CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761278Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

IND 113186

MEETING MINUTES

Chiesi Farmaceutici S.p.A.
c/o Chiesi USA, Inc.
Attention: Brant Hamel, PhD, RAC
Manager, Regulatory Affairs, Rare Diseases
175 Regency Woods Place, Ste 600
Cary, NC 27518

Dear Dr. Hamel:

Please refer to your investigational new drug application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for CHFLMZYMAA1.

We also refer to your April 26, 2021, correspondence requesting a Pre-BLA meeting to discuss the clinical data package and foreign data intended to support an Accelerated Approval of your proposed BLA.

We also refer to the teleconference between representatives of your firm and the FDA on June 29, 2021. The purpose of the meeting was to discuss the clinical data package and foreign data intended to support an Accelerated Approval of your proposed BLA.

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

If you have any questions, call Avinash Kalsi, Regulatory Project Manager at (301)348-1432.

Sincerely,

{See appended electronic signature page}

Patroula Smpokou, M.D.
Deputy Director
Division of Rare Diseases and Medical Genetics (DRDMG)
Office of Rare Diseases, Pediatrics, Urologic and Reproductive Medicine (ORPURM)
Center for Drug Evaluation and Research

ENCLOSURE: Meeting Minutes

U.S. FOOD & DRUG ADMINISTRATION

PRELIMINARY MEETING COMMENTS

Meeting Type: B
Meeting Category: Pre-BLA

Meeting Date and Time: Tuesday, June 29, 2021; 11:00 AM to 12:00 PM EDT
Meeting Location: teleconference

Application Number: IND 113186
Product Name: CHFLMZYMAA1
Indication: Enzyme replacement therapy in alpha-mannosidosis patients
Sponsor Name: Chiesi Farmaceutici S.p.A.
Regulatory Pathway: 351(a) of the Public Health Service Act

Meeting Chair: Jacqueline Karp, MD
Meeting Recorder: Avinash Kalsi

FDA ATTENDEES

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

Division of Rare Diseases and Medical Genetics
Kathleen Donohue, MD, Director
Patroula Smpokou, MD, Deputy Director
Jacqueline Karp, MD, Clinical Team Leader
Anna Choe, MD, MPH, Clinical Reviewer
Cheronda Cherry-France, MSN, BSN, Safety Regulatory Project Manager

Division of Regulatory Operations for Rare Diseases, Pediatrics, Urologic, and Reproductive Medicine
Pamela Lucarelli, Director, Project Management Staff
Avinash Kalsi, PharmD, Regulatory Health Project Manager
Diego Diaz, Regulatory Health Project Manager

Division of Pharm/Tox for Rare Diseases, Pediatric, Urologic and Reproductive Medicine
Mukesh Summan, PhD, Director

Office of Clinical Pharmacology/ Division of Translational and Precision Medicine
Jie Wang, PhD, Clinical Pharmacology Team Leader
Nayeem Hossain, PhD, Clinical Pharmacology Reviewer

Sarah Dorff, PhD, Clinical Pharmacology Reviewer

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

Office of Drug Evaluation Sciences (ODES), Division of Biomedical Informatics, Research, and Biomarker Development (BIRBD)
Y. Veronica Pei, MD, MEd, MPH, Associate Director of Biomedical Informatics (Acting)

Office of Biotechnology Products/ Division of Biotechnology Review and Research IV
LCDR Leslie Ann Rivera Rosado, PhD, Team Lead
Andrea Franco, PhD, Product Quality Assessor

Office of Pharmaceutical Manufacturing Assessment / Division of Biotechnology Manufacturing
Maxwell Van Tassell, PhD, Microbiology and Facilities Assessor

SPONSOR ATTENDEES
Chiesi USA. Inc.
Brant Hamel, PhD, RAC Manager, Regulatory Affairs – Rare Diseases
Birgitta Hedin, MSc, RAC Global Head, Regulatory Affairs – Rare Diseases
Shannon Sears, MMB Regulatory Affairs Specialist – Rare Diseases
Matt Medlin, PhD, RAC Head of US, Regulatory Affairs – Rare Diseases

Chiesi Farmaceutici S.p.A.
Ferdinando Ceravolo, MD Clinical Research Physician – Rare Diseases
Alberto D'Avino, PhD Senior Manager Regulatory CMC – Rare Diseases
Sarah Snedeker, MBA Project Leader – Rare Diseases
Diego Ardigò, MD PhD R&D Head – Rare Diseases

Others
(b) (4)

1.0 BACKGROUND

Regulatory Background
Chiesi Farmaceutici S.p.A. (Chiesi) is developing CHFLMZYMAA1, a recombinant human alpha-mannosidase (rhLAMAN) also referred to as velmanase alfa, as an enzyme replacement therapy for the treatment of alpha-mannosidosis (AM). CHFLMZYMAA1 was granted orphan drug designation on February 2, 2006, rare

pediatric disease designation on December 11, 2018, and Fast Track designation on December 12, 2019. CHFLMZYMAA1 is an approved therapy for AM in the European Union (EU), Brazil, and Ukraine.

Chiesi and the Agency discussed the design of a phase 3 clinical trial for CHFLMZYMAA1 in a type C teleconference meeting on February 26, 2019. On August 23, 2019, Chiesi submitted an IND containing a protocol for a phase 3 study CLI-LMZYAA2-01 titled "A Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel Group, Phase 3 Study to Evaluate the Efficacy and Safety of Velmanase Alfa in Patients with Alpha-Mannosidosis (SHAMAN)." Additional discussions between Chiesi and the Agency subsequently occurred, including revisions to the protocol, the acceptability of the accelerated approval pathway for CHFLMZYMAA1, and the need for a scientific rationale and justification to support the proposed surrogate endpoints and a post-approval confirmatory study.

Chiesi states that the SHAMAN study was stopped in October 2020, because of COVID-19 related issues and no subjects had been screened or enrolled in the trial. Chiesi also states that although there are requests for expanded access to CHFLMYMAA1 by U.S. physicians, no IND has been submitted and no clinical trial is ongoing in the U.S. Chiesi is now proposing to use a phase 3 randomized, double-blind, placebo-controlled trial completed in Europe (rhLAMAN-05) as the phase 3 study to support accelerated approval in the U.S.

To this end, on April 26, 2021, Chiesi requested the current Pre-BLA meeting to discuss the completed phase 3 trial to support submission of a BLA under the accelerated approval regulatory pathway, as well as to discuss the design of a proposed confirmatory study. The meeting was granted on May 5, 2021, and the meeting background package was received by FDA on May 27, 2021. FDA's preliminary comments were issued on June 25, 2021. Chelsi provided a response to the preliminary comments by email on June 30, 2021 (see Section 5.0 Attachments and Handouts). The teleconference was held on June 29, 2021, as scheduled.

Clinical Background

The Sponsor has completed the following clinical studies in Europe: a 2.5-year natural history study (rhLAMAN-01), a phase 1 dose-escalation study (rhLAMAN-02), a 12-month phase 2a open-label, randomized study of 2 doses IV 25 U/kg and 50 U/kg (rhLAMAN-03), a 20-month phase 2b open-label study with weekly IV 1 mg/kg (rhLAMAN-04), a 12-month phase 3 double-blind, randomized, placebo-controlled study (rhLAMAN-05) in AM patients 6-35 years old, and a 24-month, open-label, single-arm study in pediatric patients with AM < 6 years old (rhLAMAN-08). Patients treated in clinical trials continue treatment in 2 long-term, open-label extension studies or compassionate use programs in Europe. A post-authorization registry (SPARKLE - CLI-LMZYMAA1-12) is ongoing in Europe and has enrolled 18 patients thus far with the first enrolled patient having been on treatment for 17 months. The phase 3 study rhLAMAN-

05 included 25 patients with AM aged 6-35 years who were randomized to weekly IV 1 mg/kg velmanase (15 patients) or placebo (10 patients) for 12 months with primary efficacy endpoints of serum oligosaccharides and 3-minute stair climb test (3MSCT).

Alpha-mannosidosis (AM) is an autosomal recessive disease caused by biallelic pathogenic variants in the *MAN2B1* leading to the deficiency of alpha-mannosidase and, in turn, to the accumulation of mannose-rich oligosaccharides in various tissues, causing/contributing to disease manifestations.[1] AM has an estimated global prevalence of 1:500,000-1:1,000,000 live births but is thought to be underestimated.[2] AM is heterogeneous in clinical presentation and in the rate of clinical progression. In severe cases, death can occur in the first decade of life from infections (due to AM-related immunodeficiency) or central nervous system involvement (e.g. increased intracranial pressure) but patients with milder disease can survive into late adulthood. Manifestations include a variable combination of coarse facies, intellectual disability, recurrent infections, psychiatric symptoms, arthrosis, myopathy, ataxia, scoliosis, hearing loss, and ocular changes (hyperopia, myopia, strabismus). Recurrent infections tend to resolve after the first decade but myopathy and ataxia are progressive over time, resulting in the majority of adult patients being dependent on wheelchairs.[2, 3] No FDA-approved therapy is currently available but hematopoietic stem cell transplant (HSCT) is a treatment option for AM. HSCT has shown variable results in AM. Due to the risks of HSCT and lack of extensive experience with HSCT in AM, HSCT is not offered as standard of care to all AM patients. Otherwise, AM is managed by treating symptoms and addressing medical complications of the disease.

2.0 DISCUSSION

***Question 1a**: Does the Agency agree that serum oligosaccharides and serum IgG represent surrogate endpoints that are reasonably likely to predict clinical benefit?*

FDA Response to Question 1a:
Determination of whether changes in serum oligosaccharides and/or serum IgG are appropriate as surrogate endpoints that predict clinical benefit in AM will be made during the BLA review. In your BLA submission, provide a summary of the available evidence to support your proposal and your proposed regulatory pathway. Also, specify and justify the specific clinical benefit(s) that you believe these biomarkers are reasonably likely to predict or conclusively predict.

[1] Malm D, Nilssen Ø. Alpha-Mannosidosis. 2001 Oct 11 [Updated 2019 Jul 18]. In: Adam MP, Ardinger HH, Pagon RA, et al., editors. GeneReviews [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2021. Available from: https://www.ncbi.nlm.nih.gov/books/NBK1396/
[2] Borgwardt L, Lund AM, Dali CI. Alpha-mannosidosis - a review of genetic, clinical findings and options of treatment. Pediatr Endocrinol Rev. 2014;12 Suppl 1:185-191
[3] Malm D, Nilssen Ø. Alpha-mannosidosis. Orphanet J Rare Dis. 2008;3:21. Published 2008 Jul 23. doi:10.1186/1750-1172-3-21

In your BLA submission, summarize all available evidence (nonclinical and clinical; published studies and proprietary data) that may support each of the following points:

1. The biomarker(s) accumulate(s) in tissues where AM causes structural damage and/or functional impairment (for the specified clinical benefit).

2. This biomarker accumulation is toxic to the tissues where it accumulates.

3. The degree of biomarker accumulation correlates with the degree of tissue damage and/or organ functional impairment.

4. Reduction/ normalization of the biomarker concentration (in appropriate and relevant tissues) is associated with improvement in tissue structure and/or organ function.

5. Treatment with the product in the target population leads to consistent and durable reductions of the biomarker(s) in relevant tissues/body fluids and that the observed reductions are consistent among patient subgroups (if applicable).

6. The degree of observed biomarker reductions in treated patients are reasonably expected to lead or conclusively lead to clinical benefit in the target population and specify that benefit.

7. Quantification of the biomarker(s) is based on appropriately validated laboratory assays with performance characteristics that are fit for their intended use.

   Organize the evidence in a table similar to the following:

Senior author or protocol number (with 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)

For serum IgG, we recommend applying a similar framework as above to support its role as a surrogate endpoint.

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

Post Meeting Comment:
Subsequent to the teleconference, the Division believes that further discussion on the most appropriate regulatory pathway for your product is needed prior to a BLA submission. Specifically, we recommend a type C surrogate endpoint (SE)

meeting to discuss in more detail the evidentiary basis for the proposed surrogate endpoint(s) along with the most appropriate regulatory pathway for your product based on the available evidence collected thus far in your program, i.e., accelerated approval vs traditional approval pathway based on the proposed surrogate endpoint(s). In that meeting, the design of a potential post-approval, confirmatory trial can also be further discussed (as outlined below). Refer to *Considerations for Discussion of a New Surrogate Enpoint(s) at a Type C PDUFA Meeting Request* for information that should be included for discussion in such meeting. [4]

Question 1b: *Does the Agency agree that the rhLAMAN-05 study, supported by long-term studies with up to 48 months treatment, could serve as the pivotal study to support an accelerated approval BLA for velmanase alfa as a treatment for AM?*

FDA Response to Question 1b:
Trial rhLAMAN-05 generally appears to be an adequate and well-controlled clinical investigation that, in concert with all other completed studies, may able to support a BLA submission. However, to meet the substantial evidence of effectiveness standard based on a single adequate and well-controlled clinical trial, additional confirmatory evidence of the treatment effect must also be provided in your BLA. The confirmatory evidence may include nonclinical and/or clinical evidence that further corroborates the findings of effectiveness observed in your trial(s). Specify the confirmatory evidence in your BLA submission and refer to the FDA guidance *Substantial Evidence of Effectiveness for Human Drug and Biological Products* for more details.[5]

Meeting Discussion: **The Division inquired about the dose used in the animal studies assessing pharmacology of the drug (including studies in the animal model of disease) relative to the dose assessed in the clinical trial(s). The Sponsor was not able to provide a response during the meeting and stated that they would provide a post-meeting response. The Division also inquired about the timing of the assessment of serum oligosaccharide levels relative to drug administration in the phase 3 trial. The Sponsor stated that serum oligosaccharides levels were assessed in between the weekly doses, and that they would submit more specific information in a post-meeting response.**

Question 2: Does the Agency agree that the data from studies conducted in European AM patients are representative for AM patients in the US and will support a BLA pursuant to 21CFR 314.106?

FDA Response to Question 2:
It appears reasonable to use data from studies conducted in European AM patients to support a BLA based on the general information provided in your meeting package. The final determination will be made during BLA review. In your BLA submission, submit

[4] https://www.fda.gov/media/115120/download
[5] https://www.fda.gov/media/133660/download

appropriate justification that the completed trials fulfill the criteria set forth in 21CFR 314.106. For further details, refer to *FDA Acceptance of Foreign Clinical Studies Not Conducted Under an IND: Frequently Asked Questions: Guidance for Industry and FDA Staff.*[6]

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

Question 3a: Does the Agency agree that the rhLAMAN-10 study report and a Module 2.7.3 document summarizing individual study and integrated results presents a sufficient integrated efficacy analysis and that no separate ISE will be required?

FDA Response to Question 3a:
Your proposal not to submit a separate ISE appears reasonable. To facilitate our review of the various study reports, include the following additional information in your BLA submission:

1. Provide a side-by-side comparison of key demographic and clinical variables at baseline for studies rhLAMAN-05 and rhLAMAN-02. Please include all the variables that are shown in Table 11-1 of the CSR for rhLAMAN-05 and follow the format of the table shown below.

	rhLAMAN-02	**rhLAMAN-05**	
Variables*	**(N = 9)**	**CHFLMZYMAA1 (N = 15)**	**placebo (N = 10)**
Age, years Mean (SD) Range			
…			

* Include all the variables shown in Table 11-1 of the CSR for rhLAMAN-05.

2. For figures showing the time profile of the primary and key secondary endpoints (e.g. Figure 6 in the briefing document), provide the number of subjects (n) at each time point of the analysis within each figure.

3. For each patient that was randomized to the placebo arm of rhLAMAN-05, provide a table showing change at 1-year (placebo-period change from baseline) vs. the change after 1 year of receiving treatment (on-treatment period change using baseline as the last pre-treatment value).

4. For each patient originally treated in trial rhLAMAN-05, provide a panel of 4 plots showing the time profile of 6MWT, 3MSCT, FVC and serum oligosaccharides. Please use a different color to indicate the placebo-period and on-treatment period.

[6] https://www.fda.gov/media/83209/download

5. Provide a scientific justification for each of the MCID responder thresholds shown in table 12 of your meeting package.

6. Confirm that efficacy assessment procedures implemented during the Comprehensive Evaluation Visit (CEV) of study rhLAMAN-10 were the same as those in the parental studies rhLAMAN-02 and rhLAMAN-05.

7. For the analysis of efficacy endpoints (6MWT and 3MSCT), your analysis was conducted using the best (or maximum) of two consecutive measurements obtained one day apart. Provide a rationale for choosing the best of the two measurements. Perform additional analysis by using the average of the two measurements. We recommend both consecutive measurements be included in your ADaM dataset.

8. Provide an explanation for why the placebo group experienced a statistically significant decline in serum oligosaccharides during the first year.

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

Question 3b: *Does the Agency agree that the efficacy results from the rhLAMAN-08 study in pediatric patients <6 years of age will be presented as stand-alone data and should not be pooled with other efficacy data?*

FDA Response to Question 3b:
Your proposal to not pool efficacy results from rhLAMAN-08 appears reasonable.

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

Question 4: *Does the Agency agree to the planned presentation of integrated and individual study safety data in 2.7.4 and that no separate Integrated Summary of Safety (ISS) document will be necessary?*

FDA Response to Question 4:
In general, your proposal to provide integrated and individual safety summaries in Module 2 of the BLA submission is acceptable. For all integrated analyses, you should provide details of your pooling strategy, rationale for inclusion or exclusion of trials from the pooled population(s), and analytic strategies to manage differences in trial designs (e.g., in length, randomization ratio imbalances, study populations, etc.).

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

Question 5: *Does the Agency agree that the extent of data described in the Immunogenicity Report is sufficient to enable a reliable assessment of the impact immunogenicity on the overall clinical benefit vs. risk of velmanase alfa?*

FDA Response to Question 5:

No, we cannot agree at this time. You have characterized the neutralizing antibodies (NAb) by its inhibitory effect on enzyme activity. Because CHFLMZYMAA1 is a lysosomal ERT which requires cellular internalization to achieve its pharmacological activity, antibodies inhibiting the cellular uptake of CHFLMZYMAA1 are expected to reduce the drug effect and should be considered as neutralizing antibodies. Clarify whether you have developed cellular uptake assays to further characterize the potential neutralizing activities of anti-drug antibodies (ADA).

Regarding the immunogenicity analysis plan:

1. We note that you have not assessed baseline cross-reactive immunologic material (CRIM) status in patients treated in the completed clinical studies. In your BLA submission, provide an immunogenicity risk assessment based on the patients' genotype.

2. For the evaluation of the impact of anti-drug antibodies (ADA) on PK, we recommend that you include between-patients comparisons (i.e., between ADA positive subjects and ADA negative subjects) as well as within-patient comparisons (i.e., before ADA positivity and after ADA positivity) of PK data. For ADA positive patients, further evaluate the effects of antibody titer and neutralizing antibodies on PK.

3. We acknowledge that you plan to conduct population pharmacokinetic (PK) analysis to support PK and dose selection in your BLA. When conducting modeling, consider evaluating patients' ADA status including ADA titer as a potential covariate in the population PK/PD analysis. In the population PK/PD analysis, further explore the necessity of treating the patient's ADA status as a time-varying variable for ADA positive patients.

4. Submit the following CDISC datasets (IS, PC, and SL) for each study that contains immunogenicity and PK data and a combined dataset containing all these studies. The IS domain is described in SDTM Implementation Guide 3.2, which is on the FDA Data Standards Catalog.

SDTM or ADaM Dataset	(Minimum) Required variables for OCP review	Comments
IS or ADIS	STUDYID, USUBJID, AVISIT (or VISIT), PARAM, and AVALC (or ADASTAT, NABSTAT, LBSTRESC)	PARAM should contain ADA and NAB Test.
PC or ADPC	USUBJID, AVISIT (or VISIT), AVAL, AVALC	AVAL contains PK concentration values and AVALC contain characters containing BLQ or missing values.
SL or ADSL	USUBJID, ARM.	

Table 1. Minimum data requirement of SDTM or ADaM tables for studies with immunogenicity and pharmacokinetics data

In addition, for all clinical studies with PK data, we request that, at a minimum, the following SDTM tables be submitted: DM, PP, PC, EX, and SUPPDM. Please refer to FDA Guidance *Providing Regulatory Submissions In Electronic Format — Standardized Study Data*[7] for more details on electronic data submission requirements.

5. Refer to FDA guidance for industry *Immunogenicity Testing of Therapeutic Protein Products — Developing and Validating Assays for Anti-Drug Antibody Detection*,[8] for more information.

Additional general comments:

1. We remind you that you should use validated bioanalytical assays to determine the drug and pharmacodynamic (PD) biomarker concentrations in all pharmacokinetic (PK) and PD samples from your clinical studies. The assays should be demonstrated to be specific, sensitive, and reproducible. For PK and each PD biomarker assessment, the same assay method should be used across the study sites (if there is more than one study site) and throughout the study duration or a central laboratory should analyze all the PK and PD samples to minimize data variability among laboratories. If multiple bioanalytical assay methods or laboratories are used, we recommend that cross-validation be performed to allow comparison of results obtained by different assay methods or laboratories. Refer to the following guidance for more information: *Bioanalytical Method Validation*.[9,10]

[7] https://www.fda.gov/media/82716/download
[8] https://www.fda.gov/media/119788/download
[9] 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.
[10] https://www.fda.gov/media/70858/download

2. In addition to the assay validation reports, submit bioanalytical method performance summary tables for all the bioanalytical methods used for the PK and PD assessments in your clinical studies. Use the format of summary tables as in the guidance *Bioanalytical Methods Templates*.[11] 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 or columns are not applicable. Include any other additional bioanalytical information that might be relevant to your BLA review in a separate table.

3. We recommend that you conduct exposure-response analyses for both efficacy and safety to support the proposed dosing regimen. Refer to the "Model/Data Format"[12] for general guidance on submitting pharmacometric data. Also refer to the FDA guidance for additional information related to population PK[13] and E-R analyses.[14]

Meeting Discussion: **The Sponsor stated that a neutralizing antibody (NAb) assay based on cellular uptake will not be available at the time of BLA submission. The Sponsor also stated that development of a new cellular uptake NAb assay is still ongoing and they may request a type C guidance meeting with the Agency to discuss their bioanalytical methodology. The Sponsor stated that they plan to use the cellular uptake NAb assay, once developed, in the later confirmatory (post-approval) clinical trial. The Agency stated that the lack of cellular uptake NAb assay and associated immunogenicity data from the completed trials will be a review issue during BLA review and asked the Sponsor to evaluate (and submit data in the BLA) the impact of anti-drug antibodies (ADA) on PK, PD, efficacy, and safety based on all currently available data.**

The Agency asked whether baseline CRIM status data are available in treated patients. The Sponsor informed that baseline CRIM status was not evaluated in the completed studies, but the Sponsor is working on the CRIM assay with plans to use it in the later confirmatory (post-approval) trial.

Regarding the IS dataset, the Sponsor informed that the LB dataset will be submitted instead of IS dataset for individual studies; however, for the integrated immunogenicity evaluation, the Sponsor will submit an IS dataset. The Agency agreed with this proposal but reminded the Sponsor that the datasets should have the required variables that are specified in the preliminary comments above. When the Sponsor inquired about the dataset format, the Agency recommended that the dataset should be submitted in accordance with the CDISC dataset guidelines.

[11] https://www.fda.gov/media/131425/download
[12] https://www.fda.gov/about-fda/center-drug-evaluation-and-research-cder/modeldata-format
[13] https://www.fda.gov/media/128793/download
[14] https://www.fda.gov/media/71277/download

Question 6: *Does the Agency agree that data from the legacy studies rhLAMAN-02, rhLAMAN-03, and rhLAMAN-04 will not be provided in Clinical Data Interchange Standards Consortium (CDISC) format?*

FDA Response to Question 6:
Yes, it is acceptable to submit legacy data for studies that initiated prior to Dec 17, 2016. Although submission of study data in conformance to the standards listed in the FDA Data Standards Catalog will not be required in such studies, we strongly encourage you to use the FDA supported data standards for the submission to facilitate review of data. Please confirm that all other studies (including rhLAMAN-05, and rhLAMAN-10) will use the CDISC format.

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

Question 7: *Does the Agency agree to the design of the planned confirmatory study?*

FDA Response to Question 7:
Even though a randomized, placebo-controlled trial design would be the most informative and robust study design for a potential post-approval confirmatory study, the feasibility of such study in the context of AM is questionable given that AM is a very rare disease and that patient recruitment and retention is expected to be very challenging in the post-marketing setting, especially if the product is commercially available. In addition, it is unclear whether observable changes in the proposed clinical endpoints will be seen within the specified trial duration given the limited knowledge of the disease natural history and the wide spectrum of disease severity and progression of AM. You may want to consider alternative study designs that may be feasible as a post-marketing study while being able to provide robust data.

Meeting Discussion: **The Sponsor acknowledged the Division's concerns about the feasibility of the proposed randomized, placebo-controlled trial as a post-approval confirmatory trial. However, the Sponsor stated that they have conducted a feasibility analysis (working with patient organizations and including patient mapping) and that the proposed trial appears to be feasible to conduct in countries where patients may not have access to the product (outside the US). Alternatively, the Sponsor proposed a single arm, open-label study of long duration (10 years or more) as a confirmatory trial. Because there are no prospective long-term natural history studies for AM, the Sponsor inquired if a retrospective natural history study would be acceptable as a control arm for such single-arm confirmatory trial. Regarding a potential externally-controlled, single arm, open-label post-approval trial, the Division indicated that this would not be acceptable due to the inherently high risk of bias with this type of study design (especially if the control cohort contributes data collected retrospectively) and stated that a long duration, such as 10 years, would not adequately address the high potential for bias, especially using non-objective, effort-dependent endpoints (i.e. endpoints other than survival).**

The Division recommended that the Sponsor request a type C meeting (also see Post Meeting Comment under question 1 above) to further discuss confirmatory trial designs that may be informative and feasible in the post-approval setting. A feasibility assessment, including specific and detailed evidence, should be included to support any potential trial design for confirmation of benefit in the post-approval setting. In addition, given the uncertainties surrounding the appropriate duration of follow up needed to observe changes in clinical endpoints in AM, the Division strongly recommended consideration of an adaptive trial design with prespecified interim analyses to permit extension of the trial duration if necessary in order to generate substantial evidence of effectiveness. Details of such design can be discussed at a future meeting.

The Division and the Sponsor discussed the potential of expanded access use requests for U.S. patients and the Sponsor stated that they have already received requests for expanded access use, which underlines the sense of urgency of the BLA submission. In terms of the timing of a post-approval confirmatory trial, the Sponsor stated that the earliest start of such trial will be in Q2 of 2022. The Division recommended that a post-approval confirmatory trial should be fully enrolled at the time of BLA submission.

Question 8a*: Does the Agency agree to the primary endpoint in the planned confirmatory study?*

FDA Response to Question 8a:
The 6MWT is a reasonable functional assessment in general. However, see our specific concerns in our response to question 7. Depending on the patient age and/or degree of baseline impairment, the 2MWT may be more suitable in general.

For your planned measurement of the primary endpoint, provide a rationale for choosing the best of the two consecutive test results instead of taking the average. Provide additional details regarding the timeframe between the two consecutive measurements. Additionally, the assumed treatment difference (improvement of 30 meters compared to placebo) appears too optimistic given the data from the uncontrolled integrated study (approximately 22 meters). Provide further justification for the anticipated treatment difference of 30 meters.

Meeting Discussion: The Sponsor stated that the assumed treatment difference is reasonable based on the treatment effect from the integrated analysis and the phase 3 trial. Given the heterogeneity of disease, the Division did not find the assumed treatment difference to be realistic and advised the Sponsor to consider a global test of multiple endpoints to include all outcomes that are clinically meaningful in AM in a future post-approval confirmatory trial. The Division also advised that a multi-domain responder index (MDRI) approach is not recommended to analyze the primary endpoint, as this approach decreases the

power of the analysis in clinically heterogeneous diseases such as AM and also requires pre-determination of clinically meaningful thresholds for change in individual domain endpoints which is often difficult to determine and support with evidence in rare diseases such as AM.

Question 8b: *Does the Agency agree to the key secondary endpoint in the planned confirmatory study?*

FDA Response to Question 8b:
We do not agree with the key secondary endpoint of "total number of days with infection" and instead you may consider using the rate of infection over 12 months.

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

Question 8c*: Does the Agency agree to the other secondary endpoints in the planned confirmatory study?*

FDA Response to Question 8c:
The other secondary endpoints appear generally reasonable.

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

Question 9a: *Does the Agency agree to the statistical analysis for the primary endpoint in the planned confirmatory study?*

FDA Response to Question 9a:
Your overall analysis approach appears generally reasonable; however, further details on the following elements should be incorporated in your protocol:

1. Confirm that your primary analysis is targeting the treatment-policy estimand as discussed in the International Council on Harmonization (ICH)-E9 addendum.[15]

2. To minimize missing data, measures should be taken to encourage patients who prematurely discontinue study treatment to remain in the study for their scheduled safety and efficacy assessments.

3. As a supportive efficacy evaluation, consider performing an analysis to estimate the while-on-treatment estimand (i.e. use the last available endpoint measurement prior to initiating rescue therapy).

4. State your statistical approach (if any) for handling missing data.

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

[15] *E9(R1) Statistical Principles for Clinical Trials: Addendum: Estimands and Sensitivity Analysis in Clinical Trials* (https://www.fda.gov/media/148473/download)

Question 9b: *Does the Agency agree to the statistical analysis for the key secondary endpoint in the planned confirmatory study?*

FDA Response to Question 9b:
Your proposed analysis approach seems generally reasonable. When discussing analysis of secondary endpoints in your protocol, utilize the estimand framework as discussed in the ICH-E9 addendum. In your full protocol, specify a multiple-testing strategy for the many "Other Secondary Endpoints" specified in your protocol synopsis.

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

Question 10: *Does the Agency anticipate that an Advisory Committee Meeting would be held for velmanase alfa prior to a potential approval decision?*

FDA Response to Question 10:
The determination of the need for an Advisory Committee will be made during BLA review.

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

Question 11a: *Does the Agency agree that the proposed content would constitute a complete application for the velmanase alfa BLA?*

FDA Response to Question 11a:
The proposed table of contents of the BLA provided in Appendix 3 of the meeting briefing package appears reasonable based on the organization of the content for electronic submissions. The final determination on the acceptability of the content for a complete BLA submission will be made upon filing the BLA.

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

Question 11b: *Does the Agency agree that a risk evaluation and mitigation strategy will not be required for velmanase alfa?*

FDA Response to Question 11b:
At this time, we have insufficient information to determine whether a risk evaluation and mitigation strategy (REMS) will be necessary to ensure that the benefits of the product outweigh the risks, and, if a REMS is necessary, what the required elements may be. The need or not for a REMS will be determined during BLA review.

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

3.0 ADDITIONAL FDA COMMENTS

A. Protocol and Data Submission and Analysis

Protocol:

1. Submit all versions of the protocol for the pivotal study(ies) and the date when changes were implemented. Include a Summary of Changes for each version.

2. Submit all versions of the Statistical Analysis Plan (SAP) for your pivotal study(ies). Include a Summary of Changes for each version.

3. Submit all informed consent document(s) and describe any country- or region-specific variations.

Data Submission and Analyses:

4. CDISC standards should be followed when preparing the define file. The define files should include possible responses for all variables when the meaning is not obvious. General considerations include the following:

    - Topline summary/description of what is included in each analysis dataset (i.e., a dataset table of contents)
    - For each analysis dataset, document the following:
        - For derived or imputed variables, a description and/or algorithm of how the variable was derived or imputed from the source data
        - Clear definition of analysis flags
        - Codes and decodes of all categorical variables (e.g., 1=mild, 2=moderate, 3=severe; 0 = age < 18, 1 = age ≥ 18)

5. Submit all program code (including any macros) and datasets used to create your analyses found in the main sections of your ISE and ISS.

6. The ISS must include all deaths, serious adverse events and dropouts for adverse events for all controlled trials regardless of treatment arm assignment.

7. For the pivotal study(s), submit a table including the following information:

    - Dates of first patient and last patient visits
    - Dates of data lock
    - Dates for each interim analysis
    - Dates of the initial protocol and all revisions with a hyperlink to the protocol and each revision; include a hyperlink to Summary of Changes for each version

- Dates of all versions of the Statistical Analysis Plan (SAP) with a hyperlink to each SAP; include a hyperlink to Summary of Changes for each version and specify the number of subjects enrolled in the trial at the time of each protocol change.

8. Submit a dataset that contains all subjects who were unblinded. The dataset should include the unique subject ID, the treatment received, who requested unblinding, date of unblinding, and the reason for unblinding.

9. Submit a table that indicates those subjects for whom a CRF, narrative, or adjudication package was submitted, and the reason it was submitted (e.g., death, SAE, AE leading to medication discontinuation, adjudication package submitted). We recommend you provide this information in tabular format with the patient identifier hyperlinked to the narrative and/or CRF in the ISS.

10. When creating the disposition dataset, for discontinuations due to "other," perform medical review to ensure appropriate categorization e.g., discontinuation due to AE or meeting study discontinuation criteria, etc. For discontinuations due to "other" that are not appropriate for pre-defined categories, provide the specific reason.

11. For your safety analyses, prioritize a list of adverse events of special interest (AESIs) including those previously observed and of anticipated safety issues to be evaluated, and describe your planned analytic strategy including any MedDRA 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.

12. We recommend that you include hypersensitivity and anaphylaxis in addition to infusion-related reactions as an AESI in your safety analysis.

    For each study, provide a flag in the AE dataset or a separate dataset that maps preferred terms to the adverse events of special interest (AESIs).

13. Identify potential cases of anaphylaxis.

    a. Perform a broad standard MedDRA query (SMQ) for "Anaphylactic Reaction" in your integrated safety database. Then identify the subset with onset of reaction within 24 hours of study drug administration.

    b. In addition, any cases reported by investigators or other healthcare professionals as "anaphylaxis" or "anaphylactoid" should be accepted as cases of anaphylaxis, even if they are not captured by a MedDRA query.

c. Generate patient narratives for all cases of anaphylaxis. Include details pertinent to adjudication using the NIAID/FAAN criteria (Sampson HA et al., 2006). These should include:

   i. Timing of symptoms relative to the product infusion
   ii. Pre-medications given (and which ones)
   iii. Respiratory, skin, oropharyngeal, gastrointestinal, or cardiovascular signs and symptoms.
   iv. Pre- and post-infusion vital signs with age-appropriate reference ranges for each for pediatric patients.
   v. Rescue treatments administered (e.g. antihistamines, epinephrine, corticosteroids, oxygen, airway management, intubation, hemodynamic support).
   vi. Whether treatment with the product was discontinued, or, if continued, whether symptoms recurred after subsequent administration and when
   vii. Whether the investigator classified the reaction as anaphylaxis or anaphylactoid

d. Include alternative explanations for each case of anaphylaxis, such as food allergy or other allergy, e.g. if a child is under the care of an allergist and had a known food allergy confirmed by positive food challenge or specific IgE test in the past. Note the timing of the food allergen exposure relative to infusion of the product and the onset of signs and symptoms of possible anaphylaxis.

14. Evaluate adverse events based on **logical groupings** of preferred terms (PTs) using standard MedDRA queries or other appropriate means. Include in your submission the procedures and rationale used for grouping of preferred terms. Given the large number of relative MedDRA PTs, FDA recognizes that the list of proposed PTs and findings in the Sponsor's submission is not meant to be exhaustive. The intent of grouping PTs for safety analyses is to avoid splitting of PTs to ensure that adverse events are adequately captured (e.g., PTs such as "ABDOMINAL PAIN LOWER", "ABDOMINAL PAIN UPPER", "ABDOMINAL PAIN" should be grouped in the assessment for abdominal pain).

15. Analysis of liver safety should be included in your overall safety assessments. You should incorporate and summarize investigator reports and PTs related to potential hepatic injury which should not be limited to only specific liver biochemistry elevations. Refer to the FDA guidance *FDA* guidance for industry *Drug-Induced Liver Injury: Premarketing Clinical Evaluation*.[16]

[16] https://www.fda.gov/media/116737/download

B. Product Quality: General Comments

1. To facilitate the Agency's review of the drug substances (DS), and drug products (DP) manufacturing processes for CHFLMZYMAA1, 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 Clinical 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.

2. To facilitate the Agency's review of the control strategy for CHFLMZYMAA1, 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.

3. Regarding your immunogenicity assay validation reports for CHFLMZYMAA1, we recommend that you submit an Integrated Summary of Immunogenicity (ISI) as described in Section VIII of the 2019 FDA guidance for industry: *Immunogenicity Testing of Therapeutic Protein Products — Developing and Validating Assays for Anti-Drug Antibody Detection*. The ISI report can be submitted to eCTD Section 5.3.5.3 <Reports of Analysis of Data from More than One Study>.

For additional information, refer to the FDA Guidance *Immunogenicity Testing of Therapeutic Protein Products —Developing and Validating Assays for Anti-Drug Antibody Detection*.[17]

C. Product Quality: Microbiology Comments

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.

1. 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:

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[17] https://www.fda.gov/media/119788/download

4.0 OTHER IMPORTANT INFORMATION

DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

- Major components of the application are expected to be submitted with the original application and are not subject to agreement for late submission. We note that you have not proposed late submission of minor application components. Therefore, your application is expected to be complete at the time of original submission.

- 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.

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[19] and Pregnancy and Lactation Labeling Final Rule[20] websites, which include:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products.
- The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information related to pregnancy, lactation, and females and males of reproductive potential.
- Regulations and related guidance documents.
- A sample tool illustrating the format for Highlights and Contents, and
- The Selected Requirements for Prescribing Information (SRPI) − a checklist of important format items from labeling regulations and guidances.
- FDA's established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

Pursuant to the PLLR, you should include the following information with your application

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

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.

SECURE EMAIL COMMUNICATIONS

Secure email is required for all email communications from FDA when confidential information (e.g., trade secrets, manufacturing, or patient information) is included in the message. To receive email communications from FDA that include confidential information (e.g., information requests, labeling revisions, courtesy copies of letters), you must establish secure email. To establish secure email with FDA, send an email request to SecureEmail@fda.hhs.gov. Please note that secure email may not be used for formal regulatory submissions to applications (except for 7-day safety reports for INDs not in eCTD format).

ABUSE POTENTIAL ASSESSMENT

Drugs that affect the central nervous system, are chemically or pharmacologically similar to other drugs with known abuse potential, or produce psychoactive effects such as mood or cognitive changes (e.g., euphoria, hallucinations) need to be evaluated for their abuse potential and a proposal for scheduling will be required at the time of the NDA submission [21 CFR 314.50(d)(5)(vii)]. For information on the abuse potential evaluation and information required at the time of your NDA submission, see the guidance for industry *Assessment of Abuse Potential of Drugs*.[21]

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

[21] 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.

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[22] and the guidance for industry, *Identification of Manufacturing Establishments in Applications Submitted to CBER and CDER Questions and Answers*[23]. 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.

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

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 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*.[24]

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

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

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 ISSUES REQUIRING FURTHER DISCUSSION:

Appropriate regulatory pathway (in a future type C surrogate endpoint meeting) and trial design of potential post-approval confirmatory trial. See post-meeting comment under question 1a.

5.0 ATTACHMENTS AND HANDOUTS

On June 30, 2021, Chiesi provided via email their "Items for Further Discussion" document in response to the FDA's preliminary comments dated June 25, 2021.

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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/

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DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

PIND 113186

MEETING MINUTES

Zymenex A/S
c/o Chiesi Pharmaceuticals Inc
US Agent for Zymenex A/S
Attention: Erika Panico, RAC
Vice President and Managing Director
905 Medical Center Drive, Suite 380
Rockville, MD 20850

Dear Ms. Panico:

Please refer to your Pre-Investigational New Drug Application (PIND) file for recombinant human alpha-mannosidase (rhLAMAN).

We also refer to the meeting between representatives of your firm and the FDA on June 17, 2014. The purpose of the meeting was to discuss the ongoing Phase 3 study, the CMC, and regulatory aspects of the program.

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

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

Sincerely,

{See appended electronic signature page}

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

Enclosure:
Meeting Minutes

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type: Type B
Meeting Category: EoP2

Meeting Date and Time: June 17, 2014, from 1:00 to 2:00 PM
Meeting Location: 10903 New Hampshire Ave
White Oak Building 22, Conference Room 1313
Silver Spring, MD 20903

Application Number: PIND 113186
Product Name: rhLAMAN
Indication: treatment of alpha-mannosidosis
Sponsor/Applicant Name: Zymenex

Meeting Chairperson: Emanuela Lacana
Meeting Recorder: Kevin Bugin

Attendees:

Division of Gastroenterology and Inborn Errors Products
Donna Griebel, M.D., Director
Lara Dimick, M.D., Clinical Team Leader
Teresa Buracchio, M.D., Medical Officer
Sushanta Chakder, Ph.D., Nonclinical Team Leader
Kelly Richards, R.N., M.S.N., Capt., Regulatory Health Project Manager
Kevin Bugin, M.S., R.A.C., Senior Regulatory Health Project Manager

Office of Translational Sciences
Office of Clinical Pharmacology/Division of Clinical Pharmacology 3
Christine Hon, Pharm.D., Clinical Pharmacology Reviewer

Office of Biotechnology Products
Emanuela Lacana, Ph.D.

Division of Therapeutic Proteins
Jee Chung, Ph.D., Quality Team Leader
Leslie Rivera Rosado, Ph.D., Quality Reviewer
Laura Salazar-Fontana, Ph.D., Staff Fellow

Office of Orphan Products Development

Henry Startzman, M.D., Director, Drug Designation Program

Chiesi/Zymenex Attendees

Erika Panico, RAC	Head of US Regulatory Affairs, Chiesi Pharmaceuticals Inc.
Alex Bloom, PhD	Regulatory Lead, Chiesi UK Ltd
Giovanni Milazzo, MD	Head of Biotech Regulatory Affairs, Chiesi Farmaceutici S.p.A.
Diego Ardigó, MD PhD	Project Leader, Chiesi Farmaceutici S.p.A.
Claes Anderson, PhD	Head of R&D, Zymenex A/S
(b) (4)	(b) (4)

1.0 BACKGROUND

Zymenex (the Sponsor) has developed recombinant human alpha-mannosidase (rhLAMAN) for the treatment of alpha-mannosidosis, a rare, autosomal recessive, lysosomal storage disorder. The disorder is caused by a deficiency of alpha-mannosidase, a lysosomal enzyme which is involved in the catabolism of N-linked glycoproteins through the sequential degradation of high-mannose, hybrid and complex oligosaccharides. The developed product is intended to be used as an enzyme replacement therapy (ERT). It is expected to be given for the duration of life, with the aim of normalizing mannose-rich oligosaccharide levels in the tissues, altering the progression of the disease, and resulting in improving the patient's condition and quality of life.

On May 08, 2014 the Sponsor submitted a request to discuss the ongoing Phase 3 study, the CMC, and regulatory aspects of the program. The meeting was granted and took place as scheduled on June 17, 2014.

2.0 DISCUSSION

CMC

1. To support a future BLA, the Company has developed a process validation strategy to demonstrate that the manufacturing process is capable of consistently delivering a defined quality of drug substance and drug product. This process validation strategy will be summarized in the meeting package. Does FDA agree with the process validation approach?

FDA Response:
The overall approach for drug substance (DS) and drug product (DP) process validation appears reasonable. However, a final determination on the adequacy of the DS and DP process validation will be made upon review of your application.
In the BLA, please provide the following information and data to support licensure of your product:

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Regulatory
6. The Company plans to apply for Breakthrough Designation status in the near future. Given the information the Company has provided on the clinical program thus far, does FDA have any concerns or feedback regarding the applicability of Breakthrough Designation to CHF-LMZYM?

FDA Response:
The Breakthrough Therapy designation is intended to help expedite drug development and the approval process through frequent FDA interactions and guidance throughout the development program. In order to be considered for Breakthrough therapy you must submit a request at the time of IND submission or thereafter, but ideally no later than the end of Phase 2 (EOP2) meeting. Your submission should include relevant information to support that CHF-LMZYM is intended to treat a serious condition and that it has the potential to address an unmet medical need, as well as an explanation of how this potential is being evaluated in the planned drug development program.

Based on the data submitted in the briefing package, we have concerns that the Phase 2b data may not fulfill the criteria for a substantial improvement on a clinically significant

endpoint required to obtain a Breakthrough Therapy designation. Although the Phase 2b data appears promising, it is unclear if the drug provides a substantial clinical improvement compared to natural history data that also showed considerable variability in the 6MWT and an improvement in the 3MSCT over a 2 year period. The pulmonary function tests showed a small trend toward improvement that was not clearly clinically significant.

The eligibility for priority review designation, which is determined separately from breakthrough designation, is determined once the application has been submitted. The Division will inform the applicant in writing of a priority review designation by Day 60 of the review.
Please refer to the Guidance for Industry: Expedited Programs for Serious Conditions-Drugs and Biologics, dated June 2013, available at:
http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM358301.pdf.

7. The Company plans to apply for a Rare Pediatric Disease Priority Review Voucher at the time of BLA filing. Does FDA have any feedback regarding this approach?

FDA Response:
We are still attempting to interpret the law and the answers provided below represent our current thinking. A Guidance is being developed.

A sponsor may submit a request for pediatric rare disease designation for the use of their drug for the treatment of the disease at any time prior to submission of a marketing application. This request for pediatric rare disease designation is voluntary. If the request is submitted at the same time as submitting a request for orphan drug designation or fast-track designation, the FDA must make a decision on whether to designate the drug and the application within 60 days. If a request for pediatric rare disease designation is to be submitted, it should contain a statement that the sponsor is requesting pediatric rare disease designation for the use of the name of the sponsor's drug (or descriptive name) for use (treatment, prevention, or diagnosis) of the specific disease or condition, name and address of sponsor, resident agent for sponsor if a foreign sponsor, description of the rare disease or condition, description of the drug and a discussion of the scientific rationale for use of the drug for the rare disease or condition, documentation with authoritative references that the disease or condition affects fewer than 200,000 people in the United States and documentation that the disease primarily affects the pediatric population. The FDA's current interpretation of a disease that primarily affects the pediatric population is that greater than 50% of the patients living in the United States that have been diagnosed with the disease or condition are 0 through 18 years of age. The sponsor should also provide a regulatory history that provides whether the drug that is the subject of the pediatric rare disease designation request contains an active ingredient (including any ester or salt of the active ingredient) that has previously been approved in any other application under section 505(b)(1), 505(b)(2), or 505(j) of the FD&C Act or section 351(a) or 351(k) of the PHS Act.

If you are granted pediatric rare disease designation, it means that you have a potential new drug for a "rare pediatric disease" as defined in section 529(a)(3) of the Federal Food, Drug, and Cosmetic Act (FD&C Act)(21 U.S.C. 360ff(a)(3).

Whether or not you request pediatric rare disease designation, if you desire a pediatric rare disease priority review voucher, you will need to submit a request for a pediatric rare disease priority review voucher at the time of submission of your marketing application.. The following eligibility criteria must be met as set forth in section 529(a)(4) of the FD&C Act:

It is a human drug application as defined in section 735(1) of the FD&C Act and submitted under section 505(b)(1) of the FD&C Act or section 351(a) of the PHS Act:

- **For prevention or treatment of a rare pediatric disease as defined in section 529(a)(3) of the FD&C Act;**
- **That contains no active ingredient (including any ester or salt of the active ingredient) that has been previously approved in any other application under section 505(b)(1), 505(b)(2), or 505(j) of the FD&C Act or section 351(a) or 351(k) of the PHS Act;**
- **That the FDA deems eligible for priority review.**

- **Relies on clinical data derived from studies examining a pediatric population and dosages of the drug intended for that population.**

- **Does not seek approval for an adult indication in the original rare pediatric disease product application;**

- **Is submitted on or after October 7, 2012 and approved after July 9, 2012.**

The final answer to whether your marketing application qualifies as a "rare pediatric disease product application" as defined by statute will come in the form of an award or non-award of a pediatric disease priority review voucher at the time of marketing approval, should you request such a voucher in your marketing application.

If you have further questions about this program, please contact Henry Startzman at 301-796-8663.

8. The Company understands that a Pediatric Study Plan (PSP) is not applicable to products that have obtained Orphan Drug Designation status; therefore, the Company does not plan to provide an initial PSP. Does FDA agree?

FDA Response:

You will not need to submit a PSP; however, because this disease impacts very young children, we encourage you to continue with your plans for a pediatric development program in patients less than 6 years of age. To increase the likelihood of success, we encourage you to meet with us as you are in the process of developing your pediatric program.

Post-Meeting Comment:

During the June 17, 2014 meeting, you requested the Agency's input on your proposed stability plan. However, we were not able to provide you with a thorough assessment of your plan at that time, because of significant gaps in information related to the chemistry, manufacture, and control (CMC) of your product. In order to assess the adequacy of your stability plan, and to avoid major filing and review issues upon submission of the Biologics Licensing Application (BLA), we need to conduct a more thorough review of your product quality information (*e.g.*, product characterization, manufacturing process, and overall control strategy). We strongly recommend that you provide a comprehensive CMC package for review. Please be sure to address the following areas in your submission:

1. **The information provided as part of the briefing package suggests that there have been changes in the manufacturing process between the lots used for toxicology studies, for clinical studies, and the proposed commercial lots. In order to support the use of the safety and toxicology study results, product specifications, and stability plan, you should provide results from comparability exercises, including, where possible, side-by-side comparisons of lots used in the non-clinical, clinical studies, and the proposed commercial material with qualitative and quantitative information. Please refer for ICH Q5E for guidance regarding comparability.**

2. **In addition to the comparability data, please provide a complete description of the current and proposed commercial manufacturing process (including in-process controls), the drug substance and drug product specifications (including analytical methods), and the stability plan.**

Furthermore, all manufacturing facilities should be ready for inspection at the time of the BLA submission. Please be advised that a pre-license inspection, during which the manufacturing facilities must be in operation and manufacturing the product under review, is required (21 CFR 600.21); therefore a production schedule should be provided with the BLA.

3.0 PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the

product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Please be advised that under the Food and Drug Administration Safety and Innovation Act (FDASIA), you must submit an Initial Pediatric Study Plan (PSP) within 60 days of an End of Phase (EOP2) meeting. The PSP must contain an outline of the pediatric study or studies that you plan to conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation, and any previously negotiated pediatric plans with other regulatory authorities. The PSP should be submitted in PDF and Word format.

For additional guidance on the timing, content, and submission of the PSP, including a PSP Template, please refer to the draft guidance for industry, *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans* at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM360507.pdf. In addition, you may contact the Pediatric and Maternal Health Staff at 301-796-2200 or email pdit@fda.hhs.gov. For further guidance on pediatric product development, please refer to: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm.

4.0 DATA STANDARDS FOR STUDIES

CDER strongly encourages IND sponsors to consider the implementation and use of data standards for the submission of applications for investigational new drugs and product registration. Such implementation should occur as early as possible in the product development lifecycle, so that data standards are accounted for in the design, conduct, and analysis of clinical and nonclinical studies. CDER has produced a web page that provides specifications for sponsors regarding implementation and submission of clinical and nonclinical study data in a standardized format. This web page will be updated regularly to reflect CDER's growing experience in order to meet the needs of its reviewers. The web page may be found at: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm

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/s/

KEVIN B BUGIN
07/17/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

PIND 113186

MEETING MINUTES

Zymenex A/S
c/o Chiesi Pharmaceuticals Inc
US Agent for Zymenex A/S
Attention: Erika Panico, RAC
Vice President and Managing Director
905 Medical Center Drive, Suite 380
Rockville, MD 20850

Dear Ms. Panico:

Please refer to your Pre-Investigational New Drug Application (PIND) file for recombinant human alpha-mannosidase (rhLAMAN).

We also refer to the meeting between representatives of your firm and the FDA on June 03, 2014. The purpose of the meeting was to discuss the development program for rhLAMAN.

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

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

Sincerely,

{See appended electronic signature page}

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

Enclosure:
Meeting Minutes

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEETING MINUTES

Meeting Type: Type B
Meeting Category: EoP2

Meeting Date and Time: June 03, 2014
Meeting Location: 10903 New Hampshire Ave
White Oak Building 22, Conference Room 1421
Silver Spring, MD 20903

Application Number: PIND 113186
Product Name: rhLAMAN
Indication: treatment of alpha-mannosidosis
Sponsor/Applicant Name: Zymenex

Meeting Chairperson: Lara Dimick-Santos, MD, FACS
Meeting Recorder: Kevin Bugin

Attendees:

Division of Gastroenterology and Inborn Errors Products
Donna Griebel, M.D., Director
Lara Dimick, M.D., Clinical Team Leader
Teresa Buracchio, M.D., Medical Officer
Sushanta Chakder, Ph.D., Nonclinical Team Leader
Kevin Bugin, M.S., R.A.C., Senior Regulatory Health Project Manager

Office of Translational Sciences
Office of Clinical Pharmacology/Division of Clinical Pharmacology 3
Yow-Ming Wang, Ph.D., Biologics Team Leader
Christine Hon, Pharm.D., Clinical Pharmacology Reviewer

Office of Biotechnology Products
Division of Therapeutic Proteins
Laura Salazar-Fontana, Ph.D., Staff Fellow

Office of Biostatistics/Division of Biometrics III
Freda Cooner, Ph.D., Statistics Team Leader

Office of New Drugs/Immediate Office
Rare Diseases Program
Larissa Lapteva, M.D., Medical Officer

Office of Orphan Products Development
Henry Startzman, M.D., Director, Drug Designation Program

Division of Neurology Products
Ronald Farkas, M.D., Medical Officer

Chiesi/Zymenex Attendees

Erika Panico, RAC	Head of US Regulatory Affairs, Chiesi Pharmaceuticals Inc.
Alex Bloom, PhD	Regulatory Lead, Chiesi UK Ltd
Giovanni Milazzo, MD	Head of Biotech Regulatory Affairs, Chiesi Farmaceutici S.p.A.
Diego Ardigó, MD PhD	Project Leader, Chiesi Farmaceutici S.p.A.
Federica Cattaneo, MD	Clinical Program Lead, Chiesi Farmaceutici S.p.A.
Marcello Trevisano, PhD	Nonclinical Team Leader, Chiesi Farmaceutici S.p.A.
Marta Toschi	Regulatory Assistant, Chiesi Farmaceutici S.p.A.

Consultants Representing Chiesi/Zymenex:

(b) (4)

1.0 BACKGROUND

Zymenex (the Sponsor) has developed recombinant human alpha-mannosidase (rhLAMAN) for the treatment of alpha-mannosidosis, a rare, autosomal recessive, lysosomal storage disorder. The Sponsor concludes that the disorder is caused by a deficiency of alpha-mannosidase, a lysosomal enzyme which is involved in the catabolism of N-linked glycoproteins through the sequential degradation of high-mannose, hybrid and complex oligosaccharides. The developed product is intended to be used as an enzyme replacement therapy (ERT). It is expected to be given for the duration of life, with the aim of normalizing mannose-rich oligosaccharide levels in

the tissues, altering the progression of the disease and resulting in improving the patient's condition and quality of life.

On April 01, 2014, the Sponsor submitted a meeting request to discuss the plans for filing a BLA in 2015. Specific focus is on the clinical and nonclinical aspects of the development program. Additional meetings are expected to be requested to discuss the ongoing Phase 3 study, the CMC, and regulatory aspects of the program. The meeting requested on April 01, 2014, was granted and scheduled to occur on June 03, 2014. The meeting occurred as scheduled.

2.0 DISCUSSION

Nonclinical

1. The nonclinical program includes multiple studies using α-mannosidase-deficient (Tg-KO) and immunotolerant α-mannosidase-deficient (Tg+KO) mice, assessing the pharmacodynamics, biodistribution, pharmacokinetics / toxicokinetics and chronic toxicity (26 week) of CHF-LMZYM. The Company believes that the immunotolerant α-Mannosidosis (Tg+KO) mouse model is a suitable and biologically-relevant model for addressing key preclinical questions, in particular chronic toxicity. The Company is of the opinion that the chronic toxicity of CHF-LMZYM has been suitably evaluated, and that further toxicology studies are not required, provided that ongoing reproductive toxicology studies are successfully completed. Does FDA agree with the Company's position?

   FDA Response:

   Yes. Your completed and ongoing nonclinical studies appear to be adequate.

2. The Company has designed a toxicological program to support the development of CHF-LMZYM with a view to a future BLA. Pharmacology, pharmacokinetics and biodistribution studies have used both *in vitro* and *in vivo* assessments, where necessary. Toxicology studies – including assessments of toxicokinetics - have been conducted in mouse (using an immunotolerant α-Mannosidosis (Tg+KO) mouse model) and Cynomolgus monkey. Furthermore, reproductive and developmental toxicology studies have been conducted in adult rat, rabbit and juvenile rat. The nonclinical program presented to FDA at the Type B meeting held in February 2012 will be complemented with a package of reproductive toxicology studies in both rats and rabbits (Segments I, II, III), and these ongoing studies are briefly described in detail in the meeting package. The Company believes that these new studies, in addition to the nonclinical package presented in 2012, satisfy the requirements for the filing of a BLA for CHF-LMZYM from a nonclinical perspective. Does FDA agree with the Company's position?

   FDA Response:

   Yes, we agree.

3. A meeting was held between Zymenex and FDA on 14 February 2012, during which several recommendations for the CHF-LMZYM program were made (see Appendix 1 for

official meeting minutes). Does FDA agree that the Company has adequately addressed all the recommendations made from the February 2012 meeting, from a nonclinical perspective?

FDA Response:

Yes, we agree.

Clinical

4. The Company has implemented a clinical development program to assess the safety, tolerability and efficacy of CHF-LMZYM. The clinical program includes an observational natural history study (rhLAMAN01), and Phase 1 (rhLAMAN02), Phase 2a/2b (rhLAMAN03/04) and Phase 3 (rhLAMAN05) clinical trials. An additional post-approval study, rhLAMAN08, will assess pharmacokinetics, safety and efficacy of CHF-LMZYM in patients from birth to less than 6 years of age. The Company believes that the clinical program is suitable and sufficient to support a BLA filing for CHF-LMZYM. Assuming that positive data are obtained from rhLAMAN05, does FDA agree with the Company's position?

   FDA Response:

   No, we do not agree. We are concerned that your phase 3 trial, as currently proposed, may not be adequate and sufficient to demonstrate efficacy of CHF-LMZYM for the proposed indication. While we recognize the challenges of conducting trials in rare disease populations, the deficiencies of your phase 3 trial as described below may not qualify this trial for a marketing approval.

   - **The trial was not properly powered and the sample size was increased during the trial.**

     Discussion:
     The Sponsor presented evidence of incidence of alpha-Mannosidosis in the EU (refer to Sponsor Presentation) and clarified that the increase in sample size, was due to the identification of 5 additional patients who could be eligible for the study, which occurred prior to the start of the trial. The FDA recognizes the limitations of patient population, but reiterates that evidence of effectiveness should still be statistically significant and clinically meaningful. The FDA indicated that it looks forward to additional discussions with the Sponsor in a pre-NDA meeting when the Phase 3 data is available.

   - **We note in your protocol and SAP for the phase 3 trial that demonstration of efficacy is defined as a statistically significant improvement in the two primary endpoints, serum oligosaccharides and 3MSCT (under significance levels of 0.025 and 0.05, respectively), at the 26 week midterm analysis; or a statistically significant reduction in serum oligosaccharides (under a significance level of 0.025) and a trend for improvement in the 3MSCT and one of the prioritized secondary endpoints at the 52 week analysis. The**

study-wise type I error rate would generally be considered unacceptably large for a phase 3 trial.

- **Your trial consists of a very small sample size (25 subjects); for this reason, the linear regression model specified in your protocol and the ANCOVA model specified in your SAP may not be appropriate due to over-parameterization.**
- **Your proposed LOCF for missing data imputation method is not appropriate for the primary analysis.**
- **The magnitude of change on the primary clinical endpoint, the 3MSCT, should represent a clinically meaningful improvement for the patient. You will need to define what constitutes a clinically meaningful change or "treatment response" on these measures in your BLA submission in order for FDA to evaluate and interpret the data.**

In order to qualify for accelerated approval using a surrogate endpoint (CFR21 314.510 Subpart H), you must provide evidence in your BLA submission to support that a change in serum oligosaccharides is reasonably likely to predict a clinical benefit in the intended population. The correlational analyses of urinary oligosaccharides and the 3MSCT and FVC previously provided at the February 14, 2012 Pre-IND meeting will not be sufficient to support a prediction of clinical benefit. Additionally, approval based on a surrogate reasonably likely to predict clinical benefit, under accelerated approval, generally requires that clinical studies are underway at the time of the marketing approval with a primary clinical endpoint agreed upon by the FDA.

We agree with your inclusion of a placebo group in the phase 3 trial; however, we have some concerns about the choice of endpoints for the development program. The 3MSCT and 6MWT as global measures capture some relevant aspects of motor function; however, they were primarily developed to measure cardiorespiratory function and it is not clear that these measures are the most clinically relevant scales for this disease. Additionally, these scales are effort-dependent and intra-individual performance on these scales can be quite variable, making it difficult to interpret changes on these scales. This is particularly notable in the 2 year natural history study for alpha-mannosidosis where the measures show considerable variability and some improvement over a 2 year period.[1] As previously mentioned, you will need to define a clinically meaningful change compared to the placebo group on these scales in order to interpret the treatment effect of CHF-LMZYM.

Discussion:

The Sponsor presented data on the results of the 3MSCT and 6MWT from the Phase 2 trials (refer to Sponsor Presentation). The Sponsor acknowledges that these two tests

[1] Beck M, Olsen KJ, Wraith JE, Zeman J, Michalski JC, Saftig P, Fogh J, Malm D. Natural history of alpha mannosidosis a longitudinal study. Orphanet J Rare Dis. 2013 Jun 20;8:88.

are not the most optimal tests but the sponsor proposes that these are the most suitable for evaluation of a clinically meaningful treatment benefit for this disease. The FDA states that this will be a review issue and looks forward to continued discussion with Zymenex when the Phase 3 data are available.

Although pulmonary function measures appear to be reduced at baseline in alpha-mannosidosis patients compared to normative data, impaired pulmonary function has not previously been identified in the literature as a significant clinical sign for alpha-mannosidosis and it is not clear that these tests represent clinically meaningful endpoints for this disease. Additionally, these measures showed only a small improvement in the Phase 2b studies and the clinical significance of these improvements are questionable. As with the 3MSCT and 6MWT, the natural history study demonstrated significant variability and some improvement in pulmonary function tests over a 2 year period making it difficult to interpret small changes on these scales.

The BOT2 and Leiter scales do offer the potential for more clinically relevant disease measures of motor and cognitive function; however, these scales have not been previously validated in this population.

We are concerned that your development program has very limited PK information in either the pediatric (6-17 year olds) or the adult population. We are concerned that there will be insufficient data for the assessments of steady state PK, drug accumulation, dose proportionality, and immunogenicity impact on PK. Therefore, we recommend that you add PK assessment after multiple dosing to characterize steady state PK in both the pediatric and adult patients in your phase 3 trial (rhLAMAN-05). We remind you that you need to characterize PK properties of CHF-LMZYM following administration of your to-be-marketed drug product in an adequate number of patients in the target population(s) to inform product labeling. In general, PK information should be available for a minimum of 6 pediatric patients per age category. As far as adult patients, we recommend that you collect as much PK information as possible (i.e., all adult patients in your phase 3 trial) to strengthen the PK database as well as the exposure-response evaluations to inform product labeling.

In your briefing document, you stated that a population PK analysis was conducted, and simulations of steady state exposure were performed using the final population PK model to justify the dose selection for pediatric patients in different age groups. However, no information about this population PK model or the analysis has been included in the meeting package for our review. Therefore, the appropriateness of the model and its use in selecting the dose for different patient populations remain to be evaluated. Additional comments regarding dose selection are provided in our response to Question 5.

We noted that you performed immunogenicity assessment in your clinical trials. We remind you to assess the impact of immunogenicity on PK, pharmacodynamics,

safety, and efficacy. In general, the assessment of immunogenicity impact on PK can be performed by comparing PK data between patients who are positive for anti-drug antibodies (ADA) and/or neutralizing antibodies (NAb) vs. patients who are negative for ADA and/or NAb. Additionally, we recommend that you compare PK data before and after the development of antibodies in individual patients who seroconverted during treatment to evaluate the impact of ADA and/or NAb.

5. A pre-IND meeting was held between Zymenex and FDA in February 2012 (see Appendix 1 for official meeting minutes). Discussions regarding the clinical program for CHF-LMZYM at that meeting centered on the suitability of the phase 2b study protocol. Since the time of the meeting, the phase 2b study has been initiated and completed (see Section 3.4.2.3 on page 57) and a phase 3 study has begun (see Section 3.4.2.4 on page 75). Based on the information provided in this meeting package, does FDA agree that recommendations from the February 2012 meeting have been adequately addressed?

   FDA Response:

   No, we do not agree that you have addressed all of our concerns.

   In our previous Meeting Minutes dated March 14, 2012 for the February meeting, we informed you that we could not agree to your proposed dose selection because you provided limited clinical and safety data from your earlier phase trials. In this meeting package, you have provided various pharmacodynamic responses after 18 months of treatment in your phase 2b trial. However, the data that you provided are aggregated results from the 25 U/kg and the 50 U/kg dose groups. These data do not allow dose-response evaluation and comparison of the effects between the two dose groups. Therefore, we cannot comment on the appropriateness of the dose selection. We recommend that you perform dose-response and/or exposure-response analyses for efficacy and safety endpoints to support the proposed dosing regimen in your patient populations. Please refer to the following guidance for more details.

   http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072109.pdf

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You have adequately addressed the concerns raised in minutes from the February 14, 2012 meeting regarding stratifying the patient population by subtype. As you noted, this appears to be a heterogeneous disease population with no clear genotype-phenotype correlation and considerable overlap between clinical presentations. Therefore, we agree that it is not useful to stratify the patient population by subtype for these clinical trials. Given the use of bone marrow transplantation as first line treatment for the severe infantile form of the disease, we agree that it is not feasible at this time to conduct a clinical trial in this population. However, as you consider your development plans for patients less than 6 years of age, we advise you that children younger than 6 years of age may not be able to perform the efficacy measures currently included in the phase 3 trial (e.g., the 6MWT, 3MSCT, or FVC), as young children may not have the cognitive ability to follow instructions. We encourage you to explore other efficacy endpoints in addition to these measures. Exploratory efficacy endpoints should be clinically relevant for this disease and developmentally appropriate. Depending on your phase 3 data, partial extrapolation of efficacy data may be appropriate (See link to Guidance above). We also note that currently only 3 subjects are planned for enrollment in this study and this may not be a sufficient sample size for approval. Please include a rationale for the sample size, including availability of patients for recruitment in this age range, when you submit your study protocol for review.

<u>Additional comments</u>:

You provided narrative on IgG-mediated hypersensitivity reactions (described as infusion-related reactions or IRR) in 2 out of the 10 patients enrolled in the completed phase 2 trial. You further mention the use of a non-validated anti-rhLAMAN IgE antibody assay and report the presence of anti-rhLAMAN IgG antibodies that you claim are responsible for mediating the observed hypersensitivity reactions. You also describe testing for anti-rhLAMAN binding and neutralizing antibodies as part of the safety evaluation of rhLAMAN therapy in Phase 1, 2 and Phase 3 trials.

Our current recommendations for immunogenicity evaluation are that fully validated assays should be used to test samples collected from your phase 3 studies.

In preparation for your BLA application, we recommend that:

1. **You submit the results of the assay validation exercise, corresponding SOPs, and relevant development data not evaluated during validation to obtain the Agency's feedback on their adequacy before testing the phase 3 clinical samples.**

2. **Testing of serum samples for ADA is performed at baseline, at times of peak antibody responses (usually days 14, 28, 90, 180 etc.), and concurrently to PK samples to allow assessment of the impact of ADA in the PK, PD, safety, and efficacy of rhLAMAN therapy. Your phase 3 protocol mentions immunogenicity testing at baseline and at week 4. Justify the selection for immunogenicity testing only at day 0 and day 28 during your trial.**

Additional guidance on assay development and immunogenicity risk assessment can be found in:

1. **Guidance for Industry: Assay Development for Immunogenicity Testing of Therapeutic Proteins**
   http://www.fda.gov/downloads/Drugs/.../Guidances/UCM192750.pdf

2. **Guidance for Industry: Immunogenicity Assessment for Therapeutic Protein Products**
   http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM338856.pdf

Additional Discussion Comment:

The Sponsor indicated that they have plans to modify the SAP prior to data unblinding and would like the FDA's feedback on the proposed changes. The FDA indicated that the sponsor should submit their proposed changes to the IND along with a letter to the Project Manager to request feedback from the Agency on the proposal.

3.0 PREA REQUIREMENTS

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

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6.0 ATTACHMENTS

The Sponsor's Slide Presentation that was presented at the meeting on June 03, 2014 is attached.

12 Page(s) 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 and this page is the manifestation of the electronic signature.

/s/

KEVIN B BUGIN
06/24/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

PIND 113186

MEETING MINUTES

Zymenex A/S
c/o B&H Consulting Services, Inc. (Regulatory Agent)
Attention: Sandy Lee, M.S.
Senior Project Manager
50 Division Street, Suite 206
Somerville, NJ 08876

Dear Ms. Lee:

Please refer to your Pre-Investigational New Drug Application (PIND) file for Recombinant Human alpha-Mannosidase (rhLAMAN).

We also refer to the meeting between representatives of your firm and the FDA on February 14, 2012. The purpose of the meeting was to discuss your phase 1-2 clinical development plan.

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

If you have any questions, call me, at (301) 796-0193.

Sincerely,

{See appended electronic signature page}

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

ENCLOSURE:
Meeting Minutes

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type: B
Meeting Category: End of Phase 2

Meeting Date and Time: February 14, 2012, 12:00 PM – 1:00 PM
Meeting Location: WO 22, Room 1415

Application Number: PIND 113186
Product Name: Recombinant Human alpha-Mannosidase (rhLAMAN)
Indication: Treatment of Human alpha-Mannosidosis
Sponsor/Applicant Name: Zymenex A/S

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

FDA ATTENDEES

Division of Gastroenterology and Inborn Error Products (DGIEP)
Andrew Mulberg, M.D., Deputy Director
Lynne Yao, M.D., Clinical Team Leader
Ali Niak, M.D., Clinical Reviewer
Sushanta Chakder, Ph.D., Nonclinical Team Leader
Sruthi King, Ph.D., Nonclinical Reviewer
Elizabeth A.S. Ford, R.N., Senior Regulatory Health Project Manager

Office of Translational Sciences
Office of Clinical Pharmacology/Division of Clinical Pharmacology 3
Yow-Ming Wang, Ph.D., Biologics Team Leader
Dionna Green, M.D., Clinical Pharmacology Reviewer

Office of Biotechnology Products
Division of Therapeutic Proteins
Emanuela Lacana, Ph.D., Associate Lab Chief
Yan Wang, Chemistry Reviewer

Office of New Drugs/Immediate Office
Anne Pariser, M.D., Acting Associate Director for Rare Diseases
Larry Bauer, R.N., M.A., Regulatory Health Project Manager

Office of Orphan Products Development
Henry Startzman, M.D., Medical Officer

SPONSOR ATTENDEES

Zymenex A/S:

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Jens Fogh, DVM; President, CEO, Zymenex A/S
Pia Ringholm Gulstad, MSc Pharm; Director of Regulatory Affairs and Quality Assurance, Zymenex A/S

(b) (4)

B&H Consulting Services, Inc. (US Agent):
Helen M. Ribbans, FRAPS; President, B&H Consulting Services, Inc.
Sandy Lee, M.S.; Senior Project Manager, B&H Consulting Services, Inc.

1.0 BACKGROUND

US Agent (B&H Consulting Services, Inc), acting on behalf of Zymenex A/S, submitted a Type B Meeting Request to FDA on September 2, 2011, received September 6, 2011, to discuss PIND 113186/recombinant human alpha-Mannosidase (rhLAMAN) for the treatment of human alpha-Mannosidosis. The meeting was requested to discuss the clinical development of rhLAMAN. The meeting was granted on September 23, 2011, and scheduled to take place on December 13, 2011.

Preliminary responses were sent to the sponsor on December 9, 2011. However, on December 10, 2011, the sponsor requested the meeting be postponed to January or February due to the unexpected inability of a key sponsor-participant to attend the meeting. At the sponsor's request, the meeting was rescheduled for February 14, 2012.

2.0 DISCUSSION

CHEMISTRY MANUFACTURING AND CONTROLS

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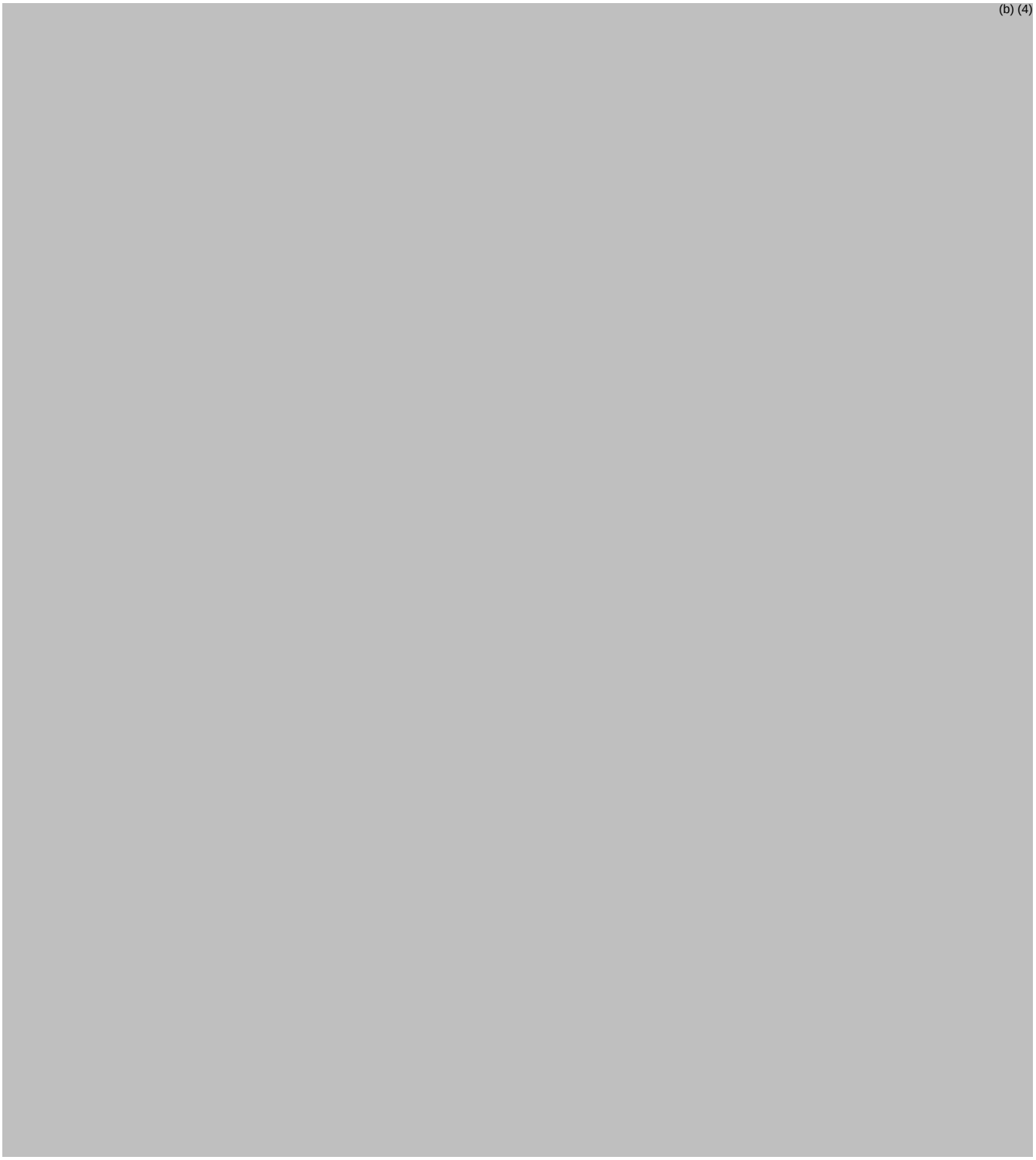

NONCLINICAL

Question 3: Does the Agency agree that the current nonclinical data are adequate to support the proposed clinical study and subsequent marketing applications?

FDA Response to Question 3:

No, we do not agree. The 10-week juvenile rat and 13-week monkey studies do not support the proposed 6-month clinical trial. Toxicity studies of at least 6-months in duration in rodents and nonrodents are necessary to support your proposed clinical trial. Toxicity studies in a transgenic model may be acceptable only if there are no other relevant species. Segment I fertility and early embryonic development, Segment II embryofetal development (2 species), and Segment III pre- and post-natal development studies should be conducted in order to support the marketing application for the product.

Additional Discussion:

Zymenex proposed to use a 6 month transgenic mouse model for their 6 month chronic toxicity studies. FDA reiterated that transgenic models may be acceptable only if there are no other relevant species. As such, justification will be required for use of this model in the chronic toxicity studies.

Zymenex agreed to provide all the available relevant nonclinical data to the IND in support of the phase 2 clinical study.

FDA reminded the sponsor that segment I reproductive toxicity studies will need to be completed prior to entering phase 2 studies, as per the ICH guidance. If these studies are not complete at the time of your IND submission, Zymenex must provide a justification and supporting data.

CLINICAL/CLINICAL PHARMACOLOGY

Question 4: Does the Agency agree that the available clinical data are adequate to support the proposed clinical study?

FDA Response to Question 4:

You are reminded to provide the clinical and nonclinical data to support the opening of your IND. Overall, we agree that your clinical development program includes important elements such as a planned natural history of study of patients with alphamannosidosis, and your phase 1 and 2a studies in patients with alpha-mannosidosis.

The data obtained from these studies will likely help to guide your planned phase 2b study. We understand that this study will likely serve as a pivotal trial and would like to discuss your plans for future phase trials. However, you did not include sufficient information from these studies to agree to the design of your proposed phase 2b study. Therefore, we have the following recommendations for you to consider in design of your phase 2b trial:

1. **We note that alpha-mannosidosis may present with three distinct phenotypes (Type 1, Type 2, and Type 3 alpha-mannosidosis). Therefore, studies should be designed to adequately evaluate the efficacy and safety of each of these clinical phenotypes. Alternatively, if your product is not intended to treat all patients with alpha-mannosidosis, then your clinical development program must be designed to treat a specific type of disease. Your briefing package did not include information**

regarding the baseline demographic information for patients treated in your phase 2a study and therefore, it is not clear whether the patients studied all have the same phenotype of alpha-mannosidosis, or whether differences in patient phenotype were associated with differences in clinical effect. Further more, it is not clear whether different phenotypic presentations are more common in different geographic locations and how studies enrolling U.S. vs. ex-U.S. patients may be affected by these geographic/phenotypic differences. You should evaluate these potential geographic differences and plan your future phase studies accordingly. Additionally, it appears that you are not planning to study patients with Type 3 disease in your proposed phase 2b trial. If this is the case, you must have a prospective plan to address how Type 3 patients will be studied and/or treated. We recommend that clinical trials should be designed to demonstrate a clinically meaningful benefit of your product in all alpha-mannosidosis populations.

2. (b) (4)

3. **Your dose selection should be based on clinical efficacy and safety data as well as any available clinical pharmacology data (e.g., pharmacokinetic and pharmacodynamic data) obtained from earlier phase trials. You have provided limited clinical efficacy and safety data from your earlier phase trials and therefore, we cannot agree to your proposed dose selection. Furthermore, it appears that a dose-response was not established based on many of the clinical endpoints measured in your phase 2a study (i.e., results from 25 U/kg dosing group appear better compared to the 50 U/kg dosing group). We recommend that prior to moving forward with future phase studies that you carefully review all available data in selecting a proposed dose, dosing interval, and length of treatment.**

4. **As noted above, alpha-mannosidosis can present with three distinct phenotypes. Therefore, selection of clinical endpoints in future studies should be selected based on clinically meaningful effects for each of the distinct subtypes. For example, improvement in survival in patients with Type 3 disease would be considered clinically meaningful and could be assessed in these patients. Additionally, other**

clinically meaningful effects that may be measured in specific phenotypes of the disease including hearing loss, cognitive impairment, cerebellar ataxia, destructive polyarthropathy and other skeletal abnormalities. While we agree that changes in overall motor function (i.e., 6MWT and 3MSC) have been used as clinical endpoints in other enzyme replacement therapy (ERT) clinical development programs, you have not yet clearly established that the etiology of the motor decline is consistent or caused by the same mechanism in all patients (see item 2). Furthermore, it is not clear that this decline occurs during a period that could be reasonably studied (i.e., months vs. years). We recommend that you review the data collected from your natural history and early phase studies to identify clinically meaningful endpoints, and the timecourse of disease progression for each phenotype of alpha-mannosidosis that could be reasonably studied.

5. **We would also recommend that you consider evaluating any potential biomarkers of alpha-mannosidosis that could also be used to understand the clinical effect of your product. You have measured urinary and serum oligosaccharides in your phase 2a study, but you have not explained which urinary oligosaccharides are most likely to correlate with effects of treatment or how these changes correlate with dose, dosing interval, and clinical endpoints. We recommend that you explore other potential biomarkers associated with alpha-mannosidosis as well.**

6. **Please clarify how you intend to quantify oligosaccharides in plasma and urine (e.g., measurement of total oligosaccharide or measurement of specific oligosaccharides).**

7. **The bioanalytical assay(s) for PK characterization, PD measurement, as well as the immunogenicity assay(s) to be used in your clinical trials should be adequately validated. Please refer to the following guidance documents (1) Guidance for Industry: Bioanalytical Method Validation and (2) Guidance for Industry: Assay Development for Immunogenicity Testing of Therapeutic Proteins.**

8. **Safety monitoring in your trial should adequately address any potential safety concerns identified in nonclinical studies (i.e., cytokine release). Safety monitoring should also include assessments for immunogenicity. Monitoring for immunogenicity must to be continued throughout the clinical development program in order to evaluate the impact of immunogenicity on PK, PD, safety and efficacy.**

Additional Discussion (FDA comments 1,2,3 and 5):
Zymenex acknowledged FDA comments, and agreed to take these comments under advisement as they move forward with their clinical development plans.

Question 5: Does the Agency agree with the proposed Phase 2b study design?

FDA Response to Question 5:
It is premature to answer this question (see FDA response to question 4).

Additional Discussion: ***None.***

Question 6: Does the Agency agree with the endpoints outlined in the proposed Phase 2b study?

FDA Response to Question 6:
No (see FDA response to question 4).

Additional Discussion:
FDA acknowledged the review of the phase 2a data that Zymenex presented. However, FDA continued to recommend that Zymenex review the recommendations that have been made as they move forward with the clinical development plan for the product.

Question 7: Does the Agency agree with the patient population included in the proposed Phase 2b study?

FDA Response to Question 7:
No (see FDA response to question 4). Additionally, we recommend that you also carefully consider the population of alpha-mannosidosis patients to be enrolled in your phase 2b study based on severity of the disease and how you will address differences in baseline severity of disease in the assessment of treatment effect of your product based on the endpoints you have selected.

Additional Discussion: ***None.***

3.0 ABUSE POTENTIAL ASSESSMENT

Drugs that affect the central nervous system, are chemically or pharmacologically similar to other drugs with known abuse potential, or produce psychoactive effects such as mood or cognitive changes (e.g., euphoria, hallucinations) need to be evaluated for their abuse potential and a proposal for scheduling will be required at the time of the NDA submission [21 CFR 314.50(d)(5)(vii)]. For information on the abuse potential evaluation and information required at the time of your NDA submission, see the draft guidance for industry, "Guidance for Industry Assessment of Abuse Potential of Drugs", available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM198650.pdf.

4.0 ATTACHMENTS AND HANDOUTS

Sponsor slides attached

25 Page(s) 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 and this page is the manifestation of the electronic signature.

/s/

ELIZABETH A FORD
03/14/2012