NEW DRUG APPROVAL

Brand Name	Lamzede®
Generic Name	velmanase alfa-tycv
Drug Manufacturer	Chiesi Farmaceutici S.p.A

Indications for Use

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.

New Drug Approval

FDA approval date: February 16, 2023

Review designation: N/A; Orphan

Type of review: Biologic License Application (BLA): 761278

Dispensing restriction: N/A

Therapeutic Class

Enzyme

Place in Therapy

DISEASE DESCRIPTION & EPIDEMIOLOGY

Alpha-mannosidosis (OMIM 248500) is a rare autosomal recessive lysosomal storage disorder (LSD) caused by the deficient activity of the enzyme alpha-mannosidase owing to mutations in the *MAN2B1* gene (609458) located on chromosome 19 (19p13.13). This deficiency affects intra-lysosomal degradation pathways and leads to the progressive accumulation of undigested mannose-oligosaccharides and subsequently, impaired cell function.

Children with alpha-mannosidosis appear normal at birth, with manifestations developing at an early age and the condition progressively worsening. The disorder encompasses a broad spectrum of clinical manifestations including mental and cognitive impairment, sensorineural hearing loss, facial dysmorphism, skeletal abnormalities, ataxia, motor function disturbances, immunodeficiency, recurrent infections and in older patients, behavioural problems and psychotic episodes. Clinical phenotypes are not clearly distinguishable due to the broad heterogeneity of the disease and patients present with a continuum of clinical manifestations of varying severity which makes disease progression difficult to predict. Although there is no obvious correlation between genotype and clinical phenotypes, recent studies have indicated a relationship between *MAN2B1* genotypes and cognitive, pulmonary and motor function. Even for patients with mild and moderate forms, prognosis is poor, with disease progression exerting a high impact not only on patients, but also on their families and caregivers, sometimes for several decades.

Alpha-mannosidosis is present worldwide and although its exact prevalence is not known, it is estimated at 1:500,000 live births. Currently, 162 mutations of the *MAN2B1* gene are reported in The Human Gene Mutation Database.

Efficacy

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 alphamannosidase activity below 11% of normal and in the range of 8 to 29 µmol/h/mg at baseline. All patients but one was 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 oligosaccaride concentrations are presented in Table 1.

Table 1: 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 (µmol/L)			
Baseline mean (SD)	6.8 (1.2)	6.6 (1.9)	--

Table 1: 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)
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) µmol/L and -65.8% (23.1%) respectively.

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

Safety

ADVERSE EVENTS

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 males, 6 female) with alpha-mannosidosis. 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.

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

Table 2: 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

Table 2: 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 (%)**
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. 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-mannosodosis. 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%).

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.

WARNINGS & PRECAUTIONS

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.

In the 5 patients who experienced anaphylaxis or severe hypersensitivity requiring medical treatment, 4 (80%) were anti-drug antibody (ADA) positive.

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

Prior to Lamzede® administration, consider pre-treating 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 readministering 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.

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 pre-treatment 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 pre-treating with antihistamines, antipyretics, and/or corticosteroids to reduce the risk of infusion-associated reactions (IARs). However, IARs may still occur in patients after receiving pre-treatment.

- 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.

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.

CONTRAINDICATIONS

None reported.

Clinical Pharmacology

MECHANISMS 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. Alphamannosidase 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 alphamannosidase. 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.

Dose & Administration

ADULTS

- For females of reproductive potential, verify that the patient is not pregnant prior to initiating treatment.
- Consider pre-treating with antihistamines, antipyretics, and/or corticosteroids prior to Lamzede® administration.
- Recommended Lamzede® dosage is 1 mg/kg (actual body weight) administered once every week as an intravenous infusion.

PEDIATRICS

- Consider pre-treating with antihistamines, antipyretics, and/or corticosteroids prior to Lamzede® administration. Lamzede® -treated pediatric patients reported a higher incidence of hypersensitivity reactions compared to Lamzede® -treated adult patients.
- Refer to adult dosing.

GERIATRICS

Refer to adult dosing.

RENAL IMPAIRMENT

None

HEPATIC IMPAIRMENT

None

Product Availability

DOSAGE FORM(S) & STRENGTH(S)

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