CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761278Orig1s000

OTHER REVIEW(S)

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING
Division of Medication Error Prevention and Analysis 2 (DMEPA 2)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	February 10, 2023
Requesting Office or Division:	Division of Rare Diseases and Medical Genetics (DRDMG)
Application Type and Number:	BLA 761278
Product Name and Strength:	Lamzede (velmanase alfa -tycv) for injection, 10 mg
Applicant/Sponsor Name:	Chiesi Farmaceutici S.p.A
OSE RCM #:	2022-1157-2
DMEPA 2 Safety Evaluator:	Sali Mahmoud, PharmD, BCPS
DMEPA 2 Team Leader:	Ashleigh Lowery, PharmD, BCCCP

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised container label and carton labeling received on January 31, 2023 for Lamzede. Division of Rare Diseases and Medical Genetics (DRDMG) requested that we review the revised container label and carton labeling for Lamzede (Appendix A) to determine if it is acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[a]

2 CONCLUSION

The Applicant implemented all of our recommendations and we have no additional recommendations at this time.

2 Pages of Draft Labeling have been Withheld in Full as B4(CCI/TS) Immediately Following this Page

[a] Mahmoud, S. Label and Labeling Review for Lamzede (BLA 761278). Silver Spring (MD): FDA, CDER, OSE, DMEPA 2 (US); 2023 JAN 23. RCM No.: 2022-1157-1.

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/

SALI MAHMOUD
02/10/2023 11:23:54 AM

ASHLEIGH V LOWERY
02/10/2023 11:27:10 AM

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

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

Memorandum

Date: January 26, 2023

To: Avinash K. Kalsi, Regulatory Project Manager, Division of Rare Diseases and Medical Genetics (DRDMG)

Sarah R. Fuchs, Clinical Reviewer, DRDMG

Mona G. Patel, Associate Director for Labeling, DRDMG

From: Elvy Varghese Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: James Dvorsky, Team Leader, OPDP

Subject: OPDP Labeling Comments for LAMZEDE (velmanase alfa-tycv) for injection, for intravenous use

BLA: 761278

Background:

In response to DRDMG's consult request dated July, 25, 2022, OPDP has reviewed the proposed Prescribing Information (PI) and carton and container labeling for the original BLA submission for LAMZEDE (velmanase alfa-tycv) for injection, for intravenous use [Lamzede].

PI:

OPDP's review of the proposed PI is based on the draft labeling accessed from SharePoint on January 23, 2023, and our comments are provided below.

Carton and Container Labeling:
OPDP's review of the proposed carton and container labeling is based on the draft labeling submitted by the sponsor to the electronic document room on January 11, 2023, and our comments are provided below.

Thank you for your consult. If you have any questions, please contact Elvy Varghese at Elvy.Varghese@fda.hhs.gov.

20 Pages of Draft Labeling have been Withheld in Full as B4(CCI/TS) Immediately Following this Page

---

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

ELVY M VARGHESE
01/26/2023 09:03:48 AM

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING
Division of Medication Error Prevention and Analysis 2 (DMEPA 2)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	January 23, 2023
Requesting Office or Division:	Division of Rare Diseases and Medical Genetics (DRDMG)
Application Type and Number:	BLA 761278
Product Name and Strength:	Lamzede (velmanase alfa-tycv) for injection, 10 mg
Applicant/Sponsor Name:	Chiesi Farmaceutici S.p.A.
OSE RCM #:	2022-1157-1
DMEPA 2 Safety Evaluator:	Sali Mahmoud, PharmD, BCPS
DMEPA 2 Team Leader:	Ashleigh Lowery, PharmD, BCCCP

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised container label and carton labeling received on January 11, 2023 for Lamzede. Division of Rare Diseases and Medical Genetics (DRDMG) requested that we review the revised container label and carton labeling for Lamzede (Appendix A) to determine if it is acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[a]

2 CONCLUSION

The Applicant implemented all of our recommendations, however the revised container label and carton labeling is unacceptable from a medication error perspective. The container label and carton labeling can be improved to reduce the risk of medication errors.

3 RECOMMENDATIONS FOR CHIESI FARMACEUTICI S.P.A.

We recommend the following be implemented prior to approval of this BLA:

A. Container Label and Carton Labeling
    1. As currently presented in narrow typography, the nonproprietary name lacks prominence and can be difficult to read. We recommend increasing the

[a] Mahmoud, S. Label and Labeling Review for Lamzede (BLA 761278). Silver Spring (MD): FDA, CDER, OSE, DMEPA2 (US); 2022 DEC 14. RCM No.: 2022-1157.

prominence of the nonproprietary name taking into account all pertinent factors, including typography, layout, contrast, and other printing features in accordance with 21 CFR 201.10(g)(2).

B. Container Label

1. Revise the word “reconstitution” on the PDP to begin with a lowercase “r” so that the statement “For Intravenous infusion after reconstitution” appears uninterrupted.

APPENDIX A. IMAGES OF LABEL AND LABELING RECEIVED ON JANUARY 11, 2023

Container labels

Carton labeling

1 Page of Draft Labeling has been Withheld in Full as B4(CCI/TS) Immediately Following this Page

---

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/

SALI MAHMOUD
01/23/2023 04:32:35 PM

ASHLEIGH V LOWERY
01/24/2023 10:20:27 AM

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Center for Drug Evaluation and Research
Office of New Drugs
Office of Rare Diseases, Pediatrics,
Urologic and Reproductive Medicine
Division of Pediatrics and
Maternal Health
Silver Spring, MD 20993
Telephone 301-796-2200
FAX 301-796-9855

Division of Pediatrics and Maternal Health Review

Review Date: December 22, 2022 **Date of Consult Request**: July 28, 2022	
From:	Christos Mastroyannis, M.D., Medical Officer, Maternal Health, Division of Pediatrics and Maternal Health (DPMH)
Through	Tamara Johnson, M.D., MS, Team Leader, Maternal Health, DPMH And Lynne Yao, M.D., Division Director, DPMH
To:	Division of Rare Diseases and Medical Genetics (DRDMG)
BLA Number:	761278
Drug:	LAMZEDE (Velmanase alfa-tycv)
Applicant:	Chiesi Farmaceutici S.p.A.
Consult request:	DRDMG requests DPMH to assist in labeling review
Indication:	For the treatment of patients with a confirmed diagnosis of alpha-mannosidosis in adult and pediatric patients.

Materials Reviewed

- Applicant's submission of June 17, 2022
- Division's Consult request of July 28, 2022, in DARRTS and Reference ID: 5020463
- Applicant's response of August 9th, 2022 to the Agency's Information Request (IR) of June 17th, 2022.

BACKGROUND

Regulatory History

The applicant, Chiesi Farmaceutici S.p.A., submitted BLA 761278 velmanase alfa-tycv on June 17, 2022. Velmanase alfa-tycv is indicated for the treatment of patients with a confirmed diagnosis of alpha-mannosidosis. The applicant has submitted this original application for velmanase alfa-tycv, a

lyophilized powder for solution for intravenous infusion once a week, for approval under the 351(a) pathway.

Velmanase alfa-tycv has been approved throughout the European Union on March 23, 2018, as "enzyme replacement therapy for the treatment of non-neurological manifestations in patients with mild to moderate alpha-mannosidosis. This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information." It was authorized under exceptional circumstances, because the applicant was unable to provide comprehensive data on the efficacy and safety of the medicine under normal conditions of use. It has also been designated as an orphan medicine.[1]

DRDMG has requested DPMH to assist with the labeling of velmanase alfa-tycv to comply with the Pregnancy and Lactation Labeling Rule (PLLR) format.

Pharmacological Class and Mode of Action

Velmanase alfa-tycv is an enzyme replacement therapy (ERT) biologic that contains the active substance recombinant human lysosomal alpha-mannosidase (rhLAMAN), alpha-D-mannoside, mannohydrolase. Velmanase alfa-tycv is produced by recombinant DNA technology in a Chinese Hamster Ovary (CHO) expression system. Genetic deficiency of LAMAN results in lysosomal accumulation of non-degraded oligosaccharides, leading to signs of the lysosomal storage disease alpha-mannosidosis. The reduction in serum oligosaccharides is representative of the intracellular lysosomal activity of velmanase alfa-tycv, which substitutes for the enzyme that is lacking in alpha-mannosidosis patients.

Drug Characteristics[2]

Molecular weight	108,713 Da
Glycosylated product	130 KDa
Half life (plasma)	30 hours
Half-life based on mouse kidney	14 days
Protein	Monomeric , identical to human enzyme, alpha mannosidase
Mutagenic potential	Not studied

Alpha-Mannosidosis and Pregnancy

Alpha-mannosidosis is a lifelong multi-systemic progressive disease, with neuromuscular and skeletal deterioration over decades.[3]

The timing of the appearance of symptoms correlates with the severity of the disease. Most neonates with alpha-mannosidosis are asymptomatic and only rarely severely affected.[4,5] While some children may have severe, rapidly progressive illness, others have very few symptoms that are mild in nature. Children with alpha-mannosidosis may present with

[1] European Medicines Agency, Science Medicines Health at https://www.ema.europa.eu/en/documents/overview/lamzede-epar-summary-public_en.pdf / accessed on October 24, 2022

[2] (b) (4)

[3] Malm D, Nilssen O (2008). "Alpha-mannosidosis". Orphanet J Rare Dis. 3 (1): 21.

[4] Roces DP, Lüllmann-Rauch R, Peng J, et al. (2004). "Efficacy of enzyme replacement therapy in alpha-mannosidosis mice: a preclinical animal study". Hum. Mol. Genet. 13 (18): 1979–88.

[5] Alpha Mannosidosis. National Organization for Rare Diseases (NORD) Factsheet 2015. https://rarediseases.org/rare-diseases/alpha-mannosidosis/

symptoms shortly after birth or may not show signs or symptoms until later in life.[6]

Symptoms may include:

- characteristic facial features (large head, low hairline, prominent forehead)
- excessive growth of the gums
- enlarged tongue
- skeletal abnormalities
- immune deficiency
- difficulty coordinating movements
- muscle weakness
- delay in motor skills development
- speech impairments
- frequent infections
- enlarged liver and spleen
- hearing loss
- cataracts
- psychiatric disturbances

The onset of the most severe form of the disease occurs within the first months of life and involves skeletal abnormalities and intellectual disability, with rapid progression leading to death from primary central nervous system involvement or myopathy.[3] This delays diagnosis, particularly as milder forms of the disease involve only mild to moderate intellectual disability, which progresses gradually during childhood or adolescence.[7] Alpha-mannosidosis is inherited in an autosomal recessive manner. At conception, each sibling of an affected individual has a 25% chance of being affected, a 50% chance of being an asymptomatic carrier, and a 25% chance of being unaffected and not a carrier. Carrier testing for at-risk relatives is possible if the pathogenic variants in the family are known. Prenatal testing for a pregnancy at increased risk is possible by assay of acid alpha-mannosidase enzymatic activity or molecular genetic testing once the pathogenic variants have been identified in the family. There is no further information how the disease may affect pregnancy and what are the effects on fertility.

Pathophysiology

A defective alpha-mannosidase enzyme, which normally helps to break down complex sugars derived from glycoproteins in the lysosome, causes progressive lysosomal accumulation of mannose-rich oligosaccharides in all tissues, resulting in impaired cellular function and apoptosis.[3,8] Complete absence of functionality in this enzyme leads to death during early childhood due to deterioration of the central nervous system.[6] Enzymes with low residual activity lead to a milder form of the disease, with symptoms such as impaired hearing, cognitive impairment, susceptibility to bacterial infections, and skeletal deformities. The course of the disease is progressive.[3,6]

REVIEW

Pregnancy

[6] Boston Children's Hospital Patient portal

[7] Guide to understanding mannosidosis. Society for Mucopolysaccharide Diseases. http://www.mpssociety.org.uk/wp-content/uploads/2016/07/guide-alphamannosidosis-2013.pdf

[8] Beck M Olsen KJ, Wraith JE et al. Natural history of alpha-mannosidosis: a longitudinal study. Orphanet J Rare Dis 2013;8:88.

Non clinical Data

As per the applicant, the reproductive toxicity program for velmanase alfa-tycv consisted of a standard package of reproductive toxicity studies (i.e., a fertility and early embryonic development study in the rat, two embryo-fetal development studies, one in the rat and one in the rabbit, and a prenatal and postnatal development study in the rat). (b) (4) per the applicant.

The nonclinical team, Shawna Weis, Ph.D. and Mukesh Summan, Ph.D., did not agree with this assessment. Nonclinical concluded that:

> In an embryo-fetal development study in the rat, velmanase alfa-tycv was administered during the period of organogenesis from gestation day (GD) 6 to GD 17. Numerous major and visceral malformations and variations were observed at exposures that were approximately 7-fold greater than those observed in patients treated at the 1 mg/kg dose level. Treatment-related major malformations included cleft palate, cleft palatine skull, severely bent pelvic girdle, and duplicated sternebrae.
>
> In an embryofetal development study in rabbit, velmanase alfa-tycv was administered from GDs 6 through 18 and was associated with skeletal and/or visceral malformations at exposures that were approximately 2.5-fold those observed in patients treated at the 1 mg/kg dose level. Major malformations observed in rabbits included incomplete intraventricular septum; severely reduced size of one or more lung lobe; unilateral renal agenesis; unilateral ureter; diaphragmatic hernia involving one or more lobe of the liver; hydrocephaly; single olfactory lobe; cystic dilatation of the cerebellum; malformed cervical, thoracic, caudal, and/or sacral vertebrae; and fused, absent, or vestigial ribs.
>
> In the pre- and post-natal development study in rats, velmanase alfa-tycv was administered intravenously every 3 days at 0, 3.3, 10, and 30 mg/kg from GD 6 to lactation day 20. Velmanase alfa-tycv did not induce effects on maternal reproductive function or on developmental and reproductive parameters of male and female offspring; thus, the maternal and developmental NOAELs were 30 mg/kg. Exposures at this dose, based on the embryo-fetal development study, were estimated to be approximately 10-fold the 1mg/kg dose of velmanase alfa-tycv.

Therefore, they concluded “Based on findings from animal reproduction studies, LAMZEDE may cause embryo-fetal harm when administered to a pregnant female.”

Reviewer Comment

In animal reproduction studies, the use of healthy normal animals is the standard approach, not enzyme-deficient animals. One must consider that if the recombinant human enzyme produces adverse developmental effects in offspring of healthy normal animals, interpretation of these findings may not translate to adverse developmental effects in offspring of enzyme-deficient humans.

Clinical Data

Chiesi performed a literature search by using Embase and Medline databases. The following Terms were applied: Lamzede OR "velmanase alpha" OR Lamazym OR Zymenex OR "LAMAN enzyme" OR rhLAMAN OR "Recombinant human alpha-mannosidase" OR "Recombinant human alpha mannosidase" OR "Recombinant human LAMAN" OR "human alpha-mannosidase" and Pregnancy OR gestation OR gravidity OR "child-bearing" OR perinatal complication* OR perinatal death.

Reviewer Comment
Lamzede is the trade name for velmanase alfa-tycv in the European Union where it is already approved. The other names like Lamazyn, Zymenex, Laman are names used during the development program.

The literature search criteria retrieved 63 publications, however, none reported data specifically on velmanase alfa-tycv use in pregnancy. A review of the pharmacovigilance (PV) database by the applicant states: "in the pharmacovigilance database from the time of velmanase alfa-tycv development to present, there have been no reported cases of pregnancy, perinatal complications, livebirths, still births, miscarriages or congenital anomalies".
This reviewer also searched PubMed, Reprotox/Micromedex and GG Briggs & RF Freeman Drugs in Pregnancy and Lactation: A Reference Guide to Fetal and Neonatal Risk. No entries were identified.

Summary
There are no data with velmanase alfa-tycv use in pregnant women to determine a drug-associated risk for major birth defects, miscarriage, or other adverse maternal or fetal outcomes. In embryo-fetal development studies, velmanase alfa-tycv administered intravenously to pregnant rats and rabbits during the period of organogenesis showed in the rat numerous major malformations and variations at exposures that were approximately 7-fold greater than those observed in patients treated at the 1 mg/kg dose level; in the rabbit, administration of velmanase alfa-tycv was associated with skeletal and/or visceral malformations, which occurred at exposures that were approximately 2.5-fold greater than those observed in patients treated at the 1 mg/kg dose level.

Lactation
As per applicant, there are no data on the presence of velmanase alfa-tycv in either human or animal milk, the effects of velmanase alfa-tycv on the breastfed infant, or its effects on milk production. Chiesi performed a literature search by using Embase and Medline databases. The following terms were applied: Lamzede OR "velmanase alpha" OR Lamazym OR Zymenex OR "LAMAN enzyme" OR rhLAMAN OR "Recombinant human alpha-mannosidase" OR "M-0011" OR "M0011" OR "Recombinant human alpha mannosidase" OR "Recombinant human LAMAN" OR "human alpha-mannosidase" and Breastfeeding OR lactation OR drug exposure during lactation OR lactational exposure OR Breast Feeding. No data specifically on velmanase alfa-tycv use in lactation were identified.
A review of PV by the applicant states, ". . . in the pharmacovigilance database from the time of velmanase alfa-tycv development to present, there have been no reported cases of breastfeeding".
Assessment by this reviewer of PubMed, Reprotox/Micromedex, GG Briggs & RF Freeman in Drugs in Pregnancy and Lactation: A Reference Guide to Fetal and Neonatal Risk and Halesmeds.com identified no entries related to velmanase alfa-tycv.

Females and Males of Reproductive Potential
In a rat fertility study, no adverse effects were observed following twice-weekly intravenous administration for two weeks prior to pairing, through day 6 of gestation. No human data are available on the effects of velmanase alfa-tycv on fertility to inform a potential clinical risk or any effects on hormonal contraception. In the PV, "no cases of adverse events related to male and/or female fertility have been reported in the pharmacovigilance database from the time of velmanase alfa-tycv development to present".

Drug Utilization
Chiesi is aware of a total of 78 patients who received velmanase alfa-tycv since its initial approval based on Chiesi's commercial data. However, details about gender and reproductive potential of each patient are not available.
The WHO[9] calculates that worldwide, 49.5 percent of the population is female, and amongst females, 49.2 percent are between the ages of 15-49 years. Accordingly, 19 of the 78 patients can be estimated to be females of reproductive potential.

Chiesi states that there is no pregnancy registry established during the velmanase alfa-tycv development program.

DISCUSSION/CONCLUSION
Pregnancy
There are no data with velmanase alfa-tycv use during pregnancy to determine a drug-associated risk for major birth defects, miscarriage, or other adverse maternal or fetal outcomes. In animal embryo-fetal development studies, velmanase alfa-tycv administered intravenously to pregnant rats and rabbits during the period of organogenesis showed numerous major malformations and variations at exposures 7-fold and skeletal and/or visceral malformations, which occurred at exposures that were approximately 2.5-fold greater than those observed in patients treated at the 1 mg/kg dose level, respectively.

DPMH is concerned about the findings from animal reproduction studies because of interpretability. If the recombinant human enzyme produces adverse developmental effects in offspring of normal healthy animals, we question whether it is appropriate to conclude that these findings translate to adverse developmental effects in offspring of enzyme-deficient humans. Based on this concern, DPMH proposes the following statement for inclusion in labeling subsections 5.3 Warnings and Precautions and in 8.1 Pregnancy, "The applicability of the findings from normal healthy animals to humans who have a deficiency of this enzyme is unclear." Per discussion with the Nonclinical team, they are not in agreement with including the proposed statement in the labeling.

A post-approval descriptive pregnancy safety study (DPSS) is not recommended for this application because there are no pregnancies or lactation cases reported in the PV from the time of velmanase alfa-tycv development to present and, also with no pregnancies reported in individuals with alpha-mannosidosis, it will be difficult to identify any patients for meaningful evaluation.

Lactation
There are no data on the presence of velmanase alfa-tycv in either human or animal milk, the effects on the breastfed infant, or the effects on milk production. Therefore, the risk/benefit statement will be inserted in subsection 8.2 Lactation, Risk Summary stating:

> The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for velmanase alfa-tycv and any potential adverse effects on the breastfed infant from velmanase alfa-tycv or from the underlying maternal condition.

[9] https://www.who.int/data/maternal-newborn-child-adolescent-ageing/indicatorexplorer-new/mca/women-of-reproductive-age-(15-49-years)-population-(thousands) accessed 31 Aug 2022.

Females and Males of Reproductive Potential

In a rat fertility study, no adverse effects were observed following twice-weekly intravenous administration for two weeks prior to pairing, through day 6 of gestation. No other human or animal data are available on the effects of velmanase alfa-tycv on fertility to inform a potential clinical risk or any effects on hormonal contraception.

Based on animal reproduction studies, LAMZEDE may cause embryo-fetal harm when administered during the first trimester of pregnancy. DRDMG seeks to include risk mitigation language to verify pregnancy status prior to initiating treatment and to use effective contraception for females of reproductive potential in labeling subsections 5.3 Warnings and Precautions and 8.3 Females and Males of Reproductive Potential. For this population, where no pregnancies have been reported for individuals who have alpha-mannosidosis, DPMH questions whether the risk mitigation language is helpful to the prescriber and suggests in its place to use language that encourages prescriber-patient discussion and decision-making. Per discussion with the Clinical team, they decided to retain the following risk mitigation language in labeling subsection 8.3 Females and Males of Reproductive Potential as it aligns with the approach to previous enzyme replacement therapy labeling.

Pregnancy Testing

For females of reproductive potential, verify that the patient is not pregnant prior to initiating treatment with LAMZEDE**.**

Contraception

Females

Advise females of reproductive potential to use effective contraception during treatment and for14 days after the last dose if LAMZEDE is discontinued.

LABELING RECOMMENDATIONS

DPMH revised Highlights, subsections 5.3, 8.1, 8.2, 8.3 and section 17 of labeling for compliance with the PLLR (see below). These are DPMH's recommendations, and they do not reflect discussions with the team. DPMH refers to the final BLA action for final labeling.

(b) (4)

2 Pages of Draft Labeling have been Withheld in Full as B4(CCI/TS) Immediately Following this Page

---

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

CHRISTOS MASTROYANNIS
12/22/2022 05:01:00 PM

TAMARA N JOHNSON
12/22/2022 05:24:41 PM

LYNNE P YAO
12/30/2022 09:39:24 AM

LABEL AND LABELING REVIEW
Division of Medication Error Prevention and Analysis 2 (DMEPA 2)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

*** This document contains proprietary information that cannot be released to the public***

Date of This Review:	December 14, 2022
Requesting Office or Division:	Division of Rare Diseases and Medical Genetics (DRDMG)
Application Type and Number:	BLA 761278
Product Name, Dosage Form, and Strength:	Lamzede (velmanase alfa-tycv) for injection, 10 mg
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Chiesi USA, Inc
FDA Received Date:	June 17, 2022; September 14, 2022
OSE RCM #:	2022-1157
DMEPA 2 Safety Evaluator:	Sali Mahmoud, PharmD, BCPS
DMEPA 2 Team Leader:	Ashleigh Lowery, PharmD, BCCCP

1 REASON FOR REVIEW

As part of the approval process for Lamzede (velmanase alfa-tycv) for injection, the Division of Rare Diseases and Medical Genetics (DRDMG) requested that we review the proposed Lamzede prescribing information (PI), container label, and carton labeling for areas of vulnerability that may lead to medication errors.

2 MATERIALS REVIEWED

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

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

N/A=not applicable for this review

*We do not typically search FAERS or ISMP Newsletters for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

Upon review of the proposed container labels, carton labeling, and PI we note areas of the labels and labeling that could be improved to promote the safe use of this product and so provide related recommendations in Section 4 below.

4 CONCLUSION & RECOMMENDATIONS

We conclude that the proposed container label, carton labeling, and PI, may be improved to promote the safe use of the product as described in Sections 4.1 and 4.2.

4.1 RECOMMENDATIONS FOR DIVISION OF RARE DISEASES AND MEDICAL GENETICS (DRDMG)

A. Prescribing Information

1. Dosage and Administration Section, Highlights of PI

a. Add "See full prescribing information for reconstitution, and administration instructions (2.x)" to guide reader to the appropriate section of FPI.

2. Dosage and Administration Section, Full PI

a. Recommend separating preparation and administration into two separate sections to facilitate information retrieval.

b. Recommend deleting (b) (4) to reduce clutter and decrease potential for (b) (4) errors. Suggest presenting (b) (4) as follows:

(b) (4)

c. (b) (4) We defer to CMC to determine if light protection is necessary; if so, we recommend adding instructions.

d. The abbreviation "µm" is error-prone and therefore we recommend using "micron" when referring to the 0.2 micron filter required for administration.

e. We recommend deleting (b) (4) to reduce complexity and potential for error. Consider the following edit for rates of infusion:

"The total volume of infusion is determined by the patient's actual body weight and should be administrated over a minimum of 60 minutes.

(b) (4)

(b) (4)

i. We recommend 60 minutes instead of (b) (4) " because 60 minutes to simplify calculation of the mL/hr infusion rate.

ii. We recommend the addition of further instructions on how to titrate the administration rate in the case of hypersensitivity reactions (b) (4)

f. Recommend changing the storage statement of the reconstituted solution to account for the duration of infusion if data is available to support (b) (4)

4.2 RECOMMENDATIONS FOR CHIESI USA, INC

We recommend the following be implemented prior to approval of this BLA:

A. General Comments (Container labels & Carton Labeling)
   1. Change "(b) (4)" to "For Intravenous infusion after Reconstitution" to minimize errors due to incorrect preparation or administration.
   2. Increase the prominence of the strength statement to better distinguish from surrounding text per 21 CFR 201.15(a)(6).

B. Container Labels
   1. To "Single-dose vial." add "Discard unused portion" where space allows for completion.

C. Carton Labeling
   1. Add the resultant concentration (in XX mg/mL) to the instructions for reconstituting the product. The concentration will inform persons responsible for preparing the product the amount of drug contained in each milliliter once reconstituted.

      Consider revising the statement to read:
      "Reconstitute with 5 mL Sterile Water for Injection, USP prior to use. After reconstitution, the final concentration is 2 mg/mL." or "(b) (4) ."
   2. To ensure consistency with the Prescribing Information, revise the statement, "(b) (4)" to read "Recommended Dosage: See prescribing information."

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Lamzede received on June 17, 2022 from Chiesi USA, Inc.

Table 2. Relevant Product Information for Lamzede	
Initial Approval Date	NA
Nonproprietary Name	velmanase alfa-tycv
Indication	indicated for the treatment of patients with a confirmed diagnosis of alpha-mannosidosis.
Route of Administration	Intravenous
Dosage Form	for injection
Strength	10 mg
Dose and Frequency	1 mg/kg (actual body weight) once every week
How Supplied	Lyophilized powder for injection for infusion in single-dose (b) (4) glass 10 mL vials. Packs of 1, 5, or 10 vials •NDC 10122-180-02: carton containing 1 vial •NDC 10122-180-05: carton containing 5 vials •NDC 10122-180-10: carton containing 10 vials
Storage	Store refrigerated at 2°C to 8°C (36°F to 46°F) in the original package. Protect from light.
Container Closure	(b) (4) rubber stopper

APPENDIX B. PREVIOUS DMEPA REVIEWS

On July 26, 2022, we searched for previous DMEPA reviews relevant to this current review using the terms, velmanase. Our search identified no previous reviews.

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[a] along with postmarket medication error data, we reviewed the following Lamzede labels and labeling submitted by Chiesi USA, Inc.

- Container label received on September 14, 2022
- Carton labeling received on September 14, 2022
- Prescribing Information (Image not shown) received on June 17, 2022, available from \\CDSESUB1\evsprod\bla761278\0001\m1\us\1-14-1-3-draft-labeling-text.docx

G.2 Label and Labeling Images

Container label

(b) (4)

2 Pages of Draft Labeling have been Withheld in Full as B4(CCI/TS) Immediately Following this Page

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

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/

SALI MAHMOUD
12/14/2022 10:34:06 AM

ASHLEIGH V LOWERY
12/15/2022 03:18:51 PM

Clinical Inspection Summary

Date	December 14, 2022
From	Cheryl Grandinetti, Pharm.D. Clinical Pharmacologist Good Clinical Practice Assessment Branch Division of Clinical Compliance Evaluation Office of Scientific Investigations
To	Avinash Kalsi, Regulatory Project Manager Sarah Fuchs, MD, Medical Officer Jacqueline Karp, MD, Medical Team Lead Kathleen Donohue, MD, Division Director Division of Rare Diseases and Medical Genetics (DRDMG)
BLA #	761278
Applicant	Chiesi Farmaceutici S.p.A.
Drug	Lamzede (velmanase alfa)
NME	Yes
Proposed Indication	For the treatment of patients with confirmed diagnosis of alpha-mannosidosis
Consultation Request Date	July 28, 2022
Summary Goal Date	December 17, 2022
Action Goal Date	February 14, 2023
PDUFA Date	February 17, 2023

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Drs. Hennermann and Lund were inspected in support of BLA 761278 covering two clinical trials, Protocols rhLAMAN-05 and CCD-LMZYMAA1-08. The studies appear to have been conducted adequately, and the data generated by these sites appear acceptable in support of the respective indication.

During the clinical investigator inspections, the source records related to the primary and key efficacy endpoint as noted in Section II of this Clinical Inspection Summary (CIS) [e.g., 3-minute stair climb test (3MSCT), 6-minute walk test (6MWT), pulmonary function tests, Peabody Developmental Motor Scale, Mullen Scale for Early Learning, Bruininks-Oseretsky Test of Motor Proficiency, hearing evaluations, cerebral spinal fluid (CSF) biomarkers] were reviewed and verified against the sponsor's data line listings for the 25 subjects randomized in Protocols rhLAMAN-05 and 1 subject enrolled in Protocol CCD-LMZYMAA1-08 at the two sites inspected. No discrepancies or issues were noted.

In addition, source records documenting the primary efficacy endpoint of the change from baseline to week 52 in serum and CSF oligosaccharides were neither maintained and retained at the central site (i.e., Dr. Lund's site) nor available during inspection for data verification. In

a 22 Nov 2022 response to an IR, the applicant submitted to the BLA, certified copies of the source records related to the oligosaccharide serum and CSF levels at Baseline and Week 52 for the 25 randomized subjects. An internal OSI review of the certified copies was performed by this reviewer, verifying them against the sponsor's data line listings for the 25 randomized subjects. No discrepancies were noted.

II. BACKGROUND

BLA 761278 was submitted in support of the use of Lamzede (velmanase alfa) for the treatment of alpha-mannosidosis. The studies supporting the application were the following:

- rhLAMAN-05, "A multi-center, double-blind, randomized, Placebo-controlled, parallel group trial, investigating the efficacy and safety of repeated Lamazym treatment of subjects with alpha-mannosidosis"
- CCD-LMZYMAA1-08 (also known as rhLAMAN08), "A 24-month multicenter, open-label Phase II trial investigating the safety and efficacy of repeated velmanase alfa (recombinant human alpha mannosidase) treatment in pediatric patients below 6 years of age with alpha-mannosidosis"

Protocol rhLAMAN-05

- ***Subjects:*** A total of 26 subjects were screened; 25 were randomized (i.e., 15 subjects received Lamzede and 10 subjects received placebo) and all 25 subjects completed the study.

- ***Sites:*** The study was conducted at 8 study sites in 6 European Union (EU) countries

- ***Study Initiation and Completion Dates:*** 10 Sep 2012 (First Subject First Visit) to 02 May 2014 (Last Subject Last Visit)

- ***Initial Database Lock:*** 29 Aug 2014; Final Database Lock: 16 Nov 2015

- ***Study Unblinding Date:*** 12 Nov 2015

This was a multi-center, double-blind, randomized, placebo-controlled, parallel group trial investigating the efficacy and safety of repeated velmanase alfa treatment of subjects with alpha-mannosidosis. The overall objective of this trial was to evaluate the efficacy and safety of repeated velmanase alfa treatment compared to placebo in subjects 5 to 35 years of age with alpha-Mannosidosis. The primary objective of this study was to demonstrate the efficacy of velmanase alfa over placebo in terms of 3-minute stair climbing test (3MSCT) improvement and serum oligosaccharide reduction over 52 weeks of treatment. The key secondary objective of this study was to demonstrate a positive trend of velmanase alfa over placebo in terms of improvement of 6-minute walk test (6MWT) and forced vital capacity (FVC) percent of predicted normal value over 52 weeks of treatment.

The trial consisted of the following:

- A screening visit (visit -1)
- A baseline visit (visit 0, prior to first dose) in order to evaluate inclusion/exclusion criteria and to perform the baseline procedures
- A first dose visit (visit 1)
- Up to 55 dose visits
- A midterm evaluation after 26 weeks (visit 26a)
- An end evaluation after 52 weeks (visit 52a)
- An additional last EOT visit was performed at week 56 (visit 56).

Subjects, aged 5 to 35 years, with a confirmed diagnosis of alpha-Mannosidosis as defined by alpha-Mannosidase activity <10% of normal activity (historical data), and who met all other protocol eligibility criteria were stratified by age and randomized in a 2:3 ratio to receive one of the following:

- Lamzede 1 mg/kg IV, infused at a maximum rate of 45 mL/hour once a week for a period of 12 months
- Matching placebo IV, infused at a maximum rate of 45 mL/hour once a week for a period of 12 months

The study drug may have been infused over a longer duration at the Investigator's discretion. Medical personnel were to continuously observe the subjects for evidence of AEs including infusion-related reactions (IRR) until one hour after the end of each infusion.

For the purpose of achieving standardized assessments, efficacy measurements were consistently conducted at a central site (Copenhagen University Hospital), while dose administration not combined with a functional evaluation was allowed at patients local site. Thus, all the visit assessments for efficacy (i.e., Baseline Visit, Visit 26a, midterm evaluation, and Visit 52a, end evaluation), were centralized at the Department of Pediatrics, Copenhagen University Hospital, Denmark. A midterm evaluation was done at week 26 for demonstration on efficacy evaluation of the 3MSCT and serum oligosaccharide values.

Safety, including AEs and SAEs, were monitored at every visit (i.e., for both visits that took place at the patient's local hospital and those that took place at the central site)

At the central site (i.e., Copenhagen University Hospital) baseline, midterm evaluation, and end evaluation, all subjects underwent serum sample for oligosaccharides, 3-minute stair climb test (3MSCT), 6-minute walk test (6MWT), pulmonary function test, Bruininks-Oseretsky test of motor proficiency 2nd edition (BOT2), cognitive function test (Leiter R), and test for biomarker proteins in CSF sampled during a lumbar puncture. In addition, pure tone audiometry and a Parents Questionnaire were performed.

The *primary efficacy endpoints* of this study were:

- Change from baseline to week 52 in serum oligosaccharides
- Change from baseline to week 52 in the 3MSCT

The *key secondary efficacy endpoints* of this study were:

- Change from baseline to week 52 in 6MWT
- Change from baseline to week 52 in FVC percent of predicted normal value (FVC %)

Serum oligosaccharides were performed centrally at the Danish Technology Institute. Investigators did not have access to these test results during the conduct of the study as well as after the study. The source records for these results were maintained at the (b) (4)

The 3MSCT and 6MWT should have been administered by a trained physiotherapist at the Copenhagen University Hospital, the central site. These tests were performed twice and the better result of the 2 tests were used.

Pulmonary function was assessed using spirometry conducted in accordance with the American Thoracic Society/European Respiratory Society statement on pulmonary function using reference values for growing lungs. Following at least 3 measurements of the series, the largest of the acceptable and reproducible maneuvers was considered and the true values were captured in the CRF. All spirometry curves were reviewed blindly by a certified pulmonologist to evaluate the quality of the test. Pulmonary function testing values judged as not reliable owing to poor quality were not used (i.e., excluded) in the analysis.

Protocol CCD-LMZYMAA1-08 (also known as rhLAMAN-08):

- ***Subjects:*** A total of 5 subjects were enrolled in the study

- ***Sites:*** The study was conducted at 7 study sites in 5 European Union (EU) countries

- ***Study Initiation and Completion Dates:*** 12 Dec 2016 (First Subject First Visit) to 03 Jul 2020 (Last Subject Last Visit)

- ***Database Lock Date:*** 19 Nov 2020

This was a 24-month multicenter, open-label, Phase II study. Patients were administered IV infusions of velmanase alfa once weekly during a period of at least 24 months. The main objectives of this study were to evaluate safety and efficacy of repeated velmanase alfa IV infusions in pediatric alpha-mannosidosis patients aged less than 6 years.

Patients attended a Screening Visit (V1) where informed consent was obtained and eligibility for inclusion in the study was determined, followed by a Baseline Visit (V0) during which baseline procedures were performed. Blood and CSF assessments at baseline were performed over 2 weeks.

Subjects received velmanase alfa infusions once weekly during a period of at least 24 months. Subjects attended the First Dose Visit (V1), followed by dose visits every 7 ± 3 days (V2 to V109), and for the patient enrolled in France, V2 to V171).

Evaluation visits occurred after the following timepoints:

- Week 26 ± 5 weeks (6 months evaluation visit, V26a)
- Week 52 ± 5 weeks (12 months evaluation visit, V52a)
- Week 78 ± 5 weeks (18 months evaluation visit, V78a) and
- Week 104 ± 5 weeks (final 24 months evaluation visit, V104a)

Each Visit lasted approximately 1 week. For the patient enrolled in France, there was a further evaluation visit at 166 ± 5 weeks (V166a).

Efficacy was assessed at the investigators site or at coordinating site at baseline (prior to first dose), at the 6 months evaluation visit (after 26 ± 5 weeks, referred to as V26a), at the 12 months evaluation visit (after 52 ± 5 weeks, referred to as V52a), at the 18 months evaluation visit (after 78 ± 5 weeks, referred to as V78a), and at the final 24 months evaluation visit (after 104 ± 5 weeks, referred to as V104a).

Safety was assessed in terms of physical examination findings, vital signs, adverse events (AEs), routine clinical laboratory evaluations including hematology, blood chemistry and urinalysis, and immunoglobulin (Ig) G immunogenicity monitoring.

Safety, including adverse events and serious adverse events (SAEs), was assessed at the Baseline Visit (V0), all dose visits and in connection with the dosing performed in the evaluation weeks.

An End of Trial visit (V110) was completed as soon as possible after the final evaluation visit.

The primary endpoints include:

- Safety and tolerability of velmanase alfa as per AEs (including infusion-related reactions), vital signs, and clinical laboratory parameters (hematology, biochemistry, and urinalysis).
- Detection of anti-velmanase alfa antibodies

- Secondary efficacy endpoints were many and included changes from baseline to 24 months for the following parameters:
    - Serum oligosaccharides
    - Functional capacity:
        - Peabody Developmental Motor Scale – 2nd Edition (PDMS-2)
        - Mullen Scale of Early Learning (MSEL)
        - Bruininks-Oseretsky Test Of Motor Proficiency–2nd Edition (BOT-2)
    - Endurance:
        - 3MSCT (in patients from 4 years of age)
        - 6-Minute Walk Test (6MWT) (in patients from 4 years of age)
        - 2-Minute Walk Test (2MWT) (in patients below the age of 4 years)
    - Hearing evaluation:
        - Otoacoustic emissions (OAE) testing
        - Automatic auditory brainstem response (AABR) audiometry
    - Immunological profile, when applicable upon judgment of the physician
        - serum IgG, IgA and IgM

        - in vitro synthesis of IgG
        - in vitro proliferative response to anti-cluster of differentiation [CD]3, interleukin [IL]-2, phytohemagglutinin [PHA] and anti-CD3+ anti-CD28
        - immunophenotype - CD3/CD4/CD8 for T-lymphocytes; and CD19/CD20 for B-lymphocytes
    - CSF biomarkers (assessments occurred at baseline, 12 months, and 24 months)
        - Tau protein
        - neurofilament protein light [NFL]
        - glial fibrillary acidic protein (GFAP)
        - oligosaccharides
    - Assessment of quality of life via questionnaire to parents
    - Pediatric Evaluation of Disability Inventory (PEDI) questionnaire to patient's parents
    - Brain magnetic resonance spectroscopy (MRS) (for mannose-rich oligosaccharides) (performed at baseline, 12 months, and 24 months)
    - MRI (of white matter, grey matter and centrum semiovale) and diffusion-MRI (performed at baseline, 12 months, and 24 months)

No primary efficacy analysis was defined.

Rationale for Site Selection

The clinical sites were selected based on enrollment, participation in the 2 clinical trials being inspected, and previous inspection history

III. RESULTS (by site):

1. **Julia Hennermann, MD**
   Sites# 2 (rhLAMAN-05) and #276 (for CCD-LMZYMAA1-08)
   Universitätsmedizin Mainz
   Zentrum für Kinderund Jugendmedizin Langenbeckstrasse. 1
   Mainz, 55131, Germany
   PDUFA Inspection Dates: October 10 to 13, 2022

Of note, for Protocol rhLAMAN-05, this site was a local study drug infusion site where dose administration visits not combined with a functional evaluation was allowed to occur. Thus, all visits, other than visits where assessments for efficacy (i.e., Baseline Visit, Visit 26a, midterm evaluation, and Visit 52a, end evaluation) were performed, took place at this local site for 7 of the 25 randomized subjects. For Protocol CCD-LMZYMAA1-08, 2 subjects were screened, 2 were enrolled, and 1 of the 2 received treatment at another site in Hamburg, Germany.

A full audit of the study records for the 7 subjects receiving study drug infusions in Protocol rhLAMAN-05 and 1 of the 2 enrolled subjects in CCD-LMZYMAA1-08 was conducted. Records reviewed during the inspection included, but were not limited to, the study protocol

and amendments; EC submissions, approvals, and correspondence; subject eligibility criteria; informed consent process and forms; source records including those related to verification of the primary and key secondary efficacy endpoints in Protocol CCD-LMZYMAA1-08; adverse event reporting; protocol deviations; drug accountability logs and processes and procedures in place for blinding the study medication; monitor logs and follow-up letters; and other regulatory documentation (e.g., financial disclosures, Statement of Investigator).

No issues with the conduct of Protocols rhLAMAN-05 and CCD-LMZYMAA1-08 were noted during inspection. There was no evidence of under-reporting of adverse events. In addition, the source records documenting the laboratory tests and primary and secondary efficacy endpoint data (i.e., detection of anti-velmanase alfa antibodies, serum oligosaccharides, 3MSCT, 6MWT, 2MWT, Peabody Developmental Motor Scale, Mullen Scale for Early learning, Bruininks-Oseretsky Test of Motor Proficiency, hearing evaluation, immunological profile, and CSF biomarkers) at baseline and 6-, 12- and 18-month evaluation visits were reviewed and verified against the sponsor's data line listings for Subject 2761, enrolled in Protocol CCD-LMZYMAA1-08. No discrepancies or issues were noted.

2. Allan Lund, MD
Sites# 3 (rhLAMAN-05) and #208 (for CCD-LMZYMAA1-08)
Center for Metabolic Diseases
Department of Clinical Genetics
Juliane Marie Centre, Copenhagen University Hospital
Blegdamsvej, 9
Copenhagen, 2100, Denmark
PDUFA Inspection Dates: October 31 to November 3, 2022

Of note, for Protocol rhLAMAN-05, this site was considered the central site and, therefore, all assessments for efficacy (i.e., Baseline Visit, Visit 26a, midterm evaluation, and Visit 52a, end evaluation) were performed at this site for all 25 randomized subjects. At this site for Protocol rhLAMAN-05, 26 subjects were screened, 25 were randomized, and 25 subjects completed the study. For Protocol CCD-LMZYMAA1-08, 1 subject was screened but not enrolled as this subject was determined to be a screen failure.

A full audit of the study records for the 26 screened subjects in Protocol rhLAMAN-05 and the 1 screened subject in CCD-LMZYMAA1-08 was conducted. Records reviewed during the inspection included, but were not limited to, the study protocol and amendments; EC submissions, approvals, and correspondence; subject eligibility criteria; informed consent process and forms; source records including those related to verification of the primary and key secondary efficacy endpoints of change from baseline to week 52 in the serum and cerebral spinal fluid (CSF) oligosaccharides, 3MSCT, 6MWT and in FVC % of predicted normal value; adverse event reporting; protocol deviations; drug accountability logs and processes and procedures in place for blinding the study medication; monitor logs and follow-up letters; and other regulatory documentation (e.g., financial disclosures, Statement of Investigator).

There was no evidence of under-reporting of adverse events. The source records documenting the primary and key secondary efficacy endpoint data (i.e., 3MSCT, 6MWT, and FVC % at baseline and Week 52) were reviewed and verified against the sponsor's data line listings for the 25 randomized subjects. No discrepancies were noted.

Of note, source records documenting the change from baseline to week 52 in serum and CSF oligosaccharides were neither maintained and retained at the clinical trial site nor available during inspection for data verification. In a 22 Nov 2022 response to an IR, the applicant submitted to the BLA certified copies of the source records related to the oligosaccharide serum and CSF levels at Baseline and Week 52 for the 25 randomized subjects. An internal OSI review of the certified copies of these source records submitted to the NDA was performed by this reviewer, verifying them against the sponsor's data line listings for the 25 randomized subjects. No discrepancies were noted.

{See appended electronic signature page}

Cheryl Grandinetti, Pharm.D.
Clinical Pharmacologist
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

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

CONCURRENCE:

{See appended electronic signature page}

Jenn Sellers, M.D.
Acting Branch Chief
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

cc:

Central Doc. Rm. BLA 761278
DRDMG/Project Manager/Avinash Kalsi
DRDMG/Medical Reviewer/Sarah Fuchs, MD
DRDMG/Medical Team Leader/Jacqueline Karp
DRDMG/Division Director/Kathleen Donohue
OSI/Office Director/David Burrow
OSI/DCCE/Division Director/Kassa Ayalew
OSI/DCCE/Acting Branch Chief/Jenn Sellers
OSI/DCCE/Team Leader/Phillip Kronstein
OSI/DCCE/GCP Reviewer/Cheryl Grandinetti
OSI/GCP Program Analysts/Yolanda Patague

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/

CHERYL A GRANDINETTI
12/14/2022 01:41:40 PM

PHILLIP D KRONSTEIN
12/14/2022 02:00:04 PM

JENN W SELLERS
12/14/2022 02:09:14 PM

M E M O R A N D U M

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

DATE: 12/8/2022

TO: Division of Rare Diseases and Medical Genetics (DRDMG)
Office of Rare Diseases, Pediatrics, Urologic, and Reproductive Medicine (ORPURM)

AND

Office of Product Quality
Office of Biologic Products

FROM: Office of Study Integrity and Surveillance (OSIS)

SUBJECT: **Decline to conduct on-site inspections**

RE: BLA 761278

OSIS received an inspection request consult from the Office of Product Quality on August 11, 2022 and the Division of Rare Diseases and Medical Genetics (DRDMG) on August 25, 2022, for the below sites. The PDUFA date is February 17, 2023.

The Office of Study Integrity and Surveillance (OSIS) declines to conduct inspections for the sites listed below. The rationale for this decision is noted below.

Rationale

Inspections of the sites listed below cannot be accomplished to provide the review division an OSIS Review by the PDUFA goal date of February 17, 2023.

We note that OSIS's inspection histories for the sites are listed below.

(b) (4): OSIS conducted a Remote Regulatory Assessment (RRA) for the site in (b) (4), which falls within the surveillance interval. The RRA was conducted under the following submissions: (b) (4)

The following objectionable conditions were observed:

(b) (4)

After review of the observations and the site's response, OSIS concluded that that some observations may impact data reliability from the reviewed studies. (Final OSIS Review – (b) (4))

[redacted] (b) (4): OSIS has no inspection history for this site.

[redacted] (b) (4): OSIS has no inspection history for this site.

[redacted] (b) (4): OSIS has no inspection history for this site.

[redacted] (b) (4): OSIS has no inspection history for this site.

[redacted] (b) (4): OSIS has no inspection history for this site.

Sites

Facility Type	Facility Name	Facility Address
Analytical	[redacted]	(b) (4)
Analytical		
Analytical		
Analytical		
Analytical		
Analytical		

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/

WENDY NG
12/08/2022 01:47:29 PM

M E M O R A N D U M

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

DATE: September 14, 2022

TO: Shawna L. Weis
Senior Pharmacologist
Division of Pharmacology/Toxicology-ORDPURM

Mukesh Summan
Director, Division of Pharmacology/Toxicology-ORDPURM
Office of New Drugs (OND)

FROM: Zhou Chen, M.D., Ph.D.
Division of New Drug Study Integrity (DNDSI)
Office of Study Integrity and Surveillance (OSIS)

Lynda Lanning, D.V.M., DABT
Division of New Drug Study Integrity (DNDSI)
Office of Study Integrity and Surveillance (OSIS)

THROUGH: Charles Bonapace, Pharm.D.
Director
Division of New Drug Study Integrity (DNDSI)
Office of Study Integrity and Surveillance (OSIS)

SUBJECT: BLA 761278

t (b) (4)

Summary

The OSIS GLP Team received a GLP consult request from the Division of Pharmacology/Toxicology for CDER OND's Office of Rare Diseases, Pediatrics, Urologic and Reproductive Medicine on September 7, 2022 regarding one developmental and reproductive toxicology study (IZU0007) submitted to BLA 761278. Study number IZU0007 entitled "rhLAMAN: Intravenous (Slow Bolus) Pre-and Post-Natal Development Study in the Rat" was conducted at (b) (4) and finalized in (b) (4) It was noted that the study design did not include a dose formulation analysis or toxicokinetic evaluation (TK). The review division has concerns regarding study

animal exposure and the lack of TK data that are needed for the BLA's labeling evaluation.

OSIS Review:
Study IZU0007 (rhLAMAN: Intravenous (Slow Bolus) Pre- and Post-N [redacted] as conducted by [redacted] to assess the test article's effects on the embryonic, fetal and post-natal development in Crl:WI(Han)rats. The study was finalized on January 7, 2015 and submitted to BLA 761278 on June 17, 2022. The sponsor of the BLA is Chiesi Farmaceutici S.p.A in Italy. The drug is velmanase alfa (rhLAMAN) and the indication is alpha-mannosidosis, an inherited disorder impacting the production of alpha-D-mannosidase.

In this study, timed-pregnant Han Wistar rats were treated with rhLAMAN at 0, 3.3, 10, or 30 mg/kg by slow intravenous bolus injection approximately every three days from gestation Day 6 to lactation Day 20 (Days 6, 9, 12, 15, 18 and 20 of gestation and 1, 4, 7, 10, 14, 17 and 20 of lactation). Dose levels in different animal groups were achieved by varying the dose volume of a fixed concentration of sponsor-provided dose formulation (3 mg/mL, 1.1, 3.3 and 10 mL/kg in low, mid and high dose groups). Treated rats were allowed to litter and rear their offspring to weaning. Twenty males and 20 females per group from the F1 generation were selected at weaning and allowed to mature untreated. The potential effects of the test article on growth, development, behavior and reproductive performance were assessed.

Mortality was noted in all test article-treated parental groups:

High dose group: Two animals were moribund sacrificed on gestation Days 15 and 16. Macroscopic findings at necropsy for the Day 15 sacrificed animal included a reddened cecum and ileum and a gelatinous pancreas. The vagina contained red fluid and all embryos were dead. Necropsy of the animal sacrificed in moribund condition on Day 16 revealed pale liver and kidneys, red fluid in the vagina and all of the embryos were dead.

Mid dose group: One animal was found dead on gestation Day 16 with no abnormalities found at necropsy.

Low dose group: Two animals had clonic convulsions on Days 1 and 8 of lactation and were terminated. No macroscopic abnormalities were identified.

Clinical observations:

High dose group: Swollen muzzles, piloerection, cold body surface, pale extremities, bleeding from vulva and anus, decreased

activities with slow breathing, prostrate, unsteady gait, and partially closed eyes.

Mid dose group: Piloerection, decreased activities with slow breathing, and prostrate.

Low dose group: Clonic convulsions in two animals.

There were no effects of rhLAMAN on pregnancy parameters or litter survival at any dose level.

No biologically significant differences in body weights and food consumption were noted across the groups.

F1 Generation (post-weaning): There were no premature deaths or clinical observations related to maternal administration of rhLAMAN. There were no post-natal effects of rhLAMAN on the F1 generation.

OSIS Evaluation:

Lack of dose formulation analysis: In this study, the test article, rhLAMAN, was pre-formulated at a fixed concentration of 3 mg/mL and provided by the sponsor. The sponsor supplied the Certificate of Analysis (COA) that confirmed the concentration of the pre-prepared formulation. As indicated in the study report, the stability for the test article formulation was also established under conditions of use. The dose was achieved for each dose group by varying the administered volume of the supplied formulation, and no dose formulation preparation was performed by the testing facility. The OSIS reviewer considers that adequate information is available for the test article formulation provided by the sponsor, and there are no concerns with the lack of dose formulation analysis.

Lack of TK evaluation: In this study, maternal toxicity was noted at all dose levels as evidenced by mortalities and clinical observations. The NOAEL was not established. There were no effects of maternal administration with rhLAMAN on the F1 generation throughout the pre- or post-weaning period. The No Observed Effect Level (NOEL) for pre- and post-natal development was considered to be 30 mg/kg. The OSIS reviewer considers the developmental toxicity in this study was adequately addressed at the given dose levels. The TK evaluation was not included in the study protocol, and thus the lack of a TK evaluation is considered a study design deficiency and not a compliance issue or GLP violation. The review division may request the sponsor perform a bridging TK study in the same strain of rats that will help with the labeling review.

Conclusion and Recommendation:
The test article formulation was supplied by the sponsor and administered without preparation of test article mixtures. Thus, the sponsor-supplied COA supports the concentration and stability of the test article formulation under the conditions of use. The lack of dose formulation analysis is not a concern for this study.

A TK evaluation was not planned for the study and included in the study protocol. Therefore, the lack of TK evaluation is a study design deficiency. Because no GLP compliance issues were identified by OSIS, a GLP inspection of the testing facility is not warranted. It is recommended that the review division request a bridging TK study in the same strain of animal to support the labeling review.

cc: via DARRTS BLA 761278
OSIS/Kassim/Fenty-Stewart/Johnson
CDER-OSIS-GLP@fda.hhs.gov
OSIS/DNDSI/Bonapace/ChenZ/Lanning

Draft: ZC 09/08/2022

Edit: LL 09/08/2022; CB 9/14/2022

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/

ZHOU CHEN
09/14/2022 04:49:10 PM

CHARLES R BONAPACE
09/15/2022 07:21:01 AM