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Enzyme-Replacement Therapy for Lysosomal Storage Disorders

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Related Policies (if applicable)
None

Disclaimer

Medical policies are a set of written guidelines that support current standards of practice. They are based on current peer-reviewed scientific literature. A requested therapy must be proven effective for the relevant diagnosis or procedure. For drug therapy, the proposed dose, frequency and duration of therapy must be consistent with recommendations in at least one authoritative source. This medical policy is supported by FDA-approved labeling and/or nationally recognized authoritative references to major drug compendia, peer reviewed scientific literature and acceptable standards of medical practice. These references include, but are not limited to: MCG care guidelines, DrugDex (IIa level of evidence or higher), NCCN Guidelines (IIb level of evidence or higher), NCCN Compendia (IIb level of evidence or higher), professional society guidelines, and CMS coverage policy.

Carefully check state regulations and/or the member contract.

Each benefit plan, summary plan description or contract defines which services are covered, which services are excluded, and which services are subject to dollar caps or other limitations, conditions or exclusions. Members and their providers have the responsibility for consulting the member's benefit plan, summary plan description or contract to determine if there are any exclusions or other benefit limitations applicable to this service or supply. **If there is a discrepancy between a Medical Policy and a member's benefit plan, summary plan description or contract, the benefit plan, summary plan description or contract will govern.**

Legislative Mandates

EXCEPTION: For Illinois only: Illinois Public Act 103-0458 [Insurance Code 215 ILCS 5/356z.61] (HB3809 Impaired Children) states all group or individual fully insured PPO, HMO, POS plans amended, delivered, issued, or renewed on or after January 1, 2025 shall provide coverage for therapy, diagnostic testing, and equipment necessary to increase quality of life for children who have been clinically or genetically diagnosed with any disease, syndrome, or disorder that includes low tone neuromuscular impairment, neurological impairment, or cognitive impairment.

EXCEPTION: For HCSC members residing in the state of Ohio, § 3923.60 requires any group or individual policy (Small, Mid-Market, Large Groups, Municipalities/Counties/Schools, State Employees, Fully-Insured, PPO, HMO, POS, EPO) that covers prescription drugs to provide for the coverage of any drug approved by the U. S. Food and Drug Administration (FDA) when it is prescribed for a use recognized as safe and effective for the treatment of a given indication in one or more of the standard medical reference compendia adopted by the United States Department of Health and Human Services or in medical literature even if the FDA has not approved the drug for that indication. Medical literature support is only satisfied when safety and efficacy has been confirmed in two articles from major peer-reviewed professional medical journals that present data supporting the proposed off-label use or uses as generally safe and effective. Examples of accepted journals include, but are not limited to, Journal of American Medical Association (JAMA), New England Journal of Medicine (NEJM), and Lancet. Accepted study designs may include, but are not limited to, randomized, double blind, placebo controlled clinical trials. Evidence limited to case studies or case series is not sufficient to meet the standard of this criterion. Coverage is never required where the FDA has recognized a use to be contraindicated and coverage is not required for non-formulary drugs.

Coverage

Continuation Therapy:
Continuation of Cerezyme (imiglucerase) and Elelyso (taliglucerase alfa) therapy for Gaucher Disease **is considered medically necessary** for all members (including new members):

- Who are currently receiving the requested medication for an indication listed below AND
- Who are experiencing benefit from therapy as evidenced by disease stability or disease improvement; AND
- When dosing is in accordance with an authoritative source.

Initial Therapy
Vpriv® (velaglucerase alfa) is the preferred product for Gaucher Disease Type 1 and coverage will be provided contingent on the coverage criteria in this Medical Policy.

Coverage for non-preferred agents, including but not limited to, Cerezyme® (imiglucerase) and Elelyso® (taliglucerase alfa) will be provided contingent on the criteria in this section and the coverage criteria in the Medical Policy. For individuals initiating therapy with an enzyme agent for Gaucher Disease, the following criteria would apply prior to Cerezyme (imiglucerase) and Elelyso (taliglucerase alfa) use:

- Individual has a history of failure to meet clinical goals (e.g., improvement or stabilization of hemoglobin, platelet counts, liver or spleen volume, or bone disease measures), adverse reaction, intolerance, or has a clinical contraindication to (the preferred agent(s)).

AND

- Physician attests that in their clinical opinion, the history of failure to meet the clinical goals, adverse reaction, intolerance, or clinical contraindication, would not be expected to occur with (non-preferred agents(s)).

OR

- The individual is currently receiving the medication covered by their current or previous health plan and is stable on the medication, with the physician attesting a change would be harmful to the individual or potentially cause reduced clinical efficacy; **OR**
- Cerezyme is requested for a member that is > 2 years old and < 4 years old.

State specific Drug Criteria may apply.

Enzyme-replacement therapy when utilized for the treatment of lysosomal storage disorders (LSD) **may be considered medically necessary** for the specific indications noted under each of the following enzyme-replacements therapies:

Product	**Criteria For Use**
Agalsidase beta (Fabrazyme®)	Agalsidase beta (Fabrazyme) **may be considered medically necessary** when: • The individual is 2 years of age or older; AND • The individual has a confirmed diagnosis of Fabry disease. Agalsidase beta (Fabrazyme) **is considered experimental, investigational and/or unproven** for the treatment of all other indications.
Avalglucosidase alfa-NGPT (Nexviazyme®)	Avalglucosidase alfa-NGPT (Nexviazyme®) **may be considered medically necessary** for the treatment of individuals 1 year of age and older with a diagnosis of late-onset Pompe disease (lysosomal acid alpha-glucosidase [GAA] deficiency). Avalglucosidase alfa-NGPT (Nexviazyme®) **is considered experimental, investigational and/or unproven** for all other indications.
Idursulfase (Elaprase®)	Idursulfase (Elaprase®) **may be considered medically necessary** when: • The individual is 5 years of age or greater; AND • The individual has a diagnosis of Hunter's syndrome (mucopolysaccharidosis II [MPS II]). Idursulfase (Elaprase®) **is considered experimental, investigational and/or unproven** for the treatment of all other indications.
Alglucosidase alfa (Lumizyme®; formerly known as Myozyme)	Alglucosidase alfa (Lumizyme®, formerly known as Myozyme) **may be considered medically necessary** for individuals with Pompe disease (GAA deficiency). Alglucosidase alfa (Lumizyme®; formerly known as Myozyme) **is considered experimental, investigational and/or unproven** for the treatment of all other indications.
Asfotase alfa (Strensiq®)	Asfotase alfa (Strensiq®) **may be considered medically necessary** for the treatment of individuals with perinatal/infantile-and juvenile-onset hypophosphatasia (HPP).

	Asfotase alfa (Strensiq®) **is considered experimental, investigational and/or unproven** for all other indications.
Cipaglucosidase alfa-atga (Pombiliti™)	Cipaglucosidase alfa-atga (Pombiliti™) **may be considered medically necessary** for treatment of late-onset Pompe disease when all of the following criteria are met: • Individual is 18 years of age or older; and • Individual weighs greater than or equal to 40 kg; and • Will be taken in combination with Opfolda; and • Individual is not improving on current enzyme replacement therapy (ERT). Cipaglucosidase alfa-atga (Pombiliti™) **is considered experimental, investigational and/or unproven** for all other indications.
Elosulfase alfa (Vimizim®)	Elosulfase alfa (Vimizim®) **may be considered medically necessary** for individuals 5 years of age or older with a documented clinical diagnosis of mucopolysaccharidosis type IVA (MPS IVA; Morquio A syndrome). Elosulfase alfa (Vimizim®) **is considered experimental, investigational and/or unproven** for all other indications.
Galsulfase (Naglazyme®)	Galsulfase (Naglazyme®) **may be considered medically necessary** for individuals with Mucopolysaccharidosis VI (MPS VI; Maroteaux-Lamy syndrome). Galsulfase (Naglazyme®) **is considered experimental, investigational and/or unproven** for all other indications.
Imiglucerase (Cerezyme®) **Non-preferred for Type 1 Gaucher disease**	Imiglucerase (Cerezyme®) **may be considered medically necessary** for individuals 2 years of age or greater with a confirmed diagnosis of Type 1 Gaucher disease that results in one or more of the following conditions: • Anemia; or • Bone disease; or • Hepatomegaly or splenomegaly; or • Thrombocytopenia. Imiglucerase (Cerezyme®) **is considered experimental, investigational and/or unproven** for all other indications.
Laronidase (Aldurazyme®)	Laronidase (Aldurazyme®) **may be considered medically** necessary for individuals 6 months of age or greater with one of the following: • Hurler and Hurler-Scheie forms of Mucopolysaccharidosis I (MPS I); or • Scheie form who have moderate to severe symptoms. Laronidase (Aldurazyme®) **is considered experimental, investigational and/or unproven** for all other indications, including but not limited to treatment of individuals with the Scheie form of MPS I who have mild symptoms.

Olipudase alfa-rpcp (Xenpozyme®)	Olipudase alfa-rpcp (Xenpozyme®) **may be medically necessary** for the treatment of non–central nervous system manifestations of acid sphingomyelinase deficiency (ASMD). Olipudase alfa-rpcp (Xenpozyme®) **is considered experimental, investigational and/or unproven** for all other indications.
Pegunigalsidase alfa-iwxj (Elfabrio®)	Pegunigalsidase alfa-iwxj (Elfabrio®) **may be considered medically necessary** in adults with a confirmed diagnosis of Fabry disease. Pegunigalsidase alfa-iwxj (Elfabrio®) **is considered experimental, investigational and/or unproven** for all other indications.
Sebelipase alfa (Kanuma®)	Sebelipase alfa (Kanuma®) **may be considered medically necessary** when: • The individual is one month of age or greater; AND • The individual has a diagnosis of lysosomal acid lipase (LAL) deficiency (i.e., Wolman's Disease). Sebelipase alfa (Kanuma®) **is considered experimental, investigational and/or unproven** for all other indications.
Taliglucerase alfa (Elelyso®) **Non-preferred for Type 1 Gaucher disease**	Taliglucerase alfa (Elelyso®) **may be considered medically necessary** for individuals 4 years of age or older with a confirmed diagnosis of Type 1 Gaucher disease. Taliglucerase alfa (Elelyso®) **is considered experimental, investigational and/or unproven** for all other indications.
Velaglucerase alpha (VPRIV®) **Preferred for Type 1 Gaucher disease**	Velaglucerase alpha (VPRIV®) **may be considered medically necessary** for long-term ERT for individuals 4 years of age or greater with type 1 Gaucher disease. Velaglucerase alpha (VPRIV®) **is considered experimental, investigational and/or unproven** for all other indications.
Vestronidase alfa-vjbk (Mepsevii®)	Vestronidase alfa-vjbk (Mepsevii®) **may be considered medically necessary** in individuals 5 months of age or greater with a diagnosis of Mucopolysaccharidosis VII (MPS VII, Sly syndrome). Vestronidase alfa-vjbk (Mepsevii®) **is considered experimental, investigational and/or unproven** for all other indications.

Policy Guidelines

None.

Description

Lysosomal storage disorders (LSD) are a group of inherited metabolic diseases that are characterized by the accumulation of waste products in the body's cells due to an enzyme deficiency. There are more than 70 lysosomal disorders and additional disorders continue to be identified. These individual disorders are rare inborn errors of metabolism, which results in the absence or deficiency of an enzyme which causes cellular deficiency. LSDs affect different parts of the body, including but not limited to the skeleton, brain, skin, heart, and central nervous system. As a group, lysosomal storage diseases are believed to have an estimated frequency of about one in every 5,000 live births. Although the individual diseases are rare, the group together affects many people globally. (1, 2)

There is no cure for lysosomal storage disorders, however, enzyme-replacement therapy can greatly improve the quality of life in select patients. The decision to start enzyme-replacement therapy for lysosomal disorders is based on the patient's symptoms or deterioration of those over time in each affected patient. Early initiation of treatment for mucopolysaccharidosis (MPS) type 1, MPS II and MPS VI can also result in clinical benefit for patients with these conditions. Although, enzyme-replacement therapy is not effective for neurological symptoms, it may bring significant improvement in the quality of life of patients with severe clinical forms of MPS I, MPS II and neuronopathic Gaucher disease. (1, 2)

A comprehensive list of lysosomal disorders can be located at the National Organization of Rare Disorders website (https://www.rarediseases.org) as the descriptions below only addresses conditions/diseases that specifically apply within the context of this policy.

Acid Sphingomyelinase Deficiency (ASMD)
Acid sphingomyelinase deficiency (ASMD), also known as Neiman-Pick disease (NPD), is a rare progressive genetic disease resulting from a deficiency of the enzyme acid sphingomyelinase. This enzyme is required to break down or metabolize the fatty lipid sphingomyelin. At the severe end of the spectrum is a fatal neurodegenerative disorder that presents in infancy (Niemann-Pick disease type A). At the mild end of the spectrum, affected individuals have no or only minimal neurological symptoms and survival into adulthood is common (Niemann-Pick disease type B). Intermediate forms of the disorder exist as well. ASMD is caused by mutations in the SMPD1 gene and is inherited in an autosomal recessive manner. Generally, Type A causes severe neurodegenerative disease during infancy, while type B is generally not considered to be a neurologic disease. Since there are some cases that fall in between these two extremes, such broad designations can be misleading, therefore, some examiners use acid sphingomyelinase disease type B to refer to all mild and intermediate forms of the disease, which can include those that have neurological findings. (3)

ASMD affects males and females equally. It is estimated that 1 in 250,000 individuals in the general population are affected with ASMD. The severe, infantile form (Niemann-Pick type A) can affect different ethnic groups but occurs with greater frequency in individuals of Ashkenazi Jewish descent. Later-onset forms (Niemann-Pick type B) can affect all ethnic groups. (3)

Fabry Disease

Fabry disease is a rare, inherited X-linked lysosomal disorder resulting from the absent or deficient activity of the lysosomal enzyme, α-galactosidase A (α-Gal A) causing excessive deposits of neutral glycosphingolipids (fat) in the vascular endothelium of several organs and in epithelial and smooth muscle cells. Progressive endothelial accumulation of glycosphingolipids accounts for the associated clinical abnormalities of skin, eye, kidney, heart, brain, and peripheral nervous system. (4, 5)

Fabry disease is subdivided into 2 phenotypes (4):

- Type 1 "classic" phenotype has little or no functional α-galactosidase A (α-Gal A) enzymatic activity (<3% of normal mean activity) and marked accumulation of GL-3/Gb3 and related glycolipids in capillaries and small blood vessels. This accumulation results in acroparesthesias (excruciating pain in the hands and feet with exercise, fevers, stress etc.), anhidrosis/hypohidrosis (absent or markedly decreased sweating), angiokeratomas (clusters of red to blue rash-like discolorations on the skin), corneal dystrophy (star-burst pattern of the cornea that does not affect vision), and gastrointestinal symptoms (e.g., abdominal pain, cramping, frequent bowel movements) in childhood and adolescents. With increasing age, symptoms progress to cardiac disorders (arrhythmias, left ventricular hypertrophy, hypertrophic cardiomyopathy), renal disorders (progressive proteinuria, renal insufficiency, and renal failure) and cardiovascular conditions (cerebrovascular disease including transient ischemic attacks and strokes). Additional symptoms may include chronic fatigue, dizziness, headache, generalized weakness, nausea, and/or vomiting, delayed puberty, altered hair growth, malformation of the joints of the fingers (rare), and lymphedema.
- Type 2 "later-onset" phenotype have residual α-Gal A activity, lack GL-3/Gb3 accumulation in capillaries and small blood vessels and do not exhibit early symptoms like type 1. Individuals typically experience a normal childhood and present with renal and/or cardiac disease within the third to seventh decade of life.

The diagnosis and treatment of Fabry disease can be very challenging. Signs and symptoms may be nonspecific and isolated in different organs resulting in a difficult and often missed diagnosis. The diagnosis of Fabry disease has considerable implications regarding treatment, management, and counseling. Specifically, physicians may be observant of the involvement of other organs in addition to the central nervous system (CNS), thus making early intervention possible. Treatment involves a multidisciplinary approach and should be initiated to minimize irreversible end-organ damage. (4, 5)

Gaucher Disease Types I, II, and III

Gaucher disease is the most common type of lysosomal storage disorders and occurs when both parents are carriers of the disease. (1) Gaucher disease, also known as glucocerebrosidase deficiency, is caused by low levels of glucocerebrosidase an enzyme that breaks down a fatty chemical in the body called glucocerebroside. Gaucher cells are normal scavenger cells called macrophages that become full of unprocessed glucocerebroside which accumulates in areas such as the bone marrow, lungs, spleen, liver and sometimes the brain. Even though the disease consists of a phenotype with varying degrees of severity, it has been sub-divided in three subtypes according to the presence or absence of neurological involvement. Depending

on the type, Gaucher disease symptoms can include fatigue, anemia, bruising and bleeding, severe bone pain, fractures and enlarged spleen/liver. (1, 6)

There are 3 distinct types of Gaucher disease based upon the absence (type I) or presence and extent of (types II and III) neurological complications. Most affected individuals have type I, and they may experience easy bruising, chronic fatigue, and an abnormally enlarged liver and/or spleen (hepatosplenomegaly). Brain development is normal in Type 1 disease. Gaucher disease type II is occurs in newborns and infants and is characterized by severe neurological complications that may include involuntary muscle spasms, difficulty swallowing and the loss of previously acquired motor skills. Gaucher disease type III appears during the first decade of life. Neurological complications may include mental deterioration, an inability to coordinate voluntary movements, and muscle spasms of the arms, legs, or entire body. (1, 6)

Hypophosphatasia (Perinatal/Infantile-And Juvenile-Onset)
Hypophosphatasia (HPP), also known as Rathbun disease, is a rare genetic disorder with highly variable clinical severity caused by loss of function mutations in the gene encoding tissue nonspecific alkaline phosphatase (TNSALP). HPP affects males and females equally and is characterized by impaired mineralization (calcification) of bones and teeth making them prone to deformity and fractures. Depending on the specific form, HPP can be inherited in an autosomal recessive (among brothers and sisters) or autosomal dominant (multiple generations) manner. (7)

HPP is classified into categories depending on the age at diagnosis. The severity is based on how much alkaline phosphatase activity resides in the body, with less enzyme activity causing more severe disease. Categories of HPP include (7):

- Perinatal HPP presents with clinical features noted prenatally (per ultrasound) or at birth. Typically, clinical exam reveals skeletal abnormalities including chest wall deformities, as well as short or bowed long bones. The skeleton is hypomineralized, which can be identified by X-ray. This form of HPP is almost universally fatal shortly after birth due to respiratory failure secondary to chest deformities.
- Prenatal benign HPP is less severe than perinatal HPP. Clinical features include bowed limbs and skeletal deformities identified via ultrasound. In this form, skeletal malformations gradually improve post birth, and the signs and symptoms vary from infantile HPP symptoms to odontohypophosphatasia (characterized by isolated dental symptoms in the absence of skeletal abnormalities).
- Infantile HPP may not exhibit noticeable abnormalities at birth although characteristics usually become apparent by 6 months of age. Characteristic changes of rickets may be noted on X-ray and fractures are often present. Infants fail to grow and gain weight appropriately, (failure to thrive) and some will experience vitamin B-6 responsive seizures. Hypercalcemia, craniosynostosis (early fusion of the bones of the skull), intracranial hypertension, episodic fever, painful/tender bones, hypotonia, headaches, bulging of the eyes (proptosis), nephrocalcinosis, chest and rib deformities resulting in higher risk for pneumonia have also been noted. Mortality in the infantile form of HPP is substantial.

- Childhood HPP (severe or mild) is typically apparent by 2 to 3 years of age. Children often exhibit a delay in gross motor milestones (i.e., delay in walking, waddling gait) due to bone and joint pain and/or fractures, skeletal abnormalities, premature loss of deciduous teeth. Children also may develop craniosynostosis with intracranial hypertension. Symptoms may improve in young adulthood although they may reoccur in middle age to late adulthood.
- Adult HPP is characterized by a wide variety of symptoms including osteomalacia, stress fractures, history of childhood rickets, history of stress fractures, bone pain, severe arthritis, joint inflammation (calcific periarthritis), loss of adult teeth. Many adults with HPP will report having had symptoms during childhood, which may include nonspecific musculoskeletal type complaints.
    - Odontohypophosphatasia, the least severe form of HPP and is diagnosed when dental abnormalities are present, but no other skeletal disease or bone issues are identified.
    - Pseudohypophosphatasia is an extremely rare form of HPP in which the individual has a normal alkaline phosphatase level versus a low alkaline phosphatase level.

Lysosomal Acid Lipase (LAL) Deficiency

Lysosomal acid lipase (LAL) deficiency is a metabolic lipid storage disorder characterized by a genetic defect resulting in a marked decrease or loss in activity of the LAL enzyme. The two rare conditions that may occur due to this enzyme deficiency include:

- Wolmans disease: This congenital disease typically occurs within the first few weeks of life as a result of a mutation in the *LIPA* gene which provides instructions to make LAL. Characteristics of this autosomal recessive condition include impaired lipid metabolism causing lipids to accumulate in body organs and calcium deposits in the adrenal glands. Additional symptoms include, but are not limited to hepatosplenomegaly, poor weight gain, jaundice, gastrointestinal symptoms, malabsorption, anemia, and developmental delay. As symptoms progress, children develop multiple organ failure and severe malnutrition therefore making this a life-threatening condition.
- Cholesteryl ester storage disease: This condition is less severe and presents later in life compared to Wolmans disease. Symptoms may include hepatosplenomegaly, cirrhosis and malabsorption and gastrointestinal symptoms. (8, 9)

Mucopolysaccharidosis (MPS)

MPS are a group of rare inherited lysosomal storage disorders where there is a deficiency or malfunction of specific lysosomal enzymes. This deficiency leads to an abnormal accumulation of certain complex carbohydrates (mucopolysaccharides or glycosaminoglycans) in the arteries, skeleton, eyes, joints, ears, skin, and/or teeth. These accumulations may also be found in the respiratory system, liver, spleen, central nervous system, blood, and bone marrow. This accumulation eventually causes damage to cells, tissues, and various organ systems. There are several types and subtypes of MPS. These disorders, with one exception, are inherited as autosomal recessive traits.

Seven distinct clinical types and numerous subtypes of the MPS have been identified. Although each MPS differs clinically, most individuals experience a period of normal development

followed by a decline in physical and/or mental function. The subtypes of MPS include, but are not limited to the following conditions (10, 11):

- MPS Type I
  MPS Type I is caused by a deficiency of alpha-L-iduronidase which is needed to break down glyclosaminoglycans. It is subdivided into 3 separate syndromes based on severity of symptoms: Scheie syndrome (MPS I S), Hurler/Scheie syndrome (MPS IH/S) and Hurler syndrome (MPS IH).
  a) *Scheie syndrome (mucopolysaccharidosis type I-S; MPS I-S):*
     The mildest form of MPS. Individuals with Scheie syndrome have a deficiency of alpha-L-iduronidase with an accumulation of dermatan sulfate. Individuals have normal intelligence, height, and life expectancy. Symptoms usually occur around age 5 and include stiff joints, carpal tunnel syndrome, aortic regurgitation, and cataracts that may result in the loss of visual acuity.
  b) *Hurler-Scheie syndrome (mucopolysaccharidosis type I-H/S; MPS-IH/S*):
     The intermediate form of MPS is extremely rare where symptoms usually become apparent between 3 and 6 years of age. Individuals may develop coarse facial features, joint stiffness, short stature, cataracts, hepatosplenomegaly, skeletal and cardiac abnormalities. Intelligence may be normal or a mild to moderate intellectual disability may develop.
  c) *Hurler syndrome (mucopolysaccharidosis type 1H; MPS 1H):*
     The most severe form of MPS in which symptoms usually become evident by the end of the first year of life. Affected infants may experience symptoms including but not limited to developmental delays, progressive mental and physical decline, limited language due to hearing loss, feeding difficulties, short stature, multiple skeletal abnormalities, hernias, enlarged organs.
- MPS II (Hunter Syndrome) is a rare inborn error of metabolism that is inherited as a X-linked trait resulting in a deficiency of iduronate sulfatase (IDS) which breaks down the glycosaminoglycans heparin sulfate and dermatan sulfate inside cells. The disease is almost exclusively found in young males. Children with a less severe form of MPS II are often diagnosed in the second decade of life. Intellect and social development are not affected. Physical characteristics in these children are less obvious and progress at a much slower rate, and skeletal problems may be less severe. Individuals with less severe MPS II may live into their 50s or beyond, although respiratory and cardiac complications can contribute to premature death. Children with the more severe form of MPS II share many of the neurological and physical features associated with severe MPS I but with milder symptoms. Onset of symptoms usually start between the ages of 2 and 4. Developmental decline is usually observed between the ages of 18 and 36 months, followed by progressive loss of motor skills. Other symptoms may include increased intracranial pressure, joint stiffness, retinal degeneration, macrocephaly, and progressive hearing loss. Whitish skin lesions may be found on the upper arms, back, and upper legs.
- MPS IV A and B, also known as Morquio Syndrome exists in two forms (Morquio syndromes type A and type B) and occurs because of a deficiency of the enzyme N-acetyl-galactosamine-6-sulfatase (type A) and beta-galactosidase (type B) resulting in the accumulation of keratan and chondroitin sulfate (type A) and keratan sulfate (type B). A

deficiency of either enzyme leads to the buildup of MPS in the body resulting in abnormal skeletal development. Typically, onset is between ages 1 to 3. The clinical features of MPS IV B are usually fewer and milder than those associated with MPS IV A. Clinical symptoms include but are not limited to, progressive skeletal changes (i.e., odontoid hypoplasia, protruded sternum, knock knees), joint stiffness, restricted breathing, heart disease, hearing loss and cloudy corneas. In most cases, intelligence is normal unless hydrocephalus develops and is untreated. (10, 11)

- MPS VI (Maroteaux-Lamy syndrome, mucopolysaccharidosis type VI) is characterized by a deficiency of the enzyme N-acetylgalactosamine-4-sulfatase, resulting in the accumulation of dermatan sulfate. Symptoms of MPS VI vary significantly among affected individuals and range from mild to severe. Clinical symptoms mimic other lysosomal disorders but also may include progressive skeletal changes, neurological symptoms due to thickening of the dura, deafness, ocular conditions (i.e., glaucoma, clouded cornea, optic nerve edema/degeneration) and heart disease. Growth is initially normal but usually ceases by age 8. In most cases, intelligence is normal. (10)
- MPS VII (Sly syndrome, mucopolysaccharidosis type VII) is an inherited, rare genetic disorder that is caused by a deficiency of the enzyme beta-glucuronidase, resulting in the accumulation of three glycosaminoglycans: dermatan sulfate, heparan sulfate and chondroitin sulfate. Intellectual disability can range from mild to severe by the age of 3. Additional clinical manifestations include skeletal abnormalities restricting movement, short stature, heart disease, hernias, hydrocephalus, hepatosplenomegaly, cloudy corneas, and a history of pneumonia. In rare cases, the infant or newborn may develop hydrops fetalis, an abnormal accumulation of fluid in various tissues of the body. (10, 11)

Pompe Disease (acid a-glucosidase [GAA] deficiency, acid maltase deficiency [AMD], or Glycogen Storage Disease Type II)

Pompe disease is a rare, inherited autosomal recessive trait that is characterized by a mutation in the gene that makes an enzyme called acid alpha-glucosidase (GAA). The GAA enzyme is required to metabolize the complex carbohydrate glycogen and convert it into the simple sugar glucose. Failure to properly break down glycogen results in accumulation of lysosomal glycogen in cells throughout the body, particularly in cardiac, smooth, and skeletal muscle cells. The onset for Pompe disease varies from birth to adulthood and it progresses rapidly with greater disease severity. There are 2 relatively distinct clinical forms of Pompe Disease which include (12, 13):

- Early onset (Infantile) Pompe disease: This disease is a result of a complete or near complete deficiency of GAA and typically occurs within the first few months of life. Patients with this form of Pompe disease are the most severely affected. Infants may present with feeding difficulties, enlarged tongue, poor weight gain, muscle weakness, floppiness, head lag and severe muscle weakness. Respiratory difficulties are often complicated by lung infections. Additional abnormalities may include hearing loss, cardiomegaly/hypertrophic cardiomyopathy, hypertrophic cardiomyopathy, hepatomegaly, and macroglossia. Infants typically do not meet or have a severe delay in meeting developmental milestones. Without treatment, progressive cardiac and respiratory failure usually causes life-threatening complications within the first year of life.

- Late-onset Pompe disease (also known as juvenile/adult Pompe disease): This disease is a result of a partial deficiency of GAA and can present within the first decade of life or as late as the eighth decade of adulthood. The extent of organ involvement varies among affected individuals. Symptoms include progressive muscle weakness mainly involving the proximal muscles (limb girdle, upper arms, and upper legs) progressing to respiratory failure, difficulty with balance, swallowing difficulties, and ptosis. Late-onset Pompe disease typically does not involve cardiac problems. Initial symptoms of late-onset Pompe disease may be subtle and may go unrecognized for years. Typically, the later the onset, the slower the progression of the disease.

Regulatory Status

The following enzyme-replacement therapies are U.S. Food and Drug Administration (FDA) approved for the treatment of specific Lysosomal Storage Disorders:

- Agalsidase beta (Fabrazyme®) was approved in 2003 by the U.S. FDA for the treatment of adult and pediatric individuals 2 years of age and older with confirmed Fabry disease. The safety and effectiveness of Fabrazyme has not been established in individuals less than 2 years of age. (14)
- Avalglucosidase alfa-NGPT (Nexviazyme®) was U.S. FDA approved in 2021 for the treatment of individuals 1 year of age and older with late-onset Pompe disease (lysosomal acid alpha-glucosidase [GAA] deficiency). The safety and effectiveness of Nexviazyme® has not been established in pediatric patients less than 1 year of age. (15)
- Idursulfase (Elaprase®) was approved in 2006 by the U.S. FDA for the treatment for Mucopolysaccharidosis II (MPS II, Hunter syndrome) based on clinical studies on children 5 years of age or older. (16)
- Alglucosidase alfa (Lumizyme®; formerly known as Myozyme) was approved in 2010 by the U.S. FDA for the use in individuals 8 years of age and older with late-onset Pompe disease that has not shown evidence of cardiac hypertrophy. In August 2014, the U.S. FDA label was modified to state that alglucosidase alfa is indicated for all individuals with Pompe disease. The restrictions for age and cardiac hypertrophy were removed. The FDA also reviewed available information and determined that Lumizyme and Myozyme are chemically and biochemically comparable therefore, the safety and effectiveness of Lumizyme and Myozyme are expected to be comparable. (17, 18)
- Asfotase alfa (Strensiq®) was approved in 2015 by the U.S. FDA for the treatment of individuals with perinatal/infantile-and juvenile-onset hypophosphatasia (HPP). (19)
- Cipaglucosidase alfa-atga (Pombiliti™) was approved in September 2023 by the U.S. FDA when used in combination with Opfolda, an enzyme stabilizer, for the treatment of adults with late-onset Pompe disease (lysosomal acid alpha-glucosidase [GAA] deficiency) in individuals weighing ≥40 kg who are not improving on their current enzyme replacement therapy (ERT). (20)
- Elosulfase alfa (Vimizim®) is the first orphan drug approved by the U.S. FDA to treat individuals with mucopolysaccharidosis type IVA (MPS IVA), also known as Morquio A syndrome. The safety and efficacy has not been established in patients below 5 years of age. (21)

- Naglazyme® (Galsulfase) was U.S. FDA approved in 2005 for the use in individuals with Mucopolysaccharidosis VI (MPS VI; Maroteaux-Lamy syndrome). (22)
- Imiglucerase (Cerezyme®) is U.S. FDA approved for individuals 2 years of age or older with Type 1 Gaucher disease that results in one or more of the following conditions: anemia, bone disease, hepatomegaly or splenomegaly, or thrombocytopenia. The safety and efficacy of Cerezyme has not been established in children younger than 2 years of age. (23)
- Laronidase (Aldurazyme®) was originally U.S. FDA approved in 2003 and is indicated for adult and pediatric individuals with Hurler and Hurler-Scheie forms of mucopolysaccharidosis I (MPS I) and for individuals with the Scheie form who have moderate to severe symptoms. Pretreatment with antipyretics and/or antihistamines is recommended prior to the infusion to reduce the risk of infusion-related allergic reactions. The FDA approval was based on clinical trials on individuals 6 months of age and greater. (24)
- Olipudase alfa (Xenpozyme®) was U.S FDA approved in August 2022 to treat pediatric and adult individuals with acid sphingomyelinase deficiency (ASMD). This is the first FDA approved medication to treat symptoms that are not related to the central nervous system in individuals with ASMD. Olipudase is an enzyme replacement therapy (ERT) that replaces the missing enzyme, acid sphingomyelinase, with a genetically engineered (recombinant) form and helps reduce sphingomyelin accumulation in the liver, spleen and lung. (3, 25).
- Pegunigalsidase alfa-iwxj (Elfabrio®) was U.S. FDA approved on May 9, 2023 for adults with a confirmed diagnosis of Fabry disease. (26)
- Sebelipase alfa (Kanuma®) was U.S. FDA approved in December 2015 for individuals with a diagnosis of lysosomal acid lipase (LAL) deficiency. The FDA approval was based on clinical trials on individuals greater than 1 month of age. (27)
- Taliglucerase alfa (Elelyso®) is U.S. FDA approved for the treatment of individuals 4 years and older with a confirmed diagnosis of Type 1 Gaucher disease. (28)
- Velaglucerase alpha (VPRIV®) was approved by the U.S. FDA in 2010 for the long term ERT for individuals with Type 1 Gaucher disease. The safety and efficacy has not been established in individuals below 4 years of age. (29)
- Vestronidase alfa-vjbk (Mepsevii®) was approved by the U.S. FDA in November 2017 for pediatric and adult individuals for the treatment of Mucopolysaccharidosis VII (MPS VII, Sly syndrome). Clinical studies involved individuals 5 months of age and older. (30)

NOTE: As with any intravenous protein product, hypersensitivity reactions are possible, therefore appropriate medical support should be readily available when the above products are administered. If a severe reaction occurs, current medical standards for emergency treatment are to be followed. Per the FDA, individuals should be monitored closely for hypersensitivity reactions. Individuals with compromised respiratory function or acute respiratory disease may be at risk of serious acute exacerbation of their respiratory compromise due to infusion reactions and may require additional monitoring. Please refer to the U.S. FDA label for specific individual precautions for ERT therapy for Lysosomal Storage Disorders.

Rationale

This medical policy was created in 2008 and is based on U.S. Food and Drug Administration (FDA) approved labeled indications and published literature. The most recent literature search of the PubMed database was performed through February 27, 2024. Following is the key literature to date.

Agalsidase beta (Fabrazyme®)
In 2003, the U.S. FDA approved agalsidase for patients with Fabry disease. The safety and efficacy of Fabrazyme were assessed in the following clinical studies, although the safety and effectiveness has not been established in pediatric patients less than 2 years of age. (14):

Study 1 was a randomized, double blind, placebo-controlled, multinational, multicenter study of 58 Fabry patients (56 males and 2 females), ages 16 to 61 years, all naïve to enzyme replacement therapy (ERT). Patients received either 1 mg/ kilogram (kg) of agalsidase beta (Fabrazyme) or placebo every 2 weeks for 5 months (20 weeks) for a total of 11 infusions. All patients were pretreated with acetaminophen and an antihistamine to decrease or prevent infusion associated reactions. Oral steroids were an additional option to the pretreatment regimen for patients who exhibited severe or recurrent infusion reactions. The primary efficacy endpoint of GL-3 inclusions in renal interstitial capillary endothelial cells, was assessed by light microscopy and was graded on an inclusion severity score ranging from 0 (normal or near normal) to 3 (severe inclusions). A GL-3 inclusion score of 0 was achieved in 20 of 29 (69%) patients treated with Fabrazyme compared to 0 of 29 treated with placebo ($p<0.001$). Similar reductions in GL-3 inclusions were observed in the capillary endothelium of the heart and skin. No differences between groups in symptoms or renal function were observed during this 5-month study.

All 58 patients in Study 1 participated in an open label extension study of Fabrazyme at 1 mg/kg every 2 weeks, which continued for an additional 54 months. At the end of 6 months of open label treatment, most patients achieved a GL-3 inclusion score of 0 in capillary endothelium. GL-3 was decreased to normal or near normal levels in mesangial cells, glomerular capillary endothelium, interstitial cells, and non-capillary endothelium. GL-3 deposition was still present in vascular smooth muscle cells, tubular epithelium and podocytes, at variably reduced levels. Forty-four of the 58 patients completed 54 months of the open label extension study. Thirty-six of these 44 patients underwent follow-up skin biopsy, and 31 of these patients showed sustained GL-3 clearance in the capillary endothelium of the skin. Follow-up heart and kidney biopsies were assessed in only 8 of the 44 patients, which showed sustained GL-3 clearance in the capillary endothelium of the kidney in 8 patients, and sustained GL-3 clearance in the capillary endothelium of the heart in 6 patients. Plasma GL-3 levels were reduced to normal levels (≤ 7.03 µg/ml) and remained at normal levels after up to 60 months of treatment. The reduction of GL-3 inclusions suggests that Fabrazyme may ameliorate disease expression; however, the relationship of GL-3 inclusion reduction to specific clinical manifestations of Fabry disease has not been established.

Study 2 was a randomized (2:1 Fabrazyme to placebo), double blind, placebo-controlled, multinational, and multicenter study of 82 patients (72 males and 10 females), ages 20 to 72 years, all naïve to ERT. Patients received either 1 mg/kg of Fabrazyme or placebo every 2 weeks for up to a maximum of 35 months (median 18.5 months). There was significant difference in post-baseline plasma GL-3 levels in the Fabrazyme-treated patients compared to placebo. The reduction in plasma GL-3 levels in the Fabrazyme group compared to the placebo group was significant at 1 year ($p<0.0001$) and at 2 years ($p=0.0019$). Fourteen patients (8 in Fabrazyme treated and 6 in placebo) had skin biopsies at first infusion and final visit. All Fabrazyme treated patients had capillary endothelium and deep vessel endothelium scores of zero at the final visit. Four of 6 placebo patients had non-zero capillary endothelium scores ($p=0.0150$), and 6 of 6 had non-zero deep vessel endothelium scores ($p=0.0003$). Sixty-seven patients who participated in Study 2 were subsequently entered into an open-label extension study in which all patients received 1 mg/kg of Fabrazyme every 2 weeks for up to a maximum of 18 months. There was a statistically significant reduction in mean plasma GL-3 levels with durability in effect through the additional 18 months of treatment in the extension study from pretreatment baseline.

Study 3 focused on the pediatric population and was an open label uncontrolled, multinational, multicenter study to evaluate the safety, pharmacokinetics, and pharmacodynamics of Fabrazyme treatment in 16 pediatric patients with Fabry disease (14 males, 2 females), who were ages 8 to 16 years at first treatment. All patients received Fabrazyme 1 mg/kg every 2 weeks for up to 48 weeks. At baseline, all 14 males had elevated plasma GL-3 levels (i.e., > 7.03 µg/mL), whereas the 2 female patients had normal plasma GL-3 levels. Median eGFR was normal (112.1 mL/min/1.73 m^2) at baseline and did not change during treatment, and median urinary protein was 151.0 mg/24 hr. (range: 70.0, 431.0). No new safety concerns were identified in pediatric patients in this study, and the overall safety and efficacy profile of Fabrazyme treatment in pediatric patients was found to be consistent with that seen in adults.

Study 5 was a long-term, observational study assessing the rate of decline in renal function (eGFR slope) in 122 patients with Fabry disease aged 16 years and older treated with Fabrazyme. Treated patients were matched 1:1 based on age (at Fabrazyme initiation), sex, Fabry disease subtype (classic or non-classic), and baseline eGFR to a historical cohort of untreated patients with Fabry disease. The median follow-up time was 3 years in the untreated group and 4.5 years in the treated group (maximum follow-up time 5 years in both groups). In the matched cohort, the median age (at Fabrazyme initiation) was 35 years, 72% of patients were male, 84% of patients had the classic Fabry disease subtype, and the median baseline eGFR was 93 mL/min/1.73 m^2. The estimated mean eGFR slope was -1.5 mL/min/1.73 m^2/year in the Fabrazyme-treated group and -3.2 mL/min/1.73 m^2/year in the untreated group (eGFR slope difference: 1.7 mL/min/1.73 m^2/year; 95% CI: 0.5, 3.0).

In 2014, Sirrs et al. evaluated 5-year outcomes of patients treated through the Canadian Fabry disease initiative (CFDI). This initiative tracks outcomes of subjects with Fabry disease that were treated with ERT. At enrollment, 86 subjects had previously received ERT (Cohort 1a) and 67 subjects were newly started (Cohort 1b) and randomized to agalsidase alfa or agalsidase beta.

209 subjects did not initially meet ERT criteria (Cohort 1c), 25 of whom met ERT criteria in follow-up and were moved to Cohort 1b (total n=178 ERT treated subjects). Use of supportive therapies such as aspirin (78%), renin-angiotensin blockade (59%), and statins (55%) was common in ERT treated subjects. In Cohort 1a, 32 subjects met the composite endpoint with 8 deaths. In Cohort 1b, 16 subjects met the composite endpoint with 1 death. Cohort 1b had fewer clinical events than Cohort 1a (p=0.039) suggesting that the treatment protocol was effective in targeting subjects at an earlier stage. 19.4% of Cohort 1b subjects on agalsidase alfa and 13.3% on agalsidase beta had a clinical event (p=0.57). Ten Cohort 1c subjects had clinical events, none of which would have been prevented by earlier use of ERT. The study concluded that Cardiovascular risk factor modification and targeted use of ERT reduce the risk of adverse outcomes related to Fabry disease. (31)

Avalglucosidase alfa-NGPT (Nexviazyme®)

In August 2021, the FDA approved Avalglucosidase alfa-NGPT (Nexviazyme®) for the treatment of patients 1 year of age and older with late-onset Pompe disease (lysosomal acid alpha-glucosidase (GAA) deficiency). The safety and effectiveness of Nexviazyme has not been established in pediatric patients younger than 1 year of age. The FDA approval is based on the following study: (15)

Study 1 (NCT02782741) was a randomized, double-blinded, multinational, multicenter trial comparing the efficacy and safety of Nexviazyme to alglucosidase alfa in 100 treatment-naive patients with late-onset Pompe disease. Patients were randomized in a 1:1 ratio based on baseline forced vital capacity (FVC), gender, age, and country to receive 20 mg/kg of Nexviazyme or alglucosidase alfa administered intravenously once every 2 weeks for 49 weeks. The trial included an open-label, long-term, follow-up phase of up to 5 years, in which patients in the alglucosidase alfa group were switched to Nexviazyme treatment. Of the 100 randomized patients, 52 were males, the baseline median age was 49 years old (range 16 to 78), median baseline weight was 76.4 kg (range 38 to 139 kg), median length of time since diagnosis was 6.9 months (range 0.3 to 328.4 months), mean age at diagnosis was 46.4 years old (range 11 to 78), mean FVC (% predicted) at baseline was 62.1% (range 32 to 85%) and mean 6-minute walk test (6-MWT) at baseline was 388.9 meters (range 118 to 630 meters). The primary endpoint of Study 1 was the change in FVC (% predicted) in the upright position from baseline to Week 49. At Week 49, the least squares (LS) mean change in FVC (% predicted) for patients treated with Nexviazyme and alglucosidase alfa was 2.9% and 0.5%, respectively. The estimated treatment difference was 2.4% (95% CI: -0.1, 5.0) favoring Nexviazyme (see Table 1).

Table 1: Summary Results of FVC (% predicted) in Upright Position in Treatment-Naive Patients with LOPD (Study 1)*

		Nexviazyme (n=51)	Alglucosidase Alfa (n=49)
Pretreatment baseline	Mean (SD)	62.5 (14.4)	61.6 (12.4)
Week 49	Mean (SD)	65.5 (17.4)	61.2 (13.5)

Estimated change from baseline to week 49	LS mean (SE)	2.9† (0.9)	0.5† (0.9)
Estimated difference between groups in change from baseline to week 49	LS mean (95% CI)	2.4†‡ (-0.1, 5.0)	

Table key: *All randomized patients, LOPD: Late-onset Pompe disease
† Estimated using a mixed model for repeated measures (MMRM) including baseline FVC (% predicted, as continuous), sex, baseline age (years), treatment group, visit, and treatment-by-visit interaction term as fixed effects.
‡ Noninferiority margin of 1.1% (p=0.0074). Statistical superiority of Nexviazyme over alglucosidase alfa was not achieved (p=0.06).

The key secondary endpoint of Study 1 was change in total distance walked in 6 minutes (6-Minute Walk Test, 6-MWT) from baseline to Week 49. At Week 49, the LS mean change from baseline in 6-MWT for patients treated with Nexviazyme and alglucosidase alfa was 32.2 meters and 2.2 meters. The estimated treatment difference was 30 meters (95% CI: 1.3, 58.7) favoring Nexviazyme (Table 2).

Table 2: Summary Results of 6-Minute Walk Test in Treatment-Naive Patients with LOPD (Study 1)*

		Nexviazyme (n=51)	**Alglucosidase Alfa (n=49)**
Pretreatment baseline	Mean (SD)	399.3 (110.9)	378.1 (116.2)
Week 49	Mean (SD)	441.3 (109.8)	383.6 (141.1)
Estimated change from baseline to week 49	LS mean (SE)	32.2† (9.9)	2.2† (10.4)
Estimated difference between groups in change from baseline to week 49	LS mean (95% CI)	30.0†‡ (1.3, 58.7)	

Table key: *All randomized patients; LOPD: Late-onset Pompe disease.
† The MMRM model for 6-MWT distance adjusts for baseline FVC (% predicted), baseline 6-MWT (distance walked in meters), baseline age (years), gender, treatment group, visit, and treatment-by-visit interaction as fixed effects.
‡ p-value at nominal level, without multiplicity adjustment (p=0.04).

Idursulfase (Elaprase®)

In 2006, the FDA evaluated clinical studies specific to the safety and efficacy of recombinant human iduronate-2-sulfatase (idursulfase) in the treatment of Hunter syndrome. This double blind, placebo-controlled trial was a phase II/III clinical study and incorporated 96 patients

between 5 and 31 years of age with a diagnosis of mucopolysaccharidosis II (Hunter syndrome). Patients were randomized to placebo infusions, weekly idursulfase (0.5 mg/kg) infusions or every other week infusions of idursulfase (0.5 mg/kg). Efficacy was evaluated using a composite endpoint consisting of distance walked in 6 minutes and the percentage of predicted forced vital capacity based on the sum of the ranks of change from baseline. Patients in the weekly and every other week idursulfase groups exhibited significant improvement in the composite endpoint compared to placebo (P = 0.0049 for weekly and P = 0.0416 for every other week) after 1 year. The weekly dosing group experienced a 37-m increase in the 6-minute walk distance (P = 0.013), a 2.7% increase in percentage of predicted forced vital capacity (P = 0.065), and a 160-mL increase in absolute forced vital capacity (P = 0.001) compared to placebo group at 53 weeks. Idursulfase was generally well tolerated, but infusion reactions did occur.

Patients who participated in the placebo-controlled trial were eligible to continue treatment in an open-label extension trial in which all patients received Idursulfase (Elaprase) 0.5mg/kg once weekly for 24 months. Patients who were treated with Elaprase once weekly and every other week in the placebo-controlled trial demonstrated improvement in distance walked in the 6-minute walk test for an additional 8 months of treatment. There was no change in mean %-predicted FVC in all Hunter syndrome patients after 6 months of treatment in the extension trial; however, a slight decrease in mean %-predicted FVC was demonstrated through month 24 of the extension trial. This study supports the use of idursulfase (Elaprase) in the treatment of mucopolysaccharidosis II/Hunter syndrome. (16, 32)

In 2012, Muenzer and colleagues stated that intravenous (IV) ERT with idursulfase for Hunter syndrome has not been demonstrated and is not predicted to cross the blood-brain barrier. Nearly all published experience with ERT with idursulfase has therefore been in patients without cognitive impairment (attenuated phenotype). Little formal guidance is available on the issues surrounding ERT in cognitively impaired patients with the severe phenotype. An expert panel was therefore convened to provide guidance on these issues. The clinical experience of the panel with 66 patients suggested that somatic improvements (e.g., reduction in liver volume, increased mobility, and reduction in frequency of respiratory infections) may occur in most severe patients. Cognitive benefits have not been seen. It was agreed that, in general, severe patients are candidates for at least a 6 to 12-month trial of ERT, excluding patients who are severely neurologically impaired, those in a vegetative state, or those who have a condition that may lead to near term death. It is imperative that the treating physician discuss the goals of treatment, methods of assessment of response, and criteria for discontinuation of treatment with the family before ERT is initiated. The authors concluded that the decision to initiate ERT in severe Hunter syndrome should be made by the physician and parents and must be based on realistic expectations of benefits and risks, with the understanding that ERT may be withdrawn in the absence of demonstrable benefits. (33)

Currently there is no data available to demonstrate improvement in disease related symptoms or long-term clinical outcome in children from age 16 months to 5 years; however, treatment with Elaprase has reduced spleen volume similarly to that of adults and children 5 yrs. of age and older. (16)

Alglucosidase alfa (Lumizyme®, formerly known as Myozyme)
Infantile-Onset Pompe Disease
The safety and efficacy of alglucosidase alfa were assessed in 57 treatment-naïve infantile-onset Pompe disease patients, age 0.2 months to 3.5 years of age at the time of first infusion. (17)

Study 1 was an international, multicenter, open label, clinical trial of 18 infantile-onset Pompe disease patients (acid a-glucosidase [GAA] deficiency). This study was conducted between 2003 and 2005. Patients were randomized equally to either 20 mg/kg or 40 mg/kg alglucosidase alfa every 2 weeks, with length of treatment ranging from 52 to 106 weeks. Enrollment was restricted to patient's ages 7 months or less at first infusion with clinical signs of Pompe disease, with cardiac hypertrophy, and who did not require ventilatory support at study entry. Fourteen patients were cross reactive immunologic material (CRIM) positive (residual GAA enzyme activity of at least 1%) and 4 patients were CRIM negative (no residual GAA enzyme activity).

Efficacy was assessed by comparing the proportions of alglucosidase alfa treated patients who died or needed invasive ventilator support with the mortality experience of an historical cohort of untreated infantile-onset Pompe patients with similar age and disease severity. In the historical cohort, 61 untreated patients with infantile-onset Pompe disease diagnosed by age 6 months were reviewed. By 18 months of age, 15 of the 18 (83%) alglucosidase alfa treated patients were alive without invasive ventilatory support, 3 patients (17%) required ventilator support, whereas only 1 patient (2%) of the in the historical control group remained alive. There were no differences in outcome were observed between patients who received 20 mg/kg versus 40 mg/kg. Other outcome measures in this study include unblinded assessments of motor function by the Alberta Infant Motor Scale (AIMS). The AIMS are a measure of infant motor performance that assesses motor maturation of the infant through age 18 months and is validated for comparison to normal, healthy infants. AIMS assessed gains in motor function which occurred in 13 patients. In the majority of patients, motor function was substantially delayed compared to normal infants of comparable age. Two of 9 patients who had demonstrated gains in motor function after 12 months of alglucosidase alfa treatment regressed despite treatment. Changes from baseline to month 12 in left ventricular mass index (LVMI), an evaluation of bioactivity, were measured by echocardiography. For the 15. patients with both baseline and Month 12 echocardiograms, all had decreases from baseline in LVMI (mean decrease 118 g/m^2, range 45 to 193 g/m^2). The magnitude of the decrease in LVMI did not correlate with the clinical outcome measure of ventilator-free survival.

Study 2 was an international, multicenter, nonrandomized, open label clinical trial that enrolled 21 patients who were ages 3 months to 3.5 years at first treatment. Eighteen patients were CRIM positive, and 3 patients were CRIM negative. All patients received 20 mg/kg alglucosidase alfa every other week for up to 104 weeks. Five of 21 patients were receiving ventilatory support at the time of first infusion. The primary outcome measure was the proportion of patients alive at the conclusion of treatment. At the 52–week interim analysis, 16 of 21 patients

were alive. Sixteen patients were free of ventilatory support at the time of first infusion; of these, 4 died, 2 required invasive ventilatory support, and 10 were free of invasive ventilatory support after 52 weeks of treatment. For the 5 patients who were receiving invasive ventilatory support at baseline, 1 died, and 4 remained on invasive ventilatory support at Week 52. (17)

Study 3 was an open label, single center trial in 18 infantile-onset Pompe disease patients who had a confirmed diagnosis of Pompe disease as identified through a newborn screening program. All patients were CRIM-positive. Patients were treated with alglucosidase alfa prior to 6 months of age (0.2 to 5.8 months at first infusion). Sixteen patients reached 18 months of age at the time of analysis, and all (100%) were alive without invasive ventilator support. (17)

In 2014, the FDA reviewed available data and determined that alglucosidase alfa (Lumizyme) and alglucosidase alfa (Myozyme) are chemically and biochemically comparable therefore, the safety and effectiveness of these products are expected to be comparable. Both products are manufactured by Genzyme Corporation and are produced from the same cell line at different production scales. Study 3 (noted above) provides further support that infantile-onset patients treated with alglucosidase alfa (Lumizyme) will have a similar improvement in ventilator-free survival as those treated with alglucosidase alfa (Myozyme). (18)

In 2022, Zhu et al. (34) evaluated the safety and efficacy of alglucosidase alfa in Chinese patients with infantile-onset Pompe disease due to the high prevalence of this disease in the Chinese population. This multicenter, single-arm, prospective, open-label clinical trial was performed at 4 sites in China. Ten eligible Chinese subjects (mean age 5.36 ± 1.56 months) with infantile-onset Pompe disease received an infusion of alglucosidase alfa at a dose of 20 mg/kg every 2 weeks for up to 52 weeks. The primary endpoints of clinical efficacy were the survival rate and changes in the left ventricular mass index. The safety assessment was based on the incidence of adverse events. Nine subjects survived after 52 weeks of treatment. One subject discontinued the study and died after mechanical ventilation was withdrawn. The intent-to-treat analysis demonstrated that the survival rate was 90.0% (95% CI: 55.5–99.7%). The mean left ventricular mass index at week 52 was 70.59 ± 39.93 g/m^2 compared to that of 298.02 ± 178.43 g/m^2 at baseline, with a difference of -227.60 ± 155.99 g/m^2. All subjects had left ventricular mass Z scores >10 at baseline, and 8 subjects (80%) achieved Z scores <5 at week 52. No treatment-related adverse events were identified, and no adverse events led to the discontinuation of treatment. This study noted that alglucosidase alfa has favorable efficacy and safety for the treatment infantile-onset Pompe disease in the Chinese population.

Late-Onset Pompe Disease

The safety and efficacy of alglucosidase alfa were assessed in 90 patients with late-onset Pompe disease, aged 10 to 70 years, in a randomized, double blind, placebo-controlled trial. The youngest alglucosidase alfa treated patient was 16 years of age, and the youngest placebo treated patient was 10 years of age. All patients were naïve to ERT. Patients were allocated in a 2:1 ratio and received 20 mg/kg alglucosidase alfa (n=60) or placebo (n=30) every other week for 78 weeks (18 months). The study population included 34 males and 26 females (n=60) in the alglucosidase alfa group and 11 males and 19 females (n=30) in the placebo group. At baseline,

all patients were ambulatory (some required assistive walking devices), did not require invasive ventilator support or non-invasive ventilation while awake and sitting upright, and had a forced vital capacity (FVC) between 30 and 79% of predicted in the sitting position. Patients who could not walk 40 meters in 6 minutes or were unable to perform appropriate pulmonary and muscle function testing was excluded from the study. A total of 81 of 90 patients completed the trial. Of the 9 patients who discontinued, 5 were in the alglucosidase alfa group and 4 were in the placebo group. Three patients discontinued the study due to an adverse event; 2 patients were in the alglucosidase alfa treatment group and 1 patient was in placebo group. At study entry, the mean % predicted FVC in the sitting position among all patients was about 55%. After 78 weeks, the mean % predicted FVC increased to 56.2% for alglucosidase alfa-treated patients and decreased to 52.8% for placebo treated patients indicating an alglucosidase alfa treatment effect of 3.4% (95% confidence interval: [1.3% to 5.5%]; p=0.004). Stabilization of % predicted FVC in the alglucosidase alfa treated patients was observed. At study entry, the mean 6-MWT among all patients was about 330 meters. After 78 weeks, the mean 6-MWT increased by 25 meters for alglucosidase alfa treated patients and decreased by 3 meters for placebo treated patients indicating an alglucosidase alfa treatment effect of 28 meters (95% confidence interval [-1 to 52 meters]; p=0.06). (17)

In 2012, van der Ploeg et al. completed an open label extension study following the late-onset treatment study (LOTS) of alglucosidase alfa to determine the durability, efficacy and safety of alglucosidase alfa. Patients who completed the LOTS study were eligible for this open label extension study and received alglucosidase alfa 20mg/kg biweekly for an additional 26 weeks. The primary efficacy assessments were the distance walked during a 6-MWT and the percentage of predicted forced vital capacity in the upright position. Data are reported as change from patient's original LOTS baseline for each measure. The benefit of alglucosidase alfa treatment observed in LOTS at week 78 was, in general, maintained at Week 104. The mean increase in distance walked measured 28.2 ± 66.5m from LOTS baseline to Week 78 and 21.3 ± 78.0m from LOTS baseline to Week 104. The mean change from baseline in percentage of predicted forced vital capacity was 1.3% ± 5.7% from LOTS baseline to Week 78 and 0.8% ± 6.7% from LOTS baseline to Week 104. Treatment related adverse events were mainly infusion associated reactions observed in 35% of patients. No deaths or anaphylactic reactions were observed during the extension study. The LOTS Extension study concluded that patients treated with alglucosidase alfa for up to 104 weeks maintained the improved walking distance and stabilization in pulmonary function observed in the first 78 weeks of alglucosidase alfa therapy. (35)

Asfotase alfa (Strensiq®)

Hypophosphatasia (Perinatal/Infantile Onset)

The FDA approved Asfotase alfa (Strensiq™) based on 4 studies. (19) Study 1 was a 24-week prospective single arm trial in 11 patients, aged 3 weeks to 39.5 months with severe perinatal/infantile-onset HPP. Severe perinatal/infantile-onset HPP was defined as biochemical, medical history and radiographic evidence of HPP as well as the presence of any of the following: rachitic chest deformity, vitamin B6 dependent seizures, or failure to thrive. Ten of 11 patients completed the 24-week trial and continued treatment in the extension phase. Nine

patients were treated for at least 216 weeks (54 months) and 4 patients were treated for over 240 weeks (60 months). Patients received Strensiq at 3 mg/kg per week for the first month; subsequently, the dose was increased up to 9 mg/kg per week due to changes based on the patient's weight and/or for lack of efficacy. All 10 patients required dose increases of up to 6 mg/kg per week or higher; 9 patients increased between 4 and 24 weeks after starting treatment and 1 patient increased after 70 weeks due to suboptimal clinical response. One patient's dose was decreased from 9 mg/kg per week to 6 mg/kg per week based on data.

Study 2 was a prospective open label study in 59 patients, age 1 day to 78 months with perinatal/ infantile-onset HPP. Patients received strensiq at 6 mg/kg per week for the first 4 weeks. Ten patients received dose increases higher than 6 mg/kg per week due to suboptimal clinical response, with dose increases occurring between 8 and 24 weeks after treatment initiation. The recommended dosage regimen of Strensiq for the treatment of perinatal/infantile- onset HPP is up to 9 mg/kg per week administered subcutaneously as 3 mg/kg 3 times per week. Forty-one patients were treated for at least 24 weeks (6 months) and 15 patients were treated for at least 96 weeks (24 months).

Survival and invasive ventilation free survival were compared in Strensiq treated patients (Studies 1 and 2) with a historical cohort of untreated patients with similar clinical characteristics (Table 3).

Table 3: Survival and Invasive Ventilation Free Survival in Strensiq Treated versus Historical Control Patients with Perinatal/ Infantile- Onset HPP

	Strensiq Treated	**Historical Controls**
Survival	n = 68	n = 48
• Alive at Point of Last Contact (%)	91	27
• Hazard Ratio (STRENSIQ/Historical Control), 95% Confidence Interval*	0.14 (0.05, 0.39)	
• Kaplan-Meier Estimate and Alive at Age 1 Year (Week 48) (%)	97	42
Invasive Ventilation Free Survival**	n = 54	n =48
• Alive and Not on Ventilation at Point of Last Contact (%)	85	25
• Hazard Ratio (STRENSIQ/Historical Control), 95% Confidence Interval*	0.21 (0.09, 0.51)	
• Kaplan-Meier Estimate of Alive and Not on Ventilation at Age 1 Year (Week 48) (%)	99	31

Table Key: *Adjusted for year of diagnosis. **Alive and not initiating invasive ventilation after start of Strensiq treatment. Strensiq treated patients on invasive ventilation at baseline were excluded from this analysis.

In patients who required any form of respiratory support, 21 of 26 (81%) of the treated patients survived through their last assessment (median age at last assessment was 3.2 years of age), versus 1 of 20 (5%) of historical controls. (19)

Skeletal Manifestations
Radiographs from 68 Strensiq treated perinatal/infantile-onset HPP patients, including 64 patients in Studies 1 and 2, and 4 patients in Study 3, were examined to assess HPP-related rickets using the 7-point Radiographic Global Impression of Change (RGI-C) scale. Patients with a minimum RGI-C score of +2 were defined as "responders". Radiologic improvements could be seen by Month 24; at last assessment, 50/68 [74%] treated patients were rated as RGI-C responders. No comparative data were available from historical controls. The mean time interval between the baseline and last RGI-C assessment was 24 months (range was 1 month to 67 months). Eighteen perinatal/infantile-onset HPP patients experienced fractures during treatment. There were insufficient data to determine the effect of Strensiq on fractures.

Long-Term Extension Trials
Long term data was collected in 68 Strensiq treated patients with perinatal/infantile onset HPP in both Study 1 and Study 2 with an additional 10 patients in Study 2. The longest duration of follow up in the 78 patients was 7 years (84 months) which identified 69/78 survival rate in Strensiq treated patients.

Hypophosphatasia (Juvenile-Onset)
Study 3 was a prospective open label 24-week trial that included 8 juvenile-onset HPP patients and 5 perinatal/ infantile-onset HPP patients. All 8 juvenile-onset patients, 6 to 12 years of age, entered the extension study and were treated for at least 48 months. Patients were randomized to receive Strensiq at 6 mg/kg per week or 9 mg/kg per week. Two patients received dose reductions during the primary treatment period, including 1 patient who experienced a decrease in vitamin B6 levels and 1 patient who experienced recurrent injection site reactions. During the extension phase, the dosing regimen for all patients was initially changed to 3 mg/kg per week. Dosing was subsequently increased to 6 mg/kg per week, with no patients requiring doses higher than 6 mg/kg per week. The recommended dosage regimen of Strensiq for the treatment of juvenile-onset HPP is 6 mg/kg per week.

Skeletal Manifestations
Radiographs from 8 Strensiq treated patients and 32 historical controls were compared to assess HPP related rickets using the 7-point RGI-C (Radiographic Global Impression of Change) scale. Patients who achieved an RGI-C score of 2 or higher (corresponding to substantial healing of rickets) were classified as being responders to treatment. All 8 treated patients were rated as responders by Month 54 of treatment. The mean duration between the baseline and last RGI-C assessments for control patients was 56 months (range was 8 to 95 months). At last assessment, 2/32 (6%) of control patients were rated as responders. Eight of 20 (40%) patients with juvenile-onset HPP experienced new fractures during the course of treatment. There were insufficient data to assess the effect of Strensiq on fractures.

Gait/Mobility
Gait was assessed using a modified Performance Oriented Mobility Assessment-Gait (MPOMA-G) scale) in 8 Strensiq treated patients at 6-month intervals out to 36 months. Mobility was also

assessed using the 6-MWT in 7 of the 8 patients. Step length improved by at least 1 point in either foot in 6/8 patients compared to 1/6 (17%) control patients. The proportion of patients who had 6-MWT percent predicted values within the normal range for age, sex, and height matched peers increased from 0/8 patients at baseline to 6/6 patients (100%) by Month 48 and all 6 were also able to walk longer distances at this time point compared to baseline.

Long-Term Extension Trials
Long term data was collected in 8 patients with juvenile-onset HPP treated with Strensiq for a minimum of 7 years (72 months). Seven patients with available MWT results had maintained improvements in their gait/mobility. (19)

In 2020, Genest et al. (36) stated that hypophosphatasia is a rare, inherited, metabolic disease characterized by tissue-nonspecific alkaline phosphatase deficiency resulting in musculoskeletal and systemic clinical manifestations. In an observational study, researchers examined the effectiveness of ERT with asfotase alfa on physical function and health-related quality of life (HRQOL) among adults with pediatric-onset hypophosphatasia who received asfotase alfa for 12 months at a single center. Primary outcomes evaluated physical function with the 6-minute walk test (6-MWT), timed up-and-go (TUG) test, Short Physical Performance Battery (SPPB), and hand-held dynamometry (HHD). Secondary outcome measures included the Lower Extremity Functional Scale (LEFS), pain prevalence/intensity, and pain medication use; HRQOL was evaluated using the 36-Item Short-Form Health Survey version 2 (SF-36v2). Safety data were collected throughout the study. All 14 patients (11 women) had compound heterozygous ALPL gene mutations and greater than or equal to 1 hypophosphatasia bone manifestation, including history of greater than or equal to 1 fracture. Mean (min, max) age was 51 (19 to 78) years. From baseline to 12 months of treatment, median 6-MWT distance increased from 267 m to 320 m (n = 13; p = 0.023); median TUG test time improved from 14.4 s to 11.3 s (n = 9; p = 0.008). Specific components of the SPPB also improved significantly: median 4-m gait speed increased from 0.8 m/s to 1.1 m/s (n= 10; p = 0.007) and median repeated chair-rise time improved from 22 s to 13 s (n = 9; p = 0.008). LEFS score improved from 24 points to 53 points (n = 10; p = 0.002). Improvements in HHD were not clinically significant. SF-36v2 Physical Component Score (PCS) improved after 12 months of treatment (n = 9; p = 0.010). Pain level did not change significantly from baseline to 12 months of treatment. There were significant improvements on chair-rise time and SF-36v2 PCS by 3 months, and on TUG test time after 6 months. No new safety signals were identified. The authors concluded that these findings showed the real-world effectiveness of asfotase alfa in improving physical functioning and HRQOL in adults with pediatric onset hypophosphatasia.

<u>Hypophosphatasia (Adult-Onset)</u>
In 2022, Dahir et al. (37) noted that the clinical signs and symptoms of HPP can manifest during any stage of life. The age at which a patient's symptoms were reported could impact access to targeted treatment with ERT (asfotase alfa), as this treatment is indicated for patients with pediatric-onset HPP in most countries. As such, many patients reported to have adult-onset HPP typically, do not receive treatment. Comparison of the disease in treated and untreated adult patients are confounded by the approved indication. To avoid this confounding factor, a

comparison between baseline disease manifestations prominent among treated versus untreated adult patients was limited to those with pediatric-onset HPP using data collected from the Global HPP Registry. The hypothesis was that treated adults will have a greater disease burden at baseline than untreated adults. The analysis of disease manifestations in adults with adult-onset HPP was conducted separately. A total of 398 adults with HPP were included; 213 with pediatric-onset (114 treated, 99 untreated) and 141 with adult-onset HPP (2 treated and 139 untreated). The treated, pediatric-onset patients were more likely to have a history of pain (prevalence ratio [PR]: 1.3, 95 % confidence interval [CI]: 1.1 to 1.4), skeletal (PR: 1.3, 95 % CI: 1.1 to 1.6), constitutional/metabolic (PR: 1.7, 95 % CI: 1.3 to 2.0), muscular (PR: 1.8, 95 % CI: 1.4 to 2.1) and neurological (PR: 1.7, 95 % CI: 1.1 to 2.3) manifestations of HPP, and also had poorer measures for HRQOL, pain, and disability compared with untreated pediatric-onset patients. In patients with adult-onset HPP, the most frequent signs and symptoms were chronic bone pain (52.5 %), dental manifestations (42.6 %), fatigue (23.4 %), recurrent fractures or pseudo-fractures (22.0 %), and generalized body pain (22.0 %). The authors concluded that along with the more classical skeletal signs and symptoms, pain, muscular, and constitutional/metabolic manifestations are common in adults with HPP, regardless of age of disease onset, highlighting a full spectrum of HPP manifestations.

Asfotase alfa (Strensiq®) is the first FDA approved treatment for use in patients with perinatal/infantile-and juvenile-onset hypophosphatasia. Additional studies and FDA approval are warranted in this subset of patients. (19)

Cipaglucosidase alfa-atga (Pombiliti™)

In September 2023, the U.S. FDA approved Pombiliti™, a hydrolytic lysosomal glycogen-specific enzyme when used in combination with Opfolda (an enzyme stabilizer) for the treatment of adult patients with late-onset Pompe disease (lysosomal acid alpha-glucosidase [GAA] deficiency) weighing ≥40 kg and who are not improving on their current enzyme replacement therapy (ERT). Per the FDA label, the safety and effectiveness of Pombiliti in combination with Opfolda have not been established in pediatric patients with late-onset Pompe disease. (20)

The FDA approved the use of Pombiliti based on the following clinical trials: Trial 1 was a randomized, double-blind, active-controlled, international, multi-center clinical trial (NCT03729362) in patients ≥18 years old diagnosed with late-onset Pompe disease (LOPD). Patients were randomized 2:1 to receive Pombiliti (20 mg/kg by intravenous infusion) in combination with Opfolda (260 mg orally for those ≥50 kg or 195 mg orally for those ≥40 kg to <50 kg) or a non-U.S.-approved alglucosidase alfa product with placebo every other week for 52 weeks. The efficacy population included a total of 123 patients of whom 95 (77%) had received prior treatment with U.S.-approved alglucosidase alfa or a non-U.S.-approved alglucosidase alfa product (ERT experienced) and 28 (23%) were ERT-naïve. More than two thirds (n=64, 67%) of ERT experienced patients had been on ERT treatment for more than 5 years prior to entering Trial 1 (mean of 7.4 years). Demographics, baseline sitting forced vital capacity (FVC) (% predicted), and 6-minute walk distance (6MWD) were generally similar between the 2 treatment groups (see Table 4 for baseline sitting FVC [percent predicted] values). Of the 123 randomized patients, 56 were males, baseline mean age was 47 years old (range from 19 to 74

years old), and mean age at diagnosis was 39 years old (range from 1 to 66). The racial groups for the patients consisted of 104 White (85%), 6 Japanese (5%), 6 Other racial group (5%), 4 Asian (3%), 1 Native Hawaiian or other Pacific Islander (1%), 1 American Indian or Alaska Native (1%), and 1 African American (1%). Key efficacy endpoints included assessment of sitting FVC (% predicted) and 6MWD (Table 4 and Table 5).

Sitting FVC (Percent-Predicted) at 52 Weeks

Patients treated with Pombiliti in combination with Opfolda showed a mean change in sitting FVC from baseline at Week 52 of -1.1% as compared with patients treated with a non-U.S. approved alglucosidase alfa product with placebo of -3.3%; the estimated treatment difference was 2.3% (95% CI: 0.02, 4.62).

The ERT experienced patients treated with Pombiliti in combination with Opfolda showed a numerically favorable change in sitting FVC from baseline at Week 52 (Table 4 and Figure 2).

Table 4: Summary of Sitting FVC in Adults with LOPD by ERT Status at 52 Weeks in Trial 1

Efficacy Endpoint	ERT-experienced		ERT-naïve*	
Sitting FVC (% predicted)	**Pombiliti in Combination with Opfolda**	**A Non-U.S.-Approved Alglucosidase alfa Product† with Placebo**	**Pombiliti in Combination with Opfolda**	**A Non-U.S.-Approved Alglucosidase alfa Product† with Placebo**
Baseline				
n	n=65	n=30	n=20	n=8
Mean (SD)	67.9 (19.1)	67.5 (21.0)	80.2 (18.7)	79.6 (21.0)
Median	68.0	69.0	82.3	88.5
Change from baseline at Week 52				
n	n=55	n=26	n=19	n=7
Mean (SD)	0.1 (5.9)	-3.5 (4.7)	-4.7 (6.2)	-2.4 (6.3)
Median	0.5	-2.5	-4.5	-3.0
Change to Week 52				
Diff. of means (SE)	3.5 (1.3)		-1.9 (2.7)	
(95% CI)	(1.0, 6.0)‡		(-7.3, 3.6)	

Table key: FVC: forced vital capacity; LOPD: late-onset Pompe disease; ERT: enzyme replacement therapy; SD: standard deviation; Diff.: difference; SE: standard error; CI: confidence interval.

*Pombiliti in combination with Opfolda is not approved for use in ERT-naïve patients with LOPD. The ERT-naïve patient subgroup enrolled too few patients to conclusively interpret the data. For the ERT-naïve group, the treatment difference was estimated using a 2-sample t-test.

† A U.S.-approved alglucosidase alfa product was not used in this clinical trial. Conclusions cannot be drawn from this clinical trial regarding comparative effectiveness between a U.S.-approved alglucosidase alfa product and Pombiliti in combination with Opfolda for the treatment of adult patients with LOPD weighing ≥40 kg and who are not improving on their current ERT.

‡ For the ERT-experienced group, the treatment difference of the mean was estimated by analysis of covariance which included treatment, gender, baseline FVC, age, weight, height in the model. Nominal p=0.006. Missing data at Week 52 was imputed using last observed values.

Figure 2. Mean Change (± SE) in Sitting FVC (% predicted) from Baseline to Week 52 in ERT experienced Adults with LOPD in Trial 1*

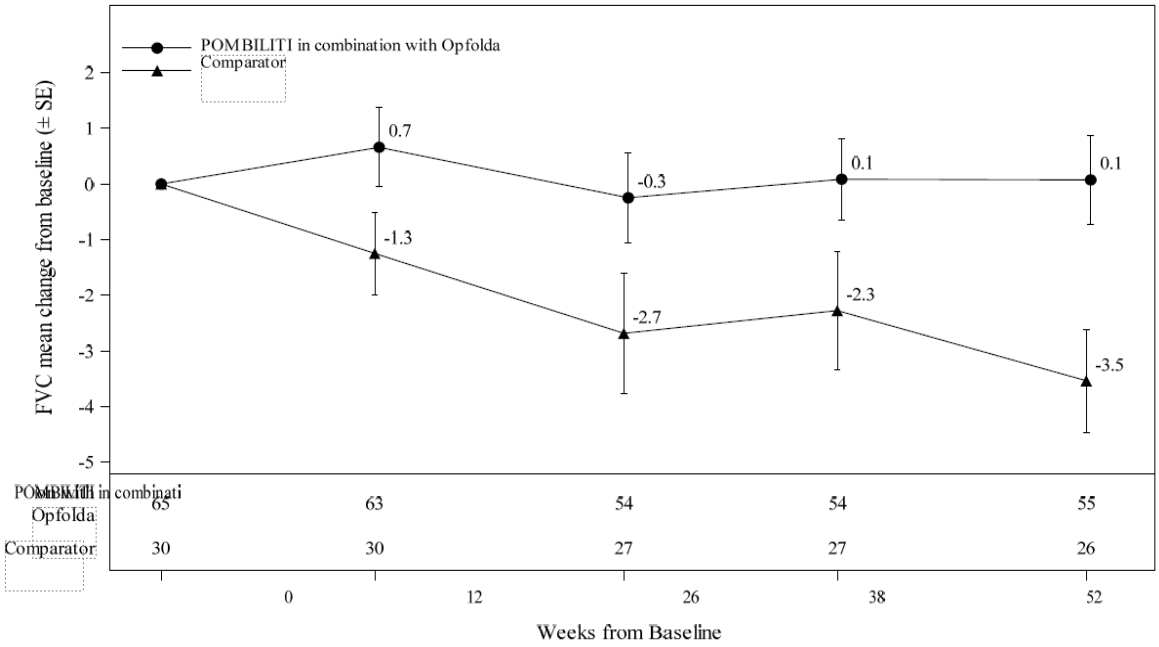

Table key: SE: standard error; FVC: forced vital capacity; ERT: enzyme replacement therapy; LOPD: late-onset Pompe disease.
*A U.S.-approved alglucosidase alfa product was not used in this clinical trial. Conclusions cannot be drawn from this clinical trial regarding osidase alfa product and POMBILITI in combination with Opfolda for the treatment adult patients with LOPD weighing ≥40 kg and who are not improving on their current ERT.

6-Minute Walk Distance (6MWD) at 52 Weeks

Patients treated with POMBILITI in combination with Opfolda walked on average 21 meters farther from baseline as compared to those treated with a non-U.S.-approved alglucosidase alfa product with placebo who walked 8 meters farther from baseline; the estimated treatment difference was 14 meters (95% CI: -1, 28).

The ERT-experienced patients treated with Pombiliti in combination with Opfolda showed a numerically favorable change in 6MWD from baseline at Week 52 (Table 5 and Figure 3).

Table 5. Summary of 6MWD in Adults with LOPD by ERT Status at 52 Weeks in Trial 1

Efficacy Endpoint	ERT-experienced		ERT-naïve*	
6MWD	**Pombiliti in Combination with Opfolda**	**A Non-U.S.-Approved Alglucosidase alfa Product†**	**Pombiliti in Combination with Opfolda**	**A Non-U.S.-Approved Alglucosidase Product†**

		with Placebo		**with Placebo**
Baseline n Mean (SD) Median	 n=65 347 (110) 353	 n=30 335 (114) 344	 n=20 394 (112) 375	 n=7 421 (136) 386
Change from baseline at Week 52 n Mean (SD) Median	 n=61 16 (39) 10	 n=29 1 (40) -9	 n=20 33 (49) 24	 n=7 38 (29) 34
Change to Week 52 Diff. of means (SE) (95% CI)	17 (8) (0.2, 33)‡		-5 (20) (-45, 36)	

Table key: 6MWD: 6-minute walk distance; LOPD: late-onset Pompe disease; ERT: enzyme replacement therapy; SD: standard deviation; Diff.: difference; SE: standard error; CI: confidence interval.

* POMBILITI in combination with Opfolda is not approved for use in ERT-naïve patients with LOPD. The ERT-naïve patient subgroup enrolled too few patients to conclusively interpret the data. For the ERT-naïve group, the treatment difference was estimated using a 2-sample t-test. One ERT-naïve subject in the control arm was excluded from this table because their change of 355 meters in 6MWD from baseline at Week 52 was a statistical outlier and not considered clinically plausible.

† A U.S.-approved alglucosidase alfa product was not used in this clinical trial. Conclusions cannot be drawn from this clinical trial regarding comparative effectiveness between a U.S.-approved alglucosidase alfa product and POMBILITI in combination with Opfolda for the treatment of adult patients with LOPD weighing ≥40 kg and who are not improving on their current ERT.

‡ For the ERT-experienced group, the treatment difference of the mean was estimated by nonparametric analysis of covariance which included gender, baseline 6MWD, age, weight, and height in the model. Nominal p=0.047. Missing data at Week 52 was imputed using last observed values.

Figure 3. Mean Change (± SE) of 6MWD from Baseline to Week 52 in ERT-experienced Adults with LOPD in Trial 1*

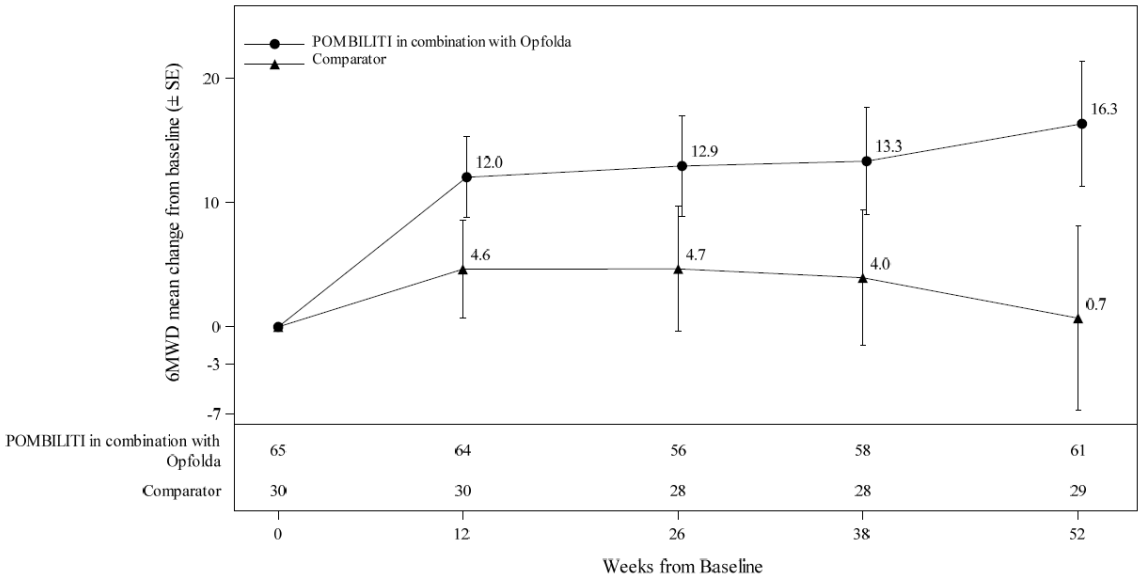

Table key: SE: standard error; 6MWD: 6-minute walk distance; ERT: enzyme replacement therapy; LOPD: late-onset
Pompe disease.
*A U.S.-approved alglucosidase alfa product was not used in this clinical trial. Conclusions cannot be drawn from this clinical trial regarding comparative effectiveness between a U.S. approved alglucosidase alfa product and Pombiliti in combination with Opfolda for the treatment adult patients with LOPD weighing ≥40 kg and who are not improving on their current ERT.

Elosulfase alfa (Vimizim®)

In February 2014, the U.S. FDA approved elosulfase alfa (Vimizim®) for patients with mucopolysaccharidosis type IVA (MPS IVA; Morquio A syndrome). The safety and efficacy of Vimizim were assessed in a 24-week, randomized, double blind, placebo-controlled clinical trial of 176 patients with MPS IVA. The age of patients ranged from 5 to 57 years. Most of the patients (82%) presented with a medical history of musculoskeletal conditions, which includes knee deformity (52%), kyphosis (31%), hip dysplasia (22%), prior spinal fusion surgery (22%) and arthralgia (20%). At baseline, all enrolled patients could walk more than 30 meters (m) but less than 325 m in 6 minutes.

Patients received Vimizim 2 mg/kg once per week (n=58), Vimizim 2 mg/kg once every other week (n=59), or placebo (n=59). The primary endpoint was the change from baseline in the distance walked in six minutes (6-MWT) at Week 24. The other endpoints included changes from baseline in the rate of stair climbing in 3 minutes (3-minute stair climb test, 3-MSCT) and changes from baseline in urine KS levels at Week 24. The treatment effect in the distance walked in 6 minutes, compared to placebo, was 22.5 m (CI 95, 4.0, 40.9; p=0.0174) in patients who received Vimizim 2 mg/kg once per week. There was no difference in the rate of stair

climbing between patients who received Vimizim 2 mg/kg once per week and those who received placebo. Patients who received Vimizim 2 mg/kg once every other week performed similarly in the 6-MWT and 3-MSCT as those who received placebo. The reduction in urinary KS levels from baseline, a measure of pharmacodynamic effect, was greater in the Vimizim treatment groups compared to placebo. The relationship between urinary KS and other measures of clinical response has not been established. (21)

Patients who participated in the placebo-controlled trial (MOR-004) were eligible to continue treatment in an open-label multicenter, phase 3 extension trial (MOR-005). In 2018, Hendriksz et al. (38) published data related to the long-term safety and efficacy of elosulfase alfa (Vimizim) ERT in 173 patients with Morquio A syndrome (mucopolysaccharidosis IVA). This 96-week extension study evaluated efficacy endpoints over 120 weeks, from the MOR-004 baseline to MOR-005 week 96. This study evaluated the impact of ERT on activities of daily living (ADL) across 3 domains (mobility, self-care, and caregiver-assistance), as assessed by the Mucopolysaccharidosis Health Assessment Questionnaire (MPS-HAQ) after 72 and 120 weeks or approximately 1 and 2 years. The mean baseline MPS-HAQ domain scores showed impairments in mobility, self-care, and independence. The MOR-005 intent-to-treat population (ITT; N=169, including 158 with 2 years follow-up) showed sustained significant reductions (representing improvements) in mobility and self-care domain least square (LS) mean scores vs. baseline at 1 and 2 years and a non-significant decrease in the caregiver-assistance domain at 2 years. At week 120, LS mean (SE) changes from baseline were -0.5 (0.1) for mobility (P=0.002), -0.4 (0.1) for self-care (P=0.001), and -1.0 (0.5) for caregiver-assistance (P=0.06) (ITT population). Improvements in MPS-HAQ domain scores vs. baseline at 1 and 2 years were greater in patients continuously treated weekly than in the total MOR-005 population and statistically significant across domains. A comparable untreated cohort of patients from the Morquio A Clinical Assessment Program (MorCAP) natural history study (ITT population, N=94, including 37 with 2 years follow-up) showed no improvement over 2 years, with two of the three domains worsening (LS mean (SE) changes from baseline: 0.3 (0.3) for mobility, 0.4 (0.2) for self-care, -0.5 (0.8) for caregiver-assistance). Changes in LS mean scores vs. baseline were statistically significantly different between MOR-005 and MorCAP for the mobility domain (-0.7 (SE 0.4), P=0.0490) and the self-care domain (-0.7 (SE 0.3), P=0.0146) at 2 years. The study concluded that these findings suggest that long-term elosulfase alfa ERT is associated with partial recovery of functional abilities, improving Morquio A patients' abilities to perform ADLs.

Per the FDA label, the safety and effectiveness of elosulfase alfa (Vimizim) in pediatric patients under the age of 5 years of age has not been established. (21)

Galsulfase (Naglazyme®)

On May 31, 2005, Galsulfase (Naglazyme®, BioMarin Pharmaceutical Inc., Novato, CA) was granted orphan drug status by the FDA for the treatment of MPS VI (Maroteaux-Lamy syndrome). Galsulfase (Naglazyme®) has been reported to improve endurance as shown by the 12-minute walk test as well as the 3-minute stair climb. It reduces the urinary excretion of GAGs indication of enzymatic bioactivity, in patients with MPS VI. A total of 56 patients with MPS VI, ages 5 years to 29 years, were enrolled in four clinical studies. The majority of patients had

severe manifestations of the disease as evidenced by poor performance on a test of physical endurance. In a randomized, double blind, multicenter, placebo-controlled clinical trial, 38 patients with MPS VI received 1 mg/kg Naglazyme or placebo, once-weekly for 24 weeks. The patients' ages ranged from 5 to 29 years. Enrollment was restricted to patients with a 12-minute walk distance of 5 to 400 meters. All patients were treated with antihistamines prior to each infusion. The Naglazyme treated group showed greater mean increases in the distance walked in 12 minutes (12-minute walk test, 12-MWT) and in the rate of stair climbing in a 3-minute stair climb test, compared with the placebo group. Following the 24-week placebo-controlled study period, 38 patients received open-label Naglazyme for 72 weeks. Among the 19 patients who were initially randomized to Naglazyme and who continued to receive treatment for 72 weeks (total of 96 weeks), increases in the 12-MWT distance and in the rate of stair climbing were observed compared to the start of the open label period (mean [+ SD] change): 72 + 116 meters and 5.6 + 10.6 stairs/minute, respectively). Among the 19 patients who were randomized initially to placebo for 24 weeks, and then crossed over to treatment with Naglazyme, the increases after 72 weeks of Naglazyme treatment compared to the start of the open label period, (mean [+ SD] change): were 118 + 127 meters and 11.1 + 10.0 stairs/minute, for the 12-MWT and the rate of stair climbing, respectively. Bioactivity was evaluated with urinary GAG concentration. Overall, 95% of patients showed at least a 50% reduction in urinary GAG levels after 72 weeks of treatment with Naglazyme. No patient receiving Naglazyme reached the normal range for urinary GAG levels. In an additional open label extension study, patients receiving Naglazyme showed maintenance of initial improvement in endurance for approximately 240 weeks. (22)

In 2019, Gomes et al. (39) sought to evaluate the effectiveness of the ERT with galsulfase for the treatment of MPS VI therefore they performed a systematic review of observational studies. The databases of PubMed, Cochrane Library, Lilacs, and Journal of Inherited Metabolic Disease were reviewed. The selection of studies, data mining, and methodological quality assessment were independently conducted by 2 authors. Eighteen studies fulfilled the inclusion criteria: 2 studies were cohorts, 1 was a longitudinal study, 1 was cross-sectional, 1 was a case-control, 8 were case series, and 5 were case reports. A total of 362 participants with MPS type VI were evaluated, and 14 different outcomes related to the treatment effect were identified. Seven outcomes showed positive results, characterized by the patient survival, QOL, respiratory function, joint mobility, physical resistance, reduction of urinary glycosaminoglycans, and growth. The hearing function and the cognitive development were stable after the treatment. Other outcomes related to the cardiac function, visual acuity, sleep apnea, and the size of the liver and spleen presented inconclusive outcomes. Concerning safety, light adverse reactions of hypersensitivity were reported. Overall, this review provided a broader panoramic view of the outcomes related to MPS type VI and determined that regardless of the inherent limitations of observational studies, the outcomes indicate that the ERT has a positive effect on most of the outcomes associated with the disease.

Imiglucerase (Cerezyme®)

In 1994, the U.S. FDA approved the use of imiglucerase (Cerezyme®) as enzyme replacement therapy. The current FDA label states imiglucerase (Cerezyme**)** is indicated for the treatment of

adults and pediatric patients 2 years of age and older with Type 1 Gaucher disease that results in one or more of the following conditions: anemia, thrombocytopenia, bone disease, hepatomegaly or splenomegaly. (23)

In clinical trials, Cerezyme improved anemia and thrombocytopenia, reduced spleen and liver size, and decreased cachexia to a degree similar to that observed with Ceredase. Per the U.S. FDA label, the safety and effectiveness of Cerezyme® has been established in patients between 2 and 16 years of age. Cerezyme® has previously been administered to patients younger than 2 years of age, however the safety and effectiveness in patient's younger than 2 have not been established. (23)

In 2007, Weinreb et al. investigated the impact of imiglucerase treatment on HRQOL of patients with type 1 Gaucher disease and bone involvement. Thirty-two previously untreated type 1 Gaucher disease patients with skeletal manifestations including bone pain, medullary infarctions, avascular necrosis, and lytic lesions received biweekly imiglucerase (at 60 U/kg). The Short Form-36 Health Survey (SF-36) was administered at regular intervals to assess HRQOL. Mean baseline SF-36 physical component summary (PCS) scores were diminished relative to U.S. general population norms. Low PCS scores were more common in patients with medullary infarction, lytic lesions, and higher bone pain severity scores. Statistically significant improvements were observed for all 8 SF-36 subscales after 2 years of treatment. Mean PCS and mental component summary (MCS) scores increased to within the normal range after 2 years of treatment and were maintained through year 4. Large HRQOL gains were observed even in patients with the most advanced disease and lowest baseline PCS scores. Imiglucerase treatment has a significant positive impact on HRQOL of type 1 GD patients with skeletal disease, including those with bone infarctions, lytic lesions, and avascular necrosis. (40)

In 2021, Weinreb et al. reported on outcomes in patients with Gaucher disease treated for 20 (±3) years with Imiglucerase with a subset analyses based on pre-treatment severity, genotype, and age at treatment initiation. Gaucher disease type 1 patients in the ICGG Gaucher Registry with complete sets at baseline, 10-year, and 20-year data are included (N = 475). Ten-year and 20-year data are compared to pre-treatment baseline, stratified by splenectomy status. Non-splenectomy patients had improvements observed at 10 years which were maintained at 20 years for most outcomes. Mean changes from baseline at 10 and 20 years, respectively, were: spleen volume: 18.2 multiples of normal (MN) to 5.1 MN and 4.2 MN; liver volume: 1.8 MN to 1.0 MN and 1.0 MN; hemoglobin: 11.4 g/dL to 13.7 g/dL and 13.8 g/dL; platelet count: 91.6 × 109/L to 168.0 × 109/L and 169.1 × 109/L; without bone crisis: 85.0% to 98.2% and 96.5%; without bone pain: 52.5% to 72.0% at 10 years, no significant change at 20 years (58.5%). Splenectomized patients had significant changes related to liver volume: 2.3 MN to 1.1 MN and 1.0 MN; hemoglobin: 11.7 g/dL to 13.3 g/dL and 13.4 g/dL; platelet count: 229.1 × 109/L to 288.1 × 109/L and 257.0 × 109/L; without bone crisis: 52.2% to 91.3% and 100%; without bone pain: 16.3% to 30.6% (not significant) and 46.9%. Similar results were found in each of the subset analyses. Patients who started treatment during childhood had normal weight and height in young adulthood. Many treated adult patients are overweight or obese; however, this is consistent with body mass index trends observed within the general population. The data

concluded that Imiglucerase is an effective, long-term treatment for Gaucher disease type 1. In a long-term observational setting, improvements seen during early treatment years are sustained by continuing treatment for 20 years, except for bone pain in non-splenectomized patients. These results are consistent when analyzed by different patient subsets, including by disease severity. (41)

Laronidase (Aldurazyme®)

In 2003, Laronidase (Aldurazyme®) was U.S. FDA approved based on the following clinical studies: Study 1 was a randomized, double blind, placebo-controlled study in 45 patients with MPS I, ages 6 to 43 years old, including 1 patient with the Hurler form, 37 patients with Hurler-Scheie form, and 7 patients with Scheie form of MPS I. All patients had a baseline percent predicted forced vital capacity (FVC) less than or equal to 77%. Patients received Aldurazyme at 0.58 mg/kg of body weight once weekly or placebo once weekly for 26 weeks. All patients were treated with antipyretics and antihistamines prior to each infusion. The primary efficacy outcome assessments were percent predicted FVC and distance walked in 6 minutes (6-MWT). After 26 weeks, patients treated with Aldurazyme showed improvement in percent predicted FVC and in 6-MWT compared to placebo-treated patients (Table 6). Evaluations of bioactivity were changes in liver size and urinary GAG levels. Liver size and urinary GAG levels decreased in patients treated with Aldurazyme compared to patients treated with placebo. No patient in the group receiving Aldurazyme reached the normal range for urinary GAG levels during this 6-month study. (24)

Table 6: Primary Efficacy Outcomes in the Placebo-controlled Study (Study 1)

		Aldurazyme (N=22)	**Placebo (N=23)**
Forced Vital Capacity (percent of predicted normal)			
Pretreatment Baseline	Mean ± s.d.	48 ± 15	54 ± 16
Week 26	Mean ± s.d.	50 ± 17	51 ± 13
Change from Baseline to Week 26	Mean ± s.d.	1 ± 7	-3 ± 7
	Median	1	-1
Difference in Change from Baseline Between Groups	Mean	4	
	Median (95 CI)	2 (0.4, 7), p=0.02*	
6-Minute Walk Distance (meters)			
Pretreatment Baseline	Mean ± s.d.	319 ± 131	367 ± 114
Week 26	Mean ± s.d.	339 ± 127	348 ± 129
Change from Baseline to Week 26	Mean ± s.d.	20 ± 69	-18 ± 67
	Median	28	-11
Difference in Change from	Mean	38	
	Median (95% CI)	39 (-2, 79), p=0.07*	

Baseline to Week 26 Between Groups		

Table Key: *By Wilcoxon Rank Sum Test; CI: confidence interval; s.d.; standard deviation

Study 2 was a 182-week, open label, uncontrolled extension study of all 45 patients who completed Study 1. Patients received Aldurazyme at 0.58 mg/kg body weight once weekly. For patients treated with Aldurazyme the mean increase in 6-MWT distance was maintained for an additional 182 weeks through completion of Study 2. At the end of Study 2, the decrease in mean urinary GAG was similar to the decrease in urinary GAG reported in Aldurazyme treated patients at the end of Study 1. The relationship of urinary GAG to other measures of clinical response has not been established.

Study 3 was a 52-week, open label, uncontrolled clinical study in 20 pediatric patients with MPS I, ages 6 months to 5 years old (at enrollment), including 16 patients (80%) with the Hurler form and 4 patients (20%) with the Hurler-Scheie form. All 20 pediatric patients received Aldurazyme at 0.58 mg/kg of body weight once weekly for 26 weeks. After 26 weeks of treatment, 16 patients continued to receive 0.58 mg/kg of body weight once weekly through Week 52, and 4 patients received 1.16 mg/kg of body weight once weekly from Week 26 through Week 52. Reduction in mean urinary GAG was demonstrated at Week 13 and was maintained through Week 52. No patient receiving Aldurazyme reached the normal range for urinary GAG levels during this 52-week study. Changes in urinary GAG levels in children 6 years and younger were similar to changes reported in older patients in Studies 1 and 2 (6 through 43 years old). The relationship of urinary GAG to other measures of clinical response has not been established.

The most serious adverse reactions reported with Aldurazyme treatment during clinical trials were anaphylactic and allergic reactions. Most adverse reactions reported in clinical trials were considered disease related and unrelated to study drug. The most common adverse reactions were infusion reactions. The frequency of infusion reactions decreased over time with continued use of Aldurazyme, and most of the reactions were classified as being mild to moderate in severity. Most infusion reactions requiring intervention were ameliorated with slowing of the infusion rate, temporarily stopping the infusion, with or without administering additional treatments including antihistamines, antipyretics, or both. Because of the potential for infusion reactions, patients should receive antipyretics and/or antihistamines prior to infusions.

Patients with compromised respiratory function, or acute respiratory disease may be at risk of serious acute exacerbation of their respiratory compromise due to infusion reactions and will require additional monitoring. Caution should also be exercised when patients with a compromised cardiac function for whom fluid restriction is indication.

Aldurazyme has been shown to improve pulmonary function and walking capacity. Currently, the risks and benefits of treating mildly affected patients with the Scheie form of MPS I have

not been established. In addition, Aldurazyme has not been evaluated for effects on central nervous system in patients less than 6 months of age. (24)

Olipudase alfa (Xenpozyme®).
The efficacy of Olipudase alfa for the treatment of non–central nervous system manifestations of acid sphingomyelinase deficiency (ASMD) has been evaluated in 3 clinical trials involving a total of 61 patients with ASMD (25):

- Trial 1 in adult patients (NCT02004691),
- Trial 2 in pediatric patients (NCT02292654), and
- Trial 3 a long-term trial in pediatric patients (NCT02004704).

Adult Patients with ASMD
Trial 1 was a multicenter, randomized, double-blinded, placebo-controlled, repeat-dose phase II/III trial in adult patients with ASMD (clinical diagnosis consistent with ASMD type B and A/B). In this trial, patients received either Xenpozyme or placebo. Treatment was administered in both groups as an intravenous infusion once every 2 weeks. Xenpozyme was dosed as follows: 0.1 mg/kg (Day 1, Week 0), 0.3 mg/kg (Weeks 2 and 4), 0.6 mg/kg (Weeks 6 and 8), 1 mg/kg (Week 10), 2 mg/kg (Week 12), and then a maintenance dose of 3 mg/kg (Week 14 onwards). The trial was divided into 2 consecutive periods: a randomized placebo-controlled, double-blinded primary analysis period (PAP) which lasted to Week 52, followed by an extension treatment period (ETP) for up to 4 years. Patients randomized to the placebo arm in the PAP crossed over to receive Xenpozyme treatment in the ETP to reach the targeted dose of 3 mg/kg, while patients in the original Xenpozyme arm continued treatment. Patients enrolled in the trial had a diffusion capacity of the lungs for carbon monoxide (DLco) ≤70% of the predicted normal value and a spleen volume ≥6 multiples of normal (MN) measured by magnetic resonance imaging (MRI). The trial population included 87% White, 7% Asian and 7% other; for ethnicity, 32% identified as Hispanic/Latino, 65% as non-Hispanic/Latino and 3% were not reported. Five males and 13 females with a median age of 34 years (range: 18 to 66) were included in the placebo arm and 8 males and 5 females with a median age of 34 years (range: 20 to 59) were included in the Xenpozyme arm. The Xenpozyme and placebo groups included 1 patient (8%) and 2 patients (11%) with mild renal impairment (60 mL/minute ≤ creatinine clearance <90 mL/minute), respectively. There were no patients with moderate or severe renal impairment. Key efficacy endpoints included assessment of % predicted DLco, spleen volume, liver volume and platelet count.

At Week 52 during the PAP, an increase of 21% in the mean percent change in % predicted DLco was observed in the Xenpozyme-treated patients compared to the placebo-treated patients (Table 5). A reduction in spleen volume of 39% was observed in the Xenpozyme- treated patients compared to the placebo-treated patients. The changes in % predicted DLco and spleen volume were noted at Week 26 of treatment, the first post-dose endpoint assessment. A decrease in mean liver volume and an increase in mean platelet count were noted in the Xenpozyme-treated patients compared to the placebo-treated patients at Week 52 (see Table 7).

Table 7: Observed Value and Percentage Change from Baseline to Week 52 in Key Endpoints in Adult Patients with ASMD Type B, A/B on Xenpozyme or Placebo (Trial 1)

	Placebo	Xenpozyme	Difference [95% CI]
DLco			
n	18	13	
Mean % predicted DLco at baseline (SD)	48.5 (10.8)	49.1 (9.7)	NA
n	17	12	
Mean % predicted DLco at Week 52 (SD)	49.9 (11.1)	59.4 (9.6)	NA
n	17	12	
LS Mean Percent change in % predicted DLco at Week 52 (SE)	3.0 (3.3)	23.9 (3.8)	20.9 (5.0) * [10.6, 31.2]
Spleen volume			
n	18	13	
Mean spleen volume (MN) at baseline (SD)	11.2 (3.8)	11.5 (4.7)	NA
n	17	13	
Mean spleen volume (MN) at Week 52 (SD)	11.2 (4.2)	7.2 (3.9)	NA
n	17	13	
LS Mean Percent change in Spleen Volume (in MN) at Week 52 (SE)	0.5 (2.62)	-38.9 (3.0)	-39.4 (4.0) † [-47.6, -31.2]
Liver volume			
n	18	13	
Mean liver volume (MN) at baseline (SD)	1.6 (0.5)	1.4 (0.3)	NA
n	17	12	
Mean liver volume (MN) at Week 52 (SD)	1.6 (0.5)	1.0 (0.2)	NA
n	17	12	
LS Mean Percent change in Liver volume from baseline to Week 52 (SE)	-1.8 (2.7)	-26.5 (3.2)	-24.7 (4.2) † [-33.4, -16.1]
Platelet count			
n	18	13	
Mean platelet count (10^9/L) at baseline (SD)	115.6 (36.3)	109.3 (30.6)	NA
n	16	13	NA
Mean platelet count (10^9/L) at Week 52 (SD)	120.2 (43.2)	126.4 (29.0)	
n	16	13	+15.6 (6.7) ‡
LS Mean Percent change in Platelet Count from baseline to Week 52 (SE)	2.7 (4.5)	18.3 (5.0)	[1.8, 29.4]

Table key: DLco; diffusing capacity of the lungs for carbon monoxide; NA; non-applicable; Nominal p value: *p value = 0.0003; † p value <0.0001; ‡ p value= 0.0280

Seventeen of 18 patients previously receiving placebo and 13 of 13 patients previously treated with Xenpozyme for 52 weeks (in the PAP) started or continued treatment with Xenpozyme, respectively, for up to 4 years. At Week 104, patients initially randomized to placebo had

received Xenpozyme for 52 weeks and demonstrated the following LS mean (SE) percent changes in clinical parameters from baseline (before first administration of Xenpozyme: increase in % predicted DLco was 26.8% (6.2); reduction in spleen volume (MN) was 36.5% (2.5); reduction in liver volume (MN) was 29.5 (2.6); and increase in platelet count was 19.5 (6.7). Patients in the previous Xenpozyme group demonstrated improvement from baseline to Week 104 in the following parameters: LS mean (SE) percent increase in % predicted DLco was 34.1% (7.9); LS mean (SE) percent reduction in spleen volume (MN) was 48.3 (2.9); LS mean (SE) percent reduction in liver volume (MN) was 31.7 (2.9); LS mean (SE) percent increase in platelet count was 24.0 (8.2).

Pediatric Patients with ASMD

Trial 2 was a multi-center, open-label, repeated-dose trial of Xenpozyme administered intravenously once every 2 weeks via infusion for 64 weeks in pediatric patients aged <18 years with a clinical diagnosis consistent with ASMD type B and A/B. Exploratory efficacy endpoints related to organomegaly, pulmonary and liver functions, and linear growth were evaluated at Week 52. Xenpozyme was dosed as follows: 0.03 mg/kg (Day 1, Week 0),0.1 mg/kg (Weeks 2), 0.3 mg/kg (Weeks 4 and 6), 0.6 mg/kg (Week 8 and 10), 1 mg/kg (Week 12), 2 mg/kg (Week 14) and then a maintenance dose of 3 mg/kg (Week 16 onwards). In Trial 2, 8 patients (7 patients from 2 to <12 years old, and 1 patient <2 years old) received an initial dose of 0.03 mg/kg Xenpozyme and all but one completed the dose escalation up to the maintenance dose of 3 mg/kg within 22 weeks. All patients were White and of non- Hispanic/Latino ethnicity. Patients enrolled in the trial had a spleen volume ≥5 MN measured by MRI. Age of patients treated with Xenpozyme ranged from 1 to 10 years old, with both sexes equally represented. Treatment with Xenpozyme resulted in improvements in mean percent change in % predicted DLco, spleen and liver volumes, platelet counts, and linear growth progression (as measured by height Z-scores) at Week 52 as compared to baseline (see Table 8).

Table 8: Efficacy Results in Xenpozyme-Treated Pediatric Patients with ASMD (Trial 2)

	Baseline Values	**Week 52 Values**
Mean % predicted DLco (SD) LS mean Percent change in % predicted DLco* (SE) 95% CI	(n=3) 48.5 (8.1)	(n=3) 70.9 (13.7) 45.9 (22.7) -12.5, 104.3
Mean spleen volume (MN) (SD) LS Mean Percent change in Spleen Volume (in MN) (SE) 95% CI	(n=8) 18.3 (5.6)	(n=8) 9.50 (2.4) -46.7 (3.6) -55.5, -37.9
Mean liver volume (MN) (SD) LS Mean Percent change in Liver Volume (in MN) (SE) 95% CI	(n=8) 2.5 (0.5)	(n=8) 1.6 (0.3) -38.1 (2.9) -44.1, -32.0

Mean platelet count (10^9/L) (SD) LS Mean Percent change in Platelet Count (SE) 95% CI	(n=8) 136.7 (33.2)	(n=7) 184.5 (54.2) 37.6 (13.7) 8.5, 66.7
Mean height Z-scores (SD) LS Mean Change in height Z-scores (SE) 95% CI	(n=8) -1.9 (0.8)	(n=7) -1.5 (1.0) 0.5 (0.1) 0.2, 0.8

Table key: ASMD: acid sphingomyelinase deficiency; CI: confidence interval; DLco; diffusing capacity of the lungs for carbon monoxide; MN: multiples of normal; SD: standard deviation; SE: standard error of the mean

Extension Trial in ASMD Pediatric Patients

The 8 pediatric patients 2 to <12 years of age from Trial 2 continued treatment in an open label long term trial (Trial 3) and were treated with Xenpozyme for 2.5 to 3.2 years. Efficacy analyses showed continued improvements in the 3 patients evaluated for % predicted DLco, 6 patients evaluated for platelet counts, and all 8 patients evaluated for spleen and liver volumes, compared to baseline, during the additional 6 months extension. In addition, the height Z-score increased by 1.3 from baseline when evaluated through 24 months of Xenpozyme treatment. Bone age, as assessed by hand x-ray, was delayed by a mean of 26.4 months at baseline in the 7 pediatric patients enrolled in Trial 2 with a bone age measured at Month 24 in Trial 3. The bone age improved to within a mean of 12 months of the chronological age when assessed at Month 24 in these 7 patients. (25)

Use of Xenpozyme is supported by evidence from an adequate, and well controlled trial (Trial 1) in adults with supportive efficacy, safety, and tolerability data in pediatric patients (Trial 2 and Trial 3. Compared to adults, a higher percentage of pediatric patients experienced treatment related serious adverse reactions, anaphylaxis, hypersensitivity reactions, and infusion-associated reaction within 24 hours of infusion. (25)

Pegunigalsidase alfa-iwxj (Elfabrio®)

Trial 1 was an open-label dose-ranging trial in adults diagnosed with Fabry disease (NCT01678898). Patients received Elfabrio at 0.2 mg/kg, 1 mg/kg, or 2 mg/kg given intravenously every other week for 52 weeks. The 0.2 mg/kg and 2 mg/kg dosage regimens are not approved and are not recommended. Trial 1 enrolled 18 patients who were ERT-naïve or who had not received ERT for more than 26 weeks and had a negative test for anti-pegunigalsidase alfa-iwxj IgG antibodies prior to enrollment. Two patients in the 1 mg/kg treatment group discontinued the trial after their first infusion; one discontinued due to a severe hypersensitivity reaction. Among the remaining 16 patients who completed Trial 1, 9 (56%) were males and 7 (44%) were females ranging in age from 17 to 54 years with a median age of 30 years. Twelve patients were White (75%) and 3 were Black or African American (19%). Three patients were Hispanic/Latino and 13 patients were non-Hispanic/Latino. Of the 9 males,

7 (78%) had the classic phenotype. The median baseline eGFR and proteinuria was 115 mL/min/1.73 m² and 0.11 g/g respectively. Among the male patients, the median value of residual alpha-galactosidase A activity was 2.4% (range: 0.0%-9.3%) in plasma and 1.3% (range: 0.0%-3.4%) in leukocytes. The average number of globotriaosylceramide (Gb3) inclusions per renal peritubular capillary (PTC) in renal biopsy specimens of patients was assessed by light microscopy using the quantitative Barisoni Lipid Inclusion Scoring System (BLISS). Evaluable renal biopsies were obtained at baseline and at 26 weeks of treatment in 14 of the 16 patients who completed Trial 1. (26)

Table 9 shows the changes from baseline to 26 weeks in the BLISS score (average number of Gb3 inclusions per renal PTC) for these 14 Elfabrio treated patients.

Table 9: Summary of the Renal Biopsy BLISS Score[1] of Gb3 Inclusions at Baseline and after 26 Weeks of Elfabrio Treatment in Adults with Fabry Disease (Trial 1)

	All Patients (N = 14)	**Males (N = 8)**	**Females (N = 6)**
Median (range)			
Baseline	3.2 (0.4, 9.0)	6.8 (0.4, 9.0)	1.2 (0.8, 3.3)
Week 26	0.7 (0.3, 2.5)	0.7 (0.3, 2.5)	0.7 (0.3, 1.4)
Change at Week 26	-2.5 (-8.5, 0.5)	-5.3 (-8.5, 0.5)	-0.7 (-2.5, 0.1)
Mean Change at Week 26 (95% CI)	-3.1 (-4.8, -1.4)	-4.7 (-7.1, -2.3)	-1.0 (-2.1, 0.1)

Table Key: CI: confidence interval; N: number.
The BLISS methodology counts the number of Gb3 inclusions in each renal PTC contained in a biopsy specimen. For each biopsy specimen (slide), approximately 300 renal PTCs were scored, and the final biopsy score for each patient was determined as the average number of Gb3 inclusions per peritubular capillary (PTC).

Trial 2 was a randomized, double-blind, and active-controlled trial (NCT03566017) in ERT experienced adults diagnosed with Fabry disease. Eligible patients were treated with agalsidase beta for at least 1 year prior to trial entry (the mean duration of agalsidase beta treatment prior to enrollment was 5.7 years). Patients were randomized 2:1 to receive Elfabrio (1 mg/kg intravenous infusion) or agalsidase beta (1 mg/kg intravenous infusion) every 2 weeks for 104 weeks.

A total of 77 patients were randomized and received at least one dose of Elfabrio (N = 52, 68%) or agalsidase beta (N = 25, 32%). Of these patients, 47 (61%) were males and 30 (39%) were females. Patients were 18 to 60 years of age with a median age of 46 years at baseline; 72 (94%) were White, 3 (4%) were Black or African American and 2 (3%) were Asian. Two patients were Hispanic/Latino and 75 patients were non-Hispanic/Latino. Forty-one (53%) patients had

the classic phenotype. The median baseline eGFR and proteinuria was 75 mL/min/1.73 m² and 0.11 g/g, respectively.

The primary efficacy endpoint was the annualized rate of change in eGFR (eGFR slope) assessed over 104 weeks. The estimated mean eGFR slope was -2.4 and -2.3 mL/min/1.73 m²/year on Elfabrio and agalsidase beta respectively. The estimated treatment difference was -0.1 (95% CI: -2.3, 2.1) mL/min/1.73 m²/year.

Per the FDA label, the safety and effectiveness of Elfabrio has not been established in pediatric patients. (26)

Sebelipase Alfa (Kanuma®)

Infants with Rapidly progressive LAL Deficiency Presenting within the First 6 Months of Life

The 2012 U.S. FDA approval for Sebelipase Alfa (Kanuma®) is based on the following studies:
A multicenter, open label, single-arm clinical study of Sebelipase Alfa (Kanuma®) was conducted in 9 infants with lysosomal acid lipase (LAL) deficiency who had growth failure or other evidence of rapidly progressive disease prior to 6 months of age. The age range at entry was 1 to 6 months. Patients received Sebelipase Alfa at 0.35 mg/kg once weekly for the first 2 weeks and then 1 mg/kg once weekly. Due to suboptimal clinical response, doses in all 6 surviving patients were escalated to 3 mg/kg once weekly, between 4 and 88 weeks (median 11 weeks) after starting treatment at 1 mg/kg. In 1 patient, the dose was escalated to 5 mg/kg once weekly between week 4 and 88 due to decreased growth velocity in a setting of positive neutralizing anti-drug antibodies to Sebelipase Alfa. The recommended dosage for these patients is 1 mg/kg to 3 mg/kg once weekly. Efficacy of Sebelipase Alfa was assessed by comparing the survival of 9 Sebelipase Alfa treated patients at 12 months of age with an untreated historical cohort of 21 patients with a similar age at disease presentation and clinical characteristics. Of the 9 Sebelipase Alfa treated infants, 6 patients survived beyond 12 months of age, compared to 0 of 21 patients in the historical cohort, all of whom died by 8 months of age. The median age of the 6 surviving Sebelipase Alfa treated patients was 18.1 months (range 12 to 42.2 months). Following initiation of treatment with Sebelipase Alfa 1 mg/kg once weekly: weight for age z scores improved in 3 of 5 surviving patients with growth failure, and all surviving patients demonstrated improvements in weight for age z scores following dose escalation to 3 mg/kg once weekly.

Across Study 1 and another study, Study 3, in infants with rapidly progressive LAL Deficiency, 9 patients received successive dose escalations up to 5 mg/kg once weekly due to suboptimal clinical response. The median duration of exposure to 5 mg/kg for the 9 patients whose doses were escalated to 5 mg/kg once weekly was 33 months (range 27 to 39 months) for patients in Study 1 and 15 months (range 5 to 24 months) in Study 3. Of the 9 patients whose Sebelipase Alfa dose was escalated to 5 mg/kg once weekly, 6 were alive at their last follow up at 3 years, and 2 were alive at their last follow up at 5 years. Of these 9 patients, 6 experienced normalization of ALT and/or AST which had remained abnormal on the lower Sebelipase Alfa dose.

Pediatric and Adult Patients with LAL Deficiency

The safety and efficacy of Sebelipase Alfa was also evaluated in a study that assessed 66 pediatric and adult patients with LAL deficiency, aged 4 to 58 (71% were less than 18 years old), in a multicenter, double blind, placebo-controlled trial. Patients were randomized to receive Sebelipase Alfa at a dose of 1 mg/kg (n=36) or placebo (n=30) once every other week for 20 weeks in the double-blind period. Sixty-two of the 66 patients (94%) had LDL C of 130mg/dL or greater at study entry. Most patients (58%) had LDL C above 190 mg/dL at study entry, and 24% of patients with LDL C above 190 mg/dL remained on lipid lowering medications. At the completion of the 20-week double-blind period of the trial, statistically significant improvement in percent change from baseline in LDL C was observed in the Sebelipase Alfa treated group as compared to the placebo group (mean difference and 95% CI). LDL C less than 130 mg/dL was achieved in 13 of 32 Sebelipase Alfa treated patients and in only 2 of 30 placebo treated patients with a baseline LDL C of less than 130 mg/dL or greater. A significant improvement in percentage change from baseline at 20 weeks was also noted in the Sebelipase Alfa treated group compared to the placebo group for other parameters related to LAL deficiency, including decreases in non-HDL C (mean difference and 95% C.I.: -21%, [-30%, -15%]; $p<0.0001$) and triglycerides (mean difference and 95% C.I.: -14%, [-28%, -1%]; $p=0.0375$), and increases in HDL C (mean difference and 95% C.I.: 20%, [12%, 26%]; $p<0.0001$). The effect of Sebelipase Alfa on cardiovascular morbidity and mortality has not been established. Patients treated with Sebelipase Alfa had larger reductions from baseline in ALT values and liver fat content (per Magnetic resonance imaging), compared to patients treated with placebo. The significance of these findings as they relate to the progression of liver disease has not been established.

Pediatric and adult patients who participated in the randomized, placebo-controlled trial were eligible to continue treatment in an open label extension. Sixty-five of 66 patients entered in which all patients received Sebelipase Alfa at a dose of 1mg/kg once every other week. Patients treated with Sebelipase Alfa for up to 36 months demonstrated improvements in lipid parameters, including LDL C levels, HDL C levels, and ALT.

Continuation of Treatment

Across Study 2 and another study, Study 4, in children and adults with LAL Deficiency, 23 of 97 patients received dose escalations from the protocol-defined starting dose of 1 mg/kg every other week (12 patients in Study 2 and 11 patients in Study 4). The median duration of exposure to the 3 mg/kg every other week regimen was 28 months (range 6 to 33 months) for patients in Study 2 and 12 months (range 3 to 27 months) in Study 4. Before being escalated to 3 mg/kg every other week, patients were on 1 mg/kg every other week for a median of 19 months (range 6 to 33 months), and most dose escalations were initiated in response to an increase in serum transaminase levels, an increase in serum lipids, or a decrease in WFA z-scores in children. Of the 23 patients whose Sebelipase Alfa dose was escalated to 3 mg/kg every other week, 20 were children. After the dose escalation, 14 of the 23 patients experienced normalization of one or more of the following biomarkers which had remained abnormally high on the lower Sebelipase Alfa dose: serum transaminases, triglycerides, and/or LDL-c.

The FDA approval was based on clinical trials on individuals greater than 1 month of age therefore the safety and efficacy has not been demonstrated in infants less than 1 month of age. Across all clinical trials, anaphylaxis occurred in 3% of patients (n=106). Appropriate medical support should be readily available when Sebelipase Alfa is administered. (27)

Additional Studies

Lysosomal acid lipase deficiency is characterized by hepatomegaly and dyslipidaemia, which can lead to cirrhosis and premature atherosclerosis. In a 2020 open-label extension study by Malinova et al., (42) adults with LAL deficiency who received sebelipase alfa treatment for 1 year reduced serum transaminase levels and liver fat content and improved serum lipid levels. Overall, the data from this study (LAL-CL04) reported on long term data out to 5 years. Of 8 patients enrolled, 7 received sebelipase alfa for 224-260 weeks; 1 was lost to follow-up. Median baseline levels of alanine aminotransferase and aspartate aminotransferase (81.5 and 50.0 U/L, respectively) were decreased through the end-of-study visit (54.0 and 34.0 U/L). Median low-density lipoprotein cholesterol decreased from 113 to 78 mg/dL, total cholesterol decreased from 171 to 132 mg/dL, and high-density lipoprotein cholesterol increased from 37 to 42 mg/dL. Most treatment-emergent events were not serious (99%), mild/moderate (98%) and unrelated to the use of sebelipase alfa (87%); no patient discontinued as a result of treatment-emergent events. One patient had 2 serious treatment-emergent events (cholecystitis and cholelithiasis; assessed as unlikely related to sebelipase alfa. Two patients had 20 nonserious infusion-associated reactions in weeks 6-38; all were manageable. One patient tested positive for antidrug antibodies (single occurrence). Sebelipase alfa was well tolerated and improved serum transaminase and lipid levels for up to 5 years in adults with LAL deficiency.

In 2022 Burton et al. (43) performed a single-arm, open-label study that evaluated the efficacy and safety of sebelipase alfa when used in patients with LAL deficiency. Patients >8 months of age diagnosed with LAL deficiency received sebelipase alfa 1.0 mg/kg by intravenous infusion every other week (qow) for up to 144 weeks. Dose was increased to 3.0 mg/kg qow and subsequently to 3.0 mg/kg weekly per protocol. Dose reductions for tolerability were permitted to 0.35 mg/kg qow. Thirty-one patients were enrolled and treated. Baseline median alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels were 63.5 and 65.5 U/L, respectively. Twenty-eight patients completed 96 weeks of treatment, and 25 continued into the extended treatment period; 19 completed 144 weeks. From baseline to week 144, median ALT and AST levels changed by -42.0 and -22.0 U/L, respectively, median liver and spleen volumes decreased from 1.4 to 1.3 and from 2.6 to 2.3 multiples of normal. Median low-density lipoprotein cholesterol levels decreased by 52.6 mg/dL, and median high-density lipoprotein cholesterol increased by 9.8 mg/dL. Liver biopsies showed improved or stable histopathology at 48 and 96 weeks compared to baseline. Infusion-associated reactions were mild (n = 1) or moderate (n = 2). One patient (a candidate for liver transplant at baseline) discontinued treatment because of liver transplant (unrelated to treatment). Two patients tested positive for nonneutralizing, anti-drug antibodies on 1 occasion each. Overall, Sebelipase alfa was well tolerated and resulted in sustained improvements in liver and lipid parameters.

Taliglucerase alfa (Elelyso)

The safety and efficacy of taliglucerase alfa (Elelyso®) were assessed in 31 adult patients with Type 1 Gaucher disease. The trial was a 9-month, multicenter, double blind, randomized trial in patients with Gaucher disease related enlarged spleens (>8 times normal) and thrombocytopenia (<120,000 /mm^3). Sixteen patients had enlarged livers and 10 patients had anemia at baseline. All patients were naïve to ERT. Patients with severe neurological symptoms were excluded from the trial. Patients were 19 to 74 years of age (mean age 36 years), and 48% were male. Patients were randomized to receive Elelyso at a dosage of either 30 units/kg (n=15) or 60 units/kg (n=16) every other week. The recommended dosage in treatment naïve adult patients is 60 units/kg every other week.

The spleen volume, liver volume, platelet count, and hemoglobin were evaluated per MRI after 9 months of treatment with Elelyso and reported as percentage of body weight (% BW) and multiples of normal (MN). The observed change from baseline in the primary endpoint, reduction in spleen volume, was considered to be clinically meaningful in light of the natural history of untreated Gaucher disease. (See table 10)

Table 10: Mean (SD) changes in clinical parameters from baseline to 9 months in treatment-naïve adults with type 1 Gaucher disease initiating therapy with Eleyso (n=31)

	Clinical Parameter	**30 units/kg* (n=15) Mean (SD)**	**60 units/kg (n=16) Mean (SD)**
Spleen Volume (% BW)	Baseline	3.1 (1.5)	3.3 (2.7)
	Month 9	2.2 (1.3)	2.1 (1.9)
	Change	-0.9 (0.4)	-1.3 (1.1)
Spleen Volume (MN)	Baseline	15.4 (7.7)	16.7 (13.4)
	Month 9	11.1 (6.3)	10.4 (9.4)
	Change	-4.5 (2.1)	-6.6. (5.4)
Liver Volume (% BW)	Baseline	4.2 (0.9)	3.8 (1.0)
	Month 9	3.6 (0.7)	3.1 (0.7)
	Change	-0.6 (0.5)	-0.6 (0.4)
Liver Volume (MN)	Baseline	1.7 (0.4)	1.5 (0.4)
	Month 9	1.4 (0.3)	1.2 (0.3)
	Change	-0.2 (0.2)	-0.3 (0.2)
Platelet Count (mm^3)	Baseline	75,320 (40,861)	65,038 (28,668)
	Month 9	86,747 (50,989)	106,531 (53,212)
	Change	11,427 (20,214)	41,494 (47,063)
Hemoglobin (g/dl)	Baseline	12.2 (1.7)	11.4 (2.6)
	Month 9	14.0 (1.4)	13.6 (2.0)
	Change	1.6 (1.4)	2.2 (1.4)

Table Key: BW: body weight; g/dl: grams per deciliter; Kg: kilogram; mm^3: cubic millimeter; MN: multiples of normal; N: number; SD: standard deviation.
*The recommended Elelyso dosage in treatment naïve adult patients is 60 units/kg every other week. Elelyso 30 units/kg every other week is not a recommended dosage.

Twenty-six of the 31 patients in this clinical trial continued blinded treatment with Elelyso in an extension trial for a total treatment duration of 24 months. The following data are the changes in clinical parameters from baseline to month 24 for the 30 units/kg (n=17) and 60 units/kg (n=14) dose groups, respectively: mean (SD) spleen volume (% BW) decreased -1.4 (0.6) and -2.0 (2.0); hemoglobin increased 1.3 (0.7) g/dL and 2.4 (2.3) g/dL; liver volume (% BW) decreased -1.1 (0.5) and -1.0 (0.7); and platelet count increased 28,433 (31,996) /mm^3 and 72,029 (68,157) /mm^3. Twenty-three of the 26 patients who continued the open label treatment for an additional 12 months demonstrated stability within the clinical parameters.

The safety and efficacy of Elelyso were assessed in 9 pediatric patients with Type 1 Gaucher disease. The trial was a 12-month, multicenter, double blind, randomized study in treatment naïve patients. Patients were 2 to 13 years of age (mean age 8.1 years), and 67% were male. Patients were randomized to receive Elelyso at a dosage of either 30 units/kg (n=4) or 60 units/kg (n=5) every other week. The recommended Elelyso dosage in treatment naïve pediatric patients is 60 units/kg every other week. Elelyso 30 units/kg every other week is not a recommended dosage. The following data are the changes in clinical parameters from baseline to Month 12 for the 60 units/kg dose group (n=5): spleen volume decreased from 18.4 MN to 11.0 MN; hemoglobin increased from 11.1 g/dL to 11.7 g/dL; liver volume decreased from 2.1 MN to 1.6 MN; platelet count increased from 80,000/mm^3 to 131,000/mm^3. Nine pediatric patients in the 12-month clinical trial continued blinded treatment with Eleyso in an extension trial for a total treatment duration of 24 months. The following data are the changes in clinical parameters from baseline to Month 24 for the 60 units/kg dose group (n=5): spleen volume decreased by 19.0 MN; hemoglobin increased by 2.5 g/dl; liver volume decreased by 0.8 MN; and platelet count increased by 76,000/mm^3.

A clinical trial in patients switching from imiglucerase treatment to Elelyso was assessed in 31 patients (26 adults and 5 pediatric patients) with Type 1 Gaucher disease. The trial was a 9-month, multicenter, open label, single-arm study in patients who had been receiving treatment with imiglucerase at dosages ranging from 9.5 units/kg to 60 units/kg every other week for a minimum of 2 years. Patients were required to be clinically stable and have a stable biweekly dose of imiglucerase for at least 6 months prior to enrollment. Patients were 6 to 66 years of age (mean age 42 years, including pediatric patients), and 55% were male. Imiglucerase therapy was stopped, and treatment with Elelyso was administered every other week at the same number of units as each patient's previous imiglucerase dose. If needed, adjustment of dosage was allowed during the study in order to maintain stability of clinical parameters (i.e., spleen volume, liver volume, platelet count, and hemoglobin). Mean (±SD) organ volumes and hematologic values remained stable through 9 months of the Elelyso treatment. At baseline, spleen volume was 5.2 (±0.9) MN, liver volume was 1.0 (±0.1) MN, platelet count was 161,137 (±73,387)/mm^3, and hemoglobin was 13.5 (±1.4) g/dL. After 9 months of Elelyso treatment,

spleen volume was 4.8 (±0.9) MN, liver volume was 1.0 (±0.0) MN, platelet count was 161,167 (±80,820)/mm^3, and hemoglobin was 13.4 (±1.5) g/dL. Elelyso dose remained unchanged in 30 of 31 patients. One patient required a dose increase at Week 24 (from 9.5 units/kg to 19 units/kg) for a platelet count of 92,000/mm^3 at Week 22, which subsequently increased to 170,000/mm^3 at Month 9.

Eighteen of the 26 adult patients who completed the 9-month clinical trial continued treatment with Elelyso in an open-label extension trial for additional 27 months (total treatment 36 months). Patients maintained stability in clinical parameters (spleen volume, liver volume, platelet count and hemoglobin); however only 10 of 18 adult patients completed 27 months of Elelyso treatment in the extension trial and 7 patients had their spleen and liver volumes assessed at 36 months.

Five pediatric patients in the 9-month clinical trial who continued open-label treatment with Elelyso for an additional 24 months demonstrated stability in these clinical parameters. Per the FDA label, there are insufficient data to inform dosing in patients less than 4 years of age. (28)

In 2015, Zimran et al. completed a multicenter, randomized, double blind, parallel-dose, 12-month study assessing efficacy and safety of taliglucerase alfa in pediatric patients (age 2-18) with Gaucher disease. Eleven children (n=11) were randomized to taliglucerase alfa 30U/kg (n=6) or 60U/kg (n=5) per infusion every other week. From baseline to month 12, the following changes were noted in the taliglucerase alfa 30-U/kg and 60-U/kg dose groups, respectively: median hemoglobin concentrations increased by 12.2% and 14.2%; the interquartile ranges of median percent change in hemoglobin levels from baseline were 20.6 and 10.4, respectively; mean spleen volume decreased from 22.2 to 14.0 multiples of normal (MN) and from 29.4 to 12.9 MN; mean liver volume decreased from 1.8 to 1.5 MN and from 2.2 to 1.7 MN; platelet counts increased by 30.9% and 73.7%; and chitotriosidase activity was reduced by 58.5% and 66.1%. Nearly all adverse events were mild/moderate, unrelated to treatment, and transient. One patient presented with treatment related gastroenteritis reported as a serious adverse event due to the need for hospitalization for rehydration. No patient discontinued treatment. The data suggest that taliglucerase alfa has the potential to be a therapeutic treatment option for children with Gaucher disease. Although results are promising, additional long-term data with larger sample sizes is needed to validate safety and efficiency in pediatric patients less than 4 years of age. (44)

Velaglucerase alpha (VPRIV)

The efficacy of VPRIV was assessed in 3 clinical studies in a total of 99 patients with type 1 Gaucher disease: 82 patients aged 4 years and older received VPRIV and 17 patients aged 3 years and older received imiglucerase. Studies I and II were conducted in patients who were not currently receiving Gaucher disease therapy. Study III was conducted in patients who were receiving imiglucerase treatment immediately before starting VPRIV. The long-term safety of VPRIV was assessed in Study IV, an open-label extension trial in a total of 93 patients with type 1 Gaucher disease ages 3 years and older. Patients who had completed Studies I to III were eligible to participate in Study IV. In Studies I through IV, VPRIV was administered intravenously

over 60 minutes at a maximum dose of 60 Units/kg every other week. Doses above 60 Units/kg were not studied in these trials.

Study I was a 12 month, randomized, double blind, parallel dose group, multinational study in 25 patients aged 4 years and older with Gaucher disease related anemia and either thrombocytopenia or organomegaly. Patients were not allowed to have had disease specific therapy for at least the previous 30 months; all but 1 had no prior therapy. The mean age was 26 years and 60% were male. Patients were randomized to receive VPRIV at a dose of either 45 units/kg (n=13) or 60 units/kg (n=12) every other week.

At baseline, mean hemoglobin concentration was 10.6 g/dL, mean platelet count was 97 x 109/L, mean liver volume was 3.6 % of body weight (% BW), and mean spleen volume was 2.9 % BW. For all studies, liver and spleen volumes were measured by MRI. The changes in clinical parameters after 12 months of treatment are shown in Table 11. The observed change from baseline in the primary endpoint, hemoglobin concentration, was considered to be clinically meaningful in the 60 units/kg dose, in light of the natural history of untreated Gaucher disease.

Table 11: Mean Change From Baseline to Month 12 For Clinical Parameters in Patients with Type 1 Gaucher Disease Initiating Therapy with VPRIV in Study I

	Mean Changes from Baseline ± Std. Err. of the Mean	
	VPRIV Dose (given every other week)	
	45 units/kg N = 13	**60 units/kg N = 12**
Hemoglobin concentration change (g/dL)	2.4 ± 0.4*	2.4 ± 0.3**
Platelet count change (x 109/L)	41 ± 14*	51 ± 12*
Liver volume change (% BW)	-0.30 ± 0.29	-0.84 ± 0.33
Spleen volume change (% BW)	-1.9 ± 0.6*	-1.9 ± 0.5*

Table Key: BW: body weight; VPRIV: Velaglucerase alpha

Study II was a 9 month, randomized, double blind, active-controlled (imiglucerase), parallel-group, multinational study in 34 patients aged 3 years and older. Patients were required to have Gaucher disease related anemia and either thrombocytopenia or organomegaly. Patients were not allowed to have had disease specific therapy for at least the previous 12 months. The mean age was 30 years of age and 53% were female; the youngest patient who received VPRIV was age 4 years. Patients were randomized to receive either 60 units/kg of VPRIV (n=17) or 60 units/kg of imiglucerase (n=17) every other week. At baseline, the mean hemoglobin concentration was 11.0 g/dL, mean platelet count was 171 x 109/L, and mean liver volume was 4.3 % BW. For the patients who had not had splenectomy (7 in each group) the mean spleen volume was 3.4 % BW. After 9 months of treatment, the mean absolute increase from baseline in hemoglobin concentration was 1.6 g/dL ± 0.2 (SE) for patients treated with VPRIV. The mean treatment difference in change from baseline to 9 months [VPRIV–imiglucerase] was 0.1 g/dL ±

0.4 (SE). In Studies I and II, examination of age and gender subgroups did not identify differences in response to VPRIV among these subgroups. The number of non-Caucasian patients in these studies was too small to adequately assess any difference in effects by race.

Study III was a 12-month, open label, single-arm, multinational study in 40 patients aged 9 years and older who had been receiving treatment with imiglucerase at doses ranging between 15 units/kg to 60 units/kg for a minimum of 30 consecutive months. Patients also were required to have a stable biweekly dose of imiglucerase for at least 6 months prior to enrollment. The mean age was 36 years and 55% were female. Imiglucerase therapy was stopped, and treatment with VPRIV was administered every other week at the same number of units as the patient's previous imiglucerase dose. Adjustment of dosage was allowed by study criteria if needed to maintain clinical parameters. Hemoglobin concentrations and platelet counts remained stable on average through 12 months of VPRIV treatment. After 12 months of treatment with VPRIV the median hemoglobin concentration was 13.5 g/dL (range: 10.8, 16.1) vs. the baseline value of 13.8 g/dL (range: 10.4, 16.5), and the median platelet count after 12 months was 174 x 109/L (range: 24, 408) vs. the baseline value of 162 x 109/L (range: 29, 399). No patient required dosage adjustment during the 12-month treatment period.

In Study IV, patients who had previously been receiving imiglucerase treatment were administered VPRIV. Patients previously treated with imiglucerase maintained stability in clinical parameters (hemoglobin concentration, platelet count, liver volume) compared with baseline for up to 60 months of treatment with ERT.

The most common adverse reactions (.10%) include headache, dizziness, abdominal pain, nausea, back pain, joint pain, activated PTT prolonged, fatigue/asthenia, and pyrexia. The most serious adverse reactions in patients treated with VPRIV were hypersensitivity reactions,

The safety and effectiveness of VPRIV has been established for ERT in patients between 4 and 17 years of age. Use of VPRIV in this age group is supported by evidence from adequate and well controlled studies of VPRIV in 70 adult patients and 20 pediatric patients. The safety and efficacy profiles were similar between pediatric and adult patients. The safety of VPRIV has not been established in pediatric patients younger than 4 years of age. (29)

Vestronidase Alfa-vjbk (Mepsevii®)

The safety and efficacy of Mepsevii was established in a clinical trial that enrolled a total of 23 patients with MPS VII ranging in age from 5 months to 25 years. Patients received treatment with Mepsevii at doses up to 4 mg/kg once every 2 weeks for up to 164 weeks. Efficacy was primarily assessed via the 6-MWT in 10 patients. After 24 weeks of treatment, the mean difference in distance walked relative to placebo was 18 meters. Additional follow-up for up to 120 weeks displayed continued improvement in 3 patients and stabilization in the others. Two patients experienced marked improvement in pulmonary function. The effect of Mepsevii on the central nervous system manifestations of MPS VII has not been determined. The most common side effects after treatment included infusion site reactions, diarrhea, rash and

anaphylaxis therefore the labeling includes a black box warning related to anaphylaxis with the use of Mepsevii. (30)

Professional Guidelines and Position Statements

American College of Medical Genetics (ACMG)

In 2011, the ACMG published guidelines for lysosomal storage diseases with individual recommendations for Fabry disease, Gaucher disease and Pompe diseases that state:

- "Agalsidase beta is suggested as the standard of care for individuals with symptoms of Fabry disease. It is noted that ERT slows progression of renal insufficiency in individuals with sufficient proteinuria, improves pulmonary and gastrointestinal symptoms and reduces renal, cardiac and CNS events.
- During the first year of treatment, ERT demonstrates improvements in peripheral symptoms in type I Gaucher disease; however, bone effects lag behind and may take several years to realize improvement. ACMG suggests using substrate reduction therapy (SRT) as second line treatment in adults who experience severe side effects with ERT or who refuse ERT and/or have a milder form of the disease.
- Alglucosidase alfa (Myozyme/Lumizyme; Genzyme Corporation) has been shown to be effective in the treatment of patients with early and late-onset Pompe disease. The individual response to ERT may vary due to the development of rhGAA specific antibodies, age of presentation, rate of progression of disease, muscle fiber type, defective autophagy, and underlying genotype. It is important to identify patients with infantile PD because ERT needs to be initiated as early as possible." (45)

Coding

Procedure codes on Medical Policy documents are included **only** as a general reference tool for each policy. **They may not be all-inclusive.**

The presence or absence of procedure, service, supply, or device codes in a Medical Policy document has no relevance for determination of benefit coverage for members or reimbursement for providers. **Only the written coverage position in a Medical Policy should be used for such determinations.**

Benefit coverage determinations based on written Medical Policy coverage positions must include review of the member's benefit contract or Summary Plan Description (SPD) for defined coverage vs. non-coverage, benefit exclusions, and benefit limitations such as dollar or duration caps.

CPT Codes	None
HCPCS Codes	C9399, G0138, J0180, J0218, J0219, J0220, J0221, J1203, J1322, J1458, J1743, J1786, J1931, J2508, J2840, J3060, J3385, J3397, J3490, J3590 [C9085: deleted 4/1/2022]

*Current Procedural Terminology (CPT®) ©2023 American Medical Association: Chicago, IL.

References

1. National Organization of Rare Disorders. Rare disease database: Lysosomal storage disorder. (Mar 2008). Available at <https://www.rarediseases.org> (accessed February 28, 2024).
2. Cleveland Clinic. Lysosomal storage diseases (Jun 2022). Available at <https://my.clevelandclinic.org> (accessed February 28, 2024).
3. National Organization of Rare Disorders. Rare disease database: Acid sphingomyelinase deficiency. (Sep 2022). Available at <https://www.rarediseases.org> (accessed February 28, 2024).
4. National Organization of Rare Disorders. Rare disease database: Fabry disease. (Jun 6, 2019). Available at <https://www.rarediseases.org> (accessed February 29, 2024).
5. Ahsan N. Fabry Disease. (May 23, 2023). Available at <https://www.emedicine.medscape.com> (accessed February 29, 2024).
6. National Gaucher Foundation, Inc. Gaucher disease: What is Gaucher disease. (2024). Available at <https://www.gaucherdisease.org> (accessed February 29, 2024).
7. National Organization of Rare Disorders: Hypophosphatasia. (Feb 26, 2021). Available at <https://www.rarediseases.org> (accessed February 29, 2024).
8. National Organization of Rare Disorders. Lysosomal acid lipase deficiency. (2024). Available at <https://www.rarediseases.org> (accessed March 1, 2024).
9. National Organization of Rare Disorders. Wolman disease. (Aug 2016). Available at <https://rarediseases.info.nih.gov> (accessed March 1, 2024).
10. National Organization of Rare Disorders. Mucopolysaccharidoses. (Aug 2016). Available at <https://www.rarediseases.org> (accessed March 1, 2024).
11. National Institute of Neurological Disorders and Stroke (NINDS). Mucopolysaccharidoses. (Nov 2023). Available at <https://www.ninds.nih.gov> (accessed March 1, 2024).
12. National Organization of Rare Disorders. Pompe Disease. (Jan 2024). Available at <https://www.rarediseases.org> (accessed March 1, 2024).
13. National Institute of Neurological Disorders and Stroke (NINDS). Pompe Disease Information Page. (Nov 2023). Available at <https://www.ninds.nih.gov> (accessed March 1, 2024).
14. FDA-Highlights of prescribing information. Fabrazyme® (Agalsidase Beta). Food and Drug Administration. (Feb 2024). Available at <https://www.accessdata.fda.gov> (accessed February 26, 2024).
15. FDA- Highlights of prescribing information. Avalglucosidase alfa-NGPT (Nexviazyme®). Food and Drug Administration. (Aug 2021). Available at <https://www.accessdata.fda.gov> (accessed February 26, 2024).
16. FDA- Highlights of prescribing information. Elaprase® (idursulfase). Food and Drug Administration. (Nov 2018). Available at <https://www.accessdata.fda.gov> (accessed February 26, 2024).
17. FDA- Highlights of prescribing information. Lumizyme® (alglucosidase alfa). Food and Drug Administration. (May 2023). Available at <https://www.accessdata.fda.gov> (accessed February 26, 2024).
18. FDA expands approval of drug to treat Pompe disease to patients of all ages; removes risk mitigation strategy requirements (Aug 2014). Available at <https://drugs.com> (accessed March 1, 2024).

19. FDA- Highlights of prescribing information. Strensiq® (Asfotase alfa). Food and Drug Administration. (Jun 2020). Available at <https://www.accessdata.fda.gov> (accessed February 26, 2024).
20. FDA- Highlights of prescribing information. Pombiliti™ (Cipaglucosidase alfa-atga). Food and Drug Administration. (Sep 2023). Available at <https://www.accessdata.fda.gov> (accessed February 26, 2024).
21. FDA- Highlights of prescribing information. Vimizim® (elosulfase alfa). Food and Drug Administration. (Dec 2019). Available at <https://www.accessdata.fda.gov> (accessed February 26, 2024).
22. FDA- Highlights of prescribing information. Naglazyme® (Galsulfase). Food and Drug Administration. (Dec 2019). Available at <https://www.accessdata.fda.gov> (accessed February 27, 2024).
23. FDA- Highlights of prescribing information. Cerezyme® (imiglucerase). Food and Drug Administration. (Dec 2021). Available at <https://www.accessdata.fda.gov> (accessed February 27, 2024).
24. FDA- Highlights of prescribing information. Aldurazyme (Laronidase). Food and Drug Administration. (Dec 2023). Available at <https://www.accessdata.fda.gov> (accessed February 27, 2024).
25. FDA- Highlights of prescribing information. Olipudase alfa (Xenpozyme®). (Dec 2023). Food and Drug Administration. Available at <https://www.accessdata.fda.gov> (accessed February 27, 2024).
26. FDA- Highlights of prescribing information. Pegunigalsidase alfa-iwxj (Elfabrio®) Olipudase alfa (Xenpozyme®). (May 9, 2023). Food and Drug Administration. Available at <https://www.accessdata.fda.gov> (accessed February 27, 2024).
27. FDA- Highlights of prescribing information. Kanuma® (sebelipase alfa). Food and Drug Administration. (Nov 2021). Available at <https://www.accessdata.fda.gov> (accessed February 27, 2024).
28. FDA- Highlights of prescribing information. Elelyso® (Taliglucerase Alfa). Food and Drug Administration. (May 2023). Available at <https://www.accessdata.fda.gov> (accessed February 27, 2024).
29. FDA- Highlights of prescribing information. VPRIV® (velaglucerase alfa). Food and Drug Administration. (Dec 2020). Available at <https://www.accessdata.fda.gov> (accessed February 27, 2024).
30. FDA- Highlights of prescribing information. Mepsevii® (Vestronidase alfa-vjbk). Food and Drug Administration. (Dec 2020). Available at <https://www.accessdata.fda.gov> (accessed February 27, 2024).
31. Sirrs SM, Bichet DG, Casey R, et. al. Outcomes of patients treated through the Canadian Fabry disease initiative. Mol Genet Metab. Apr 2014; 111(4):499-506. PMID 24534763
32. Muenzer J, Wraith, JE, Beck M, et al. A phase II/III clinical study of enzyme replacement therapy with idursulfase in mucopolysaccharidosis II (Hunter syndrome). Genet Med. Aug 2006; 8(8):465-473. PMID 16912578
33. Muenzer J, Bodamer O, Burton B, et al. The role of enzyme replacement therapy in severe Hunter syndrome-an expert panel consensus. Eur J Pediatr. Jan 2012; 171(1):181-188. PMID 22037758

34. Zhu D, Zhu J, Qiu W, et al. A multi-centre prospective study of the efficacy and safety of alglucosidase alfa in Chinese patients with infantile-onset pompe disease. Front Pharmacol. 2022; 13:903488. PMID 35833019
35. van der Ploeg A, Barohn R, Carlson L, et al. Open-label extension study following the Late-Onset Treatment Study (LOTS) of alglucosidase alfa. Mol Genet Metab. Nov 2012; 107(3):456-461. PMID 23031366
36. Genest F, Rak D, Petryk A, et al. Physical function and health-related quality of life in adults treated with asfotase alfa for pediatric-onset hypophosphatasia. JBMR Plus. Aug 2020; 4(9):e10395. PMID 32995696
37. Dahir k, Seefried L, Kishnani P, et. al. Clinical profiles of treated and untreated adults with hypophosphatasia in the global HPP registry. Orphanet J Rare Dis. 2022; 17:277. PMID 35854311
38. Hendriksz C, Parini R, AlSayed M, et al. Impact of long-term elosulfase alfa on activities of daily living in patients with Morquio A syndrome in an open-label, multi-center, phase 3 extension study. Clinical Trial Mol Genet Metab. Feb 2018; 123(2):127-134. PMID 29248359
39. Gomes D, Gallo L, Leite B et al. Clinical effectiveness of enzyme replacement therapy with galsulfase in mucopolysaccharidosis type VI treatment: Systematic review. J Inherit Metab Dis. Jan 2019; 42(1):66-76. PMID 30740728
40. Weinreb N, Barranger J, Packman S, et al. Imiglucerase (Cerezyme) improves quality of life in patients with skeletal manifestations of Gaucher disease. Clin Genet. Jun 2007; 71(6):576-588. PMID 17539908
41. Weinreb NJ, Camelo JS Jr, Charrow J, et al. Gaucher disease type 1 patients from the ICGG Gaucher Registry sustain initial clinical improvements during twenty years of imiglucerase treatment. Mol Genet Metab. Feb 2021; 132(2):100-111. PMID 33485799.
42. Malinová V, Balwani M, Sharma R, et al. Sebelipase alfa for lysosomal acid lipase deficiency: 5-year treatment experience from a phase 2 open-label extension study. Sep 2020; 40(9):2203-2214. PMID 32657505
43. Burton B, Consuelo Sanchez A, Kostyleva M, et al. Long-term sebelipase alfa treatment in children and adults with lysosomal acid lipase deficiency. J Pediatr Gastroenterol Nutr. Jun 2022; 74(6):757-764. PMID 35442238
44. Zimran A, Gonzalez-Rodriguez DE, Abrahamov A, et al. Safety and efficacy of two dose levels of taliglucerase alfa in pediatric patients with Gaucher disease. Blood Cells Mol Dis. Jan 2015; 54(1):9-16. PMID 25453586
45. Wang RY, Bodamer OA, Watson MS, et al. American College of Medical Genetics (ACMG). Lysosomal storage diseases: Diagnostic confirmation and management of presymptomatic individuals. 2011; 13(5):57-484. PMID 21502868

Centers for Medicare and Medicaid Services (CMS)

The information contained in this section is for informational purposes only. HCSC makes no representation as to the accuracy of this information. It is not to be used for claims adjudication for HCSC Plans.

The Centers for Medicare and Medicaid Services (CMS) does not have a national Medicare coverage position. Coverage may be subject to local carrier discretion.

A national coverage position for Medicare may have been developed since this medical policy document was written. See Medicare's National Coverage at <http://www.cms.hhs.gov>.

Policy History/Revision	
Date	**Description of Change**
07/15/2024	Document updated with literature review. The following changes were made in Coverage: 1) Added "Cipaglucosidase alfa-atga (Pombiliti™) may be considered medically necessary for treatment of late-onset Pompe disease when all of the following criteria are met: a) Individual is 18 years of age or older; and b) Individual weighs greater than or equal to 40 kg; and c) Will be taken in combination with Opfolda; and d) Individual is not improving on current enzyme replacement therapy (ERT)"; 2) Added "Cipaglucosidase alfa-atga (Pombiliti™) is considered experimental, investigational and/or unproven for all other indications"; 3) Updated the term "patient(s)" to "individual(s)" in each section of Coverage. Added reference 20; others updated.
06/01/2024	Document updated. The following change was made to Continuation Therapy in Coverage: Removed "through a previously authorized pharmacy or medical benefit" in the statement: "Continuation of Cerezyme (imiglucerase) and Elelyso (taliglucerase alfa) therapy for Gaucher Disease is considered medically necessary for all members (including new members…" No new references added.
07/01/2023	Document updated with literature review. The following changes were made in coverage: 1) Added new coverage/section specific to Olipudase alfa-rpcp (Xenpozyme) 2) Added new coverage/section specific to Pegunigalsidase alfa-iwxj (Elfabrio®) 3) Removed section specific to Myozyme and added "formerly known Myozyme" to the existing Lumizyme coverage 4) Removed "for long-term enzyme replacement therapy (ERT)" to the existing Imiglucerase (Cerezyme) coverage statement. Added references 2, 3, 24, 32, 34, 36, 39, 40, 43, 44; others updated, some removed.
04/01/2022	Document updated with preferred drug criteria.
02/15/2022	Document updated with literature review. The following changes were made to Coverage: 1) Agalsidase beta (fabrazyme®): Added "confirmed" prior to diagnosis 2) Taliglucerase alfa (Elelyso™): removed "for long term ERT" and changed term to "4 years of age or older" 3) avalglucosidase alfa-NGPT (Nexviazyme™): added conditional coverage for late-onset Pompe disease. 4) Added references 7, 13, 31, 33; others updated/some removed.
05/01/2021	Document updated with literature review. The following changes were made to Coverage: a) "Enzyme-replacement therapy when utilized for the treatment of lysosomal storage disorders (LSD) may be considered medically

	necessary for the specific indications noted under each of the following enzyme-replacements therapies" b) Added 2 years of age or older to the Agalsidase beta (Fabrazyme®) criteria. Added reference 8; others updated, some removed.
01/15/2019	Reviewed. No changes.
05/01/2018	The following was added to Coverage: 1) Asfotase alfa (Strensiq™) may be considered medically necessary for the treatment of patients with perinatal/infantile-and juvenile-onset hypophosphatasia (HPP). 2) Asfotase alfa (Strensiq™) is considered experimental, investigational and/or unproven for all other indications. 3) Vestronidase alfa-vjbk (Mepsevii™) may be considered medically necessary in patients 5 months of age or greater with a diagnosis of Mucopolysaccharidosis VII (MPS VII, Sly syndrome). 4) Vestronidase alfa-vjbk (Mepsevii™) is considered experimental, investigational and/or unproven for all other indications. 5) Agalsidase beta (Fabrazyme) and Idursulfase (Elaprase™): changed the wording on the experimental, investigational and/or unproven coverage statement from "disease and conditions" to "all other indications".
01/15/2017	Document updated with literature review. The following changes were made to Coverage: 1) 5 years of age or greater added to section II as conditional coverage for Idursulfase (Elaprase™) 2) 6 months of age or greater added to section VII as conditional coverage for Laronidase (Aldurazyme®) 3) Expanded experimental, investigational and/or unproven coverage statement to contain "including but not limited to treatment of members with the Scheie form of MPS I who have mild symptoms" to section VII Laronidase (Aldurazyme®) 4) Patients 4 years of age or greater added to section X as conditional coverage for Taliglucerase alfa (Elelyso™) 5) patients 4 years of age or greater added to section XI as conditional coverage for Velaglucerase alpha (VPRIV).
07/01/2016	Document updated with literature review. The following was added to Coverage: 1) Sebelipase Alfa (Kanuma™) may be considered medically necessary when the patient is one month of age or greater; and the patient has a diagnosis of Lysosomal Acid Lipase (LAL) deficiency. 2) Sebelipase Alfa (Kanuma™) is considered experimental, investigational and/or unproven for all other indications. Description, References and Rationale were updated to reflect change in Coverage.
01/01/2016	Document updated with literature review. The following medically necessary drugs and indications were added to Coverage: 1) Agalsidase beta (Fabrazyme) 2) Galsulfase (Naglazyme) 3) Imiglucerase (Cerezyme) 4) Taliglucerase alfa (Elelyso ™) 5) Laronidase (Aldurazyme) 6) Taliglucerase alfa (Elelyso ™). The following experimental, investigational and/or unproven drugs and indications were added to Coverage: 1) Agalsidase beta (Fabrazyme) 2) Galsulfase (Naglazyme) 3) Imiglucerase (Cerezyme) 4)

	Taliglucerase alfa (Elelyso ™) 5) Laronidase (Aldurazyme) 6) Taliglucerase alfa (Elelyso ™). Entire policy was completely revised.
12/15/2014	Document updated with literature review. The following change was made to the coverage of Lumizyme: the restrictions for age and cardiac hypertrophy were removed.
07/01/2014	Document updated with literature review. The following added to the coverage position 1) Elosulfase alfa (Vimizim) may be considered medically necessary for patients 5 years of age or older with a documented clinical diagnosis of mucopolysaccharidosis type IVA (MPS IVA; Morquio A syndrome). 2) Elosulfase alfa (Vimizim) is considered experimental, investigational and/or unproven for all other indications.
06/01/2012	Document updated with literature review. No coverage change.
10/01/2010	Document updated with literature review. The following was added: Alglucosidase alfa (Lumizyme™) may be considered medically necessary for use in patients eight years and older with late-onset (non-infantile) Pompe disease that has not shown evidence of cardiac hypertrophy. Alglucosidase alfa (Lumizyme™) for the treatment of all other indications is considered experimental, investigational and unproven.
02/15/2008	New medical document.