Policy Number	RX501.067
Policy Effective Date	10/01/2026

Enzyme-Replacement Therapy for Lysosomal Storage Disorders

Table of Contents
Coverage
Policy Guidelines
Description
Rationale
Coding
References
Policy History
Appendix

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 generally accepted standards of and developed by nonprofit professional association(s) for the relevant clinical specialty, third-party entities that develop treatment criteria, or other federal or state governmental agencies. 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 generally accepted standards of medical care. 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.**

Medical Benefit Therapeutic Alternatives

Certain prescription drugs administered by a health care provider in a clinical or professional setting have therapeutic equivalents or alternatives. Benefits may be limited to certain therapeutic equivalents or alternatives unless a coverage exception is granted. Members and their providers may visit the plan website for more information or may call the number on the member's ID card for further assistance.

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 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

NOTE 1: See the Appendix for exception criteria for medications in this class. The Appendix is not applicable to plans regulated by the Illinois Department of Insurance or Medicare or Medicaid plans.

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 non-Food and Drug Administration (FDA) approved 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 non-FDA approved 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 non-FDA approved 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 non-FDA approved 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 non-FDA approved indications.
Cipaglucosidase alfa-atga (Pombiliti™)	Cipaglucosidase alfa-atga (Pombiliti™) **may be considered medically necessary** for treatment of late-onset Pompe disease when **ALL** 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 non-FDA approved indications.
Elosulfase alfa (Vimizim®)	Elosulfase alfa (Vimizim®) **may be considered medically necessary** for individuals 5 years of age or older with mucopolysaccharidosis type IVA (MPS IVA; Morquio A syndrome).

	Elosulfase alfa (Vimizim®) **is considered experimental, investigational, and/or unproven** for all other non-FDA approved 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 non-FDA approved indications.
Imiglucerase (Cerezyme®)	Imiglucerase (Cerezyme®) **may be considered medically necessary** for individuals 2 years of age and older with a 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 non-FDA approved 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 non-FDA approved 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 non-FDA approved 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 non-FDA approved 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 non-FDA approved indications.
Taliglucerase alfa (Elelyso®)	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 non-FDA approved indications.
Velaglucerase alpha (VPRIV®)	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 non-FDA approved indications.
Vestronidase alfa-vjbk (Mepsevii®)	Vestronidase alfa-vjbk (Mepsevii®) **may be considered medically necessary** in individuals with a diagnosis of Mucopolysaccharidosis VII (MPS VII, Sly syndrome) Vestronidase alfa-vjbk (Mepsevii®) **is considered experimental, investigational, and/or unproven** for all other non-FDA approved indications.

Enzyme-replacement therapy when utilized for the treatment of lysosomal storage disorders (LSD) **is considered not medically necessary** as noted below:

Product	**Criteria For Use**
Tividenofusp alfa-eknm (Avlayah™)	Tividenofusp alfa-eknm (Avlayah™) for the treatment of neurologic manifestations of Hunter syndrome (Mucopolysaccharidosis type II, MPS II **is considered not medically necessary** as a clinical benefit has not been established.

	Tividenofusp alfa-eknm (Avlayah™) **is considered experimental, investigational, and/or unproven** for all other non-FDA approved 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 1 in 40,000-60,000. Although individual diseases are rare, the group together affects many people globally. (17, 18)

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 neurologic 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. (17, 18)

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 address 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 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 ASMD type B to refer to all mild and intermediate forms of the disease, which can include those that have neurological findings. NPD type C is due to disease-causing variants in 1 of 2 different genes and does not involve a deficient enzyme; therefore, it is considered a separate disorder, distinct from NPD types A and B. (19)

ASMD affects males and females equally. It is estimated that 1 in 250,000 individuals in the general population are affected by 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. (19)

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). The enzyme deficiency causes excessive deposits of glycosphingolipids (GL-3 or Gb3), resulting in cell abnormalities and organ dysfunction affecting small blood vessels, the heart, and the kidneys. (20)

Fabry disease is subdivided into 2 phenotypes (20):

- 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 children 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 has residual α-Gal A activity, lacks GL-3/Gb3 accumulation in capillaries and small blood vessels, and does 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 decades 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 both type 1 and 2 males is confirmed by demonstrating the enzyme deficiency and by identifying the specific *GLA* gene mutation. Treatment involves a

multidisciplinary approach and should be initiated to minimize irreversible end-organ damage. (20)

Gaucher Disease (Types I, II, and III)
Gaucher disease is the most common lysosomal storage disorder and occurs when both parents are carriers of the disease. Gaucher disease is caused by a deficiency in 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 into 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. (21, 22)

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.

- Gaucher disease type 1: The most common form in western countries. Symptoms include spleen and liver enlargement, bone problems, and fatigue. Brain development is normal.
- Gaucher disease type 2: This type of Gaucher disease is rare and involves severe neurological (brain stem) abnormalities. It is usually fatal within the first 2 years, and it is currently untreatable because of severe, irreversible brain damage.
- Gaucher disease type 3: This type of Gaucher disease is rare in the United States and Europe; however, it is the most common form of the disease worldwide. Gaucher disease type 3 has a severity between types 1 and 2, causing the same symptoms as type 1 plus some neurological involvement. While patients typically have a shortened lifespan, some can live into their fifties with treatment. (21)

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 mutations in the *ALPL* gene. 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. (23)

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 (24):

- Perinatal HPP presents 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 hypo mineralized, which can be identified by X-ray. This form of HPP was frequently fatal although ERT has altered the progression of the disease resulting in increased survival.

- Infantile HPP characteristics usually become apparent by 6 months of age. Characteristic changes of rickets may be noted on X-rays and fractures are often present. Infants fail to grow, and some will experience vitamin B-6 responsive seizures. Hypercalcemia and nephrocalcinosis are common. Mortality in the infantile form of HPP has been reduced with ERT treatment.
- Childhood HPP is diagnosed when the disease manifests after 6 months of age. Children often exhibit delays in meeting gross motor milestones and static myopathy. A common feature is premature loss of deciduous teeth (before 5 years of age) with intact roots. X-rays reveal changes consistent with rickets and often a radiolucent band extending from growth plate into the metaphysis.
- Adult HPP is characterized by a wide variety of symptoms including non-specific musculoskeletal complaints and slow to heal metatarsal or subtrochanteric femoral fractures. Many adults with HPP will report having had symptoms during childhood, despite formal diagnosis not being made until later in life.
- Odontohypophosphatasia is the least severe form of HPP and is diagnosed when dental abnormalities are present, but no other skeletal diseases such as rickets or osteomalacia are present.

Lysosomal Acid Lipase Deficiency

Lysosomal acid lipase (LAL) deficiency is a lipid storage disorder characterized by a genetic defect resulting in a marked decrease or loss of activity of the LAL enzyme. The two rare conditions that may occur due to this enzyme deficiency include (25-27):

- Wolmans disease: This rare, congenital disease typically occurs in early childhood due to the complete absence of the enzyme known as lysosomal acid lipase (LIPA or LAL). This enzyme is needed to metabolize certain lipids in the body. Without this enzyme, lipids may accumulate in the tissues and organs causing persistent vomiting and diarrhea, abdominal distention, Jaundice, hepatosplenomegaly, and premature cardiovascular events.
- Cholesteryl ester storage disease (CESD): This condition is less severe and presents later in life compared to Wolmans disease. In CESD, the LIPA gene variant results in some enzyme activity. Symptoms may include hepatosplenomegaly, cirrhosis and malabsorption, and gastrointestinal symptoms.

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. (28)

Several clinical types and subtypes of 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 (28, 29):

- MPS Type I is caused by a missing or deficiency enzyme alpha-L-iduronidase which is needed to break down glyclosaminoglycans dermatan sulphate and heparan sulphate. 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. Like Scheie syndrome, affected individuals have a deficiency of the alpha-L-iduronidase specific for accumulation of dermatan sulfate. Affected 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 is characterized by a deficiency of the enzyme alpha-L-iduronidase, resulting in an accumulation of dermatan and heparan sulfates. Symptoms usually become evident between 6 months and 2 years of age. Children usually stop developing between ages 2 and 4 followed by progressive mental decline and loss of physical skills. 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 an 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 but are not limited to increased intracranial pressure, joint stiffness, retinal degeneration, macrocephaly, and progressive hearing loss.
- MPS IV (Morquio Syndrome) 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, curvature of the spine, 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.

- 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.
- 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. Some clinical manifestations include mild to severe intellectual disability, 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.

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 simple 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 of 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 (30):

- 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. Symptoms may include but are not limited to hypertrophic cardiomyopathy, hepatomegaly due to heart failure, weakness of skeletal muscle (especially proximal muscles), and progressive diaphragm weakness resulting in respiratory difficulties. Patients with this form of Pompe disease are the most severely affected. Infants may present with feeding difficulties due to an enlarged tongue. 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 at any age. The extent of organ involvement varies among affected individuals. Symptoms include progressive muscle weakness mainly involving the shoulders and hips, progressive diaphragm weakness leading 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. (1)
- 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. (2)
- 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. (3)
- 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 on 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. (4, 31)
- 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). (5)
- 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). (6)
- 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. Safety and efficacy have not been established in patients below 5 years of age. (7)
- Naglazyme® (Galsulfase) was U.S. FDA approved in 2005 for the use in individuals with Mucopolysaccharidosis VI (MPS VI; Maroteaux-Lamy syndrome). (8)

- 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, thrombocytopenia, bone disease, hepatomegaly, or splenomegaly. The safety and efficacy of Cerezyme has not been established in children younger than 2 years of age. (9)
- 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. The FDA approval was based on clinical trials on individuals 6 months of age and greater. (10)
- Olipudase alfa (Xenpozyme®) was approved by the U.S FDA in August 2022 to treat pediatric and adult individuals with non-central nervous system manifestations of acid sphingomyelinase deficiency (ASMD). (11)
- Pegunigalsidase alfa-iwxj (Elfabrio®) was U.S. FDA approved on May 9, 2023 for adults with a confirmed diagnosis of Fabry disease. (12)
- 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. (13)
- 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. (14)
- Velaglucerase alpha (VPRIV®) was approved by the U.S. FDA in 2010 for the long term ERT for individuals with Type 1 Gaucher disease. Safety and efficacy have not been established in individuals younger than 4 years of age. (15)
- 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. (16)
- Tividenofusp alfa-eknm (Avlayah™) was approved in March 2026 for the treatment of neurologic manifestations of Hunter syndrome (Mucopolysaccharidosis type II, MPS II) when initiated in presymptomatic or symptomatic pediatric patients weighing at least 5 kg prior to advanced neurologic impairment. This indication was FDA approved under an accelerated approval based on a reduction of cerebrospinal fluid heparan sulfate observed in individuals treated with Avlayah. Per the FDA label, continued approval for this indication may be contingent upon verification of clinical benefit in confirmatory trial(s). (33)

NOTE 2: Per the FDA labels, when receiving ERT for lysosomal disorders, individuals should be monitored closely for hypersensitivity reactions, including anaphylaxis. Appropriate medical monitoring and support measures, including cardiopulmonary resuscitation equipment, should be readily available when ERT is administered. Please refer to the U.S. FDA label for precautions for each individual ERT therapy.

Rationale

This policy was developed in 2008 and is based on the U.S. Food and Drug Administration (FDA) labeled indications.

Agalsidase beta (Fabrazyme®)
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 were randomized 1:1 to receive either Fabrazyme 1 mg/ kilogram (kg) every 2 weeks or placebo for 20 weeks. Patients had a median age of 24 years in the placebo group and 33 years in the Fabrazyme group at baseline. At baseline, all patients had plasma αGAL (alpha-galactosidase A) activity below the detection limit and 79% had leukocyte αGAL activity below the detection limit. The median plasma GL-3 at baseline was 14.4 ng/uL in the placebo group and 14.7 ng/uL in the Fabrazyme group with the overall range of <1.2 to 36 ng/uL. The median eGFR at baseline was 98.5 mL/hr in the placebo group and 83.0 mL/hr in the Fabrazyme group (overall range 24 to 153 mL/hr). All patients were pretreated with acetaminophen and antihistamine. Oral steroids were an additional option to the pretreatment regimen for patients who exhibited severe or recurrent infusion-associated reactions. (1)

Tissue biopsy specimens (kidney, heart, skin) were evaluated at baseline and at week 20 by light microscopy for the presence and number of GL-3 inclusions using a semi-quantitative methodology. Renal interstitial capillaries were scored based on the number of GL-3 (globotriaosylceramide) inclusions on a scale of 0 to 3 (0 defined as “nearly none” or “trace,” 1 defined as “mild,” 2 defined as “moderate,” and 3 defined as “severe”). The primary endpoint was the proportion of patients in either group with a renal capillary GL-3 inclusion score of zero at week 20. In the Fabrazyme group, 20 of 29 (69%) patients achieved a score of zero while 0 of 29 placebo treated patients achieved a score of zero ($p<0.001$). Similar reductions in GL-3 inclusions were observed in the capillary endothelium of the heart and skin (Table 1). All 58 patients who completed Study 1 were subsequently treated with Fabrazyme 1 mg/kg every two weeks in an open-label extension study. After six months of open-label treatment, most patients with available biopsy data achieved a GL-3 inclusion score of 0 in capillary endothelium (Table 1).

Table 1: Proportion of Patients with Tissue GL-3 Inclusion Score of Zero (Study 1 and open-label treatment)

	20 weeks of randomized treatment in Study 1		**6 months of Fabrazyme open-label treatment**	
	Placebo (n=29)	Fabrazyme (n=29)	Placebo/ Fabrazyme (n=29)*	Fabrazyme/ Fabrazyme (n=29)*
Kidney	0/29	20/29	24/24	23/25
Heart	1/29	21/29	13/18	19/22
Skin	1/29	29/29	25/26	26/27

* Results reported where biopsies were available.

Study 2 was a randomized (2:1 Fabrazyme to placebo), double-blind, placebo-controlled, multinational, multicenter study of 82 patients (72 males and 10 females) with Fabry disease, all naive to enzyme replacement therapy. Of the 82 enrolled patients, 51 and 31 patients were randomized to the Fabrazyme and placebo groups, respectively. Patients were 20 to 72 years of age with a median age of 45 years at baseline, a median age of 36 years at Fabry disease diagnosis, and a median of 10 years at symptom onset. The median plasma GL-3 at baseline was 9.3 ug/mL in the placebo group and 8.9 ug/mL in the Fabrazyme group with the overall range of 2.8 to 18.9 ug/mL. At baseline, patients had median plasma αGAL activity 1.5 nmol/hour/mL (range: 0 to 1.5), leukocyte αGAL activity 1.8 nmol/hour/mL (range: 0 to 4.0), eGFR 52 mL/min/1.73 m^2 (range: 25 to 113), and protein to creatinine ratio 0.9 mg/mg (range: 0 to 7.3). Patients received either 1 mg/kg Fabrazyme IV (intravenous) or placebo every two weeks for up to 35 months (median follow-up 18.5 months). The primary efficacy endpoint was the time to first occurrence of a clinically significant event (renal, cardiac, or cerebrovascular event, or death). A total of 14 of 51 (28%) Fabrazyme-treated patients and 13 of 31 (42%) placebo-treated patients experienced a clinically significant event (HR 0.57, 95% CI: 0.27, 1.22).

Study 3 (Pediatric Study) was an open-label, single-arm, multinational, multicenter study in 16 pediatric patients with Fabry disease (14 males, 2 females), aged 8 to 16 years (median 12 years). At baseline, patients had median plasma αGAL activity 0.2 nmol/hour/mL (range: 0.0, 2.0) and median leukocyte αGAL activity 0.5 nmol/hour/mg (range: 0.0, 12.5). All 14 males had elevated plasma GL-3 levels (i.e., >7.03 µg/mL) at baseline, whereas the two females 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). All patients received Fabrazyme 1 mg/kg every two weeks for up to 48 weeks.

In Study 3, at baseline, all 14 males had elevated plasma GL-3 levels (i.e., >7.03 µg/mL), whereas the two female patients had normal plasma GL-3 levels. At weeks 24 and 48 of treatment, all 14 males had plasma GL-3 within the normal range. The two female patients' plasma GL-3 levels remained normal through study week 48. Histological evaluation of the capillary endothelium (vasculature), deep vessel endothelium, deep vessel smooth muscle cells, and perineurium of biopsied skin was conducted using histochemistry with light microscopy. Scoring was on a scale of 0 to 3 (0 defined as none; 1 as mild, 2 as moderate, and 3 as severe). At baseline, 12 of the 14 males had GL-3 inclusions present on skin biopsy (scores 1, 2, or 3) and all 12 achieved GL-3 inclusion scores of 0 at weeks 24 and 48 of treatment. The two females had no GL-3 inclusions in skin at baseline.

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 was 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).

Use in the Pediatric Population

The safety and effectiveness of Fabrazyme have been established in pediatric patients based on adequate and well-controlled studies in adults, a single-arm, open-label study in 16 pediatric patients with Fabry disease aged 8 to 16 years, and additional data in 24 patients with Fabry disease aged 2 to 7 years. The overall safety profile of Fabrazyme was similar between the pediatric and the adult population. Safety and effectiveness have not been established in pediatric patients less than 2 years of age.

Avalglucosidase alfa-NGPT (Nexviazyme®)

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. One hundred patients (51 in Nexviazyme and 49 in alglucosidase alfa) were randomized in a 1:1 ratio based on baseline forced vital capacity ([FVC] % predicted; <55% or ≥55%), sex, age (<18 years or ≥18 years), and country (Japan or not-Japan) to receive 20 mg/kg of Nexviazyme or alglucosidase alfa administered IV once every two weeks for 49 weeks. After 49 weeks, all randomized patients in Study 1 had the option to enter an open-label extension treatment period to receive Nexviazyme and continue treatment up to at least Week 145. (2)

Demographic and Disease Characteristics

Of the 100 randomized patients, 52 were males, the baseline median age was 49 years old (range from 16 to 78), median baseline weight was 76.4 kg (range from 38 to 139 kg), median length of time since diagnosis was 6.9 months (range from 0.3 to 328.4 months), mean age at diagnosis was 46.4 years old (range from 11 to 78), mean FVC (% predicted) at baseline was 62.1% (range from 32 to 85%), and mean 6 Minute Walk Test (6-MWT) at baseline was 388.9 meters (range from 118 to 630 meters). The racial groups for the patients consisted of 94 White (94%), 3 Black or African American (3%), and 3 Asian (3%). Fifteen patients were Hispanic/Latino (15%), 76 non-Hispanic/Latino (76%) and 9 were not reported. Five patients (all in the alglucosidase alfa arm) discontinued the study prior to Week 49: four due to adverse events (acute myocardial infarction, arthritis, dyspnea, and urticaria), and one due to withdrawal of consent. All 95 patients who did not discontinue the study prior to Week 49 entered the open-label period (51 from the Nexviazyme arm and 44 from the alglucosidase alfa arm). Of the 95 patients, 77 patients had follow-up data on FVC (% predicted) at Week 145 (44 from the Nexviazyme arm and 33 from the alglucosidase alfa arm) and 80 patients had follow-up data on 6-MWT at Week 145 (45 from the Nexviazyme arm and 35 from the alglucosidase alfa arm). Fourteen (14%) patients (7 in each group) discontinued treatment during the extension treatment period (5 for adverse events, 1 for poor compliance to protocol and 8 for other reasons).

Primary Efficacy Results from the 49-Week Active-Controlled Period and Open-Label Period up to Week 145 in Study 1

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 2). Figure 1 presents the LS mean change from baseline in FVC (% predicted) over time by treatment group up to Week 49.

Table 2: 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)	

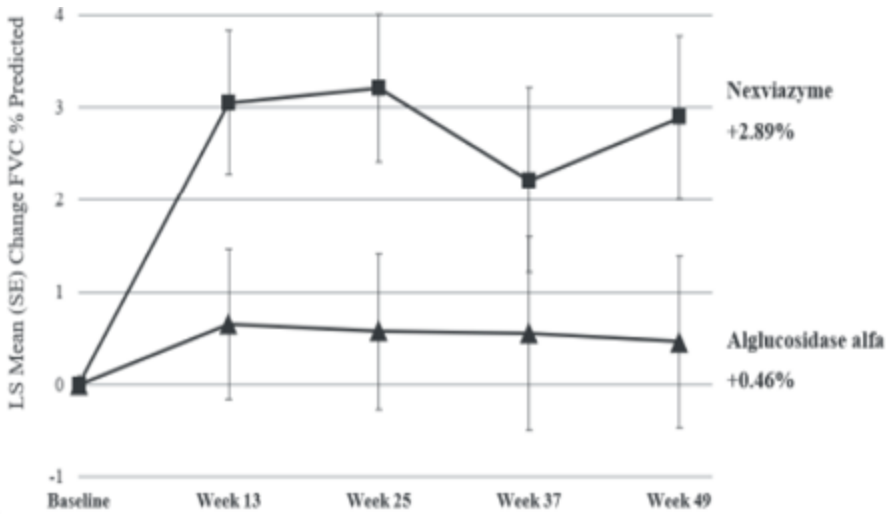
CI: confidence interval; LOPD: Late-onset Pompe disease; LS: Least squares.

*All randomized patients,

† 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).

Figure 1: Plot of LS Mean (SE) Change From BaseLine of FVC (% predicted) in Upright Position over Time in ERT-Naïve Patients with LOPD (Study 1)



Number of patients	Baseline	Week 13	Week 25	Week 37	Week 49
Nexviazyme	51	51	51	51	49
Alglucosidase alfa	49	47	45	44	43

* All randomized patients

For patients who continued to receive Nexviazyme after Week 49 the mean change from baseline to Week 145 in FVC (% predicted) was 1.7 (SD=8.6, 95% CI: -0.9, 4.2), and the mean change from Week 49 to Week 145 was -0.8 (SD=6.2, 95% CI: -2.7, 1.0). For patients who switched from alglucosidase alfa to Nexviazyme after Week 49 the mean change from baseline to Week 145 was 0.5 (SD=8.3, 95% CI: -2.3, 3.4), and the mean change in FVC (% predicted) from Week 49 to Week 145 was 0.8 (SD=6.9) (95% CI: -1.6, 3.1).

Efficacy Results for Total Distance Walked in 6 Minutes from the 49-Week Active-Controlled Period and Open-Label Period up to Week 145 in Study 1

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 end 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 3).

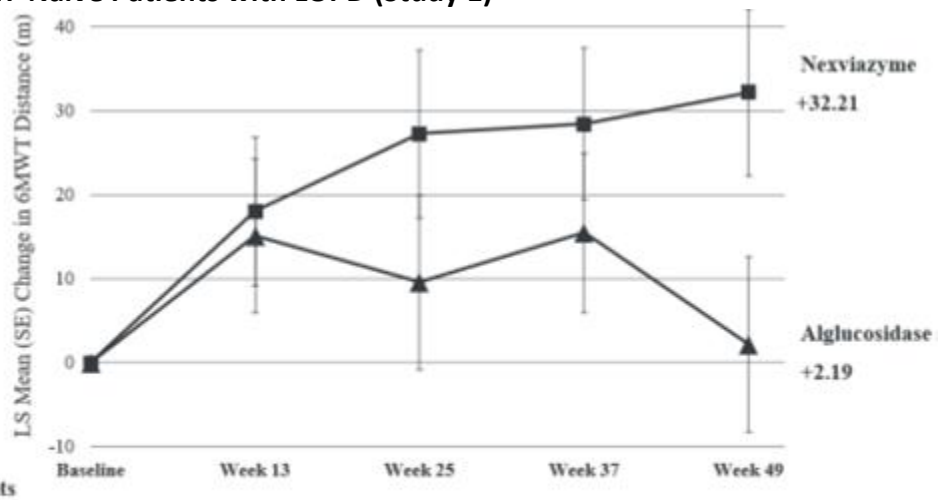
Table 3: Summary Results of 6-MWT in ERT-Naive Patients with LOPD (Study 1)*

		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)	

6-MWT: 6-Minute Walk Test; ERT: Enzyme replacement therapy; LOPD: Late-onset Pompe disease.
*All randomized patients.

† 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).

Figure 2: Plot of LS Mean (SE) Change from Baseline of 6-MWT (distance walked, in meters) over Time in ERT-Naïve Patients with LOPD (Study 1)



Number of patients	Baseline	Week 13	Week 25	Week 37	Week 49
Nexviazyme	51	51	49	50	48
Alglucosidase alfa	49	47	45	45	43

* All randomized patients

For patients who continued to receive Nexviazyme after Week 49, the mean change from baseline to Week 145 in 6MWT was 24.9 (SD=68.6, 95% CI: 4.8, 44.9), and the mean change from Week 49 to Week 145 was -11.0 (SD=33.5, 95% CI: -20.8, -1.2). For patients who switched from alglucosidase alfa to Nexviazyme after Week 49 the mean change from baseline to Week 145 in 6-MWT was -4.1 (SD=90.4, 95% CI: -34.1, 25.8), and the mean change from Week 49 to Week 145 was -7.7 (SD=50.3, 95% CI: -24.4, 9.0).

Idursulfase (Elaprase®)

The safety and efficacy of Elaprase were evaluated in a 53-week, randomized, double-blind, placebo-controlled clinical trial of 96 patients with Hunter syndrome. The trial included patients with deficiency in iduronate-2-sulfatase enzyme activity and a percent predicted forced vital capacity (% predicted FVC) less than 80%. The ages of patients ranged from 5 to 31 years. Patients received Elaprase 0.5 mg/kg once per week (n=32), Elaprase 0.5 mg/kg once every other week (n=32), or placebo (n=32). The primary efficacy outcome assessment was a two-component composite score based on the sum of the ranks of the change from baseline to Week 53 in distance walked in six minutes (6-MWT) and the ranks of the change in %-predicted FVC. This two-component composite primary endpoint differed statistically significantly between the three groups, and the difference was greatest between the placebo group and the once weekly treatment group (once weekly Elaprase versus placebo, p=0.0049). Examination of

the individual components of the composite score showed that, in the adjusted analysis, the weekly Elaprase-treated group experienced a 35-meter greater mean increase in the distance walked in six minutes compared to placebo. The changes in %-predicted FVC were not statistically significant (Table 4). (3)

Table 4. Clinical Trial Results

	Elaprase Weekly n=32*			**Placebo n=32***			**Elaprase Once Weekly-Placebo**
	Baseline	**Week 53**	**Change†**	**Baseline**	**Week 53**	**Change†**	**Difference in Change**
Results from the 6-Minute Walk Test (Meters)							
Mean ± SD	392 ± 108	436 ± 138	44 ± 70	393 ± 106	400 ± 106	7 ± 54	37 ± 16‡ 35 ± 14§ (p=0.01)
Median	397	429	31	403	412	-4	
Percentiles (25th, 75th)	316, 488	365, 536	0, 94	341, 469	361, 460	-30, 31	
Results from the Forced Vital Capacity Test (% of Predicted)							
Mean ± SD	55.3 ± 15.9	58.7 ± 19.3	3.4 ± 10.0	55.6 ± 12.3	56.3 ± 15.7	0.8 ± 9.6	2.7 ± 2.5‡ 4.3 ± 2.3§ (p=0.07)
Median	54.9	59.2	2.1	57.4	54.6	-2.5	
Percentiles (25th, 75th)	43.6, 69.3	44.4, 70.7	-0.8, 9.5	46.9, 64.4	43.8, 67.5	-5.4, 5.0	

* One patient in the placebo group and one patient in the Elaprase group died before Week 53; imputation was by last observation carried forward in the intent-to-treat analysis.
† Change, calculated as Week 53 minus Baseline
‡ Observed mean ± SE
§ ANCOVA model-based mean ± SE, adjusted for baseline disease severity, region, and age.

Pharmacodynamic assessments included urinary glycosaminoglycans (GAG) levels and changes in liver and spleen size. Urinary GAG levels were elevated in all patients at baseline. Following 53 weeks of treatment, mean urinary GAG levels were reduced in the Elaprase once weekly group, although GAG levels remained above the upper limit of normal in half of the Elaprase treated patients. Urinary GAG levels remained elevated and essentially unchanged in the placebo group. Sustained reductions in both liver and spleen volumes were observed in the Elaprase once weekly group through Week 53 compared to placebo. There were essentially no changes in liver and spleen volumes in the placebo group.

Extension trial patients who participated in the placebo-controlled trial were eligible to continue treatment in an open-label extension trial. During the extension trial, all patients received 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-MWT for an additional 8 months of treatment in the extension trial. 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. The long-term effect of Elaprase on pulmonary function in Hunter syndrome patients is unclear.

There were no further reductions in mean urinary GAG levels in patients initially treated with Elaprase once weekly; however, the patients treated with Elaprase every other week during the placebo-controlled trial experienced further reductions in mean urinary GAG levels after changing to a more frequent dosing regimen during the extension trial. The persistence of reduced urinary GAG levels did not correlate with the long-term effect demonstrated by the 6-MWT distance or %-predicted FVC.

Clinical Trial in Patients 7 Years and Younger

A 53-week, open-label, multicenter, single-arm trial was conducted to assess the safety, pharmacokinetics, and pharmacodynamics of Elaprase 0.5 mg/kg once weekly in male Hunter syndrome patients aged 7 years and younger. Safety results demonstrated that patients with complete gene deletion or large gene rearrangement mutations are more likely to develop antibodies, including neutralizing antibodies, and to experience hypersensitivity reactions with Elaprase administration. In patients who remained antibody negative, the pharmacokinetic profile, reduction in urinary GAG excretion levels, and reduction in spleen volume were similar to those of adults and children 5 years and older. In patients who were persistently antibody positive, the presence of anti-idursulfase antibody was associated with reduced systemic exposure of idursulfase and a less pronounced decrease in urinary GAG levels.

Use in the Pediatric Population

Clinical trials with Elaprase were conducted in 96 patients with Hunter syndrome, ages 5 to 31 years old, with the majority of the patients in the pediatric age group (median age 15 years old). In addition, an open-label, uncontrolled clinical trial was conducted in 28 patients with Hunter syndrome, ages 16 months to 7.5 years old. Patients 16 months to 5 years of age demonstrated a reduction in spleen volume that was similar to that of adults and children 5 years and older. However, there is no data to support improvement in disease-related symptoms or long-term clinical outcome in patients 16 months to 5 years of age. The safety and effectiveness of Elaprase have not been established in pediatric patients less than 16 months of age.

Alglucosidase alfa (Lumizyme®, formerly known as Myozyme)

Infantile-Onset Pompe Disease

The safety and effectiveness of alglucosidase alfa in the treatment patients with infantile-onset Pompe disease (IOPD) were assessed in 57 treatment-naive infantile-onset Pompe disease patients, aged 0.2 month to 3.5 years at first alglucosidase alfa infusion, in three separate open label, single-arm clinical trials (Trials 1, 2, and 3). (4)

Trial 1 (Patients with IOPD)

Trial 1 was an international, multicenter, open-label, clinical trial of 18 patients with IOPD. This trial was conducted between 2003 and 2005. Patients were randomized 1:1 to receive either 20 mg/kg or 40 mg/kg of IV alglucosidase alfa every two weeks, with length of treatment ranging from 52 to 106 weeks. Enrollment was restricted to patients 7 months of age or younger at first infusion with clinical signs of Pompe disease and cardiac hypertrophy, and who did not require ventilatory support at trial entry. Fourteen patients were cross reactive immunologic material (CRIM) positive, and 4 patients were CRIM negative.

Efficacy was assessed by comparing the proportions of alglucosidase alfa-treated patients who died or needed invasive ventilator support at 18 months of age with the mortality experience of a historical cohort of untreated patients with IOPD with similar age and disease severity. In the 16 historical cohort, 61 untreated patients with IOPD diagnosed by age 6 months, born between 1982 and 2002, were identified by a retrospective review of medical charts. By 18 months of age, 15 of 18 (83%) alglucosidase alfa-treated patients were alive without invasive ventilatory support and 3 (17%) required invasive ventilator support, whereas only one of the 61 (2%) historical control patients was alive. No differences in outcome were observed between patients who received 20 mg/kg versus 40 mg/kg.

Other outcome measures in this trial included unblinded assessments of motor function by the Alberta Infant Motor Scale (AIMS), a measure of infant motor performance that assesses motor maturation of the infant through age 18 months. Although gains in motor function were noted in 13 patients, the motor function was substantially delayed compared to normal infants of comparable age in the majority of patients. Two of 9 patients who had initially demonstrated gains in motor function after 12 months of alglucosidase alfa treatment regressed despite continued treatment.

Changes from baseline to Month 12 in left ventricular mass index (LVMI), a measure of pharmacodynamic effect, were evaluated by echocardiography. Fifteen patients who underwent both baseline and Month 12 echocardiograms demonstrated decreases from baseline in LVMI (mean decrease 118 g/m^2, range 45 to 193 g/m^2). However, the magnitude of the decrease in LVMI did not correlate with the clinical outcome measure of ventilator-free survival.

Trial 2 (Patients with IOPD)

Trial 2 was an international, multicenter, non-randomized, open-label clinical trial that enrolled 21 patients with IOPD aged 3 months to 3.5 years at first infusion. Eighteen patients were CRIM positive and 3 patients were CRIM negative. All patients received IV 20 mg/kg alglucosidase alfa every other week for up to 104 weeks. Five of 21 patients were receiving invasive ventilatory support at the time of the 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 invasive 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.

Trial 3 (Patients with IOPD)
Trial 3 was an open-label, single-center trial in 18 patients with IOPD who had a confirmed diagnosis of Pompe disease as identified through a newborn screening program. All patients were CRIM positive. Patients were treated with IV 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.

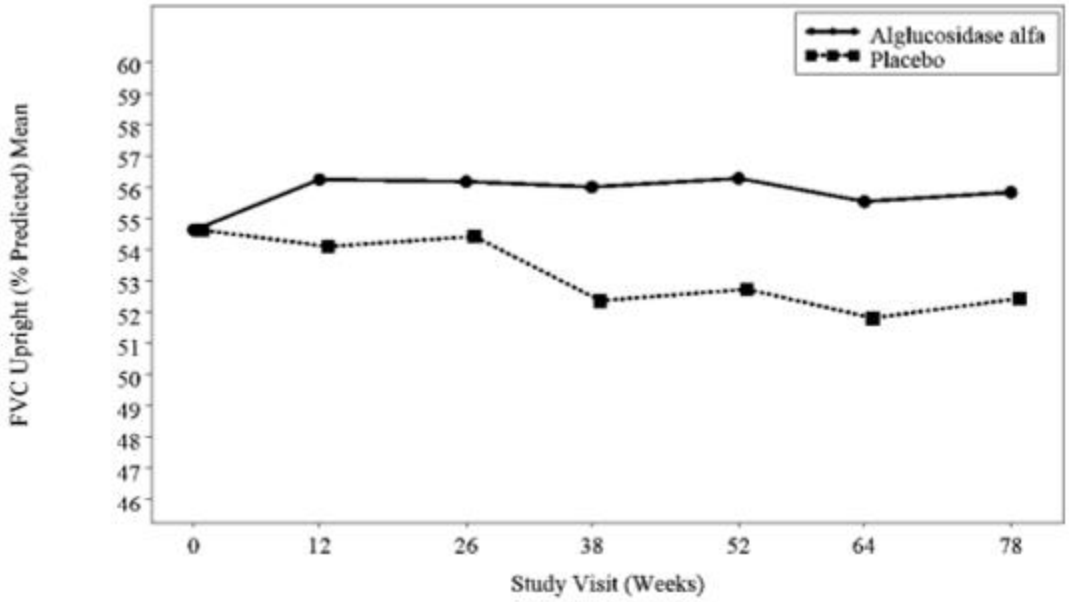
Clinical Trials in Late-Onset Pompe Disease
The safety and efficacy of alglucosidase alfa were assessed in 90 patients with late-onset Pompe disease (LOPD), aged 10 to 70 years, in a randomized, double-blind, placebo-controlled trial (Trial 4). All patients were naive to ERT. Patients were allocated in a 2:1 ratio and received 20 mg/kg of IV alglucosidase alfa (n=60) or IV placebo (n=30) every other week for 78 weeks (18 months).

The youngest alglucosidase alfa-treated patient was 16 years of age, and the youngest placebo treated patient was 10 years of age. The trial 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 were 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; two patients were in the alglucosidase alfa treatment group and one patient was in placebo group.

At trial 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 (see Figure 3).

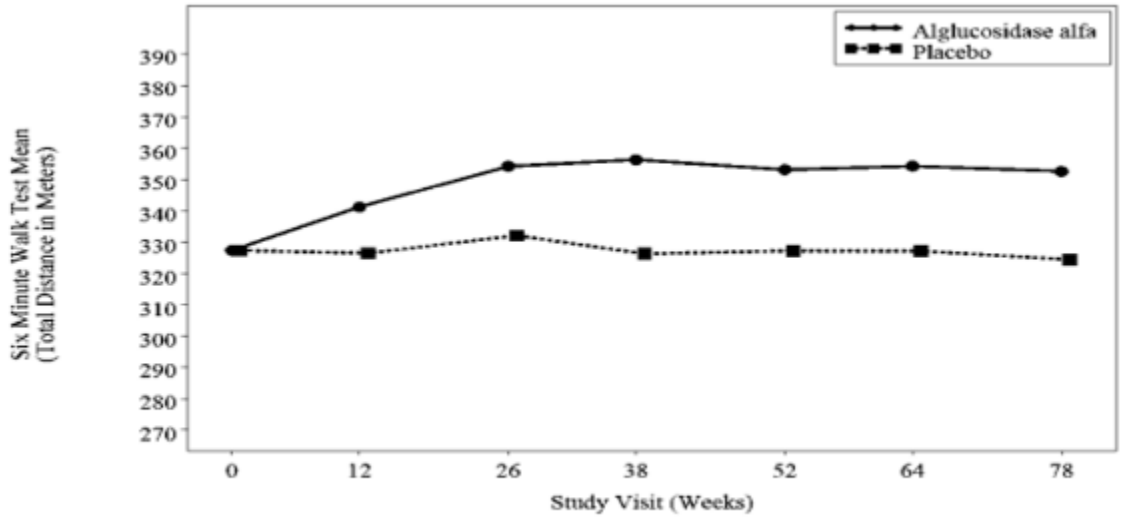
Figure 3: Mean FVC Upright (% Predicted) over Time in Patients with LOPD (Trial 4)



Note: ANCOVA least squares means adjusting for baseline values

At trial 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% CI: [-1 to 52 meters]; p=0.06) (see Figure 4).

Figure 4: Mean Six Minute Walk Test Total Distance Walked Over Time In Patients with LOPD (Trial 4)



Note: ANCOVA least squares means adjusting for baseline values

<u>Use in the Pediatric Population</u>

Per the FDA label, the safety and effectiveness of alglucosidase alfa (Lumizyme) has been established in pediatric patients with Pompe disease. The use of (Lumizyme for this pediatric indication is supported by evidence from an adequate and well-controlled trial in 57 treatment naive pediatric patients with IOPD treated with alglucosidase alfa, aged 0.2 month to 3.5 years at first infusion, (Trials 1, 2, and 3) and 90 adult and pediatric patients with LOPD in a randomized, double-blind, placebo-controlled trial including 2 patients 16 years of age or less.

Asfotase alfa (Strensiq®)

Perinatal/Infantile Onset Hypophosphatasia

Study 1 was a 24-week prospective single-arm trial in 11 patients with severe perinatal/infantile-onset hypophosphatasia (HPP). In this study, 7/11 (64%) were female and 10/11 (91%) patients were white, and age ranged from 3 weeks to 39.5 months. 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 have been treated for at least 216 weeks (54 months) and 4 patients have been treated for over 240 weeks (60 months). Patients received subcutaneous Strensiq 3 mg/kg per week for the first month; subsequently, dose increases up to 9 mg/kg per week were allowed for changes in weight and/or for lack of efficacy. All 10 patients required dose increases 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 pharmacokinetic (PK) data. (5)

Study 2 was a prospective open-label study in 59 patients with perinatal/infantile-onset HPP. In this study, 32/59 (54%) were female, 46/59 (78%) were white, and age ranged from 1 day to 78 months. Patients received subcutaneous 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 starting treatment. 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 three 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 ventilation-free survival in Perinatal/Infantile-Onset HPP

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 5).

Table 5. Survival and Invasive Ventilation-Free Survival in Strensiq Treated versus Historical Control Patients with Perinatal/ Infantile Onset HPP (Pooled Studies 1 and 2)

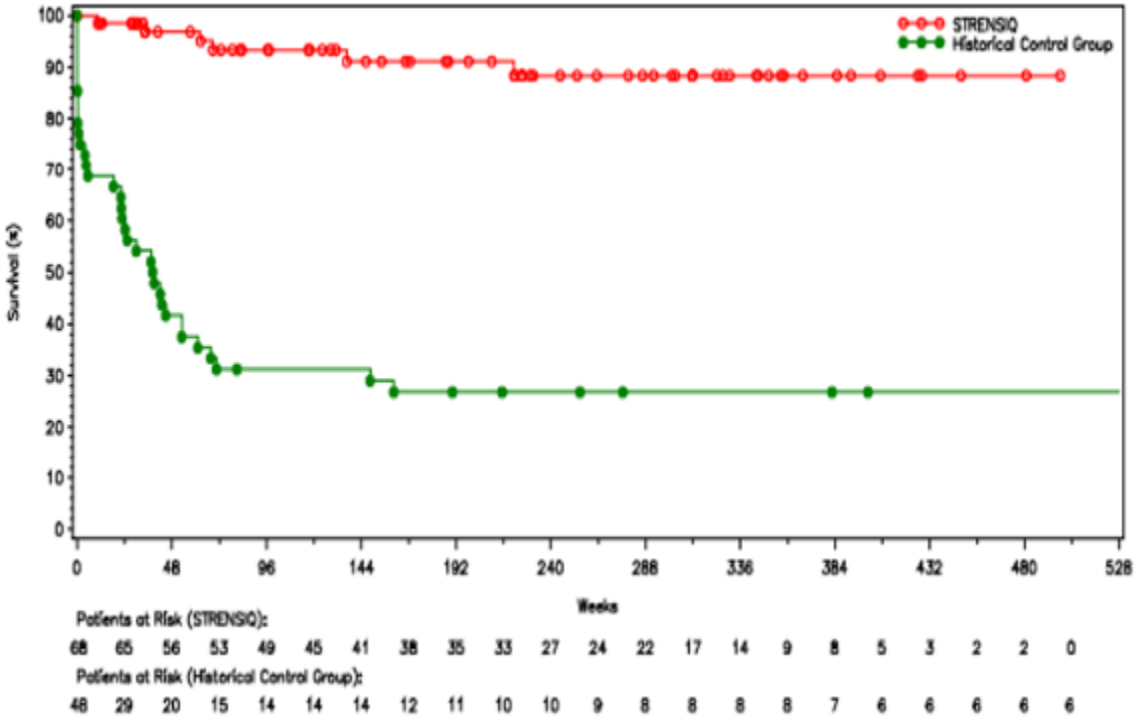
	Strensiq Treated	**Historical Controls**
Survival	n = 68	n = 48

• 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) (%)	96	31

HPP: hypophosphatasia
* 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.

Figure 5: Overall Survival in Strensiq-Treated versus Historical Control Patients with Perinatal/Infantile-Onset HPP (Pooled Studies 1 and 2)



Skeletal Manifestations in Perinatal/Infantile-Onset HPP

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 was 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 the course of treatment. There was insufficient data to determine the effect of Strensiq on fractures.

Growth in Perinatal/Infantile-Onset HPP

Height and weight measurements (as measured by Z-scores) were available post treatment for 72 perinatal/infantile-onset HPP patients, including 68 patients enrolled in Studies 1 and 2, and 4 patients enrolled in Study 3 (Table 6).

Table 6: Perinatal/Infantile-Onset Height and Weight Measurements as Measured by Z-Score (Studies 1 and 2)

	Height Z-score				**Weight Z-score**			
	Baseline		**Last Assessment**		**Baseline**		**Last Assessment**	
	Mean	Min, Max	Mean	Min, Max	Mean	Min, Max	Mean	Min, Max
Studies 1 and 2* (N=68)	-3.3	-10.1, 0.9	-2.9	-10.6, 0.4	-3.2	-23.8, 0	-2.4	-20.9. 1.1
Study 3 (N=4)**	-2.6	-6.6, -0.7	-1.5	-5.8, 0.4	-2.5	-8.2, -1.0	-1.5	-5.4, 0.5

*The mean time interval between baseline and last assessment was 21 months (range was 1 month to 72 months).

**The mean time between baseline and last assessment was 56 months (range was 53 months to 60 months).

Long-Term Extension Trials in Perinatal/Infantile-Onset HPP

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). At point of last contact, 69/78 (88%) Strensiq-treated patients had survived.

<u>Juvenile-Onset Hypophosphatasia</u>

Study 3 was a prospective open-label 24-week trial that included 8 juvenile-onset HPP patients and 5 perinatal/ infantile-onset HPP patients; 11/13 (85%) were male and 12/13 (92%) were white. On study entry, patients were 6 to 12 years of age. All 8 juvenile-onset patients entered the extension study and were treated for at least 48 months. At trial entry, patients were randomized to receive subcutaneous Strensiq 6 mg/kg per week or 9 mg/kg per week. Two

patients received dose reductions during the primary treatment period, including one patient who experienced a decrease in vitamin B6 levels and one 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 treatment of juvenile-onset HPP is 6 mg/kg per week.

Growth in Juvenile-Onset HPP

Height and weight measurements (as measured by Z-scores) in 8 Strensiq-treated juvenile-onset HPP patients were compared with a historical cohort of 32 untreated patients with similar clinical characteristics (Table 7). Height and weight data for historical patients were collected from medical records.

Table 7: Juvenile-Onset Height and Weight Measurements as Measured by Z-Score (Study 3)

	Height Z-score				**Weight Z-score**			
	Baseline		**Last Assessment**		**Baseline**		**Last Assessment**	
	Mean	**Min, Max**	**Mean**	**Min, Max**	**Mean**	**Min, Max**	**Mean**	**Min, Max**
Srensiq (N=8)*	-1.5	-3.8, 0	-0.9	-2, 0	-1.1	-3.5, 2.3	0	-1.3, 2.2
Control (N=32)	-1.1	-4.9, 2.6	-1.1	-4.9, 1.8	-1.2	-5, 2.1	-1	-5.7, 2.1

* The mean time interval between baseline and last assessment was 55 months (range was 53 months to 60 months).

** The mean time interval between baseline and last assessment was 61 months (range was 19 months to 109 months).

Skeletal Manifestations

Radiographs from 8 Strensiq treated juvenile-onset HPP 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 was insufficient data to assess the effect of Strensiq on fractures.

Gait/Mobility in Juvenile-Onset HPP

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 in Juvenile-Onset HPP
Long term data was collected in 8 patients with juvenile-onset HPP treated with Strensiq for at least 6 years (72 months). At last assessment, 7 patients with available 6MWT results had maintained improvements in gait/mobility.

Cipaglucosidase alfa-atga (Pombiliti™)
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 IV 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 7.4 years). (6)

Demographics, baseline sitting forced vital capacity (FVC) (% predicted), and 6-MWD were generally similar between the 2 treatment groups (see Table 8 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 6-MWD (Table 8 and Table 9).

<u>Sitting FVC (Percent-Predicted) at 52 Weeks</u>
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 8 and Figure 6).

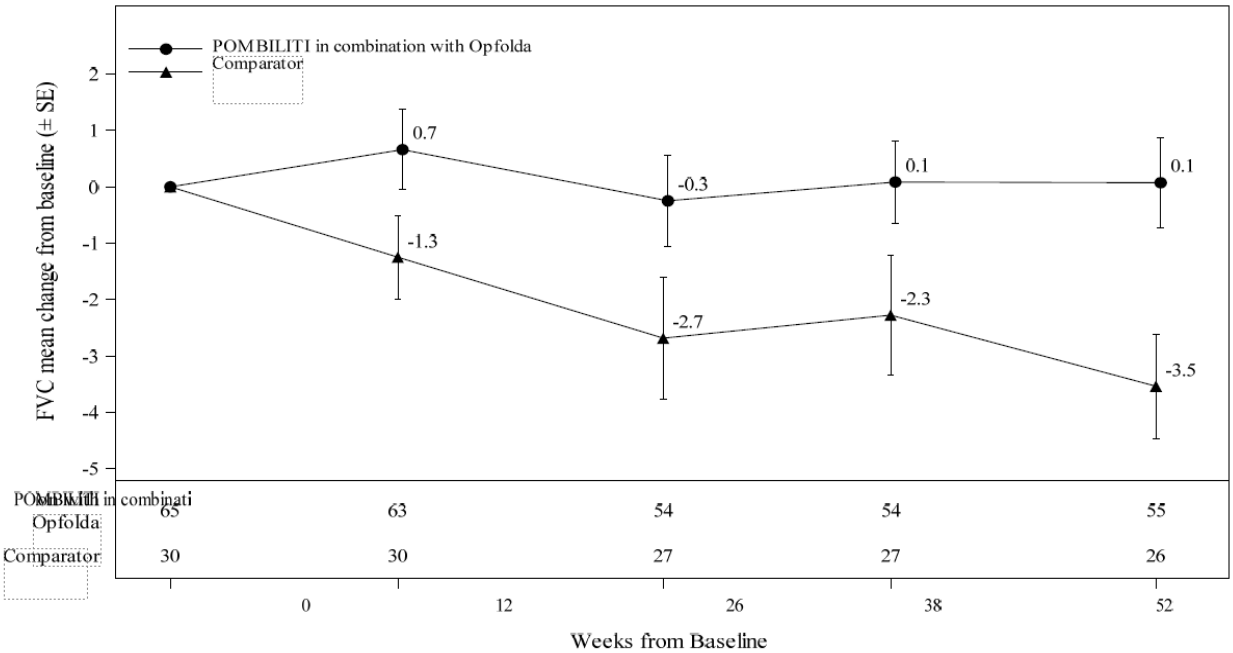
Table 8: Summary of Sitting FVC in Adults with LOPD by ERT Status at 52 Weeks in Trial 1

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)	

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 6: Mean Change (± SE) in Sitting FVC (% Predicted) From Baseline to Week 52 in ERT Experienced Adults with LOPD in Trial 1*



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.

<u>6-Minute Walk Distance (6-MWD) at 52 Weeks</u>

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 6-MWD from baseline at Week 52 (Table 9 and Figure 7).

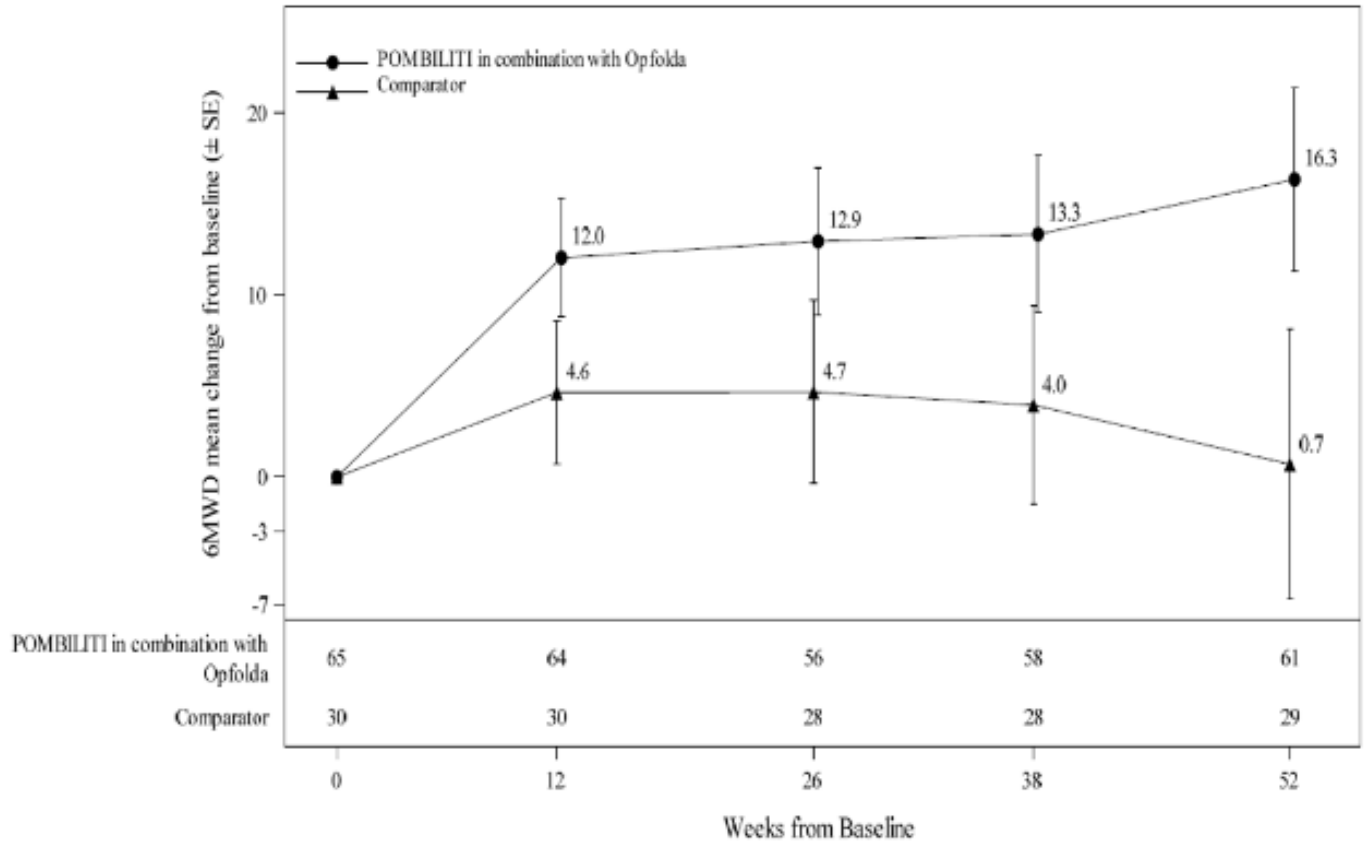
Table 9: Summary of 6MWD in Adults with LOPD by ERT Status at 52 Weeks in Trial 1

Efficacy Endpoint	ERT-experienced		ERT-naïve*	
6MWD	**Pombiliti in Combination with Opfolda**	**A Non-U.S.-Approved Alglucosidase alfa Product† with Placebo**	**Pombiliti in Combination with Opfolda**	**A Non-U.S.-Approved Alglucosidase Product† with Placebo**
Baseline n Mean (SD)	 n=65 347 (110)	 n=30 335 (114)	 n=20 394 (112)	 n=7 421 (136)

Median	353	344	375	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)	

6-MWD: 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 7: Mean Change (± SE) of 6-MWD From Baseline to week 52 in ERT-experienced Adults with LOPD in Trial 1*



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.

Per the FDA label, the safety and effectiveness of Pombiliti in combination with Opfolda has not been established in pediatric patients with late-onset Pompe disease.

Elosulfase alfa (Vimizim®)
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. (7)

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 keratan sulfate (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.

Table 10: Results from Placebo-Controlled Clinical Trial

	Vimizim 2 mg/kg once per week			**Placebo**			**Vimizim versus Placebo**
	Baseline	**Week 24**	**Change**	**Baseline**	**Week 24**	**Change**	**Mean Difference in Changes**
N	58	57*	57	59	59	59	
Six-Minute Walk Test (Meters)							
Mean ± SD	203.9 ± 76.32	243.3 ± 83.53	36.5 ± 58.49	211.9 ± 69.88	225.4 ± 83.22	13.5 ± 50.63	23.0† (CI95, 2.9, 43.1)
Median	216.5	251.0	20.0	228.9	229.4	9.9	22.5‡ (CI95, 4.0, 40.9) (p=0.0174)‡,§
Min, Max	42.4, 321.5	52.0, 399.9	-57.8, 228.7	36.2, 312.2	50.6, 501.0	-99.2, 220.5	

* One patient in the Vimizim group dropped out after 1 infusion.
† Observed Vimizim mean change –Placebo mean change.
‡ ANCOVA Model-based Vimizim mean change – Placebo mean change, adjusted for baseline 6MWT categories (less than or equal to 200 meters, greater than 200 meters) and age groups (5-11, 12-18, 19 or older).
§ p-value based on the model-based difference in means.

Extension Trial

Patients who participated in the placebo-controlled trial were eligible to continue treatment in an open-label extension trial. One hundred seventy-three of 176 patients enrolled in the extension trial in which patients received Vimizim 2 mg/kg once per week (n=86) or Vimizim 2 mg/kg once every other week (n=87). In patients who continued to receive Vimizim 2 mg/kg once per week for another 48 weeks (for a total 72-week exposure), walking ability showed no further improvement beyond the first 24 weeks of treatment in the placebo-controlled trial.

Use in the Pediatric Population

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.

Galsulfase (Naglazyme®)

The FDA approved the use of galsulfase (Naglazyme®) based on the following 4 clinical studies with a total of 56 patients (ages 5 years to 29 years) with Mucopolysaccharidosis VI (MPS VI; Maroteaux-Lamy syndrome). The majority of patients had severe manifestations of the disease as evidenced by poor performance on a test of physical endurance. (8):

In the 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-MWD 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 (Table 11).

Table 11: Results from Placebo-Controlled Clinical Study

	Naglazyme			**Placebo**			**Naglazyme Versus Placebo**
	Baseline	**Week 24**	**Change**	**Baseline**	**Week 24**	**Change**	**Difference in Changes**
N	19	19	19	20	19*	19	
Results from the 12-Minute Walk Test (Meters)							
Mean ± SD	227 ± 170	336 ± 227	109 ± 154	381 ± 202	399 ± 217	26 ± 122	83 ± 45† 92 ± 40‡ (p = 0.025)‡,§
Median Percentiles (25th, 75th)	210 90, 330	316 125, 483	48 7, 183	365 256, 560	373 204, 573	34 –3, 89	
Results from 3-Minute Stair Climb Test (Stairs/Minute)							
Mean ± SD	19.4 ± 12.9	26.9 ± 16.8	7.4 ± 9.9	31.0 ± 18.1	32.6 ± 19.6	2.7 ± 6.9	4.7 ± 2.8† 5.7 ± 2.9‡ (p = 0.053)‡,§
Median Percentiles (25th, 75th)	16.7 10.0, 26.3	22.8 14.8, 33.0	5.2 2.2, 9.9	24.7 18.1, 51.5	29.0 14.2, 57.9	4.3 1.0, 6.2	

* One patient in the placebo group dropped out after 4 weeks of infusion.

† Observed mean of Naglazyme - Placebo ± SE

‡ Model-based mean of Naglazyme - Placebo ± SE, adjusted for baseline.

§ p-value based on the model-based mean difference.

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 50% reduction in urinary GAG levels after 72 weeks of treatment with Naglazyme. No patient receiving Naglazyme reached the normal range for urinary glycosaminoglycan (GAG) levels. In an additional open-label extension study, patients receiving Naglazyme showed maintenance of initial improvement in endurance for approximately 240 weeks.

Use in the Pediatric Population

Per the FDA label, clinical studies with Naglazyme were conducted in 56 patients, ages 5 to 29 years, with the majority of these patients in the pediatric age group. In addition, an open-label study was conducted in four infants (3 months to 12.7 months) treated with 1 mg/kg (n = 2) or 2 mg/kg (n = 2) of Naglazyme. Safety results in infants were consistent with results observed in patients 5 to 29 years old.

Imiglucerase (Cerezyme®)

Study RC 91-0110 was a randomized, double-blind, active-controlled study of 30 patients (17 male and 13 female), aged 12 to 69 years (mean age of 38 years in the Cerezyme group and mean age of 28 years in the alglucerase group at baseline), with Gaucher disease type 1 and a hemoglobin of at least 1 g/dL below the lower age limit for age and sex. Patients were randomized 1:1 to receive either Cerezyme 60 units/kg every other week or alglucerase for 6 months. Primary efficacy parameters were an increase in hemoglobin concentration of at least 1 g/dL, increase in platelet count and decrease in spleen and liver volume at 6 months. Efficacy results are shown in Table 12. (9)

Table 12: Change from Baseline to Month 6 in Clinical Efficacy Parameters in a Randomized, Double-Blind Active-Controlled Trial of Cerezyme Compared to Alglucerase in Patients 12 Years of Age and Older with Gaucher Disease Type 1

Clinical Parameter		Cerezyme (N=15)	Alglucerase (N=15)	Difference (Cerezyme – Alglucerase) [95% CI]*
Hemoglobin concentration (g/dL)	Baseline	10.7	10.9	-
	Absolute Change from Baseline	1.9	1.6	0.3 [-0.6, 1.3]

Platelet count ($\times 10^3/mL^3$)	Baseline	68.5	74.2	-
	Absolute Change from Baseline	22.7	15.8	6.9 [-10.4, 24.1]
Liver volume (mL)	Baseline	2521	2788	-
	Absolute Change from Baseline	-310	-307	-3 [-246, 240]
	Percent Change from Baseline (%)	-11	-10	-1 [-9, 7]
Spleen volume (mL)	Baseline	2369	2603	-
	Absolute Change from Baseline	-902	-874	-28 [-652, 596]
	Percent Change from Baseline (%)	-35	-30	-5 [-14, 4]

CI: confidence interval; g/dL: grams per deciliter; mL: milliliter
* Confidence intervals were calculated using the t distribution (appropriate for small sample sizes) and the standard error of the difference in sample means (i.e. the pooled estimate of the common standard deviation, computed as the weighted average of the standard deviations in the two treatment groups); there was no evidence that the assumption of equal variances between the groups was violated.

Bone x-rays showed improvements in cortical thickness and lucencies in 7 of 11 Cerezyme treated patients.

In study RC 92-0501, twenty-nine patients continued treatment for a total duration of 24 months. Patients were unblinded at 9 months and allowed to cross-over to Cerezyme treatment. At 24 months, mean increase in hemoglobin was 2.4 g/dL, mean increase in platelet count was $40 \times 10^3/mL^3$, mean change in liver volume was -20%, and mean change in spleen volume was -57%.

Use in the Pediatric Population

The safety and effectiveness of Cerezyme for treatment of Type 1 Gaucher disease that results in one or more of the following conditions: anemia, thrombocytopenia, bone disease, hepatomegaly or splenomegaly have been established in pediatric patients 2 years of age and older. Use of Cerezyme for this indication is supported by evidence from adequate and well-controlled studies of Cerezyme and alglucerase in adults and pediatric patients 12 years of age and older, with additional data obtained by the FDA from the medical literature and post marketing experience in pediatric patients as young as 2 years of age. The safety and effectiveness of Cerezyme has not been established in pediatric patients younger than 2 years of age.

Laronidase (Aldurazyme®)

Study 1 (NCT00912925) was a randomized, double-blind, placebo-controlled study in 45 patients with MPS I, including 1 patient with the Hurler form, 37 patients with Hurler-Scheie form, and 7 patients with Scheie form of MPS I. Among the 45 patients who completed Study 1, 22 (49%) were male and 23 (51%) were female ranging in age from 6 to 43 years with a mean age of 15.5 years. Thirty seven (82%) were White, 2 (4%) were Asian, 6 (13%) were Other and no patients were Black or African American. For ethnicity, 4 (9%) were Hispanic. All patients had a baseline percent predicted forced vital capacity (FVC) less than or equal to 77%. Patients

received Aldurazyme IV at 0.58 mg/kg of body weight once weekly or placebo once weekly for 26 weeks. All 45 randomized patients completed the study. (10)

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 13).

Table 13: Change from Baseline in FVC[1] and 6 Minute Walk Distance in Aldurazyme or Placebo Treated Adult and Pediatric Patients with MPS I over 26 Weeks (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 Baseline to Week 26 Between Groups	Mean	38	
	Median (95% CI)	39 (-2, 79), p=0.07*	

MPS I: Mucopolysaccharidosis I
*By Wilcoxon Rank Sum Test; CI: confidence interval; s.d.; standard deviation
[1] Forced Vital Capacity

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.

Study 2 (NCT00146770) was a 182-week, open-label, uncontrolled extension study of all 45 patients who completed Study 1. Patients received Aldurazyme IV at 0.58 mg/kg body weight once weekly. Forty (89%) patients completed the study through Week 182. Five (11%) patients, all of whom received placebo in Study 1 and subsequently received Aldurazyme in Study 2, discontinued prematurely. Of these, 2 patients discontinued due to an adverse event, 2 patients due to patient wishes, and 1 patient due to pregnancy. 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.

Clinical Studies in Patients 6 Years and Younger

Study 3 (NCT00146757) was a 52-week, open-label, uncontrolled clinical study in 20 pediatric patients with MPS I, including 16 patients (80%) with the Hurler form and 4 patients (20%) with the Hurler-Scheie form. Among the 20 patients who participated in Study 3, 12 (60%) were male and 8 (40%) were female ranging in age from 6 months to 5 years old with a mean age of 2.9 years. Eighteen (90%) were White, 1 (5%) were Black or African American and 1 (5%) were Other. A total of 18 patients completed the study. All 20 patients received Aldurazyme IV 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.

Use in the Pediatric Population

Per the FDA label, the safety and effectiveness of Aldurazyme have been established for the treatment of pediatric patients with Hurler and Hurler-Scheie forms of MPS I and the treatment of pediatric patients with the Scheie form of MPS I who have moderate to severe symptoms. The safety and effectiveness of Aldurazyme for the treatment of mildly affected pediatric patients with the Scheie form has not been established. Use of Aldurazyme for these indications is supported by evidence from an adequate and well controlled clinical study (Study 1) with an open label extension (Study 2) in adult and pediatric patients with MPS I, and from an open label, uncontrolled clinical study in pediatric patients with MPS I, 6 months to 5 years of age (Study 3). The safety and effectiveness of Aldurazyme in pediatric patients 6 months of age to 5 years of age was found to be similar to pediatric patients 6 to 18 years of age and adults for these indications.

The FDA label offers the following black box warnings:

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

require additional monitoring. Appropriate respiratory support should be available during infusion.

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 manifestations of the disorder.

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 (11):

- Trial 1 in adult patients (NCT02004691),
- Trial 2 in pediatric patients (NCT02292654), and
- Trial 3 is 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 IV 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 placebo-treated patients (Table 14). A reduction in spleen volume of 39% was observed in the Xenpozyme-treated patients compared to placebo-treated patients. The changes in % predicted DLco and spleen volume were noted at Week 26 of treatment, the first post-dose endpoint assessment (Figures 8 and 9). 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 14).

Table 14: 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)	

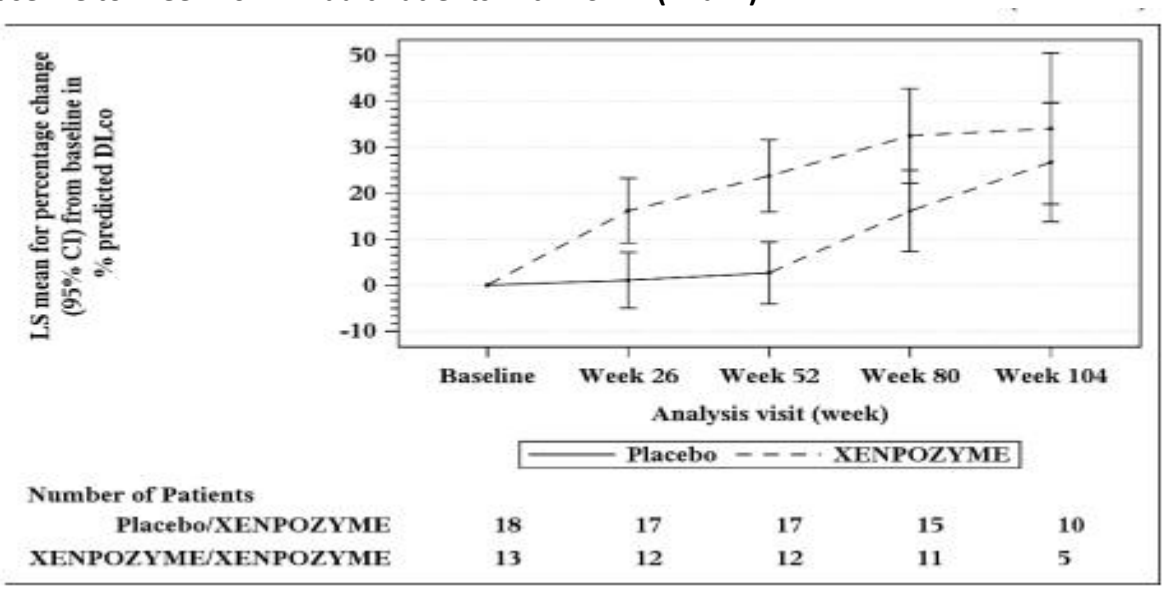
n LS Mean Percent change in Platelet Count from baseline to Week 52 (SE)	16 2.7 (4.5)	13 18.3 (5.0)	+15.6 (6.7) ‡ [1.8, 29.4]

ASMD: acid sphingomyelinase deficiency; CI: confidence interval; 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).

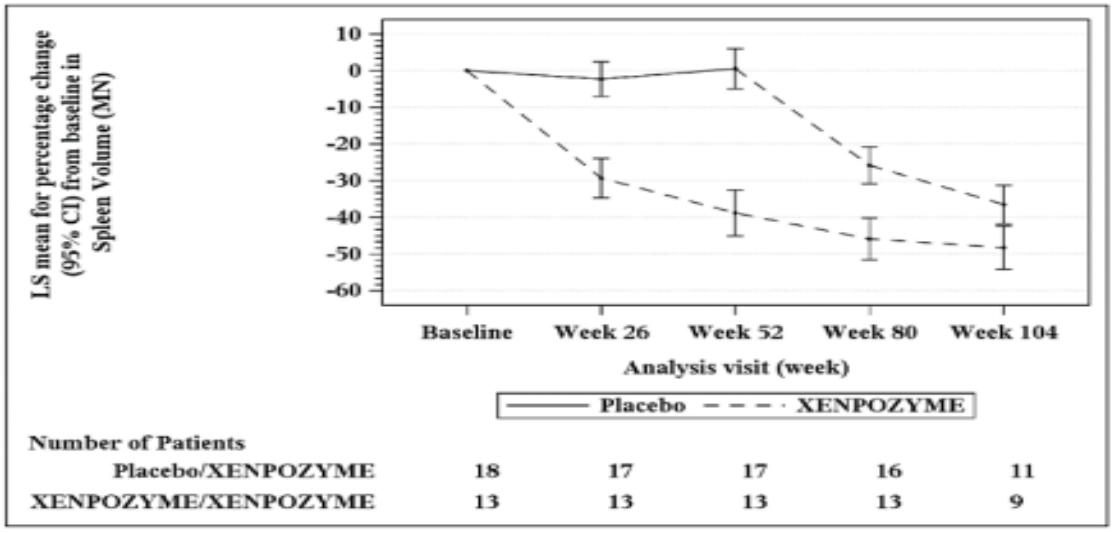
Patients in the previous Xenpozyme group demonstrated improvement from baseline to Week 104 in the following parameters: LS mean (SE) percent increase in % predicted DLco was 34.1% (7.9); LS mean (SE) percent reduction in spleen volume (MN) was 48.3 (2.9); LS mean (SE) percent reduction in liver volume (MN) was 31.7 (2.9); LS mean (SE) percent increase in platelet count was 24.0 (8.2).

Figure 8: Plot of the LS Means (95% CI) of the Percentage Change in DLco (% predicted) From Baseline to Week 104 in Adult Patients with ASMD (Trial 1)



The vertical bars represent the 95% CIs for the LS means.
The LS means and 95% CIs are based on a mixed model for repeated measures approach, using data up to Week 104. Patients in placebo/Xenpozyme group received placebo by Week 52 and switched to Xenpozyme thereafter.

Figure 9: Plot of the LS Means (95%CI) Of the Percentage Change in Spllen Volume (MN) From Baseline to Week 104 in Patients with ASMD (Trial 1)



The vertical bars represent the 95% CIs for the LS means. The LS means and 95% CIs are based on a mixed model for repeated measures approach, using data up to Week 104. Patients in placebo/Xenpozyme group received placebo by Week 52 and switched to Xenpozyme thereafter.

Clinical Trial in Pediatric Patients with ASMD

Trial 2 was a multi-center, open-label, repeated-dose trial of Xenpozyme administered IV 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 15).

Table 15: Efficacy Results in Xenpozyme-Treated Pediatric Patients with ASMD (Trial 2)

	Baseline Values	**Week 52 Values**
Mean % predicted DLco (SD)	(n=3)	(n=3)

LS mean Percent change in % predicted DLco* (SE) 95% CI	48.5 (8.1)	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

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.

Use in the Pediatric Population

The safety and effectiveness of Xenpozyme for the treatment of non-central nervous system manifestations of acid sphingomyelinase deficiency (ASMD) have been established in pediatric patients down to birth. Use of Xenpozyme for this indication 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) and Clinical Studies. Compared to adults, a higher percentage of pediatric patients experienced treatment related serious adverse reactions, anaphylaxis, hypersensitivity reactions, and infusion-associated reactions shat occurred within 24 hours of infusion. Two pediatric patients, an 18 month old receiving Xenprozyme and a 16 month old with ASMD type A that received a version of olipudase alfa manufactured from a different process developed anaphylaxis.

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 IV every other week for 52 weeks. The 0.2 mg/kg and 2 mg/kg dosage regimens are not approved and are not recommended. (12)

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 m^2 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.

Table 16 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 16: 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)

CI: confidence interval; N: number.
[1] The BLISS methodology counts the number of Gb3 inclusions in each renal peritubular capillary (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 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 IV infusion) or agalsidase beta (1 mg/kg IV 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 m^2 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 m^2/year on Elfabrio and agalsidase beta respectively. The estimated treatment difference was -0.1 (95% CI: -2.3, 2.1) mL/min/1.73 m^2/year.

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

Sebelipase Alfa (Kanuma®)

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

A multicenter, open-label, single-arm clinical study of Kanuma® was conducted in 9 infants with lysosomal acid lipase (LAL) deficiency who had growth failure of other evidence of rapidly progressive disease prior to 6 months of age. The age range at entry was 1 to 6 months. Patients received Kanuma 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. (13)

The efficacy of Kanuma was assessed by comparing the survival of the 9 Kanuma-treated patients (followed in the open-label, single-arm trial) at 12 months of age to the survival in an

untreated, historical cohort of 21 patients with a similar age at disease presentation and clinical characteristics. Of the 9 Kanuma-treated patients, 6 patients survived beyond 12 months of age, compared to 0 of 21 patients who survived in the historical cohort, all of whom had died by 8 months of age. The median age of the 6 surviving Kanuma-treated patients was 18.1 months (range 12 to 42.2 months).

Following initiation of treatment with Kanuma 1 mg/kg once weekly: weight for age z scores improved in 3 of 5 surviving patients with growth failure, and all 6 surviving patients demonstrated improvements in weight for age z scores following dose escalation to 3 mg/kg once weekly.

Continuation Treatment

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 Kanuma 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 Kanuma dose.

Pediatric and Adult Patients with LAL Deficiency

The safety and efficacy of Kanuma were accessed in 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 Kanuma 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. The majority of 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 Kanuma 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 Kanuma 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 statistically significant improvement in percentage change from baseline at 20 weeks was also noted in the Kanuma 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 Kanuma on cardiovascular morbidity and mortality has not been established.

Patients treated with Kanuma 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.

Open Label Treatment

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 Kanuma at a dose of 1mg/kg once every other week. Patients treated with Kanuma 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-cores in children. Of the 23 patients whose Kanuma 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 Kanuma dose: serum transaminases, triglycerides, and/or LDL-c.

Use in the Pediatric Population

The safety and effectiveness of Kanuma has been established in pediatric patients aged 1 month and older. Clinical trials with Kanuma were conducted in 56 pediatric patients (range 1 month to <18 years old).

Taliglucerase alfa (Elelyso)

Clinical Trial in Adult Patients: Initial Therapy

The safety and efficacy of taliglucerase alfa (Elelyso®) in the treatment of adult patients with Type 1 Gaucher disease was assessed in a 9-month, multi-center, double-blind, randomized trial (Trial 1) in 31 adult patients with Gaucher disease-related enlarged spleens (>8 times normal) and thrombocytopenia (<120,000 /mm^3). Sixteen patients had enlarged livers and ten patients had anemia at baseline. All patients were naïve to enzyme replacement therapy (ERT). Patients with severe neurological symptoms were excluded from the trial. (14)

Patients were randomized to receive Elelyso at an IV dosage of either 30 units/kg (n=15; 50% of the recommended dosage) or 60 units/kg (the recommended dosage; n=16) every other week. After 9 months, 26 of the 31 patients continued in the blinded portion of the long-term extension trial for a total treatment duration of 24 months at the same IV dosage every other week. Twenty three of those 26 patients continued open-label Elelyso treatment (30 or 60

units/kg given IV every other week) for an additional 12 months (total duration of Elelyso treatment was 36 months).

Baseline Demographics
In Trial 1, patients were 19 to 74 years of age (mean age 36 years), 48% were male, 97% were White and 29% and 71% were Hispanic/Latino and non-Hispanic/Latino, respectively.

Efficacy Results
Table 17 shows the baseline values and mean (SD) changes in clinical parameters (spleen volume, liver volume, platelet count, and hemoglobin) after 9 months of Elelyso treatment in Trial 1. Liver and spleen volumes were measured by MRI and are reported as percentage of body weight (% BW) and multiples of normal (MN). The observed reduction from baseline in spleen volume (the primary endpoint), was considered to be clinically meaningful in light of the natural history of untreated Gaucher disease.

Table 17: Mean (SD) Changes in Clinical Parameters from Baseline to 9 Months in Treatment-Naïve Adults with Type 1 Gaucher Disease Treated with Elelyso (N=31) (Trial 1)**

	Clinical Parameter	**Elelyso 30 units/kg* (n=15) Mean (SD)**	**Elelyso 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)

BW: body weight; g/dl: grams per deciliter; Kg: kilogram; mm^3: cubic millimeter; N: number.
*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.
** SD = standard deviation
ǂ % BW = percentage of body weight
ǂǂ MN = multiples of normal

The following data are the changes in clinical parameters from baseline to Month 24 (including the 9-month initial period and the 15-month first long-term extension) for the 30 units/kg (n=12; 50% of the recommended dosage) and 60 units/kg (the recommended dosage; n=14) treatment groups, respectively: mean (SD) spleen volume (% BW) decreased by 1.4 (0.6) and 2.0 (2.0), in MN by 6.8 (3.0) and 10.2 (9.8); hemoglobin increased by 1.3 (1.7) g/dL and 2.4 (2.3) g/dL; liver volume (% BW) decreased by 1.1 (0.5) and 1.0 (0.7), in MN by 0.4 (0.2) and 0.4 (0.3) and platelet count increased 28,433 (31,996)/mm^3 and 72,029 (68,157)/mm^3 . The 23 patients who continued open-label Eleleyso treatment for additional 12 months demonstrated stability in these clinical parameters.

Clinical Trial in Pediatric Patients 16 Years of Age and Younger

The safety and efficacy of Elelyso in the treatment of pediatric patients with Type 1 Gaucher disease was assessed in a 12-month, multi-center, double-blind, randomized trial (Trial 2) in 9 treatment-naïve patients. Patients were randomized to receive Elelyso at an IV dosage of either 30 units/kg (n=4) (50% of the recommended dosage) or 60 units/kg (the recommended dosage; n=5) every other week. After 12 months, all 9 patients entered a blinded portion of the long-term extension trial (24-months of total treatment) where they continued treatment with Elelyso at the same dosage every other week.

Baseline Demographics

In Trial 2, patients were 2 to 13 years of age (mean age 8.1 years), 67% were male, 89% were White and 44% and 56% were Hispanic/Latino and non-Hispanic/Latino, respectively.

Efficacy Results

The following data in Trial 2 are the changes [median (Q1, Q3)] in clinical parameters from baseline to Month 12 for the 60 units/kg dose group (n=5): spleen volume decreased from 18.4 (14.2, 35.1) MN to 11.0 (8.3, 14.5) MN; hemoglobin increased from 11.1 (9.2, 11.3) g/dL to 11.7 (11.5, 12.9) g/dL; liver volume decreased from 2.1 (2.0, 2.3) MN to 1.6 (1.5, 1.9) MN; platelet count increased from 80,000 (79,000, 87,000)/mm^3 to 131,000 (119,000, 215,000)/mm^3.

The following data are the changes [median (Q1, Q3)] in clinical parameters from baseline to Month 24 (including the initial 12-month period and the 12-month long-term extension) for the 60 units/kg dose group (n=5): spleen volume decreased by 19.0 (8.3, 41.2) MN; hemoglobin increased by 2.5 (1.9, 3.0) g/dL; liver volume decreased by 0.8 (0.6, 1.1) MN; and platelet count increased by 76,000 (67,000, 100,000)/mm^3.

Clinical Trial in Patients Switching from Imiglucerase Treatment to Elelyso

The safety and efficacy of Elelyso were assessed in 31 patients (26 adult and 5 pediatric patients) with Type 1 Gaucher disease who were switched from imiglucerase to Elelyso (Trial 3). Trial 3 was a 9-month, multi-center, open-label, single arm study in patients who had been receiving IV 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 dosage of imiglucerase for at least 6 months prior to enrollment. 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 (9.5 units/kg to 60 units/kg given IV every other week). 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).

Eighteen of the 26 adult patients who completed the 9-month clinical trial continued treatment with Elelyso (9.5 units/kg to 60 units/kg given IV every other week) in an open-label extension trial for additional 27 months (total duration of Elelyso treatment was 36 months).

Five of the pediatric patients who completed the 9-month trial continued open-label treatment with Elelyso (9.5 units/kg to 60 units/kg given IV every other week) for an additional 24 months (total duration of Elelyso treatment was 33 months).

Baseline Demographics
In Trial 3, patients were 6 to 66 years of age (mean age 42 years, including pediatric patients), 55% were male, 97% were White, and 16% and 84% were Hispanic/Latino and non-Hispanic/Latino, respectively.

Efficacy Results
In Trial 3, at baseline, spleen volume was 5.2 (4.5) MN, liver volume was 1.0 (0.3) MN, platelet count was 161,137 (73,387)/mm^3, and hemoglobin was 13.5 (1.4) g/dL. Mean (SD) organ volumes and hematologic values remained stable through 9 months of ELELYSO treatment. After 9 months of ELELYSO treatment, spleen volume was 4.8 (4.6) MN, liver volume was 1.0 (0.2) MN, platelet count was 161,167 (80,820)/mm^3, and hemoglobin was 13.4 (1.5) g/dL. The Elelyso dosage 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.

During the 36-month period, 18 Elelyso-treated adult 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 only 7 patients had their spleen and liver volumes assessed at 36 months. During the 33-month period, the 5 Elelyso-treated pediatric patients demonstrated stability in these clinical parameters.

<u>Use in the Pediatric Population</u>

The safety and effectiveness of Elelyso for the treatment of pediatric patients 4 years of age and older with a confirmed diagnosis of Type 1 Gaucher disease has been established. The use of Elelyso for this indication is supported by evidence of effectiveness from adequate and well-controlled trials of Elelyso in adults, with additional pharmacodynamic data from 5 pediatric patients and pharmacokinetic data from 9 pediatric patients who participated in clinical trials. Data from 14 pediatric patients were included in the safety evaluation. The safety and effectiveness of Elelyso has not been established in patients less than 4 years of age.

Pediatric patients experienced a higher frequency of vomiting during Elelyso treatment (4 of 9 treatment-naïve patients) than adult patients, and this may be a symptom of hypersensitivity reaction. The frequencies of other adverse reactions were similar between pediatric and adult patients treated with Elelyso.

Velaglucerase alpha (VPRIV)

The efficacy of VPRIV was assessed in three clinical trials 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 IV 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. (15)

Clinical Trials of VPRIV as Initial Therapy

Study I was a 12 month, randomized, double blind, parallel dose group, multinational trial 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 10^9/L, mean liver volume was 3.6% 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 18. 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 18: Mean Change From Baseline to Month 12 For Clinical Parameters in Patients with Type 1 Gaucher Disease Initiating Therapy with VPRIV in Study I

Clinical Parameter	VPRIV 45 units/kg # N = 13 Mean ± SE	VPRIV 60 units/kg N = 12 Mean ± SE
Hemoglobin concentration change (g/dL)	2.4 ± 0.4†	2.4 ± 0.3*
Platelet count change (x 10^9/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†

BW: body weight; SE = standard error of the mean; VPRIV: velaglucerase alpha
The recommended starting dose in naïve patients is 60 Units/kg. The 45 Units/kg dosage is not recommended as a starting dose in naïve patients.
† Statistically significant changes from baseline after adjusting for performing multiple tests
* Primary study endpoint was hemoglobin concentration change in the 60 Units/kg group, $p<0.001$

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 10^9/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 both studies, 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.

In Study IV, treatment naïve patients were administered VPRIV. Treatment-naïve patients continued to show improvements in clinical parameters (hemoglobin concentration, platelet count, liver volume, and spleen volume) compared with baseline for up to 60 months of treatment with ERT.

Clinical Trial in Patients Switching from Imiglucerase Treatment to VPRIV

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 10^9/L (range: 24, 408) vs. the baseline value of 162 x 10^9/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, and spleen volume) compared with baseline for up to 60 months of treatment with ERT.

Use in the Pediatric Population

The safety and effectiveness of VPRIV has been established for ERT in patients between 4 and 17 years of age with type 1 Gaucher disease. The use of VPRIV in this age group is supported by evidence from adequate and well-controlled studies of VPRIV in 74 adult patients and 20 pediatric patients. The safety and efficacy profiles were similar between pediatric and adult patients. The efficacy and safety of VPRIV has not been established in pediatric patients younger than 4 years of age.

Vestronidase Alfa-vjbk (Mepsevii®)

The clinical program for Mepsevii included 23 patients with MPS VII, 17 of whom were evaluable for efficacy, 20 for safety, and 23 for immunogenicity. Patients were enrolled in clinical trials and expanded access protocols receiving treatment at doses up to 4 mg/kg once every two weeks for up to 187 weeks. The patients ranged in age from 5 months to 25 years. Sixteen patients were younger than 18 years of age. (16)

Studies 301 and 202

Study UX003-CL301 (referred to as Study 301, NCT02230566) was a randomized start trial of Mepsevii 4 mg/kg every two weeks in patients with MPS VII. Twelve patients were randomized to one of four placebo durations before crossing over to active treatment. Three patients received Mepsevii immediately for a duration of 48 weeks, 3 patients received placebo for 8 weeks then Mepsevii for 40 weeks, 3 patients received placebo for 16 weeks then Mepsevii for 32 weeks, and 3 patients received placebo for 24 weeks then Mepsevii for 24 weeks. Of the 12 patients enrolled in the trial, 4 were male and 8 were female and ranged in age from 8 to 25 years (median 14 years). Nine patients were younger than 18 years of age. The majority of the patients were White (75%), with 50% of Hispanic or Latino ethnicity. Patients who were enrolled in Study 301 were eligible to roll over to Study UX003-CL202 (referred to as Study 202, NCT02432144), an open-label extension trial in which patients received additional doses of Mepsevii at 4 mg/kg IV every other week for up to 144 weeks. Ten patients rolled over directly

from the end of Study to Week 0 of Study 202, while 2 patients (17%) had treatment gaps before enrolling in Study 202.

In Study 301, motor function, forced vital capacity, and visual acuity were assessed after 24 weeks of Mepsevii treatment and measured against pre-specified minimal important differences. The extremely small population of patients with MPS VII globally necessitated the enrollment of all patients able to participate, resulting in a highly heterogeneous group. Clinical endpoints were not assessable in some patients due to their extent of disease, age or level of cognition. Repeated assessments of the 6-MWT were feasible in ten of 12 patients and are described further below. Of the three patients who improved on their 6-MWT (Figure 10, left panel), two also were noted to have improvement in balance and gross motor proficiency as assessed by the Bruininks Oseretsky Test of Motor Proficiency (BOT-2).

In this trial, the mean difference in 6MWT distance between Mepsevii and placebo treatment periods in patients able to perform the test at baseline and subsequent visits through Week 24 is shown in Table 19. The mean difference in 6-MWT distance increases with increased treatment duration. However, due to the small size of the trial, standard errors are large.

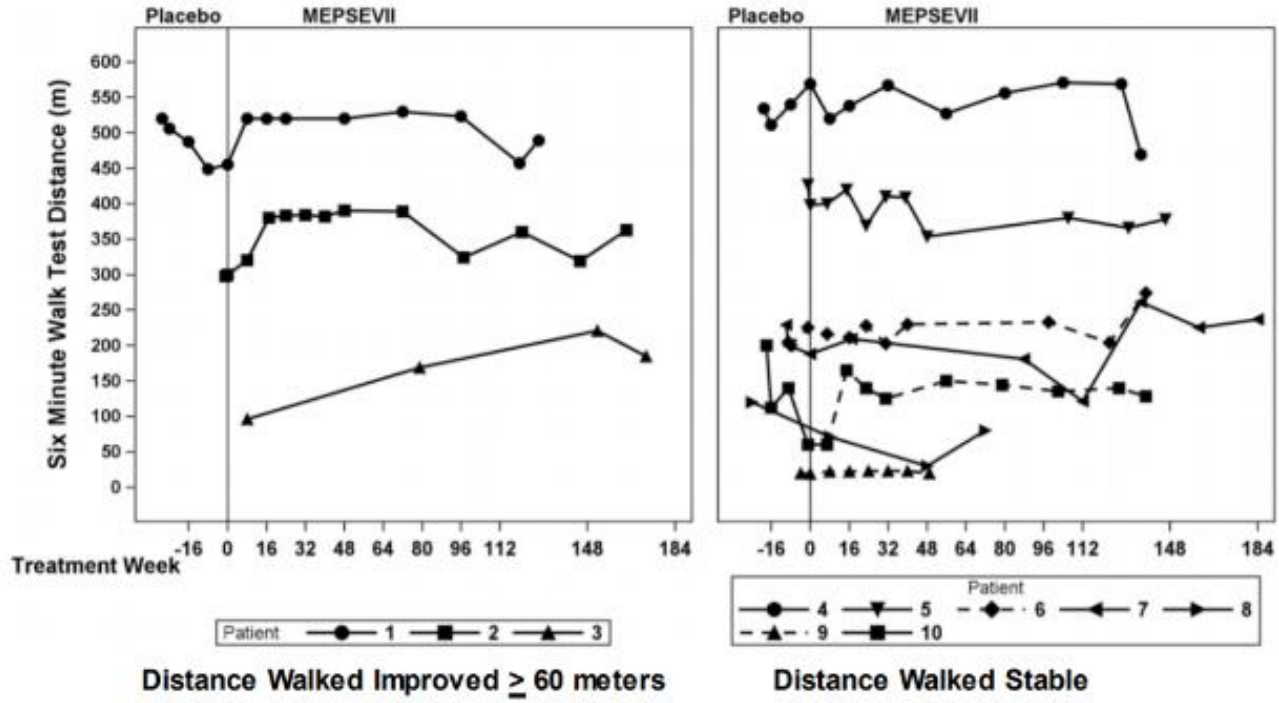
Table 19. Mean Difference in 6-MWT Distance (meters) Between Mepsevii and Placebo Treatment (Study 301) in Patients with MPS VII

Duration of MEPSEVII Treatment	LS mean 6MWT (meters) (± Standard Error)*	Number and Treatment Assignment of Patients Included in Analyis**
8 weeks	-11 (± 24)	5 placebo period; 8 MEPSEVII period
16 weeks	13 (± 32)	5 placebo period; 8 MEPSEVII period
24 weeks	18 (± 33)	5 placebo period; 8 MEPSEVII period

6-minute walk test (6-MWT); MPS: mucopolysaccharidosis.
*ANCOVA analysis of change from baseline in least squares (LS) mean between placebo and MEPSEV II for different periods, after adjusting for study cohort, age, and baseline 6MWT distance. Patients who used assistive devices were imputed as zeros in the analysis.
**Number and treatment assignment of patients included in the analysis was based upon a randomized start trial design and patient ability to complete testing. Due to no placebo period for the three patients who received 48 weeks of Mepsevii in the first cohort of the randomized start design, more data were available for analyses during the treatment period (n=8) than during the placebo period (n=5). While data from 8 participants were available at each time point, due to missing observations, the 8 participants were not the same across all time points.

The observed individual 6-MWT distances for the 10 patients who could perform the test in Study 301 and Study 202 through Week 184 are presented in Figure 10. The course of three patients with improvement in distance walked of at least 60 meters during the 301 Study compared to the start of Mepsevii treatment (Week 0) is shown in the left panel; the relatively stable course in the remaining seven patients, including those who used assistive devices, is shown in the right panel.

Figure 10: 6MWT Distance for MPS VII Patients in Studies 301 and 202



Patient 10 did not use an assistive device at baseline but started using an assistive device postbaseline from Treatment Week 8. Patients 6 and 9 consistently used an assistive device at all visits. A solid line indicates the unassisted assessments and a dotted line indicates the assisted assessments.

Liver and Spleen Volume

In Study 301, imaging by MRI or ultrasound to assess liver and spleen volume was performed in seven of the 12 patients. Most liver volumes were normal or below normal size at baseline (mean 1,591 mL, range 742 to 2,207 mL), and on average were unchanged after treatment (mean 1,459 mL, range 876 to 1,851 mL).

Spleen volumes generally were normal or below normal size at baseline (mean 325 mL, range 131 to 491 mL) and on average were unchanged after treatment (mean 360 mL, range 200 to 582 mL).

Study 203

UX003-CL203 (referred to as Study 203; NCT02418455) was an open-label, uncontrolled single arm study that enrolled 8 patients less than 5 years of age who received Mepsevii at a dose of 4 mg/kg every two weeks for 48 weeks of treatment and up to an additional 240 weeks during an optional continuation period. The study evaluated urinary GAG excretion, growth, and hepatosplenomegaly. With long-term treatment, urinary GAG levels remained decreased upon exposure to Mepsevii. At baseline, all 8 patients had impaired growth, and height remained near the 5th percentile relative to age-matched gender norms throughout the trial. No significant changes in hepatosplenomegaly were observed.

Other Investigations

Study UX003-CL201 (referred to as Study 201, NCT01856218) was a single arm, open-label, dose exploration trial completed outside the United States that enrolled three MPS VII patients, ranging in age from 5 years to 25 years. Two patients were male; two patients were white and one was Asian. After 120 weeks of exposure to Mepsevii, one patient demonstrated a 21% improvement over baseline in forced vital capacity (FVC % predicted) on pulmonary function testing in addition to a 105-meter improvement in the 6-MWT. Two other patients with baseline hepatosplenomegaly had a reduction in liver volume (24% and 53%) and spleen volume (28% and 47%) after 36 weeks of Mepsevii treatment. Expanded access to Mepsevii treatment was provided to a pediatric patient with MPS VII who required continuous ventilatory support at the start of treatment and was subsequently able to tolerate 9 hours daily off ventilator support after 164 weeks of Mepsevii treatment.

Use in the Pediatric Population

The safety and effectiveness of Mepsevii have been established in pediatric patients less than 18 years of age.

Limitations of Use

The effect of Mepsevii on the central nervous system manifestations of MPS VII has not been determined.

Tividenofusp alfa-eknm (Avlayah™)

Tividenofusp alfa-eknm (Avlayah™) is FDA approved for the treatment of neurologic manifestations of Hunter syndrome (Mucopolysaccharidosis type II, MPS II) when initiated in presymptomatic or symptomatic pediatric patients weighing at least 5 kg prior to advanced neurologic impairment. This indication is approved under accelerated approval based on reduction of cerebrospinal fluid/heparan sulfate observed in patients treated with Avalah. Per the FDA label, continued approval for this indication may be contingent upon verification of clinical benefit in a confirmatory trial(s). (33)

Trial 1 (NCT04251026) was a Phase 1/2 multi-center, international, multi-cohort, single-arm, open-label trial of Avlayah in 47 pediatric patients with Hunter syndrome including 44 patients with neuronopathic Hunter syndrome and 3 patients with non-neuronopathic Hunter syndrome. Of the 47 patients enrolled, 46 patients completed part 1 of the study (up to Week 24) and 1 patient discontinued the study due to an adverse reaction prior to Week 24. In part 1 of Trial 1, patients received a starting dosage of Avlayah ranging from 3 mg/kg to 15 mg/kg weekly and a maximum dosage ranging from 3 mg/kg to 30 mg/kg weekly (0.2 to 2 times the approved recommended maintenance dosage). Patients who received 30 mg/kg weekly dosage (2 times the approved recommended maintenance dosage) did not show additional reductions from baseline in cerebrospinal fluid (CSF) or urine heparan sulfate (HS) concentration compared to patients who received 15 mg/kg weekly. The most common Avlayah dosage (57% of the patients) in Trial 1 was 15 mg/kg administered once weekly.

All 47 patients in Trial 1 were male, with a baseline median age of 5 years (range: 3 months to 13 years of age). The patient population consisted of 27 White (57%), 4 Black or African American (9%), 4 Asian (9%), 3 who were more than one race (6%), 1 of another race (2%), and 8 of an unknown race (17%). Ethnicity consisted of 7 patients who were Hispanic or Latino (15%), 38 who were Not Hispanic or Latino (81%), and 2 of an unknown ethnicity (4%). Of the 47 patients, 15 patients were enzyme replacement therapy (ERT)-naïve, and 32 patients were ERT-experienced, 2 of whom had a history of prior treatment for Hunter syndrome with hematopoietic stem cell transplantation (HSCT), and 2 of whom had a history of prior treatment for Hunter syndrome with gene therapy. The median duration of previous ERT treatment was 26 months (range: 1 to 134 months).

In Trial 1, treatment with Avlayah resulted in a significant reduction of CSF HS. For the 44 patients who had measurements at Week 24, the CSF HS mean percent reduction from baseline was 91% (95% CI: 89%, 92%); the minimum and maximum percent change in CSF HS from baseline were 72% and 98%, respectively. At baseline, 0% (0 of 47) of patients had CSF HS levels below the upper limit of normal (ULN). At Week 24, 93% (41 of 44) of Avlayah-treated patients had CSF HS levels below the upper limit of normal (ULN).

The safety and effectiveness of Avalah have not been established in pediatric patients weighing less than 5 kg.

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 (32):

- "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 (PD). 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."

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, J1757, J1786, J1931, J2508, J2840, J3060, J3385, J3397, J3490, J3590.

*Current Procedural Terminology (CPT®) ©2025 American Medical Association: Chicago, IL.

References

U.S. Food and Drug Administration Labels:

1. FDA-Highlights of prescribing information. Fabrazyme® (agalsidase beta). Food and Drug Administration. (Jul 2024). Available at: <https://www.accessdata.fda.gov> (accessed June 13, 2025).
2. FDA- Highlights of prescribing information. Avalglucosidase alfa-NGPT (nexviazyme®). Food and Drug Administration. (Sep 2023). Available at: <https://www.accessdata.fda.gov> (accessed June 11, 2025).
3. FDA- Highlights of prescribing information. Elaprase® (idursulfase). Food and Drug Administration. (Nov 2018). Available at: <https://www.accessdata.fda.gov> (accessed June 12, 2025).
4. FDA- Highlights of prescribing information. Lumizyme® (alglucosidase alfa). Food and Drug Administration. (Dec 2024). Available at: <https://www.accessdata.fda.gov> (accessed June 12, 2025).
5. FDA- Highlights of prescribing information. Strensiq® (asfotase alfa). Food and Drug Administration. (Jul 2024). Available at: <https://www.accessdata.fda.gov> (accessed June 12, 2025).
6. FDA- Highlights of prescribing information. Pombiliti™ (Cipaglucosidase alfa-atga). Food and Drug Administration. (Jul 2024). Available at: <https://www.accessdata.fda.gov> (accessed June 12, 2025).
7. FDA- Highlights of prescribing information. Vimizim® (elosulfase alfa). Food and Drug Administration. (Dec 2019). Available at: <https://www.accessdata.fda.gov> (accessed June 12, 2025).
8. FDA- Highlights of prescribing information. Naglazyme® (galsulfase). Food and Drug Administration. (Sep 2024). Available at: <https://www.accessdata.fda.gov> (accessed June 12, 2025).
9. FDA- Highlights of prescribing information. Cerezyme® (imiglucerase). Food and Drug Administration. (Dec 2024). Available at: <https://www.accessdata.fda.gov> (accessed June 12, 2025).

10. FDA- Highlights of prescribing information. Aldurazyme (laronidase). Food and Drug Administration. (Dec 2023). Available at: <https://www.accessdata.fda.gov> (accessed June 12, 2025).
11. FDA- Highlights of prescribing information. Olipudase alfa (Xenpozyme®). (Dec 2024). Food and Drug Administration. Available at: <https://www.accessdata.fda.gov> (accessed June 13, 2025).
12. FDA- Highlights of prescribing information. Pegunigalsidase alfa-iwxj (Elfabrio®). (May 2023). Food and Drug Administration. Available at: <https://www.accessdata.fda.gov> (accessed June 13, 2025).
13. FDA- Highlights of prescribing information. Kanuma® (sebelipase alfa). Food and Drug Administration. (Jul 2024). Available at: <https://www.accessdata.fda.gov> (accessed June 13, 2025).
14. FDA- Highlights of prescribing information. Elelyso® (taliglucerase Alfa). Food and Drug Administration. (Jan 2025). Available at: <https://www.accessdata.fda.gov> (accessed June 13, 2025).
15. FDA- Highlights of prescribing information. VPRIV® (velaglucerase alfa). Food and Drug Administration. (Jul 2024). Available at: <https://www.accessdata.fda.gov> (accessed June 13, 2025).
16. FDA- Highlights of prescribing information. Mepsevii® (vestronidase alfa-vjbk). Food and Drug Administration. (Dec 2020). Available at: <https://www.accessdata.fda.gov> (accessed June 13, 2025).
33. Prescribing Label: Tividenofusp alfa-eknm (Avlayah) for injection, for intravenous use. Mar 2026. Available at: <https://www.accessdata.fda.gov> (accessed April 1, 2026).

Other:

17. National Organization of Rare Disorders. Rare disease database: Lysosomal storage disorder. (Mar 2008). Available at: <https://www.rarediseases.org> (accessed July 8, 2025).
18. Cleveland Clinic. Lysosomal storage diseases (Jun 2022). Available at: <https://my.clevelandclinic.org> (accessed July 8, 2025).
19. National Organization of Rare Disorders. Rare disease database: Acid sphingomyelinase deficiency. (Jan 2025). Available at: <https://www.rarediseases.org> (accessed July 8, 2025).
20. National Organization of Rare Disorders. Rare disease database: Fabry disease. (Jun 6, 2019). Available at: <https://www.rarediseases.org> (accessed July 8, 2025).
21. National Gaucher Foundation, Inc. Gaucher disease: What is Gaucher disease. (2025). Available at: <https://www.gaucherdisease.org> (accessed July 8, 2025).
22. National Organization of Rare Disorders: Gaucher Disease. (Sep 2024). Available at: <https://www.rarediseases.org> (accessed July 8, 2025).
23. National Organization of Rare Disorders: Hypophosphatasia. (May 2025). Available at: <https://www.rarediseases.org> (accessed July 9, 2025).
24. Mayo Clinic. Hypophosphatasia: Clinical updates and therapeutic advances. (Jan 2020). Available at: <https://mayoclinic.org> (accessed July 9, 2025).
25. National Organization of Rare Disorders. Wolman disease. (Aug 2016). Available at: <https://www.rarediseases.info.nih.gov> (accessed July 9, 2025).

26. American Liver Foundation. Lysosomal Acid Lipase Deficiency (LADL). (Jun 25, 2025). Available at: <https://www.liverfoundation.org> (accessed July 9, 2025).
27. National Organization of Rare Disorders. Cholesteryl ester storage disease. (Apr 2023). Available at: <https://www.rarediseases.info.nih.gov> (accessed July 9, 2025).
28. National Organization of Rare Disorders. Mucopolysaccharidoses. (Jun 23, 2017). Available at: <https://www.rarediseases.org> (accessed July 9, 2025).
29. National Institute of Neurological Disorders and Stroke (NINDS). Mucopolysaccharidoses. (Jul 19, 2024). Available at: <https://www.ninds.nih.gov> (accessed July 9, 2025).
30. National Organization of Rare Disorders. Pompe Disease. (Jan 2024). Available at: <https://www.rarediseases.org> (accessed July 10, 2025).
31. FDA expands approval of drug to treat Pompe disease to patients of all ages. (Aug 2014). Available at: <https://www.drugs.com> (accessed July 10, 2025).
32. 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 <https://www.cms.hhs.gov>.

Policy History/Revision

Date	Description of Change
10/01/2026	Document updated. The following changes were made to Coverage: 1) Added “Tividenofusp alfa-eknm (Avlayah™) for the treatment of neurologic manifestations of Hunter syndrome (Mucopolysaccharidosis type II, MPS II) is considered not medically necessary as a clinical benefit has not been established; and 2) Added Tividenofusp alfa-eknm (Avlayah™) is considered experimental, investigational, and/or unproven for all other non-FDA approved indications. Added reference 33.
01/01/2026	Document updated with literature review. The following changes were made in Coverage: 1) Modified enzyme replacement therapies to be in line with each United States Food and Drug Administration label; 2) Added “non-Food and Drug Administration (FDA) approved” to the existing experimental, investigational and/or unproven statement for each enzyme replacement therapy; and 3) Removed statements related to preferred and non-preferred

	agents, and initial/continuation of therapy. Added references 22, 24, 26, 27; others updated and/or removed.
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.

Appendix

The Appendix is not applicable to plans regulated by the Illinois Department of Insurance or Medicare or Medicaid plans.

Continuation Therapy:
Continuation of therapy with non-preferred agents **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:
Coverage for non-preferred agents will be provided contingent to the criteria in this section. For individuals initiating therapy, the following criteria would apply prior to non-preferred agent use:

- Individual has tried and failed, is intolerant to, or has a clinical contraindication to the preferred agent; AND
- Physician attests that in their clinical opinion, the same intolerance, contraindications, lack of clinical efficacy, or adverse event would not be expected to occur with non-preferred agent;

OR

- The preferred drugs are experiencing documented drug shortages or recalls from a wholesaler, manufacturer, the ASHP (American Hospital of Health-System Pharmacist) Drug Shortage web page or the US Food and Drug Administration.

OR

- Cerezyme is requested for a member that is > 2 years old and < 4 years old.

State specific drug criteria my apply.

Preferred Drugs	Non-Preferred Drugs
Vpriv	Cerezyme Elelyso