocol Submission:	MM/DD/YYYY
	Study/Trial Completion:	MM/DD/YYYY
	Final Report Submission:	04/29/2016
	Other: _____	MM/DD/YYYY

- **ADD MORE AS NEEDED USING THE SAME TABULAR FORMAT FOR EACH PMC.**
- **INCLUDE DESCRIPTIONS AND MILESTONES IN THE TABLE ABOVE FOR ALL CMC/OBP NON-REPORTABLE PMCS *FOR WHICH THE FOLLOWING ANSWERS WILL BE IDENTICAL.*USE A SEPARATE TEMPLATE FOR EACH PMR/PMC FOR WHICH THE ANSWERS TO THE FOLLOWING QUESTIONS DIFFER.**
- ***DO NOT USE THIS FORM* IF ANY STUDIES WILL BE REQUIRED UNDER FDAAA OR WILL BE PUBLICALY REPORTABLE**

1. During application review, explain why this issue is appropriate for a PMC instead of a pre-approval requirement. Check reason below and describe.

   ☐ Need for drug (unmet need/life-threatening condition)
   ☒ Long-term data needed (e.g., stability data)
   ☐ Only feasible to conduct post-approval
   ☒ Improvements to methods
   ☐ Theoretical concern
   ☐ Manufacturing process analysis
   ☐ Other

   The endotoxin test method under-reports the amount of endotoxin spiked in unformulated drug substance, (b) (4), and drug substance samples, suggesting that the endotoxin tests, including the drug substance release test may not be able to detect the presence of contaminated endotoxin. The sponsor demonstrated that a modification of the USP method involving (b) (4) sample treatment may be effective in enabling the recovery of endotoxin from spiked samples. The endotoxin method using an (b) (4) sample treatment needs to be validated with samples generated from the next product campaign. This is appropriate for a PMC because the rabbit pyrogen test is used for drug product release to ensure patient safety.

2. Describe the particular review issue and the goal of the study.

Reference ID: 3856695

The sponsor needs to develop and validate a reliable endotoxin test for the unformulated drug substance sample. In addition, the sponsor needs to validate the modified endotoxin method involving the use of (b) (4) sample preparation system for the (b) (4) and drug substance samples.

3. [OMIT – for PMRs only]

4. What type of study is agreed upon (describe and check type below)?

   Select only one. Fill out a new sheet for each type of PMR/PMC study.

   - ☐ Dissolution testing
   - ☒ Assay
   - ☐ Sterility
   - ☐ Potency
   - ☐ Product delivery
   - ☐ Drug substance characterization
   - ☐ Intermediates characterization
   - ☐ Impurity characterization
   - ☐ Reformulation
   - ☐ Manufacturing process issues
   - ☐ Other

   Describe the agreed-upon study:

   Develop and validate a reliable endotoxin test for the unformulated drug substance sample. In addition, validate the (b) (4) and drug substance endotoxin test using the modified endotoxin method involving the use of (b) (4) sample preparation system. Provide the validation information and data.

5. To be completed by ONDQA/OBP Manager:

   - ☒ Does the study meet criteria for PMCs?
   - ☒ Are the objectives clear from the description of the PMC?
   - ☒ Has the applicant adequately justified the choice of schedule milestone dates?
   - ☒ Has the applicant had sufficient time to review the PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

☒ *This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

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(signature line for BLAs only)

Reference ID: 3856695

PMR/PMC Development Template: Product Quality (CMC)

This template should be completed by the review chemist (ONDQA), biologist (OBP), or microbiologist (DMA) and included for *each* type of CMC PMR/PMC in the Action Package. See #4 for a list of CMC PMR/PMC types

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PMC 2920-6	Validate the [redacted] (b) (4) If the [redacted] (b) (4) is revised based on the validation study, update the BLA file accordingly.

PMC Schedule Milestones:		
	Final Protocol Submission:	
	Study/Trial Completion:	
	Final Report Submission:	01/31/2016
	Other:	

- **ADD MORE AS NEEDED USING THE SAME TABULAR FORMAT FOR EACH PMC.**
- **INCLUDE DESCRIPTIONS AND MILESTONES IN THE TABLE ABOVE FOR ALL CMC/OBP NON-REPORTABLE PMCS *FOR WHICH THE FOLLOWING ANSWERS WILL BE IDENTICAL.*USE A SEPARATE TEMPLATE FOR EACH PMR/PMC FOR WHICH THE ANSWERS TO THE FOLLOWING QUESTIONS DIFFER.**
- ***DO NOT USE THIS FORM* IF ANY STUDIES WILL BE REQUIRED UNDER FDAAA OR WILL BE PUBLICALY REPORTABLE**

1. During application review, explain why this issue is appropriate for a PMC instead of a pre-approval requirement. Check reason below and describe.

   - ☐ Need for drug (unmet need/life-threatening condition)
   - ☐ Long-term data needed (e.g., stability data)
   - ☒ Only feasible to conduct post-approval
   - ☐ Improvements to methods
   - ☐ Theoretical concern
   - ☒ Manufacturing process analysis
   - ☐ Other

   This study was requested to confirm that the [redacted] (b) (4) procedure at the newly added drug product manufacturing site is effective. The post-use integrity test results from the process validation lots manufactured at a different site were not highly variable. This suggests tha [redacted] (b) (4)

2. Describe the particular review issue and the goal of the study.

Reference ID: 3856695

(b) (4)

3. [OMIT – for PMRs only]

4. What type of study is agreed upon (describe and check type below)?

   Select only one. Fill out a new sheet for each type of PMR/PMC study.

   - ☐ Dissolution testing
   - ☐ Assay
   - ☐ Sterility
   - ☐ Potency
   - ☐ Product delivery
   - ☐ Drug substance characterization
   - ☐ Intermediates characterization
   - ☐ Impurity characterization
   - ☐ Reformulation
   - ☒ Manufacturing process issues
   - ☐ Other

   Describe the agreed-upon study:

   The sponsor will perform a study to establish th (b) (4)

5. To be completed by ONDQA/OBP Manager:

   - ☒ Does the study meet criteria for PMCs?
   - ☒ Are the objectives clear from the description of the PMC?
   - ☒ Has the applicant adequately justified the choice of schedule milestone dates?
   - ☒ Has the applicant had sufficient time to review the PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

☒ *This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

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(signature line for BLAs only)

Reference ID: 3856695

PMR/PMC Development Template: Product Quality (CMC)

This template should be completed by the review chemist (ONDQA), biologist (OBP), or microbiologist (DMA) and included for *each* type of CMC PMR/PMC in the Action Package. See #4 for a list of CMC PMR/PMC types

NDA/BLA #	125561/0
Product Name:	KANUMA (sebelipase alfa)
PMC 2920-7	Perform a microbial retention study to support the proposed (b) (4) time limit for (b) (4). Limit the validated time for (b) (4) to (b) (4) until the (b) (4) time limit has been approved by the Agency.

PMC Schedule Milestones:	Final Protocol Submission:	
	Study/Trial Completion:	
	Final Report Submission:	01/31/2016
	Other:	

- **ADD MORE AS NEEDED USING THE SAME TABULAR FORMAT FOR EACH PMC.**
- **INCLUDE DESCRIPTIONS AND MILESTONES IN THE TABLE ABOVE FOR ALL CMC/OBP NON-REPORTABLE PMCS *FOR WHICH THE FOLLOWING ANSWERS WILL BE IDENTICAL.*USE A SEPARATE TEMPLATE FOR EACH PMR/PMC FOR WHICH THE ANSWERS TO THE FOLLOWING QUESTIONS DIFFER.**
- ***DO NOT USE THIS FORM* IF ANY STUDIES WILL BE REQUIRED UNDER FDAAA OR WILL BE PUBLICALY REPORTABLE**

1. During application review, explain why this issue is appropriate for a PMC instead of a pre-approval requirement. Check reason below and describe.

   ☐ Need for drug (unmet need/life-threatening condition)
   ☐ Long-term data needed (e.g., stability data)
   ☒ Only feasible to conduct post-approval
   ☐ Improvements to methods
   ☐ Theoretical concern
   ☐ Manufacturing process analysis
   ☐ Other

   The validated time limit for (b) (4) is (b) (4). Section 3.2.P.3.4 of the BLA states that an additional microbial retention study will be performed to validate a (b) (4) time limit for (b) (4). This study is currently in progress.

2. Describe the particular review issue and the goal of the study.

Reference ID: 3856695

The goal of the study is to increase the validated time limit for (b) (4) from (b) (4) to (b) (4).

3. [OMIT – for PMRs only]

4. What type of study is agreed upon (describe and check type below)?

   Select only one. Fill out a new sheet for each type of PMR/PMC study.

   ☐ Dissolution testing
   ☐ Assay
   ☒ Sterility
   ☐ Potency
   ☐ Product delivery
   ☐ Drug substance characterization
   ☐ Intermediates characterization
   ☐ Impurity characterization
   ☐ Reformulation
   ☐ Manufacturing process issues
   ☐ Other

   Describe the agreed-upon study:

   A microbial retention study will be performed to validate a (b) (4) time limit for (b) (4) (b) (4)

5. To be completed by ONDQA/OBP Manager:

   ☒ Does the study meet criteria for PMCs?
   ☒ Are the objectives clear from the description of the PMC?
   ☒ Has the applicant adequately justified the choice of schedule milestone dates?
   ☒ Has the applicant had sufficient time to review the PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

☒ *This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

_____ (signature line for BLAs only)

Reference ID: 3856695

PMR/PMC Development Template: Product Quality (CMC)

This template should be completed by the review chemist (ONDQA), biologist (OBP), or microbiologist (DMA) and included for *each* type of CMC PMR/PMC in the Action Package. See #4 for a list of CMC PMR/PMC types

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NDA/BLA #	125561/0
Product Name:	KANUMA (sebelipase alfa)
PMC 2920-8	Perform a study to confirm that the dye ingress test method used for drug product stability samples is capable of detecting small defects that could allow microbial ingress. The study should be performed with a range of small defect sizes (b) (4) Revise the positive control defect size used for stability testing based on the results of the study and update the BLA file accordingly.

PMC Schedule Milestones:		
	Final Protocol Submission:	
	Study/Trial Completion:	
	Final Report Submission:	01/31/2016
	Other:	

PMC 2920-9	Conduct a study to understand the mechanism of endotoxin masking and/or interference in the drug product. Explore alternative test methods and develop a more suitable *in vitro* test method for the drug product.

PMC Schedule Milestones:		
	Final Protocol Submission:	
	Study/Trial Completion:	04/29/2016
	Final Report Submission:	
	Other:	

- **ADD MORE AS NEEDED USING THE SAME TABULAR FORMAT FOR EACH PMC.**
- **INCLUDE DESCRIPTIONS AND MILESTONES IN THE TABLE ABOVE FOR ALL CMC/OBP NON-REPORTABLE PMCS *FOR WHICH THE FOLLOWING ANSWERS WILL BE IDENTICAL.*USE A SEPARATE TEMPLATE FOR EACH PMR/PMC FOR WHICH THE ANSWERS TO THE FOLLOWING QUESTIONS DIFFER.**
- ***DO NOT USE THIS FORM* IF ANY STUDIES WILL BE REQUIRED UNDER FDAAA OR WILL BE PUBLICALY REPORTABLE**

1. During application review, explain why this issue is appropriate for a PMC instead of a pre-approval requirement. Check reason below and describe.

   ☐ Need for drug (unmet need/life-threatening condition)
   ☐ Long-term data needed (e.g., stability data)
   ☐ Only feasible to conduct post-approval
   ☒ Improvements to methods
   ☐ Theoretical concern
   ☐ Manufacturing process analysis
   ☐ Other

Reference ID: 3856695

2920-8: The container closure integrity (CCI) test was shown to detect defects as small as (b) (4) The parameters used for the CCI test are typical for dye ingress testing, and the method is probably capable of detecting smaller leaks. CCI was demonstrated during process validation, and CCI testing is included in the post-approval stability protocol.

2920-9: The sponsor's interim plan for drug product release testing complies with the regulations. The sponsor will use rabbit pyrogen testing for drug product release until a more suitable *in vitro* assay is developed and validated. Due to issues with the *in vitro* endotoxin test method, every drug product lot manufactured thus far has been subjected to rabbit pyrogen testing. None of the lots failed rabbit pyrogen testing.

2. Describe the particular review issue and the goal of the study.

2920-8: The defective positive control used during method validation was a container prepared with a (b) (4) micron defect. However, current CCI test methods are capable of detecting leaks (b) (4) microns. Use of positive controls with defects (b) (4) microns is standard industry practice for method validation and routine CCI testing. The goal of the study is to confirm that the dye ingress method is capable of detecting leaks (b) (4) microns. The CCI test method will be revised to include a positive control with a (b) (4) micron defect based on the results of the validation study.

2920-9: (b) (4) The goal of the study is to develop and validate a more suitable *in vitro* release test method for bacterial endotoxin which will replace the rabbit pyrogen test.

3. [OMIT – for PMRs only]

4. What type of study is agreed upon (describe and check type below)?

<u>Select only one. Fill out a new sheet for each type of PMR/PMC study.</u>

- ☐ Dissolution testing
- ☒ Assay
- ☐ Sterility
- ☐ Potency
- ☐ Product delivery
- ☐ Drug substance characterization
- ☐ Intermediates characterization
- ☐ Impurity characterization
- ☐ Reformulation
- ☐ Manufacturing process issues
- ☐ Other

Reference ID: 3856695

Describe the agreed-upon study:

2920-8: The sponsor will perform an additional method validation study for the dye ingress test. Defective units with a range of small defect sizes (b) (4) will be subjected to the assay conditions and then checked for dye ingress.

2920-9: The sponsor will perform endotoxin (b) (4) studies and (b) (4) studies with alternative and/or (b) (4) *in vitro* (b) (4) test methods.

5. To be completed by ONDQA/OBP Manager:

☒ Does the study meet criteria for PMCs?
☒ Are the objectives clear from the description of the PMC?
☒ Has the applicant adequately justified the choice of schedule milestone dates?
☒ Has the applicant had sufficient time to review the PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

☒ *This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

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(signature line for BLAs only)

Reference ID: 3856695

PMR/PMC Development Template: Product Quality (CMC)

This template should be completed by the review chemist (ONDQA) or biologist (OBP) and included for *each* type of CMC PMR/PMC in the Action Package. See #4 for a list of CMC PMR/PMC types

BLA # 125561
Product Name: Kanuma

PMC 2920-21 Description: Conduct worst-case simulated or worst-case real world shipping studies for both the drug substance and the drug product to assess the potential impact of shipping conditions on product quality.

PMC Schedule Milestones:

Final Protocol Submission:	
Study/Trial Completion:	
Final Report Submission:	10/31/2016
Other:	

PMC 2920-13 Description: Conduct a study to improve the formulation to reduce or eliminate the potential for formation of visible proteinaceous particles and other insoluble protein aggregates. If a significantly improved formulation is identified, develop the improved formulation for the commercial product.

PMC Schedule Milestones:

Final Protocol Submission:	
Study/Trial Completion:	
Final Report Submission:	02/29/2016
Other:	

1. During application review, explain why this issue is appropriate for a PMC instead of a pre-approval requirement. Check reason below and describe.

   - ☒ Need for drug (unmet need/life-threatening condition)
   - ☐ Long-term data needed (e.g., stability data)
   - ☒ Only feasible to conduct post-approval
   - ☐ Improvements to methods
   - ☐ Theoretical concern
   - ☒ Manufacturing process analysis
   - ☐ Other

Reference ID: 3856695

Upon approval, Kanuma (sebelipase alfa) will be the only available therapy for patients with Lysosomal Acid Lipase Deficiency (LAL-D), which is a rare, serious, life-threatening lysosomal storage disease. Kanuma drug substance and final drug product were developed under an abbreviated schedule because of Kanuma was granted with a breakthrough therapy status. Data from characterization studies indicate sebelipase alfa in its current formulation, is prone to form aggregates. (b) (4) Although formation of aggregates is a safety concern, the risk is mitigated due to the requirement of an in-line filter during administration. The issue is therefore not a pre-approval requirement. However, a better formulation that minimizes aggregate formation is beneficial from both safety and efficacy perspectives.

2. Describe the particular review issue and the goal of the study.

The study of aggregates formation under real life shipping conditions will provide a more realistic evaluation of promotion of aggregates formation during commercial shipping of Kanuma drug substance and drug product. (b) (4) The formulation study will provide additional evidence to guide future improvements to the stability of the product.

3. [OMIT – for PMRs only]

4. What type of study is agreed upon (describe and check type below)?

Select only one. Fill out a new sheet for each type of PMR/PMC study.

- ☐ Dissolution testing
- ☐ Assay
- ☐ Sterility
- ☐ Potency
- ☐ Product delivery
- ☐ Drug substance characterization
- ☐ Intermediates characterization
- ☐ Impurity characterization
- ☐ Reformulation
- ☒ Manufacturing process issues
- ☐ Other

Describe the agreed-upon study:

(b) (4)

5. To be completed by ONDQA/OBP Manager:

- ☒ Does the study meet criteria for PMCs? Yes
- ☒ Are the objectives clear from the description of the PMC? Yes

Reference ID: 3856695

☒ Has the applicant adequately justified the choice of schedule milestone dates? Yes
☒ Has the applicant had sufficient time to review the PMCs, ask questions, determine feasibility, and contribute to the development process? Yes

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PMR/PMC Development Coordinator:

☒ *This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

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(signature line for BLAs only)

Reference ID: 3856695

PMR/PMC Development Template: Product Quality (CMC)

This template should be completed by the review chemist (ONDQA) or biologist (OBP) and included for *each* type of CMC PMR/PMC in the Action Package. See #4 for a list of CMC PMR/PMC types

BLA # 125561
Product Name: Kanuma

PMC 2920-12 Description: To improve control of the N-linked glycan profile, identify for the current HPAEC-PAD method peaks representative of [redacted] (b) (4) and establish drug substance release specifications for the critical peaks or groups of peaks. Alternatively, develop an alternative method with better resolution to control the glycan profile, such as (but not limited to) the [redacted] (b) (4) characterization tests.

PMC Schedule Milestones:

Final Protocol Submission:	
Study/Trial Completion:	
Final Report Submission:	04/30/2017
Other:	

1. During application review, explain why this issue is appropriate for a PMC instead of a pre-approval requirement. Check reason below and describe.

   - ☒ Need for drug (unmet need/life-threatening condition)
   - ☐ Long-term data needed (e.g., stability data)
   - ☒ Only feasible to conduct post-approval
   - ☐ Improvements to methods
   - ☐ Theoretical concern
   - ☒ Manufacturing process analysis
   - ☐ Other

   Upon approval, Kanuma (sebelipase alfa) will be the only available therapy for patients with Lysosomal Acid Lipase Deficiency (LAL-D), which is a rare, serious, life-threatening lysosomal storage disease. Kanuma drug substance and final drug product were developed under an abbreviated schedule because Kanuma was granted breakthrough therapy status. Currently, the sponsor has an assay in place to measure critical glycans that affect product potency. However, the assay doesn't provide sensitive and comprehensive quantitation of these glycans. Because data from clinical lots have demonstrated the current assay provides a range within which the product tends to remain potent, the issue is not a pre-approval requirement. However, a better assay for the critical glycans will greatly enhance the manufacturer's ability to maintain product consistency throughout post-licensure product management.

2. Describe the particular review issue and the goal of the study.

Reference ID: 3856695

(b) (4)

The goal of the study is to develop a more comprehensive and quantitative method or methods to control the overall glycan profile (b) (4)

(b) (4)

3. [OMIT – for PMRs only]

4. What type of study is agreed upon (describe and check type below)?

   Select only one. Fill out a new sheet for each type of PMR/PMC study.

   ☐ Dissolution testing
   ☒ Assay
   ☐ Sterility
   ☐ Potency
   ☐ Product delivery
   ☐ Drug substance characterization
   ☐ Intermediates characterization
   ☐ Impurity characterization
   ☐ Reformulation
   ☐ Manufacturing process issues
   ☐ Other

   Describe the agreed-upon study:

   1. To improve the current HPAEC-PAD method for better glycan quantitation or profiling.
   2. Or, to develop new methods to better characterize the glycans.

5. To be completed by ONDQA/OBP Manager:

   ☒ Does the study meet criteria for PMCs? Yes
   ☒ Are the objectives clear from the description of the PMC? Yes
   ☒ Has the applicant adequately justified the choice of schedule milestone dates? Yes
   ☒ Has the applicant had sufficient time to review the PMCs, ask questions, determine feasibility, and contribute to the development process? Yes

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PMR/PMC Development Coordinator:

☒ *This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

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(signature line for BLAs only)

Reference ID: 3856695

PMR/PMC Development Template: Product Quality (CMC)

This template should be completed by the review chemist (ONDQA) or biologist (OBP) and included for *each* type of CMC PMR/PMC in the Action Package. See #4 for a list of CMC PMR/PMC types

BLA # 125561
Product Name: Kanuma

PMC 2920-14 Description: Develop and implement an improved SDS-PAGE test or another purity test to quantitate high molecular weight product-related species with greater sensitivity and precision than the current SDS-PAGE test.

PMC Schedule Milestones:

Final Protocol Submission:	
Study/Trial Completion:	
Final Report Submission:	01/31/2017
Other:	

PMC 2920-22 Description: Characterize the potential of rhLAL to form oxidized variants and deamidated variants and determine whether variants identified are stability-indicating. Implement changes to the drug substance and drug product control strategies as warranted by the data.

PMC Schedule Milestones:

Final Protocol Submission:	
Study/Trial Completion:	
Final Report Submission:	07/31/2016
Other:	

PMC 2920-10 Description: Characterize the potential levels of [redacted] (b) (4) in the drug substance.

PMC Schedule Milestones:

Final Protocol Submission:	
Study/Trial Completion:	
Final Report Submission:	03/31/2016
Other:	

PMC 2920-11 Description: Develop and implement a drug substance release test to quantify the percent compositions of the N-terminal variants.

PMC Schedule Milestones:

Final Protocol Submission:	
Study/Trial Completion:	
Final Report Submission:	01/31/2017
Other:	

Reference ID: 3856695

1. During application review, explain why this issue is appropriate for a PMC instead of a pre-approval requirement. Check reason below and describe.

   ☒ Need for drug (unmet need/life-threatening condition)
   ☐ Long-term data needed (e.g., stability data)
   ☐ Only feasible to conduct post-approval
   ☒ Improvements to methods
   ☐ Theoretical concern
   ☒ Manufacturing process analysis
   ☐ Other

Upon approval, Kanuma (sebelipase alfa) will be the only available therapy for patients with Lysosomal Acid Lipase Deficiency (LAL-D), which is a rare, serious, life-threatening lysosomal storage disease. Kanuma drug substance, and final drug product was developed under an abbreviated schedule because of Kanuma was granted with a breakthrough therapy status. Because of the rapid product and process development, the application lacks sensitive tests for some product variants, product-related and process-related impurities. Our review of clinical and commercial Kanuma drug substance and drug product lots concluded that the currently approved impurity assays are capable of control for the major impurities to ensure safety. The issues identified above are therefore not pre-approval requirement. They are aimed at providing better control in post-licensure product management to ensure product consistency and safety.

2. Describe the particular review issue and the goal of the study.

(b) (4) [redacted] However, these impurities should be fully characterized and monitored to ensure process and product consistency. The goal of these PMCs is to provide sensitive and more comprehensive means to measure these impurities to maintain product consistency and to further ensure safety in post-marketing product management.

3. [OMIT – for PMRs only]

4. What type of study is agreed upon (describe and check type below)?

   Select only one. Fill out a new sheet for each type of PMR/PMC study.

   ☐ Dissolution testing
   ☐ Assay
   ☐ Sterility
   ☐ Potency
   ☐ Product delivery
   ☐ Drug substance characterization
   ☐ Intermediates characterization
   ☒ Impurity characterization
   ☐ Reformulation
   ☐ Manufacturing process issues

Reference ID: 3856695

☐ Other

Describe the agreed-upon study:

1. A more sensitive assay to control for [redacted] (b) (4)
2. Characterizing and developing additional controls for the presence of [redacted] (b) (4)

5. To be completed by ONDQA/OBP Manager:

☒ Does the study meet criteria for PMCs? Yes
☒ Are the objectives clear from the description of the PMC? Yes
☒ Has the applicant adequately justified the choice of schedule milestone dates? Yes
☒ Has the applicant had sufficient time to review the PMCs, ask questions, determine feasibility, and contribute to the development process? Yes

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PMR/PMC Development Coordinator:

☒ *This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

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(signature line for BLAs only)

Reference ID: 3856695

PMR/PMC Development Template: Product Quality (CMC)

This template should be completed by the review chemist (ONDQA) or biologist (OBP) and included for *each* type of CMC PMR/PMC in the Action Package. See #4 for a list of CMC PMR/PMC types

BLA # 125561
Product Name: Kanuma

PMC 2920-15 Description: Implement the [redacted] (b) (4) test method for drug product release specifications

PMC Schedule Milestones:

Final Protocol Submission:	
Study/Trial Completion:	
Final Report Submission:	04/30/2016
Other:	

PMC 2920-16 Description: Implement an assay for uptake of sebelipase alfa into [redacted] (b) (4) for drug product release specifications.

PMC Schedule Milestones:

Final Protocol Submission:	
Study/Trial Completion:	
Final Report Submission:	06/30/2016
Other:	

PMC 2920-17 Description: Develop and implement a [redacted] (b) (4) receptor binding assay for drug product release specifications.

PMC Schedule Milestones:

Final Protocol Submission:	
Study/Trial Completion:	
Final Report Submission:	01/31/2017
Other:	

PMC 2920-19 Description: Improve the enzyme activity assay to increase the range of sebelipase alfa dilutions over which the assay will yield consistent values for specific activity.

PMC Schedule Milestones:

Final Protocol Submission:	
Study/Trial Completion:	
Final Report Submission:	01/31/2016
Other:	

1. During application review, explain why this issue is appropriate for a PMC instead of a pre-approval requirement. Check reason below and describe.

Reference ID: 3856695

☒ Need for drug (unmet need/life-threatening condition)
☐ Long-term data needed (e.g., stability data)
☐ Only feasible to conduct post-approval
☒ Improvements to methods
☐ Theoretical concern
☒ Manufacturing process analysis
☐ Other

Upon approval, Kanuma (sebelipase alfa) will be the only available therapy for patients with Lysosomal Acid Lipase Deficiency (LAL-D), which is a rare, serious, life-threatening lysosomal storage disease. Kanuma drug substance and final drug product were developed under an abbreviated schedule because of Kanuma was granted breakthrough therapy status. Because of the rapid product and process development, the enzyme activity assay and (b) (4) content assays, while providing reasonable control for the potency of the product and ensuring efficacy, may not be sufficiently precise or sensitive at the time of approval of Kanuma license application to monitor product quality changes throughout the lifecycle of the product. Additionally, the application lacks several other assays to control for attributes that may be relevant to the mechanism of action of the product. Because our review of clinical and commercial Kanuma drug substance and drug product lots concluded that the currently approved assays are capable of control for the majority of critical quality attributes to ensure safety and efficacy, the issues identified above are not pre-approval requirements. These PMCs are aimed at providing better control in post-licensure product management to ensure product consistency.

2. Describe the particular review issue and the goal of the study.

(b) (4)

Control of sebelipase alfa enzyme activity and of affinity to these receptors is critical to ensure clinical efficacy. (b) (4) . Additionally, the tests for (b) (4) and (b) (4) content serve only as surrogates for receptor binding. The goals of these PMCs are 1) to expand the range of enzyme concentrations over which the current enzyme activity assay performs to enhance consistency of the results, 2) to measure enzyme activity with a more sensitive enzyme kinetic assay (b) (4) to better evaluate enzymatic activity, and 3) to directly measure the affinity of the enzyme molecule to its target receptors and the resulting efficiency of cellular uptake. The completion of the PMCs will provide methods to enable more comprehensive evaluation of the attributes most relevant to the mechanism of action in post-licensure product management.

3. [OMIT – for PMRs only]

4. What type of study is agreed upon (describe and check type below)?

Select only one. Fill out a new sheet for each type of PMR/PMC study.

☐ Dissolution testing
☐ Assay
☐ Sterility
☒ Potency
☐ Product delivery
☐ Drug substance characterization

Reference ID: 3856695

☐ Intermediates characterization
☐ Impurity characterization
☐ Reformulation
☐ Manufacturing process issues
☐ Other

Describe the agreed-upon study:

1. Implement an enzyme kinetic study (b) (4)
2. Directly measure uptake of the enzyme by a relevant cell line in cell culture
3. Directly measure binding affinity of the enzyme to its receptor using an *in vitro* method
4. Expand the range of concentrations over which the current enzyme activity assay is accurate

5. To be completed by ONDQA/OBP Manager:

☒ Does the study meet criteria for PMCs? Yes.
☒ Are the objectives clear from the description of the PMC? Yes.
☒ Has the applicant adequately justified the choice of schedule milestone dates? Yes.
☒ Has the applicant had sufficient time to review the PMCs, ask questions, determine feasibility, and contribute to the development process? Yes.

PMR/PMC Development Coordinator:

☒ *This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

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(signature line for BLAs only)

Reference ID: 3856695

PMR/PMC Development Template: Product Quality (CMC)

This template should be completed by the review chemist (ONDQA) or biologist (OBP) and included for *each* type of CMC PMR/PMC in the Action Package. See #4 for a list of CMC PMR/PMC types

BLA # 125561
Product Name: Kanuma

PMC 2920-18 Description: Conduct studies to determine whether the [redacted] (b) (4) receptor binding assays are stability-indicating. Implement the stability-indicating assays into the drug product stability specifications with acceptance criteria supported by stability data.

PMC Schedule Milestones:

Final Protocol Submission:	
Study/Trial Completion:	
Final Report Submission:	01/31/2018
Other:	

PMC 2920-20 Description: Evaluate and revise as warranted all release and stability specifications after manufacture of sufficient commercial batches for meaningful statistical analyses.

PMC Schedule Milestones:

Final Protocol Submission:	
Study/Trial Completion:	
Final Report Submission:	12/31/2016
Other:	

1. During application review, explain why this issue is appropriate for a PMC instead of a pre-approval requirement. Check reason below and describe.

   ☒ Need for drug (unmet need/life-threatening condition)
   ☒ Long-term data needed (e.g., stability data)
   ☒ Only feasible to conduct post-approval
   ☐ Improvements to methods
   ☐ Theoretical concern
   ☐ Manufacturing process analysis
   ☐ Other

Reference ID: 3856695

Upon approval, Kanuma (sebelipase alfa) will be the only available therapy for patients with Lysosomal Acid Lipase Deficiency (LAL-D), which is a rare, serious, life-threatening lysosomal storage disease. Kanuma drug substance and final drug product were developed under an abbreviated schedule because Kanuma was granted breakthrough therapy status. Because of the rapid product and process development, the current assays, although sufficient to support approval of the product, are inadequate to provide comprehensive product evaluation for lifecycle management. As a result, the sponsor committed to develop and potentially implement more assays post-approval. To evaluate if these assays should be included in release and stability testing and to establish appropriate acceptance criteria, the sponsor will need to collect data from a large data set.

2. Describe the particular review issue and the goal of the study.

To collect a statistically meaningful dataset from long term stability data and lot release data to establish new or refine current acceptance criteria for release and stability specifications.

3. [OMIT – for PMRs only]

4. What type of study is agreed upon (describe and check type below)?

Select only one. Fill out a new sheet for each type of PMR/PMC study.

☐ Dissolution testing
☐ Assay
☐ Sterility
☐ Potency
☐ Product delivery
☐ Drug substance characterization
☐ Intermediates characterization
☐ Impurity characterization
☐ Reformulation
☐ Manufacturing process issues
☒ Other: Refine release and stability specification

Describe the agreed-upon study:

Data collection and statistical analysis of release and stability data

5. To be completed by ONDQA/OBP Manager:

☒ Does the study meet criteria for PMCs? Yes
☒ Are the objectives clear from the description of the PMC? Yes
☒ Has the applicant adequately justified the choice of schedule milestone dates? Yes

Reference ID: 3856695

☒ Has the applicant had sufficient time to review the PMCs, ask questions, determine feasibility, and contribute to the development process? Yes

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PMR/PMC Development Coordinator:

☒ *This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

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(signature line for BLAs only)

Reference ID: 3856695

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/s/

JESSICA J LEE
12/07/2015

Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research

Office of Biotechnology Products
Division of
Division of Biotechnology Review and Research III
FDA, White Oak Campus

Immunogenicity Addendum

Date: 10/6/2015

To: File: IND 108460/BLA 125561, Kanuma (Sebelipase Alfa /SBC-102)

From: Joao A. Pedras-Vasconcelos, Ph.D.
Susan Kirshner, PhD, Review Chief
Division of Biotechnology Review and Research III (DBRR III)
Office of Biotechnology Products
CDER/FDA

Subject: Amendment 90 immunogenicity update for Sebelipase-alfa (SBC-102).

Product: Kanuma (Sebelipase alfa) is a recombinant human lysosomal acid lipase (rhLAL) expressed in transgenic chicken eggs.

Indication:

- Enzyme replacement Therapy for lysosomal storage diseases caused by LAL deficiency (Wolman Disease and Cholesteryl Ester Storage Disease)

Sponsor: Synageva Biopharma Corp.
111 River Bend Road, Athens GA 30605

Summary:

The validation reports provided to the BLA indicate that the binding assay and the in vitro and cell-based neutralizing antibody assays are suitable to monitor immunogenicity to Kanuma (Sebelipase-alfa/SBC-102) during enzyme replacement therapy for LAL deficiency (Wolman Disease and Cholesteryl Ester Storage Disease) .

Submission:

Sebelipase alfa (SBC-102) is a recombinant human lysosomal acid lipase (rhLAL) that catalyzes the lysosomal hydrolysis of cholesteryl esters and triglycerides to free cholesterol, glycerol and free fatty acids. It is developed for the treatment of Wolman Disease and Cholesteryl Ester Storage Disease (CSED). The sponsor submitted BLA 125561 for Kanuma (Sebelipase alfa) on 01/08/15 with a PDUFA date of 08/08/15. Due

to unresolved facilities issues, the BLA was granted a three month extension and the PDUFA date delayed till 11/8/2015.

The immunogenicity memo was completed and archived under DARTS during the initial review cycle. However, there remained an outstanding information request regarding cut point analysis of CSED patient pre-study sera for the two neutralizing antibody assays- the enzymatic activity and the cell based neutralizing antibody assay. The sponsor needed to submit data after approval, but given the clock extension, the sponsor submitted the immunogenicity update to the BLA file under Amendment 90 (10/5/2015).

Based on normal donor sera, the current cut point for the enzymatic activity neutralizing antibody assay method (8291-329) is (b) (4)%. The sponsor used patient sera from the LAL-CL02 study, to calculate the cut point using pre-study samples. The updated analysis resulted in a cut point of (b) (4)% (8291-329 addendum 1). Similarly based on normal donor sera, the current cut point for the cell based neutralizing antibody assay method (8298-036) is (b) (4)%. Using patient sera from the LAL-CL02 study, the updated analysis resulted in a cut point of (b) (4)% (8298-036 addendum 1).
In both the enzyme activity neutralizing assay and the cell-based neutralizing antibody assay, using sera from patient donors resulted in cut points that were higher than those from normal sera. In the enzyme activity assay, the cut point was statistically different for patient sera vs. normal sera (p=0.035). Given that the cut point is greater in patient sera compared to normal donor sera, the sponsor proposes to continue to use the original, more conservative, cut point for each of the two neutralizing antibody assays, to determine neutralizing antibody status in patients. Thus no sample reanalysis will be required.

Reviewer's comment: *Although the cut points changed using the CSED patient population, it would likely lead to fewer patients being considered NAb+ because the patient cut points are higher for the two assays. By choosing to maintain the lower cut points derived from normal donor sera, the sponsor will keep current NAb positive rates and avoids having to retest the confirmed ADA+ samples. This is acceptable as it is the more conservative approach and does not lead to increased risk to patient safety.*

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

/s/

JOAO A PEDRAS VASCONCEL
10/16/2015
Immunogencitity addendum to primary immunogenicity review-No further action required

SUSAN L KIRSHNER
10/19/2015

Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Biotechnology Products

FINAL LABEL AND LABELING REVIEW

Date: August 12 2015

Reviewer: Jibril Abdus-Samad, PharmD, Labeling Reviewer
Office of Biotechnology Products

Jibril Abdus-samad -S
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Date 2015 08 12 11 54 34 04'00'

Through: Arulvathani Arudchandran, PhD, Quality Reviewer
Division of Biotechnology Review and Research II

Arulvanthani P. Arudchandran -A
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Date: 2015.08.12 12:10:11 -04'00'

Application: BLA 125561/0

Product: Kanuma™ (sebelipase alfa)

Applicant: Alexion Pharmaceuticals Inc.

Submission Dates: November 21 2014; June 19, 22; July 14, 29; and August 8, 11 2015

Executive Summary:

The container labels and carton labeling for Kanuma™ (sebelipase alfa) were reviewed and found to comply with the following regulations: 21 CFR 610.60 through 21 CFR 610.67; 21 CFR 201.2 through 21 CFR 201.25; 21 CFR 201.50 through 21 CFR 201.57, 21 CFR 201.100 and United States Pharmacopeia (USP), USP 38/NF 33 [August 1 2015 to November 30 2015]. Labeling deficiencies were identified, mitigated, and resolved. The container label and carton labeling submitted on August 11 2015 are acceptable.

Background and Summary Description:

The Applicant submitted BLA 125561 Kanuma (sebelipase alfa) on January 8, 2015. Table 1 lists the proposed product characteristics of Kanuma (sebelipase alfa).

Table 1: Proposed Characteristics of Kanuma (sebelipase alfa)

Trade Name	Kanuma
Proper Name	sebelipase alfa
Indication	[redacted] (b) (4) for patients with Lysosomal Acid Lipase (LAL) Deficiency.
Dose	Infants up to 6 months: 1 mg/kg administered once weekly as an intravenous infusion as an initial dose followed by escalation to 3 mg/kg once weekly Pediatrics and Adults: 1 mg/kg administered once every other week as an intravenous infusion.
Route of Administration	Intravenous Infusion
Dosage Form	Injection
Strength and Container-closure	20 mg/10 mL in single-use vials
Storage and Handling	Store in a refrigerator at 36° to 46° F (2°C to 8°C). Do not freeze. Do not shake. Store in the outer carton in order to protect from light.

Materials Reviewed:
Prescribing Information
Container Label
Carton Labeling

(b) (4)

Subpart G-Labeling Standards
Subpart A-General Labeling Provisions

I. Container

A. 21 CFR 610.60 Container Label

(a) Full label. The following items shall appear on the label affixed to each container of a product capable of bearing a full label:

(1) The proper name of the product; [see 21 CFR 600.3 (k) and section 351 of the PHS Act]; *conforms*.

(2) The name, address, and license number of manufacturer; does not conform.

OBP Request: Your 365h form identifies (b) (4) as the Applicant/Licensee of your proposed product Kanuma (sebelipase alfa).

Therefore, [redacted] (b) (4) is considered the manufacturer for purposes of fulfilling 21 CFR 600.3(t), 21 CFR 610.60 (a)(2), and 21 CFR 610.61. This information should appear on the carton labeling as follows:

"Manufactured by:" or "Manufacturer:"
[redacted] (b) (4)

Applicant revised as requested.

Subsequent to a change in Applicant from [redacted] (b) (4) to Alexion submitted on June 23, 2015, the Applicant revised the manufacturing information appropriately to:

Manufactured by:
Alexion Pharmaceuticals, Inc.
Chesire, CT 06410 USA
U.S. License Number 1743

Applicant revised as requested.

(3) The lot number or other lot identification; *conforms*.

(4) The expiration date; *conforms*.

(5) The recommended individual dose, for multiple dose containers. *conforms*.

(6) The statement: "'Rx only'" for prescription biologicals. *conforms*.

(7) If a Medication Guide is required under part 208 of the chapter, the statement required under §208.24(d) of this chapter instructing the authorized dispenser to provide a Medication Guide to each patient to whom the drug is dispensed and stating how the Medication Guide is provided, except where the container label is too small, the required statement may be placed on the package label. *Not applicable*.

(b) Package label information. If the container is not enclosed in a package, all the items required for a package label shall appear on the container label. *Not applicable*.

(c) Partial label. If the container is capable of bearing only a partial label, the container shall show as a minimum the name (expressed either as the proper or common name), the lot number or other lot identification and the name of the manufacturer; in addition, for multiple dose containers, the recommended individual dose. Containers bearing partial labels shall be placed in a package which bears all the items required for a package label. *Not applicable*.

(d) No container label. If the container is incapable of bearing any label, the items required for a container label may be omitted, provided the container is placed in a package which bears all the items required for a package label. *Not applicable*.

(e) Visual inspection. When the label has been affixed to the container, a sufficient area of the container shall remain uncovered for its full length or circumference to permit inspection of the contents.

OBP Request: Indicate how the label is affixed to the vial and where the visual area of inspection is located per 21 CFR 610.60(e).
Applicant confirmed. Acceptable.

B. 21 CFR 201.2 Drugs and devices; National Drug Code numbers – The National Drug Code (NDC) number is located at the top of the label. [See 21 CFR 207.35]; *conforms*.

C. 21 CFR 201.5 Drugs; adequate directions for use; *conforms*.

D. 21 CFR 201.6 Drugs; misleading statements; *conforms*.

E. 21 CFR 201.10 Drugs; statement of ingredients; [Placement and prominence] does not conform.

OBP Request: Ensure the font size of the proper name “sebelipase alfa” is at least half the size of the proprietary name and has prominence commensurate as per 21 CFR 201.10.
Applicant revised as requested.

F. 21 CFR 201.15 Drugs; prominence of required label statements; does not conform.

OBP Requests:
Decrease the size of the multi-color graphic to the right of "Tradename" to provide more space on the label to allow for increased prominence of critical information on the PDP.
Applicant revised as requested.

Revise the font of color and style of the dosage form "Injection" to match the proper name "sebelipase alfa".
Applicant revised as requested.

Revise the strength statement so that the strength per total volume statement is more prominent than the strength per milliliter statement.

For example, change from: 20 mg/10 mL (2 mg/mL)

to: **20 mg/10 mL** (2 mg/mL)
Applicant revised as requested.

Delete [redacted] (b) (4) from the route of administration statement [redacted] (b) (4) to appear as "For Intravenous Infusion Only".
Applicant revised as requested.

Revise the statement "[redacted] (b) (4)" to read "Dilute Before Use". Additionally, revise "Dilute Before Use" to the same font and font size as "For Intravenous Infusion Only". The increased prominence of this statement emphasizes the need for dilution..
Applicant revised as requested.

Relocate Rx Only statement to the top right-side of the PDP.
Applicant revised as requested.

G. 21 CFR 201.17 Drugs; location of expiration date; *conforms*.

H. 21 CFR 201.25 Bar code; *conforms*.

I. 21 CFR 201.50 Statement of identity; *conforms*.

J. 21 CFR 201.51 Declaration of net quantity of contents; *conforms*.

K. 21 CFR 201.55 Statement of dosage; *conforms*.

L. 21 CFR 201.100 Prescription drugs for human use; *conforms*. *The list of ingredients appears on the carton labeling.*

(b) (4)

[redacted]

(b) (4)

II. Carton

A. 21 CFR 610.61 Package Label:

a) The proper name of the product; [see 21 CFR 600.3 (k) and section 351 of the PHS Act] *conforms*.

b) The name, addresses, and license number of manufacturer;
does not conform.

OBP Request: Your 365h form identifies [redacted] (b) (4) as the Applicant/Licensee of your proposed product Kanuma (sebelipase alfa). Therefore, [redacted] (b) (4). is considered the manufacturer for purposes of fulfilling 21 CFR 600.3(t), 21 CFR 610.60 (a)(2), and 21 CFR 610.61. This information should appear on the carton labeling as follows: “Manufactured by:” or “Manufacturer:” [redacted] (b) (4)

Subsequent to a change in Applicant from [redacted] (b) (4) to Alexion submitted on June 23, 2015, the Applicant revised the manufacturing information appropriately to:

Manufactured by:
Alexion Pharmaceuticals, Inc.
Chesire, CT 06410 USA
U.S. License Number 1743

Applicant revised as requested.

c) The lot number or other lot identification; *conforms*.

d) The expiration date; *conforms*.

e) The preservative used and its concentration, if no preservative is used and the absence of a preservative is a safety factor, the words “no preservative”; *conforms*.

f) The number of containers, if more than one; *not applicable*.

g) The amount of product in the container expressed as (1) the number of doses, (2) the volume, (3) units of potency, (4) weight, (5) equivalent volume (for dried product to be reconstituted), or (6) such combination of the foregoing as needed for an accurate description of the contents, whichever is applicable; *conforms*.

h) The recommended storage temperature; *conforms*.

i) The words “Do not Freeze” or the equivalent, as well as other instructions, when indicated by the character of the product; *conforms*. However, OBP recommends light protection statement to appear with storage information.

OBP Request: Combine the temperature storage and the light protection statements to appear as “Store in a refrigerator at at 2°C to 8°C (36°F to 46°F) in original carton to protect from light.”
Applicant revised as requested.

j) The recommended individual dose if the enclosed container(s) is a multiple-dose container; *not applicable.*

k) The route of administration recommended, or reference to such directions in and enclosed circular; does not conform.

OBP Requests:
Delete “[redacted] (b) (4) from the route of administration statement [redacted] (b) (4) ” to appear as “For Intravenous Infusion Only”.
Applicant revised as requested.

Revise the statement [redacted] (b) (4) to read “Dilute Before Use”. Additionally, revise “Dilute Before Use” to the same font and font size as “For Intravenous Infusion Only". The increased prominence of this statement emphasizes the need for dilution.
Applicant revised as requested.

l) Known sensitizing substances, or reference to enclosed circular containing appropriate information; *not applicable*.

m) The type and calculated amount of antibiotics added during manufacture; *not applicable*.

n) The inactive ingredients when a safety factor, or reference to enclosed circular containing appropriate information; *not applicable*

o) The adjuvant, if present; *not applicable*

p) The source of the product when a factor in safe administration; does not conform.

OBP Request: Add the following statement to the side panel of the carton labeling above the list of ingredients to comply with 21 CFR 610.61(p).

Produced in genetically engineered chicken egg whites using recombinant DNA technology.

Applicant revised as requested.

q) The identity of each microorganism used in manufacture, and, where applicable, the production medium and the method of inactivation, or reference to an enclosed circular containing appropriate information; *not applicable*.

r) Minimum potency of product expressed in terms of official standard of potency or, if potency is a factor and no U.S. standard of potency has been prescribed, the words "No U.S. standard of potency"; *conforms*.

s) The statement "Rx only" for prescription biologicals; *conforms*.

- Note: If product has a medication guide, a statement is required on the package label if it is not on the container label (see above). It is recommended on both labels. *Not applicable*.

B. 21 CFR 610.62 Proper name; package label; legible type Note: Per 21 CFR 601.2(c)(1), certain regulation including 21 CFR 610.62 do not apply to the four categories of "specified" biological products listed in 21 CFR 601.2(a)]. *Kanuma (sebelipase) is a therapeutic recombinant DNA-derived product obtained from genetically engineered hens, therefore considered as a specified biological product*

C. 21 CFR 610.63 Divided manufacturing responsibility to be shown; *not applicable*.

D. 21 CFR 610.64 Name and address of distributor:

The name and address of the distributor of a product may appear on the label provided that the name, address, and license number of the manufacturer also appears on the label and the name of the distributor is qualified by one of the following phrases: "Manufactured for _____". "Distributed by _____", "Manufactured by _____ for _____", "Manufactured for _____ by _____", "Distributor: _____", or 'Marketed by _____". The qualifying phrases may be abbreviated; *not applicable*.

E. 21 CFR 610.67 Bar code label requirements: Biological products must comply with the bar code requirements at §201.25 of this chapter; *conforms*.

F. 21 CFR 201.2 Drugs and devices; National Drug Code numbers – The National Drug Code (NDC) number is located on top of the label [See 21 CFR 207.35] ; *conforms*.

G. 21 CFR 201.5 Drugs; adequate directions for use; *conforms*.
However within the PI section (b) (4) Preparation, we clarified the preparation instructions by emphasizing "mix by inversion" and "do not shake".

H. 21 CFR 201.6 Drugs; misleading statements; *conforms*.

I. 21 CFR 201.10 Drugs; statement of ingredients [Placement and Prominence]; does not conform.

OBP Request: Ensure the font size of the proper name "sebelipase alfa" is at least half the size of the proprietary name and has prominence commensurate as per 21 CFR 201.10.
Applicant revised as requested.

J. 21 CFR 201.15 Drugs; prominence of required label statements; does not conform.

OBP Requests:
Decrease the size of the multi-color graphic to the right of "Tradename" to provide more space on the label to allow for increased prominence of critical information on the PDP.
Applicant revised as requested.

Include the finished dosage form "Injection" on the line below the proper name in the same font of color and style as the proper name "sebelipase alfa". The finished dosage form is critical information that should be displayed prominently along with the route of administration and dilution instructions. For CDER-regulated biological products, the finished dosage form should appear below the proper name.[1]
Applicant revised as requested.

Revise the strength statement so that the strength per total volume statement is more prominent than the strength per milliliter statement.
Applicant revised as requested.

Revise the statement [redacted] (b) (4) " to read "Dilute Before Use".
Applicant revised as requested.

Relocate Rx Only statement to the top right-side of the PDP.
Applicant revised as requested.

If there is space, relocate the single use only and discard statements from the side panel to the PDP.
Applicant revised as requested.

The critical information on the PDP should appear as:

Kanuma
(sebelipase alfa)
Injection

20 mg/10 mL
(2 mg/mL)

For Intravenous Infusion
Dilute Before Use
Single-Use Only. Discard Unused Portion

The top panel should appear as:

[1] See Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors. 2013 Apr [cited 2014 Jun 12]. Available from: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM349009.pdf. "For biological products, the proper name for biological products should not include the finished dosage form. The finished dosage form can appear on the line below the proper name."

Kanuma
(sebelipase alfa)
Injection

20 mg/10 mL (2 mg/mL)

For Intravenous Infusion
Dilute Before Use
Applicant revised as requested.

K. 21 CFR 201.17 Drugs; location of expiration date; *conforms*.

L. 21 CFR 201.25 Bar code label requirements; *conforms*.

M. 21 CFR 201.50 Statement of identity; *conforms*.

N. 21 CFR 201.51 Declaration of net quantity of contents; *conforms*.

O. 21 CFR 201.55 Statement of dosage; *conforms*.

P. 21 CFR 201.100 Prescription drugs for human use; does not conform. The quantity of ingredients requires clarification and

OBP Requests:
Revise the statement of ingredients to be expressed as each mL to be consistent with your Prescribing Information section 11 - DESCRIPTION. Additionally, revise the statement of ingredients to comply with USP General Chapters: <1091> Labeling of Inactive Ingredients, by listing the names of the inactive ingredients in alphabetical order in the following format: inactive ingredient (amount). For example:

Each mL contains sebelipase alfa 2 mg, citric acid monohydrate (x mg), Human Serum Albumin (x mg), and trisodium citrate dihydrate (x mg)

Applicant revised as requested.

(b) (4)

(b) (4)

[redacted]

(b) (4)

CDER Labeling Recommendations

This section describes additional container label and carton labeling recommendations provided to the Applicant that address CDER Labeling preferences. The Applicant's response to these recommendations is acceptable.

A. General Comments

1. Replace "Tradename" with "Kanuma" throughout the labels and labeling.

2. Confirm there is no text on the ferrule and cap overseal of the vials to comply with USP General Chapters: <7> Labeling, Labels and Labeling for Injectable Products, Ferrules and Cap Overseals.

B. Container Label

1. Revise the storage information to read as "Store in refrigerator at 2°C to 8°C (36°F to 46°F) in original carton to protect from light.

Conclusions

The container labels and carton labeling for Kanuma™ (sebelipase alfa) were reviewed and found to comply with the following regulations: 21 CFR 610.60 through 21 CFR 610.67; 21 CFR 201.2 through 21 CFR 201.25; 21 CFR 201.50 through 21 CFR 201.57, 21 CFR 201.100 and USP 38/NF 33 [May 1, 2015 to July 31, 2015]. Labeling deficiencies were identified, mitigated, and resolved. The container label and carton labeling submitted on August 11 2015 are acceptable (see below).

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/s/

JIBRIL ABDUS-SAMAD
08/13/2015

ARULVATHANI P ARUDCHANDRAN
08/13/2015

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	July 29, 2015
Requesting Office or Division:	Division of Gastroenterology & Inborn Error Products (DGIEP)
Application Type and Number:	BLA 125561
Product Name and Strength:	Kanuma (sebelipase alfa) Injection 20 mg/10 mL (2 mg/mL)
Submission Dates:	July 14, 2015 & July 20, 2015
Applicant/Sponsor Name:	Synageva Biopharma Corp.
OSE RCM #:	2014-2479
DMEPA Primary Reviewer:	Matthew Barlow, RN, BSN
DMEPA Team Leader:	Kendra Worthy, PharmD

1 PURPOSE OF MEMO

The Division of Gastroenterology & Inborn Error Products (DGIEP) requested that we review the revised label and labeling (Appendix A) to determine if it is acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[1]

2 CONCLUSIONS

The revised carton and container labeling is acceptable from a medication error perspective.

[1] Barlow M. Label and Labeling Review for Kanuma (BLA 125561). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2015 April 14. 11 p. OSE RCM No.: 2014-2479.

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/s/

MATTHEW J BARLOW
07/29/2015

KENDRA C WORTHY
07/29/2015

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

CLINICAL INSPECTION SUMMARY

DATE: June 19, 2015

TO: Kevin Bugin, Regulatory Project Manager
Juli Tomaino, M.D. and Lauren Weintraub, M.D., Medical Officers
Division of Gastroenterology and Inborn Errors Products

FROM: Susan Leibenhaut, M.D.
Medical Officer
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

THROUGH: Susan D. Thompson, M.D.
Team Leader
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

THROUGH: Kassa Ayalew, M.D., M.P.H
Branch Chief
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections

BLA: 125561

APPLICANT: Synageva BioPharma Corp.
BIOLOGIC: sebelipase alpha
NME: Yes
THERAPEUTIC CLASSIFICATION: Priority

INDICATION: (b) (4) for patients with lysosomal acid lipase deficiency (LAL Deficiency)

CONSULTATION REQUEST DATE: December 18, 2014
INSPECTION SUMMARY GOAL DATE: July 14, 2015
DIVISION ACTION GOAL DATE: September 8, 2015
PDUFA DATE: September 8, 2015

I. BACKGROUND:

Synageva BioPharma Corp. submitted this BLA for Sebelipase alfa (SBC-102), a recombinant human lysosomal acid lipase (rhLAL), purified from egg white of transgenic Gallus (chickens), with the same amino acid sequence as the native human enzyme. The proposed indication is (b) (4) for patients with lysosomal acid lipase deficiency (LAL Deficiency). The product received both orphan designation and breakthrough therapy designation.

Lysosomal Acid Lipase Deficiency (LALD) (Online Mendelian Inheritance in Man database number 278000) is a multisystem storage disorder caused by a marked decrease in activity of the enzyme lysosomal acid lipase (LAL). Lysosomal acid lipase is responsible for the metabolism and degradation of lipids, predominantly cholesteryl esters, and triglycerides, in the lysosomes, and its marked reduction in patients with LALD leads to accumulation of these lipids in various tissues and cell types throughout the body.

LALD presents as a clinical continuum with a two major phenotypes: early onset and late onset. In late onset LALD, also known as Cholesteryl Ester Storage Disease (CESD), liver disease is the predominant clinical manifestation, with hepatomegaly, elevation of transaminases, and progression to liver fibrosis and cirrhosis. Early onset LALD, also known as Wolman Disease, is characterized by severe malabsorption, growth failure, and hepatic failure and is usually fatal within the first year of life.

The review division requested inspection of the following clinical trials that were submitted in support of the indication:

1. Protocol LAL-CL02 entitled, “A Multicenter, Randomized, Placebo-controlled Study of SBC-102 in Patients with Lysosomal Acid Lipase Deficiency (ARISE [Acid Lipase Replacement Investigating Safety and Efficacy])”

2. Protocol LAL-CL03 entitled, “An Open Label, Multicenter, Dose Escalation Study to Evaluate the Safety, Tolerability, Efficacy, Pharmacokinetics, and Pharmacodynamics of SBC-102 in Children with Growth Failure Due to Lysosomal Acid Lipase Deficiency”

Sites chosen for inspection included clinical sites and contract research organizations (CROs). The clinical sites were chosen on the basis of high enrollment and participation in more than one study. The CROs were chosen because of their roles in central reading of important efficacy parameters for Protocol LAL-CL02. The sponsor was inspected because this product is a new molecular entity (NME).

II. RESULTS (by Site):

Type of Inspected Entity, Name, and Address	Protocol #, Site #, and # of Subjects	Inspection Date	Classification*
CI: Edward Neilan Boston Children's Hospital 3 Blackfan Circle, Room CLS-14070 Boston, MA 02115	LAL-CL02 Site 2109 3 Subjects	February 3 to 11, 2015	NAI
CI: Simon Jones, M.D. Central Manchester University Hospitals NHS Foundation Trust St. Mary's Hospital, Oxford Road Manchester M13 9 WL, UK	LAL-CL03 Site 01 3 Subjects	March 30 to April 2, 2015	NAI
CI: Vassili Valayannopoulos, M.D. Centre de Reference Maladies Metaboliques de l'enfant et de l'adulte Hopital Necker 149 Rue de Sevres 75015 Paris, France	LAL-CL03/Site 02 3 Subjects LAL-CL02 Site 701/4 Subjects	April 13 to 17, 2015	NAI
CI : Alejandra Consuelo, M.D. Hospital Infantil de México No. 162 Col. Doctores, Delegación Cuauhtémoc Mexico, 06720	LAL-CL02 Site 1302 4 Subjects	April 6 to 10, 2015	Pending NAI
CRO: (b) (4)	LAL-CL02 Central reading of MRI/sample processing for MRI fat quantitation and liver biopsy	(b) (4)	NAI
CRO: (b) (4)	LAL-CL02 Liver fat content reduction on MRI	(b) (4)	NAI
CRO: (b) (4)	LAL-CL02 Liver histopathology readings	(b) (4)	NAI
Sponsor: Synageva BioPharma Corp 33 Hayden Avenue, Lexington, Massachusetts 02421	LAL-CL03 and LAL-CL02	May 28 to June 3, 2015	Pending VAI

Key to Classifications
NAI = No deviation from regulations.
VAI = Deviation(s) from regulations.
OAI = Significant deviations from regulations.

Pending = Preliminary classification based on information in 483 or preliminary communication with the field; EIR has not been received from the field, and complete review of EIR is pending.

1. **Edward Neilan**
   Boston Children's Hospital, Boston, MA 02115

a. **What was inspected:** At this site, for Protocol LAL-CL02 there were three subjects screened and enrolled. The inspection included review of informed consent documents (ICDs), institutional review board (IRB) correspondence and approvals, source documents, sponsor correspondence, investigator agreements (1572s), financial disclosure, adverse event reports, and electronic case report forms (eCRFs).

b. **General Observations/Commentary:** There was no evidence of under-reporting of adverse events. Data listings for drug infusion, liver biochemical parameters, and concomitant medications were verifiable.

c. **Assessment of data integrity:** The study appears to have been conducted adequately, and the data generated by this site may be used in support of the respective indication

2. **Simon Jones, M.D.**
   Central Manchester University Hospitals St. Mary's Hospital, Manchester, UK

a. **What was inspected:** At this site, for Protocol LAL-CL03, three subjects were screened and enrolled. One subject died and two subjects completed the study. Source documents and informed consent documents were reviewed. In addition, ethics committee correspondence and approvals, sponsor correspondence, investigator agreements (1572s), financial disclosure, and eCRFs were reviewed.

b. **General observations/commentary:** There was no evidence of under-reporting of adverse events and the efficacy data was verifiable.

c. **Assessment of data integrity:** The study appears to have been conducted adequately, and the data generated by this site may be used in support of the respective indication.

3. **Vassili Valayannopoulos, M.D.**
   Centre de Reference Maladies Metaboliques de l'enfant et de l'adulte
   Hopital Necker, 75015 Paris, France

a. **What was inspected:** At this site, for Protocol LAL-CL03, three subjects were screened, enrolled, and completed the study. For Protocol LAL-CL02, four subjects were screened, enrolled, and completed the study. Source documents and informed consent documents were reviewed. In addition, ethics committee correspondence and approvals, sponsor correspondence, investigator agreements (1572s), financial disclosure, and eCRFs were reviewed.

b. **General Observations/Commentary:** There was no evidence of under-reporting of adverse events and the efficacy data was verifiable.

c. **Assessment of data integrity:** The studies appear to have been conducted adequately, and the data generated by this study appear acceptable in support of the respective indications.

4. **Alejandra Consuelo, M.D.**
   Hospital Infantil de México, Delegación Cuauhtémoc Mexico, 06720

Note: Observations below for this CI inspection are based on review of the draft EIR. An inspection summary addendum will be issued if conclusions change upon review of the final EIR.

a. **What was inspected:** At this site, for Protocol LAL-CL02, six subjects were screened; and four subjects were enrolled and completed the study. Source documents and informed consent documents were reviewed In addition, ethics committee correspondence and approvals, sponsor correspondence, investigator agreements (1572s), financial disclosure, and eCRFs were reviewed.

b. **General Observations/Commentary:** There was no evidence of under-reporting of adverse events and the efficacy data was verifiable.

c. **Assessment of data integrity:** The study appears to have been conducted adequately, and the data generated by this study appear acceptable in support of the respective indications.

5. [redacted] (b) (4)

a. **What was inspected:** [redacted] (b) (4) a CRO, was responsible for qualifying clinical sites for MRI and liver biopsy procurement and processing of the MRI data and liver biopsies. The central reading of magnetic resonance imaging was conducted by independent contractors of [redacted] (b) (4). The determination of the fat quantification using MRI was conducted by [redacted] (b) (4) and the liver biopsy interpretation was conducted by [redacted] (b) (4). These last two entities were also inspected by FDA, and the results are noted below. The inspection of [redacted] (b) (4) covered quality assurance, quality control, subject masking, process flows, organizational responsibilities, operating procedures for imaging and pathology, training of staff, system validation, correspondence between CRO, sponsor, sub-contracted sites and clinical sites, validation of subjects' data points, protocol deviations, storage of data, work orders and service agreements.

b. **General observations/commentary:** It appeared that the protocols were followed and no unblinding of subject data occurred. Subject data for MRI readings were verified to be consistent with the data listings provided by the sponsor to the FDA in the BLA submission.

Reviewer note: See below concerning issues noted on the inspection of the [redacted] (b) (4) *site.*

c. **Assessment of data integrity:** The MRI readings appear to have been conducted as per protocol and the data generated by this CRO may be used in support of the respective indication.

6. [redacted] (b) (4)

a. **What was inspected:** This CRO was responsible for the specific liver fat content evaluation of the MRI scans. They worked under contract for [redacted] (b) (4) who had responsibility for the overall management of subject MRI and liver biopsy evaluation generated by Protocol LAL-CL02. The inspection covered review of the firm's contract and service manuals from [redacted] (b) (4), review of the [redacted] (b) (4) written procedures, protocol, and subject data analysis. Line listings from the sponsor submission were compared with data at the site.

b. **General observations/commentary:** Data from approximately 20 subjects were reviewed and found consistent with sponsor data tables. One deviation was

noted [redacted] (b) (4) No Form FDA 483 was issued because the scan time point information was included in data entry provided by [redacted] (b) (4) and not under direct control of [redacted] (b) (4)

Reviewer note: This issue was discussed with the review division via e-mail on April 21, 2015. On April 24, 2015, the sponsor provided via e-mail an unsolicited proposed erratum to the clinical study report in which they accurately described the actual procedures used concerning the lack of blinding of the time point and the rationale for the procedure. This erratum was submitted to the NDA on May 28, 2015.

c. **Assessment of data integrity:** The study appears to have been conducted adequately, and the data generated by this site may be used in support of the respective indication.

7. [redacted] (b) (4)

a. **What was inspected:** This CRO was responsible for the slide reading methodologies and interpretation for the liver biopsy specimens generated by Protocol LAL-CL02. The inspection covered review of the contractual responsibilities including blinding of the pathologists and also covered verification of the biopsy data of the 26 subjects whose data were submitted to the FDA by the sponsor in support of the BLA.

b. **General observations/commentary:** Inspection documented that the procedures were followed and that there were no discrepancies between the line listings and the readings in the records of the CRO.

c. **Assessment of data integrity:** The liver biopsy interpretations appear to have been conducted as per protocol and the data generated by this CRO may be used in support of the respective indication.

8. Synageva BioPharma Corp
33 Hayden Avenue, Lexington, Massachusetts 02421

Note: Observations below for this sponsor inspection are based on communications with the FDA field investigator. An inspection summary addendum will be issued if conclusions change upon review of the final EIR.

a. **What was inspected:** This inspection evaluated compliance with sponsor

responsibilities for Protocols LAL-CL02 and LAL-CL03 including selection and oversight of contract research organizations, monitoring, financial disclosure, FDA Form 1572s, and quality assurance (QA). The inspection included review of general correspondence and study master files, site monitoring, and handling of adverse events and other sponsor/monitor related activities.

b. **General observations/commentary:** Results of the inspection indicated that, in general, records were well organized and available for review. Monitoring of investigators was adequate and the sponsor maintained adequate oversight of the trials. Data receipt and handling and test article accountability were considered to be adequate. A Form FDA 483 was issued for a single observation, failure to ensure that an investigation was conducted in accordance with the general investigational plan and protocols as specified in the IND. Specifically, for Protocol LAL-CL03 the sponsor did not ensure that all serious adverse events were reported by one clinical site to the sponsor or designee within 24 hours, as required by the protocol. These adverse events, specifically infusion related reaction (urticaria), abdominal adenomegalies, worsening of growth failure, and systemic infection, were reported to FDA in a timely manner once the sponsor was made aware by the clinical site. On June 11, 2015, the sponsor responded adequately to the Form FDA 483.

c. **Assessment of data integrity:** The studies appear to have been conducted adequately, and the data generated by these studies appear acceptable in support of the respective indications.

III. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Four investigator sites, three CROs, and the sponsor were inspected for this application. Inspection of the (b) (4) found that the original procedure for blinding of timepoints for liver MRI in Protocol LAL-CL02 was not followed, and the sponsor provided an erratum to the clinical study report to explain this issue. Although violations were cited during inspection of the sponsor, these violations are considered minor. Data from all clinical sites and the contract research organizations appear reliable and the sponsor appears to have adequately fulfilled the sponsor responsibilities. Classifications for inspections of Dr. Consuelo's site and for the sponsor are preliminary. An inspection summary addendum will be issued if conclusions change upon review of the final EIR.

The studies appear to have been conducted adequately, and the data generated by these studies appear acceptable in support of the respective indications.

{See appended electronic signature page}

Susan Leibenhaut, M.D.
Medical Reviewer
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

Susan D. Thompson, M.D.
Team Leader
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE:

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Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research

Office of Biotechnology Products
Division of
Division of Biotechnology Review and Research III
FDA, White Oak Campus

Immunogenicity Memorandum

Date: 12/18/2014

To: File: IND 108460/BLA 125561, Kanuma (Sebelipase Alfa /SBC-102)

From: Joao A. Pedras-Vasconcelos, Ph.D.
Cecila Tami, PhD, Team Leader
Division of Biotechnology Review and Research III (DBRR III)
Office of Biotechnology Products
CDER/FDA

Subject: Immunogenicity consult for Sebelipase-alfa (SBC-102).

Product: Kanuma (Sebelipase alfa) is a recombinant human lysosomal acid lipase (rhLAL) expressed in transgenic chicken eggs.

Indication:

- (b) (4) LAL deficiency (Wolman Disease and Cholesteryl Ester Storage Disease)

Sponsor: Synageva Biopharma Corp.
111 River Bend Road, Athens GA 30605

Summary:
The validation reports provided to the BLA indicate that the binding assay and the in vitro and cell-based neutralizing antibody assays are suitable to monitor immunogenicity to Kanuma (Sebelipase-alfa/SBC-102) during enzyme replacement therapy for LAL deficiency (Wolman Disease and Cholesteryl Ester Storage Disease) .

Submission:
Sebelipase alfa (SBC-102) is a recombinant human lysosomal acid lipase (rhLAL) that catalyzes the lysosomal hydrolysis of cholesteryl esters and triglycerides to free cholesterol, glycerol and free fatty acids. It is developed for the treatment of Wolman Disease and Cholesteryl Ester Storage Disease (CSED), two clinical conditions in a spectrum of lysosomal storage diseases characterized by LAL deficiency and accumulation of triglycerides and cholesteryl esters in macrophages in the liver, spleen,

small intestine and other organs. Hepatomegaly and splenomegaly are common clinical manifestations. The disease onset varies from early infancy, with high morbidity and mortality, to diagnosis in the fifties and beyond when the disease shows lower morbidity. This depends on the nature of the mutation to the *lipA* gene encoding for LAL on chromosome 10q23.2-q23.3.

Sebelipase alfa is a 55 kDa protein produced in transgenic chickens, (b) (4) [redacted] The product quality review is under the purview of DBRR2's Chris Downey. Briefly, the product is expressed in egg white of transgenic hens. (b) (4) [redacted]. Upon IV administration to patients, the drug product is believed to bind to macrophage mannose receptors or mannose-6-phosphate receptors on relevant cell types via the glycan antennae, and is subsequently internalized and localized to the lysosomal compartment. Once in the lysosome, sebelipase alfa will hydrolyze accumulated substrate in LAL-deficient cells, ameliorating the pathology in affected tissues.

Under IND 108468, the product received orphan designation for the spectrum of LAL deficiencies in July 2010, fast track designation for the treatment of LAL Deficiency in June 2011 and Breakthrough Therapy designation for Wolman disease, the pediatric indication, in May, 2013

The sponsor submitted BLA 125561 for Kanuma (Sebelipase alfa) on 01/08/15 with a PDUFA date of 08/08/15.

The sponsor performed four clinical studies to support efficacy and safety of sebelipase: LAL-CL01 (Adults only), LAL-CL02 (adult and pediatric>4yo) and LAL-CL03 (pediatric <2yo) and LAL-CL04 (extension of CL01).

To support the breakthrough therapy designation the sponsor performed clinical study LAL-003: An Open Label, Multicenter, Dose Escalation Study to Evaluate the Safety, Tolerability, Efficacy, Pharmacokinetics, and Pharmacodynamics of SBC-102 in Children with Growth Failure Due to Lysosomal Acid Lipase Deficiency. This study included 9 pediatric patients who received an initial weekly infusion dose of 0.35 mg/kg, a dose escalation to 1 mg/kg in all subjects, contingent upon acceptable safety and tolerability, and a further dose escalation to 3 mg/kg if there was evidence of a loss of efficacy due to the potential development of neutralizing antibodies. The primary objective of the study was to evaluate the effect of sebelipase alfa (SBC-102) therapy on survival at 12 months of age in children with growth failure due to LAL Deficiency. The study lasted up to 24 months, and no children over 2 years old were admitted. The immunogenicity sampling plan for this study included testing for ADA at prescreening, 2, 8, and 12 weeks and every 6 months till 24 months, or at the time of early withdrawal. Drug infusion was performed weekly, and immunogenicity sampling is done prior to dosing. The clinical laboratory tests were performed weekly for the first 4 weeks, and

every 2 weeks after that. Four out of the seven patients that completed the study developed ADA, and two of these patients have remained positive for neutralizing antibodies.

Comment to the file:
Given the immunological immaturity of the patient population in LAL-003, the age and their health status, the proposed immunogenicity sampling plan is acceptable. Taking additional samples would require further bleed of the infants.

To support the Cholesterol Ester Storage Disease (CESD, late onset disease) indication, the sponsor initially performed Study LAL-CL01, which was a multinational, first-in-human Phase 1/2 study in adult subjects with liver dysfunction due to LAL Deficiency. This study was an open-label dose-escalation study to assess the safety, tolerability, pharmacokinetics, and pharmacodynamics of 3 dose levels of sebelipase alfa. History of allergies to egg proteins was an exclusion criterion for this study. Nine subjects ranging in age from 19 to 45 years of age with LAL Deficiency were enrolled into 3 sequential dose cohorts: 0.35 mg/kg, 1 mg/kg, and 3 mg/kg. Subjects received 4 once-weekly IV infusions of sebelipase alfa. Antibodies to SBC-102 were tested at pre-screening, day 0 and day 28 of study, and none of the patients tested positive. Eight of 9 subjects who completed LAL-CL01 were transferred to an ongoing, long-term extension study, LAL-CL04. The objective of LAL-CL04 is to evaluate the long-term safety, tolerability and efficacy of sebelipase alfa at 2 dose levels (1 and 3 mg/kg biweekly). None of the 8 ongoing subjects have developed antibodies to SBC-102 at 52 weeks of treatment, with antibody monitoring being done every 3 months. Two subjects were reported to have developed infusion reactions. For one of those subjects, the infusion reaction was severe enough that total Ig and IgE anti-SBC-102 antibodies as well as anti-egg white antibodies were examined. This subject has since returned to treatment with no further infusion reactions.
To further study safety and efficacy the sponsor performed LAL-CLO2 as a phase 3 randomized double-blind, placebo-controlled, multinational study (35 drug, 31 placebo), with subsequent open label-extension. There were 35 patients given 1 mg/kg once every other week IV infusions. Five of 35 Kanuma-treated pediatric and adult patients that completed the 20-week double-blind period of the study treatment (14%) developed anti-drug antibodies which were transient, and negative for neutralizing antibodies. In the extension portion of the study, two older patients that were switched from the placebo group to drug-treated group developed transient binding and neutralizing antibody responses 20 weeks after the treatment initiation.

Immunogenicity assay reports

The sponsor submitted to IND 108460 under SN069 (1/17/14) a validation report for the screening, confirmation and titration of anti-SBC-102 antibodies.

Immunogenicity Report 8285-711: Validation of an Immunoassay for the detection, confirmation and titration of anti-SBC-102

The report contains three components: (1) a screening assay, which identifies initial positive or negative samples; (2) a confirmation assay, which assesses specificity of the positive screen samples; and (3) titration assay which estimates the level of antibody for the confirmed positive samples.

Assay principle:

(b) (4)

The system suitability acceptance criteria are summarized below:

(b) (4)

(b) (4)

Comment to the file:
The system suitability ranges for NC, HPC and LPC were derived from mean OD values +/- 3 SDs obtained in the initial round of experiments.

Samples are first tested for binding antibody, then confirmed for specificity by competition with excess drug product and if confirmed, are then titrated till sample reaches the assay cut point. The unknown sample acceptance criteria are summarized below.

(b) (4)

(b) (4)

(b) (4)

Cut point determination:
The sponsor determined the screening assay cut point using 50 normal human sera samples, tested by 2 analysts over several days. Because neither the raw data nor the log-transformed data were normally distributed the sponsor opted for a plate specific cut point (table below), and established a normalization factor using the formula:
Normalization factor (NF) = OD of Screening cut-point – OD of Negative control mean

Plate-specific cut points were then established using the formula:
CP = Mean OD of NC in each plate + 0.033 (NF).

Screening cut point was calculated non-parametrically as the 95th percentile.

Normalization Factor Calculations
(From Statistics)

	Mean			Negative	
N	observed response	STD	Cut-point value (95th percentile)	control mean	Normalisation factor
194	0.090954	0.016842	0.123	0.089667	0.033333

Confirmatory cut point was calculated at 99th percentile of the normal distribution (table below)

Table 5
Confirmatory CutPoint Calculation
(from Statistics)

N	Mean of percentage inhibition values	STD of percentage inhibition values	Confirmatory cut point	
115	-4.05467	15.5442	43.9771	(mean + 3.09*std)
			32.1633	(mean + 2.33*std)

Comment to the file:
The use of plate specific cut point following a statistical analysis is acceptable. Given the difficulty in getting sera from patients with Wolman Disease (n=9) and Cholesteryl Ester Storage Disease (CSED, n=60), no patient sera were tested to confirm the cut point established with sera from healthy donors. The sponsor was asked to perform limited cut point comparisons with the adult patient sera for all the ADA assays. The sponsor showed that the signal from pre-treatment adult Wolman Disease patients is not significantly different than that of healthy individuals. That response is reviewed at the end of this memo.

Assay precision:

To test screening assay precision the sponsor run the HPC, LPCs, and NC samples on six different plates by two analysts on different days. Three sets of control samples were analyzed in different locations on each precision plate. Intra-assay precision was reported for each control sample, both as pooled percent coefficient of variation (%CV) of signal (OD) and a range of within-a-plate %CV values. Inter-assay precision was determined from the %CV of the mean signal (OD) for each level of controls, pooled over six or more validation precision runs.

Assay Precision (With OD)

(b) (4)

Comment to the file:
The intra-assay variability and inter-assay variability for the screening assay are (b) (4) *% and are acceptable.*

In addition, the sponsor also evaluated inter- and intra- assay precision of the confirmatory assay using the percentage inhibition following pre incubation of HPC and LPC with drug product

Assay Precision (Confirmatory Specificity)

(b) (4)

(b) (4)

Comment to the file:
The intra-assay and inter-assay variability for %inhibition of the HPC in the confirmatory assay are (b) (4) *% and are acceptable. For the LPC, two of the runs (Val-20 and Val-22) had each one outlier value, increasing the intra-assay variability for those individual runs* (b) (4) *%. This resulted in* (b) (4) *% inter-assay variability, which is still acceptable as for LPC* (b) (4) *% are traditionally allowed.*

(b) (4)

Comment to the file
The precision for the titration assay is acceptable.

Drug tolerance and assay sensitivity
The sponsor tested the screening assay drug tolerance by spiking different amounts of drug product (25, 50, 100, and 200 ug/ml) into different concentrations of positive control (0.25, 0.5, 1.25, 2.5 and 5 ug/ml). The table below summarizes the results.

Free-Drug Tolerance

(b) (4)

Comments to the file

The assay show good drug tolerance. The half-life of the drug is reported to be 3-4 hrs and the sampling for ADA is done prior to infusion of each dosing cycle, thus it is unlikely the drug would ever be present at the tested amounts. Based on the data, the sensitivity of the assay for this control antibody is (b) (4) *ug/ml which is acceptable.*

Assay selectivity and specificity

The sponsor evaluated the selectivity of the assay in normal human sera (n=10), in lipemic sera (n=5) and hemolyzed sera (n=5). Each serum was spiked with LPC and HPC or left unspiked. For confirmatory assay purposes, these same samples were spiked in parallel with drug product. Data was provided in two tables in the report, and showed that the assay was not impacted by use of either lipemic or hemolysed sera.

For assay specificity, the sponsor used human IgG at equivalent concentrations as LPC (0.5ug/ml) and HPC (10ug/ml) in parallel with the controls. Results are summarized table below.

(b) (4)

The sponsor also tested for hook effects (b) (4)

No hook effects were observed.

Comments to the file:

The testing for assay selectivity and hook effect are acceptable. For specificity the sponsor could have used a mouse isotype control antibody as the positive control is a mouse anti-SBC102 IgG1, or at least a human antibody of an irrelevant but known

specificity, not simply generic human Ig. However, this is a minor point and does not impact the acceptability of the assay.

Robustness:
The sponsor only tested positive control stability in this validation report. (b) (4)

Results show that the positive control remained stable through all these conditions- OD values of the positive control under the conditions studies were all higher than cut point and %CV (b) (4) %.

Comment to the file:
The antibody remains stable through the conditions tested. The stability of the control preparations at (b) (4) was still ongoing. The actual assay robustness testing provided was very limited, and the sponsor refers to a prior validation report for previous robustness testing- a comment was sent to the sponsor requesting addition data assessing assay robustness. The information was provided and found acceptable.

Screening/Confirmatory/Titer Assay assessment-
Other than the limited robustness, the assay is suitable for screening, confirming and titrating anti-SBC102 antibodies in normal human serum. The sponsor did not test any Wolman Disease or Cholesteryl Ester Storage Disease (CSED) patient sera for cut-point confirmation, but as the serum is very rare, and they are using a plate specific cut point, this is acceptable.The Sponsor was requested to analyze data from pre-treatment samples of adult onset patients to confirm the assay cut point calculated with sera from normal donors. The sponsor showed that the signal from pre-treatment adult Wolman Disease patients is not significantly different than that of healthy individuals. That response is reviewed at the end of this memo.

The sponsor submitted to IND 108460 under SN0109 (10/10/14) the validation reports for two neutralizing antibody assays- an in vitro enzymatic assay and cell based assay.

Immunogenicity Report 8291-329: Validation of enzymatic activity based neutralization assay for the detection of anti-SBC-102 neutralizing antibodies in human serum

Assay principle:
(b) (4)

(b) (4)

The system suitability acceptance criteria are summarized below

Validation Parameters	Target Specifications
System Suitability	(b) (4)

Assay Cut Point:

(b) (4)

Comment to the file:
Cut point assay calculation with and without background enzyme levels are very similar. The sponsor will use the lower one 15.2% inhibition for a sample to be considered NAb+. Given the rarity of the patient population -n=9 for Wolman disease, and n=65 for CESD- only normal sera were tested. The sponsor was asked to confirm the assay cut point using pre-treatment serum samples from adult CESD patients to confirm cut point. for all the ADA assays. However, because adult CESD patients did not develop ADA they were not tested in the NAb assay so the comparison could not be done. However, some children did test NAb positive indicating that the assay was able to detect NAb. The clinical results are reviewed at the end of this memo.

Assay Precision

(b) (4)

Comment to the file:
The intra-assay inter–assay precision for HPC and LPC-1 are (b) (4) *% and are acceptable.* (b) (4) *are not acceptable. The sponsor states LPC-2 will not be used as a system suitability control.*

Assay titration and hook effects

The sponsor also tested for hook effects (b) (4) No hook effects were observed.

Comment to the file:

(b) (4)

Drug Tolerance

(b) (4)

Comment to the file:

The assay has relatively low drug tolerance ((b) (4) *ng/ml), but as the drug only has a 3-4 hr half-life, and antibody sampling is done before weekly dosing, when there is no quantifiable drug in the serum, it is unlikely to affect NAb detection.*

Method Selectivity

(b) (4)

Comment to the file:

High levels of lipids are a characteristic of Wolman Disease and Cholesteryl Ester Storage Disease sera, so testing of lipemic sera was appropriate given the patient sera from the two clinical trials is quite precious (n-9 for Wolman disease, and n=65 for CESD).

Assay Specificity

The sponsor determined the specificity of the method as with the screening ELISA using an irrelevant human IgG of unknown specificity. (b) (4)

Comment to the file

Similar to the screening/confirmatory assays, the sponsor used generic human Ig. The control antibody is a rabbit anti-LAL antibody, and they could have used an isotype

rabbit control. However, this is a minor point and does not impact the acceptability of the assay.

Assay Robustness

The sponsor only tested the positive control stability in this validation report (b) (4)

Comment to the file:

The antibody remains stable through the conditions tested. The stability of the control preparations at (b) (4) °C was still ongoing. The actual assay robustness testing provided was very limited, and the sponsor refers to prior validation report for previous robustness testing. A request for additional robustness data was sent to the sponsor. The information was provided and found acceptable.

Immunogenicity Report 8298-036: Validation of cell based neutralization assay for the detection and titration of anti-SBC-102 antibodies in human serum

Assay principle:

(b) (4)

Figure-1
Principle of the Method (illustration)

(b) (4)

Comment to the file:

(b) (4)

Assay Cut Point:

(b) (4)

Screening Cutpoint for the Detection of Anti-SBC-102 Neutralization Antibodies in Human Serum

(b) (4)

Comment to the file:
Cut point calculation for the assay is acceptable- (b) (4) *Given the rarity of the patient population n-9 for Wolman disease, and n=65 for CESD, only normal sera were tested. The sponsor was asked to confirm the assay cut point using pre-treatment serum samples from adult CESD patients to confirm cut point. for all the ADA assays. Because adult CESD patients did not*

develop ADA they were not tested in the NAb assay so the comparison could not be done. However, some children did test NAb positive indicating that the assay was able to detect NAb. The clinical results are reviewed at the end of this memo.

Assay Precision

(b) (4)

Comment to the file

(b) (4)

Drug Tolerance

(b) (4)

Comment to the file:
The assay has relatively low drug tolerance (b) (4) *g/ml), which is still higher than the in vitro enzymatic NAb assay where even this level of drug interferes with detection of NAbs. This is acceptable however, for the reasons referred to earlier.*

Method Selectivity

(b) (4)

Comment to the file:
High levels of lipids are a characteristic of Wolman Disease and Cholesteryl Ester Storage Disease sera, so testing of lipemic sera was appropriate, especially given the

patient sera from the two clinical trials is quite precious (n-9 for Wolman disease, and n=65 for CESD).

Assay Specificity

(b) (4)

Comment to the file
Similar to the screening/confirmatory assays, and the enzymatic Nab assay, the sponsor used generic human Ig to assess specificity. The control antibody is a rabbit anti-LAL antibody, and they could have used an isotype rabbit control. They could also have blocked the M6P receptor to show that cell line would not uptake the drug. However, these are minor points and do not impact the acceptability of the assay.

Assay Robustness

(b) (4)

Comment to the file:
The antibody remains stable through the conditions tested. The stability of the control preparations at (b) (4) *°C was still ongoing. The actual assay robustness testing provided was very limited, and the sponsor refers to prior validation report for previous robustness testing. A request for additional robustness data was sent to the sponsor. The information was provided and found acceptable*

Neutralizing Antibody Assay assessment-

(b) (4)

The following IR concerning assay validation was sent to the sponsor on April 24th, 2015 as part of the midcycle communication:

We 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 comments:

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 infant onset disease 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 to 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 assays 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. Update your BLA submission to include the validation reports for the assays to detect anti-SBC-102 IgE antibodies and anti-egg white antibodies.**

Sponsor response 5/27/15

Question 1 Sponsor response:

(b) (4)

Reviewer Comment:

The sponsor provided the required information, and showed that for study LAL-CL02 patient sera, the assay cut point is not significantly different from that of the healthy sera used in the validation study. The response is acceptable.

Question 2 Sponsor Response:

(b) (4)

(b) (4)

Reviewer Comment:
The sponsor provided the requested information and the response is acceptable.

Question 3 Sponsor Response:

(b) (4)

Reviewer Comment:
The sponsor provided the required information and the response is acceptable because the event that triggered the requirement for the development of anti-SBC-102 anti-IgE ELISA was a rare adverse event which was remediated with medication, and did not repeat. The patient was ADA- throughout the study and had no detectable antibody to either product or egg (clinical immunogenicity ImmnoCAP assay).
Based on the validation report submitted, however, it appears that the anti-drug IgE ELISA may not be sufficiently optimized and is fairly insensitive. (b) (4) *The assay has poor drug tolerance, and can only be used on serum samples taken when drug concentration is at trough level. The sponsor could switch to a more sensitive system such as an ECL based assay. However, as there have been no additional episodes with other patients, the requirement for assay optimization could be handled as a PMC.*

Immunogenicity data Summary
Immunogenicity samples were obtained in 4 clinical efficacy and safety studies (Table 2)- LAL-CL01/04 (Adult), LAL-CL02 (adult and pediatric>4yo) and LAL-CL03 (pediatric <2yo). Two infant patients in LAL-CL03 died in the first week of the study, and no immunogenicity data was obtained from them. The number of patients for immunogenicity assessment in this study was reduced to 7 from the original 9.

Table 2: Overview of Sebelipase Alfa Clinical Development Program

Study Identifier (Status)	Study Design	Study Objective(s)	LAL Deficiency Population	Dosage Regimen	Treatment Duration	No. of Subjects	Primary Efficacy Endpoint
LAL-CL01 (Complete)	Phase 1/2, single-arm, open-label, dose escalation	Safety, PK, and PD	Adult (≥18 years)	3 cohorts: 0.35, 1, and 3 mg/kg qw IV	4 weeks	9 (3/cohort)	N/A
LAL-CL02 (Double-blind period complete; Open-label period ongoing)	Phase 3, randomised, double-blind, placebo-controlled; followed by open-label extension	Efficacy, Safety, and PK	Pediatric / adult (≥4 years)	1 mg/kg qow IV	20 weeks double-blind followed by open-label up to 130 weeks	66 (36 sebelipase alfa / 30 placebo)	Normalisation of ALT
LAL-CL03 (Primary analysis complete; Follow-up ongoing)	Phase 2/3, single-arm, open-label	Efficacy, Safety, and PK	Pediatric (≤2 years)	Dose escalation from 0.35 to 1 mg/kg qw IV; Up to 3 or 5 mg/kg qw IV	Up to 208 weeks	9	Survival at 12 months
LAL-CL04 (Enrolment; complete; Follow-up ongoing)	Phase 2, single-arm, open-label extension for subjects who completed LAL-CL01	Efficacy and Safety	Adult (≥18 years)	0.35, 1, or 3 mg/kg, qw IV for 4 weeks; 1 or 3 mg/kg qow IV	Up to 156 weeks	8	N/A

The following tables (1.4.1A-C) provide summary immunogenicity data by clinical study (1A), by product dose (1B) and by patient age (1C).
Overall 10/84 patients (11.95%) were ADA+:

- 4/7 (57.1%) of the pediatric patients < 2yo (LAL-CL03)
- 3/24 (12.5%) of 2-12 yo
- 1/23 (4.3%) of 12-18 yo
- 2/28 (7.1%) of adult patients.

Two out of four <2yo pediatric patients (LAL-CL03/01-002 and 02-003) also tested NAb+, and these patients showed the highest ADA+ titers, (1:790, and 1:1142), while the two others in the group that were NAb negative had moderate titers (1:153, 1:223).
The timing of the response for the high titer patients ranged from d36-d664 for patient LAL-CL03/01-002, to d56- d338 for patient LAL-CL03/02-003.

In the older patient study LAL-CL02, patient (b) (6) 1 had high titer (1:816) by day 29 and was seronegative by day 142, and patient (b) (6) had titer of 1:448 by day 29 and was seronegative by day 230. Data were not provided concerning pre-existing antibodies in patients but the timing of the responses suggests that there were no pre-existing antibodies detectable by their assays. With regards to dosing, the 3 mg dose had higher incidence of ADA+ (3/8, 37.5%), compared to the 1mg dose (7/74, 9.5%).

Table 1.4.1A

Summary of Antibody Data:
By Study

Parameter	Statistic	LAL-CL01/ LAL-CL04 (N=9)	LAL-CL02 (N=66)	LAL-CL03 (N=9)	Total SA Treated (N=84)
Antibody Positive Rate	n (% of N)	1 (11.1%)	5 (7.6%)	4 (44.4%)	10 (11.9%)
Time to First Antibody Positive Result (days)	N	1	5	4	10
	Mean (SD)	242.0 (NA)	56.8 (27.75)	141.8 (184.42)	109.3 (125.04)
	Median	242.0	57.0	56.5	57.0
	Min, Max	242, 242	29, 85	36, 418	29, 418
Time to Peak Titer (days)	N	1	5	4	10
	Mean (SD)	242.0 (NA)	62.4 (23.19)	373.0 (276.16)	204.6 (222.83)
	Median	242.0	57.0	379.0	84.5
	Min, Max	242, 242	29, 85	57, 677	29, 677
Peak Titer	N	1	5	4	10
	Mean (SD)	160.000 (NA)	340.992 (315.9503)	576.750 (472.4142)	417.196 (375.0317)
	Median	160.000	309.780	506.210	266.160
	Min, Max	160.00, 160.00	20.00, 816.08	152.98, 1141.60	20.00, 1141.60

Comment to the file:

The Sponsor did not exclude from the immunogenicity calculations the two infant patients in LAL-CL03 who died in the first week of the study. Therefore, the antibody positive rate in Table 1.4.1A is lower (44.4%) than the actual antibody positive rate of 57.1% calculated excluding these two patients.

Table 1.4.1B

Summary of Antibody Data:
By Active Dose of Longest Duration [1]

Parameter	Statistic	0.35 mg/kg (N=2)	1 mg/kg (N=74)	3 mg/kg (N=8)	Total SA Treated (N=84)
Antibody Positive Rate	n (% of N)	0	7 (9.5%)	3 (37.5%)	10 (11.9%)
Time to First Antibody Positive Result (days)	N	0	7	3	10
	Mean (SD)		134.9 (144.45)	49.7 (11.85)	109.3 (125.04)
	Median		84.0	56.0	57.0
	Min, Max		29, 418	36, 57	29, 418
Time to Peak Titer (days)	N	0	7	3	10
	Mean (SD)		175.9 (231.67)	271.7 (229.75)	204.6 (222.83)
	Median		84.0	244.0	84.5
	Min, Max		29, 677	57, 514	29, 677
Peak Titer	N	0	7	3	10
	Mean (SD)		298.214 (268.7247)	694.820 (501.1184)	417.196 (375.0317)
	Median		222.540	789.880	266.160
	Min, Max		20.00, 816.08	152.98, 1141.60	20.00, 1141.60

ISS of Sebelipase alfa

Table 1.4.1C

Summary of Antibody Data:
By Age

Parameter	Statistic	<2.00 Years (N=9)	2.00-12.00 Years (N=24)	12.01-17.99 Years (N=23)	>=18.00 Years (N=28)	Total SA Treated (N=84)
Antibody Positive	n (% of N)	4 (44.4%)	3 (12.5%)	1 (4.3%)	2 (7.1%)	10 (11.9%)
Time to First Antibody Positive Result (days)	N	4	3	1	2	10
	Mean (SD)	141.8 (184.42)	75.3 (15.89)	29.0 (NA)	135.5 (150.61)	109.3 (125.04)
	Median	56.5	84.0	29.0	135.5	57.0
	Min, Max	36, 418	57, 85	29, 29	29, 242	29, 418
Time to Peak Titer (days)	N	4	3	1	2	10
	Mean (SD)	373.0 (276.16)	75.3 (15.89)	29.0 (NA)	149.5 (130.81)	204.6 (222.83)
	Median	379.0	84.0	29.0	149.5	84.5
	Min, Max	57, 677	57, 85	29, 29	57, 242	29, 677
Peak Titer	N	4	3	1	2	10
	Mean (SD)	576.750 (472.4142)	144.407 (149.1704)	816.080 (NA)	307.830 (209.0632)	417.196 (375.0317)
	Median	506.210	103.440	816.080	307.830	266.160
	Min, Max	152.98, 1141.60	20.00, 309.78	816.08, 816.08	160.00, 455.66	20.00, 1141.60

The complete listing of ADA+ subjects, along with titers and NAb status was provided in ISS table 1.4.2 (see
below).

Table 1.4.2

Listing of Subjects With Any Antibody Positive Result

(b) (4)

(b) (4)

Comment to the file:
As expected, the immunogenicity rates were higher for the infant patients<2yo than for the older patients which is related to the degree of enzyme genetic deficiency observed in the infant patients- sebilipase is "foreign" protein, and thus they are less immunological tolerant. Only this group of patients had detectable NAb responses (shown in red squares). Table 2 below from study LAL-CL03 (pediatric population) suggests that infusion associate events appear to be stronger upon seroconversion.

Table 20: Summary of IARs Before and After Initial ADA Positivity in ADA-Positive Subjects

Subject ID	Initial ADA Positivity	Last Infusion Prior to Data Cut-off	IARs Prior to Initial ADA Positivity			IARs After Initial ADA Positivity		
			Mild	Moderate	Severe	Mild	Moderate	Severe
(b) (6)	Day 36	Day 666	None	None		tachycardia (3) pallor retching agitation cough pyrexia (2) irritability increased body temperature	urticaria	
	Day 57	Day 446	None	None		None	None	
	Day 418	Day 1153	pyrexia (4) diarrhoea urticaria			vomiting (2) extravasation	infusion site oedema	
	Day 56	Day 422	pyrexia vomiting	pyrexia	tachycardia	pyrexia (5) chills (2) hyperthermia (2) vomiting tachycardia hypotonia hypertension	pyrexia (2) chills (2) oxygen saturation decreased	tachycardia pallor

Source: Listing 16.2.8.10, Listing 16.2.5.1, and Table 14.3.2.2

ADA = anti-drug antibody; ATU = Temporary Use Authorisation (Autorisation Temporaire d'Utilisation; IAR = infusion-associated reaction

[a] The subject tested positive at a single assessment at Week 8 and was ADA negative at all subsequent assessments.

[b] IARs were not reported for the subject during treatment under ATU. However, according to a publication (abstract) prepared by the Investigator, the subject experienced non-serious Grade 1 IRRs of "fever: (4); diarrhoea: (1); skin rash: (1)" (Valayannopoulos, 2014, *Mol Genet Metab*), which have been summarised in this table as pyrexia (4), diarrhoea (1), and urticaria (1)

It is unclear from table 1.4.2 above which NAb assay the sponsor used to detect Nabs, but in the text of the study reports it states that both assays were used. Similarly there are a number of ADA+ patients from study LAL-CL02 listed in the table with measurable antibody titers that do not have NAb assay results listed, but according to the study report there were no detectable NAbs.

Overall the immunogenicity rate to sebilipase alpha is low and correlates with the degree of genetic deficiency. ADA and NAb responses appear to be transient and not associated with serious adverse events.

120 day Safety update:

Two additional subjects in Study LAL-CL02 ((b) (6) and (b) (6)) tested positive for neutralizing antibodies to cellular uptake but not to enzyme activity, The first subject (b) (6) had undetectable titres after first developing ADAs at Week 4 (double blind period) then had low titres again at Week 52(open-label period) and was NAb+. The second subject (b) (6) originally in the placebo treated group, but tested ADA+ and NAb+ after initiation of treatment under the extension portion of study LAL-CLO2 . This patient appeared positive at screening and subsequently retested ADA+ positive on week 20 of treatment, and NAb+ by the cell based assay. The patient tested ADA- at weeks 52 and 56. The patient did not show loss of efficacy as evidenced by reductions in serum transaminases by week 4 following transition to sebelipase alfa.

Reviewer comment:

Unlike the Wolman Disease patients, these additional Cholesteryl Ester Storage Disease patients were only positive for neutralizing antibodies by the cell based

assay. The responses were also transient in nature, and appeared not to have impacted efficacy.

Proposed immunogenicity label:
Below is the text for the immunogenicity portion of the product label. This text was edited in collaboration with clinical reviewers Juli Tomaino and Lauren Weintraub

6.2 Immunogenicity

As with all therapeutic proteins, there is potential for immunogenicity. Patients have developed anti-drug antibodies (ADA) to Kanuma. Immunogenicity assay results are highly dependent on the sensitivity and specificity of the assay and may be influenced by several factors such as: assay methodology, sample handling, timing of sample collection, concomitant medication, and underlying disease. For these reasons, comparison of the incidence of antibodies to Kanuma with the incidence of antibodies to other products may be misleading.

Patients with Rapidly Progressive LAL Deficiency Presenting with Growth Failure in the First 6 Months of Life

Four of the patients with rapidly progressive disease who had at least one post-treatment assessment developed ADA during treatment with Kanuma. Two of the 4 ADA-positive patients were determined to be positive for neutralizing antibodies that inhibit in vitro enzyme activity and cellular uptake of the enzyme. At the time of initial ADA positivity, 3 patients were receiving a dosage of 1 mg/kg once weekly and 1 patient was receiving a dosage of 3 mg/kg once weekly. Three of the 4 ADA-positive patients had ADA titers monitored from the initiation of treatment, and developed measureable ADA titers within the first 2 months of exposure. One of the 4 ADA-positive patients had persistent ADA titers. ADA titers decreased to undetectable levels in the remaining 3 patients while receiving continued treatment at a dose of 3 mg/kg once weekly.
Hypersensitivity reactions occurred in all 4 of the ADA-positive patients vs. 1 of the 3 ADA-negative patients. None of the infants discontinued treatment. One ADA-positive infantile-onset patient had decreased efficacy attributable to the presence of neutralizing antibodies.

Pediatric and Adult Patients

Five of 35 Kanuma-treated pediatric and adult patients that completed the 20-week double-blind period of the study treatment (14%) developed ADA. All patients were receiving 1 mg/kg once every other week. All five ADA-positive patients first developed measurable ADA titers within the first 3 months of exposure. Two of the 5 ADA-positive patients had a measurable ADA titer at only one time point. In the 3 patients with measurable ADA titers at multiple time points, ADA titers decreased to undetectable levels during continued treatment. Two patients developed neutralizing antibodies during the open-label extension phase after 20 weeks and 52 weeks of treatment with Kanuma. . There is no clear association between ADA and decreased efficacy in pediatric and adult patients treated with Kanuma.

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/s/

JOAO A PEDRAS VASCONCEL
06/09/2015

Maria Cecilia TAMI
06/09/2015

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Division of Pediatric and Maternal Health
Office of New Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Silver Spring, MD 20993
Tel 301-796-2200
FAX 301-796-9744

Pregnancy and Lactation Labeling Rule (PLLR) Labeling Review

Date: 6-9-2015

From: Leyla Sahin, M.D.
Medical Officer,
Division of Pediatric and Maternal Health, Maternal Health Team

Through: Tamara Johnson, M.D., M.S.
Acting Team Leader, Maternal Health Team
Division of Pediatric and Maternal Health

Linda L. Lewis, M.D.
Acting Deputy Director,
Division of Pediatric and Maternal Health

To: Division of Gastroenterology and Inborn Errors Products

Drug: Kanuma (sebelipase alfa); BLA 125561

Subject: Pregnancy and Lactation Labeling

Applicant: Synageva Biopharma Corporation

Materials Reviewed:
- Applicant's proposed labeling
- Literature review

Consult Question: Please assist with Pregnancy and Lactation Labeling

Reference ID: 3776578

INTRODUCTION

The applicant submitted an original biologics license application for Kanuma (sebelipase alfa), (b) (4) for the treatment of lysosomal acid lipase deficiency, on November 21, 2014. The Division of Gastroenterology and Inborn Errors Products (DGIEP) consulted the Division of Pediatric and Maternal Health (DPMH) on January 16, 2015, to assist with reviewing the Pregnancy and Nursing Mothers subsections of labeling.

BACKGROUND

Product and Disease Background

Kanuma (sebelipase alfa), is a recombinant human lysosomal acid lipase enzyme developed for the treatment of lysosomal acid lipase deficiency, a rare autosomal recessive lysosomal storage disease caused by mutations in the LIPA gene.[1] The age at onset and rate of progression vary greatly and this may relate to the nature of the underlying mutations.[2] Patients presenting in infancy have the most rapidly progressive disease, developing signs and symptoms in the first weeks of life and rarely surviving beyond 6 months of age. Children and adults typically present with some combination of dyslipidemia, hepatomegaly, elevated transaminases, and microvesicular hepatosteatosis on biopsy, referred to as cholesteryl ester storage disease. Liver damage with progression to fibrosis, cirrhosis and liver failure occurs in a large proportion of patients. Elevated low-density lipoprotein cholesterol levels and decreased high-density lipoprotein cholesterol levels are common features, and cardiovascular disease may manifest as early as childhood.

Pregnancy and Lactation Labeling Rule (PLLR)

On December 4, 2014, the Food and Drug Administration (FDA) published the "*Content and Format of Labeling for Human Prescription Drug and Biological Products; Requirements for Pregnancy and Lactation Labeling*," also known as the Pregnancy and Lactation Labeling Rule (PLLR).[3] The PLLR requirements include a change to the structure and content of labeling for human prescription drug and biologic products with regard to pregnancy and lactation, and a new subsection for information with regard to females and males of reproductive potential (if applicable). Specifically, the pregnancy categories (A, B, C, D and X) will be removed from all prescription drug and biological product labeling and a new format will be required for all products that are subject to the 2006 Physicians Labeling Rule, to include information about the risks and benefits of using these products during pregnancy and lactation. The PLLR will officially take effect on June 30, 2015; however, at this time applicants may voluntarily convert labeling to the PLLR format. The recommendations in this review are consistent with the PLLR format.

---

[1] Reiner Z, Guardamagna O, Nair D, et al. Lysosomal acid lipase deficiency-an under-recognized cause of dyslipidaemia and liver dysfunction. Atherosclerosis. 2014 Jul; 235(1):21-30.
[2] Porto AF. Lysosomal acid lipase deficiency: diagnosis and treatment of Wolman and Cholesteryl Ester Storage Diseases. Pediatr Endocrinol Rev. 2014 Sep;12 Suppl 1:125-32.
[3] Content and Format of Labeling for Human Prescription Drug and Biological Products, Requirements for Pregnancy and Lactation Labeling (79 FR 72063, December 4, 2014).

Reference ID: 3776578

DISCUSSION

A search of published literature for available data on lysosomal acid lipase deficiency disease in pregnancy was performed. This reviewer identified only one published case report of a pregnancy in a woman with cholesteryl ester storage disease and she had an uncomplicated pregnancy.[4] The applicant proposed [redacted] (b) (4) .
DPMH is of the opinion that there are insufficient data to support the applicant's proposed statements and recommends not including this information.

CONCLUSION

The Pregnancy and Lactation subsections of labeling were structured to be consistent with the PLLR.

DPMH LABELING RECOMMENDATIONS

DPMH discussed labeling recommendations with DGIEP at labeling meetings. DPMH recommendations are below and reflect the discussions with DGIEP.
See final labeling for all of the labeling revisions negotiated with the applicant.

USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no available data on KANUMA in pregnant women to inform any drug associated risk. Animal reproductive studies conducted with sebelipase alfa showed no evidence of embryolethality, fetotoxicity, teratogenicity, or abnormal early embryonic development at dosages up to 164 and 526 times the [redacted] (b) (4) human dose (based on AUC), in rats and rabbits respectively [redacted] (b) (4)

The background risk of major birth defects and miscarriage for the indicated population [redacted] (b) (4) unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Data

Animal Data

[redacted] (b) (4) rats [redacted] (b) (4) up to 60 mg/kg ([redacted] (b) (4) 164 times the human AUC) at [redacted] (b) (4) 1 mg/kg) and [redacted] (b) (4) rabbits at dosages up to 50 mg/kg ([redacted] (b) (4) 526 times the [redacted] (b) (4) human [redacted] (b) (4) 1 mg/kg). In rats, [redacted] (b) (4) of sebelipase alfa [redacted] (b) (4) up to 60 mg/kg [redacted] (b) (4)

[4] Gidiri M, Lindow SW, Masson EA, Kilpatrick E. Congenital cholesteryl ester storage disease: what are the implications in pregnancy? Eur J Obstet Gynecol Reprod Biol 2009;142:86–87.

Reference ID: 3776578

(b) (4)

8.2 Lactation

Risk Summary

There are no data on the presence of sebelipase alfa in human milk, the effects on the breastfed infant, or the effects on milk production. It is not known if sebelipase alfa is present in animal milk. The development and health benefits of breastfeeding should be considered along with the mother's clinical need for KANUMA and any potential adverse effects on the breastfed infant from (b) (4) or from the underlying maternal condition.

Reference ID: 3776578

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/s/

LEYLA SAHIN
06/09/2015

TAMARA N JOHNSON
06/09/2015

LINDA L LEWIS
06/09/2015

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: June 3, 2015

To: Kevin Bugin, MS, RAC, Senior Regulatory Health Project Manager
Division of Gastroenterology and Inborn Errors Products (DGIEP)

From: Adewale Adeleye, Pharm.D., MBA, Regulatory Review Officer,
Office of Prescription Drug Promotion (OPDP)

CC: Kathleen Klemm, Pharm.D., RAC, Team Leader, OPDP

Subject: BLA # 125561 - KANUMA (sebelipase alfa) injection, for intravenous use

---

Reference is made to DGIEP's consult request dated January 16, 2015, requesting review of the proposed Package Insert (PI) and Carton/Container Labeling for KANUMA (sebelipase alfa) injection, for intravenous use (Kanuma).

OPDP has reviewed the proposed PI entitled, "Sebilipase.clean from sponsor.3.27.15.docx" that was available in SharePoint on May 27, 2015. OPDP's comments on the proposed PI are provided directly on the attached copy of the labeling (see below).

OPDP has also reviewed the proposed Carton/Container labeling entitled, "draft-carton-vial-label.pdf" that was sent from DGIEP to OPDP on June 2, 2015. OPDP has no comments at this time on the proposed Carton/Container labeling.

Thank you for your consult. If you have any questions please contact me at (240) 402-5039 or adewale.adeleye@fda.hhs.gov

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

Reference ID: 3773864

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/s/

ADEWALE A ADELEYE
06/03/2015

U.S. FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
OFFICE OF ANTIMICROBIAL PRODUCTS
DIVISION OF ANTIVIRAL PRODUCTS

MEMORANDUM

Date: June 1, 2015

From: Poonam Mishra, MD, MPH
Deputy Director for Safety
Division of Antiviral Products/DAVP

Through: Jeffrey S Murray, MD, MPH
Deputy Division Director, DAVP

To: Juli Tomaino, MD/Jessica J Lee, MD
Kevin Bugin, RPM
Division of Gastroenterology and Inborn Errors Products/DGIEP

Subject: Consult Request regarding BLA 125561

General Information:

BLA: 125561

Applicant: Synageva BioPharma Corp

Drug Name: Sebelipase alfa

Drug Class: Enzyme replacement therapy

Proposed Indication: Treatment of lysosomal acid lipase deficiency

Date of Request: January 16, 2015

Materials Reviewed: DGIEP consult request and questions
Relevant sections of submission dated 1/8/2015 under BLA 125561, Midcycle presentation

Reference ID: 3772502

Consult Request:

The following consult request was received from Division of Gastroenterology and Inborn Errors Products (DGIEP).

DGIEP requests the assistance of DAVP in the review of a new BLA to support the use of sebelipase alfa, a recombinant human lysosomal acid lipase (rhLAL) enzyme, purified from egg white of transgenic gallus, intended to treat patients with lysosomal acid lipase deficiency (LAL-deficiency).

1) Are there avian pathogens that are known to affect humans or have potential to be transmitted across species that we should be monitoring in an ongoing basis to assure product quality and safety?

LAL Deficiency is defined by two phenotypes: Wolman Disease (WD) (complete loss of enzyme activity) and Cholesteryl Ester Storage Disease (CESD) (partial loss of enzyme activity). The diagnosis of late-onset disease, CESD, is highly variable, where the majority of patients (80%) present in childhood with progressive liver disease, while others go undiagnosed until complications manifest in late adulthood.[1] Elevation of serum transaminases, dyslipidemia (high LDL-cholesterol, high triglycerides, and low HDL) and hepatosplenomegaly are the main abnormalities seen in CESD, but not universally manifested in all CESD patients.

The primary endpoint for Study LAL-CL02, the clinical trial evaluating patients with CESD, is normalization of serum ALT. Specifically, we are requesting advice on the adequacy of using serum ALT normalization as an efficacy endpoint. Note that DGIEP did not agree to the primary endpoint of ALT normalization because a correlation has not been established between ALT reduction/normalization and clinically meaningful outcomes in patients with CESD. Furthermore, 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.

2) While we acknowledge that sustained viral remission (SVR) is the primary endpoint for hepatitis C trials, please comment on whether changes in ALT have been considered as additional evidence of efficacy (i.e., key secondary or exploratory endpoints) in trials that supported product labeling for the

[1] Bernstein DL, Hülkova H, Bialer MG, Desnick RJ. Cholesteryl ester storage disease: Review of the findings in 135 reported patients with an underdiagnosed disease. J Hepatol. 2013 Feb 26.

Reference ID: 3772502

treatment of liver diseases in your Division.

3) Please include your rationale to support or refute the use of ALT normalization as an efficacy endpoint that reflects a clinically meaningful benefit in patients with CESD.

Please note that question 1) in your consult request has been addressed in a separate review archived by Dr. Lalji Mishra, Clinical Virologist (signed 5/28/15). This review focuses on clinical questions (2&3) in the consult request.

Background and Introduction

Sebelipase alfa is a recombinant human lysosomal acid lipase (rhLAL) enzyme with the proposed indication for the treatment (b) (4) for patients with lysosomal acid lipase (LAL) deficiency.

LAL deficiency is a rare autosomal recessive lysosomal storage disease resulting in cholesteryl ester (CE) accumulation and triglyceride storage in the liver, spleen and macrophages.[1] This leads to microvesicular steatosis, hepatomegaly, cirrhosis, liver failure, dyslipidemia, and accelerated atherosclerosis.[1] The biochemical findings in patients with CESD include elevated serum total cholesterol, LDL-cholesterol, triglycerides, and serum transaminases.

As noted in the Guidance document entitled Guidance for Industry Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics, “The accelerated approval regulations (21 CFR part 314, subpart H and 21 CFR part 601, subpart E), promulgated in 1992, allow use of additional endpoints for approval of drugs or biological products that are intended to treat serious or life-threatening diseases and that either demonstrate an improvement over available therapy or provide therapy where none exists. In this setting, the FDA may grant approval based on an effect on a surrogate endpoint that is *reasonably likely* to predict clinical benefit (“based on epidemiologic, therapeutic, pathophysiologic, or other evidence”).”

Furthermore, ICH Guideline E9 Statistical Principles for Clinical Trials (1998) outlines the following general principles for consideration. These are excerpts. For details, please refer to link provided in the reference section.

> The primary variable (‘target’ variable, primary endpoint) should be the variable capable of providing the most clinically relevant and convincing evidence directly related to the primary objective of the trial. The selection of the primary variable

> should reflect the accepted norms and standards in the relevant field of research. There should be sufficient evidence that the primary variable can provide a valid and reliable measure of some clinically relevant and important treatment benefit in the patient population described by the inclusion and exclusion criteria.

In reference to surrogate variables, it states,

> When direct assessment of the clinical benefit to the subject through observing actual clinical efficacy is not practical, indirect criteria (surrogate variables) may be considered. Commonly accepted surrogate variables are used in a number of indications where they are believed to be reliable predictors of clinical benefit.

DAVP's Experience from Antiviral Drug Development

DAVP would like to share some of the previous experience related to the endpoints used in the clinical trials evaluating therapies for treatment of viral infections such as chronic hepatitis C and hepatitis B as well as HIV-1 infection.

The ultimate goal for treatment of chronic hepatitis C (CHC) is to reduce the occurrence of end-stage liver disease and its complications including decompensated cirrhosis, liver transplantation and hepatocellular carcinoma. Evaluating clinical outcomes from prospective, randomized controlled clinical trials in patients infected with hepatitis C virus is challenging and not feasible because of the difficulty of maintaining patients on a randomized arm without intervening therapy for a sufficient duration (many years) to identify late-occurring clinical events such as HCC; therefore, treatment response is defined by a virological parameters. The most important virological parameter for treatment of CHC has been the sustained virological response (SVR).

Use of SVR is the primary efficacy endpoint in trials evaluating CHC treatments. The attainment of SVR has been proven to be a reliable predictor of long-term clearance of hepatitis C infection and is generally regarded as a "virological cure". Multiple observational cohorts show correlations between SVR and improvements in clinical outcomes such as development of hepatocellular carcinoma, hepatic events, fibrosis, and all-cause mortality. Attainment of SVR in chronic hepatitis C patients has shown to be associated with a decreased progression of fibrosis, and some studies have even suggested reversal of fibrosis or early cirrhosis (Poynard, et al. Hepatology 2000; 32: 1131-1137 & Gastroenterology 2002; 122: 1303-1313).

Reference ID: 3772502

Treatment of CHC with direct-acting antiviral agents (DAAs) in most patients generally results in a rapid decrease in ALT levels compared to baseline values. This decrease in ALT values is consistent with the reduction in viral load and hepatic inflammation. Elevations in liver enzymes are observed with viral breakthrough or relapse.

In chronic hepatitis B, aims of treatment are to achieve sustained suppression of hepatitis B virus replication and to induce remission of liver disease. The ultimate goal in chronic hepatitis B treatment is to prevent cirrhosis, liver failure and HCC. For hepatitis B drug approvals, DAVP has used co-primary endpoints such as improvement in liver histology, viral suppression (decrease in serum HBV DNA level), HBe antigen loss with or without detection of anti-HBe, and normalization of serum transaminases. Also for hepatitis B, trial populations are generally less advanced and clinical endpoints are not expected for years or decades.

DAVP has used HIV RNA levels as surrogate endpoint for drug trials evaluating investigational agents for the treatment of HIV -1 infection.

Discussion and Recommendations

We agree with DGIEP's position that the primary endpoint of ALT normalization will not be an appropriate primary endpoint because, as noted, a correlation has not been established between ALT reduction/normalization and clinically meaningful outcomes in patients with CESD. Elevations in serum liver enzymes do not reflect synthetic function of the liver and normal liver enzymes do not necessarily preclude significant or advanced liver disease.

Although, ALT is used as an indicator of hepatic inflammation, its correlation with hepatic disease progression is not well documented (Feld and Liang, 2006). Previous studies in individuals with chronic hepatitis C have shown that individuals with normal ALT can have advanced disease with stage 3 or 4 fibrosis and even individuals with persistently normal ALT over 3-6 years can have fibrosis progression (Kyrlagkitssis, et al. Am J Gastroenterol 2003; Hui, et al. J Hepatol 2003).

Similarly, data in HBeAg-negative chronic hepatitis B patients with persistently high-normal ALT shows that these patients are still at risk of liver disease progression (Lin, et al. Hepatology 2007).

For improvement in ALT values to be used as a surrogate endpoint under accelerated approval regulations, the surrogate endpoint is reasonably likely to predict clinical

Reference ID: 3772502

benefit, based on epidemiologic, therapeutic, pathophysiologic or other evidence. Approval under this regulation is subject to the requirement that the applicant study the drug further to verify and describe its clinical benefit (see 21CFR 314.510). For full approval, the sponsor will have to do confirmatory trial with clinical endpoints. We do acknowledge the challenges associated with the recruitment of patients with CESD. Since, a trial with primary endpoint of clinical outcomes is not feasible in this patient population; we agree that some validated surrogate endpoint could be used as a primary endpoint to make drug available for those in need in a timely manner.

We recommend considering a long-term observational follow-up registry to document improvements in long-term clinical outcomes such as progression of liver disease, liver-related mortality or liver failure requiring liver transplantation.

Thank you for this interesting consult. We look forward to further discussions with DGIEP.

Reference ID: 3772502

References

Bernstein DL, Hülkova H, Bialer MG, Desnick RJ. Cholesteryl ester storage disease: Review of the findings in 135 reported patients with an underdiagnosed disease. J Hepatol. 2013 Feb 26.

Feld and Liang. Hepatitis C – Identifying Patients with Progressive Liver Injury. Hepatology. 2006;43:S194-S206.

Guidance for Industry Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics [Available at http://www.fda.gov/downloads/Drugs/Guidances/ucm071590.pdf Accessed on May 28, 2015]

Hui CK, Belaye T, Montegrande K, Wright TL. A comparison in the progression of liver fibrosis in chronic hepatitis C between persistently normal and elevated transaminase. J Hepatol 2003;38:511-517.

International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use. E9 Statistical Principles for Clinical Trials. [Available at http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E9/Step4/E9_Guideline.pdf. Accessed on May 28, 2015].

Kyrlagkitssis I, Potmann B, Smith H, O'Grady J, Cramp ME. Liver histology and progression of fibrosis in individuals with chronic hepatitis C and persistently normal ALT. Am J Gastroenterol 2003; 98:1588-1593.

Lin CL, Liao LY, Liu CJ, Yu MW, Chen PJ, et al. Hepatitis B viral factors in HbeAg-negative carriers with persistently normal serum alanine aminotransferase levels. Hepatology. 2007 May;45(5):1193-8.

Poynard T, McHutchison J, Davis GL, Esteban-Mur R, Goodman Z, Bedossa P, Albrecht J. Impact of interferon alfa-2b and ribavirin on progression of liver fibrosis in patients with chronic hepatitis C. Hepatology. 2000 Nov; 32: 1131-1137.

Poynard T, McHutchison J, Manns M, Trepo C, Lindsay K, Goodman Z, Ling MH, Albrecht J. Impact of pegylated interferon alfa-2b and ribavirin on liver fibrosis in patients with chronic hepatitis C. Gastroenterology 2002 May; 122: 1303-1313.

Reference ID: 3772502

Reiner Ž, Guardamagna O, Nair D, Soran H, Hovingh K, Bertolini S, et al. Lysosomal acid lipase deficiency--an under-recognized cause of dyslipidaemia and liver dysfunction. Atherosclerosis. 2014 Jul;235(1):21-30.

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/s/

POONAM MISHRA
06/01/2015

JEFFREY S MURRAY
06/01/2015

DEPARTMENT OF HEALTH & HUMAN SERVICES Public
Health Service

Food and Drug Administration
Office of New Drugs, ODE-IV
Division of Pediatric and Maternal Health
Silver Spring, MD 20993
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MEMORANDUM TO FILE

From:	Ethan D. Hausman, MD, Medical Officer Division of Pediatric and Maternal Health (DPMH)
Through:	Hari Cheryl Sachs, MD, Medical Team Leader DPMH Lynne P. Yao, MD, Acting Division Director DPMH
BLA Number:	125,561
Sponsor:	Synageva Biophama Corp
Drug:	Kanuma (sebelipase)
Indication:	Lysosomal acid lipase (LAL) deficiency
Dosage form and route of administration:	Injection for intravenous (IV) use
Proposed dosing regimen:	1 to 3 mg/kg once weekly (qW)
Consult due date:	June 1, 2015

Division Consult Request: The Division of Gastroenterology and Inborn Error Products (DGIEP) requests DPMH's "assistance in crafting language appropriate for the labeling in the applicable sections of the label (Indications, D&A, Section 8, etc)"

Reference ID: 3752666

Background

Sebelipase is a lysosomal acid lipase (LAL) enzyme replacement therapy (ERT) under development for the treatment of patients with LAL deficiency. (b) (4). Sebelipase has received orphan designation for treatment of patients with LAL deficiency.

The sponsor submitted data from two clinical studies to support approval of sebelipase treatment in affected patients (b) (4). The first study was an uncontrolled trial in 9 affected patients 1 to 6 months old and the second study was a randomized, placebo-controlled study of 66 affected patients, ages 4 to 58 years.

DGIEP is still reviewing the data and the ages for which sebelipase may be approved are not yet determined.

Pediatric Use Labeling:
The Pediatric Use subsection must describe what is known and unknown about use of the drug in the pediatric population, including limitations of use, and must highlight any differences in efficacy or safety in the pediatric population versus the adult population. For products with pediatric indications, the pediatric information must be placed in the labeling as required by 21 CFR 201.57(c)(9)(iv). This regulation describes the appropriate use statements to include in labeling based on findings of safety and effectiveness in the pediatric use population.(Also see draft Guidance for Industry and Review Staff Pediatric Information Incorporated Into Human Prescription Drug and Biological Products Labeling, February, 2013). Because sebelipase may be approved in pediatric patients, 1 month and older, pediatric information can be distributed in various sections of labeling, where appropriate.

DPMH Labeling Recommendations:

The labeling is undergoing substantial revisions by DGEIP and consultant divisions. This review will focus on labeling sections 1 (Indications), 2 (Dosage and Administration), 5 (Warnings and Precautions) and 8.4 (Pediatric Use). Sections 8.1 (Pregnancy) and 8.3 (Nursing Mothers) will be addressed in the separate Maternal Health labeling review (pending). The descriptions for sections 6 (Warnings and Precautions) and 14 (Clinical Studies) requires intensive data review and is deferred to DGIEP (pending). The labeling version in the SharePoint location as of April 20, 2015 is shown below.

For each section, the proposed language is presented first, followed by recommended changes, if any, in ***bold italics***.

Indications

The proposed indication is shown below followed by DGIEP's recommended modification.

Original

(b) (4) (sebelipase alfa) is a lysosomal acid lipase indicated for (b) (4) patients with Lysosomal Acid Lipase (LAL) Deficiency."

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DGIEP Proposal

TRADENAME™ (sebelipase alfa) is a lysosomal acid lipase indicated for ***the treatment of*** *Lysosomal Acid Lipase (LAL) Deficiency.*

Reviewer comment: The proposed change is acceptable.

Dosage and Administration

This section of labeling is undergoing substantial revisions by DGIEP and FDA consultant divisions.

"2.1 Recommended Dose

(b) (4)

Reviewer comment: For the above section, DPMH recommends the following language for the second paragraph.

The recommended dosage in pediatric patients, ages 1 month to 17 years, and adults presenting with LAL deficiency is 1 mg/kg administered as an intravenous infusion once every other week.

Reviewer comment: The remainder of Dosage and Administration is shown below and is generally acceptable.

2.2 Preparation Instructions

Kanuma is for intravenous infusion only.

1. Determine the number of vials (b) (4) based on the patient's weight and (b) (4).
2. (b) (4)

Table 1: (b) (4) Infusion Volumes (b) (4) *

(b) (4)

* The infusion volume should be based on the prescribed dose and should be prepared to a final Kanuma concentration of 0.1 mg/mL to 1.5 mg/mL.

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3. Mix gently. Do not shake the vials or the prepared infusion.

4. The solution should be inspected visually for particulate matter and discoloration prior to administration. It should be a clear to slightly opalescent, colorless to slightly colored solution. Thin, translucent particles or fibers may be present in the vials or diluted solution. Do not use if the solution is cloudy or if (b) (4) observed.

5. Discard any unused product. Do not freeze.

2.3 Administration Instructions

Administer the diluted solution as an intravenous infusion using a low-protein binding infusion set with an in-line, low-protein binding 0.2 micron filter.

(b) (4). A 1-hour infusion may be considered (b) (4)

2.4 Storage (b) (4)

Kanuma contains no preservatives; therefore, product should be used immediately after dilution. If immediate use is not possible, the diluted product may be stored up to 24 hours at 2°C to 8°C (36°F to 46°F) (b) (4) Do not freeze or shake. Protect from light."

Warnings and Precautions

"5.1 Hypersensitivity Reactions Including Anaphylaxis

Hypersensitivity reactions, including anaphylaxis, have been reported in Kanuma-treated patients. (b) (4) (b) (4) reaction (b) (4) of severe respiratory distress, urticarial (b) (4), and tachycardia. (b) (4)

In clinical (b) (4) Kanuma -treated patients, including (b) (4) infants and (b) (4) and adults, experienced signs and symptoms either consistent with or that may be related to a hypersensitivity reaction. (b) (4) signs and symptoms occurring in two or more (b) (4) included abdominal pain, fever, chills, diarrhea, eczema, laryngeal edema, nausea, pallor, pruritus, rash, (b) (4), and vomiting. The majority of reactions occurred during or within 4 hours of the completion of the infusion. Patients were not routinely pre-medicated prior to infusion of Kanuma during clinical (b) (4)

The management of hypersensitivity reactions may include temporarily interrupting the infusion, lowering the infusion rate, and/or treatment with antihistamines, antipyretics, and/or corticosteroids. If interrupted, the infusion may be resumed at a slower rate with increases as tolerated. Pre-treatment with antipyretics and/or antihistamines may prevent subsequent reactions in those cases where symptomatic treatment was required.

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(b) (4)

Consider the risks and benefits of re-administering Kanuma following a severe reaction. Monitor patients, with appropriate resuscitation measures available, (b) (4) the decision is made to re-administer the product."

Reviewer comment: The above language is consistent with recent labeling descriptions for other ERTs (e.g., Aldurazyme, BLA 125058; labeling update April 3, 2013). Final labeling language is deferred to DGIEP.

6 Adverse Reactions

The description of patient exposure in the Adverse Reactions section of labeling is shown below.

(b) (4)

Reviewer comment: The description above is not consistent with section 14 (Clinical Studies), which describes treatment of 75 patients including 9 infants (ages 1 to 6 months at enrolment) in Study 1, and 66 pediatric and adult patients (ages 4 to 58 years at randomization) in Study 2, and Study 3 which included 65 of the 66 patients in Study 2. The duration of each study should also be provided.

The description of the patients studied (including the numbers of patients studied) in sections 6 and 14 should match. Alternatively, the reason for any disparity of the number of patients described in sections 6 and 14 should be clearly described. This comment also applies to section 8.4; that is, the number of pediatric patients studied and the age range of pediatric patients studied should be clear.

8.4 Pediatric Use

"Safety and effectiveness of Kanuma have been established in pediatric patients aged 1 month and older. Clinical trials with Kanuma were conducted in (b) (4) patients (b) (4) range 1 month to (b) (4) years old) (b) (4) [see Clinical Studies (14)]."

Reviewer comment: The number of pediatric patients studied is unclear and the above description is not acceptable.

Proposed language

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"Safety and effectiveness of Kanuma have been established in ***[DGIEP to insert the number of pediatric patient studied]*** *pediatric patients aged 1 month and older. Clinical trials with Kanuma were conducted in* (b) (4) *patients (* (b) (4) *, range 1 month to* (b) (4) *years old)* (b) (4) *[see Clinical Studies (14)]."*

14 Clinical Studies

As noted in the comments Adverse Reactions, the Clinical Studies section of labeling describes treatment of 75 patients including 9 infants (ages 1 to 6 months at enrollment) in Study 1, and 66 pediatric and adult patients (ages 4 to 58 years at randomization) in Study 2, and Study 3 which included 65 of the 66 patients in Study 2.

Reviewer comment: The number of pediatric and patients studied is unclear and the above descriptions are not acceptable.

DPMH defers the final text of section 14 to DGIEP; however, DPMH offers the following descriptions for Studies 1 and 2.

(b) (4)

Conclusion and Recommendations

The above comments were provided to DGIEP in advance of the internal labeling meeting on May 12, 2015. The reader is directed to final negotiated labeling (pending) for additional labeling revisions which are not described above.

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

/s/

ETHAN D HAUSMAN
05/11/2015

HARI C SACHS
05/11/2015
I agree with these recommendations.

LYNNE P YAO
05/12/2015

DMEP Consult Memo

To: Juli Tomaino, M.D.
Division of Gastroenterology and Inborn Errors Products (DGIEP)

From: Julie Golden, M.D.
Division of Metabolism and Endocrinology Products (DMEP)

Through: James Smith, M.D., M.S.
Deputy Division Director
DMEP

Re: BLA 125561
Lipid changes with sebelipase alfa for treatment of lysosomal acid lipase deficiency

Introduction

DMEP received the following consult question from DGIEP on March 11, 2015, with a requested completion date of April 11, 2015. The BLA is on a priority review clock on "The Program" with a PDUFA date of July 8, 2015.

DGIEP requests your assistance in determining whether a reduction in LDL cholesterol is potentially acceptable as a clinical endpoint in patients with lysosomal acid lipase (LAL) deficiency (cholesteryl ester storage disease (CESD) phenotype. The diagnosis of late-onset disease, CESD, is highly variable, where the majority of patients (80%) present in childhood with progressive liver disease, while others go undiagnosed until complications manifest in adulthood. The estimated prevalence is 1:150,000 to 1:300,000, approximating 750 to 1500 U.S. patients. Elevation of serum transaminases, dyslipidemia (high LDL-cholesterol, high triglycerides, and low HDL) and hepatosplenomegaly are the main abnormalities seen in CESD, but not universally manifested in all CESD patients. CESD patients experience hepatic microvesicular steatosis, which progresses to fibrosis, cirrhosis and finally, death due to liver failure. Although many CESD patients are diagnosed with dyslipidemia, the potential for premature accelerated atherosclerosis has only been reported in a small number of CESD patients; resulting in coronary artery disease, aneurysm, stroke, ulcerothrombotic atherosclerosis of the aorta and stenosis of femoral arteries.

We are in the process of reviewing the totality of the data provided in the BLA submission, receipt date 1/8/2015. While the primary endpoint of the trial evaluating sebelipase alfa (SA) in patients with CESD (Study LAL-CL02) is ALT normalization, the Division does not agree with ALT normalization as the primary endpoint for this trial. The Division remains concerned that the primary efficacy endpoint, normalization of ALT, for Study LAL-CL02 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]). Therefore, ALT normalization is unlikely to serve as the sole basis to establish

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efficacy in the CESD patient population. Instead, the totality of the clinical and laboratory parameters for which there are pre- and on-treatment data are under review. The change from baseline in LDL-c is a key secondary endpoint, along with other cholesterol parameters.

In light of recent products that received full approval based on improvements in LDL-c in small patient populations (i.e., Kynamro) and the association of dyslipidemia with increased risk of cardiovascular events, DGIEP is evaluating whether demonstrating an improvement in LDL-c would be a clinically meaningful benefit in patients with CESD. Please comment on whether a reduction in LDL-c represents a meaningful treatment benefit in this rare disease population.

Background

Lysosomal acid lipase (LAL) is the key enzyme responsible for hydrolysis of cholesteryl esters in the lysosomes; its deficiency leads to lysosomal accumulation of cholesteryl esters and triglycerides primarily in hepatocytes and macrophages. Mutations in the *LIPA* gene that encodes for LAL results in two major phenotypes: (1) Wolman's disease, which is universally fatal in the first few years of life and is characterized by hepatosplenomegaly, malabsorption, failure to thrive, and adrenal calcification, and (2) cholesteryl ester storage disease (CESD), a heterogeneous condition that can present in childhood or adulthood; patients typically present with hepatic steatosis that can lead to fibrosis/cirrhosis, but other manifestations can include dyslipidemia. Because of the heterogeneity of the disease, some patients are not diagnosed into adulthood, and some authors suggest that it may be underdiagnosed. This consult will focus on the CESD phenotype.

The primary lipid abnormalities seen in CESD are elevated LDL cholesterol (LDL-C) and low HDL-C, with a more variable finding of increased triglycerides (TG). Out of a case series of 135 CESD patients published in 2013,[1] 43 patients had reported values of LDL-C, which ranged from 119 to 360 mg/dL. (By contrast, mean LDL-C in U.S. adults is estimated to be 116 mg/dL (95% CI 114, 117) from a survey conducted between 2007 and 2010.[2]) Circulating LDL-C is regulated by LDL receptors (LDLR) that are upregulated in response to cellular cholesterol. By trapping cholesteryl esters in the lysosome, LAL deficiency prevents the generation of free cholesterol in the cell. Because cholesterol synthesis via 3-hydroxy-3-methylglutaryl-coezyme A (HMGCoA) reductase is regulated by the amount of intracellular free cholesterol, *de novo* cholesterol production is increased in LAL deficiency, which down-regulates LDLR, resulting in decreased clearance of LDL-C from the circulation.

Historically, the National Cholesterol Education Program Adult Treatment Panels (NCEP-ATP), appointed by the NHLBI, have recommended various LDL-C cut-offs to reduce cardiovascular risk. For example, the most recent ATPIII update recommended that in high-risk persons, the LDL-C goal is <100 mg/dL, but when CV risk is very high, an LDL-C

[1] Bernstein DL, et al. Cholesteryl storage disease: Review of the findings in 135 reported patients with an underdiagnosed disease. J Hepatol, 2013; 58: 1230-43.
[2] Carroll MD, et al. Trends in lipids and lipoproteins in US adults, 1988-2010. JAMA, 2012; 308(15): 1545-54.

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goal of <70 mg/dL is "a reasonable clinical strategy."[3,4] Furthermore, for moderately high-risk persons, the recommended LDL-C goal is <130 mg/dL, with an LDL-C goal <100 mg/dL being a therapeutic option. However, in 2013, the NCEP-ATP cholesterol guidelines were updated by an expert panel from the American College of Cardiology (ACC) and the American Heart Association (AHA).[5] These guidelines have changed the paradigm of cholesterol treatment from LDL-C "goals" to the identification of patients most likely to benefit from cholesterol-lowering statin therapy. This is because the only strategy that has been utilized in cardiovascular outcomes trials conducted over the last 20 years has been the use of fixed doses of cholesterol-lowering drugs to reduce atherosclerotic CV risk, as opposed to treating to a specific LDL-C goal. Furthermore, because the overwhelming body of evidence for CV risk reduction has derived from statin trials, the guidelines, and standard-of-care medical practice, focus on statins as first-line cholesterol-lowering therapy for primary and secondary prevention of atherosclerotic cardiovascular disease.

Interestingly, in the aforementioned case series,[1] only 35 (26%) patients with CESD were treated with statins. There has been speculation that LDL-C lowering by HMGCoA reductase inhibition could either improve (by decreasing endogenous cholesterol production) or worsen (by increasing cholesteryl esters to the lysosomes by enhancing LDL uptake via LDLR upregulation) the liver disease of CESD.[6] According to the Bernstein case series, of the 35 patients taking statins, 8 had no liver biopsy findings reported and 15 had biopsy findings with fibrosis, cirrhosis, or CESD-associated hepatopathology but no long-term or sequential follow-up data. In the 12 remaining patients, there were no cases whose liver histology improved, and all 12 patients had progressive liver disease that was more advanced in subsequent biopsies, consistent with the progressive nature of liver disease in CESD. Six patients required transplantation or died from liver failure. The authors concluded that *these findings emphasize the lack of efficacy of statins in ameliorating liver disease or preventing its progression.*[1] DMEP acknowledges this perspective (although this study was far from conclusive regarding whether statins have any effect on liver disease in CESD); however, for cardiovascular protection, statins – typically administered at the highest dose tolerated in patients at high CV risk – are the standard-of-care for the reasons discussed above.

Given that dyslipidemia, including increases in total cholesterol, LDL-C, and triglyceride-rich lipoproteins, as well as low HDL-C, are considered risk factors for cardiovascular disease, it would seem reasonable to assume that patients with CESD are at increased risk

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[3] Grundy SM, et al. Implications of recent clinical trials for the National Cholesterol Education Program Adult Treatment Panel III Guidelines. Circulation, 2004; 110: 227-39.

[4] Note that these recommendations also included the following advice: "when a high-risk patient has high triglycerides or low high-density lipoprotein cholesterol (HDL-C), consideration can be given to combining a fibrate or nicotinic acid with an LDL-lowering drug". Since the writing of these recommendations, <u>three</u> randomized controlled trials of fibrate or nicotinic acid on top of a statin have *failed* to demonstrate CV benefit compared to statin alone.

[5] Stone NJ, et al. 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation, 2014; 129(25 Suppl 2): S1-45.

[6] Fourchier SW and Defesche JC. Lysosomal acid lipase A and the hypercholesterolaemic phenotype. Curr Opin Lipidol, 2013; 24: 332-8.

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for CV disease. In addition, associations between the *LIPA* gene and coronary artery disease (CAD) have been identified in genome-wide association studies, although interestingly, the CAD risk allele was not associated with increased LDL-C.[6] Evidence of atherosclerotic disease in patients with CESD is limited in the literature. This may be because of the young age at which patients present with CESD. Fourchier noted in a 2013 review that five cases of cardiovascular disease in patients with CESD had been previously reported, but these cases were mostly asymptomatic and the diagnosis of CESD was made late in life.[6] Clearly, the heterogeneity of the condition makes characterizing the phenotype and natural history complicated, and more work is needed in this area.

As noted in the consult question, cholesterol homeostasis is also impacted in other genetic conditions; most notably homozygous familial hypercholesterolemia (HoFH), which is most often a result of mutations in both alleles for the LDLR. These patients have a distinctive phenotype of extremely high LDL-C from birth, cutaneous or tendinous xanthomas, and the onset of CV disease in early childhood.[7] Untreated patients with HoFH often die by 20 years of age, although recent advances in LDL-C lowering therapy (e.g., statins and LDL apheresis) have delayed CV events and prolonged survival in these patients.[7] Given this history, two drugs that have been recently approved for HoFH (but notably have serious safety concerns that would preclude studying or approving for a broader patient population) were evaluated based on changes in LDL-C. Notably, HoFH is essentially a monogenic condition of LDL-C metabolism; therefore, there is no controversy that the markedly elevated levels of LDL-C cause the cardiovascular phenotype that characterizes this syndrome. Prior to the approval of Juxtapid and Kynamro for HoFH, the last approved first-in-class LDL-C-lowering drug was ezetimibe, which was approved in 2002. Ezetimibe, like the statins, was approved based on changes in LDL-C, but given new concerns about utilizing lipid biomarkers as a CVD surrogate, particularly TG and HDL-C,[8,9,10,11,12] as well as the strong evidence of CV benefit and excellent safety profile established for the statins, it is controversial whether new LDL-C-lowering drugs being developed for broader patient populations should be approved based on changes in LDL-C alone prior to the completion of a CV outcomes trial. At present, DMEP remains willing to consider changes in LDL-C as a basis for approval, but this will be discussed at upcoming AC meetings in June 2015 with regard to the potential approval of two drugs in a new class of agents, PCSK9 inhibitors, which are currently under review. (The PCSK9 inhibitors demonstrate LDL-C lowering of 50 to 60 percent.)

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[7] Raal FJ, et al. Reduction in mortality in subjects with homozygous familial hypercholesterolemia associated with advances in lipid-lowering therapy. Circulation, 2011; 124: 2202-7.
[8] Barter PJ, et al. Effects of torcetrapib in patients at high risk for coronary events. N Engl J Med, 2007; 357: 2109-22.
[9] ACCORD Study Group. Effects of combination lipid therapy in type 2 diabetes mellitus. N Engl J Med, 2010; 362(17): 1563-74.
[10] Boden WE, et al. Niacin in patients with low HDL cholesterol levels receiving intensive statin therapy. N Engl J Med, 2011; 365: 2255-67.
[11] Schwartz GG, et al. Effects of dalcetrapib in patients with a recent acute coronary syndrome. N Engl J Med, 2012; 367: 2089-99.
[12] The HPS2-THRIVE Collaborative Group. Effects of extended-release niacin with laropiprant in high-risk patients. N Engl J Med, 2014; 371: 203-12.

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Natural History Study LAL-2-NH01

The sponsor has conducted a natural history observational study in children ≥ 5 years of age and adults with LAL deficiency. The primary objective of this study was to characterize key aspects of the clinical presentation, disease phenotype, and progression of patients with LAL deficiency.

A total of 48 patients were confirmed to have LAL deficiency and were included in the full analysis set.

Data could be collected from living and deceased patients; all but one (47 of 48) entered in the study were living. The one deceased individual had a history of liver transplant and allogeneic stem cell transplant with subsequent graft-versus-host disease, and died at age 17.6 years due to H1N1 influenza. One patient who was alive at the time of consent, died on study at age 16.0 years from a motor vehicle accident.

The mean and median duration of time from the first record collection to the last record collection was 13.9 and 12.3 years, respectively, with a range of 1.8 to 38.8 years.

A total of 29 (60%) patients were male, and 44 (92%) patients were white. More than half (27 of 48; 56%) of patients were less than 20 years of age, with eight (17%) less than 10 years of age. The maximum age at the time of consent was 48 years.

The mean and median age at the first report of signs and symptoms was 9.0 and 5.8 years, respectively (range 0 to 42 years), and mean and median ages at diagnosis was 15.2 and 9.5 years, respectively (range 1 to 46 years). A total of 36 patients (75%) had the first report of signs and symptoms by 10 years of age. The actual first sign or symptom experienced was not captured. The time from the first report of signs or symptoms to diagnosis was 5 years or less for 77%, between 5 and 10 years for 8%, and more than 10 years for 15% of patients, with a maximum time of 40 years.

A history of hepatomegaly and splenomegaly was documented in 88% and 79% of patients, respectively. A history of other conditions was less common, with no other condition documented in more than 20% of patients. Of the 48 patients, 31 (65%) had hepatic histology data. Steatosis, fibrosis, and cirrhosis were documented in 87%, 52%, and 16% of the 31 patients, respectively. Six (13%) had undergone liver transplant.

The only report of atherosclerotic cardiovascular disease was "peripheral artery disease" (not considered "significant" by the investigator) in one 28-year-old patient. This patient also had a history of subvalvular aortic stenosis, aortic insufficiency, and infrarenal aortic stenosis, and her twin sister, also participating in the study, had a history of tricuspid valve insufficiency and aortic stenosis since age 24. The third sibling in this family participating in this study, a 32-year-old male, had no significant medical history reported. No family history of early death due to cardiovascular disease was reported in this family, although 7 (15%) patients in the overall cohort reported family history of early death due to CV

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disease. There was no discussion of development of CV disease in the study population over the observational study duration.

Prior lipid-lowering medication (LLM) use, most commonly a statin, and dietary intervention were reported for 81% and 68% of patients, respectively. The mean age at first LLM use was 15.8 years.

Lipid data, including HDL-C, LDL-C, TG, and total-C, were collected from at least three time points spanning a period of at least 12 months.

LDL-C values are displayed in Figure 1; LDL-C values prior to LLM use or in patients with no LLM use are presented in solid circles and values after initiation of LLM are presented in hollow circles. The highest documented LDL-C was 409 mg/dL.

Figure 1. LDL-C Values, by Patient and LLM Use, Natural History Study

(b) (4)

Figure 2 presents a spaghetti plot of LDL-C values over time by patient age. Patients who underwent liver transplant are shown by dark lines; LDL-C values before transplant are indicated by solid circles and those after transplant by hollow circles.

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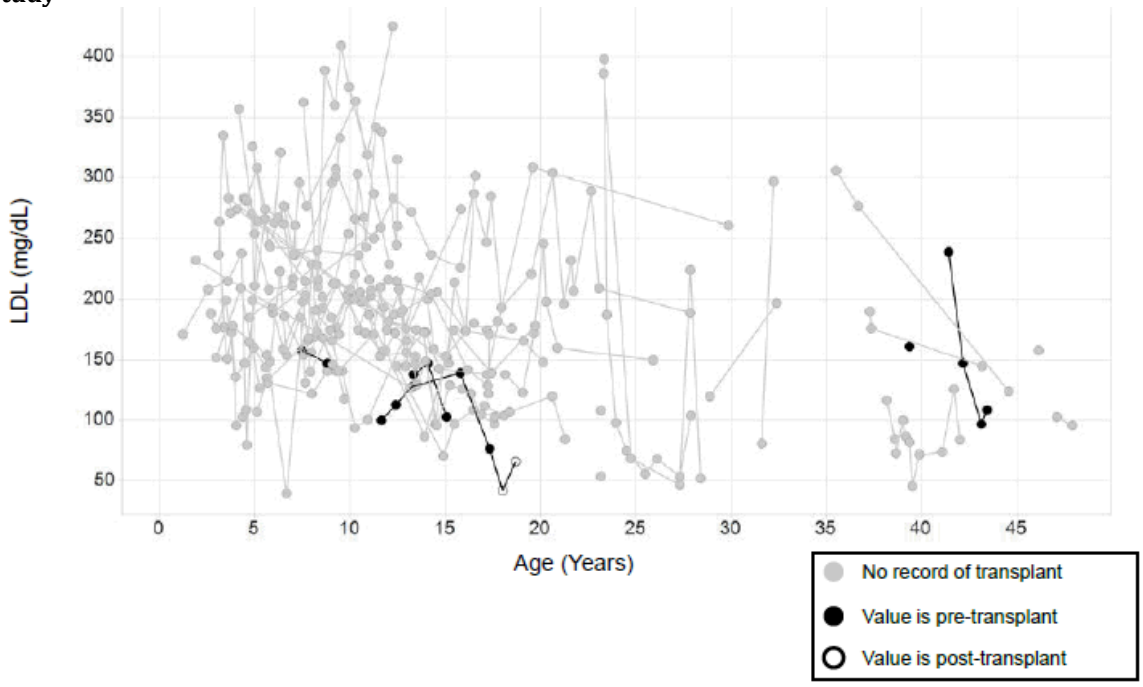
Figure 2. LDL-C Over Time by Age, in Patients With and Without Liver Transplant, Natural History Study



Source: LAL-2-NH01 CSR, Figure 26

Regarding other lipid parameters, 28 (58%) of patients had at least one TG value over 200 mg/dL, and 4 (8%) had at least one TG value ≥ 500 mg/dL. The highest value reported was 700 mg/dL. There were no reported cases of pancreatitis. A total of 42 (88%) of patients had at least one HDL-C value < 40 mg/dL.

Lipids are summarized in the following table through 24 months of observation:

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Table 1. Observed Lipid Data, Natural History Study

Laboratory Test Statistic[2]	Baseline[3]	Semi-Annual Follow-up Intervals - Observed Values[1]			
		6 Months	12 Months	18 Months	24 Months
HDL Cholesterol (mg/dL)					
N	46	13	19	17	16
ABN Low, n (%)	20 (43.5)	5 (38.5)	13 (68.4)	9 (52.9)	10 (62.5)
WNL, n (%)	26 (56.5)	8 (61.5)	6 (31.6)	8 (47.1)	6 (37.5)
ABN High, n (%)	0	0	0	0	0
Mean (SD)	37.5 (17.20)	38.5 (13.88)	30.7 (10.85)	36.8 (11.93)	29.4 (10.26)
25th Quartile	25.87	28.00	26.00	31.00	21.80
Median	36.84	39.00	30.00	34.00	31.00
75th Quartile	43.00	46.33	37.84	43.24	38.50
Min, Max	11.6, 95.0	15.4, 63.0	9.7, 56.0	14.7, 63.3	13.0, 41.3
LDL Cholesterol (mg/dL)					
N	45	11	19	17	16
ABN Low, n (%)	0	0	0	0	0
WNL, n (%)	16 (35.6)	3 (27.3)	9 (47.4)	7 (41.2)	7 (43.8)
ABN High, n (%)	29 (64.4)	8 (72.7)	10 (52.6)	10 (58.8)	9 (56.3)
Mean (SD)	202.9 (82.26)	191.7 (66.95)	183.2 (73.77)	192.0 (95.44)	201.6 (95.11)
25th Quartile	144.79	159.07	103.86	136.00	118.44
Median	189.19	176.00	199.00	197.68	188.17
75th Quartile	243.24	211.00	254.00	263.00	269.00
Min, Max	54.0, 398.1	73.0, 335.0	87.0, 297.3	46.0, 389.0	72.0, 409.0
Total Cholesterol (mg/dL)					
N	48	12	25	23	17
ABN Low, n (%)	0	0	0	0	0
WNL, n (%)	18 (37.5)	3 (25.0)	12 (48.0)	9 (39.1)	10 (58.8)
ABN High, n (%)	30 (62.5)	9 (75.0)	13 (52.0)	14 (60.9)	7 (41.2)
Mean (SD)	269.5 (90.30)	266.1 (61.10)	234.9 (64.88)	251.4 (90.98)	232.8 (89.01)
25th Quartile	213.00	233.00	177.61	167.00	170.00
Median	245.00	254.00	232.00	248.00	229.00
75th Quartile	312.80	328.19	277.00	281.85	285.00
Min, Max	120.0, 497.7	139.0, 347.5	131.3, 366.8	92.7, 458.0	119.7, 473.0

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Laboratory Test Statistic[2]	Baseline[3]	Semi-Annual Follow-up Intervals - Observed Values[1]			
		6 Months	12 Months	18 Months	24 Months
Triglycerides (mg/dL)					
N	48	12	24	19	18
ABN Low, n (%)	0	0	0	0	0
WNL, n (%)	35 (72.9)	6 (50.0)	19 (79.2)	17 (89.5)	16 (88.9)
ABN High, n (%)	13 (27.1)	6 (50.0)	5 (20.8)	2 (10.5)	2 (11.1)
Mean (SD)	184.4 (125.09)	222.6 (134.73)	160.1 (90.03)	135.9 (42.38)	134.5 (50.40)
25th Quartile	103.00	143.44	106.21	92.92	106.19
Median	146.00	201.27	126.55	133.00	122.00
75th Quartile	205.77	231.62	193.35	170.80	154.87
Min, Max	3.4, 700.0	70.0, 584.1	67.3, 436.3	78.8, 214.0	60.2, 254.0

Source: Section 14.3, Table 14.3.4.9.

ABN = abnormal; HDL = high-density lipoprotein; LDL = low-density lipoprotein; Min = minimum; Max = maximum; SD = standard deviation; WNL = within normal limits

Note: ABN-Low, WNL, ABN-High counts may not sum to the number of subjects with data (n) due to missing results assessments by the Investigator.

Note: n represents the number of subjects with an assessment of the parameter in that interval.

1 Follow-up intervals are non-overlapping, and represent time from the baseline assessment. For subjects with more than one assessment in an interval, the latest assessment in the window was used. For computation, 1 month = 30.4 days.

2 Values below (ABN Low), WNL, and above (ABN High) the normal range were determined using standardized age- and gender- stratified normal ranges based on those from a central laboratory used in Synageva Study LAL-CL01.

3 The overall baseline for each parameter was the first recorded value for that particular parameter.

Source: LAL-2-NH01 CSR, Table 19

In patients in the LLM set (patients who had at least one LLM, at least one recorded pre-medication value, and at least one recorded post-medication value for one outcome variable of interest), mean LDL-C at baseline (prior to initiating LLM, n=17) was approximately 228 mg/dL, and at 24 months (n=4), mean LDL-C was 131 mg/dL.

Trial LAL-CL02

This trial evaluating the efficacy and safety of sebelipase alfa was a phase 3, randomized, double-blind, placebo-controlled trial of 20 weeks' duration, followed by an open-label extension of 130 weeks.

A total of 66 patients 4 years of age or older with LAL deficiency (36 sebelipase alfa and 30 placebo) were randomized. LAL deficiency was confirmed by dried blood spot (DBS) testing.[13] All patients were to have abnormal ALT (≥ 1.5x ULN) to be randomized. Randomization was stratified by age (< 12 years, ≥ 12 years), average screening ALT (< 3 × ULN, ≥ 3 × ULN), and use of lipid lowering medications (LLMs) (yes, no). If receiving LLM, the patient was to be on a stable regimen for 6 weeks prior to randomization, and willing to remain on a stable dose for at least the first 32 weeks of treatment.

The dosage regimen was 1 mg/kg qow IV. During the open-label extension, dose increases to 3 mg/kg qow were permitted in the event of inadequate clinical response, and dose reductions to 0.35 mg/kg qow were permitted in the event of poor tolerability.

[13] Hamilton J, et al. A new method for the measurement of lysosomal acid lipase in dried blood spots using the inhibitor Lalistat 2. Clin Chim Acta. 2012; 413: 1207-10.

Reference ID: 3743382

The primary efficacy endpoint was normalization of ALT. In addition to the primary endpoint, a series of key secondary endpoints were evaluated, including reduction in LDL-C, TG, and non-HDL-C, and increase in HDL-C, in a fixed sequence to control for type I error.

Study Patients

A total of 86 patients were screened for study eligibility; 66 patients in 15 countries were considered eligible and enrolled in the trial over a 9-month period.

The average age at randomization was 16 years, with a range of 4 to 58 years; 50% of patients were female, 83% were white, 2% were black, and 15% were of Hispanic ethnicity. Demographics were well-balanced between groups. The following table describes LAL deficiency diagnosis and history in the patient population:

Table 2. LAL Deficiency Diagnosis and History, Trial LAL-CL02

Parameter / Statistic	Sebelipase Alfa (N=36)	Placebo (N=30)	Total (N=66)
Age at first onset of LAL Deficiency-related abnormality (years)			
N	36	30	66
Mean (SD)	7.5 (8.36)	5.4 (5.16)	6.5 (7.12)
Q1	1.0	2.0	1.0
Median	5.0	4.0	4.0
Q3	10.5	8.0	10.0
Range	0 - 42	0 – 20	0 - 42
p-value	0.3256		
First LAL Deficiency-related abnormality, n (%)			
Elevated transaminases	17 (47)	14 (47)	31 (47)
Hypercholesterolaemia	6 (17)	2 (7)	8 (12)
Hypertriglyceridaemia	1 (3)	0	1 (2)
Low HDL	0	0	0
Enlarged spleen (splenomegaly)	0	1 (3)	1 (2)
Complications of liver disease	0	0	0
Cardiovascular disease events	0	0	0
Other	12 (33)	13 (43)	25 (38)
Method of initial diagnosis, n (%)			
Enzyme activity	23 (64)	20 (67)	43 (65)
Genetic sequencing	2 (6)	3 (10)	5 (8)
Other	11 (31)	7 (23)	18 (27)

Source: LAL-CL02 CSR, Table 18

Baseline lipids were heterogeneous, with some patients in the normal/optimal range, and others abnormally high (or low, in the case of HDL-C). On average, mean LDL-C was 207 mg/dL, with a range of 70 to 378 mg/dL. Mean baseline LDL-C was somewhat higher in the placebo group than the sebelipase group. Baseline TG was only modestly elevated, and not in the range considered at risk for pancreatitis ("severe" hypertriglyceridemia is generally defined for labeling purposes as a fasting TG of ≥ 500 mg/dL). Baseline lipid parameters are shown in the table below:

Reference ID: 3743382

Table 3. Baseline Serum Lipids, Trial LAL-CL02

Parameter / Statistic	Sebelipase Alfa (N=36)	Placebo (N=30)	Total (N=66)
LDL-c (mg/dL) at baseline			
N	36	30	66
Mean (SD)	189.9 (57.16)	229.5 (69.95)	207.9 (65.85)
Median	193.0	213.0	204.0
Range	70 - 280	135 - 378	70 - 378
p-value		0.0618	
LDL-c category at baseline [n (%)]			
< 130	4 (11)	0	4 (6)
≥ 130 - < 190	14 (39)	10 (33)	24 (36)
≥ 190	18 (50)	20 (67)	38 (58)
p-value		0.1430	

Parameter / Statistic	Sebelipase Alfa (N=36)	Placebo (N=30)	Total (N=66)
Non-HDL-c (mg/dL) at baseline			
N	36	30	66
Mean (SD)	220.5 (61.48)	263.8 (75.48)	240.2 (71.06)
Median	223.5	241.5	230.5
Q3	262.5	336.0	295.0
Range	93 - 332	155 - 408	93 - 408
p-value		0.0341	
TG (mg/dL) at baseline			
N	36	30	66
Mean (SD)	152.8 (54.43)	174.4 (65.90)	162.6 (60.42)
Q1	110.0	122.0	113.0
Median	138.0	170.0	159.5
Range	65 - 307	66 - 361	65 - 361
p-value		0.1509	
TG category at baseline [n (%)]			
< 200	30 (83)	22 (73)	52 (79)
≥ 200 - < 500	6 (17)	8 (27)	14 (21)
p-value		0.3751	
Cholesterol (mg/dL) at baseline			
N	36	30	66
Mean (SD)	252.5 (60.70)	296.7 (75.38)	272.6 (70.79)
Median	253.0	278.0	261.5
Range	121 - 355	191 - 440	121 - 440
p-value		0.0341	
HDL-c (mg/dL) at baseline			
N	36	30	66
Mean (SD)	32.4 (7.09)	33.4 (7.46)	32.8 (7.22)
Median	32.0	33.5	32.5
Range	18 - 48	16 - 47	16 - 48
p-value		0.5065	

N: Number of subjects in specified treatment group; n: Number of subjects with data available; %: Percentage based on N; SD: Standard deviation; ULN: Upper limit of normal.

p-value for treatment differences (Fisher's exact test for categorical data and Wilcoxon rank sum test for numerical data); Baseline: Last measurement prior to first study drug infusion. In case of multiple pre-treatment measurements, the average of the last (up to 3) measurements.

Source: LAL-CL02 CSR, Table 24

A total of 26 patients (39%) were on LLM at baseline, the majority of which were statins. LLM history and usage at baseline is described in the table below:

Reference ID: 3743382

Table 4. History of and Baseline Lipid Lowering Medication (LLM) Use, Trial LAL-CL02

Parameter	Sebelipase Alfa (N=36) n (%)	Placebo (N=30) n (%)	Total (N=66) n (%)
History of LLM Use			
Subjects with at least one prior medication	15 (42)	11 (37)	26 (39)
Subjects with at least one prior statin	15 (42)	9 (30)	24 (36)
Subjects with at least one prior non-statin LLM	5 (14)	3 (10)	8 (12)
Subjects with at least one prior statin and at least one non-statin LLM	5 (14)	1 (3)	6 (9)
Type of Prior LLM[1]			
Lipid modifying agents, plain	14 (39)	11 (37)	25 (38)
HMG CoA reductase inhibitors	14 (39)	9 (30)	23 (35)
Other lipid modifying agents	3 (8)	1 (3)	4 (6)
Bile acid sequestrants	1 (3)	2 (7)	3 (5)
Fibrates	1 (3)	0	1 (2)
Lipid modifying agents, combinations	1 (3)	0	1 (2)
HMG CoA reductase inhibitors in combination with ezetimibe	1 (3)	0	1 (2)
Baseline LLM Use			
Baseline use of LLM	15 (42)	11 (37)	26 (39)
Baseline use of NAFLD medication	2 (6)	1 (3)	3 (5)

1 WHO Drug Standard June 2012, ATC Level 3 and ATC Level 4.
N: Number of subjects in specified treatment group; n: Number of subjects with at least one medication in the category; %: Percentage based on N.
Note: A subject may have taken more than one kind of medication; LLM, including LLM, NAFLD medications, and corticosteroids.

Source: LAL-CL02 CSR, Table 27

Notably, the proportion of patients on high-intensity statin therapy (i.e., atorvastatin 40 or 80 mg, rosuvastatin 20 or 40 mg, or simvastatin 80 mg), which is considered optimal to reduce the risk of CV events,[5] was low. In the placebo group, one patient (3%) was on atorvastatin 40 mg. In the sebelipase group, four patients (11%) were on high-intensity statin (two on atorvastatin 40 mg, one on atorvastatin 80 mg, and one on simvastatin 80 mg).

No patient had a medical history suggestive of atherosclerotic cardiovascular disease, with the exception of a 21-year-old male patient randomized to placebo with a "vascular graft". No patient had a history of xanthoma.

Efficacy Evaluation

The last double-blind assessment for the primary efficacy endpoint was defined as the last measurement prior to the Week 20 infusion. All but one patient (65 of 66; 98%) completed the double-blind period and continued in the open-label period. One 13-year-old male prematurely discontinued due to an infusion reaction.

A summary of the efficacy results are presented below:

Reference ID: 3743382

Table 5. Summary of Primary and Secondary Endpoints, Trial LAL-CL02

Parameter / Statistic	Sebelipase Alfa (N=36)	Placebo (N=30)	Statistically significant in fixed sequence test
PRIMARY EFFICACY ENDPOINT (#1):			
1. ALT normalisation [n (%)]			
N	36	30	
Yes	11 (31)	2 (7)	Yes
Difference	24%		
p-value	0.0271		
SECONDARY EFFICACY ENDPOINTS (#2 – 9)			
2. LDL reduction (percentage change from baseline)			
N	36	30	
Mean (SD)	-28.42 (22.304)	-6.25 (13.015)	
Q1	-46.32	-12.48	
Median	-28.89	4.82	Yes
Q3	-12.41	4.83	
Range	-59.41 - 45.87	-32.80 - 15.88	
Difference	-22.174		
p-value	<0.0001		
3. Non-HDL-c reduction (percentage change from baseline)			
N	36	30	
Mean (SD)	-27.97 (18.612)	-6.94 (10.922)	
Q1	-43.85	-15.67	
Median	-26.41	-5.96	Yes
Q3	-17.01	2.75	
Range	-52.98 - 35.13	-31.36 - 7.14	
Difference	-21.04		
p-value	<0.0001		
4. AST normalisation [n (%)]			
N	36	29	
Yes	15 (42)	1 (3)	Yes
Difference	39%		
p-value	0.0003		

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Parameter / Statistic	Sebelipase Alfa (N=36)	Placebo (N=30)	Statistically significant in fixed sequence test
5. Triglyceride reduction (percentage change from baseline)			Yes
N	36	30	
Mean (SD)	-25.45 (29.411)	-11.14 (28.827)	
Q1	-45.60	-35.50	
Median	-32.41	-14.90	
Q3	-11.97	4.72	
Range	-66.89 - 58.99	-50.56 - 55.96	
Difference	-14.30		
p-value	0.0375		
6. HDL-c increase (percentage change from baseline)			Yes
N	36	30	
Mean (SD)	19.57 (16.833)	-0.29 (12.360)	
Q1	10.49	-9.59	
Median	19.13	1.20	
Q3	28.29	6.82	
Range	-24.11 - 66.07	-25.37 - 20.65	
Difference	19.86		
p-value	<0.0001		
7. Liver fat content reduction (percentage change from baseline)			Yes
N	32	25	
Mean (SD)	-31.98 (26.763)	-4.21 (15.559)	
Q1	-49.74	-13.20	
Median	-35.08	-4.11	
Q3	-19.30	8.99	
Range	-74.65 - 52.39	-37.29 - 24.59	
Difference	-27.77		
p-value	<0.0001		
8. Improvement in liver histopathology [n (%)]			No
N	16	10	
Yes	10 (63)	4 (40)	
Difference	23%		
p-value	0.4216		

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Parameter / Statistic	Sebelipase Alfa (N=36)	Placebo (N=30)	Statistically significant in fixed sequence test
9. Liver volume reduction (MN) (percentage change from baseline)			No
N	33	27	
Mean (SD)	-10.28 (10.510)	-2.66 (10.107)	
Q1	-16.34	-9.79	
Median	-11.73	-4.55	
Q3	-1.80	3.13	
Range	-35.64 - 12.40	-22.39 - 18.66	
Difference	-7.62		
p-value	0.0068		

N: Number of subjects in specified treatment group; n: Number of subjects with data available; %: Percentage based on N; SD: Standard deviation; Q1, Q3: First, third quartile; Difference: Difference between mean or percentage of Sebelipase Alfa – Placebo.

p-value for treatment differences (Fisher's exact test for normalisation and liver histology endpoints, and Wilcoxon rank sum test for all other endpoints).

ALT/AST normalisation: Abnormal ALT/AST values at baseline which became normal (below the age-and gender-specific ULN) at the end of the double-blind period; If the final assessment of ALT was less than 10 weeks (70 days) after the first dose, the subject was considered with ALT normalisation = No in the analysis; Subjects with normal AST values at baseline were excluded from analysis of AST normalisation endpoint; Abnormal baseline ALT/AST was defined as exceeding the ULN from the central laboratory; Abdominal MRI was required for all subjects except 1) those with internal or otherwise non-removable metal medical items and 2) children for whom sedation was required but medically contra-indicated; Multi-echo gradient echo assessments of liver fat content were not required in children who could not hold their breath for 15-30 seconds; For subjects ≥18 years of age, biopsies were required unless medically contra-indicated; Biopsies were optional in subjects < 18 years of age.

MN: Multiples of normal; A value of MN > 1.0 indicated an organ volume which was greater than the expected normal size.

Source: LAL-CL02 CSR, Table 29

The absolute change in LDL-C at the last visit was -51.1 mg/dL in the sebelipase group and -16.2 mg/dL in the placebo group. This resulted in a mean difference of -34.9 mg/dL.

In a post hoc analysis, the proportion of patients with baseline LDL-C over 130 mg/dL who achieved LDL-C less than 130 mg/dL was 40.6% (13/32) in the sebelipase group and 6.7% (2/30) in the placebo group at the last double-blind visit.

Three patients (8.3%) receiving sebelipase, but not other LLM, demonstrated an increase from baseline to the last time point in the double-blind period in LDL-C – see figure below. The largest outlier was a patient with a baseline LDL-C of 239 mg/dL who had a 46% increase during the trial. There was no report of non-compliance or neutralizing antibodies in this patient's treatment course. Of note, during the open label period, this patient experienced a change in LDL-C at week 24 of -25% (although it was not reported what other changes might have been initiated during this time, such as concomitant LLM or dietary intervention).

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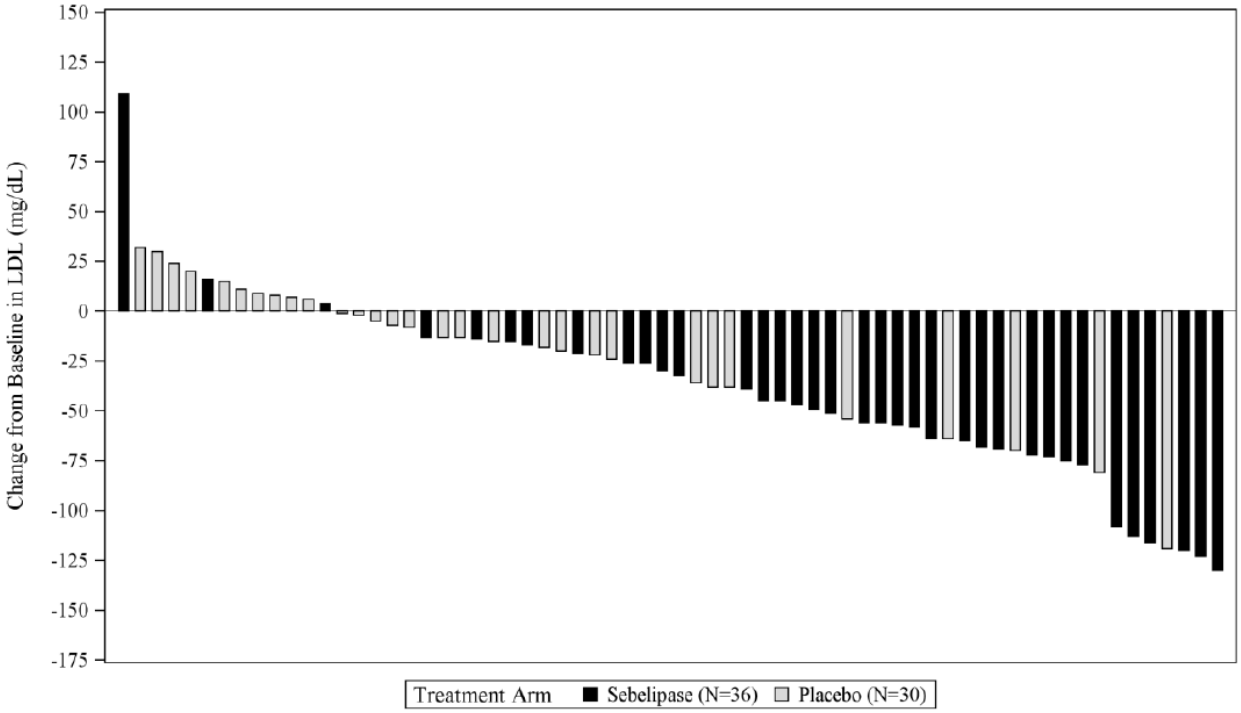
Figure 3. Waterfall Plot of Change from Baseline to the Last Time Point in the Double-blind Treatment Period in LDL-C, by Patient, Trial LAL-CL02

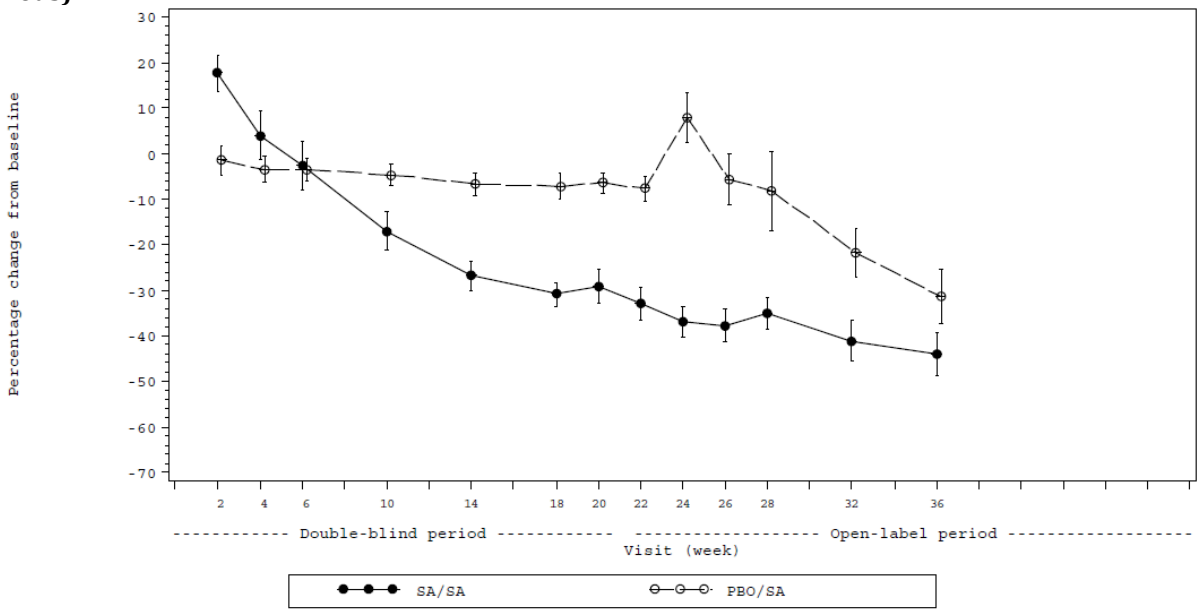


Source: LAL-CL02 CSR, Figure 5

Regarding LDL-C trajectory over time, including through the open label period, Figure 4 demonstrates that a mean percent *increase* was seen in the sebelipase group at weeks 2 and 4; a statistically significant different decrease from placebo was not observed until week 10. (Of note, from a safety perspective, mean percent increases were also seen in TG at weeks 2 and 4, with a maximum mean percent increase of 5% at week 4.)

Reference ID: 3743382

Figure 4. Mean Percent Change in LDL-C Over Time, Trial LAL-CL02 (Double-blind and Open-label Periods)



Treatment sequence: SA/SA=sebelipase alfa/sebelipase alfa; PBO/SA=placebo/sebelipase alfa.
BL = baseline, the last measurement prior to first study drug infusion in the double-blind period for both the SA/SA and placebo/SA groups. In case of multiple pre-treatment measurements, the average of the last (up to 3) measurements within 45 days was used. Visits for a treatment sequence are presented as long as at least 5 subjects had data available.

Source: LAL-CL02 OLE Interim CSR, Figure 13

The sponsor evaluated the effects of baseline LLM use on efficacy results. At baseline, patients on LLM had a mean LDL-C of 173.6 mg/dL; those not on LLM had a mean LDL-C of 230.2 mg/dL. Importantly, concomitant LLM use did not appear to attenuate the effect on lipid parameters with sebelipase (and perhaps sebelipase and LLM might even act synergistically):

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Table 6. Efficacy Endpoints by LLM Use, Trial LAL-CL02

Parameter / Statistic	LLM		No LLM	
	Sebelipase Alfa (N=15)	Placebo (N=11)	Sebelipase Alfa (N=21)	Placebo (N=19)
Primary Endpoint				
1. ALT normalisation [n (%)]				
n*	15	11	21	19
Yes	7 (47%)	0	4 (19%)	2 (11%)
Difference	47%		8%	
p-value	0.0103		0.6642	
Secondary Endpoints				
2. LDL reduction (percentage change from baseline)				
N	15	11	21	19
Mean (SD)	-36.7 (16.0)	-9.6 (15.2)	-22.5 (24.6)	-4.3 (11.5)
Difference	-27.1		-18.2	
p-value	0.0013		0.0018	
3. Non-HDL-c reduction (percentage change from baseline)				
n	15	11	21	19
Mean (SD)	-35.4 (13.5)	-9.7 (11.6)	-22.7 (20.2)	-5.3 (10.5)
Difference	-25.7		-17.4	
p-value	0.0003		0.0005	
4. AST normalisation [n (%)]				
n*	15	11	21	18
Yes	8 (53%)	0	7 (33%)	1 (6%)
Difference	53%		27%	
p-value	0.0074		0.0489	
5. Triglyceride reduction (percentage change from baseline)				
n	15	11	21	19
Mean (SD)	-28.9 (21.7)	-5.3 (31.6)	-23.0 (34.2)	-14.5 (27.4)
Difference	-23.6		-8.4	
p-value	0.0548		0.2553	

Parameter / Statistic	LLM		No LLM	
	Sebelipase Alfa (N=15)	Placebo (N=11)	Sebelipase Alfa (N=21)	Placebo (N=19)
6. HDL-c increase (percentage change from baseline)				
n	15	11	21	19
Mean (SD)	23.7 (20.0)	2.1 (10.5)	16.6 (13.9)	-1.7 (13.4)
Difference	21.6		18.3	
p-value	0.0081		0.0002	
7. Liver fat content reduction (percentage change from baseline)				
n	14	10	18	15
Mean (SD)	-26.0 (34.2)	-3.1 (15.8)	-36.6 (19.0)	-5.0 (15.9)
Difference	-23.0		-31.6	
p-value	0.0376		0.0001	
8. Improvement in liver histopathology [n (%)]				
n	7	6	9	4
Yes	4 (57%)	3 (50%)	6 (67%)	1 (25%)
Difference	7%		42%	
p-value	1.0000		0.2657	

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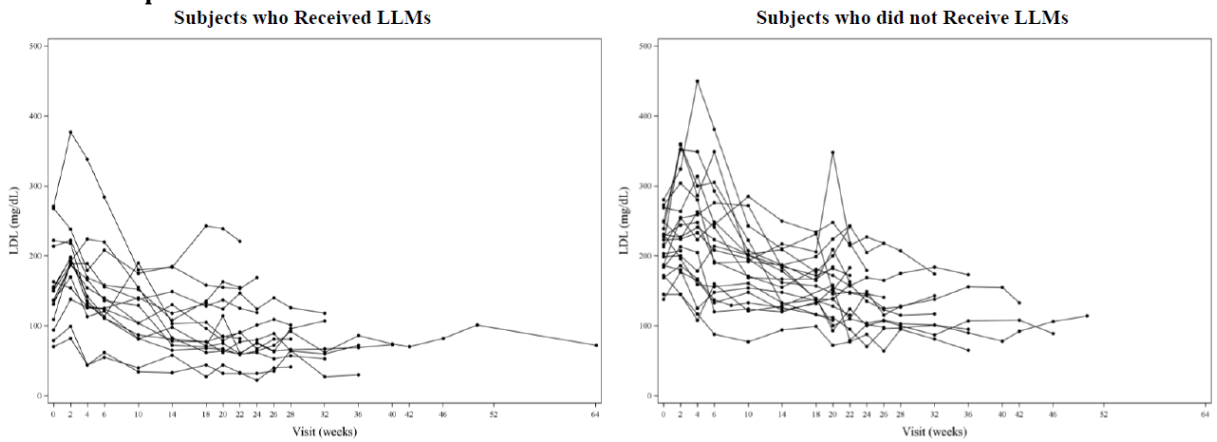
Parameter / Statistic	LLM		No LLM	
	Sebelipase Alfa (N=15)	Placebo (N=11)	Sebelipase Alfa (N=21)	Placebo (N=19)
9. Liver volume reduction (MN) (percentage change from baseline)				
n	14	11	19	16
Mean (SD)	-9.3 (11.2)	-0.9 (8.1)	-11.0 (10.2)	-3.9 (11.4)
Difference	-8.4		-7.1	
p-value	0.0350		0.0711	

Source: Table 14.2.2.11
N: Number of subjects in specified treatment group; n: Number of subjects with data available;
n*: Number of subjects who had both abnormal baseline ALT/AST and ALT/AST assessment at end of double-blind period;
%:Percentage based on n, for ALT and AST normalisation percentage based on n*;
SD: Standard deviation;
Difference: Difference between mean or percentage of Sebelipase Alfa - Placebo;
p-value for treatment differences (Fisher's exact test for normalisation and liver histology endpoints, and Wilcoxon rank sum test for all other endpoints);
ALT/AST normalisation: Abnormal ALT/AST values at baseline which became normal (below the age-and gender-specific ULN) at the end of the double-blind period; If the final assessment of ALT is less than 10 weeks (70 days) after the first dose, the subject is not considered to have ALT normalisation at last DB in the analysis; Subjects with normal AST values at baseline were excluded from analysis of AST normalisation endpoint;
Abnormal baseline ALT/AST is defined as exceeding the ULN from the central laboratory;
Serum lipid values measured in mmol/L;
Abdominal MRI was required for all subjects except 1) those with internal or otherwise non-removable metal medical items and 2) children for whom sedation was required but medically contra-indicated;
Multi-echo gradient echo assessments of liver fat content were not required in children who could not hold their breath for 15-30 seconds;
For subjects ≥18 years of age, biopsies were required unless medically contra-indicated;
Biopsies were optional in subjects < 18 years of age;
Improvement in liver histopathology from baseline is defined as an absolute decrease ≥5% in the H & E Stain Fat;
MN: Multiples of normal; A value of MN > 1.0 indicates an organ volume which is greater than the expected normal size

Source: LAL-CL02 CSR, Table 35

Figure 5. LAL-C Over Time in Patients Receiving Sebelipase by Use of LLM, Trial LAL-CL02 Double Blind and Open Label Periods



Source: LAL-CL02 OLE Interim CSR, Figure 16

Discussion and Recommendations

The dyslipidemia of CESD is a reflection of dysregulation of lipid metabolism due to the inherent lipid storage disorder caused by LAL deficiency. The phenotype is predominately one of liver disease, although CV disease has been reported less frequently.

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Of the lipid parameters reported, LDL-C has the most data to support a causal relationship with atherosclerotic cardiovascular disease. A meta-analysis of statin trials estimated that each 1.0 mmol/L (~39 mg/dL) reduction in LDL-C is associated with a reduction in the rate of major vascular events, defined in the referenced publication as the first occurrence of any major coronary event, coronary revascularization, or ischemic stroke, by ~22%.[14] In the LAL-CL02 trial, sebelipase was associated with a decrease in LDL-C of 22%, or 35 mg/dL in the trial population. If this degree of change from statin trials could be extrapolated to sebelipase in this patient population, one could estimate approximately 20% reduction in CV risk. This is speculative, however.

We note that increases in HDL-C and decreases in TG were also observed with sebelipase. Although HDL-C concentrations are inversely proportional to CV risk in epidemiological studies, it is unknown whether these observed changes with sebelipase would translate to reduction in CV risk. As noted in the background discussion, the impact of increasing HDL-C and decreasing TG with drugs on CV risk is uncertain.[8,9,10,11,12]

By contrast, very high TG concentrations (e.g., greater than 1000 mg/dL) are associated with an increase in risk for pancreatitis. Therefore, a drug that dramatically *increases* TG (particularly above 1000 mg/dL) might increase the risk for pancreatitis, particularly if it is sustained. Neither TGs of this magnitude, nor dramatic increases in TG, were observed in this trial, but it is a theoretical concern given the observed early lipid increases associated with sebelipase after initiating treatment.

The following are limitations in this clinical program with respect to characterizing the clinical significance of the observed lipid changes with sebelipase:

- There was considerable heterogeneity with respect to baseline LDL-C and other lipid parameters; in fact, some patients had lipid parameters in the normal range

- There is not strong evidence for a link between LAL deficiency and risk for premature atherosclerotic CV events, presumably due to the relatively young age of presentation

- The trials were not designed to establish LDL-C lowering; for example, patients were generally not receiving standard-of-care lipid-lowering therapy prior to receiving this drug

In addition, DMEP believes there is reason to be concerned about the extent of off-label use, if approved. For example, we note a publication in which authors have suggested that supplementing with lysosomal acid lipase in mice without LAL deficiency could treat atherosclerotic plaques, concluding *These results support the potential utility of lysosomal acid lipase supplementation for the treatment of atherosclerosis, a leading cause of mortality*

[14] Cholesterol Treatment Trialists' (CTT) Collaborators. Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170,000 participants in 26 randomised trials. Lancet (2010); 376:1670-81.

Reference ID: 3743382

and morbidity in Westernized nations.[15] Furthermore, we have concerns about apparent attempts to broaden the patient population. We note that authors in a recent sponsor-funded publication assert that LAL deficiency is likely underdiagnosed; this article provides a diagnostic algorithm for use by lipidologists, endocrinologists, cardiologists, and hepatologists to identify patients with this "under-recognized" disorder.[16] It is possible that a far greater number of patients may receive this drug, if approved, than estimated based on the pre-approval prevalence; if so, the safety database may be inadequate to support a more widespread use.

In our opinion, sebelipase should not be indicated for the treatment of dyslipidemia. If you choose to approve sebelipase for LAL deficiency and wish to describe changes in lipid parameters in another section of the label, we recommend that:

- Limitations of use should include the following or similar language:
    - Sebelipase is not indicated for use in patients with dyslipidemia without concurrent evidence of LAL deficiency.
    - The effect of sebelipase on cardiovascular morbidity and mortality has not been determined.

- Limitations to the lipid findings in the clinical trial, such as inadequate use of concomitant statin therapy, should be described.

- The increases in LDL-C and TG that were observed in the first few weeks of treatment should be described as adverse reactions. A caveat that the clinical implications of these findings are unknown can be included.

[15] Du H, et al. Reduction of atherosclerotic plaques by lysosomal acid lipase supplementation. Arterioscler Thromb Vasc Biol, 2004; 24: 147-54.
[16] Reiner Z, et al. Lysosomal acid lipase deficiency – an under-recognized cause of dyslipidemia and liver dysfunction. Atherosclerosis, 2014. 235: 21-30.

Reference ID: 3743382

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/s/

JULIE K GOLDEN
04/29/2015

JAMES P SMITH
04/29/2015

LABEL AND LABELING REVIEW

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

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Date of This Review:	April 14, 2015
Requesting Office or Division:	Division of Gastroenterology & Inborn Error Products (DGIEP)
Application Type and Number:	BLA 125561
Product Name and Strength:	Kanuma (sebelipase alfa) Injection 20 mg/10 mL (2 mg/mL)
Product Type:	Single Ingredient Product
Rx or OTC:	Rx
Applicant/Sponsor Name:	Synageva BioPharma Corp.
Submission Date:	November 21, 2014 & March 27, 2015
OSE RCM #:	2014-2479
DMEPA Primary Reviewer:	Matthew Barlow, RN, BSN
DMEPA Team Leader:	Kendra Worthy, PharmD

Reference ID: 3731875

1 REASON FOR REVIEW

The Division of Gastroenterology & Inborn Error Products (DGIEP) requested DMEPA review the proposed labels and labeling submitted by Synageva BioPharma Corp. on November 21, 2014 and March 27, 2015, and to evaluate the labels for any areas that may lead to medication error.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Label and Labeling Review	
Material Reviewed	**Appendix Section (for Methods and Results)**
Product Information/Prescribing Information	A
FDA Adverse Event Reporting System (FAERS)	N/A-B
Previous DMEPA Reviews	C
Human Factors Study	N/A-D
ISMP Newsletters	N/A-E
Other	N/A-F
Labels and Labeling	G

N/A=not applicable for this review

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

Kanuma (sebelipase alfa) is a new molecular entity under BLA 125561. The applicant submitted proposed carton and container labels coupled with the proposed Full Prescribing Information (PI) on November 21, 2014.

We performed a risk assessment of all the proposed materials submitted to further evaluate for any potential areas that may lead to medication errors. We found that there are areas of the carton and container labels that could be modified to improve clarity and increase understanding of both labels. Additionally, we found areas within the PI that can be revised to increase clarity of the presented information.

4 CONCLUSION & RECOMMENDATIONS

Based on this review, DMEPA recommends the following be implemented prior to the approval of this BLA:

4.1 RECOMMENDATIONS FOR THE DIVISION

A. Prescribing Information

1. We recommend revising the symbol "<" under the Dosage and Administration section of the Highlights of Prescribing Information, and also under section 2.1 of the Prescribing Information, to "less than." We advise

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avoiding use of all dangerous symbols, which includes the symbols “<” and “>,” as they can be easily misinterpreted[1].

4.2 RECOMMENDATIONS FOR SYNAGEVA BIOPHARMA CORP.

B. Carton Label

1. (b) (4)

C. Container Label

1. See A.1
2. Place a barcode, vertically[2], on the container label to meet with regulation 21 CFR 201.25(c)(2).
3. We recommend adding the statement “Store in a refrigerator” to align with carton label and to further emphasize the proper storage conditions for the product.

[1] ISMP’s List of Error-Prone Abbreviations, Symbols, and Dose Designations [Internet]. Horsham (PA): Institute for Safe Medication Practices. 2013 [cited 2013 Sep 16]. Available from: http://www.ismp.org/tools/errorproneabbreviations.pdf.

[2] Neuenschwander M. et al. Practical guide to bar coding for patient medication safety. Am J Health Syst Pharm. 2003 Apr 15;60(8):768-79.

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APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Kanuma that Synageva BioPharma Corp. submitted on November 21, 2014 and March 27, 2015.

Table 2. Relevant Product Information for Kanuma	
Initial Approval Date	N/A
Active Ingredient	Sebelipase Alfa
Indication	Indicated for patients with Lysosomal Acid Lipase (LAL) Deficiency.
Route of Administration	Intravenous Infusion
Dosage Form	(b) (4) Solution
Strength	20 mg/10 mL (2 mg/mL)
Dose and Frequency	The recommended starting dose is: **Infants [<6 months of age] presenting with rapidly progressive disease**: 1 mg/kg as an intravenous infusion once weekly. In clinical studies, these patients were dose escalated to 3 mg/kg once weekly. **Children and Adults:** 1 mg/kg as an intravenous infusion once every other week.
How Supplied	Kanuma 20 mg vials are supplied as a sterile, non-pyrogenic solution. Kanuma is supplied in 10 mL, single-use, clear Type I glass vials.
Storage	Store Kanuma under refrigeration between 2°C to 8°C (36°F to 46°F). Do not shake or freeze the vials. Protect (b) (4) from light.
Container Closure	See How Supplied.

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APPENDIX B. FDA ADVERSE EVENT REPORTING SYSTEM (FAERS)

B.1 Methods

N/A

B.2 Results

N/A

B.3 List of FAERS Case Numbers

N/A

B.4 Description of FAERS

The FDA Adverse Event Reporting System (FAERS) is a database that contains information on adverse event and medication error reports submitted to FDA. The database is designed to support the FDA's postmarket safety surveillance program for drug and therapeutic biologic products. The informatic structure of the FAERS database adheres to the international safety reporting guidance issued by the International Conference on Harmonisation. FDA's Office of Surveillance and Epidemiology codes adverse events and medication errors to terms in the Medical Dictionary for Regulatory Activities (MedDRA) terminology. Product names are coded using the FAERS Product Dictionary. More information about FAERS can be found at: http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/AdverseDrugEffects/default.htm.

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APPENDIX C. PREVIOUS DMEPA REVIEWS

C.1 Methods

We searched the L: Drive on April 6, 2015 using the terms, “Kanuma” and “sebelipase” to identify reviews previously performed by DMEPA.

C.2 Results

Our search identified no previous reviews related to label and labeling.

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APPENDIX D. HUMAN FACTORS STUDY

D.1 Study Design

N/A

D.2 Results

N/A

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APPENDIX E. ISMP NEWSLETTERS

E.1 Methods

N/A

E.2 Results

N/A

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APPENDIX F.

F.1 Methods

N/A

F.2 Results

N/A

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APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[3] along with postmarket medication error data, we reviewed the following Kanuma labels and labeling submitted by Synageva BioPharma Corp. on November 21, 2014 and March 27, 2014.

- Container label
- Carton labeling
- Prescribing Information

G.2 Label and Labeling Images

(b) (4)

[3] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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B. Container Label

(b) (4)

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

/s/

MATTHEW J BARLOW
04/14/2015

KENDRA C WORTHY
04/14/2015

RPM FILING REVIEW

(Including Memo of Filing Meeting)

To be completed for all new NDAs, BLAs, and Efficacy Supplements [except SE8 (labeling change with clinical data) and SE9 (manufacturing change with clinical data]

Application Information		
NDA # BLA# 125561	NDA Supplement #: S- BLA Supplement #: S-	Efficacy Supplement Category: ☐ New Indication (SE1) ☐ New Dosing Regimen (SE2) ☐ New Route Of Administration (SE3) ☐ Comparative Efficacy Claim (SE4) ☐ New Patient Population (SE5) ☐ Rx To OTC Switch (SE6) ☐ Accelerated Approval Confirmatory Study (SE7) ☐ Animal Rule Confirmatory Study (SE7) ☐ Labeling Change With Clinical Data (SE8) ☐ Manufacturing Change With Clinical Data (SE9) ☐ Pediatric
Proprietary Name: Kanuma Established/Proper Name: sebelipase alfa Dosage Form: solution (for intravenous injection) Strengths: 2 mg/ml		
Applicant: Synageva Biopharma Corp. Agent for Applicant (if applicable):		
Date of Application: 01/08/2015 Date of Receipt: 01/08/2015 Date clock started after UN:		
PDUFA/BsUFA Goal Date: 09/08/2015	Action Goal Date (if different):	
Filing Date: 03/09/2015	Date of Filing Meeting: December 16, 2014	
Chemical Classification (original NDAs only) : ☐ Type 1- New Molecular Entity (NME); NME and New Combination ☐ Type 2- New Active Ingredient; New Active Ingredient and New Dosage Form; New Active Ingredient and New Combination ☐ Type 3- New Dosage Form; New Dosage Form and New Combination ☐ Type 4- New Combination ☐ Type 5- New Formulation or New Manufacturer ☐ Type 7- Drug Already Marketed without Approved NDA ☐ Type 8- Partial Rx to OTC Switch		
Proposed indication(s)/Proposed change(s): Treatment of Lysosomal Acid Lipase Deficiency		
Type of Original NDA: AND (if applicable) Type of NDA Supplement: ***If 505(b)(2): Draft the "505(b)(2) Assessment" review found at:*** ***http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499.***	☐ 505(b)(1) ☐ 505(b)(2) ☐ 505(b)(1) ☐ 505(b)(2)	

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Type of BLA ***If 351(k), notify the OND Therapeutic Biologics and Biosimilars Team***	☒ 351(a) ☐ 351(k)
Review Classification: ***The application will be a priority review if:*** • ***A complete response to a pediatric Written Request (WR) was included (a partial response to a WR that is sufficient to change the labeling should also be a priority review – check with DPMH)*** • ***The product is a Qualified Infectious Disease Product (QIDP)*** • ***A Tropical Disease Priority Review Voucher was submitted*** • ***A Pediatric Rare Disease Priority Review Voucher was submitted***	☐ Standard ☒ Priority ☐ Pediatric WR ☐ QIDP ☐ Tropical Disease Priority Review Voucher ☐ Pediatric Rare Disease Priority Review Voucher
Resubmission after withdrawal? ☐	Resubmission after refuse to file? ☐
Part 3 Combination Product? ☐ ***If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults***	☐ Convenience kit/Co-package ☐ Pre-filled drug delivery device/system (syringe, patch, etc.) ☐ Pre-filled biologic delivery device/system (syringe, patch, etc.) ☐ Device coated/impregnated/combined with drug ☐ Device coated/impregnated/combined with biologic ☐ Separate products requiring cross-labeling ☐ Drug/Biologic ☐ Possible combination based on cross-labeling of separate products ☐ Other (drug/device/biological product)

☒ Fast Track Designation ☒ Breakthrough Therapy Designation ***(set the submission property in DARRTS and notify the CDER Breakthrough Therapy Program Manager)*** ☒ Rolling Review ☒ Orphan Designation ☐ Rx-to-OTC switch, Full ☐ Rx-to-OTC switch, Partial ☐ Direct-to-OTC Other:	☐ PMC response ☐ PMR response: ☐ FDAAA [505(o)] ☐ PREA deferred pediatric studies (FDCA Section 505B) ☐ Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) ☐ Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)
Collaborative Review Division (*if OTC product*):	
List referenced IND Number(s): IND 108460	

Goal Dates/Product Names/Classification Properties	**YES**	**NO**	**NA**	**Comment**
PDUFA/BsUFA and Action Goal dates correct in tracking system? ***If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.***	☒	☐		
Are the established/proper and applicant names correct in tracking system? ***If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name***	☒	☐		

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to the supporting IND(s) if not already entered into tracking system.				
Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, orphan drug)? ***Check the New Application and New Supplement Notification Checklists for a list of all classifications/properties at:*** ***http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm*** ***If no, ask the document room staff to make the appropriate entries.***	☒	☐	☐	
Application Integrity Policy	**YES**	**NO**	**NA**	**Comment**
Is the application affected by the Application Integrity Policy (AIP)? ***Check the AIP list at:*** ***http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm***	☐	☒		
If yes, explain in comment column.				
If affected by AIP, has OC/OMPQ been notified of the submission? **If yes,** date notified:	☐	☐		
User Fees	**YES**	**NO**	**NA**	**Comment**
Is Form 3397 (User Fee Cover Sheet)/Form 3792 (Biosimilar User Fee Cover Sheet) included with authorized signature?	☒	☐		

User Fee Status ***If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send Unacceptable for Filing (UN) letter and contact user fee staff.***	Payment for this application *(check daily email from UserFeeAR@fda.hhs.gov)*: ☐ Paid ☒ Exempt (orphan, government) ☐ Waived (e.g., small business, public health) ☐ Not required
If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.	Payment of other user fees: ☒ Not in arrears ☐ In arrears
User Fee Bundling Policy ***Refer to the guidance for industry, Submitting Separate Marketing Applications and Clinical Data for Purposes of Assessing User Fees at:*** ***http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM079320.pdf***	Has the user fee bundling policy been appropriately applied? ***If no, or you are not sure, consult the User Fee Staff.*** ☒ Yes ☐ No

505(b)(2) (NDAs/NDA Efficacy Supplements only)	**YES**	**NO**	**NA**	**Comment**
Is the application a 505(b)(2) NDA? *(Check the 356h form,*	☐	☐		

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cover letter, and annotated labeling). **If yes**, answer the bulleted questions below:				
• Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?	☐	☐		
• Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action is less than that of the reference listed drug (RLD)? **[see 21 CFR 314.54(b)(1)].**	☐	☐		
• Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug **[see 21 CFR 314.54(b)(2)]?** ***If you answered yes to any of the above bulleted questions, the application may be refused for filing under 21 CFR 314.101(d)(9). Contact the 505(b)(2) review staff in the Immediate Office of New Drugs for advice.***	☐	☐		
• Is there unexpired exclusivity on another listed drug product containing the same active moiety (e.g., 5-year, 3-year, orphan, or pediatric exclusivity)? ***Check the Electronic Orange Book at:*** ***http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm*** **If yes**, please list below:	☐	☐		

Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration

If there is unexpired, 5-year exclusivity remaining on another listed drug product containing the same active moiety, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 314.108(b)(2). Unexpired, 3-year exclusivity may block the approval but not the submission of a 505(b)(2) application.

Exclusivity	**YES**	**NO**	**NA**	**Comment**
Does another product (same active moiety) have orphan exclusivity for the same indication? ***Check the Orphan Drug Designations and Approvals list at:*** ***http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm***	☐	☒		
If another product has orphan exclusivity, is the product considered to be the same product according to the orphan drug definition of sameness **[see 21 CFR 316.3(b)(13)]**? ***If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy***	☐	☐	☒	
NDAs/NDA efficacy supplements only: Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? **If yes**, # years requested: ***Note:*** *An applicant can receive exclusivity without requesting it;*	☐	☐	☐	

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therefore, requesting exclusivity is not required.				
NDAs only: Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use?	☐	☐	☐	
If yes, did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)? ***If yes, contact the Orange Book Staff (CDER-Orange Book Staff).***	☐	☐	☐	
BLAs only: Has the applicant requested 12-year exclusivity under section 351(k)(7) of the PHS Act? ***If yes, notify Marlene Schultz-DePalo, OBP Biosimilars RPM*** ***Note**: Exclusivity requests may be made for an original BLA submitted under Section 351(a) of the PHS Act (i.e., a biological reference product). A request may be located in Module 1.3.5.3 and/or other sections of the BLA and may be included in a supplement (or other correspondence) if exclusivity has not been previously requested in the original 351(a) BLA. An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.*	☐	☒	☐	

Format and Content				
Do not check mixed submission if the only electronic component is the content of labeling (COL).	☐ All paper (except for COL) ☒ All electronic ☐ Mixed (paper/electronic) ☒ CTD ☐ Non-CTD ☐ Mixed (CTD/non-CTD)			
If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format?				
Overall Format/Content	**YES**	**NO**	**NA**	**Comment**
If electronic submission, does it follow the eCTD guidance?[1] **If not,** explain (e.g., waiver granted).	☒	☐	☐	
Index: Does the submission contain an accurate comprehensive index?	☒	☐		
Is the submission complete as required under 21 CFR 314.50 (*NDAs/NDA efficacy supplements*) or under 21 CFR 601.2 (*BLAs/BLA efficacy supplements*) including:	☒	☐		

[1] http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf

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☒ legible ☒ English (or translated into English) ☒ pagination ☒ navigable hyperlinks (electronic submissions only) **If no**, explain.				
BLAs only: Companion application received if a shared or divided manufacturing arrangement? **If yes**, BLA #	☐	☐	☒	
Forms and Certifications				
Electronic *forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise,* ***paper*** *forms and certifications with hand-written signatures must be included.* ***Forms*** *include: user fee cover sheet (3397/3792), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674);* ***Certifications*** *include: debarment certification, patent certification(s), field copy certification, and pediatric certification.*				
Application Form	**YES**	**NO**	**NA**	**Comment**
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)? ***If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].***	☒	☐		
Are all establishments and their registration numbers listed on the form/attached to the form?	☒	☐	☐	
Patent Information **(NDAs/NDA efficacy supplements only)**	**YES**	**NO**	**NA**	**Comment**
Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?	☐	☐	☐	
Financial Disclosure	**YES**	**NO**	**NA**	**Comment**
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)? ***Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].*** ***Note:*** *Financial disclosure is required for bioequivalence studies that are the basis for approval.*	☒	☐		
Clinical Trials Database	**YES**	**NO**	**NA**	**Comment**
Is form FDA 3674 included with authorized signature? ***If yes, ensure that the application is also coded with the supporting document category, "Form 3674."***	☒	☐		

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If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant				
Debarment Certification	**YES**	**NO**	**NA**	**Comment**
Is a correctly worded Debarment Certification included with authorized signature? ***Certification is not required for supplements if submitted in the original application; If foreign applicant, both the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications].*** ***Note:*** *Debarment Certification should use wording in FD&C Act Section 306(k)(1) i.e., "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as, "To the best of my knowledge…"*	☒	☐	☐	
Field Copy Certification (NDAs/NDA efficacy supplements only)	**YES**	**NO**	**NA**	**Comment**
For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included? ***Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)*** ***If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.***	☐	☐	☐	
Controlled Substance/Product with Abuse Potential	**YES**	**NO**	**NA**	**Comment**
For NMEs: Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)? ***If yes,*** *date consult sent to the Controlled Substance Staff:* For non-NMEs: *Date of consult sent to Controlled Substance Staff*:	☐	☐	☒	
Pediatrics	**YES**	**NO**	**NA**	**Comment**
PREA Does the application trigger PREA? ***If yes, notify PeRC@fda.hhs.gov to schedule required PeRC meeting***[2] ***Note****: NDAs/BLAs/efficacy supplements for new active ingredients (including new fixed combinations), new indications, new dosage*	☐	☒		Orphan Designation

[2] http://inside fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/PediatricandMaternalHealthStaff/ucm027829 htm

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forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.				
If the application triggers PREA, is there an agreed Initial Pediatric Study Plan (iPSP)? ***If no, may be an RTF issue - contact DPMH for advice.***	☐	☐	☒	
If required by the agreed iPSP, are the pediatric studies outlined in the agreed iPSP completed and included in the application? ***If no, may be an RTF issue - contact DPMH for advice.***	☐	☐	☒	
BPCA: Is this submission a complete response to a pediatric Written Request? ***If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)***[3]	☐	☒		
Proprietary Name	**YES**	**NO**	**NA**	**Comment**
Is a proposed proprietary name submitted? ***If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."***	☒	☐	☐	
REMS	**YES**	**NO**	**NA**	**Comment**
Is a REMS submitted? ***If yes, send consult to OSE/DRISK and notify OC/ OSI/DSC/PMSB via the CDER OSI RMP mailbox***	☐	☒	☐	
Prescription Labeling	☐ **Not applicable**			
Check all types of labeling submitted.	☒ Package Insert (PI) ☐ Patient Package Insert (PPI) ☐ Instructions for Use (IFU) ☐ Medication Guide (MedGuide) ☒ Carton labels ☒ Immediate container labels ☐ Diluent ☐ Other (specify)			
	YES	**NO**	**NA**	**Comment**
Is Electronic Content of Labeling (COL) submitted in SPL format? ***If no, request applicant to submit SPL before the filing date.***	☒	☐		

[3] http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/PediatricandMaternalHealthStaff/ucm027837.htm

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Is the PI submitted in PLR format?[4]	☒	☐		
If PI not submitted in PLR format, was a waiver or deferral requested before the application was received or in the submission? **If requested before application was submitted**, what is the status of the request? ***If no waiver or deferral, request applicant to submit labeling in PLR format before the filing date.***	☐	☐	☒	
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to OPDP?	☒	☐	☐	
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (*send WORD version if available*)	☐	☐	☒	
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office (OBP or ONDQA)?	☒	☐	☐	
OTC Labeling	☒ **Not Applicable**			
Check all types of labeling submitted.	☐ Outer carton label ☐ Immediate container label ☐ Blister card ☐ Blister backing label ☐ Consumer Information Leaflet (CIL) ☐ Physician sample ☐ Consumer sample ☐ Other (specify)			
	YES	**NO**	**NA**	**Comment**
Is electronic content of labeling (COL) submitted? ***If no, request in 74-day letter.***	☐	☐		
Are annotated specifications submitted for all stock keeping units (SKUs)? ***If no, request in 74-day letter.***	☐	☐	☐	
If representative labeling is submitted, are all represented SKUs defined? ***If no, request in 74-day letter.***	☐	☐	☐	
All labeling/packaging sent to OSE/DMEPA?	☐	☐	☐	
Other Consults	**YES**	**NO**	**NA**	**Comment**
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team) ***If yes, specify consult(s) and date(s) sent:***	☐	☒	☐	
Meeting Minutes/SPAs	**YES**	**NO**	**NA**	**Comment**

[4] http://inside fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/StudyEndpointsandLabelingDevelopmentTeam/ucm025576 htm

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End-of Phase 2 meeting(s)? **Date(s):** 12 Jun 2012 ***If yes, distribute minutes before filing meeting***	☒	☐		EoP1 and PrePhase 3
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? **Date(s):** 15 Aug 2014 ***If yes, distribute minutes before filing meeting***	☒	☐		
Any Special Protocol Assessments (SPAs)? **Date(s):** ***If yes, distribute letter and/or relevant minutes before filing meeting***	☐	☒		

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ATTACHMENT

MEMO OF FILING MEETING

DATE: December 17, 2014

BACKGROUND:
See attached Filing presentation.

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Kevin Bugin	Y
	CPMS/TL:	Richard Ishihara	Y
Cross-Discipline Team Leader (CDTL)	Jessica Lee		Y
Division Director/Deputy	Donna Griebel		Y
Office Director/Deputy	Julie Beitz		Y
Clinical	Reviewer:	Juli Tomaino/Lauren Weintraub	Y
	TL:	Jessica Lee	Y
Clinical Pharmacology	Reviewer:	Jing Fang	Y
	TL:	Yow-Ming Wang	Y
Biostatistics	Reviewer:	Benjamin Vali	Y
	TL:	Yeh-Fong Chen	Y

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Nonclinical (Pharmacology/Toxicology)	Reviewer:	Sruthi King	Y
	TL:	Sushanta Chakder	Y
Immunogenicity (assay/assay validation) *(for protein/peptide products only)*	Reviewer:	Joao Pedras-Vasconcelos	Y
	TL:	Daniela Vertheli	Y
Product Quality (CMC)	Reviewer:	Christopher Downey	Y
	TL:	Juhong Liu	Y
Quality Microbiology	Reviewer:	Colleen Thomas/Bo Chi	Y
	TL:	Patricia Hughes	Y
CMC Labeling Review	Reviewer:	Jibril Abdus-Samad	N
	TL:		N
Facility Review/Inspection	Reviewer:	Christina Capaci-Daniel	Y
	TL:	Peter Zhihao Qiu	N
OSE/DMEPA (proprietary name, carton/container labels))	Reviewer:	Matthew Barlow	Y
	TL:	Kendra Worthy	Y

Reference ID: 3702011

Bioresearch Monitoring (OSI)	Reviewer:	Susan Leibenhaut	Y
	TL:	Susan Thompson	N
Other attendees	Joette Meyer, Diem-Kieu Ngo, Cindy Hong, Amy Rosenberg, David Joy, Nancy Hayes, Michael Pacanowski, Kassa Ayalew, Nitin Mehrotra, Andrew Mulberg, Aleksander Winiarski, Joeseph Peacock, Susan Kirshner, Joyce Korvick, Dragos Roman, Laura Epstein, Larisa Rudenko, Kimberly Swank		

FILING MEETING DISCUSSION:

GENERAL • 505(b)(2) filing issues: ○ Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? ○ Did the applicant provide a scientific "bridge" demonstrating the relationship between the proposed product and the referenced product(s)/published literature? Describe the scientific bridge (e.g., BA/BE studies):	☒ Not Applicable ☐ YES ☐ NO ☐ YES ☐ NO
• Per reviewers, are all parts in English or English translation? **If no**, explain:	☒ YES ☐ NO
• Electronic Submission comments **List comments**:	☐ Not Applicable ☒ No comments
CLINICAL **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• Clinical study site(s) inspections(s) needed? **If no,** explain:	☒ YES ☐ NO

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• Advisory Committee Meeting needed? **Comments**: ***If no, for an NME NDA or original BLA, include the reason. For example:*** o ***this drug/biologic is not the first in its class*** o ***the clinical study design was acceptable*** o ***the application did not raise significant safety or efficacy issues*** o ***the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease***	☐ YES Date if known: ☒ NO ☐ To be determined Reason: The application did not raise significant safety or efficacy issues.
• If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? **Comments**:	☒ Not Applicable ☐ YES ☐ NO
CLINICAL PHARMACOLOGY **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• Clinical pharmacology study site(s) inspections(s) needed?	☐ YES ☒ NO
BIOSTATISTICS **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
NONCLINICAL (PHARMACOLOGY/TOXICOLOGY) **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter

IMMUNOGENICITY (protein/peptide products only)	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE

Reference ID: 3702011

Comments:	☐ Review issues for 74-day letter
PRODUCT QUALITY (CMC) **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☒ Review issues for 74-day letter
New Molecular Entity (NDAs only) • Is the product an NME?	☐ YES ☐ NO
<u>Environmental Assessment</u> • Categorical exclusion for environmental assessment (EA) requested? **If no**, was a complete EA submitted? **If EA submitted**, consulted to EA officer (OPS)? **Comments**: OBP/DTP product. OBP to manage.	☒ YES ☐ NO ☐ YES ☐ NO ☐ YES ☐ NO
<u>Quality Microbiology</u> • Was the Microbiology Team consulted for validation of sterilization? **Comments**:	☒ Not Applicable ☐ YES ☐ NO
<u>Facility Inspection</u> • Establishment(s) ready for inspection? ▪ Establishment Evaluation Request (EER/TBP-EER) submitted to OMPQ? **Comments**: OBP to manage.	☐ Not Applicable ☒ YES ☐ NO ☒ YES ☐ NO
<u>Facility/Microbiology Review</u> (BLAs only) **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☒ Review issues for 74-day letter

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CMC Labeling Review **Comments**:	☐ Review issues for 74-day letter
APPLICATIONS IN THE PROGRAM (PDUFA V) (NME NDAs/Original BLAs) • Were there agreements made at the application's pre-submission meeting (and documented in the minutes) regarding certain late submission components that could be submitted within 30 days after receipt of the original application? • If so, were the late submission components all submitted within 30 days?	☐ N/A ☐ YES ☒ NO ☐ YES ☐ NO
• What late submission components, if any, arrived after 30 days?	
• Was the application otherwise complete upon submission, including those applications where there were no agreements regarding late submission components?	☒ YES ☐ NO
• Is a comprehensive and readily located list of all clinical sites included or referenced in the application?	☒ YES ☐ NO
• Is a comprehensive and readily located list of all manufacturing facilities included or referenced in the application?	☒ YES ☐ NO
REGULATORY PROJECT MANAGEMENT	
Signatory Authority: Julie Beitz **Date of Mid-Cycle Meeting** (for NME NDAs/BLAs in "the Program" PDUFA V): 02/18/2015 **21st Century Review Milestones (see attached)** (listing review milestones in this document is optional):	

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Comments:	
REGULATORY CONCLUSIONS/DEFICIENCIES	
☐	The application is unsuitable for filing. Explain why:
☒	The application, on its face, appears to be suitable for filing. Review Issues: ☐ No review issues have been identified for the 74-day letter. ☒ Review issues have been identified for the 74-day letter. Review Classification: ☐ Standard Review ☒ Priority Review
ACTIONS ITEMS	
☒	Ensure that any updates to the review priority (S or P) and classifications/properties are entered into tracking system (e.g., chemical classification, combination product classification, orphan drug).
☐	If RTF, notify everyone who already received a consult request, OSE PM, and Product Quality PM (to cancel EER/TBP-EER).
☐	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
☐	351(k) BLA/supplement: If filed, send filing notification letter on day 60
☒	If priority review: • notify sponsor in writing by day 60 (see CST for choices) • notify OMPQ (so facility inspections can be scheduled earlier)
☒	Send review issues/no review issues by day 74
☒	Conduct a PLR format labeling review and include labeling issues in the 74-day letter
☒	Update the PDUFA V DARRTS page (for applications in the Program)
☐	Other

Annual review of template by OND ADRAs completed: September 2014

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

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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
02/12/2015

RICHARD W ISHIHARA
02/13/2015

REGULATORY PROJECT MANAGER
PHYSICIAN'S LABELING RULE (PLR) FORMAT REVIEW
OF THE PRESCRIBING INFORMATION

Complete for all new NDAs, BLAs, Efficacy Supplements, and PLR Conversion Labeling Supplements

Application: BLA 125561

Application Type: New BLA

Name of Drug/Dosage Form: Kanuma (sebelipase alfa), solution (for intravenous injection)

Applicant: Synageva BioPharma Corp.

Receipt Date: 08 Jan 2015

Goal Date: 08 Sep 2015

1. Regulatory History and Applicant's Main Proposals

Kanuma (sebelipase alfa) has been developed [redacted] (b) (4) for patients with lysosomal acid lipase (LAL) deficiency. LAL deficiency is a very rare autosomal recessive monogenic disorder in which patients are deficient for a lysosomal enzyme (lysosomal acid lipase, which leads to the lysosomal accumulation of cholesteryl ester and triglycerides in various tissues and cell types of the body. This disease is progressive, multisystem, and frequently manifests early in life leading to serious complications. This treatment is intended to directly address the root cause of the disease by providing a replacement of the missing or deficient enzyme which leads to reduction of the accumulated substrates and restoration of normal lipid metabolism. The product is being proposed for use in both the infantile form of the disease and the older children and adults.

2. Review of the Prescribing Information

This review is based on the applicant's submitted Word format of the prescribing information (PI). The applicant's proposed PI was reviewed in accordance with the labeling format requirements listed in the "Selected Requirements for Prescribing Information (SRPI)" checklist (see the Appendix).

3. Conclusions/Recommendations

No SRPI format deficiencies were identified in the review of this PI.

The following labeling issues were identified, and will be communicated to the Applicant by way of sending the draft labeling with revisions marked:

1. The nonproprietary name should not be included in the Indications and Usage (I&U) section of the Full Prescribing Information (FPI).

2. The Established Pharmacologic Class (EPC) should not be included the I&U section of the FPI. The only place it is required in labeling is the I&U statement in Highlights.

3. It is not necessary to cross-reference Clinical Studies. The Dosage and Administration section should include complete dosing information needed to use the product.

4. "Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit" is a required statement in Section 2 for all parenteral products as per 21 CFR 201.57.

5. Do not refer to clinical trials by the internal code name. Instead, number the studies as Study 1, Study 2, etc.

6. According to 21 CFR 201.57:
   The Pediatric use subsection must cite any limitations on the pediatric indication, need for specific monitoring, specific hazards associated with use of the drug in any subsets of the pediatric population (e.g., neonates), differences between pediatric and adult responses to the drug, and other information related to the safe and effective pediatric use of the drug.

   For additional information see the Pediatric labeling guidance, Section III.A: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM341394.pdf

7. The Patient Counseling section is directed at the patient/caregiver. Delete information for the prescriber.

8. Do not include the "Rx only" statement anywhere in the PI. This statement is only required for container and carton labels. *See Guidance for Industry: Implementation of Section 126 of the FDA Modernization Act of 1997 – Elimination of Certain Labeling Requirements*.

All labeling issues identified above will be conveyed to the applicant in the 74-day letter. The applicant will be asked to correct these deficiencies and resubmit the PI in Word format by April 01, 2015, The resubmitted PI will be used for further labeling review.

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Appendix

The Selected Requirement of Prescribing Information (SRPI) is a 42-item, drop-down checklist of important format elements of the prescribing information (PI) based on labeling regulations (21 CFR 201.56 and 201.57) and guidances.

Highlights

See Appendix A for a sample tool illustrating the format for the Highlights.

HIGHLIGHTS GENERAL FORMAT

YES 1. Highlights (HL) must be in a minimum of 8-point font and should be in two-column format, with ½ inch margins on all sides and between columns.

Comment:

YES 2. The length of HL must be one-half page or less unless a waiver has been granted in a previous submission. The HL Boxed Warning does not count against the one-half page requirement. Instructions to complete this item: If the length of the HL is one-half page or less, select "YES" in the drop-down menu because this item meets the requirement. However, if HL is longer than one-half page, select "NO" unless a waiver has been granted.

Comment:

YES 3. A horizontal line must separate HL from the Table of Contents (TOC). A horizontal line must separate the TOC from the FPI.

Comment:

YES 4. All headings in HL must be **bolded** and presented in the center of a horizontal line (each horizontal line should extend over the entire width of the column as shown in Appendix A). The headings should be in UPPER CASE letters.

Comment:

YES 5. White space should be present before each major heading in HL. There must be no white space between the HL Heading and HL Limitation Statement. There must be no white space between the product title and Initial U.S. Approval. See Appendix A for a sample tool illustrating white space in HL.

Comment:

YES 6. Each summarized statement or topic in HL must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contain more detailed information. The preferred format is the numerical identifier in parenthesis [e.g., (1.1)] at the end of each summarized statement or topic.

Comment:

YES 7. Section headings must be presented in the following order in HL:

Section	Required/Optional
• **Highlights Heading**	Required
• **Highlights Limitation Statement**	Required
• **Product Title**	Required

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Selected Requirements of Prescribing Information

• **Initial U.S. Approval**	Required
• **Boxed Warning**	Required if a BOXED WARNING is in the FPI
• **Recent Major Changes**	Required for only certain changes to PI*
• **Indications and Usage**	Required
• **Dosage and Administration**	Required
• **Dosage Forms and Strengths**	Required
• **Contraindications**	Required (if no contraindications must state "None.")
• **Warnings and Precautions**	Not required by regulation, but should be present
• **Adverse Reactions**	Required
• **Drug Interactions**	Optional
• **Use in Specific Populations**	Optional
• **Patient Counseling Information Statement**	Required
• **Revision Date**	Required

* RMC only applies to the BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS sections.

Comment:

HIGHLIGHTS DETAILS

Highlights Heading

YES 8. At the beginning of HL, the following heading must be **bolded** and should appear in all UPPER CASE letters: **"HIGHLIGHTS OF PRESCRIBING INFORMATION"**.

Comment:

Highlights Limitation Statement

YES 9. The **bolded** HL Limitation Statement must include the following verbatim statement: "**These highlights do not include all the information needed to use (insert name of drug product) safely and effectively. See full prescribing information for (insert name of drug product).**" The name of drug product should appear in UPPER CASE letters.

Comment:

Product Title in Highlights

YES 10. Product title must be **bolded**.

Comment:

Initial U.S. Approval in Highlights

YES 11. Initial U.S. Approval in HL must be **bolded**, and include the verbatim statement "**Initial U.S. Approval:**" followed by the **4-digit year**.

Comment:

Boxed Warning (BW) in Highlights

N/A 12. All text in the BW must be **bolded**.

Comment:

N/A 13. The BW must have a heading in UPPER CASE, containing the word "**WARNING**" (even if more than one warning, the term, "**WARNING**" and not "**WARNINGS**" should be used) and other words to identify the subject of the warning (e.g., "**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**"). The BW heading should be centered.

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Comment:

N/A 14. The BW must always have the verbatim statement "***See full prescribing information for complete boxed warning***." This statement should be centered immediately beneath the heading and appear in *italics*.

Comment:

N/A 15. The BW must be limited in length to 20 lines (this includes white space but does not include the BW heading and the statement "***See full prescribing information for complete boxed warning.***").

Comment:

Recent Major Changes (RMC) in Highlights

N/A 16. RMC pertains to only the following five sections of the FPI: BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS. RMC must be listed in the same order in HL as the modified text appears in FPI.

Comment:

N/A 17. The RMC must include the section heading(s) and, if appropriate, subsection heading(s) affected by the recent major change, together with each section's identifying number and date (month/year format) on which the change was incorporated in the PI (supplement approval date). For example, "Warnings and Precautions, Acute Liver Failure (5.1) --- 9/2013".

Comment:

N/A 18. The RMC must list changes for at least one year after the supplement is approved and must be removed at the first printing subsequent to one year (e.g., no listing should be one year older than revision date).

Comment:

Indications and Usage in Highlights

YES 19. If a product belongs to an established pharmacologic class, the following statement is required under the Indications and Usage heading in HL: "(Product) is a (name of established pharmacologic class) indicated for (indication)".

Comment:

Dosage Forms and Strengths in Highlights

N/A 20. For a product that has several dosage forms (e.g., capsules, tablets, and injection), bulleted subheadings or tabular presentations of information should be used under the Dosage Forms and Strengths heading.

Comment:

Contraindications in Highlights

YES

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21. All contraindications listed in the FPI must also be listed in HL or must include the statement "None" if no contraindications are known. Each contraindication should be bulleted when there is more than one contraindication.

    Comment:

Adverse Reactions in Highlights

YES 22. For drug products other than vaccines, the verbatim **bolded** statement must be present: "**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer's U.S. phone number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch**".

    Comment:

Patient Counseling Information Statement in Highlights

YES 23. The Patient Counseling Information statement must include one of the following three **bolded** verbatim statements that is most applicable:

If a product **does not** have FDA-approved patient labeling:

- **"See 17 for PATIENT COUNSELING INFORMATION"**

If a product **has** FDA-approved patient labeling:

- **"See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling"**
- **"See 17 for PATIENT COUNSELING INFORMATION and Medication Guide"**

Comment:

Revision Date in Highlights

YES 24. The revision date must be at the end of HL, and should be **bolded** and right justified (e.g., "**Revised: 9/2013**").

Comment:

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Contents: Table of Contents (TOC)

See Appendix A for a sample tool illustrating the format for the Table of Contents.

YES 25. The TOC should be in a two-column format.

Comment:

YES 26. The following heading must appear at the beginning of the TOC: **"FULL PRESCRIBING INFORMATION: CONTENTS"**. This heading should be in all UPPER CASE letters and **bolded**.

Comment:

N/A 27. The same heading for the BW that appears in HL and the FPI must also appear at the beginning of the TOC in UPPER CASE letters and **bolded**.

Comment:

YES 28. In the TOC, all section headings must be **bolded** and should be in UPPER CASE.

Comment:

YES 29. In the TOC, all subsection headings must be indented and not bolded. The headings should be in title case [first letter of all words are capitalized except first letter of prepositions (through), articles (a, an, and the), or conjunctions (for, and)].

Comment:

YES 30. The section and subsection headings in the TOC must match the section and subsection headings in the FPI.

Comment:

YES 31. In the TOC, when a section or subsection is omitted, the numbering must not change. If a section or subsection from 201.56(d)(1) is omitted from the FPI and TOC, the heading "FULL PRESCRIBING INFORMATION: CONTENTS" must be followed by an asterisk and the following statement must appear at the end of TOC: "*Sections or subsections omitted from the full prescribing information are not listed."

Comment:

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Full Prescribing Information (FPI)

FULL PRESCRIBING INFORMATION: GENERAL FORMAT

YES 32. The **bolded** section and subsection headings in the FPI must be named and numbered in accordance with 21 CFR 201.56(d)(1) as noted below (section and subsection headings should be in UPPER CASE and title case, respectively). If a section/subsection required by regulation is omitted, the numbering must not change. Additional subsection headings (i.e., those not named by regulation) must also be **bolded** and numbered.

BOXED WARNING
1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
6 ADVERSE REACTIONS
7 DRUG INTERACTIONS
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Labor and Delivery
8.3 Nursing Mothers
8.4 Pediatric Use
8.5 Geriatric Use
9 DRUG ABUSE AND DEPENDENCE
9.1 Controlled Substance
9.2 Abuse
9.3 Dependence
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
12.4 Microbiology (by guidance)
12.5 Pharmacogenomics (by guidance)
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
13.2 Animal Toxicology and/or Pharmacology
14 CLINICAL STUDIES
15 REFERENCES
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

Comment:

YES 33. The preferred presentation for cross-references in the FPI is the section (not subsection) heading followed by the numerical identifier. The entire cross-reference should be in *italics* and enclosed within brackets. For example, *"[see Warnings and Precautions (5.2)]"* or "[*see Warnings and Precautions (5.2)*]".

Comment:

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N/A 34. If RMCs are listed in HL, the corresponding new or modified text in the FPI sections or subsections must be marked with a vertical line on the left edge.

Comment:

FULL PRESCRIBING INFORMATION DETAILS

FPI Heading

YES 35. The following heading must be **bolded** and appear at the beginning of the FPI: "**FULL PRESCRIBING INFORMATION".** This heading should be in UPPER CASE.

Comment:

BOXED WARNING Section in the FPI

N/A 36. In the BW, all text should be **bolded**.

Comment:

N/A 37. The BW must have a heading in UPPER CASE, containing the word "**WARNING**" (even if more than one Warning, the term, "**WARNING**" and not "**WARNINGS**" should be used) and other words to identify the subject of the Warning (e.g., "**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**").

Comment:

CONTRAINDICATIONS Section in the FPI

YES 38. If no Contraindications are known, this section must state "None."

Comment:

ADVERSE REACTIONS Section in the FPI

YES 39. When clinical trials adverse reactions data are included (typically in the "Clinical Trials Experience" subsection of ADVERSE REACTIONS), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

"Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice."

Comment:

N/A 40. When postmarketing adverse reaction data are included (typically in the "Postmarketing Experience" subsection of ADVERSE REACTIONS), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

"The following adverse reactions have been identified during post-approval use of (insert drug name). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure."

Comment:

PATIENT COUNSELING INFORMATION Section in the FPI

N/A 41. Must reference any FDA-approved patient labeling in Section 17 (PATIENT COUNSELING INFORMATION section). The reference should appear at the beginning of Section 17 and

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include the type(s) of FDA-approved patient labeling (e.g., Patient Information, Medication Guide, Instructions for Use).

Comment:

N/A 42. FDA-approved patient labeling (e.g., Medication Guide, Patient Information, or Instructions for Use) must not be included as a subsection under section 17 (PATIENT COUNSELING INFORMATION). All FDA-approved patient labeling must appear at the end of the PI upon approval.

Comment:

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Appendix A: Format of the Highlights and Table of Contents

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use [DRUG NAME] safely and effectively. See full prescribing information for [DRUG NAME].

[DRUG NAME (nonproprietary name) dosage form, route of administration, controlled substance symbol]
Initial U.S. Approval: [year]

WARNING: [SUBJECT OF WARNING]
See full prescribing information for complete boxed warning.

- **[text]**
- **[text]**

----------RECENT MAJOR CHANGES----------
[section (X.X)] [m/year]
[section (X.X)] [m/year]

----------INDICATIONS AND USAGE----------
[DRUG NAME] is a [name of pharmacologic class] indicated for [text]

----------DOSAGE AND ADMINISTRATION----------
- [text]
- [text]

----------DOSAGE FORMS AND STRENGTHS----------
[text]

----------CONTRAINDICATIONS----------
- [text]
- [text]

----------WARNINGS AND PRECAUTIONS----------
- [text]
- [text]

----------ADVERSE REACTIONS----------
Most common adverse reactions (incidence > x%) are [text].

To report SUSPECTED ADVERSE REACTIONS, contact [name of manufacturer] at [phone #] or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.

----------DRUG INTERACTIONS----------
- [text]
- [text]

----------USE IN SPECIFIC POPULATIONS----------
- [text]
- [text]

See 17 for PATIENT COUNSELING INFORMATION [and FDA-approved patient labeling OR and Medication Guide].

Revised: [m/year]

FULL PRESCRIBING INFORMATION: CONTENTS*

WARNING: [SUBJECT OF WARNING]
1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
2.1 [text]
2.2 [text]
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
5.1 [text]
5.2 [text]
6 ADVERSE REACTIONS
6.1 [text]
6.2 [text]
7 DRUG INTERACTIONS
7.1 [text]
7.2 [text]
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Labor and Delivery
8.3 Nursing Mothers
8.4 Pediatric Use
8.5 Geriatric Use
9 DRUG ABUSE AND DEPENDENCE
9.1 Controlled Substance
9.2 Abuse
9.3 Dependence
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
12.4 Microbiology
12.5 Pharmacogenomics
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
13.2 Animal Toxicology and/or Pharmacology
14 CLINICAL STUDIES
14.1 [text]
14.2 [text]
15 REFERENCES
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

*Sections or subsections omitted from the full prescribing information are not listed.

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/s/

KEVIN B BUGIN
02/12/2015

RICHARD W ISHIHARA
02/13/2015