

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use LAMZEDE® safely and effectively. See full prescribing information for LAMZEDE.

LAMZEDE (velmanase alfa-tycv) for injection, for intravenous use
Initial U.S. Approval: 2023

WARNING: SEVERE HYPERSENSITIVITY REACTIONS

See full prescribing information for complete boxed warning.

Hypersensitivity Reactions Including Anaphylaxis

- Appropriate medical support measures, including cardiopulmonary resuscitation equipment, should be readily available. If a severe hypersensitivity reaction occurs, discontinue LAMZEDE immediately and initiate appropriate medical treatment. (5.1)

INDICATIONS AND USAGE

LAMZEDE is recombinant human lysosomal alpha-mannosidase indicated for the treatment of non-central nervous system manifestations of alpha-mannosidosis in adult and pediatric patients. (1)

DOSAGE AND ADMINISTRATION

- For females of reproductive potential, verify that the patient is not pregnant prior to initiating treatment. (2.1)
- Consider pretreating with antihistamines, antipyretics, and/or corticosteroids prior to LAMZEDE administration. (2.2)
- Recommended LAMZEDE dosage is 1 mg/kg (actual body weight) administered once every week as an intravenous infusion. (2.2)
- See the full prescribing information for dosage modifications due to hypersensitivity reactions or IARs. (2.3)

- See the full prescribing information for reconstitution and administration instructions. (2.4, 2.5)

DOSAGE FORMS AND STRENGTHS

For injection: 10 mg of velmanase alfa-tycv as a lyophilized powder in a single-dose vial for reconstitution. (3)

CONTRAINDICATIONS

None. (4)

WARNINGS AND PRECAUTIONS

- *Infusion-Associated Reactions (IARs)*: If severe IARs occur, discontinue LAMZEDE and initiate appropriate medical treatment. (5.2)
- *Embryo-Fetal Toxicity*: May cause fetal harm. Advise females of reproductive potential to use effective contraception during treatment and for 14 days after the last dose if LAMZEDE is discontinued. (5.3, 8.1, 8.3)

ADVERSE REACTIONS

Most common adverse reactions (incidence > 20%) are hypersensitivity reactions including anaphylaxis (5.1), nasopharyngitis, pyrexia, headache, and arthralgia. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Chiesi USA, Inc. at 1-888-661-9260 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

See 17 for PATIENT COUNSELING INFORMATION.

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FULL PRESCRIBING INFORMATION

WARNING: SEVERE HYPERSENSITIVITY REACTIONS

Hypersensitivity Reactions Including Anaphylaxis

Patients treated with LAMZEDE have experienced hypersensitivity reactions, including anaphylaxis. Appropriate medical support measures, including cardiopulmonary resuscitation equipment, should be readily available during LAMZEDE administration. If a severe hypersensitivity reaction (e.g., anaphylaxis) occurs, discontinue LAMZEDE immediately and initiate appropriate medical treatment. In patients with severe hypersensitivity reaction, a desensitization procedure to LAMZEDE may be considered [see *Warnings and Precautions (5.1)*].

1 INDICATIONS AND USAGE

LAMZEDE is indicated for the treatment of non-central nervous system manifestations of alpha-mannosidosis in adult and pediatric patients.

2 DOSAGE AND ADMINISTRATION

2.1 Important Recommendations Prior to LAMZEDE Treatment Initiation

For females of reproductive potential, verify that the patient is not pregnant [see *Use in Specific Populations (8.1, 8.3)*].

2.2 Recommended Dosage and Administration

Prior to LAMZEDE administration, consider pre-treating with antihistamines, antipyretics, and/or corticosteroids [see *Warnings and Precautions (5.1, 5.2)*].

The recommended dosage of LAMZEDE is 1 mg/kg (actual body weight) administered once every week as an intravenous infusion.

The total volume of infusion is determined by the patient's actual body weight and should be administered over a minimum of 60 minutes for patients weighing up to 49 kg. Patients weighing 50 kg and greater should be infused at a maximum infusion rate of 25 mL/hour to control the protein load [see *Dosage and Administration (2.4)*].

If one or more doses are missed, restart the treatment as soon as possible, as long as it is at least 3 days from the next scheduled dose. If it is within 3 days from the next scheduled dose, give only the next dose per schedule.

2.3 Dosage and Administration Modifications Due to Hypersensitivity Reactions and/or Infusion-Associated Reactions

In the event of a severe hypersensitivity reaction (including anaphylaxis) or severe infusion-associated reaction (IAR), immediately discontinue LAMZEDE administration and initiate appropriate medical treatment. For additional recommendations in the event of a severe hypersensitivity reaction or IAR, see *Warnings and Precautions (5.1, 5.2)*.

In the event of a *mild to moderate* hypersensitivity reaction or a *mild to moderate* IAR, consider temporarily holding the infusion for 15 to 30 minutes, slowing the infusion rate to 25% to 50% of the recommended rate, and initiating appropriate medical treatment [see *Warnings and Precautions (5.1, 5.2)*].

If symptoms:

- Persist despite temporarily holding or slowing the infusion, stop the infusion and monitor the patient. If symptoms continue to persist, discontinue the infusion, and consider re-initiating the infusion within 7 to 14 days at 25% to 50% of the recommended rate with appropriate pretreatment.
- Subside following holding or slowing the infusion, resume infusion at 25% to 50% the recommended rate. If tolerated, increase the infusion rate by increments of 25% of the recommended rate until the recommended infusion rate is reached. Closely monitor the patient.

2.4 Reconstitution Instructions

Use aseptic technique during preparation. Reconstitute LAMZEDE in the following manner:

- Determine the number of LAMZEDE vials to be reconstituted based on the patient's weight in kg and the recommended dose [see *Dosage and Administration (2.2)*]. Round the number of vials up to the next whole number.
- Remove vials from the refrigerator and set aside for approximately 30 minutes to allow vials to come to room temperature.
- Reconstitute each vial by slowly injecting 5 mL of Sterile Water for Injection, down the inside wall of each vial. Avoid adding the Sterile Water for Injection to the vial forcefully or directly onto the lyophilized powder to minimize foaming.
- Allow the reconstituted vials to stand on the table for 5 – 15 minutes. Then gently tilt and roll each vial for 15 – 20 seconds to enhance the dissolution process. Each vial will yield a concentration of 2 mg/mL. Do not invert, swirl, or shake the vials.
- Visually inspect the reconstituted solution in the vials for particulate matter and discoloration. The solution should be clear to slightly opalescent. Due to the nature of LAMZEDE, the solution may occasionally contain some proteinaceous particles in the form of thin white strands or translucent fibers which will be removed by the in line filter during infusion. Discard if opaque particles are present or the solution is discolored.
- Slowly withdraw the required volume from the vials with caution to avoid foaming in the syringe. If the volume of the solution exceeds one syringe capacity, prepare the required number of syringes in order to replace the syringe quickly during the infusion. Discard unused portion remaining in the vials.

Storage of the Reconstituted Solution

- If the reconstituted LAMZEDE vial is not used immediately, store the vial refrigerated at 2°C to 8°C (36°F to 46°F) for up to 24 hours inclusive of infusion time. Protect from light during refrigeration. Do not freeze.
- Reconstituted LAMZEDE vial must be infused within 10 hours after removal from the refrigerator, inclusive of total infusion time. Discard if not used within 10 hours.
- Infuse reconstituted solution within 24 hours from the time of preparation, which includes the storage time in the refrigerator, the time at room temperature, and the duration of the infusion.

2.5 Administration Instructions

- Use an infusion set equipped with a pump and a low protein binding, 0.2-micron, in-line filter to administer LAMZEDE. Do not shake the syringe.
- The total volume of infusion is determined by the patient's actual body weight and should be administered over a minimum of 60 minutes for patients weighing up to 49 kg. Patients weighing 50 kg and greater should be infused at a maximum infusion rate of 25 mL/hour to control the protein load.
- When the last syringe is empty, replace the dosage syringe with a 20 mL syringe filled with 0.9% Sodium Chloride Injection, and then continue to infuse an additional 10 mL of 0.9% Sodium Chloride Injection through the infusion system to infuse the remaining fraction of LAMZEDE in the line to the patient.

3 DOSAGE FORMS AND STRENGTHS

For injection: 10 mg of velmanase alfa-tycv as a white to off-white lyophilized powder with a cake-like appearance in a single-dose vial for reconstitution.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Hypersensitivity Reactions Including Anaphylaxis

Hypersensitivity reactions including anaphylaxis have been reported in LAMZEDE-treated patients. In clinical trials, 19 (50%) LAMZEDE-treated patients (5 adult patients and 14 pediatric patients) experienced hypersensitivity reactions, including 2 (5%) patients (1 adult patient and 1 pediatric patient) who experienced anaphylaxis and an additional 3 (8%) pediatric patients who experienced severe hypersensitivity reactions that required medical treatment [see *Clinical Studies (14)*].

In the 5 patients who experienced anaphylaxis or severe hypersensitivity requiring medical treatment, 4 (80%) were anti-drug antibody (ADA) positive [see *Clinical Pharmacology (12.6)*].

Anaphylaxis and severe hypersensitivity signs and symptoms included cyanosis, hypotension, emesis, urticaria, erythema, facial swelling, pyrexia, and tremor.

Prior to LAMZEDE administration, consider pretreating with antihistamines, antipyretics, and/or corticosteroids. Appropriate medical support measures, including cardiopulmonary resuscitation equipment, should be readily available during LAMZEDE administration.

- If a *severe* hypersensitivity reaction (e.g., anaphylaxis) occurs, discontinue LAMZEDE immediately and initiate appropriate medical treatment. Consider the risks and benefits of re-administering LAMZEDE following severe hypersensitivity reactions (including anaphylaxis). Patients may be rechallenged using slower infusion rates. In patients with severe hypersensitivity reaction, desensitization measures to LAMZEDE may be considered. If the decision is made to readminister LAMZEDE, ensure the patient tolerates the infusion. If the patient tolerates the infusion, the rate may be increased to reach the recommended dosage.
- If a *mild* or *moderate* hypersensitivity reaction occurs, consider slowing the infusion rate or temporarily withholding the dose [see *Dosage and Administration* (2.3)].

5.2 Infusion-Associated Reactions

Infusion-associated reactions (IARs) have been reported in LAMZEDE-treated patients. In clinical trials 19 (50%) LAMZEDE-treated patients (3 adult and 16 pediatric patients) experienced IARs. Of these 19 patients, 5 (13 % of all patients) required pretreatment in the clinical trials. One LAMZEDE-treated patient in clinical trials discontinued due to recurrent IARs.

The most frequent symptoms of IARs that occurred in >10% of the population were pyrexia, chills, erythema, vomiting, cough, urticaria, rash and conjunctivitis. Similar symptoms were observed in adult and pediatric populations.

Prior to LAMZEDE administration, consider pretreating with antihistamines, antipyretics, and/or corticosteroids to reduce the risk of infusion-associated reactions (IARs). However, IARs may still occur in patients after receiving pretreatment.

- If a *severe* IAR occurs, discontinue LAMZEDE immediately and initiate appropriate medical treatment. Consider the risks and benefits of readministering LAMZEDE following a severe IAR. Patients may be rechallenged using slower infusion rates. Once a patient tolerates the infusion, the infusion rate may be increased to reach the recommended infusion rate.
- If a *mild* or *moderate* IAR occurs, consider slowing the infusion rate or temporarily withholding the dose [see *Dosage and Administration* (2.3)].

5.3 Embryo-Fetal Toxicity

Based on findings from animal reproduction studies, LAMZEDE may cause embryo-fetal harm when administered to a pregnant female. Administration of velmanase alfa-tycv to pregnant rats during the period of organogenesis caused skeletal and visceral malformations. In rats and rabbits, skeletal and visceral malformations were observed at exposures that were approximately 7- and 2.5-fold, respectively, those observed in patients treated at the recommended dose of 1 mg/kg.

The decision to continue or discontinue LAMZEDE treatment during pregnancy should consider the female's need for LAMZEDE, the potential drug-related risks to the fetus, and the potential adverse outcomes from untreated maternal disease.

For females of reproductive potential, verify that the patient is not pregnant prior to initiating treatment with LAMZEDE. Advise females of reproductive potential to use effective contraception during treatment with LAMZEDE and for 14 days after the last dose if LAMZEDE is discontinued [see *Use in Specific Populations (8.1, 8.3)*].

6 ADVERSE REACTIONS

The following clinically significant adverse reactions are described elsewhere in the labeling:

- Hypersensitivity Reactions Including Anaphylaxis [see *Warnings and Precautions (5.1)*]
- Infusion-Associated Reactions (IARs) [see *Warnings and Precautions (5.2)*]

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Adverse Reactions From Trial 1

The safety of LAMZEDE was evaluated in Trial 1, which included a total of 15 LAMZEDE-treated patients (8 adult patients aged 18-35 years old and 7 pediatric patients aged 6-17 years old; 9 male, 6 female) with alpha-mannosidosis [see *Clinical Studies (14)*]. All patients received LAMZEDE 1 mg/kg weekly via intravenous infusion for 52 weeks.

A serious adverse reaction of acute renal failure was reported in 1 (7%) LAMZEDE-treated patient (see *Description of Selected Adverse Reactions*).

Table 1 lists adverse reactions that occurred in at least 2 LAMZEDE-treated patients in Trial 1.

Table 1: Adverse Reactions (≥2 patients) in Adult and Pediatric Patients with Alpha-Mannosidosis Treated with LAMZEDE in Trial 1

Adverse Reaction	LAMZEDE N=15 n (%)	Placebo N=10 n (%)
Nasopharyngitis	10 (66)	7 (70)
Pyrexia	6 (40)	5 (50)
Headache	5 (33)	3 (30)
Arthralgia	3 (20)	1 (10)
Acute tonsillitis	2 (13)	0
Urinary tract infection ¹	2 (13)	1 (10)
Eye pruritus	2 (13)	0
Gastroenteritis	2 (13)	0
Hypersensitivity	2 (13)	0
Influenza	2 (13)	0

Syncope	2 (13)	0
Toothache	2 (13)	0
Back pain	2 (13)	1 (10)
Ear infection	2 (13)	1 (10)

¹ "Urinary tract infection" is composed of similar terms.

Adverse Reactions from Trials 2 and 3

In Trial 2, 5 pediatric patients aged 3 to 5 years old (3 male, 2 female) with alpha-mannosidosis received LAMZEDE weekly for a mean exposure of 121 weeks [see *Clinical Studies (14)*].

One patient treated with LAMZEDE (20%) presented serious reactions (chills and hyperthermia on the same occasion). The adverse reactions that occurred in at least 2 of 5 patients (and are in addition to the adverse reactions already identified in Trial 1 above) included: cough, otitis media, rhinitis, conjunctivitis, fall, ligament sprain, oropharyngeal pain, swelling face, and upper respiratory tract infection.

Trial 3 is an integrated analysis that pooled the cumulative databases from LAMZEDE phase 1, 2, and 3 trials in patients with alpha-mannosidosis. A total of 33 patients (20 male, 13 female) aged 6 to 35 years old (14 adults, 19 pediatric) received LAMZEDE weekly for a mean exposure of 89 weeks in adult patients and 155 weeks in pediatric patients.

One patient was withdrawn from the trial due to repeated IARs and successfully reintroduced after 89 weeks of pause.

The adverse reactions that occurred in at least 10% of patients (and are in addition to the adverse reactions already identified in Trial 1 and 2 above) included abdominal pain upper, contusion, excoriation, post-lumbar puncture syndrome, wound, weight increased, erythema, rash, and tooth extraction.

Description of Selected Adverse Reactions

Acute Renal Failure

One patient out of 38 (3%) experienced one episode of acute renal failure. This patient paused LAMZEDE treatment for 4 weeks and acute renal failure resolved within 12 weeks of diagnosis. This patient is noted to have received the concomitant medication of ibuprofen.

Immunoglobulin A Vasculitis

One episode of immunoglobulin A vasculitis (IgAV), reported as *Henoch Schonlein Purpura*, occurred in one patient out of 38 (3%) who developed high anti-drug antibody (ADA) levels.

Seizure

One patient out of 38 (3%), with no prior history of seizures experienced more than one episode of seizures. A relationship between the occurrence of seizures in this patient and exposure to LAMZEDE cannot be excluded.

Pediatric Patients

Hypersensitivity reactions overall were reported in 36% of adult patients and 58% of pediatric patients.

Immunogenicity: Anti-Drug Antibody-Associated Adverse Reactions

Infusion-associated reactions (including anaphylaxis and severe hypersensitivity reactions) occurred in a higher incidence in LAMZEDE-treated patients who developed anti-velmanase alfa-tycv antibodies (anti-drug antibodies, ADA) compared to patients who were ADA-negative (80% versus 20%) [see *Clinical Pharmacology (12.6)*].

In Trial 1 following treatment with LAMZEDE for up to 52 weeks, 1 out of 5 ADA-positive patients developed severe hypersensitivity and this patient developed the highest ADA level among all the ADA-positive patients in the trial. In Trial 2 following treatment with LAMZEDE for up to 174 weeks, 2 out of 4 ADA-positive pediatric patients experienced IARs. In Trial 3, 3 out of 33 patients (9.1%) reported IARs; two of these patients were ADA positive (one of these two patients is described in Trial 1); one patient was ADA negative.

6.2 Postmarketing Experience

The following adverse reactions have been identified during postapproval use of velmanase alfa outside of the United States. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Cardiac disorders: aortic valve incompetence, palpitations, tachycardia

Ear and labyrinth disorders: deafness

Eye disorders: lacrimation increased

Gastrointestinal disorders: odynophagia

General disorders and administration site conditions: asthenia, fatigue

Infections and infestations: endocarditis, staphylococcal infection, bacterial disease carrier, furuncle

Metabolism and nutrition disorders: decreased appetite

Musculoskeletal and connective tissue disorders: joint swelling, joint warmth

Nervous system disorders: ataxia, nervous system disorder, somnolence

Psychiatric disorders: psychotic disorder, agitation, encopresis, nervousness

Respiratory, thoracic and mediastinal disorders: pharyngeal edema, wheezing

Skin, subcutaneous tissue disorders: angioedema

Vascular disorders: vascular fragility, hypotension

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Based on findings from animal reproduction studies, LAMZEDE may cause embryo-fetal harm when administered to a pregnant female. In animal reproduction studies, major visceral malformations were observed in rats and rabbits when velmanase alfa-tycv was administered in pregnant rats and rabbits during the period of organogenesis. These malformations were observed in rats at the highest dose level, at exposures that were approximately 7-fold the recommended dose in patients of 1 mg/kg. Malformations occurred at all dose levels in rabbits with the highest dose exposures approximately 2.5-fold the recommended patient dose of 1 mg/kg (*see Data*).

There are no available data on LAMZEDE use in pregnant females to evaluate a drug-associated risk of major birth defects, miscarriage or other adverse maternal or fetal outcomes. Advise the pregnant female of the potential risk to the fetus. The decision to continue or discontinue LAMZEDE treatment during pregnancy should consider the female's need for LAMZEDE, the potential drug-related risks to the fetus, and the potential adverse outcomes from untreated maternal disease.

The background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defects, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively.

Data

Animal Data

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. Major malformations and variations were observed at exposures that were approximately 7-fold greater than the recommended dose of 1 mg/kg. Treatment-related major malformations included cleft palate, cleft palatine skull, severely bent pelvic girdle, and duplicated sternebrae.

In an embryofetal development study in the rabbit, administration of velmanase alfa-tycv from GDs 6 through 18 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. 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 greater than the 1 mg/kg dose of velmanase alfa-tycv.

8.2 Lactation

Risk Summary

There are no data on the presence of velmanase alfa-tycv or its metabolite in either human or animal milk, the effects on the breastfed infant, or the effects on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for LAMZEDE and any potential adverse effects on the breastfed infant from velmanase alfa-tycv or from the underlying maternal condition.

8.3 Females and Males of Reproductive Potential

LAMZEDE may cause embryo-fetal harm when administered to a pregnant female [*see Use in Specific Populations (8.1)*].

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 for 14 days after the last dose if LAMZEDE is discontinued.

8.4 Pediatric Use

The safety and effectiveness of LAMZEDE for the treatment of alpha-mannosidosis have been established in pediatric patients.

Use of LAMZEDE for this indication is supported by evidence from an adequate and well-controlled clinical trial in adult and pediatric patients, and from an open label trial in 5 pediatric patients (younger than 6 years of age) [see *Clinical Studies (14)*].

LAMZEDE-treated pediatric patients reported a higher incidence of hypersensitivity reactions compared to LAMZEDE-treated adult patients [see *Warnings and Precautions (5.1)*, *Adverse Reactions (6.1)*].

8.5 Geriatric Use

Alpha-mannosidosis is largely a disease of pediatric and young adult patients. Clinical trials of LAMZEDE did not include patients 65 years of age and older.

11 DESCRIPTION

Velmanase alfa-tycv, is lysosomal alpha-mannosidase produced by recombinant DNA technology in Chinese Hamster Ovary (CHO) cells. The amino acid sequence of the monomeric protein is identical to the naturally occurring human enzyme, alpha-mannosidase. Velmanase alfa-tycv has an approximate molecular weight of 130 kDa.

LAMZEDE (velmanase alfa-tycv) for injection is a sterile, preservative-free, white to off-white lyophilized powder with a cake-like appearance for intravenous infusion after reconstitution. Each single-dose vial contains 10 mg of velmanase alfa-tycv and the inactive ingredients dibasic sodium phosphate (2.47 mg), glycine (10.1 mg), mannitol (227.5 mg) and monobasic sodium phosphate (0.088 mg). After reconstitution with 5 mL Sterile Water for Injection, USP the resultant concentration is 2 mg/mL with pH of 7.5 ± 0.5.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Alpha-mannosidosis is a lysosomal storage disease that results from reduced activity of the enzyme alpha-mannosidase, caused by gene variants in Mannosidase Alpha Class 2B Member 1. Alpha-mannosidase catalyzes the degradation of accumulated mannose-containing oligosaccharides. The

deficiency of alpha-mannosidase causes an intra-lysosomal accumulation of mannose-rich oligosaccharides in various tissues. Velmanase alfa-tycv provides an exogenous source of alpha-mannosidase. Velmanase alfa-tycv is internalized via binding to the mannose-6-phosphate receptor on the cell surface and transported into lysosomes where it is thought to exert enzyme activity.

12.2 Pharmacodynamics

Serum oligosaccharide concentrations are elevated in patients with alpha-mannosidosis. In clinical studies, serum oligosaccharide concentrations were quantified by assessment of 2-mannose oligosaccharides. LAMZEDE treatment resulted in reductions of serum oligosaccharide concentrations in patients with alpha-mannosidosis [see *Clinical Studies (14)*].

12.3 Pharmacokinetics

The pharmacokinetics of velmanase alfa-tycv were evaluated in adult patients with alpha-mannosidosis and are presented as mean (standard deviation, SD) unless otherwise specified. The steady state maximum plasma velmanase alfa-tycv concentration (C_{max}) was 7.9 (0.9) $\mu\text{g/mL}$ and area under the concentration-time curve (AUC_{0-t}) was 159.8 (24.4) $\mu\text{g}\cdot\text{h/mL}$ at the approved recommended dosage of 1 mg/kg.

Distribution

The volume of distribution of velmanase alfa-tycv was 276 (43) mL/kg in patients with alpha-mannosidosis.

Elimination

The total body clearance of velmanase alfa-tycv was 5.7 (0.9) mL/h/kg and the mean terminal half-life ($t_{1/2}$) was 33.6 hours in patients with alpha-mannosidosis.

Metabolism

Velmanase alfa-tycv is expected to be metabolized into small peptides by catabolic pathways.

Specific Population

Pediatric Patients

In pediatric patients (6 to 17 years of age) with alpha-mannosidosis, the C_{max} and AUC_{0-t} at steady state were 6.6 (1.0) $\mu\text{g/mL}$ and 109.8 (17.8) $\mu\text{g}\cdot\text{h/mL}$, respectively, at the recommended dose of 1 mg/kg velmanase alfa-tycv administered once a week.

In pediatric patients (3 to <6 years of age) with alpha-mannosidosis, the C_{max} and AUC_{0-t} at steady state were 7.0 (2.3) $\mu\text{g/mL}$ and 75.9 (39.7) $\mu\text{g}\cdot\text{h/mL}$ at the recommended dose of 1 mg/kg velmanase alfa-tycv administered once a week.

12.6 Immunogenicity

The observed incidence of anti-drug antibodies is highly dependent on the sensitivity and specificity of the assay. Differences in assay methods preclude meaningful comparisons of the incidence of anti-drug antibodies in the studies described below with the incidence of anti-drug antibodies in other studies, including those of velmanase alfa-tycv or of other velmanase alfa products.

In Trial 2 following 104 weeks treatment with LAMZEDE [see *Clinical Studies (14)*], 4 out of 5 pediatric patients (80%) developed anti-velmanase alfa-tycv antibodies (anti-drug antibodies, ADA). Three out of 4 ADA-positive patients (75%) developed neutralizing antibodies that inhibit velmanase alfa-tycv enzyme activity.

In Trial 3 [see *Adverse Reactions (6.1)*], 33 patients (10 adult, 23 pediatric) received LAMZEDE for up to 209 weeks. Among the 33 patients, 5 patients (1 adult and 4 pediatric) (15%) had ADA before treatment with LAMZEDE and for 1 patient the ADA level increased after treatment with LAMZEDE. Four other patients (1 adult and 3 pediatric) (12%) developed ADA after treatment with LAMZEDE. ADA positive samples were tested for neutralizing antibodies that inhibit velmanase alfa-tycv enzyme activity (NAb) during treatment in Trial 1. Four patients with ADA positive results also had positive NAb results during treatment with LAMZEDE. However, NAb positive results of similar magnitude were detected in 4 patients during treatment with placebo.

Neutralizing antibodies that inhibit cellular uptake of velmanase alfa-tycv have not been characterized.

Development of ADA was associated with lower plasma concentrations of velmanase alfa-tycv. Two pediatric patients who developed ADA had reduced pharmacodynamic responses in reduction of serum oligosaccharides at the time when high ADA levels were observed.

Infusion associated reactions (IARs) occurred in 2 patients in Trial 2 and 2 patients in Trial 3 who developed ADA compared to 2 patients in Trial 2 and 1 patient in Trial 3 who were ADA-negative [see *Warnings and Precautions (5.1) and Adverse Reactions (6.1)*].

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

Animal studies to evaluate the carcinogenic potential of velmanase alfa-tycv have not been conducted. In the pre- and postnatal development study in the rat, one female at the 30 mg/kg dose level developed a malignant histiocytic sarcoma of the ovary. A relationship to treatment for this tumor cannot be excluded. The AUC associated with tumor formation in this study was approximately 10-fold greater than those observed in patients treated at the 1 mg/kg dose level.

Mutagenesis

Studies to evaluate the mutagenic potential of velmanase alfa-tycv have not been conducted.

Impairment of Fertility

Intravenous administration of velmanase alfa-tycv twice-weekly for two weeks prior to pairing, through day 6 of gestation, showed no adverse effects on fertility parameters in rats. Based on data from the embryofetal study, exposures in the fertility study were approximately 10-fold greater than those observed in patients treated at the 1 mg/kg dose level.

14 CLINICAL STUDIES

Trial 1

Trial 1 (NCT01681953) was a phase 3 multicenter, randomized, double-blinded, placebo-controlled, parallel group trial in adult and pediatric patients with alpha-mannosidosis. The trial evaluated the efficacy of LAMZEDE over 52 weeks at a dose of 1 mg/kg given weekly as an intravenous infusion. A total of 25 patients were enrolled (14 males, 11 females), including 13 adult patients (age range: ≥ 18 to 35 years; mean: 25 years) and 12 pediatric patients (age range: ≥ 6 to < 18 years; mean: 11 years); all patients were White. Ethnicity data were not collected. All patients had alpha-mannosidase activity below 11% of normal and in the range of 8 to 29 $\mu\text{mol/h/mg}$ at baseline. All patients but one were naïve to LAMZEDE. Fifteen patients (8 adult and 7 pediatric) received LAMZEDE and 10 patients (5 adult and 5 pediatric) received placebo. All patients completed the trial.

The efficacy results for the clinical endpoints assessed at 12 months, 3-minute stair climbing test (3MSCT), 6-minute walking test (6MWT) and forced vital capacity (FVC) (% predicted), favored the LAMZEDE group and were supported by a reduction in serum oligosaccharide concentration. The results of 3MSCT, 6MWT, FVC (% predicted), and serum oligosaccharide concentrations are presented in Table 2.

Table 2: Change from Baseline in Clinical Endpoints and Serum Oligosaccharide in LAMZEDE- or Placebo-Treated Adult and Pediatric Patients with Alpha-Mannosidosis Over 12 Months

	LAMZEDE (n=15)	Placebo (n=10)	Treatment difference (95% CI)
3MSCT (steps/min)			
Baseline mean (SD)	52.9 (11.2)	55.5 (16.0)	--
Mean absolute change from baseline (SD)	0.6 (8.6)	-2.4 (5.5)	2.6 (-3.8, 9.1)
Mean relative change (%) from baseline (SD)	0.5 (16.1)	-3.6 (13.1)	3.4 (-9.5, 16.3)
FVC (% predicted)			
Baseline mean (SD)	81.7 (20.7)	90.4 (10.4)	--
Mean absolute change from baseline (SD)	8.2 (9.9)	2.0 (12.6)	5.5 (-5.0, 16.1)
Mean relative change (%) from baseline (SD)	11.4 (13.1)	1.9 (15.4)	7.4 (-5.7, 20.5)
6MWT (meters)			
Baseline mean (SD)	459.6 (72.3)	465.7 (140.5)	--
Mean absolute change from baseline (SD)	4.4 (46.1)	-4.6 (40.8)	7.4 (-30.7, 45.5)
Mean relative change (%) from baseline (SD)	1.2 (9.8)	-0.8 (10.8)	1.6 (-7.2, 10.4)
Serum oligosaccharides ($\mu\text{mol/L}$)			
Baseline mean (SD)	6.8 (1.2)	6.6 (1.9)	--
Mean absolute change from baseline (SD)	-5.1 (1.2)	-1.6 (1.7)	-3.5 (-4.4, -2.6)
Mean relative change (%) from baseline (SD)	-75.8 (11.2)	-20.3 (24.0)	-55.6 (-69.3, -41.9)

Mean = sample mean and SD = standard deviation. For each endpoint, the treatment difference in the adjusted means (95% CI) were calculated using an analysis of covariance that included baseline age, baseline value of the endpoint as covariates. Missing data of FVC (% predicted) were not imputed.

Trial 2

LAMZEDE was investigated in a single arm trial in pediatric alpha-mannosidosis patients less than 6 years of age (NCT02998879). All patients had alpha-mannosidase activity below 10% of normal at baseline. The trial enrolled five patients ranging from 3.7 to 5.9 years of age, with a mean age of 4.5 years. Four patients were White, race was not recorded for 1 patient; and 3 were male and 2 were female. Patients received LAMZEDE 1 mg/kg as intravenous infusion once weekly (4 patients for 24 months, 1 patient for 40 months).

The mean (SD) absolute and percentage changes from Baseline for serum oligosaccharides at 24 months were -7.7 (4.27) $\mu\text{mol/L}$ and -65.8% (23.1%) respectively.

16 HOW SUPPLIED/STORAGE AND HANDLING

How Supplied

LAMZEDE (velmanase alfa-tycv) for injection is supplied as a white to off-white lyophilized powder with a cake-like appearance in a single-dose vial. Each vial contains 10 mg of velmanase alfa-tycv. LAMZEDE is available as:

- One 10 mg single-dose vial in a carton: NDC 10122-180-02
- Five 10 mg single-dose vials in a carton: NDC 10122-180-05
- Ten 10 mg single-dose vials in a carton: NDC 10122-180-10

Storage and Handling

Store refrigerated at 2°C to 8°C (36°F to 46°F) in the original carton to protect from light. Do not freeze.

17 PATIENT COUNSELING INFORMATION

Hypersensitivity Reactions Including Anaphylaxis and Infusion-Associated Reactions (IARs)

Advise the patient and caregiver that reactions related to the infusion may occur during and after LAMZEDE treatment, including anaphylactic reactions, other serious or severe hypersensitivity reactions, and IARs. Inform the patient and caregiver of the signs and symptoms of hypersensitivity reactions and IARs and to seek medical care should signs and symptoms occur [see *Warnings and Precautions* (5.1, 5.2)].

Embryo-Fetal Toxicity

LAMZEDE may cause embryo-fetal harm. Advise the pregnant female of the potential risk to the fetus. Advise a female patient and caregiver to inform their healthcare provider of a known or suspected pregnancy [see *Warnings and Precautions* (5.3) and *Use in Specific Populations* (8.1)].

Advise a female of reproductive potential to use effective contraception during treatment and for 14 days after the last dose if LAMZEDE is discontinued [*see Use in Specific Populations (8.1, 8.3)*].

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