CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761261Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

IND 012757

MEETING MINUTES

Genzyme Corporation
Attention: Vanessa Davidson
Director, Global Regulatory Affairs
55 Corporate Drive, Mailstop: 55C-300
Bridgewater, NJ 08807

Dear Ms. Davidson:

Please refer to your investigational new drug application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for GZ402665.

We also refer to the teleconference between representatives of your firm and the FDA on March 24, 2021. The purpose of the meeting was to discuss your proposed plan for a Biologics License Application (BLA) submission for GZ402665 as (b) (4) treatment of non-central nervous system manifestations of acid sphingomyelinase deficiency (ASMD) in pediatric and adult patients.

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

If you have any questions, call Jenny Doan, Regulatory Project Manager, at (301) 796-1023.

Sincerely,

{See appended electronic signature page}

Kathleen M Donohue, MD, MSc
Director
Division of Rare Diseases and Medical Genetics
Office of Rare Diseases, Pediatrics, Urologic and Reproductive Medicine
Center for Drug Evaluation and Research

ENCLOSURE:
Meeting Minutes

U.S. FOOD & DRUG ADMINISTRATION

MEMORANDUM OF MEETING MINUTES

Meeting Type: B
Meeting Category: Pre-BLA

Meeting Date and Time: March 24, 2021; 11:15AM – 12:15PM EST
Meeting Location: Teleconference

Application Number: 012757
Product Name: GZ402665
Indication: Enzyme replacement therapy for (b) (4) treatment of non-central nervous system (CNS) manifestations of acid sphingomyelinase deficiency (ASMD) in pediatric and adult patients.

Sponsor Name: Genzyme Corporation
Regulatory Pathway: 351(a) of the Public Health Service Act

Meeting Chair: Anita Zaidi, MD, Clinical Team Leader
Meeting Recorder: Jenny Doan, Regulatory Project Manager

FDA ATTENDEES

Office of Rare Diseases, Pediatrics, Urologic and Reproductive Medicine (ORPURM)
Hylton Joffe, MD, MMSc, Director
Janet Maynard, MD, Deputy Director

Division of Rare Diseases and Medical Genetics (DRDMG)
Kathleen Donohue, MD, Director
Anita Zaidi, MD, Clinical Team Leader
Christine Hon, PharmD, Clinical Analyst

Division of Pharm/Tox of Rare Diseases, Pediatric, Urologic and Reproductive Medicine
Mukesh Summan, PhD, Director
Mary Ellen McNerney, PhD, Reviewer

Division of Regulatory Operations for Rare Diseases and Medical Genetics
Pam Lucarelli, Director, Project Management Staff
Michael White, PhD, Chief, Project Management Staff
Jenny Doan, MSN, BSN, Regulatory Health Project Manger

Office of Clinical Pharmacology/Division of Translational and Precision Medicine (DTPM)
Jie (Jack) Wang, PhD, Clinical Pharmacology Team Leader
Xiaohui (Michelle) Li, PhD, Clinical Pharmacology Reviewer

Lian Ma, PhD, Pharmacometrics Team Leader
Yuching, PhD, PBPK Lead

Office of Biostatistics/ Division of Biometrics IV
Yan Wang, PhD, Biostatistics Team Leader
Yared Gurmu, PhD, Biostatistics Reviewer

Office of Biotechnology Products (OBP)
Ram Sihag, PhD, CMC Team Leader
Maria Gutierrez-Hoffman, PhD, Team Leader

Office of Pharmaceutical Manufacturing Assessment (OPMA)
Maria Gutierrez-Hoffman, PhD, Reviewer
Virginia Carroll, PhD, Team Leader

Office of Biostatistics/ Division of Biometrics III/ Patient-Focused Statistical Support (PFSS)
Lili Garrard, PhD, PFSS Team Leader (Acting)
Marian Strazzeri, MS, PFSS Reviewer

Division of Clinical Outcome Assessment (DCOA)
Christopher St. Clair, PharmD, COA Reviewer
Elektra Papadopoulos, MD, MPH, Deputy Director (Acting)

Office of Surveillance and Epidemiology (OSE)
Laura Zendel, PharmD, BCPS, Team Leader, Division of Risk Management (DRM)
Theresa Ng, PharmD, BCPS, CDE, Risk Management Analyst, DRM
Sarah Vee, PharmD, Safety Evaluator, Division of Medication Errors Prevention and Analysis (DMEPA)
Idalia Rychlik, PharmD, Team Leader, DMEPA
Su-Lin Sun, RPh, PharmD, GWCPM, Safety Regulatory Project Manager
Aleksander Winiarski, PharmD, RPh, Team Leader

SPONSOR ATTENDEES
Colleen Costello, PhD, Associate Vice President, Global Regulatory Affairs – US
Vanessa Davidson, Director, Global Regulatory Affairs – US
Sandy Furey, MD, PhD, Therapeutic Area Strategy Lead Rare Diseases, Specialty PV
Don Gieseker, PharmD , AVP of US Regulatory Affairs
(b) (4) External Consultant, Clinical Outcomes Assessment
Ruth Pulikottil Jacob, PhD, Health Economics and Value Assessment Business Partner
Andreas Jessel, MD, Vice President, Global Project Head, Rare Disease Development
Barbara Kittner, MD, Therapeutic Area Head Rare Diseases, Specialty PV
Karin Knobe, MD, PhD, Vice President, Therapeutic Area Head, Development Rare Diseases and Rare Blood Disorders
Monica Kumar, MD, MPH, Senior Director, Clinical Research

Priti Lad, Senior Director, Global Regulatory Affairs – US
Jing Li, Associate Director, PK PD Modeling
Sreeraj Macha, Senior Director, PK PD modeling
Amanda Meisel, PharmD, Post-Doctoral Fellow, Global Regulatory Affairs – US
Susan Richards, PhD, FAAPS, Vice President, Translational Medicine and Early Development
Joyce Tay, PhD, Manager, Global Regulatory Affairs – CMC Biologics
Susana Zaph, PhD, Head Translational Disease Modeling- Rare
Qi Zhang, PhD, Director, Biostatistics

1.0 BACKGROUND

FDA Regulatory Background

The sponsor, Genzyme Corporation (Genzyme), is developing GZ402665, also referred to as olipudase alfa, an enzyme replacement therapy for the treatment of non-central nervous system manifestations of acid sphingomyelinase deficiency (ASMD) in pediatric and adult patients. Olipudase alfa is a recombinant human acid sphingomyelinase (rhASM), produced by mammalian cell culture technology using a Chinese hamster ovary cell line. The product is intended to be supplied as a lyophilized powder, to be reconstituted for intravenous infusion, and administered (b) (4) according to body weight.

Olipudase alfa was granted orphan drug designation for the treatment of ASMD (Niemann-Pick disease) on August 3, 2000. The IND was submitted to the FDA on October 26, 2005, granted Fast Track designation on April 23, 2007, and Breakthrough Therapy designation on May 26, 2015, both for the treatment of non-neurological manifestations of ASMD.

The olipudase alfa clinical development program had multiple changes in the manufacturing process during the course of the drug development, including a switch from Process A to Process B and Process C (b) (4) eventually to Process C (b) (4) as to-be marketed drug substance and drug product process. Highlights of the FDA interactions related to the manufacture processes for olipudase are outlined in the table below.

October 4, 2011	Type C meeting to discuss proposed clinical and manufacturing development plans for olipudase alfa. To support phase 2 and future clinical development programs for olipudase alfa, the sponsor intended to implement (b) (4) (b) (4) (b) (4) (Process B) to replace (b) (4) (Process A). Meeting minutes issued on November 4, 2011.
April 7, 2015	Type C meeting to discuss Genzyme's plan to change the manufacturing process from Process B to Process C, which is (b) (4) for the ongoing phase 2/3 and proposed pediatric clinical trials. The FDA

	requested Genzyme provide additional information to support the comparability between the two processes and raised concerns on the timing of introducing new material to the ongoing clinical studies. Meeting minutes issued on April 13, 2015.
January 25, 2017	Type B meeting to discuss FDA's concerns regarding the comparability issues, particularly due to changes in specific activity between Process B and Process C. The FDA also recommended additional clinical data would be needed to evaluate and characterize the impact of these changes. Meeting minutes issued on January 31, 2017. Additional comments were provided in an advice letter on March 3, 2017.
July 26, 2017	Type C meeting to discuss the pediatric extrapolation plan for olipudase alfa. The FDA indicated (b) (4) (b) (4) challenges for the extrapolation for safety and efficacy. Genzyme proposed to enroll at least 8 additional pediatric patients (age < 12 years) into the open-label DFI13803 trial to be initiated with Process C product. Meeting minutes issued on July 31, 2017.
July 27, 2018	FDA issued a WRO in response to a CMC-only meeting request to discuss Genzyme's additional change to the drug substance manufacturing, which includes transitioning from a (b) (4) (Process C (b) (4) to a (b) (4) (Process C (b) (4). The FDA commented on the proposed comparability assessment plan between Process C (b) (4) and Process C (b) (4). Additional FDA feedback was provided on incorporating Process C (b) (4) into the ongoing clinical studies in an advice letter on October 5, 2018.
August 28, 2019	Type B meeting to discuss Genzyme's proposed data package for a rolling review BLA for olipudase alfa. The FDA stated its concerns regarding the format and content of the BLA submission, the proposed datasets, and the timeline given the various manufacturing processes. Meeting minutes issued on September 8, 2019.
October 18, 2019	FDA issued a WRO to comment on Genzyme's clarifications for their rolling BLA submission strategy.
January 31, 2020	FDA issued an advice letter in response to the CMC amendment submitted September 20, 2019, which contains a biochemical comparability assessment between Process C (b) (4) and to-be-market Process C (b) (4) The FDA concurred that the materials from these two processes are analytically comparable.

Genzyme plans to submit a BLA rolling review with the following schedule:

BLA Submission Wave	Proposed Submission Date	Content
Wave 1	June 14, 2021	Non-clinical modules
Wave 2	September 30, 2021	CMC and Clinical modules

On January 21, 2021, Genzyme submitted a meeting request to discuss the BLA data package for olipudase. On January 27, 2021, the FDA granted a type B pre-BLA teleconference, which is scheduled to take place on March 24, 2021. The meeting briefing package was received on February 22, 2021. FDA sent preliminary comments to Genzyme on March 17, 2021. The meeting took place as scheduled.

FDA Clinical Background

Acid spingomyelinase deficiency (ASMD) is an autosomal recessive disease caused by genetic mutations in the *SMPD1* gene leading to a deficiency in the lysosomal enzyme acid sphingomyelinase (ASM), which catalyzes the degradation of sphingomyelin. ASMD has traditionally been broken down into two subgroups. Type A generally causes severe neurodegenerative disease during infancy, whereas type B is generally not considered to be a neurologic disease. There is also an intermediate phenotype known as A/B form.[1]

ASMD type B is a milder later onset form of ASMD and can develop symptoms from infancy to adulthood. It is associated with systemic disease that can vary widely in severity and extent. Patients may have hepatosplenomegaly, deterioration in lung function, liver disease, growth delays and low weight, osteopenia, and dyslipidemia. Patients with ASMD type B usually do not develop neurological symptoms but may develop mild symptoms. Some affected children and adolescents may develop nystagmus and cerebellar signs, which includes unsteady manner of walking and clumsiness. Intellectual disability and psychiatric disorders, abnormalities of the retina, and peripheral neuropathy may occur.[2]

2.0 DISCUSSION

FDA Introductory Comment

Your proposed BLA submission for adults consists of one adequate and well-controlled trial (DFI12712). In that trial, the primary endpoint that uses a patient reported outcome, the splenomegaly-related score (SRS), appears to have shown no difference between the treated and placebo arms. Therefore, your pivotal trial fails to meet the primary endpoint on a clinically meaningful outcome. As such, it is unclear how the other primary endpoints (DLco, spleen volume) directly measure how a patient feels, functions or survives. In order to receive traditional approval, you need to provide

[1] GeneReviews. Acid sphingomyelinase deficiency. Accessed March 4, 2021. https://www.ncbi.nlm.nih.gov/books/NBK1370/
[2] National Organization for Rare Disorders' Rare Disease Database. Acid sphingomyelinase deficiency. Accessed March 4, 2021. https://rarediseases.org/rare-diseases/acid-sphingomyelinase-deficiency/

justification and evidence that the other primary endpoints (DLco, spleen volume) are expected to have a clinically meaningful benefit or have been shown to predict a specific clinical benefit to patients.

Also, in order to establish substantial evidence of effectiveness, you must accompany your adequate and well-controlled trial with confirmatory evidence of treatment effect. This evidence should be specifically described in your BLA submission. We refer you to the FDA draft guidance for industry *Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products* (December 2019)[3,4] for examples of how a single trial together with confirmatory evidence can establish effectiveness.

You also do not have a well-controlled trial for the pediatric population that you propose to treat. Therefore, you will need to justify your lack of a well-controlled trial and provide all evidence that would intend to establish substantial evidence of effectiveness in the pediatric population.

Meeting Discussion: ***Refer to attached Sponsor's response to FDA Preliminary Comments (Section 5.0).***

Although the Sponsor's overall proposal appears reasonable, the Agency reiterated that the adequacy of the data package will be determined at filing after the BLA is submitted. The Sponsor's overall approach to using partial extrapolation also appears reasonable. Whether the study data and results support the partial extrapolation of efficacy from adult to pediatrics will be determined during the BLA review.

The Agency stated that detailed information is needed in the BLA to demonstrate a clinically meaningful benefit to the patients. The Sponsor should specify a clinically meaningful threshold for the selected endpoints in the target population and provide adequate justification for such thresholds. The degree of change in the biomarker should be clinically meaningful for the targeted population. Information on the correlation of the biomarker with clinical outcomes from clinical trials and/or literature should be provided. Refer to the Post-Meeting Comments below regarding how the available evidence and literature can be used to justify the use of a surrogate endpoint as a clinically meaningful endpoint.

The Sponsor also stated, when asked by the Agency, that the lack of difference in SRS in DFI12712 was due to an unexpected placebo effect. The Agency stated that the BLA should include a detailed argument summarizing the Sponsor's point of view regarding why the changes in the biomarker endpoints are clinically meaningful despite the lack of improvement seen on the PRO endpoint.

[3] We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.
[4] https://www.fda.gov/media/133660/download

Post-Meeting Comments: ***DLCO, FVC, spleen size, and platelets etc. are biomarker measures that do not directly measure how patients feel, function, and survive. To support traditional approval using these biomarkers as surrogate endpoints in ASMD, summarize the available evidence (published literature or proprietary data, in vitro, in vivo, or clinical) linking the underlying pathophysiology of the disease (e.g. sphingomyelin accumulation) with the biomarker endpoints and the clinical relevance of those changes for ASMD patients.***

1. ***Sphingomyelin is tissue toxic when it accumulates***
2. ***Sphingomyelin accumulates in all tissues where the disease causes structural damage and functional loss***
3. ***Degree of sphingomyelin accumulation is correlated with degree of tissue damage***
4. ***Reduction in sphingomyelin is associated with normalization of structure and function in surrogate endpoints (e.g. DLCO, FVC, spleen size, platelets).***
5. ***The magnitude of this reduction is clinically meaningful in the target patient population***
6. ***Drug removes sphingomyelin from disease target tissues***

Organize the evidence for each of the above six points in a table like the following:

Senior author or protocol number (w/ hyperlink)	***Year study completed or published (in ascending order)***	***Population number & type (patients, healthy volunteers, animal models, cell lines)***	***Study design***	***Intervention (e.g. dose) vs. control (e.g. placebo)***	***Results (treatment difference, 95%CI, p-value)***

Question 1: Does the Agency agree that the proposed clinical data package is sufficient to support the filing and review of the BLA for the proposed indication?

FDA Response to Question 1: The adequacy of the data package for filing will be determined during the filing review of the BLA. Refer to the Introductory Comment and the comments below.

We remind you to submit the following for study DFI12712 (ASCEND) under Section 5.3.5.3 of the eCTD[5]:

- An exact copy (e.g., screenshot) of each COA used to evaluate efficacy, safety, measurement properties, and/or meaningful change in study DFI12712 *as administered* in the trial;
- A detailed scoring algorithm for each administered COA that includes how scores were computed in the presence of missing item responses;
- A clear description of how each COA-based endpoint was constructed from COA scores;
- A final Psychometric Analysis Plan (PAP); and
- A COA Evidence Dossier compiling and synthesizing all psychometric and meaningful change results.

The evaluation of the measurement properties of the COAs (e.g., the SRS, BFI Item 3, BPI-SF Item 3, and FACIT-Dyspnea) and the interpretation of COA-based endpoints intended for labeling in study DFI12712 (ASCEND) will be review issues. If you intend to conduct patient exit interviews and include these data in the BLA, we strongly recommend submitting the interview protocol and interviewer guide(s) to the Agency for review and comment as soon as possible. We recommend that the interviews include open-ended concept elicitation regarding symptoms and impacts of ASMD and cognitive debriefing of the SRS. We refer you to the FDA Patient-Focused Drug Development guidance series[6] (particularly the Guidance 4 discussion document[7]) regarding use of qualitative data to support interpretation of meaningful change.

For safety assessment, you need to submit the narratives for deaths, serious adverse events, adverse events of special interests, and withdrawal due to adverse event for all the studies.

We recommend that you perform exploratory analyses evaluating the impact of *SMPD1* genotype on PK, PD, safety, and efficacy.

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[5] Per the FDA guidance for industry *Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims* (December 2009); accessible at: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/patient-reported-outcome-measures-use-medical-product-development-support-labeling-claims).

[6] https://www.fda.gov/drugs/development-approval-process-drugs/fda-patient-focused-drug-development-guidance-series-enhancing-incorporation-patients-voice-medical

[7] https://www.fda.gov/media/132505/download

Meeting Discussions: ***Refer to attached Sponsor's response to FDA Preliminary Comments (Section 5.0)***

The Sponsor should submit to the BLA a dossier containing all justification and evidence related to the COAs. Rationale for the selection/development of the COAs (including but not limited to SRS) should be included (relevant literature, clinical expert input, etc.). The results of psychometric analyses should also be included. It is acceptable not to include the interview protocol and interviewer guide.

The Sponsor's proposed exploratory analyses evaluating the impact of SMPD1 genotype appears reasonable. The Agency may have additional comments during the BLA review.

Post Meeting Comment: The Sponsor should also perform exploratory analyses assessing the correlation of baseline residual acid sphingomyelinase activity with PK, PD, safety, and efficacy.

Question 2: Does the Agency agree with Sanofi Genzyme's proposed plan to include clinical data and analyses related to manufacturing Processes B, C (b) (4) and C (b) (4) in the clinical study reports, Integrated Summary of Safety, Integrated Summary of Efficacy, and Integrated Summary of Immunogenicity in the BLA?

FDA Response to Question 2: Your overall proposed plan to include clinical data and analyses related to different manufacturing process drug products in the clinical study reports, ISS, ISE, and ISI appears reasonable. We have the following comments regarding some of the planned analyses. We may also have additional comments during the BLA review.

- The safety assessment of TEAEs between drug products manufactured with Process B and C (b) (4) in DFI13803 ASCEND-Peds CSR should include the evaluation of treatment emergent SAEs, hypersensitivity IARs, and anaphylaxis reactions IARs.
- For efficacy assessment between Process B and Process C (b) (4) drug products in the DFI12712 ASCEND CSR, LTS13632 CSR, and ISE, include evaluations of other efficacy/PD measurements such as DLco, liver volume, ALT, HDL, LDL, and lyso sphingomyelin, etc. in addition to the currently proposed endpoints.

Meeting Discussion: ***No further discussion occurred.***

Question 3: Does the Agency agree that the clinical data provided address the concerns from the Agency regarding comparability between Process B and Process C (b) (4)?

FDA Response to Question 3: The clinical comparability between Process B and Process C (b) (4) drug products will be a review issue and determined during the review of the BLA. Please also refer to the response to Question 2.

Meeting Discussion: ***No further discussion occurred.***

Question 4: Does the Agency agree Sanofi Genzyme's proposal to include the following data from patients treated with Process C (b) (4) in the initial BLA and in the 120 day safety update?

FDA Response to Question 4:
Your proposal appears reasonable.

Meeting Discussion: ***No further discussion occurred.***

Question 5: Does the Division agree with Sanofi Genzyme's plan to present descriptive statistics and to not include "minimum detectable difference calculations" in the analyses comparing the different manufacturing processes as requested by the Division?

FDA Response to Question 5:
Your proposed analysis plan for comparing the different manufacturing processes appears reasonable.

Meeting Discussion: ***No further discussion occurred.***

Question 6: Does the Agency agree with the planned content of Module 2.7.2 of the BLA, including modeling (population PK, exposure-response, population PK/PD and quantitative system pharmacology) analyses?

FDA Response to Question 6: The proposed content of Module 2.7.2 appears sufficient to support the review of clinical pharmacology components of your BLA.

We have the following additional clinical pharmacology comments.

- For the evaluation of the impact of anti-drug antibodies (ADA) on pharmacokinetic (PK), we recommend that you include between-subject comparison (i.e., between ADA positive subjects and ADA negative subjects) as well as within-subject comparison (i.e., before ADA positive and after ADA positive) of PK data.
- We acknowledge that you plan to conduct population PK analysis to support PK and dose selection. We encourage you to include subject's ADA status as a covariate in the population PK analysis on an exploratory basis to evaluate the impact of ADA on PK. In the population PK analysis, further explore the necessity of treating the subject ADA status as a time-varying variable for ADA positive subjects with or without the ADA titer data.

- Submit bioanalytical method performance summary tables for all the bioanalytical methods used for the PK and PD assessment in your clinical studies. Use the format of summary tables as in FDA guidance for industry *Bioanalytical Methods Templates*.[8] Include the method performance summary for each of the supported clinical studies. Do not delete any rows from the tables. State "not applicable" if certain rows of columns are not applicable. Include any other additional bioanalytical information in a separate table that might be relevant for your BLA review.
- We recommend the content and format of information in the Clinical Pharmacology section (Section 12) of labeling be consistent with FDA guidance for industry *Clinical Pharmacology Section of Labeling for Human Prescription Drug and Biological Products – Content and Format*.[9]

Meeting Discussion: ***No further discussion occurred.***

Question 7: Does the Agency agree with the content, layout, and location of the proposed patient visualization profiles?

FDA Response to Question 7: We agree with the eCTD location of the proposed patient visualization profiles. We have the following comments for the content and the layout of these patient profiles.

- We noted that you have included in the patient profiles the upper and lower reference limits (as depicted by green dotted lines) for some but not all laboratory tests. We recommend that you include the upper and lower reference values for all laboratory tests in the patient profiles.
- As shown in Appendix B, the current layout of the patient profiles is one graph for one variable/profile per page. To facilitate the review of these patient profiles and the relationship of one profile to another, we recommend that you group relevant patient profiles and plot them together in one page. Below are some example layouts of the patient profiles.
    - Dose and duration, ADA, AEs, and concomitant medications
    - Dose and duration, ceramide levels, lyso sphingomyelin CRP, IL-6, and IL-8
    - Dose and duration, iron, ferritin, and platelet count
    - Dose and duration, bilirubin, alkaline phosphate, AST, and ALT
    - Spleen and liver volumes, DLCO, FVC, FEV, and TLC
    - High resolution CT and chest X-ray evaluations
- When plotting individual profiles over time for the key outcome variables (as shown in Appendix B), use different colors to indicate the data associated with each manufacturing process.

[8] https://www.fda.gov/media/131425/download
[9] https://www.fda.gov/media/74346/download

Meeting Discussion: ***No further discussion occurred.***

Question 8: Does the Division agree with the proposed analyses related to the COVID-19 pandemic that will be included in the clinical study reports for LTS13632 and DFI12712 (ASCEND), Integrated Summary of Safety, Integrated Summary of Efficacy, and Integrated Summary of Immunogenicity?

FDA Response to Question 8: The overall approach of analyzing the clinical data to evaluate the impact of COVID-19 appears reasonable. In addition to TEAEs, we recommend that you evaluate the impact of COVID-19 on treatment emergent SAEs, hypersensitivity IARs, and anaphylaxis reactions IARs.

Meeting Discussion: ***No further discussion occurred.***

Question 9: Does the Agency agree with Sanofi Genzyme's plan to submit the DFI12712 ASCEND clinical study report and dataset?

FDA Response to Question 9: Your plan to submit the DFI12712 ASCEND clinical study report and dataset appears reasonable. You should include treatment emergent SAEs, hypersensitivity IARs, and anaphylaxis reactions IARs in the comparison report summarizing the changes to the PAP data in the DFI12712 ASCEND interim CSR version 1 vs. version 2.

Your efficacy datasets should include a flag variable indicating the manufacturing processes. Provide this flag variable for efficacy datasets from trials DFI13412, DFI13803 ASCEND Peds, LTS13632, DFI12712 ASCEND and the extension study.

Meeting Discussion: ***No further discussion occurred.***

Question 10: Does the Division agree with the proposed Study Data Standardization Plan?

FDA Response to Question 10: The overall proposed Study Data Standardization Plan appears reasonable.

Your overall plan to submit the datasets and computer program codes to support the psychometric evaluation of COAs implemented in study DFI12712 (ASCEND) appears reasonable. However, we remind you that computer program (e.g., SAS, R) code used to conduct all (not just for construct validity) scoring, psychometric analyses, meaningful change analyses should be submitted.

Meeting Discussion: ***No further discussion occurred.***

Question 11: Does the Agency agree that the safety profile as summarized in section 12.1 supports Sanofi Genzyme's position that a risk evaluation and mitigation strategy

(REMS) should not be required and that labeling would be adequate to inform health care professionals and patients about the appropriate use of olipudase alfa?

FDA Response to Question 11: We have insufficient information at this time to determine whether a risk evaluation and mitigation strategy (REMS) will be necessary to ensure that the benefits of the drug outweigh the risks, and if it is necessary, what the required elements will be. We will determine the need for a REMS during the review of your application.

Meeting Discussion: ***No further discussion occurred.***

Question 12: Does the Agency agree that the electronic Common Technical Document (eCTD) Table of Content (TOC) is acceptable for the submission?

FDA Response to Question 12: The overall eCTD TOC appears acceptable for the BLA submission. We have the following additional comments.

- Clarify the eCTD location in which the standalone report describing the clinical comparison between olipudase alfa manufactured with Process B versus Process C (b) (4) will be submitted. We recommend that you submit the data analysis datasets that were used for analyzing and comparing the two drug products manufactured with Process B and Process C (b) (4) under this section of eCTD or provide in the study report the specific eCTD locations in which such datasets are submitted.
- If referencing Drug Master Files, include letters of authorization in section 1.4 References.
- Refer to "The Comprehensive Table of Contents Headings and Hierarchy"[10] for more specific headings that may be used for the BLA.
- We note reproductive and developmental toxicology studies are listed in eCTD module 4.2.3.5. Kindly confirm that these study reports will be submitted in the June 2021 nonclinical submission.
- Refer to Additional Comments from CMC and Microbiology.

Meeting Discussion: ***No further discussion occurred.***

Question 13: Does the Agency agree with the proposed rolling submission schedule?

FDA Response to Question 13: Your proposed rolling review submission appears reasonable. Refer to the guidance for industry *Expedited Programs for Serious Conditions – Drugs and Biologics*[11] for the formal rolling review request.

[10] https://www.fda.gov/media/76444/download
[11] https://www.fda.gov/media/86377/download

Meeting Discussion: ***No further discussion occurred.***

Question 14: Does the FDA agree with Sanofi Genzyme's proposal to use data cut off dates for the olipudase alfa ongoing trials LTS13632 and DFI12712 approximately 6 months prior to the submission date of the last wave of the rolling BLA submission?

FDA Response to Question 14: No, we do not agree. Your proposed data cutoff dates for the ongoing trials LTS13632 and DFI12712 are more than 6 months from the proposed submission date of the last wave of the rolling BLA submission (i.e., September 30, 2021). The data cutoff dates for the two trials should be as close as possible to but no sooner than 6 months (i.e., April 1, 2021) from the submission date of the last wave of the rolling BLA submission (i.e., September 30, 2021). Otherwise, provide adequate justification for your proposed cutoff dates.

In addition, clarify the data cutoff dates for the ongoing trials LTS13632 and DFI12712 in Appendix A. Under Module 5.3.3.2 of Appendix A, the data cut-off date for DFI12712 Interim CSR Version 2 is missing. The data cut-off date for LTS13632 is (b) (4) (b) (4) different from the proposed data cut-off date of March 1, 2021, as described in the current meeting package.

Meeting Discussion: ***Refer to attached Sponsor's response to FDA Preliminary Comments (Section 5.0).***

The Sponsor provided justification for the proposed data cut-off dates of March 1, 2021, for LTS13632 and March 15, 2021, for DFI12712. The FDA stated that the proposed data cut-off dates for the two studies appear reasonable.

Question 15: Does the FDA agree with Sanofi Genzyme's proposal to use the submission date of the last wave of the rolling BLA as the data cut-off date for the 120 day safety update report and to submit the 120 day safety update report to the FDA within 120 calendar days after the last wave of the rolling BLA is submitted to the FDA?

FDA Response to Question 15: That appears reasonable. However, we remind you to submit the updated efficacy and safety data analysis datasets in the 120-day safety update submission.

Meeting Discussion: ***No further discussion occurred.***

Question 16: Sanofi Genzyme requests guidance on whether the BLA may be designated for Priority Review and if the Agency plans to conduct an expedited review.

FDA Response to Question 16: The determination on the priority and expedited review designation will be made during the filing review of your application.

Meeting Discussion: ***No further discussion occurred.***

Question 17a: Does the Agency agree that olipudase alfa may qualify as a rare pediatric disease product application?

FDA Response to Question 17a: Whether an application qualifies for a Rare Pediatric Disease Priority Review Voucher is a matter of review. FDA would need to evaluate the application to determine whether the BLA is eligible for a priority review voucher. Please consult the draft guidance for industry *Rare Pediatric Disease Priority Review Vouchers,*[12] for instructions on how to submit a Rare Pediatric Disease Priority Review Voucher request and the eligibility criteria.

Meeting Discussion: ***No further discussion occurred.***

Question 17b: Does the Division have any additional feedback regarding Sanofi Genzyme's justification and the potential for the olipudase alfa BLA to receive a Priority Review Voucher?

FDA Response to Question 17b: If an applicant seeks approval in both adults and pediatric patients with the rare disease for the same indication, it will not affect voucher eligibility, as described in the guidance. However, we remind applicants seeking a voucher that – whether or not they seek approval for use in an adult population – we expect them to submit data adequate for labeling the drug for use by the affected pediatric patients.

Meeting Discussion: ***No further discussion occurred.***

Question 18: Does the FDA agree that, based upon the data shared to date that an Advisory Committee is unlikely?

FDA Response to Question 18: The determination on the Advisory Committee will be made during your application review.

Meeting Discussion: ***No further discussion occurred.***

3.0 ADDITIONAL FDA COMMENTS

Human Factors

We understand that you are planning to use olipudase alfa as enzyme replacement therapy for (b) (4) treatment of non-central nervous system (CNS) manifestations of acid sphingomyelinase deficiency (ASMD) in pediatric and adult patients. However, you have not submitted a comprehensive risk analysis. It is unclear from your submission who are the intended users or the anticipated use environment. If you intend to have

[12] http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM423325.pdf

non healthcare providers (e.g., caregivers) prepare and administer your proposed product in a home setting, we are concerned that medication errors may occur.

Thus, we recommend you conduct a comprehensive use-related risk analysis if you have not already completed one. The comprehensive use-related risk analysis should include a comprehensive and systematic evaluation of all the steps involved in using your product (e.g., based on a task analysis) the errors that users might commit or the tasks they might fail to perform and the potential negative clinical consequences of use errors and task failures.

Your risk analysis should also discuss risk-mitigation strategies you employed to reduce risks you have identified and the methods you intend to use for validating the risk-mitigation strategies. This information is needed to ensure that all potential risks involved in using your product have been considered and adequately mitigated and the residual risks are acceptable.

Based on this risk analysis, you will need to determine whether you need to submit the results of a human factors (HF) validation study conducted under simulated use conditions with representative users performing necessary tasks to demonstrate safe and effective use of the product.

If you determine that you do need to submit a HF validation study for your product, the risk analysis can be used to inform the design of a human factors validation study protocol for your product. We recommend you submit your study protocol for feedback from the Agency before commencing your study. Please note we will need 60 days to review and provide comments on the HF validation study protocol. Plan your development program timeline accordingly. Note that submission of a protocol for review is not a requirement. If you decide not to submit a protocol, this approach carries some risk to you because prospective Agency review is not possible, but this is a decision for your company.

Please refer to our draft guidance *Contents of a Complete Submission for Threshold Analyses and Human Factors Submissions to Drug and Biologic Applications* for the content of a human factors validation study protocol submission.

The requested information should be submitted to the IND. Place the requested information in eCTD Section 5.3.5.4 – Other Study reports and related information.

Guidance on human factors procedures to follow can be found in the following guidance documents:

Applying Human Factors and Usability Engineering to Medical Devices

Guidance on Safety Considerations for Product Design to Minimize Medication Errors

Note that we recently published three draft guidance documents that, while not yet finalized, might also be useful in understanding our current thinking and our approach to human factors for combination products, product design, and labeling:

Human Factors Studies and Related Clinical Study Considerations in Combination Product Design and Development

Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors

Contents of a Complete Submission for Threshold Analyses and Human Factors Submissions to Drug and Biologic Applications

CMC

To facilitate the Agency's review of the drug substance (DS) and drug product (DP) manufacturing processes for olipudase alfa, in your BLA application provide the information for process parameters and in-process control, as applicable, in the following tabular format. Please provide a separate table for each unit operation. The tables should summarize information from module 3 and may be submitted either to module 1 or module 3R.

Process Parameter/ Operating Parameter/ In-Process Control	Proven Acceptable Range/ Control Limits/Targets[1] for Commercial Manufacturing Process	Criticality Classification[2]	Characterized Range/ Control Limits/Targets[1] tested in Process Development Studies	Manufactured Range/ Control Limits/ Targets[1] used for Pivotal Study Lots	Manufactured Range/ Control Limits/ Targets[1] used in Process Validation	Justification of the Proposed Commercial Acceptable Range[3]	Comment[4]

[1] As applicable
[2] For example, critical process parameter, key process parameter, non-critical process parameter, as described in module 3.
[3] This could be a brief verbal description or links to the appropriate section of the eCTD.
[4] Optional.

To facilitate the Agency's review of the control strategy for olipudase alfa, in your BLA application provide information for quality attributes and process and product related impurities for the DS and DP in the following tabular format. The tables should summarize information from module 3 and may be submitted either to module 1 or module 3R.

Quality Attributes and Process and Product Related Impurities for CI, DS and DP	Criticality Classification[1]	Impact[2]	Source[3]	Analytical Method [4]	Proposed Control Strategy[6]	Justification of the Proposed Control Strategy[6]	Comment[7]

[1] For example, critical quality attribute or non-critical quality attribute.
[2] What is the impact of the attribute, e.g. contributes to potency, immunogenicity, safety, efficacy.
[3] What is the source of the attribute or impurity, e.g. intrinsic to the molecule, fermentation, protein A column.
[4] List all the methods used to test an attribute in-process, at release, and on stability. For example, if two methods are used to test identity then list both methods for that attribute.
[5] List all the ways the attribute is controlled, for example, in-process testing, validated removal, release testing, stability testing.
[6] This could be a brief verbal description or links to the appropriate section of the eCTD.
[7] Optional.

Microbiology:

The FDA is providing additional product quality microbiology comments for you to consider during development of your commercial manufacturing process and preparation of your 351(a) BLA submission.

All facilities should be registered with the FDA at the time of the 351(a) BLA submission and ready for inspection in accordance with 21 CFR 600.21 and 601.20(b)(2). Include in the BLA submission a complete list of the manufacturing and testing sites with their corresponding FEI numbers. A preliminary manufacturing schedule for the drug substance and drug product should be provided in the BLA submission to facilitate the planning of pre-license inspections during the review cycle. Manufacturing facilities should be in operation and manufacturing the product under review during the inspection.

Information and data for CMC product quality microbiology should be submitted in the specified sections indicated below.

The CMC Drug Substance section of the 351(a) BLA (Section 3.2.S) should contain information and data summaries for microbial and endotoxin control of the drug substance. The information should include, but not be limited to the following:

- Bioburden and endotoxin levels at critical manufacturing steps should be monitored using qualified bioburden and endotoxin tests. Bioburden sampling

should occur prior to any 0.2 µm filtration step. The pre-established bioburden and endotoxin limits should be provided (3.2.S.2.4).

- Bioburden and endotoxin data obtained during manufacture of three process qualification (PPQ) lots (3.2.S.2.5).
- Microbial data from three successful product intermediate hold time validation runs at manufacturing scale. Bioburden and endotoxin levels before and after the maximum allowed hold time should be monitored and bioburden and endotoxin limits provided (3.2.S.2.5).
- Chromatography resin and UF/DF membrane lifetime study protocols and acceptance criteria for bioburden and endotoxin samples. During the lifetime studies, bioburden and endotoxin samples should be taken at the end of storage prior to sanitization (3.2.S.2.5).
- Information and summary results from the shipping validation studies (3.2.S.2.5).
- Drug substance bioburden and endotoxin release specifications (3.2.S.4).
- Summary reports and results from bioburden and endotoxin test method qualification studies performed for in-process intermediates and the drug substance. If compendial test methods are used, brief descriptions of the methods should be provided in addition to the compendial reference numbers (3.2.S.4).

The CMC Drug Product section of the 351(a) BLA (Section 3.2.P) should contain validation data summaries to support the aseptic processing operations. For guidance on the type of data and information that should be submitted, refer to the FDA guidance for industry *Submission Documentation for Sterilization Process Validation in Applications for Human and Veterinary Drug Products.*[13]

The following information should be provided in Sections 3.2.P.3.3 and/or 3.2.P.3.4, as appropriate.

- Identification of the manufacturing areas and type of fill line (e.g. open, RABS, isolator), including area classifications.

[13] http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm072171.pdf

- Description of the sterilizing filter (supplier, size, membrane material, membrane surface area, etc.); sterilizing filtration parameters (pressure and/or flow rate), as validated by the microbial retention study; wetting agent used for post-use integrity testing of the sterilizing filter and post-use integrity test acceptance criteria.
- Parameters for filling and capping for the vials.
- A list of all equipment and components that contact the sterile drug product (i.e. the sterile-fluid pathway) with the corresponding method(s) of sterilization and depyrogenation, including process parameters. The list should include single-use equipment.
- Processing and hold time limits, including the time limit for sterilizing filtration and aseptic filling.
- Sampling points and in-process limits for bioburden and endotoxin. Bioburden samples should be taken at the end of the hold time prior to the subsequent filtration step. Pre-sterile filtration bioburden limits should not exceed 10 CFU/100 mL.

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

- Bacterial filter retention study for the sterilizing filter. Include a comparison of validation test parameters with routine sterile filtration parameters.
- Sterilization and depyrogenation of equipment and components that contact the sterile drug product. Provide summary data for the three validation studies and describe the equipment and component revalidation program.
- In-process microbial controls and hold times. Three successful product intermediate hold time validation runs should be performed at manufacturing scale, unless an alternative approach can be scientifically justified. Bioburden and endotoxin levels before and after the maximum allowed hold time should be monitored and bioburden and endotoxin limits provided.
- Isolator decontamination summary data and information, if applicable.
- Three successful consecutive media fill runs, including summary environmental monitoring data obtained during the runs. Describe the environmental and personnel monitoring procedures followed during media fills and compare them to the procedures followed during routine production.

- Information and summary results from shipping validation studies.
- Validation of capping parameters, using a container closure integrity test.
- Lyophilizer sterilization validation summary data and information.

The following product testing and method validation information should be provided in the appropriate sections of Module 3.2.P:

- Container closure integrity testing. System integrity should be demonstrated initially and during stability. Container closure integrity method validation should demonstrate that the assay is sensitive enough to detect breaches that could allow microbial ingress (≤ 20 microns). Container closure integrity testing should be performed *in lieu* of sterility testing for stability samples every 12 months (annually) until expiry.
- Summary report and results for qualification of the bioburden, sterility, and endotoxin test methods performed for in-process intermediates (if applicable) and the finished drug product, as appropriate. If compendial test methods are used, brief descriptions of the methods should be provided in addition to the compendial reference numbers. Provide full descriptions and validation of non-compendial rapid microbial methods.
- Summary report and results of the Rabbit Pyrogen Test conducted on three batches of drug product in accordance with 21 CFR610.13(b).
- Low endotoxin recovery studies. Certain product formulations have been reported to mask the detectability of endotoxin in the USP <85> *Bacterial Endotoxin Test* (BET). The effect of hold time on endotoxin detection should be assessed by spiking a known amount of standard endotoxin (RSE or purified CSE) into undiluted drug product and then testing for recoverable endotoxin over time.
- Microbiological studies in support of the post-reconstitution and post-dilution storage conditions. Describe the test methods and results that employ a minimum countable inoculum (10-100 CFU) to simulate potential microbial contamination that may occur during dilution. The test should be run at the label's recommended storage conditions, be conducted for twice the recommended storage period, bracket the drug product concentrations that would be administered to patients, and use the label-recommended reconstitution solutions and diluents. Periodic intermediate sample times are recommended. Challenge organisms may include strains described in USP <51> *Antimicrobial Effectiveness Testing*, plus typical skin flora or species associated with hospital-

borne infections. *In lieu* of this data, the product labeling should recommend that the post-reconstitution and post-dilution storage period is not more than 4 hours.

***Meeting Discussion:* No further discussion occurred.**

4.0 OTHER IMPORTANT INFORMATION

DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

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

- Major components of the application are expected to be submitted with the original application and are not subject to agreement for late submission. You stated you intend to submit a complete application and therefore, there are no agreements for late submission of application components.

PREA REQUIREMENTS

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

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

PRESCRIBING INFORMATION

In your application, you must submit proposed prescribing information (PI) that conforms to the content and format regulations found at 21 CFR 201.56(a) and (d) and 201.57 including the Pregnancy and Lactation Labeling Rule (PLLR) (for applications submitted on or after June 30, 2015). As you develop your proposed PI, we encourage you to review the labeling review resources on the PLR Requirements for Prescribing Information[14] and Pregnancy and Lactation Labeling Final Rule[15] websites, which

[14] https://www.fda.gov/drugs/laws-acts-and-rules/plr-requirements-prescribing-information
[15] https://www.fda.gov/drugs/labeling/pregnancy-and-lactation-labeling-drugs-final-rule

include:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products.

- The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information related to pregnancy, lactation, and females and males of reproductive potential.

- Regulations and related guidance documents.

- A sample tool illustrating the format for Highlights and Contents, and

- The Selected Requirements for Prescribing Information (SRPI) − a checklist of important format items from labeling regulations and guidances.

- FDA's established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

Pursuant to the PLLR, you should include the following information with your application to support the changes in the Pregnancy, Lactation, and Females and Males of Reproductive Potential subsections of labeling. The application should include a review and summary of the available published literature regarding the drug's use in pregnant and lactating women and the effects of the drug on male and female fertility (include search parameters and a copy of each reference publication), a cumulative review and summary of relevant cases reported in your pharmacovigilance database (from the time of product development to present), a summary of drug utilization rates amongst females of reproductive potential (e.g., aged 15 to 44 years) calculated cumulatively since initial approval, and an interim report of an ongoing pregnancy registry or a final report on a closed pregnancy registry. If you believe the information is not applicable, provide justification. Otherwise, this information should be located in Module 1. Refer to the draft guidance for industry *Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products – Content and Format*.

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

DISCUSSION OF SAFETY ANALYSIS STRATEGY FOR THE ISS

After initiation of all trials planned for the phase 3 program, you should consider requesting a Type C meeting to gain agreement on the safety analysis strategy for the Integrated Summary of Safety (ISS) and related data requirements. Topics of discussion at this meeting would include pooling strategy (i.e., specific studies to be

pooled and analytic methodology intended to manage between-study design differences, if applicable), specific queries including use of specific standardized MedDRA queries (SMQs), and other important analyses intended to support safety. The meeting should be held after you have drafted an analytic plan for the ISS, and prior to programming work for pooled or other safety analyses planned for inclusion in the ISS. This meeting, if held, would precede the Pre-NDA meeting. Note that this meeting is optional; the issues can instead be addressed at the pre-NDA meeting.

To optimize the output of this meeting, submit the following documents for review as part of the briefing package:

- Description of all trials to be included in the ISS. Please provide a tabular listing of clinical trials including appropriate details.

- ISS statistical analysis plan, including proposed pooling strategy, rationale for inclusion or exclusion of trials from the pooled population(s), and planned analytic strategies to manage differences in trial designs (e.g., in length, randomization ratio imbalances, study populations, etc.).

- For a phase 3 program that includes trial(s) with multiple periods (e.g., double-blind randomized period, long-term extension period, etc.), submit planned criteria for analyses across the program for determination of start / end of trial period (i.e., method of assignment of study events to a specific study period).

- Prioritized list of previously observed and anticipated safety issues to be evaluated, and planned analytic strategy including any SMQs, modifications to specific SMQs, or sponsor-created groupings of Preferred Terms. A rationale supporting any proposed modifications to an SMQ or sponsor-created groupings should be provided.

When requesting this meeting, clearly mark your submission "**DISCUSS SAFETY ANALYSIS STRATEGY FOR THE ISS**" in large font, bolded type at the beginning of the cover letter for the Type C meeting request.

MANUFACTURING FACILITIES

To facilitate our inspectional process, we request that you clearly identify *in a single location*, either on the Form FDA 356h, or an attachment to the form, all manufacturing facilities associated with your application. Include the full corporate name of the facility and address where the manufacturing function is performed, with the FEI number, and specific manufacturing responsibilities for each facility.

Also provide the name and title of an onsite contact person, including their phone number, fax number, and email address. Provide a brief description of the manufacturing operation conducted at each facility, including the type of testing and

DMF number (if applicable). Each facility should be ready for GMP inspection at the time of submission.

Consider using a table similar to the one below as an attachment to Form FDA 356h. Indicate under Establishment Information on page 1 of Form FDA 356h that the information is provided in the attachment titled, "Product name, NDA/BLA 012345, Establishment Information for Form 356h."

Site Name	Site Address	Federal Establishment Indicator (FEI) or Registration Number (CFN)	Drug Master File Number (if applicable)	Manufacturing Step(s) or Type of Testing [Establishment function]
(1)				
(2)				

Corresponding names and titles of onsite contact:

Site Name	Site Address	Onsite Contact (Person, Title)	Phone and Fax number	Email address
(1)				
(2)				

To facilitate our facility assessment and inspectional process for your marketing application, we refer you to the instructional supplement for filling out Form FDA 356h[16] and the guidance for industry, *Identification of Manufacturing Establishments in Applications Submitted to CBER and CDER Questions and Answers*[17]. Submit all related manufacturing and testing facilities in eCTD Module 3, including those proposed for commercial production and those used for product and manufacturing process development.

OFFICE OF SCIENTIFIC INVESTIGATIONS (OSI) REQUESTS

The Office of Scientific Investigations (OSI) requests that the items described in the draft guidance for industry, *Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions,* and the associated conformance guide, *Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications,* be provided to facilitate

[16] https://www.fda.gov/media/84223/download
[17] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/identification-manufacturing-establishments-applications-submitted-cber-and-cder-questions-and

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

Please refer to the draft guidance for industry *Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions* (February 2018) and the associated *Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications*.[18]

NONPROPRIETARY NAME

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

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

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

To the extent that your proposed 351(a) BLA is within the scope of this guidance, FDA will assign a four-letter suffix for inclusion in the proper name designated in the license at such time as FDA approves the BLA.

5.0 ATTACHMENTS AND HANDOUTS

On March 22, 2021, Genzyme sent via email a response to the FDA preliminary comments as read-ahead materials for the teleconference.

[18] https://www.fda.gov/media/85061/download

22 Pages have 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. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

JENNY N DOAN
03/26/2021 04:09:17 PM
Signed on behalf of Dr. Donohue.

CDER Medical Policy Council Brief
Breakthrough Therapy Designation
Division of Gastroenterology and Inborn Errors Products
May 22, 2015

Summary

1. IND 012757
2. Sponsor: Genzyme Corporation
3. Product: olipudase alfa (recombinant human acid sphingomyelinase [rhASM])
4. Indication: treatment of nonneurological manifestations of acid sphingomyelinase deficiency
5. Is the drug intended, alone or in combination with one or more other drugs, to treat a serious or life-threatening disease or condition? Yes
6. Does the preliminary clinical evidence indicate that the drug may demonstrate substantial improvement over existing therapies on one or more clinically significant endpoints? Yes

Medical Officer: Dina Zand, MD
Clinical TL: Laurie Muldowney, MD

1. Brief description of the drug

Olipudase alfa is a recombinant form of human acid sphingomyelinase (rhASM), manufactured by DNA recombinant technology in a Chinese hamster ovary cell line. Olipudase alfa is predominately a disulfide linked rhASM dimer with an apparent molecular weight of 140 kilodaltons. In clinical trials, olipudase alfa is administered once every 2 weeks by intravenous (IV) infusion. Due to size, olipudase alfa does not cross the blood-brain barrier and is not expected to affect neurological manifestations of ASMD when administered intravenously.

Physiologically, acid sphingomyelinase is responsible for the hydrolysis of sphingomyelin to ceramide and phosphocholine in lysosomes, and deficiency in this enzyme leads an abnormal accumulation of sphingomyelin throughout the body, primarily in monocyte-macrophages within the reticuloendothelial system in liver, spleen, bone marrow, and lungs. In the most severe, or "neuronopathic" form, the characteristic foam cells (a histologic marker of substrate deposition) also accumulate in the CNS.

2. Brief description of the disease and intended population

Acid sphingomyelinase deficiency (ASMD) is a rare autosomal recessive lysosomal storage disease with an estimated incidence of 0.4 to 0.6 in 100,000 newborns. Historically, ASMD was classified into two phenotypes previously known as Niemann-Pick type A (NPD A) and Niemann-Pick type (NPD B). Patients with NPD A (also known as acute neuronopathic ASMD) typically present in

infancy with failure to thrive, hepatosplenomegaly, rapid progression of neurodegenerative disease, and death by 3 to 4 years of age. NPD B (or non-neuronopathic ASMD) is typically a somatic disease with minimal neurological involvement. These diseases, in fact, represent a continuum of clinical manifestations, and an intermediate, chronic neuronopathic phenotype (NPD A/B) has also been described, hence the current re-classification under the common term ASMD.

Because olipudase alfa does not cross the blood-brain barrier, it is currently intended as treatment of the non-neuronopathic form of ASMD. The onset and clinical course of non-neuronopathic ASMD is highly variable, and the age of onset varies from early childhood to the fourth and fifth decades of life. Patients may present with any combination of clinical manifestations, including hepatosplenomegaly, interstitial lung disease, bleeding, thrombocytopenia, atherogenic lipid profile, liver dysfunction, osteoporosis, growth retardation and delayed puberty. In a recent natural history study of 103 patients with intermediate or attenuated subtypes of ASMD, the mean age of death was 25 years and ranged from 2 to 72 years. Patients typically died of complications from their disease, including pulmonary insufficiency, respiratory infection, splenic rupture, hemorrhage, premature coronary artery disease, and cirrhosis.

3. Endpoints used in the available clinical data, endpoints planned for later studies, and endpoints currently accepted by the review division in the therapeutic area

No drug has been approved to date for the treatment of acid sphingomyelinase deficiency and there are no clinical trials, published or ongoing, that have established clinically relevant endpoints for this indication. Because absence of a qualified endpoint poses significant challenges to designing a successful clinical program, the Division has held multiple discussions with Genzyme, its consultants as well as experts within the Agency in an effort to identify endpoints that would capture clinically meaningful changes in response to treatment in the challenging context of such a rare and heterogeneous disease. A consensus was recently reached with Genzyme regarding several endpoints that evaluate treatment-related reductions in substrate deposition in organs typically affected by this enzyme deficiency (i.e., spleen and liver), as well as the impact of treatment on lung diffusing capacity for carbon monoxide (DLco) (see endpoint discussion below).

Change in DLco: The Division discussed with Genzyme the merits of DLco in ASMD, and agreement was reached to use change in DLco as a co-primary endpoint in their phase 2/3 trial of adults with ASMD (it is anticipated that this trial, should it provide positive results, will likely be the "pivotal" registration trial). The Division believes that improvement in DLco could be considered clinically relevant in patients with baseline abnormalities in DLco, presuming the change meets a clinically meaningful threshold. This is because the lung is a target organ in ASMD, and pulmonary dysfunction contributes to the morbidity and mortality of patients with ASMD. The pathophysiology of pulmonary disease in ASMD is reasonably well understood and a positive effect on DLco would reflect of an improvement in lung gas exchange secondary to a reduction in lung sphingomyelin deposits. DPARP has been previously consulted and provided input and support on the use of DLco as a clinical endpoint in ASMD.

Change in spleen size: In the Division's judgment, a reduction in spleen size (or reduction in size of any other organ such as the liver for that matter), although an important marker of pharmacodynamic activity, poses important challenges in establishing a true clinical benefit, particularly as it relates to how patients with ASMD feel, function, or survive. For example, patients with ASMD can have significant splenomegaly (> 8x multiples of normal), but only a subset of patients describe symptoms associated with splenomegaly (e.g., early satiety, abdominal discomfort, and body image concerns). Moreover, splenomegaly does not correlate well with changes in platelet counts in ASMD. Therefore, the Division does not regard a decrease in spleen size by itself as a sufficient demonstration of a clinically meaningful effect. This issue has been discussed with Genzyme on multiple occasions and the Division has proposed, among others, that reductions in spleen size should be evaluated in combination with improvement in spleen-related symptoms (e.g., abdominal pain, early satiety), in the subset of patients with such symptoms. In the end Genzyme decided to assess the change in spleen size as a co-primary endpoint with DLco in their phase 2/3 trial of adults with ASMD, and improvement in spleen-related symptoms will be assessed as a secondary endpoint. This has been found acceptable by the Division.

4. Brief description of available therapies (if any)

There are no approved treatments for ASMD. Current management strategies include palliative care and supportive care to treat specific disease manifestations; none of these interventions modify or alter the rate of disease progression.

Bone marrow transplantation has been undertaken in a small number of ASMD patients. , It has not been shown, however, to impact neurological symptoms associated with the neuronopathic phenotype, and complications from the procedure have limited its use in the non-neuronopathic subtype. Partial or full splenectomy has been used for the management of splenomegaly in ASMD. This procedure, however, has not been demonstrated to impact disease progression, and there are reports of subsequent increased risk for pulmonary infection.

5. Brief description of any drugs being studied for the same indication that received breakthrough therapy designation

None.

6. Description of preliminary clinical evidence

- **Overview of clinical development program**

  Olipudase alfa is being developed to treat the nonneurological manifestations of ASMD. To date, two Genzyme-sponsored clinical trials have been completed with olipudase alfa, both phase 1 studies in adults with ASMD. An open-label extension study is currently ongoing for patients who completed the phase 1 multiple dose study. A pediatric phase 1/2 study and an adult phase 2/3 study are planned. The Division and Genzyme reached a general agreement regarding the latter study and a final statistical analysis plan is under final discussion. The Division has provided advice regarding the primary efficacy analysis, favoring either a co-primary endpoint incorporating DLco and spleen reduction, or a hierarchical approach in which DLco is the first statistic to be tested followed by spleen volume.

Table 1: Overview of Clinical Development Program

Study Number	Phase/patient population	Study Design	Number planned/ enrolled/ completed	Endpoints/Objectives
Completed Studies				
SPHINGO00605	Phase 1/Adults with ASMD	Single-center, single dose, dose-escalation study	23/11/11	Safety
DFI13412	Phase 1b/Adults with ASMD	Open-label, multicenter, ascending dose, multiple dose study	5/5/5	Primary: safety and tolerability Exploratory Efficacy Endpoints include: - percent change from baseline in spleen and liver volumes - pulmonary imaging, PFTs - Exercise capacity - Physician global assessment, QoL assessments - Hematology, fasting lipid profile
Ongoing Studies				
LTS13632	Phase 2/Adults with ASMD who completed DFI13412	Multinational, multicenter, non-randomized, open-label, long-term treatment study	~65 – 70/5/5	Primary: Safety Secondary: - spleen and liver volume - pulmonary imaging and function tests - Exercise capacity - Hematology

Planned Studies				
DFI12712	Phase 2/3 in adult patients with ASMD	Multicenter, randomized, double-blind, placebo-controlled, repeat-dose, dose-comparison study	35	-Primary Endpoints: - percentage change in spleen volume (in MN) from baseline to week 52 - percentage change in DLco (in % predicted of normal) from baseline to week 52
DFI13803	Phase 1/2 in pediatric patients with non-neuronopathic ASMD	Multi-national, multi-center, open-label, ascending dose study	Minimum of 12	Primary: safety and tolerability Exploratory Efficacy: - spleen and liver volume - infiltrative lung disease scoring - patient growth (z-score) - pulmonary function testing - bone age, bone biomarkers - Physician's global assessment, health outcome questionnaires - cognitive and adaptive function testing

- **Efficacy data available to support breakthrough therapy designation**

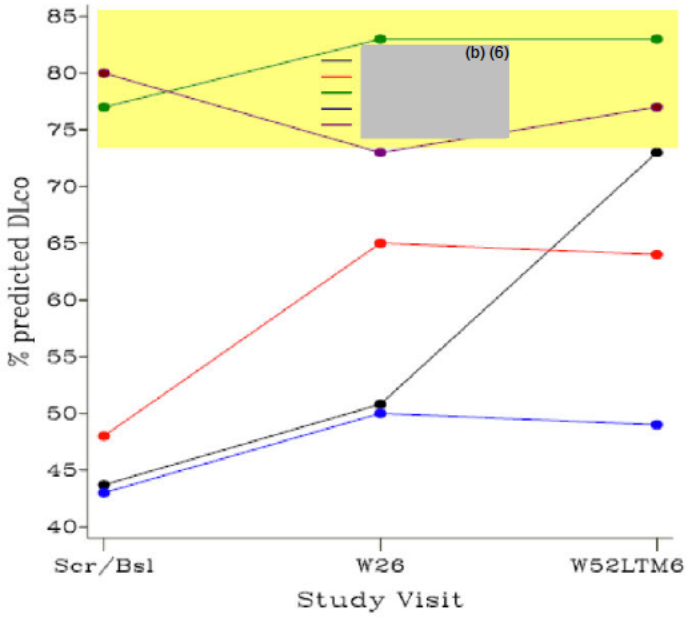
The preliminary clinical evidence provided to support breakthrough therapy designation is from 5 adult patients with ASMD who completed a 26-week phase 1b trial DFI13412 with enrollment in an ongoing extension trial to 52 weeks.

Study DFI13412 was a phase 1b, open-label, multicenter, ascending multiple-dose study of adult patients with ASMD. The primary objective of this study was to determine the safety and tolerability of dose escalation to 3.0 mg/kg given IV every 2 weeks for a duration of 26 weeks. Of the 5 patients enrolled, 3 were men and 2 were women, with an age range between 22 and 47 years. Clinical response was assessed for hepatic, splenic, and pulmonary endpoints, with comparison of changes at 26 weeks relative to baseline, each patient serving as his own control. All 5 patients continued in the ongoing extension trial where the same evaluations were conducted for up to 52 weeks.

Pulmonary Function/DLco:

The effect of olipudase alfa upon lung function was assessed via measurement of DLco as percentage of normal predicted values. The mean baseline DLco of 58% reflected moderate disease severity. At 26 weeks and 52 weeks, the DLco mean improved from baseline by 13.4% and 23.4% respectively. DLco severity scores consistently improved in 3 of 5 patients as displayed in the graph below. All three patients with baseline DLco below 50% of normal improved on treatment. Two patients (highlighted in yellow) who had at baseline DLco values of 77% and 80% of normal showed very small changes on treatment. These two patients appear to have had milder manifestations of the disease at baseline (they are displayed in the same green and purple in in subsequent graphs).

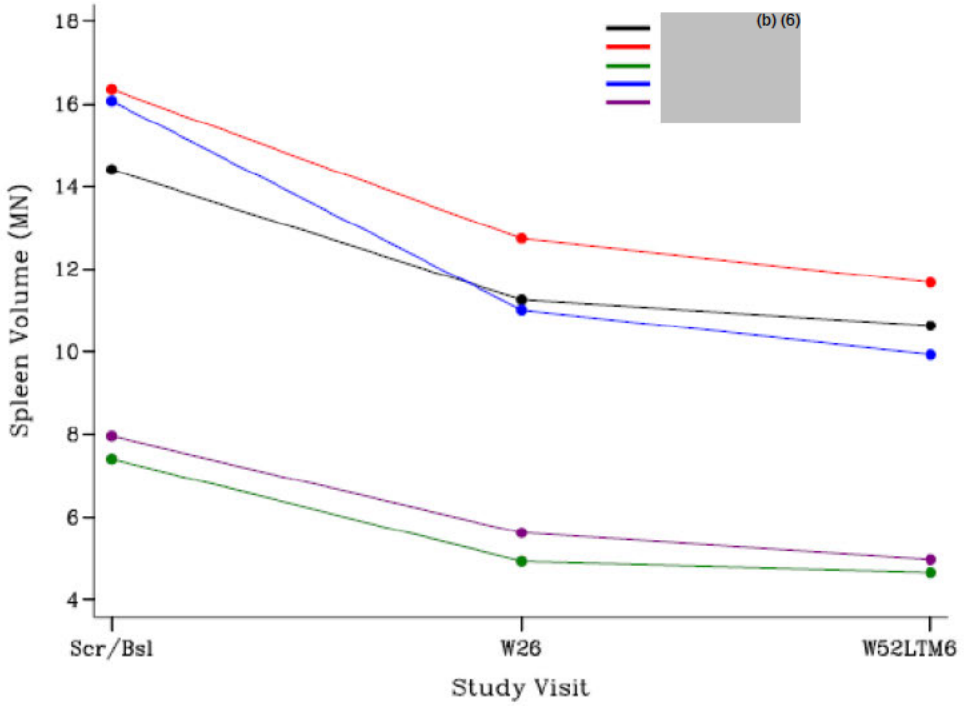
Figure 3 By-patient percent predicted DL_{CO} with 12 months olipudase alfa treatment



Change in Spleen Size:

All patients had splenomegaly at baseline, with spleen sizes ranging from approximately 8 to 16.5 multiples of normal (MN). Spleen volume in cm^3 decreased in all patients with a mean reduction of 25.3% by week 26 and 29.2% by week 52. Mean spleen volume reduction as multiples of normal was 27.6% and 33.5% at week 26 and week 52, respectively. Absolute changes for individual patients are displayed in Figure 4 of the BT application, reproduced below. Please note that the reduction was smallest in the two patients who had the mildest degree of spleen enlargement at baseline (i.e. green and purple profile).

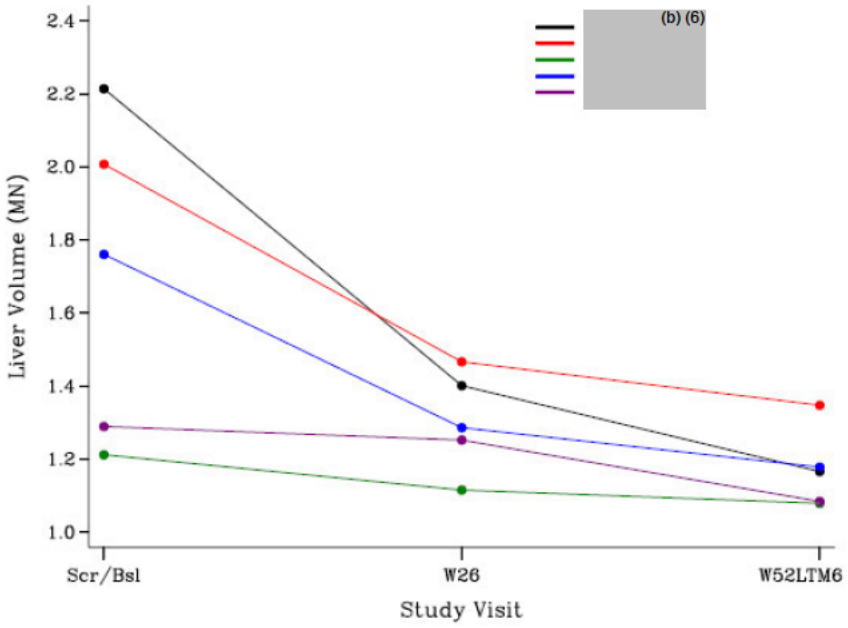
Figure 4 - Reduction in spleen volume over 12 months (DFI13412 and LTS13632)



Change in Hepatic Size and Reduction of Hepatic Sphingomyelin:

As calculated via MRI imaging, hepatic volumes decreased in 4 of 5 patients at 26 weeks, with a reduction in mean liver volume (cm^3) from baseline of 17.1%. Hepatic volumes decreased in all patients at 52 weeks with a mean liver volume reduction from baseline of 22.8% (Fig 5 and Table 1, below). Similar to observations described in the previous figures, the two patients with the smallest degree of liver enlargement at baseline showed the least change on treatment (see green and purple profiles).

Figure 5: Reduction in Liver Volume Over 52 weeks



The same changes are presented in table format below:

Table 1 - Change in liver volume by time point (baseline, week 26, week 52)

Patient ID	Liver volume (cm^3)					Liver volume (MN)				
	BL	W26	chg from BL	W52	chg from BL	BL	W26	chg from BL	W52	chg from BL
(b) (6)	4029	2610	-35.2%	2192	-45.6%	2.21	1.4	-36.7%	1.17	-47.3%
	3262	2247	-31.1%	2153	-34%	2.01	1.47	-27%	1.35	-32.9%
	1806	1757	-2.7%	1697	-6%	1.21	1.12	-8%	1.08	-10.9%
	2971	2274	-23.5%	2245	-24.4%	1.76	1.29	-26.9%	1.18	-33.1%
	1934	2072	7.1%	1854	-4.1%	1.29	1.25	-2.9%	1.08	-15.9%
Mean (SD)	2800.6 (934.4)	2191.9 (311.3)	-17.1%	2028.3 (239.3)	-22.8%	1.697 (0.438)	1.304 (0.136)	-20.3%	1.171 (0.109)	-28.0%

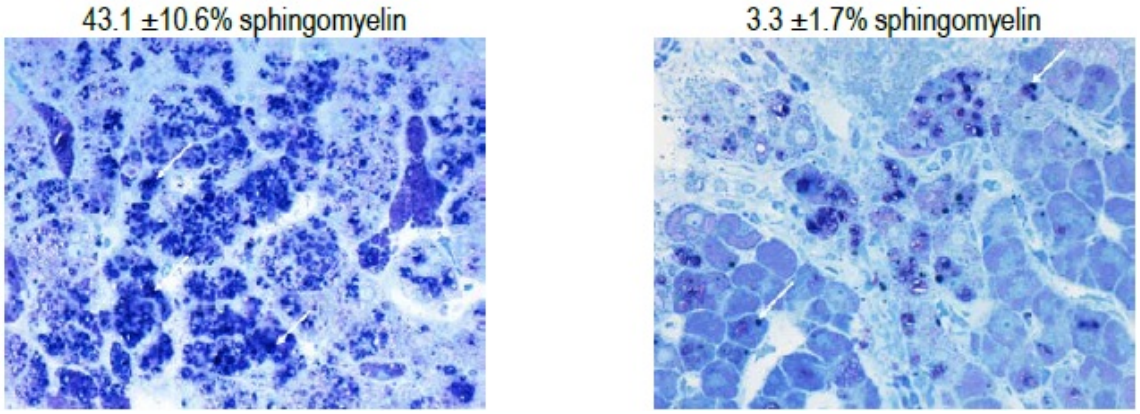
Abbreviations: BL = baseline; MN = multiples of normal; W26 = week 26; W52 = week 52

Normal liver volume in MN is 25 cm^3/kg x body weight (kg)

To ascertain histologic changes that may be associated with olipudase alfa exposure, liver biopsies were completed at baseline and after 26 weeks of infusion. Sphingomyelin concentrations were assessed histomorphometrically using high-resolution light microscopy (HRLM). All samples that could be analyzed (4 of 5 patients) showed a reduction of sphingomyelin that was calculated to range from 9 to 44 percentage points. Figure 2 presents an example from a single patient.

Sphingomyelin levels were also measured biochemically via LC/MS/MS with demonstration of mean reduction from baseline assessed at 66.3%

Figure 1: Histopathology images of Patient 840001003 showing sphingomyelin accumulation by HRLM at baseline and week 26



Magnification 600x
White arrows indicate sphingomyelin accumulation in lysosomes of hepatocytes and Kupffer cells. Sections from resin-embedded samples from patients were stained with a modified toluidine blue stain (Patient, (b) (6) shown)

Other Clinical Assessments:

- Fatigue severity and impact on daily function were assessed using the Brief Fatigue Inventory (BFI), a self-administered PRO. At baseline, all patients reported mild to moderate fatigue. After 26 weeks, three patients noted improvement from "moderate" to "mild" or absence of fatigue, and two patients reported no changes. At week 52, 4 patients reported either no changes in fatigue or improvement. The patient with lupus reported worsening fatigue.
- Pain was assessed at baseline, 26 and 52 weeks using the Brief Pain Inventory (BPI), another self-administered PRO. Of the 4 patients with baseline pain, three improved to a lower BPI at 26 and 52 weeks, while the 4th noted worsening (the patient with lupus).
- Liver enzymes were presented descriptively and tended to decrease or normalize; however, these changes did not correlate with degree of reduction in hepatic size.

- **Safety data (a brief explanation of the safety profile would be helpful, especially if it affects the division's recommendation)**

As with other enzyme replacement therapy the potential risk of immune mediated adverse reactions (e.g., hypersensitivity reactions) is present and will require monitoring throughout the clinical program.

An animal toxicity signal of acute phase reaction, thought to be related to the rapid conversion of sphingomyelin to its main catabolite ceramide, was identified in a murine model of ASMD. This safety signal was successfully attenuated in humans by modifying the dose escalation regimen. Few adverse events consistent with acute phase reactions (fever, nausea, vomiting, fatigue, pain) have been observed since the implementation of an intrapatient dose escalation, and these were reported to be of mild severity. No deaths, serious adverse events or severe treatment-emergent adverse events have been identified to date. Additionally, there were no reported changes in vital signs, coagulation or EKG parameters. At the end of 52 weeks, none of the 5 patients had developed IgG antibodies to olipudase alfa.

7. Division's recommendation and rationale

Based on the preliminary clinical data provided, the Division recommends that a Breakthrough Therapy designation should be granted for olipudase alfa to treat the nonneurological manifestations of ASMD. Although the data provided in this BT submission are limited to a small number of patients (5), one has to take into consideration that this is about one seventh of number of patients to be enrolled in what is anticipated to be the "pivotal" trial for this indication (35 patients). With this in mind the Division's recommendation is based on the following:

- Nonneuronopathic ASMD is a serious medical condition for which there are no available pharmacological therapies. It is a condition which, if left untreated, progresses to serious complications such as pulmonary insufficiency, splenic rupture, hyperspenism, premature coronary artery disease, and/or cirrhosis.
- The preliminary clinical data submitted in support of the Breakthrough Therapy designation indicate that olipudase reduces substrate deposition in spleen and liver, and most importantly, improves pulmonary function, the latter being assessed via an endpoint that the Division considers to be clinically significant for this new indication (lung diffusing capacity for carbon monoxide or DLco).

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

As previously indicated, Genzyme intends to initiate a multicenter, randomized, double-blind, placebo-controlled, Phase 2/3 study in adult patients with ASMD (Study DFI12712). Efficacy will be assessed using a co-primary endpoint of percentage change in spleen volume from baseline to week 52 and percentage change in DLco from baseline to week 52. The Sponsor and the Division have had extensive discussion regarding the endpoints and statistical analysis plan for this study and are close to agreement. The Sponsor is also initiating a phase 1/2 study in pediatric patients with non-neuronopathic ASMD to assess the safety and tolerability of olipudase alfa in pediatric patients.

9. References

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/s/

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05/26/2015

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