



# Effective Health Care Program

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Technical Brief  
Number 12

## Enzyme-Replacement Therapies for Lysosomal Storage Diseases



Agency for Healthcare Research and Quality  
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## **Enzyme-Replacement Therapies for Lysosomal Storage Diseases**

**Prepared for:**

Agency for Healthcare Research and Quality  
U.S. Department of Health and Human Services  
540 Gaither Road  
Rockville, MD 20850  
[www.ahrq.gov](http://www.ahrq.gov)

**Contract No. 290-2007-10058-I**

**Prepared by:**

Blue Cross and Blue Shield Association Technology Evaluation Center  
Evidence-based Practice Center  
Chicago, IL

**Investigators:**

Thomas A. Ratko, Ph.D.  
Anne Marbella, M.S.  
Sarah Godfrey, M.P.H.  
Naomi Aronson, Ph.D.

This report is based on research conducted by the Blue Cross and Blue Shield Association Technology Evaluation Center Evidence-based Practice Center (EPC) under contract to the Agency for Healthcare Research and Quality (AHRQ), Rockville, MD (Contract No. 290 2007-10058-I). The findings and conclusions in this document are those of the author(s), who are responsible for its contents; the findings and conclusions do not necessarily represent the views of AHRQ. Therefore, no statement in this report should be construed as an official position of AHRQ or of the U.S. Department of Health and Human Services.

The information in this report is intended to help health care decisionmakers—patients and clinicians, health system leaders, and policymakers, among others—make well-informed decisions and thereby improve the quality of health care services. This report is not intended to be a substitute for the application of clinical judgment. Anyone who makes decisions concerning the provision of clinical care should consider this report in the same way as any medical reference and in conjunction with all other pertinent information, i.e., in the context of available resources and circumstances presented by individual patients.

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None of the investigators have any affiliations or financial involvement that conflicts with the material presented in this report.
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**Suggested citation:** Ratko TA, Marbella A, Godfrey S, Aronson N. Enzyme-Replacement Therapies for Lysosomal Storage Diseases Technical Brief. No. 12. (Prepared by Blue Cross and Blue Shield Association Technology Evaluation Center Evidence-based Practice Center under Contract No. 290-2007-10058-I.) Rockville, MD: Agency for Healthcare Research and Quality. January 2013. [www.effectivehealthcare.ahrq.gov/reports/final.cfm](http://www.effectivehealthcare.ahrq.gov/reports/final.cfm).

## Preface

The Agency for Healthcare Research and Quality (AHRQ), through its Evidence-based Practice Centers (EPCs), sponsors the development of evidence reports and technology assessments to assist public- and private-sector organizations in their efforts to improve the quality of health care in the United States. The reports and assessments provide organizations with comprehensive, science-based information on common, costly medical conditions and new health care technologies and strategies. The EPCs systematically review the relevant scientific literature on topics assigned to them by AHRQ and conduct additional analyses when appropriate prior to developing their reports and assessments.

This EPC evidence report is a Technical Brief. A Technical Brief is a rapid report, typically on an emerging medical technology, strategy or intervention. It provides an overview of key issues related to the intervention—for example, current indications, relevant patient populations and subgroups of interest, outcomes measured, and contextual factors that may affect decisions regarding the intervention. Although Technical Briefs generally focus on interventions for which there are limited published data and too few completed protocol-driven studies to support definitive conclusions, the decision to request a Technical Brief is not solely based on the availability of clinical studies. The goals of the Technical Brief are to provide an early objective description of the state of the science, a potential framework for assessing the applications and implications of the intervention, a summary of ongoing research, and information on future research needs. In particular, through the Technical Brief, AHRQ hopes to gain insight on the appropriate conceptual framework and critical issues that will inform future comparative effectiveness research.

AHRQ expects that the EPC evidence reports and technology assessments will inform individual health plans, providers, and purchasers as well as the health care system as a whole by providing important information to help improve health care quality.

We welcome comments on this Technical Brief. They may be sent by mail to the Task Order Officer named below at: Agency for Healthcare Research and Quality, 540 Gaither Road, Rockville, MD 20850, or by email to [epc@ahrq.hhs.gov](mailto:epc@ahrq.hhs.gov).

Carolyn M. Clancy, M.D.  
Director  
Agency for Healthcare Research and Quality

Jean Slutsky, P.A., M.S.P.H.  
Director, Center for Outcomes and Evidence  
Agency for Healthcare Research and Quality

Stephanie Chang, M.D., M.P.H.  
Director, EPC Program  
Center for Outcomes and Evidence  
Agency for Healthcare Research and Quality

Supriya Janakiraman, M.D., M.P.H.  
Task Order Officer  
Center for Outcomes and Evidence  
Agency for Healthcare Research and Quality

## **Acknowledgments**

The authors gratefully acknowledge the following individuals for their contributions to this project: Claudia Bonnell, R.N., M.L.S.; Sharon Flaherty, M.A.; Lisa Garofalo, B.A.; Lisa Sarsany, M.A.; and Kathleen Ziegler, Pharm.D.

## **Peer Reviewers**

Barbara Burton, M.D.  
Professor of Pediatrics  
Feinberg School of Medicine and  
Director, Adult Phenylketonuria (PKU) Program  
Children's Memorial Research Center  
Chicago, IL

Robert Steiner, M.D.  
Credit Unions for Kids Professor of Pediatric Research  
and Vice Chair for Research  
Oregon Health & Science University  
Portland, OR

Jeanine Utz, Pharm.D., B.C.O.P., B.C.P.S.  
Medication Therapy Management, Advanced Therapies  
Adjunct Assistant Professor  
Department of Experimental and Clinical Pharmacology  
University of Minnesota, Fairview  
Minneapolis, MN

# Enzyme-Replacement Therapies for Lysosomal Storage Diseases

## Structured Abstract

**Background.** Lysosomal storage diseases (LSDs) comprise about 50 unique monogenic autosomal or X-linked diseases with an estimated combined incidence of 1 in 7,000 to 8,000 live births. They occur secondary to genetic mutations that result in deficiency or reduced activity of native intracellular enzymes that catabolize biological macromolecules. These enzyme defects result in accumulation of specific macromolecular compounds within lysosomes in various tissues and organs, causing progressive damage that can become life-threatening in some diseases. LSD management traditionally involved supportive care measures tailored to disease stage, the organs and systems involved, and the degree of impairment. However, enzyme-replacement therapy (ERT) is now commercially available for six LSDs, typically used lifelong with traditional management practices for each.

**Purpose.** The objective of this Technical Brief is to provide an overview of U.S. Food and Drug Administration (FDA)-approved ERT for the treatment of six LSDs. The purpose of a Technical Brief is to report what outcomes (benefits and harms) have been studied for a technology, drug or procedure; it does not enumerate those outcomes. The Technical Brief also addresses research gaps identified during its preparation. It is not intended as a comparative effectiveness review or systematic review that draws conclusions as to the clinical benefits and harms of a drug, device, or procedure. It does not assess study quality or the strength of the body of evidence on specific outcomes.

**Methods.** Four Guiding Questions were used to frame this Technical Brief. An inspection of the literature from 1990 through mid-April 2012 included primary studies, as well as narrative and systematic review articles to create an overview of potential clinical outcomes. Other information sources included dosing and other treatment-related information from the FDA-approved product labels; scientific information packages from the product manufacturers that included unpublished data; and, interviews with physician Key Informants and patient advocates.

**Findings.** Published clinical studies report a variety of outcomes associated with nine FDA-approved ERT products. They include disease-specific intermediate outcomes, such as plasma or urinary levels of macromolecular compounds. Others were common hematological measures (e.g., anemia, thrombocytopenia), bone pain and skeletal abnormalities, renal function, cardiac function, pulmonary function, growth, and walking tests. Harms reported to the FDA and in clinical studies were primarily allergic, including infusion-associated reactions and anaphylaxis. Immunogenic responses, primarily an IgG-type antibody response and neutralizing antibodies, have been reported. This Technical Brief identified a number of research gaps, including the need for comparative effectiveness studies, dose optimization, optimal timing for initiation of ERT, and mechanisms involved in uptake and distribution of ERT products.

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# Background

## Lysosomal Storage Diseases

Lysosomes are generally spherical, subcellular organelles bounded by a single layer membrane within eukaryotic cells. They are ubiquitous structures that contain an array of glycoprotein acid hydrolase enzymes, all of which are synthesized in the endoplasmic reticulum and modified in the Golgi apparatus. Lysosomal enzymes catabolize all major classes of biological macromolecules such as proteins, nucleic acids, glycosphingolipids, mucopolysaccharides, and glycogen, as well as sequestered bacteria, viruses, and other foreign substances that are taken up by phagocytosis into white blood cells and macrophages. Lysosomes are also responsible for autophagy, the gradual turnover of each cell's own components as they age and become obsolescent. They may be considered the main site of intracellular digestion and housekeeping.

Lysosomal storage diseases (LSDs) comprise a group of unique monogenic autosomal or X-linked diseases that occur secondary to genetic defects (e.g., single nucleotide substitutions, frameshift mutations, gene deletions) that cause total deficiency or reduced activity of specific native enzymes within the lysosomes.<sup>1-4</sup> This allows macromolecular compounds that are normally enzymatically catabolized to accumulate within these organelles, expanding them and causing progressive damage in connective tissue, skeletal structure, various organs, and, in some cases, the central nervous system. The damage caused by substrate accumulation results in physical deterioration, functional impairment, and, potentially, death.

Some fifty different LSDs have been identified, broadly divided into categories that are defined by accumulation of a specific macromolecule.<sup>1-4</sup> Although each LSD is individually somewhat rare, as a group they have an incidence of about 1 per 7,000 to 8,000 live births, with regional and genetic population variations.<sup>4-6</sup> LSDs may be variably expressed as infantile, juvenile, or adult forms. In adult-onset diseases, the pathogenesis is usually slower than in the infantile or juvenile forms, and may include peripheral and CNS symptoms. By contrast, infantile and juvenile forms often involve progressive central nervous system involvement in addition to peripheral symptoms. LSDs also often exhibit significant heterogeneity in ultimate expression, with early or late presentation of symptomatic pathology that may be a function of mutation type and residual enzyme levels. Although specific mutations or types of mutations may be connected to discrete disease effects, genotype-phenotype correlations are often not strong.<sup>4</sup>

## Therapeutic Measures for Lysosomal Storage Diseases

### Enzyme-Replacement Therapy

Within the United States, the term “enzyme replacement therapy” (ERT) refers to a group of nine commercially available glycoprotein products, each intended to augment or replace the activity of a specific endogenous catabolic enzyme within cellular lysosomes.<sup>2, 3, 7-13</sup> All ERT products are administered by intravenous infusion, at dosages typically based on patient body weight, usually weekly or every other week, typically for the life of a patient. The infused enzymes are taken up by cells and transported into lysosomes, where they catabolize the specific macromolecule that has accumulated.

Six ERT products are produced using recombinant DNA methods in Chinese hamster ovary cell cultures (imiglucerase, agalsidase beta, galsulfase, laronidase, alglucosidase alfa [Myozyme® and Lumizyme®]). One (idursulfase) is produced using recombinant DNA methods in a human cell line. One (velaglucerase alfa) is produced using gene-activation technology and a human fibroblast cell culture. One product (taliglucerase) is uniquely produced by recombinant DNA technology in genetically modified carrot cells, rather than in mammalian cell culture.<sup>14</sup> Each ERT product is specific for only one LSD. However, three (imiglucerase, velaglucerase alfa, taliglucerase) have been developed to treat type I Gaucher disease, the most common LSD. Two alglucosidase alfa products [Myozyme® and Lumizyme®] are available to treat Pompe disease, although the FDA-approved labels differ as outlined later in this Technical Brief.

## **Supportive Care**

Prior to the advent of ERT, only supportive care measures were available to manage patients; they are now used in addition to ERT as indicated. These may vary according to the organs and systems that are affected, and the level of physical impairment.<sup>1-3, 15, 16</sup> Supportive care is not curative, and once a certain degree of tissue or organ damage develops, it may become difficult or impossible to reverse, even with ERT. Therefore, early diagnosis and timely treatment is crucial to optimal management of LSDs. For example, patients with Type 1 Gaucher disease, the most common LSD, may develop visceral problems (e.g., hepatomegaly, splenomegaly), anemia, thrombocytopenia, lung disease, severe bone pain (acute or chronic), avascular necrosis, and have growth impairment and pubertal delay.<sup>17</sup> Supportive care prior to the development of specific ERT may have comprised combinations of therapies that could include blood transfusion, bed rest, analgesia, anti-inflammatory agents, hyperbaric oxygen, and surgery (splenectomy, orthopedic procedures). In the age of ERT, however, many of these are no longer used nor recommended (e.g., splenectomy).

## **Substrate Reduction Therapy**

Substrate reduction therapy (SRT) has been proposed as another potential strategy to treat LSDs.<sup>18-27</sup> SRT refers to the inhibition of synthesis of macromolecules that accumulate in the lysosomes of tissues and organs of patients with LSDs. The effectiveness of SRT depends on the existence of residual catabolic enzyme activity specific to the substance and disease for which it is used. Thus, if the rate of synthesis of a macromolecule is reduced, residual enzyme levels may be sufficient to degrade it, thereby reducing accumulation.

One SRT product—miglustat—has received FDA marketing approval for treatment of adult patients with mild to moderate type I Gaucher disease for whom ERT is not a therapeutic option.<sup>22, 25</sup> This agent is not an ERT product and will not be considered further in this Technical Brief.

## **Allogeneic Hematopoietic Stem-Cell Transplantation (HSCT)**

Allogeneic HSCT has been investigated as a curative option for selected patients with several of the LSDs considered in this Technical Brief. The success of HSCT is variable, depending on the LSD and the underlying condition of the patient. A comprehensive comparative effectiveness review (CER) is available from AHRQ that assesses the body of evidence on the use of allogeneic HSCT to treat all the LSDs considered in this Technical Brief.<sup>28</sup>

The AHRQ CER concludes that overall there appears to be a favorable risk-benefit profile for the treatment of MPS I with HSCT for severe cases with stable cardiopulmonary function, if the disease is diagnosed at 2 years of age or younger and the disability quotient (DQ) is 70 or greater. There also appears to be a favorable risk-benefit profile for the treatment of MPS I with HSCT for rare attenuated cases in which the diagnosis is made at older than 2 years of age and the DQ is 70 or greater.<sup>29</sup> Likewise, overall there appears to be a favorable risk-benefit profile for the treatment of MPS VI with HSCT when enzyme replacement is not available or after failure of enzyme replacement. ERT may be used in conjunction with allogeneic HSCT, or to prepare patients with an LSD for the procedure. Supplemental treatment may include physical therapy, occupational therapy, and treatment-related surgery and medications.<sup>30</sup>

## Technical Brief Objective

The objective of this Technical Brief is to provide an overview of FDA-approved ERT for the treatment of six lysosomal storage diseases shown in Table 1. Four Guiding Questions (following) address the clinical indications for each ERT, potential benefits and harms associated with each ERT product, and dosing and administration details of each ERT. An electronic scan of the literature provides a picture of published evidence on clinical use of these agents for each LSD. This Technical Brief also discusses unresolved or controversial issues surrounding the use of ERT to treat lysosomal storage diseases, based on the literature and information obtained through semi-structured, one-on-one telephone interviews with Key Informants.

## Guiding Questions

1. What FDA-approved enzyme-replacement therapy (ERT) products are available for lysosomal storage diseases (LSDs)?
  - a. What are the clinical indications for each FDA-approved ERT product?
  - b. What are the potential benefits of ERT for LSDs?
  - c. What are the potential safety issues and harms with ERT?
2. What is the context in which each FDA-approved ERT product is used?
  - a. What are the FDA-approved dose regimens for each ERT product?
  - b. Where and by whom is ERT administered?
  - c. What adjunct treatments are used with each FDA-approved ERT product?
3. What published and unpublished studies have reported on the use and safety of this intervention?
  - a. Type of ERT
  - b. Indication/patient inclusion criteria
  - c. Study design/size
  - d. Comparator used in comparative studies
  - e. Concurrent/prior treatments
  - f. Length of followup
  - g. Outcomes measured
4. What are key unresolved or controversial issues with ERT in LSDs?

**Table 1. Lysosomal storage diseases with U.S. Food and Drug Administration (FDA)-approved enzyme-replacement therapy**

Disease	Deficient Enzyme (FDA-Approved Product)	Pathological Lysosomal Macromolecule	Clinical Description and Expression
Fabry Disease	$\alpha$ -galactosidase A (Fabrazyme®)	glycosphingolipids, predominantly globotriaosylceramide and galabiosylceramide	<p>Fabry disease is an X-linked disorder with an onset of symptoms and severity of symptoms that vary widely among patients. Males may exhibit symptoms in childhood or adolescence, or remain asymptomatic into adulthood. Females may have no early symptoms and only mild symptoms in later years or have symptoms as severe as affected males.</p> <p>Early symptoms include a whorl-like pattern visible in the cornea, skin lesions, pain in the extremities, decreased ability to sweat, gastrointestinal symptoms such as chronic abdominal pain and diarrhea, followed by slow decline in kidney function. Cardiomyopathy, arrhythmia, and stroke may occur. Fabry pain may present as chronic pain (acroparesthesia, which is near-constant tingling or numbness, nagging, burning pain in the hands and feet), or acute pain crises, which are episodes of excruciating pain, usually in the extremities and radiating inward, and often accompanied by fever and elevated erythrocyte sedimentation rate (ESR). Both are common early signs of Fabry disease, especially in boys.</p> <p>Prior to the development of dialysis, HSCT, or ERT, life expectancy was 40- 50 years, with cause of death usually due to a decline in kidney function or to cardiovascular disease.</p>
Type 1 Gaucher disease	glucocerebrosidase (Cerezyme®, VPRIV™, Elvelyo™)	glucosylceramide	<p>Type 1 Gaucher disease is the most common lysosomal storage disease. The onset of symptoms is variable, from early childhood to late adulthood. The majority of patients with Gaucher disease have symptoms in childhood, although the age of onset can vary markedly. Patients presenting in early childhood have a more severe course of the disease compared to those presenting later in life.</p> <p>Signs and symptoms include anemia, hepatosplenomegaly, skeletal diseases and very rarely, lung or liver impairment. Growth deficiencies and pubertal delay may be common. The clinical course, disease progression, and severity among the different organ systems vary markedly among cases. Type 1 Gaucher disease is typically defined by a lack of CNS involvement.</p> <p>Life expectancy varies widely, depending on the severity of symptoms, and can extend to near normal expectancy.</p>

**Table 1. Lysosomal storage diseases with U.S. Food and Drug Administration (FDA)-approved enzyme-replacement therapy (continued)**

Disease	Deficient Enzyme (FDA-approved product)	Pathological Lysosomal Macromolecule	Clinical Description and Expression
Glycogen Storage Disease type II (Pompe disease)	acid alpha-glucosidase (Myozyme®, Lumizyme®)	glycogen	<p>Pompe disease is often grouped into early and late onset forms, although in reality a spectrum of disease may occur with differing age of onset and rapidity of progression.</p> <p>Symptoms appear in the first few months of life in the infantile form of the disease. Many patients with Pompe disease with late onset have symptoms in early childhood, sometimes even in infancy. There are feeding problems, poor weight gain, muscle weakness, floppiness, head lag, respiratory difficulties, and an enlarged heart. Life expectancy is less than 1 year, with cause of death usually from cardiorespiratory failure or respiratory infection.</p> <p>Onset of symptoms in the late onset form of the disease ranges from the first decade to the sixth decade of life. Severity of symptoms varies markedly among patients. Patients experience muscle weakness, progressive respiratory weakness, and either no or mild cardiac insufficiencies.</p> <p>Prior to the availability of ERT, survival depended on the severity and rate of disease progression, with cause of death usually due to respiratory failure.</p>

**Table 1. Lysosomal storage diseases with U.S. Food and Drug Administration (FDA)-approved enzyme-replacement therapy (continued)**

Disease	Deficient Enzyme (FDA-approved product)	Pathological Lysosomal Macromolecule	Clinical Description and Expression
MPS I (Hurler, Hurler-Scheie, or Scheie syndrome)	alpha-L-iduronidase (Aldurazyme®)	glycosaminoglycans dermatan sulfate and heparan sulfate	<p>MPS I comprises a wide spectrum of severity, with a wide range of symptoms that differ from patient to patient with regard to age of onset and severity. Individuals may be categorized anywhere from severe to attenuated (less severe). The classifications Hurler, Hurler-Scheie, and Scheie are now considered to be oversimplifications that do not adequately reflect the tremendous variation in symptoms, presentation and progression. The term “attenuated” rather than “mild” is used to describe the less severe individuals because of effects of the disease on a less severe individuals are too significant to be considered mild. Though the symptoms manifest in a continuous spectrum among patients, for clinical purposes, they often are categorized into the following three groups:</p> <p>MPS IH (Hurler) is the most severe form with symptoms presenting within the first 12 months of age. Symptoms may include respiratory insufficiency, hearing loss, joint movement restriction, enlargement of the heart, spleen, and liver, and progressive cognitive deterioration, coarse facial features, growth deficits, heart disease, clouded corneas, and inguinal and umbilical hernias. Prior to the availability of HSCT, life expectancy was less than 12 years, with cause of death most commonly due to obstructive airway disease, upper respiratory infections, or cardiac complications.</p> <p>MPS IH/S (Hurler-Scheie) is an intermediate form of the disease with symptoms presenting usually from 3-6 years of age. Symptoms and signs may include growth deficiencies, deafness, coarse facial features, clouded corneas, inguinal and umbilical hernia, and heart disease. Life expectancy for Hurler-Scheie is late teens to early twenties.</p> <p>MPS IS (Scheie) is the attenuated form of the disease with symptoms presenting from 5-12 years of age. Symptoms may include stiff joints, clouded corneas, cardiac valve disease, normal intelligence or mild learning disabilities. Life expectancy extends into adulthood, though significant morbidity occurs.</p>

**Table 1. Lysosomal storage diseases with U.S. Food and Drug Administration (FDA)-approved enzyme-replacement therapy (continued)**

Disease	Deficient Enzyme (FDA-approved product)	Pathological Lysosomal Macromolecule	Clinical Description and Expression
MPS II (Hunter disease)	iduronate sulfatase (Elaprase®)	glycosaminoglycans dermatan sulfate and heparan sulfate	<p>MPS II is an X-linked disorder. Although most patients are male, females can also be affected. However, for clinical purposes, women are almost never affected.</p> <p>The clinical symptoms of MPS II are highly variable, differing among patients in which symptoms develop, age of onset and severity.</p> <p>MPS II exhibits a continuous spectrum of disease, ranging from severe on one end to an attenuated form on the other, with a range in between. The more severe form has CNS involvement with symptoms presenting between 2 and 5 years of age. Symptoms may include short stature, organomegaly, joint stiffness, hearing loss, progressive cognitive deterioration, behavioral disorders, progressive airway disease, and cardiac disease.</p> <p>Prior to the advent of ERT, life expectancy ranged from 10-20 years. Death usually results from cardiorespiratory disease due to progressive obstructive and restrictive lung disease along with cardiac valvular disease.</p> <p>Patients with the attenuated form of the disease may not be diagnosed until school-age, adolescence, or adulthood. The physical symptoms may include the same as the severe form, but are milder in nature. Usually the CNS is not involved. Prior to ERT, life expectancy was 20-60 years.</p>

**Table 1. Lysosomal storage diseases with U.S. Food and Drug Administration (FDA)-approved enzyme-replacement therapy (continued)**

Disease	Deficient Enzyme (FDA-approved product)	Pathological Lysosomal Macromolecule	Clinical Description and Expression
MPS VI (Maroteaux-Lamy syndrome)	arylsulfatase B (Naglazyme™)	dermatan sulfate glycosaminoglycan	<p>As with the other forms of MPS, the following vary among patients: which symptoms develop, age of onset of symptoms, and severity of symptoms. Growth and development can be normal the first few years of life, but appear to stop around age 6. Linear growth is severely limited in MPS VI, and these patients without ERT have marked short stature, and the effects of ERT on growth are not yet completely understood.</p> <p>The clinical characteristics are much like MPS I, except with a later onset and a slower progression of symptoms. In comparison to MPS I, skeletal deformities tend to be more prominent, joint symptoms are characterized by hypermobility rather than stiffness, and cognitive involvement is very rare. Psychomotor skills are affected by the physical and visual impairments of the disease.</p> <p>Prior to ERT, life expectancy depended on severity of symptoms, ranging from less than 20 years to later adulthood, with cause of death usually from cardiorespiratory disease due to progressive obstructive and restrictive lung disease along with cardiac valvular disease.</p>

**\*Textbook Sources:**

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## Methods

Several sources were used to inform this Technical Brief. Information was collected in a review of published medical literature, narrative review articles, a search of the grey literature, and discussions with Key Informants.

Guiding Questions 1 and 2 relied on information from published narrative reviews and information in the grey literature. The latter may include information culled from Web sites of pharmaceutical companies, patient advocacy groups, and other sources such as the FDA-approved prescribing information for each ERT product.

Guiding Question 3 was addressed through a systematic scan and description that enumerates select study elements of interest (e.g., study design, sample size) to provide an overview of the published literature including primary and secondary (narrative and systematic reviews) articles. Key Informants provided guidance on the potential clinical outcomes of interest and the potential benefits and harms of ERT as the review was conducted.

Guiding Question 4 relied on integrating information from Key Informants, grey literature, published primary studies and narrative reviews.

## Data Sources

### Discussions With Key Informants

The Key Informants comprised a group of physician specialists in metabolic diseases, lysosomal storage diseases, and rare diseases. In addition, one payer representative was part of the Key Informant group. Unless otherwise specified, the views presented in this report are those of the authors.

Two Key Informant group conference calls were conducted that included the clinicians mentioned in the preceding paragraph. The Key Informants provided input on the literature review, for example, years to include in the search and potential clinical outcomes. As a follow-up to the group conference calls, the Key Informants were interviewed individually by telephone, using a semi-structured interview outline that provided opportunity to share their clinical experiences with patients with lysosomal storage diseases, their experience with ERT, and their opinions on unresolved or controversial issues relating to ERT. The seven questions we asked in the interviews follow:

1. Have you seen patients in your practice with any of the six diseases covered in this report (MPS I, MPS II, MPS VI, Gaucher, Fabry, Pompe)?
2. What challenges, successes, and failures have you experienced in treating these patients?
3. What factors do you consider before starting ERT with your patients?
4. What outcomes, beneficial and harmful, have you seen in your patients treated with ERT?
5. What do you believe are unresolved issues surrounding ERT?
6. In your view, what needs to be done to resolve these issues, for example by pharmaceutical companies, researchers, or practitioners?
7. Are you aware of any new ERT products or developments in the development or testing phase that are not common knowledge?

## Discussions With Patient Advocates

One call with the patient advocates was conducted. Many patients with an LSD are children, but many are surviving well into adulthood. Patients with late-onset disease are often not diagnosed until the 3rd, 4rd, 5th, or even 6th, decade of life. Therefore, one adult patient and one parent of a child patient were consulted. The adult patient and the parent were asked about their experiences with the disorder prior to ERT and subsequent to ERT. They were asked to describe symptoms, clinical outcomes of importance to them, and factors involved in the decision to begin treatment with ERT. We recognize that the report deals with six unique diseases; however, we primarily sought a broad perspective on the challenges that caregivers and LSD patients face.

## Grey Literature Search

The U.S. Food and Drug Administration (FDA) Web site concerning the nine commercially available ERT treatments was accessed. Information was gathered to inform Guiding Questions 1 and 2.

ERT manufacturers provided scientific information packages (SIPs) that contained product information, unpublished data, and a bibliography. Their Web sites were accessed to inform Guiding Questions 1 and 2, using the following Web links:

Biomarin Pharmaceuticals

[www.bmrn.com/products/naglazyme.php](http://www.bmrn.com/products/naglazyme.php)

[www.bmrn.com/products/aldurazyme.php](http://www.bmrn.com/products/aldurazyme.php)

Genzyme Corporation

[www.fabrazyme.com/global/fz\\_us\\_hp\\_homepage.asp](http://www.fabrazyme.com/global/fz_us_hp_homepage.asp)

[www.cerezyme.com/](http://www.cerezyme.com/)

[www.myozyme.com/](http://www.myozyme.com/)

[www.lumizyme.com/patients.aspx](http://www.lumizyme.com/patients.aspx)

Pfizer Labs

[www.elelyso.com/](http://www.elelyso.com/)

[www.elelyso.com/](http://www.elelyso.com/)

Shire Human Genetic Therapies, Inc.

[www.vpriv.com](http://www.vpriv.com)

[www.elaprase.com](http://www.elaprase.com)

Registries and patient advocate Web sites for each of the six LSDs were accessed. Examples included:

[www.lysosomallearning.com/support/lsd\\_sup\\_registries.asp](http://www.lysosomallearning.com/support/lsd_sup_registries.asp)

[www.marlow.org/PATIENT/Undrstd\\_Disease\\_Treat/Lrn\\_about\\_Disease/Metabolic\\_Storage/Hurler\\_and\\_Treatment/index.html](http://www.marlow.org/PATIENT/Undrstd_Disease_Treat/Lrn_about_Disease/Metabolic_Storage/Hurler_and_Treatment/index.html)

[www.mppsociety.org/](http://www.mppsociety.org/)

[www.mppsociety.co.uk/index.php?page=hunter-disease](http://www.mppsociety.co.uk/index.php?page=hunter-disease)

[www.mppsociety.org.au/MPS%20Diseases/mpsviregistry.htm](http://www.mppsociety.org.au/MPS%20Diseases/mpsviregistry.htm)

[www.registrynxt.com/Gaucher/Pages/RegistryNXTHome.aspx](http://www.registrynxt.com/Gaucher/Pages/RegistryNXTHome.aspx)

[www.lsdregistry.net/fabryregistry/](http://www.lsdregistry.net/fabryregistry/)  
[www.pompe.com/en/healthcare-professionals/pompe-registry.aspx](http://www.pompe.com/en/healthcare-professionals/pompe-registry.aspx)

Current clinical studies involving ERT were identified by searching ClinicalTrials.gov/ct.

## **Published Literature Search**

We searched the published medical literature in MEDLINE®, Embase®, the Cochrane Database, and the Health Technology Assessment Database to address Guiding Question 3. Based on input from the Key Informants, the initial searches encompassed the years 1990 through September 16, 2011, as outlined in Appendix A. Initiation in 1991 corresponds to the year the first ERT product (alglucerase, no longer marketed) received FDA marketing approval. The search was updated on April 24, 2012, while the draft was under peer review.

The DistillerSR® Systematic Review Tool was utilized to facilitate the screening and study selection process. Titles and abstracts were examined using Distiller® to identify articles for potential inclusion. We retrieved selected narrative or systematic review articles on ERT for the pertinent LSDs to provide background materials.

Preclinical studies, meeting abstracts, foreign-language articles, editorials, comments, and letters to the editor were excluded in the first-level title and abstract screen. Reports were eligible for full-text screening if the abstract provided clinical outcomes in patients who received an FDA-approved ERT product; if an abstract wasn't available but the title was deemed potentially relevant, we retrieved the full text article for further examination. The search was limited to English-language reports based on evidence that suggests language restrictions do not change results of systematic review for conventional medical interventions.<sup>31</sup>

In the second-level screen, full-text clinical studies were retrieved and screened for inclusion or exclusion in the literature compilations. We sought all randomized controlled trials (RCTs), in particular the pivotal trial or study submitted by the manufacturer for FDA approval for each ERT product. To alert readers and avoid oversampling, if more than one study was available with the same (or nearly same) study population, as in an extension study, we cross-indexed the trials in the tables. We also sought prospective phase I or II nonrandomized studies that included patient subgroups with specific disease manifestations not well represented in RCTs, or treatment protocols or settings that were not reported in RCTs. If higher-level studies (RCTs, prospective phase I and II) were not available, case series (single-arm studies), case-control studies, case reports, and prospective registry studies were eligible for the main evidence compilations.

We also sought registry reports to ascertain whether clinical outcomes reported in that type of publication were consistent with outcomes reported in clinical studies. Reference lists of the included studies and recent review articles were examined to identify other relevant articles. A resource bibliography that lists all the citations we examined in the second-level literature screen is available in Appendix E. We did not assess study quality or the overall strength of the evidence.

# **Data Organization and Presentation**

## **Information Management**

Three main sources of information were consulted for this Technical Brief: published literature, grey literature, and Key Informants. Data from studies published in the medical literature were abstracted into Microsoft Word® tables (Appendix B). Data collected include: study design, number of study subjects, subject age, severity of disease, ERT dosing and administration details, length of follow-up, and type of clinical outcome measures.

Information about clinical indications, ERT dosing, and administration, abstracted from review articles and from the FDA-approved prescribing information for each ERT product, was organized in tables. Information from Key Informants and patient advocates was managed in a Microsoft Word® document.

## **Data Presentation**

Summary tables present selected published studies for each disease, and include the following information: study design, patient population, interventions, dose regimen, follow-up duration, and clinical outcomes that were measured. A narrative summary integrates information gathered from the medical literature, FDA-approved documentation, the grey literature, and the Key Informants, to describe the current state of ERT treatment, clinical indications, dosing and administration details, and a discussion of the key unresolved or controversial issues regarding the treatment.

## **Peer Review**

A draft of this Technical Brief was posted to the AHRQ Web site for four weeks, during which invited peer reviewers, the Key Informants, and the general public were invited to comment on it. All comments received were compiled by AHRQ and provided to the authors for reconciliation. The disposition of comments was posted to the public AHRQ Web site.

## Findings

### Guiding Question 1: What FDA-approved enzyme-replacement therapy (ERT) products are available for lysosomal storage diseases (LSDs)?

All commercially available ERT products in the United States were approved under stipulations of the FDA Orphan Drug Act (ODA) of 1983, which provides for granting special status to a product to treat a rare disease or condition upon request of a sponsor ([www.fda.gov/RegulatoryInformation/Legislation/FederalFoodDrugandCosmeticActFDCAAct/SignificantAmendmentsToTheFDCAAct/OrphanDrugAct/default.htm](http://www.fda.gov/RegulatoryInformation/Legislation/FederalFoodDrugandCosmeticActFDCAAct/SignificantAmendmentsToTheFDCAAct/OrphanDrugAct/default.htm)).

According to the ODA, a product intended to treat a rare disease or condition must meet certain criteria, particularly that the disease or condition for which the drug is intended affects fewer than 200,000 people in the United States or, if the drug is a vaccine, diagnostic drug, or preventive drug, the persons to whom the drug will be administered in the United States are fewer than 200,000 per year. This status is referred to as orphan designation. The approval of an orphan designation request does not alter the standard regulatory requirements and process for obtaining marketing approval. The safety and efficacy of a compound must be established through adequate and well-controlled studies.

Due to the massive financial investment required to produce orphan drugs, prior to the passage of the ODA, very few companies invested in the development of these drugs. Additionally, because the target population for orphan drugs is extremely small, the long-term return on investment for these drugs is extremely low. The ODA provides pharmaceutical companies who develop orphan drugs with a tax credit to help offset the cost to conduct clinical trials. The Act also grants a 7-year period of market exclusivity to prevent other companies from developing and competing with similar products.

### What are the Clinical Indications for Each FDA-Approved ERT Product?

Table 2 lists nine FDA-approved ERT products and the clinical indications for each, according to the FDA-approved prescribing information. Off-label use is not relevant for these agents, with the exception of dose regimen variations, for example in patients with type I Gaucher disease.<sup>32-34</sup>

The indications shown in Table 2 are specific to the disease in question and are based on evidence from clinical studies, some of which are shown in summary tables under Guiding Question 3 of this Technical Brief. For example, in three published clinical studies of agalsidase beta for Fabry disease (reviewed later), a key endpoint was the extent of globotriaosylceramide (GL-3) inclusions in the capillary endothelium of the kidney, heart, and skin, measured by light microscopy in biopsy specimens.<sup>35-37</sup> In a randomized, placebo-controlled trial, accumulation of GL-3 in these cells was considered to be a surrogate marker for the subsequent development of renal, cardiac, and cerebrovascular disease, which lead to high morbidity and premature mortality.<sup>36</sup> A subsequent postapproval randomized, double-blind placebo-controlled trial was required by FDA to demonstrate clinical benefit. This trial examined correlations between inclusion clearance and subsequent composite clinical outcomes related to renal, cardiac and cerebrovascular disease.<sup>35</sup>

**Table 2. FDA-approved prescribing information for enzyme-replacement therapy products for lysosomal storage diseases**

<b>Disease</b>	<b>Product (Generic Name)</b>	<b>Manufacturer</b>	<b>FDA Approval Date</b>	<b>Clinical Indication From the FDA-Approved Prescribing Information (Source)</b>
Fabry Disease	Fabrazyme® (agalsidase beta)	Genzyme Corporation	April 2003	Fabrazyme is indicated for use in patients with Fabry disease. ( <a href="http://www.fabrazyme.com/hcp/pi/fz_us_hc_pi.pdf">www.fabrazyme.com/hcp/pi/fz_us_hc_pi.pdf</a> )
Type 1 Gaucher disease	Cerezyme® (imiglucerase)	Genzyme Corporation	May 1994	Cerezyme (imiglucerase for injection) is indicated for long-term enzyme-replacement therapy for pediatric and adult patients with a confirmed diagnosis of type 1 Gaucher disease that results in one or more of the following conditions: <ul style="list-style-type: none"> <li>• anemia</li> <li>• thrombocytopenia</li> <li>• bone disease</li> <li>• hepatomegaly or splenomegaly</li> </ul> ( <a href="http://www.cerezyme.com/~media/Files/CerezymeUS/pdf/cerezyme_pi.pdf">www.cerezyme.com/~media/Files/CerezymeUS/pdf/cerezyme_pi.pdf</a> )
	VPRIV™™ (velaglucerase alfa)	Shire Human Genetic Therapies, Inc.	March 2010	VPRIV (velaglucerase alfa for injection) is a hydrolytic lysosomal glucocerebroside-specific enzyme indicated for long-term enzyme-replacement therapy (ERT) for pediatric and adult patients with type 1 Gaucher disease. ( <a href="http://www.accessdata.fda.gov/drugsatfda_docs/label/2010/022575lbl.pdf">www.accessdata.fda.gov/drugsatfda_docs/label/2010/022575lbl.pdf</a> )
	Elelyso™ (taliglucerase)	Pfizer Labs	May 2012	ELELYSO™ (taliglucerase alfa) for injection is a hydrolytic lysosomal glucocerebroside-specific enzyme indicated for long-term enzyme replacement therapy (ERT) for adults with a confirmed diagnosis of Type 1 Gaucher disease. ( <a href="http://www.elelyso.com/pdf/ELELYSO_Prescribing_Information.pdf">www.elelyso.com/pdf/ELELYSO_Prescribing_Information.pdf</a> )
Glycogen Storage Disease type II (Pompe disease)	Myozyme® (alglucosidase alfa)	Genzyme Corporation	April 2006	Myozyme (alglucosidase alfa) is indicated for use in patients with Pompe disease. Myozyme has been used in patients with infantile-onset Pompe disease, whereas use of Myozyme in patients with other forms of Pompe disease has not been adequately studied. ( <a href="http://www.accessdata.fda.gov/drugsatfda_docs/label/2008/125141_74lbl.pdf">www.accessdata.fda.gov/drugsatfda_docs/label/2008/125141_74lbl.pdf</a> )
	Lumizyme® (alglucosidase alfa)	Genzyme Corporation	May 2010	Lumizyme (alglucosidase alfa) is a lysosomal glycogen-specific enzyme indicated for patients 8 years and older with late (non-infantile) onset Pompe disease who do not have evidence of cardiac hypertrophy. The safety and efficacy of Lumizyme have not been evaluated in controlled clinical trials in infantile-onset patients, or in late (non-infantile) onset patients less than 8 years of age. ( <a href="http://www.accessdata.fda.gov/drugsatfda_docs/label/2010/125291lbl.pdf">www.accessdata.fda.gov/drugsatfda_docs/label/2010/125291lbl.pdf</a> )

**Table 2. FDA-approved prescribing information for enzyme-replacement therapy products for lysosomal storage diseases (continued)**

<b>Disease</b>	<b>Product (Generic Name)</b>	<b>Manufacturer</b>	<b>FDA Approval Date</b>	<b>Clinical Indication From the FDA-Approved Prescribing Information (Source)</b>
MPS I (Hurler, Hurler- Scheie, or Scheie syndrome)	Aldurazyme® (laronidase)	Genzyme Corporation	April 2003	Aldurazyme is a hydrolytic lysosomal glycosaminoglycan (GAG)-specific enzyme indicated for patients with Hurler and Hurler-Scheie forms of Mucopolysaccharidosis I (MPS I) and for patients with the Scheie form who have moderate to severe symptoms. The risks and benefits of treating mildly affected patients with the Scheie form have not been established. Aldurazyme has not been evaluated for effects on the central nervous system manifestations of the disorder. ( <a href="http://www.aldurazyme.com/pdf/az_us_hc_pi.pdf">www.aldurazyme.com/pdf/az_us_hc_pi.pdf</a> )
MPS II (Hunter disease)	Elaprase® (idursulfase intravenous)	Shire Human Genetic Therapies, Inc.	July 2006	Elaprase is indicated for patients with Hunter syndrome (Mucopolysaccharidosis II, MPS II). ( <a href="http://www.elaprase.com/pdf/Elaprase_US_PI_v6.pdf">www.elaprase.com/pdf/Elaprase_US_PI_v6.pdf</a> )
MPS VI (Maroteaux - Lamy syndrome)	Naglazyme™ (galsulfase)	BioMarin Pharmaceutical, Inc.	June 2005	Naglazyme is a hydrolytic lysosomal glycosaminoglycan (GAG)-specific enzyme indicated for patients with Mucopolysaccharidosis VI (MPS VI; Maroteaux-Lamy syndrome). ( <a href="http://www.naglazyme.com/en/documents/Naglazyme_Prescribing_Information.pdf">www.naglazyme.com/en/documents/Naglazyme_Prescribing_Information.pdf</a> )

The first ERT product for type I Gaucher disease (alglucerase, no longer marketed) received approval based on effects on surrogate markers, including hemoglobin levels and platelet counts; splenic and hepatic volumes measured by computed tomography (CT) or magnetic resonance imaging (MRI); and, skeletal involvement reflected by serum acid phosphatase activity.<sup>38</sup> As shown later in this Technical Brief, subsequent studies for the more recently approved products for type I Gaucher disease (imiglucerase, velaglucerase, taliglucerase alfa) used similar disease surrogates, as well as clinical outcomes such as bone pain, bone crisis, pathologic fractures, mobility, and quality of life (SF-36 general health survey).<sup>39-44</sup>

As shown in Table 2, and the summary tables for clinical studies of these diseases under Guiding Question 3, the other commercially available ERT products received approval based on their effects on disease-specific clinical outcomes, including, but not limited to, walking (laronidase for MPS I, idursulfase (intravenous) for MPS II, galsulfase for MPS VI) or stair-climbing capacity (galsulfase) and pulmonary capacity and function (alglucosidase alfa for Pompe disease, laronidase for MPS I).

## What are the Potential Benefits of ERT for LSDs?

Potential beneficial responses to ERT are outlined according to disease in Table 3, based on information obtained from the FDA-approved product labels and from narrative review articles.<sup>1, 2, 7-9, 12, 16, 45, 46</sup>

**Table 3. Potential beneficial responses to ERT for lysosomal storage diseases**

Disease	Outcome Measure <sup>1, 2, 7-9, 12, 16, 45, 46</sup>
Fabry Disease	<ul style="list-style-type: none"> <li>• Renal function</li> <li>• Vascular lesions</li> <li>• Myocardial function</li> <li>• Nerve fiber conduction</li> <li>• Neuropathic pain</li> <li>• Tolerance to cold and heat</li> <li>• Exercise tolerance</li> <li>• Quality of life</li> </ul>
Type 1 Gaucher disease	<ul style="list-style-type: none"> <li>• Hepatic or splenic volume</li> <li>• Hematological measures</li> <li>• Bone manifestations</li> <li>• Growth benefits</li> </ul>
Glycogen Storage Disease type II (Pompe disease)	<ul style="list-style-type: none"> <li>• Lifespan</li> <li>• Cardiac symptoms</li> <li>• Myocardial function</li> <li>• Skeletal muscle function</li> <li>• Walking ability</li> <li>• Sleep disordered breathing</li> <li>• Respiratory or pulmonary function</li> <li>• Quality of life</li> </ul>
MPS I H-S and S (Hurler, Hurler-Scheie, or Scheie syndrome) disease)	<ul style="list-style-type: none"> <li>• Urinary glycosaminoglycan levels</li> <li>• Hepatic or splenic volume</li> <li>• Airway patency and sleep apnea</li> <li>• Myocardial function</li> <li>• Range of motion in joints</li> <li>• Growth rate</li> <li>• 6-minute walk test</li> </ul>



**Table 3. Potential beneficial responses to ERT for lysosomal storage diseases (continued)**

Disease	Outcome Measure <sup>1, 2, 7-9, 12, 16, 45, 46</sup>
MPS II (Hunter disease)	<ul style="list-style-type: none"> <li>• Urinary glycosaminoglycan levels</li> <li>• Hepatic and splenic volume</li> <li>• Airway patency and sleep apnea</li> <li>• Myocardial function</li> <li>• Range of motion in joints</li> <li>• Growth rate</li> <li>• 6-minute walk test</li> </ul>
MPS VI (Maroteaux-Lamy syndrome)	<ul style="list-style-type: none"> <li>• Urinary glycosaminoglycan levels</li> <li>• Hepatic and splenic volume</li> <li>• Airway patency and sleep apnea</li> <li>• Myocardial function</li> <li>• Range of motion in joints</li> <li>• Growth rate</li> <li>• 6-minute walk test</li> <li>• 12-minute walk test</li> <li>• Stair climbing test</li> <li>• Pulmonary function</li> <li>• Endurance</li> <li>• Growth</li> </ul>

According to interviews with Key Informant clinical experts, the responses to ERT may vary within each LSD for which it is indicated, related to the clinical manifestations and stage of disease at the time ERT is initiated. Our Key Informants further suggested that the optimal timing of ERT initiation is not established, although earlier in the disease course is surmised to be better than later.

## What are the Potential Safety Issues and Harms With ERT?

The FDA-approved prescribing information for each ERT product indicates infusion-associated adverse events may occur in recipients. These include pyrexia, chills, hypertension, tachycardia, cutaneous reactions (rash, pruritis, erythema, urticaria), burning, swelling, headache, nausea, fatigue, malaise, joint pain, dyspnea, facial edema, dizziness, bronchospasm, and others (Table 4).

**Table 4. Adverse effects of ERT reported in the FDA-approved label**

Disease	Generic Name	Infusion-Related	IgG-Positivity	Black Box Warning
Fabry Disease	agalsidase beta	•	•	
Type 1 Gaucher disease	imiglucerase velaglucerase taliglucerase	•	•	
Glycogen Storage Disease type II (Pompe disease)	aglucosidase alfa (two products with same generic name)	•	•	•
MPS I H-S and S (Hurler, Hurler-Scheie, or Scheie syndrome)	laronidase	•	•	•
MPS II (Hunter disease)	idursulfase (intravenous)	•	•	•
MPS VI (Maroteaux-Lamy syndrome)	galsulfase	•	•	

The FDA-approved label for each ERT product also reports immunogenic effects, primarily elicitation of IgG-type antibodies, including neutralizing antibodies, in varying proportions of study subjects (Table 4). The prescribing information for these products cautions that interpretation of immunogenicity results is affected by the sensitivity and specificity of the assay, and that the incidence of antibody positivity may be influenced by a number of factors related to assay methodology, sample handling, timing of sample collection relative to dosing, concomitant medications, and underlying disease. The influence of elicited IgG antibodies on long-term efficacy of ERT products was not reported in the clinical studies cited under Guiding Question 3 in this Technical Brief.

Black box warnings appear on the FDA-approved label for four ERT products (alglucosidase alfa [Myozyme® and Lumizyme®]; idursulfase (intravenous) [Elaprase®]; laronidase [Aldurazyme®]), indicating life-threatening anaphylactic reactions have been observed in some patients during infusion (Table 4). The label for a fourth product, agalsidase beta [Fabrazyme®] indicates that life-threatening anaphylactic reactions and severe allergic reactions have been observed in some patients during infusions, but the information is not specifically included as a black box warning.

The prescribing information for each product reports adverse events were noted in a low proportion of ERT recipients, but none have been attributed to a specific action of the glycoprotein itself. This concurs with the clinical experience reported by the Key Informants for this Technical Brief, who reported infusion-related reactions and immunogenic events in their patients; it also concurs with results reported in the clinical studies summarized under Guiding Question 3.

**Guiding Question 2: What is the context in which each FDA-approved ERT product is used?**

## **What are the FDA-Approved Dose Regimens for Each ERT Product?**

The dose regimen specified in the FDA-approved label for each ERT product is shown in Table 5. All ERT products are infused intravenously, typically over periods of 1 to 4 hours, as specified.

**Table 5. FDA-approved label dose regimens for ERT products**

Disease	Product	Dose Regimen (Link)
Fabry Disease	Fabrazyme® (agalsidase beta)	<ul style="list-style-type: none"> <li>The recommended dosage of Fabrazyme is 1 mg/kg body weight infused every two weeks as an intravenous (IV) infusion. Patients should receive antipyretics prior to infusion.</li> <li>The initial IV infusion rate should be no more than 0.25 mg/min (15 mg/hr). The infusion rate may be slowed in the event of infusion reactions. After patient tolerance to the infusion is well established, the infusion rate may be increased in increments of 0.05 to 0.08 mg/min (increments of 3 to 5 mg/hr) with each subsequent infusion. For patients weighing &lt; 30 kg, the maximum infusion rate should remain at 0.25 mg/min (15 mg/hr). For patients weighing ≥ 30 kg, the administration duration should not be less than 1.5 hours (based on individual patient tolerability).</li> <li>Patients who have had a positive skin test to Fabrazyme or who have tested positive for anti-Fabrazyme IgE may be successfully re-challenged with Fabrazyme. The initial re-challenge administration should be a low dose at a lower infusion rate, e.g., 1/2 the therapeutic dose (0.5 mg/kg) at 1/25 the initial standard recommended rate (0.01 mg/min).</li> <li>Once a patient tolerates the infusion, the dose may be increased to reach the approved dose of 1 mg/kg and the infusion rate may be increased by slowly titrating upwards (doubled every 30 minutes up to a maximum rate of 0.25 mg/min), as tolerated.</li> </ul> <p>(<a href="http://www.fabrazyme.com/hcp/pi/fz_us_hc_pi.pdf">www.fabrazyme.com/hcp/pi/fz_us_hc_pi.pdf</a>)</p>
Type 1 Gaucher disease	Cerezyme® (imiglucerase)	<ul style="list-style-type: none"> <li>Cerezyme® (imiglucerase for injection) is administered by intravenous infusion over 1-2 hours. Dosage should be individualized to each patient.</li> <li>Initial dosages range from 2.5 U/kg of body weight 3 times a week to 60U/kg once every 2 weeks. 60 U/kg every 2 weeks is the dosage for which the most data are available. Disease severity may dictate that treatment be initiated at a relatively high dose or relatively frequent administration.</li> <li>Dosage adjustments should be made on an individual basis and may increase or decrease, based on achievement of therapeutic goals as assessed by routine comprehensive evaluations of the patient's clinical manifestations.</li> </ul> <p>(<a href="http://www.cerezyme.com/~media/Files/CerezymeUS/pdf/cerezyme_pi.pdf">www.cerezyme.com/~media/Files/CerezymeUS/pdf/cerezyme_pi.pdf</a>)</p>
	VPRIV™ (velaglucerase alfa)	<ul style="list-style-type: none"> <li>60 Units/kg administered every other week as a 60-minute intravenous infusion.</li> <li>Patients currently being treated with imiglucerase for Gaucher disease can be switched to VPRIV. Patients previously treated on a stable dose of imiglucerase are recommended to begin treatment with VPRIV at that same dose when they switch from imiglucerase to VPRIV.</li> <li>Physicians can make dosage adjustments based on achievement and maintenance of each patient's therapeutic goals. Clinical trials have evaluated doses ranging from 15 Units/kg to 60 Units/kg every other week.</li> </ul> <p>(<a href="http://www.accessdata.fda.gov/drugsatfda_docs/label/2010/022575lbl.pdf">www.accessdata.fda.gov/drugsatfda_docs/label/2010/022575lbl.pdf</a>)</p>
	Elelyso™ (taliglucerase)	<ul style="list-style-type: none"> <li>The recommended dose is 60 Units/kg of body weight administered once every 22 weeks as a 60-120 minute intravenous infusion.</li> <li>Patients currently being treated with imiglucerase for Type 1 Gaucher disease can be switched to ELELYSO. Patients previously treated on a stable dose of imiglucerase are recommended to begin treatment with ELELYSO at that same dose when they switch from imiglucerase to ELELYSO.</li> <li>Dosage adjustments can be made based on achievement and maintenance of each patient's therapeutic goals. Clinical studies have evaluated dose ranges from 11 Units/kg to 73 Units/kg every other week.</li> <li>The initial infusion rate should be 11.3 mL/min. After patient tolerability to the infusion rate is established, the rate of infusion may be increased to 2.3 mL/min. The total volume of the infusion solution should be delivered over a period of no less than 1 hour.</li> </ul> <p>(<a href="http://www.elelyso.com/pdf/ELELYSO_Prescribing_Information.pdf">www.elelyso.com/pdf/ELELYSO_Prescribing_Information.pdf</a>)</p>

**Table 5. FDA-approved label dose regimens for ERT products (continued)**

Disease	Product	Dose Regimen (Link)
Glycogen Storage Disease type II (Pompe disease)	Myozyme® (αglucosidase alfa)	<ul style="list-style-type: none"> <li>The recommended dosage regimen of Myozyme is 20 mg/kg body weight administered every 2 weeks as an intravenous infusion. The total volume of infusion is determined by the patient's body weight and should be administered over approximately 4 hours.</li> <li>Infusions should be administered in a step-wise manner using an infusion pump. The initial infusion rate should be no more than 1 mg/kg/hr. The infusion rate may be increased by 2 mg/kg/hr every 30 minutes, after patient tolerance to the infusion rate is established, until a maximum rate of 7 mg/kg/hr is reached. Vital signs should be obtained at the end of each step. If the patient is stable, Myozyme may be administered at the maximum rate of 7 mg/kg/hr until the infusion is completed. The infusion rate may be slowed and/or temporarily stopped in the event of infusion reactions.</li> </ul> <p>(<a href="http://www.accessdata.fda.gov/drugsatfda_docs/label/2008/125141_74lbl.pdf">www.accessdata.fda.gov/drugsatfda_docs/label/2008/125141_74lbl.pdf</a>)</p>
	Lumizyme® (αglucosidase alfa)	<ul style="list-style-type: none"> <li>The recommended dosage of Lumizyme is 20 mg/kg body weight administered every 2 weeks as an intravenous infusion.</li> <li>The total volume of infusion is determined by the patient's body weight and should be administered over approximately 4 hours. Infusions should be administered in a step-wise manner using an infusion pump.</li> <li>The initial infusion rate should be no more than mg/kg/hr. The infusion rate may be increased by 2 mg/kg/hr every 30 minutes, after patient tolerance to the infusion rate is established, until a maximum rate of 7 mg/kg/hr is reached. Vital signs should be obtained at the end of each step. If the patient is stable, Lumizyme may be administered at the maximum rate of 7 mg/kg/hr until the infusion is completed. The infusion rate may be slowed or temporarily stopped in the event of infusion reactions.</li> </ul> <p>(<a href="http://www.accessdata.fda.gov/drugsatfda_docs/label/2010/125291lbl.pdf">www.accessdata.fda.gov/drugsatfda_docs/label/2010/125291lbl.pdf</a>)</p>
MPS I H-S and S (Hurler, Hurler-Scheie, or Scheie syndrome)	Aldurazyme® (laronidase)	<ul style="list-style-type: none"> <li>The recommended dosage regimen of Aldurazyme is 0.58 mg/kg of body weight administered once weekly as an intravenous (IV) infusion.</li> <li>Pretreatment is recommended 60 minutes prior to the start of the infusion and may include antihistamines, antipyretics, or both.</li> <li>The final volume of the infusion is determined by the patient's body weight. Patients with a body weight of 20 kg or less should receive a total volume of 100 mL. Patients with a body weight greater than 20 kg should receive a total volume of 250 mL. For patients with underlying cardiac or respiratory compromise and weighing up to 30 kg, physicians may consider diluting Aldurazyme in a volume of 100 mL and administering at a decreased infusion rate.</li> </ul> <p>(<a href="http://www.aldurazyme.com/pdf/az_us_hc_pi.pdf">www.aldurazyme.com/pdf/az_us_hc_pi.pdf</a>)</p>
MPS II (Hunter disease)	Elaprase® (idursulfase intravenous)	<ul style="list-style-type: none"> <li>The recommended dosage regimen of Elaprase is 0.5 mg/kg of body weight administered every week as an intravenous infusion.</li> <li>Elaprase is a concentrated solution for intravenous infusion.</li> <li>The total volume of infusion may be administered over a period of 1 to 3 hours. Patients may require longer infusion times due to infusion reactions; however, infusion times should not exceed 8 hours.</li> <li>The initial infusion rate should be 8 mL/hr for the first 15 minutes. If the infusion is well tolerated, the rate may be increased by 8 mL/hr increments at 15 minute intervals in order to administer the full volume within the desired period of time. However, at no time should the infusion rate exceed 100 mL/hr. The infusion rate may be slowed and/or temporarily stopped, or discontinued for that visit, based on clinical judgment, if infusion reactions were to occur. Elaprase should not be infused with other products in the infusion tubing.</li> </ul> <p>(<a href="http://www.elaprase.com/pdf/Elaprase_US_PI_v6.pdf">www.elaprase.com/pdf/Elaprase_US_PI_v6.pdf</a>)</p>

**Table 5. FDA-approved label dose regimens for ERT products (continued)**

Disease	Product	Dose Regimen (Link)
MPS VI (Maroteaux-Lamy syndrome)	Naglazyme™ (galsulfase)	<ul style="list-style-type: none"> <li>The recommended dosage regimen of Naglazyme is 1 mg per kg of body weight administered once weekly as an intravenous infusion.</li> <li>Pretreatment with antihistamines with or without antipyretics is recommended 30 to 60 minutes prior to the start of the infusion.</li> <li>The total volume of the infusion should be delivered over a period of time of no less than 4 hours. The initial infusion rate should be 6 mL per hour for the first hour. If the infusion is well tolerated, the rate of infusion may be increased to 80 mL per hour for the remaining 3 hours. The infusion time can be extended up to 20 hours if infusion reactions occur.</li> <li>For patients 20 kg and under or those who are susceptible to fluid volume overload, physicians may consider diluting Naglazyme in a volume of 100 mL. The infusion rate (mL per min) should be decreased so that the total infusion duration remains no less than 4 hours.</li> </ul> <p>(<a href="http://www.naglazyme.com/en/documents/Naglazyme_Prescribing_Information.pdf">www.naglazyme.com/en/documents/Naglazyme_Prescribing_Information.pdf</a>)</p>

The dose regimens shown in Table 5 reflect those in the FDA-approved prescribing information for each agent. According to the Key Informants, dose optimization is of significant interest, particularly determining a minimum effective dose for each disease, given the burden on the family unit of weekly or fortnightly infusions. Published studies (see findings for Guiding Question 3) have evaluated more than one dose regimen for some ERT products, including agalsidase beta for Fabry disease;<sup>47</sup> imiglucerase for type I Gaucher disease;<sup>41, 48</sup> laronidase for MPS I;<sup>49</sup> idursulfase (intravenous) for MPS II;<sup>50, 51</sup> and galsulfase for MPS VI.<sup>52, 53</sup>

## Where and By Whom is ERT Administered?

In the United States, ERT has typically been administered in an outpatient infusion clinic under the direction of a physician and team experienced in the use of these agents.<sup>54</sup> Such well-controlled settings are initially required to ensure immediate access to care to address serious infusion-associated adverse reactions, particularly immediate-type (IgE-mediated) hypersensitivity, or anaphylactic, events. Furthermore, medically fragile patients may more appropriately receive infusions in an inpatient or short stay infusion unit setting.<sup>55</sup>

Because these agents must be administered on a weekly or every other weekly basis for the life of the patient, ERT can be onerous, leading to missed school or workplace absence on the day it is received, and ultimately missed doses. To lessen the burden on patients and their families, some patients may be transitioned to home therapy.<sup>56-58</sup> Home infusion of ERT was initially studied in patients with type I Gaucher disease.<sup>59</sup> It has been reported as an option for patients with Fabry disease,<sup>60</sup> MPS I,<sup>61</sup> and MPS II, and MPS VI.<sup>56, 62, 63</sup> However, patients with infantile Pompe disease may not be able to transfer to home care because of an increased risk for serious adverse events during an infusion.<sup>55</sup> In general, the outcomes measured in these studies and the follow-up durations were similar to those reported by disease in the clinical studies summarized under Guiding Question 3. Safety was the main focus of most home infusion studies, as the patients had already been receiving ERT in a more controlled setting.

In the United States, individual access to home therapy is typically determined by the patient's health insurance plan.<sup>64</sup> Although the chronology may vary by patient and disease, transition to home therapy typically is considered after an initial 6 months of clinic treatment free from infusion-associated reactions.<sup>56, 62, 65</sup> The attending physician determines whether patients are recommended for home infusion. Home infusions are conducted under the care of trained infusion personnel, though the physician is available via phone if additional direction is

necessary.<sup>62</sup> Essential elements of a home infusion program include a home health care team, a defined protocol with careful patient selection, good vascular access either through a peripheral line or central access device, and a detailed management plan for infusion-associated reactions and anaphylaxis.<sup>62, 65</sup> An algorithm has been proposed for home infusion to treat MPS II, based on data from the international Hunter Outcome Survey.<sup>66</sup> This protocol commences ERT in clinic, with subsequent evaluation for home therapy. If successful, the patient is referred to a home care team for assessment, with agreement of all parties for transition, and followed by initiation of home treatment.<sup>65</sup> According to this approach, a patient who does not fulfill criteria for home therapy will continue treatment in clinic.

## What Adjunct Treatments Are Used With Each FDA-Approved ERT Product?

Therapeutic management of LSDs comprises measures that address specific symptoms of each disease, but offering no possibility for cure.<sup>1-3, 15, 16</sup> Similar organ-specific manifestations may appear in various combinations as a function of disease and disease stage, including the gastrointestinal tract, the central nervous system, the upper and lower respiratory tract, the visual system, the musculoskeletal system, and the hematopoietic system. For example, untreated patients with Type 1 Gaucher disease, the most common LSD, may develop hepatomegaly or splenomegaly, anemia, thrombocytopenia, impaired lung function, acute or chronic severe bone pain, avascular necrosis, and have growth impairment and pubertal delay.<sup>17</sup> Supportive care prior to development of ERT may have comprised combinations of therapies that could include blood transfusion, bed rest, analgesia, anti-inflammatory agents, hyperbaric oxygen, and surgery (splenectomy, orthopedic procedures). In the age of ERT, however, many of these are no longer used nor recommended (e.g., splenectomy).

In addition to disease-specific adjunct measures, a number of common drugs may be used to prevent or treat infusion-associated reactions, some examples of which are shown in Table 6.<sup>62</sup> Dose regimens for antihistamines, corticosteroids and epinephrine are typically age-dependent, and may vary by physician choice, experience, or availability. Those presented in Table 6 have been reported in the context of home infusion of idursulfase (intravenous).<sup>62</sup> Given the common immune pathogenesis and physiology involved in infusion-associated reactions, and mechanism of action of the drugs, these treatments will be effective regardless of the ERT in question.

**Table 6. Drugs potentially used for the treatment of ERT infusion-associated reactions**

Severity of Reaction	Antipyretic	Antihistaminic	Anti-inflammatory	Sympathomimetic	H2 Receptor Antagonist
Mild	Acetaminophen Ibuprofen	Chlorpheniramine Hydroxyzine	NA	NA	NA
Moderate	Acetaminophen Ibuprofen	Chlorpheniramine (IV)	Hydrocortisone (IV)	NA	NA
Severe (anaphylaxis)	Acetaminophen Ibuprofen	Chlorpheniramine (IV)	Hydrocortisone (IV)	Epinephrine (IM) Albuterol (nebulized)	Ranitidine (IV)

IM = intramuscular; IV = intravenous; NA = not applicable

Guiding Question 3: What published and unpublished studies have reported on the use and safety of this intervention?

## Published Clinical Studies

### Search Results

The primary goal of the literature search was to show the relative scope and extent of studies that have been published since 1990. MEDLINE®, EMBASE®, the Cochrane Controlled Trial Database, and the Health Technology Assessment Database were searched electronically, as shown in Appendix A.

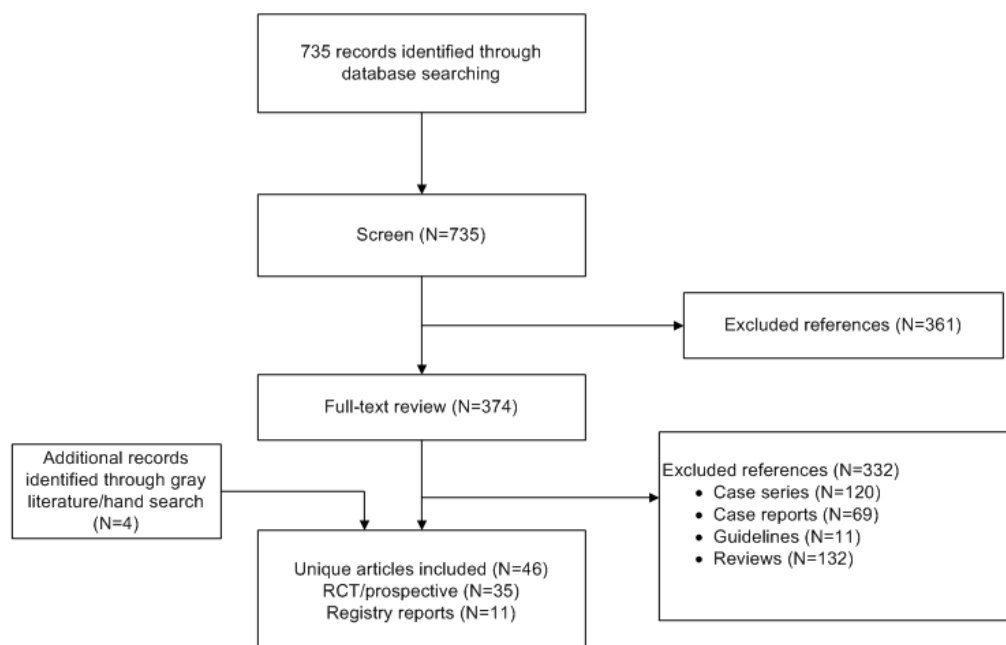
An initial electronic search encompassing the period January 1990 through September 16, 2011 yielded a total of 585 citations. During peer review of the draft report, the search was updated for the period September 16, 2011 through April 24, 2012, yielding an additional 150 items. Among all 735 citations, 361 were excluded as not relevant by title and abstract screen, leaving 374; four additional citations were identified through hand searches of bibliographies or at peer review, bringing the total to 378 shown in Table 7. Clinical studies and registry reports were retrieved for full-text (second-level) examination. Appendix E contains a resource bibliography of all the articles that we enumerate in Table 7.

**Table 7. Second-level literature screen results**

Study Type	Fabry Disease	Type 1 Gaucher Disease	Type II Glycogen Storage Disease (Pompe)	MPS I	MPS II	MPS VI	Total
RCT/Prospective phase I/II	8	7	8	5	4	3	35
Case Series	29	53	20	10	7	1	120
Case Reports	16	14	13	12	8	6	69
Guidelines	4	3	1	1	1	1	11
Registry Reports	3	4	0	0	3	1	11
Reviews	41	32	22	18	12	7	132
Total	101	113	64	46	35	19	378

Figure 1 is a PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses)<sup>67</sup> diagram depicting the flow of articles through this Technical Brief.

**Figure 1. PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) diagram depicting the flow of articles through this Technical Brief**



## Evidence Compilations

In Table 8 through Table 13, we present information on clinical outcomes from a total of 35 RCTs and other prospective studies on each disease and ERT product. Because we had a sufficient number of RCTs and prospective studies to adequately map the clinical evidence, we did not include case series or case reports in the tables.

Harms associated with ERT are reviewed under Guiding Question 1. Those are primarily infusion-related or immune-mediated. Among the clinical studies that were abstracted for Guiding Question 3 (Table 8 through Table 13), there were no reports of adverse events attributed to an ERT product. Long-term adverse sequelae of ERT have not been delineated for most products. Our Key Informants universally indicated the adverse events they have observed were infusion-related or allergic type, not associated with specific actions of the glycoproteins themselves.

## Fabry Disease

Characteristics of eight studies of agalsidase beta therapy for Fabry disease are summarized in Table 8.<sup>35-37, 47, 68-71</sup> A total of 288 symptomatic patients were enrolled, counting the 58 patients in the extension study of Germain<sup>36</sup> that followed the pivotal trial of Eng.<sup>69</sup> Reported ages ranged from 9<sup>37</sup> to 76<sup>70</sup> years with the length of follow-up ranging from 20<sup>68, 69</sup> weeks up to 234<sup>36</sup> weeks. The ERT dose in all studies ranged from 0.2 mg/kg<sup>47, 70</sup> to 1.0 mg/kg every other



**Table 8. Selected clinical studies of agalsidase beta for the treatment of Fabry Disease**

Author, Year, Country, Sample Size	Study Design	Treatment Groups and Dose	Disease Stage/Type	Mean age at Study Onset (range) Yrs	Length of Followup (wks)	Substrate Level	Substrate Deposits	Renal Function	Cardiac Function	Pain Scores	Cerebrovascular	Growth	Quality of Life
Vedder <sup>47</sup> 2008, Netherlands n=13 n=21	dose-optimization study	1) 0.2 mg/kg every other week (eow) 2) 1.0 mg/kg eow	no information provided	1) 49 (25-73) 2) 48 (27-70)	52	•		•	•				
Wraith <sup>37</sup> 2008, international n=16	open-label study in children	1 mg/kg eow	symptomatic	12 (9-12)	48	•		•	•			•	•
Banikazemi <sup>35</sup> 2007, international agalsidase beta: n=51 placebo: n=31	randomized double blind, placebo controlled trial	1 mg/kg eow placebo	symptomatic	47±10 44±9	up to 152			•	•		•		
Germain <sup>36</sup> 2007, international n=58	open-label extension study	1 mg/kg eow	symptomatic	31 (17-62)	up to 234	•		•	•	•			
Tahir <sup>71</sup> 2007, USA N = 11	open-label	1 mg/kg eow	symptomatic	19-58	120			•					

**Table 8. Selected clinical studies of agalsidase beta for the treatment of Fabry Disease (continued)**

Author, Year, Country, Sample Size	Study Design	Treatment Groups and Dose	Disease Stage/Type	Mean age at Study Onset (range) Yrs	Length of Followup (wks)	Substrate Level	Substrate Deposits	Renal Function	Cardiac Function	Pain Scores	Cerebrovascular	Growth	Quality of Life
Vedder <sup>70</sup> 2007, Netherlands n=16	open-label randomized, controlled trial	0.2 mg/kg eow	treatment groups stratified by disease severity	48 (24-76)	52-104	•		•	•	•			
Eto <sup>68</sup> 2005, Japan n=13	open-label Phase II bridging study	1 mg/kg eow	symptomatic	27 (16-34)	20	•		•					
Eng <sup>69</sup> 2001, international n=58 agalsidase beta: n=29 placebo: n=29	randomized double blind, placebo controlled trial	1 mg/kg eow placebo	symptomatic	32±9 28±11	20	•	•			•			

**Table 9. Selected clinical studies of imiglucerase, velaglucerase, and taliglucerase for the treatment of Type 1 Gaucher disease**

Author, Year, Country, Sample Size	ERT	Study Design	Treatment Groups and Dose	Disease Stage/Type	Mean Age at Study Onset (Range) Yrs	Length of Followup (wks)	Hematologic	Liver Size	Spleen Size	Skeletal Pathology	QoL Physical Score	QoL Mental Score
Zimran <sup>44</sup> 2011, international n = 15 n = 16	taliglucerase alfa	Phase III, double-blind, randomized, parallel-group, comparison-dose multinational clinical trial	30 U/kg eow 60 U/kg eow	symptomatic	36 (19-74)	36	•	•	•			
Kishnani <sup>41</sup> 2009, international 1) n=33 2) n=62	imiglucerase	open-label, randomized, Phase IV, dose frequency trial	2 treatment groups: 20-60 IU/kg 1) monthly dose eow 2) monthly dose every 4 weeks	at least 2 yrs on imiglucerase	age at initial imiglucerase infusion: 1) 36 (10-74) 2) 42 (11-75)	104	•	•	•	•	•	•
Sims <sup>42</sup> 2008, United States n=33		open-label, single cohort prospective study	60 IU/kg eow	symptomatic	median 43 (12 -70)	208	•	•	•	•		
de Fost <sup>48</sup> 2007, Netherlands 1) n=5 2) n=6		randomized, controlled trial	2 treatment groups: 1) 3.45 IU/kg weekly or 7.5 IU/kg eow 2) 15 IU/kg every 4 weeks	symptomatic	51 (34-75)	52	•	•	•			
Grabowski <sup>40</sup> 1995, United States n=15		randomized, double-blind, parallel trial	60 IU/kg eow	symptomatic	39 (13-69)	39	•	•	•			

**Table 9. Selected clinical studies of imiglucerase, velaglucerase, and taliglucerase for the treatment of Type 1 Gaucher disease (continued)**

Author, Year, Country, Sample Size	ERT	Study Design	Treatment Groups and Dose	Disease Stage/Type	Mean Age at Study Onset (range) Yrs	Length of Followup (wks)	Hematologic	Liver Size	Spleen Size	Skeletal Pathology	QoL Physical Score	QoL Mental Score
Elstein <sup>39</sup> 2011, Israel  n = 8 (same study population as Zimran <sup>43</sup> 2010)	velaglucerase alfa	extension of Phase I/II open-label study	60 IU/kg eow tapered to 30 IU/kg eow	symptomatic	39 (18-62)	208	•	•	•	•		
Zimran <sup>43</sup> 2010, Israel (same study population as Elstein <sup>39</sup> 2011)  Phase I/II: n=11 extension: n=8		Phase I/II open-label study	60 IU/kg eow tapered to 30 IU/kg eow	symptomatic	41 (18-69)	39	•	•	•			

**Table 10. Selected clinical studies of alglucosidase alfa for the treatment of glycogen storage disease type II (Pompe Disease)**

Author, Year, Country, Sample Size	Study Design	Treatment Groups and Dose*	Disease Stage/Type	Mean Age at Study Onset (Range) Yrs	Length of Followup (wks)	Enzyme Level	6-Min Walk Test	Pulmonary Function	Cardiac Function	Muscle Function	Quality of Life	Survival
Orlikowski <sup>72</sup> 2011, France n=5	open-label study in adults	20 mg/kg eow	juvenile/adult form	48 (28-62)	52	•		•		•	•	
van der Ploeg <sup>73</sup> 2010, international 1) n=60 2) n=30	randomized, double-blind, placebo controlled trial	20 mg/kg eow (Lumizyme) placebo	juvenile/adult form	45 (16-70) 2) 43 (10-68)	78		•	•		•		
Strothotte <sup>74</sup> 2010, Germany n=44	open-label study	20 mg/kg eow	juvenile/adult form	49 (21-69)	52	•	•	•		•		
Kishnani <sup>75</sup> 2009, United States n=16	open-label randomized trial extension to Kishnani, 2006 <sup>76</sup>	20-40 mg/kg eow	infantile form	mean age at end of study: 3 (2-4)	60-150			•	•	•		•
Nicolino <sup>77</sup> 2009, United States n=21	open-label study	20-40 mg/kg eow	infantile and juvenile form	16 months (4-43)	up to 168			•	•	•	•	•
Levine <sup>78</sup> 2008, international n=8	open-label, Phase II trial for children, extension study to Kishnani 2006 <sup>76</sup>	10-20 mg/kg eow	infantile form	6 months (3-15)	52			•	•			
McDowell <sup>79</sup> 2008, international 1) n=7 2) n=31	retrospective study on patients who were in open-label trial for children	1) patients with arrhythmias 2) patients without arrhythmias dose not reported	infantile form	1) median 7 months (6-13) 2) median 8 months (1-43)	78				•			
Kishnani <sup>76</sup> 2006, international n=8	Phase II, open-label study in children	10-20 mg/kg weekly or 20 mg/kg eow	infantile form	median age at first treatment: 5 months (3-15)	up to 153			•	•	•		•

week (fortnightly). The type of outcomes reported varied, including plasma substrate level, renal function, cerebrovascular disease, pain, growth, and quality of life. Plasma substrate levels and capillary substrate inclusions were reported in the randomized, placebo-controlled pivotal trial.<sup>69</sup>

## Gaucher Disease

Table 9 summarizes characteristics of seven studies of ERT (four imiglucerase<sup>40-42, 48</sup>; two velaglucerase<sup>39, 43</sup>; one taliglucerase<sup>44</sup>) for type I non-CNS Gaucher disease. Two studies were performed in the United States,<sup>40, 42</sup> five were international.<sup>39, 41, 43, 44, 48, 80</sup> A total of 212 patients (counting patients from the Elstein velaglucerase extension study<sup>39</sup>) with mild-to-moderate symptoms including anemia, thrombocytopenia, hepatomegaly, splenomegaly, and early bone lesions were enrolled. They ranged in age from as young as 10 years<sup>41</sup> to 75 years<sup>48</sup> with length of follow-up ranging from 18 weeks<sup>39</sup> to 208 weeks.<sup>39, 42</sup> Doses ranged from 3.5 IU/kg weekly<sup>48</sup> to 60 IU/kg every other week (fortnightly).<sup>39-43</sup> The type of outcomes reported varied, including primarily hematological measures (e.g., anemia, thrombocytopenia), hepatomegaly, splenomegaly, and skeletal abnormalities. Different dose regimens were evaluated in two randomized trials involving imiglucerase.<sup>41, 48</sup>

## Glycogen Storage Disease type II (Pompe Disease)

Eight studies of alglucosidase alfa as treatment for glycogen storage disease type II (Pompe disease) are summarized in Table 10.<sup>72-79</sup> Two are categorized as randomized trials.<sup>73, 75</sup> Among the latter, one was the pivotal trial for Lumizyme®.<sup>73</sup> All other studies cited in Table 10 involved the other available alglucosidase alfa product, Myozyme®. Two studies were performed in the United States.<sup>75, 77</sup> A total of 230 patients, 139 with the juvenile/adult form,<sup>72-74</sup> and 91 with infantile Pompe disease<sup>75-79, 81</sup> were enrolled, ranging in age from 1 month<sup>79</sup> to 70 years.<sup>73</sup> Adult or juvenile patients mostly had moderate-to-severe disease manifested by respiratory impairment, myopathy and reduced muscle strength, and impaired mobility.<sup>72-74</sup> Patients with infantile Pompe disease had severe manifestations marked by left ventricular hypertrophic cardiomyopathy, profound muscle weakness and hypotonia, and ventilator dependency.<sup>64-68, 72</sup> Across all studies, ERT was infused at doses ranging from 10 to 40 mg/kg, weekly or fortnightly. One study evaluated two different dose regimens of alglucosidase alfa.<sup>75</sup> The type of outcomes reported varied by type of disease, with cardiac, pulmonary, and muscle function being the most common measures.

## MPS I (Hurler, Hurler-Scheie, or Scheie syndrome)

Table 11 shows summaries of five clinical studies of  $\alpha$ -L-iduronidase (laronidase) therapy that enrolled a total of 148 patients with severe or attenuated forms of MPS I (Hurler, Hurler-Scheie, or Scheie syndrome).<sup>49, 82-85</sup> One of the studies was performed solely in the United States.<sup>85</sup> Patients ranged in age from as young as 1 year<sup>49, 83</sup> to 43 years.<sup>82, 84</sup> Symptoms ranged from mild to severe, including impaired pulmonary function, left-ventricular hypertrophy, hepatomegaly, impaired mobility, impaired growth, sleep apnea, and decreased functional quality of life reflected by the Child Health Assessment Questionnaire/Health Assessment Questionnaire disability index. Doses of laronidase ranged from 100-200 IU/kg weekly to 300 IU/kg fortnightly, with length of follow-up ranging from 26 weeks<sup>49, 84</sup> to 182 weeks.<sup>82</sup> One study was reported as a randomized, open-label dose-optimization trial using three alternative regimens, shown in Table 11.<sup>49</sup> The type of outcomes reported varied, most commonly including plasma substrate level, liver volume, 6-minute walk test, and sleep apnea.

## **MPS II (Hunter Disease)**

Table 12 shows five studies that enrolled a total of 334 patients (counting patients in the Phase II/III extension study of Muenzer<sup>51</sup>) with MPS II (Hunter disease).<sup>50, 51, 86-88</sup> One was performed in the United States.<sup>50</sup> Patients ranged in age from less than 6<sup>87</sup> to 54<sup>88</sup> years, with symptoms of MPS II, including hepatosplenomegaly, radiographic evidence of dystosis multiplex, cardiomyopathy, valvular heart disease, joint mobility, and evidence of upper airway obstruction. Two studies were randomized, placebo-controlled trials that evaluated idursulfase (intravenous) in several dose regimens ranging from 0.15 mg/kg weekly<sup>50</sup> to 1.5 mg/kg fortnightly.<sup>50</sup> The length of follow-up ranged from 24 weeks<sup>50</sup> to 53 weeks<sup>51</sup> in the initial trials, with one extended to 104 weeks.<sup>86</sup> The type of outcomes reported varied, but most commonly included the 6-minute walk test (6MWT) and pulmonary function. The Muenzer 2011 extension study reported the parent- and child-assessed Child Health Assessment Questionnaire Disability Index Score.<sup>86</sup> The Hunter Outcome Survey<sup>87</sup> is a key prospective database study that reported outcomes in children younger than six years old (mean age 3.8 years), the time at which the MPS II phenotype becomes evident and damage irreversible.

## **MPS VI (Maroteaux-Lamy Disease)**

Table 13 shows three international clinical studies of galsulfase in a total of 56 enrolled patients to treat symptomatic or rapidly progressive MPS VI (Maroteaux-Lamy syndrome).<sup>52, 89, 90</sup> A fourth article cited in Table 13 is a pooled analysis<sup>53</sup> of all 56 patients included in the three original trials shown there. Symptoms included impaired pulmonary function, impaired walking ability, impaired joint range of motion, skeletal dysplasia, joint stiffness and pain, hepatosplenomegaly, and impaired visual acuity. Patient age ranged from 5<sup>90</sup> to 29 years.<sup>53</sup> Galsulfase was administered at 0.2-1.0 mg/kg weekly, with follow-up ranging from 48 weeks<sup>89</sup> to 240 weeks.<sup>53</sup> The primary outcome of the 2010 Harnatz study<sup>53</sup> was long-term pulmonary function and growth. A 2006 Phase III randomized, double-blind, placebo-controlled trial reported the primary efficacy variable was the distance walked in a 12-minute walk test (12MWT), whereas the secondary efficacy variables were the number of stairs climbed in a 3-minute stair climb (3MSC) and the level of urinary glycosaminoglycan (GAG) excretion.<sup>90</sup> The 2004<sup>52</sup> and 2005<sup>75</sup> Harnatz studies reported liver volume, 6-minute walk test, joint range of motion and other outcomes.

**Table 11. Selected clinical studies of laronidase for the treatment of Mucopolysaccharidosis I (MPS I, Hurler, Hurler-Scheie, or Scheie syndrome)**

Author, Year, Country, Sample Size	Study Design	Treatment Groups and Dose	Disease Stage/Type	Mean age at study onset (Range) yrs	Length of Follow-up (wks)	Substrate level	Liver Volume	6-min Walk Test	Range of Motion	Mental Development	Pulmonary Function	Cardiac Symptoms	Sleep Apnea	Visual Acuity	Growth
Clarke <sup>82</sup> 2009, international n=40	open-label extension study to Wraith <sup>84</sup> 2004	100 IU/kg weekly	attenuated	16 (6-43)	182	•	•	•	•	•	•		•	•	
Giugliani <sup>49</sup> 2009, international  1) n=8 2) n=8 3) n=8 4) n=9	dose-optimization trial	1) 100 IU/kg weekly 2) 200 IU/kg eow 3) 200 IU/kg weekly 4) 300 IU/kg eow	severe (n=10) and attenuated (n=23)	overall: 9 (1-21) 1) 8 (3-17) 2) 9 (5-17) 3) 9 (1-20) 4) 9 (4-21)	26	•	•	•							
Wraith <sup>83</sup> 2007, international n=20	open-label study on children <5 yrs of age	100-200 IU/kg weekly	severe (n=16) and attenuated (n=4)	3 (1-5)	52	•	•			•		•	•		•
Wraith <sup>84</sup> 2004, international  laronidase: n=22 placebo: n=23	Phase III randomized, double-blind, placebo-controlled trial	100 IU/kg weekly placebo	severe (n=1) and attenuated (n=44)	16 (7-43) 15 (6-39)	26	•	•	•	•		•		•		
Kakkis <sup>85</sup> 2001 United States  laronidase: n=10	Phase II trial	125 IU/kg weekly	intermediate	5-22	52	•	•		•		•	•		•	•



**Table 12. Selected clinical studies of idursulfase (intravenous) for the treatment of Mucopolysaccharidosis II (Hunter Disease)**

Author, Year, Country, Sample Size	Study Design	Treatment Groups and Dose	Disease Stage/Type	Mean Age at Study Onset (Range) Yrs	Length of Followup (Wks)	Substrate Level	Spleen Volume	Liver Volume	6-Min Walk Test	Range of Motion	Pulmonary Function	Cardiac Symptoms	Sleep Apnea	Child Health Disability Index
Okuyama <sup>88</sup> 2010, Japan n=10	open-label study in adults	0.5 mg/kg weekly	attenuated	30 (21-54)	52	•	•	•	•	•	•	•	•	
Muenzer <sup>87</sup> 2011, international n=124	prospective database study (Hunter Outcome Survey)	0.5 mg/kg eow	attenuated or severe	3.8 ± 1.8	92	•		•						
Muenzer <sup>86</sup> 2011, International n=94	open-label extension study of Phase II/III randomized double-blind, placebo-controlled trial (Muenzer <sup>51</sup> 2006)	0.5 mg/kg weekly	treatment groups had same distribution baseline disease scores from 2-6	5-31	104		•	•	•	•	•			•
Muenzer <sup>50</sup> 2007, United States  idursulfase (intravenous): n=9 placebo: n=3	Phase I/II, randomized, double-blind, placebo-controlled trial	1) 0.15 mg/kg eow 2) 0.5 mg/kg eow 3) 1.5mg/kg eow 4) placebo	attenuated	overall: 14 (6-20) 1) 11 (9-14) 2) 20 (20) 3) 8 (6-10) 4) 17 (13-20)	trial: 24  extension: 26	•	•	•	•	•	•	•	•	
Muenzer <sup>51</sup> 2006, international  1) idursulfase (intravenous): n=32 2) idursulfase (intravenous): n=32 3) placebo: n=32	Phase II/III, randomized double-blind, placebo-controlled trial	1) 0.5 mg/kg weekly 2) 0.5 mg/kg eow 3) placebo	treatment groups had same distribution baseline disease scores from 2-6	1) 15 (6-26) 2) 14 (5-31) 3) 13 (5-29)	53	•	•	•	•	•	•			

**Table 13. Selected clinical studies of galsulfase for the treatment of Mucopolysaccharidosis VI (Maroteaux-Lamy Syndrome)**

Author, Year, Country, Sample Size	Study Design	Treatment Groups and Dose	Disease Stage/Type	Mean Age at Study Onset (Range) Yrs	Length of Followup (Wks)	Liver Volume	Stair Climb (3 min)	Walk Test (6 or 12 min)	Range of Motion	Pulmonary Function	Ophthalmologic Evaluation	Sleep Apnea	Growth
Harmatz <sup>53</sup> 2010, international n=56	pooled analysis including Phase I/II, II, III studies including extension Phases to 48 weeks	0.2 mg/kg or 1.0 mg/kg weekly	symptomatic	Phase I/II: 12 (7-16) Phase II: 12 (6-21) Phase III: 14 (5-29)	up to 240					•			•
Harmatz <sup>90</sup> 2006, international n=39	Phase III, randomized, double-blind placebo-controlled trial	1.0 mg/kg weekly	symptomatic	14 (5-29)	48		•	•					
Harmatz <sup>89</sup> 2005, international n=10	open-label study	1.0 mg/kg weekly	rapidly advancing disease	13 (6-22)	48	•		•	•		•	•	•
Harmatz <sup>52</sup> 2004, international n=7	Phase I/II randomized, two-dose, double-blind	0.2 mg/kg weekly n=4 1.0 mg/kg weekly n=3	entire severity spectrum	11 (7-16)	48	•	•	•	•	•	•	•	•

## **Published Registry Studies**

Summaries of 11 published registry studies of ERT for Fabry disease, type I Gaucher, MPS II, and MPS VI are shown in Appendix C. These generally reported the same types of outcomes as reported in the clinical studies summarized, previously. However, the actual percentages of outcomes associated with each disease and its treatment may not be as informative as possible, given uncertainty in the real denominators (patient numbers) associated with each registry as participation is voluntary. As noted at a manufacturer-sponsored Web site ([www.lysosomallearning.com/support/lsd\\_sup\\_registries.asp](http://www.lysosomallearning.com/support/lsd_sup_registries.asp)), no single database or registry exists for all LSDs.

## **Unpublished Studies and Ongoing Clinical Studies**

For this Technical Brief, the ERT product manufacturers supplied the EPC with compilations of information that included abstracts and posters presented at scientific meetings, as well as product bibliographies and monographs. We cross-indexed the bibliographies we received with published literature identified in our search as well as through NCBI PubMed®. In this exercise, our team did not identify key information, for example novel outcomes or studies, that would extend the general findings we had not already found in the course of this project in published studies, review articles, FDA documents, Key Informant interviews, or manufacturers or advocacy Web sites.

Appendix D shows 29 current clinical studies (Phase I-IV) identified through a search of the ClinicalTrials.gov Web site. These are being performed for all ERT products, with similar endpoints and outcomes as reported for each specific disease as outlined in Table 8 through Table 13 in this Technical Brief. Notably, two studies (NCT0638547, NCT 00852358) are evaluating intrathecal administration of laronidase to treat CNS symptoms of MPS I (MPS I, Hurler, Hurler-Scheie, or Scheie syndrome). Two studies (NCT00920647, NCT 01506141) are evaluating intrathecal administration of idursulfase (intravenous) to treat CNS symptoms of MPS II (Hunter's disease).

## **Guiding Question 4: What are key unresolved or controversial issues with ERT in LSDs?**

We sought to address this Guiding Question through integration of information from published clinical studies, narrative review articles, FDA summary documents, and a series of semi-structured interviews with five highly experienced Key Informant physicians and end-users of ERT. The complete discussions are not summarized; rather, we present key clinical concurrences.

## **Key Informant Semistructured Telephone Interviews**

In the following discussion, unless otherwise stated, the views expressed are those of the authors of this Technical Brief. Views of the Key Informants are specified as such.

The Key Informants universally asserted that CNS neuronopathic aspects of any LSD do not respond to ERT, because the large glycoproteins do not penetrate the blood–brain barrier. One proposed approach to overcome this obstacle is direct intrathecal administration of ERT products. Our literature scan identified two case reports on the intrathecal approach, one in a

patient with MPS I,<sup>91</sup> the other a patient with MPS VI.<sup>92</sup> Intrathecal administration of ERT is the subject of current clinical studies in patients with MPS I and MPS II (see Appendix D).

In our discussions, the Key Informants further indicated that in their experience ERT does not generally reverse established disease-associated damage in patients with any LSD. However, it is not clear what “established” means in terms of type, site, and extent of damage. How this topic could be explored in clinical studies is not clear.

A key point raised in our Key Informant interviews was the importance of timing initiation of ERT prior to or at first appearance of symptoms. We identified published clinical studies that investigated the timing of ERT relative to symptom onset and clinical outcomes for a few LSDs. These include renal function and disease progression in adult patients with Fabry disease treated with agalsidase beta,<sup>93</sup> and, avascular necrosis and other manifestations of type I Gaucher disease.<sup>94, 95</sup> Several published clinical studies have investigated the impact of early initiation of ERT in infants with Pompe disease.<sup>75, 96-100</sup> A key factor in the response of infants with Pompe to ERT is the absence of cross-reacting immunologic material and development of antibodies that may impede response to alglucosidase alfa.<sup>101</sup> A study conducted in Germany reported the influence of idursulfase (intravenous) on growth in patients with MPS II, particularly the effect of beginning ERT before the age of 10 years.<sup>102</sup>

## **Patient Advocate Telephone Interviews**

Two individuals participated in these anecdotal interviews, a patient affected with an LSD and a caregiver of a patient affected with an LSD. We did not investigate their statements in relationship to the literature. The discussion touched on a variety of issues including clinical outcomes of importance to patients and parents; the importance of “community” in ongoing ERT; information of importance to patients and caregivers; bone marrow transplantation; and, the influence of disease on family members.

The patient with an LSD described several personally important clinical outcomes associated with ERT. These included improved joint range of motion, improved ability to walk, increased energy and feeling of well-being, and independence in daily living. The patient further described how ERT was associated with stabilized cardiac function; improved ability to breathe; improved bone health in terms of reduced pain; and, fewer infections presumably related to immune suppression secondary to the LSD. These types of improvements were of great significance in the patient’s view because they directly affect the quality of life. Quality life with ERT has been studied in patients with type I Gaucher disease,<sup>103-105</sup> Fabry disease,<sup>106</sup> and MPS I (Hurler, Hurler-Scheie, or Scheie syndrome) disease.<sup>107</sup> The patient reported that a shortage-related ERT hiatus resulted in rapid loss of cognitive function and energy, and led to increased bone aching and pain, all of which improved with resumption of ERT. Although cognitive function is not typically affected by the LSD afflicting this patient, a decline was apparent to the patient during the involuntary treatment hiatus. The patient expressed a degree of “guilt” about use of substantial health care resources in times of ERT product shortage. Similar concerns were reported in 2011 among a group of fifty patients with adult type I Gaucher disease in Spain during a 6-month shortage of imiglucerase secondary to viral contamination and manufacturing problems in Europe;<sup>108</sup> a similar situation occurred in Australia in 2009.<sup>109</sup> Shortages of Cerezyme® and Fabrazyme® in the United States were reported by the manufacturer in Fall 2011 ([www.gaucherdisease.org/cerezyme\\_shortage\\_letter\\_2011.pdf](http://www.gaucherdisease.org/cerezyme_shortage_letter_2011.pdf)).

The caregiver we interviewed described the patient under care as full of energy on ERT, social, and no longer readily identifiable (from a distance) as having an LSD. The caregiver

further indicated the patient's doctor has discussed hematopoietic stem-cell transplantation as an option, but cautioned it would not necessarily stabilize cognitive function, carries a high risk of harms, and may not yield any more improvement than ERT. The caregiver also indicated the community aspect of hospital-based therapy as important to a family sense of well-being.

## Summary and Implications

This Technical Brief addresses four Guiding Questions to examine the state of evidence on the use of ERT in patients with an LSD for which an FDA-approved product is available. To address Guiding Questions 1 and 2, we summarized indications and dose regimens from the FDA-approved prescribing information for each of nine available products, as well as information from review articles on how, where, and by whom ERT may be administered. Results summarized under Guiding Question 3 provide a picture of clinical studies for each product, from a search of the published literature. Guiding Question 4 integrates information from a series of semi-structured interviews with five highly experienced Key Informant physicians and end-users of ERT, relevant published clinical studies, narrative review articles, and FDA summary documents. The information compiled in this Technical Brief is intended as a resource with which health care providers and decision-makers may educate themselves about the ERT products available, how they are used, and clinical issues articulated by clinical experts and patient advocates.

Given the rarity of these diseases individually, the overall evidence base comprises small randomized, controlled trials, cohort studies, prospective single-arm studies, case series, case reports, and registry summaries. The volume of published literature correlates roughly with the FDA marketing approval dates. Thus, about 34 percent of the articles we identified in our scan were about ERT (all available products) in type I Gaucher disease, which was followed by articles on Fabry disease, which comprised 25 percent of the literature volume. The other four LSDs together make up about 31 percent of the published articles we found.

We recognize that our outcome reporting could be construed as limited by the inclusion primarily of randomized and other complementary prospective studies, excluding a larger number of case series, case reports, and foreign-language articles. The inclusion of higher-level evidence in the form of RCTs is supportable in that the trials were typically complete in capturing the key clinical outcomes of importance with a lower risk of bias than case series and case reports. Furthermore, as we state in the Methods section of this report, exclusion of non-English language reports has been shown to have little effect on the findings of systematic reviews.<sup>31</sup> All of the citations we considered in the second-level literature screen are compiled in Appendix E of this report.

The clinical studies compiled in the Technical Brief map the characteristics of available evidence, including patient populations, sample size, study methods, and what outcomes have been reported for each product. Across the six LSDs, as outlined in Table 1, and clinical studies (Table 8 through Table 13), the reported patient characteristics are highly heterogeneous, as each exhibits a disease-specific constellation of signs and symptoms. Further, the expression of symptoms often varies greatly among and within the six diseases, ranging from early infancy for Pompe disease to perhaps mid-adulthood for type I Gaucher disease. However, some commonalities in symptoms clearly exist between these LSDs: for example hepatomegaly or splenomegaly, bone and other skeletal abnormalities, abnormal hematological measures (anemia, thrombocytopenia), cardiac dysfunction, pulmonary dysfunction, and impaired ambulation.

The conundrum of these orphan diseases is that they are very rare and genetically unique within and between types; however, because the macromolecular compounds accumulate within lysosomes—which are found in every cell type in the body—they can exhibit similar individual pathologies. Yet, each ERT product is effective for only one LSD, and ERT outcomes may vary among patients with the same disorder. This heterogeneity may complicate decision-making as it relates to initiating ERT—when is the optimal time? The majority of clinical studies we

examined for this Technical Brief did not address this issue; all patients in the studies we summarized were symptomatic, to a greater or lesser degree, and required therapy. However, several of the Key Informants indicated that timing of treatment is very important as it relates to disease progression and development of irreversible damage.

We identified a few reports that showed the effect of early initiation of ERT. For example, the impact of early initiation of agalsidase beta on renal function and disease progression has been studied in adult patients with Fabry disease.<sup>93</sup> Others reported the impact of early ERT on manifestations of type I Gaucher disease.<sup>94, 95</sup> Several published clinical studies have investigated the impact of early detection and initiation of ERT in infants with Pompe disease.<sup>75, 96-100</sup> A sibling-control study in two children (8 weeks and 3.6 years old) reported a benefit of earlier initiation of galsulfase to slow or prevent the development of significant pathological changes of MPS VI.<sup>110</sup>

Information contained in several sources, including the FDA-approved label for each product; narrative and systematic reviews; clinical studies; and, Key Informant interviews suggests that ERT glycoproteins have few, if any, specific adverse effects on recipients. The vast majority of adverse events are infusion-associated reactions, which are generally mild and easily controlled or self-limiting. Immune sensitization and anaphylactic responses have been reported; the former may rarely affect therapy, whereas the latter will usually preclude further administration of the specific agent and are the subject of FDA-mandated Black Box warnings on the approved label for alglucosidase alfa, laronidase, and idursulfase (intravenous).

Our scan of the literature, the Key Informant discussions, and other publicly available information revealed a number of unanswered questions with regard to clinical use of the agents. Thus, optimal dose regimens have not been established. One article cited in Table 9 reported dose optimization studies for imiglucerase in patients with type I Gaucher disease, investigating variation of the amount of product administered or frequency of administration.<sup>41</sup> There are many other clinical reports, editorials, and commentaries on this issue, dating back to the mid-1990s, soon after the first ERT product for type I Gaucher disease became commercially available.<sup>33, 34, 111-119</sup> We also identified reports on the effect of dose variation for ERT in patients with Fabry disease<sup>70, 120</sup> and MPS I.<sup>49</sup> The evidence base is substantially more robust for type I Gaucher disease than for the others, as would be expected given the relative prevalence of these diseases and the chronology of FDA marketing approvals.

Although we did not investigate this issue, some Key Informants voiced concern that the mechanism of action of ERT agents is not well understood. How they are taken up by lysosomes, and how they are distributed into various compartments and tissues is unclear.<sup>15</sup> This bears directly on clinical outcomes of ERT achieved in organs or compartments that are less accessible to large glycoproteins. For example, the blood–brain barrier represents a significant impediment to intravenous ERT for diseases that have a CNS neuronopathic component. Approaches to this obstacle may entail the use of combined therapy comprising chaperone molecules, combined with ERT, or perhaps with intrathecal administration of enzymes.<sup>19-21, 25, 26</sup> However, chaperone and combination therapies are purely investigational at present.

Several potential issues of interest were raised by peer reviewers of the draft Technical Brief. These include: port infections and repeat port surgeries as a harm associated with ERT, and the apparent lack of Phase IV clinical trials that were mandated by FDA as a condition for accelerated approval. We did not investigate literature on these topics.

In considering the implications of this Technical Brief, the issues are not merely technical or clinical. Although patients with so-called classic symptoms of an LSD can be apparent,

atypically presenting patients often require greater consideration.<sup>121</sup> The Key Informants suggested earlier initiation of ERT is preferable compared to later in patients for whom a diagnosis has been made. However, they expressed uncertainty as to whether it is appropriate to initiate ERT in an undiagnosed, asymptomatic individual in whom only a genetic mutation predictive of an LSD has been identified. This reticence is congruent with literature showing the disease genotype-phenotype relationship is not exact.<sup>80, 121, 122</sup> Furthermore, the phenotypic expression of an LSD may significantly vary among individuals; it may not express itself at all or, symptoms may not manifest for a very long period of time.<sup>3, 123</sup> Thus, whether to initiate ERT in patients with a genetic mutation specific for an LSD is an issue for which further study will be required.

Information concerning whether or when to stop ERT is also unclear. In our Key Informant interviews, we heard anecdotally of experience where the burden of therapy on the family of a patient with a rapidly progressing or nonresponsive LSD drove a decision to cease and turn to supportive comfort care alone. This raises complex questions related to the psychosocial dynamics of the family unit and also around the ethics of treatment withdrawal. We did not identify clinical studies relating such family issues and ERT. However, it is reasonable to envision disease registries as storehouses and conveyances for this type of information to physicians. Disease registries represent a means to establish treatment benefits as well as understand disease natural history and epidemiology. They can be used to collect long-term longitudinal data on clinical outcomes of rare LSDs, and information related to effects of treatment cessation and the parameters used to make such determinations. However, we are not aware of existing registry data on this topic.

The rarity of the LSDs in typical primary care or pediatric practice, and thus physician recognition and timely initiation of ERT, is a topic that has not been well studied.<sup>80, 122</sup> In the United States, the National Organization for Rare Disorders and the National Institutes of Health Office of Rare Diseases, estimate that 25 million Americans suffer from a rare disease.<sup>80</sup> The latter seems a large number, but the LSDs considered in this Technical Brief are individually very rare. Clinical vigilance therefore becomes key to ensure timely initiation of ERT for LSDs.<sup>6</sup> Primary care physicians—who typically manage common problems in unselected patients—must learn to recognize the occasional zebra in a herd of horses, without working up every horse, because common patients can present with rare diseases.<sup>124</sup>

A generic primary care practice approach to patients with rare disease has been published.<sup>80</sup> According to the authors, this approach may reduce problems that include a lack of coordinated care, lack of information about rare diseases, delayed diagnosis, and delayed therapy.<sup>80</sup> The authors of this paper further suggest this approach may ultimately enable primary care physicians to systematically address the problems posed by individuals who present with an unrecognized or rare disorder, presumably including an LSD. Most LSD patients present with symptoms secondary to existing damage. Once an LSD is diagnosed, a comprehensive treatment plan can be developed involving a multidisciplinary team headed by a biochemical geneticist or other physician experienced in treating these diseases.

## Next Steps

Several key areas of investigation were identified by our scan of the published literature and other information sources, and our discussions with Key Informants, as follows:



## **Comparative Effectiveness of ERT Products and Selective Outcome Assessment**

During the preparation of this Technical Brief, a third ERT product gained FDA marketing approval in the United States for use in patients with type I Gaucher disease. This product, taliglucerase alfa (Elelyso™) is produced using a carrot cell-based process, which is distinct from processes used for the other two products available for this disease (imiglucerase [Cerezyme®] and velaglucerase alfa [VPRIV™]). The comparative effectiveness and safety of these products has not been reported, particularly the potential effects of switching a patient from one to another in terms of efficacy and safety. Similarly, the comparative effectiveness of two available ERT products [Myozyme®, Lumizyme®] for forms of Pompe disease not specified in the FDA-approved label for each has not been reported, but studies could now be undertaken. Knowledge of the comparative effectiveness of products labeled for the same disease would benefit patients, particularly in times of specific product shortage.

In considering comparative studies, a related consideration is selective outcome assessment. Examination of the outcomes reported across studies compiled in Table 8 through Table 13 of this Technical Brief shows that a number of clinical outcomes that were deemed important in our Key Informant and Patient Advocate interviews are not consistently represented. For example, two important outcomes for Fabry patients—renal and cardiac function—were reported in most studies shown in Table 8. However, relatively little information is available on the effect of agalsidase beta on pain, cerebrovascular pathology, growth, and quality of life measures. Similarly, our affected Patient Advocate mentioned bone and joint pain and function, physical function and overall feeling of well-being (quality of life) as key attributes improved by ERT, yet as shown in Table 8 through Table 13, these have not been consistently reported in clinical trials, regardless of the disease under study. Survival is reported only in studies of ERT among patients with infantile or juvenile onset Pompe disease, as shown in Table 10. Whether survival can be studied for other LSDs with slower progression and uncertain onset remains to be established. Given the rarity of these diseases, and difficulty in reliably predicting their expression and rate of progression among individual patients, it is difficult to study ERT in rigorous randomized trials. Nonetheless, additional study is warranted to establish efficacy for a broader range of outcomes than currently available for each disease.

## **Pharmacodynamic and Pharmacokinetic Issues**

We did not review published studies along these lines of investigation. However, several Key Informants suggested the need for more basic research on the mechanism of action of ERT products. They suggested areas of interest to include efforts to improve cellular targeting, enhance ERT cellular uptake, and improve pharmacokinetic parameters to enhance distribution of these agents within body compartments. Improved ERT product formulations have significant potential to enhance therapeutic effectiveness and safety. Molecular modifications designed to increase enzyme delivery to minimally or nonaccessible physiologic compartments would have significant therapeutic benefit. This would particularly benefit patients with diseases that affect the CNS and are not treatable with current agents, and diseases that cause bone lesions and damage, which do not respond well to ERT due to limited uptake into those sites. In theory, depot products, similar to those developed for intravenous immune globulin therapy, with subcutaneous administration and prolonged release, would potentially ease the burden of therapy on patient and family alike by simplifying administration.

## **ERT Dose Regimen Optimization**

A majority of our Key Informants agreed that optimal ERT dose regimens are not known for any of the LSDs, although as discussed above in this Technical Brief, some information is available in the literature on this topic. Ideally, comparative randomized dose studies using standardized protocols would address dose optimization for all indications, including initiation and maintenance dosing. However, there are practical difficulties in performing comparative randomized dose studies using standardized protocols for very small and very heterogeneous patient populations, where the underlying disease severity and extent of disease progression before ERT is begun are critical variables in determining optimal dose. One useful approach may be the concept of establishing therapeutic goals and individualizing dose to enable patients to reach and maintain those goals. This question bears on issues that include clinical effectiveness, resource utilization, and patient compliance.

## **Early Treatment Initiation**

Our Key Informants generally agreed that the earliest possible initiation of ERT, prior to or at first appearance of symptoms, is necessary to reap the most benefits by preventing or delaying irreversible tissue damage with disease progression. Early treatment initiation is predicated on a high level of clinical acumen on the part of primary care and pediatric physicians to recognize the possible presence of an LSD based on perhaps subtle signs, family history, and clinical experience, and to make prompt referrals to specialists. The timing of treatment initiation has been investigated for a few diseases, as alluded to earlier in this Technical Brief. In an ideal world, studies that compare treatment timing would involve symptomatic and asymptomatic patients. However, any clinical study withholding ERT in symptomatic patients to study the effect of timing on outcomes would be unethical.

All these endeavors will require the combined efforts of physician investigators, bench scientists, pharmaceutical manufacturers, and patient advocacy groups. Given the individual rarity of the LSDs, patient accrual for clinical studies is difficult. Ideally, cooperative efforts—perhaps analogous to the Children’s Oncology Group—may provide a pathway toward ensuring that studies are standardized in conduct and reporting. Disease-specific registries, with standardized operating procedures for data submission and reporting will remain important to enhance knowledge of natural history and therapeutic outcomes. Such efforts would hasten referrals to specialists in metabolic disease, obviously benefitting patients and their families, but also potentially benefitting the overall health care system as the result of earlier care and reduced disease morbidity.

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## Appendix A. Electronic Database Search Strategies

### Search 1 -

"Mucopolysaccharidosis I"[Mesh] OR ("mucopolysaccharidosis" AND "type I") OR  
"mucopolysaccharidosis I" OR "mucopolysaccharidosis-I" OR "MPS I" OR "Hurler disease" OR  
"hurler syndrome"

AND

laronidase OR aldurazyme

AND

English language, humans

Results in PubMed = 36

29 additional studies identified using the search in EMBASE = 15 appeared to be unique and possibly relevant

Cochrane search found 4 trials – all are in the database.

### Search 2 –

"Mucopolysaccharidosis II"[Mesh] OR (mucopolysaccharidosis AND "type II") OR  
"mucopolysaccharidosis II" OR "mucopolysaccharidosis-II" OR "MPS II" OR "Hunter disease"  
OR "hunter syndrome"

AND

"idursulfase" [Supplementary Concept] OR idursulfase OR elaprase

AND

English language, humans

Results in PubMed = 34

67 additional studies identified using the search in EMBASE = 3 appeared to be unique and possibly relevant

Cochrane search found 1 protocol and 2 trials that were unique and added to the database.

### Search 3 –

"Mucopolysaccharidosis VI"[Mesh] OR (mucopolysaccharidosis AND "type VI") OR  
"mucopolysaccharidosis VI" OR "mucopolysaccharidosis-VI" OR "MPS VI" OR "maroteaux-  
lamy syndrome"

AND

"galsulfase" [Supplementary Concept] OR galsulfase OR naglazyme

AND

English language, humans

Results in PubMed = 21

24 additional studies identified using the search in EMBASE = 6 appeared to be unique and possibly relevant

Cochrane search found 1 new technology assessment which was added. Everything else was already there.

### Search 4 –

"Fabry Disease"[Mesh] OR "fabry disease" OR "alpha-Galactosidase A Deficiency"

AND

"agalsidase beta" [Supplementary Concept] OR "agalsidase beta" OR fabrazyme

AND

English language, humans

Results in PubMed =132

130 studies identified using the search in EMBASE = 13 appeared to be unique and possibly relevant

Cochrane search found 2 additional trials which were added.

#### Search 5 -

"Gaucher Disease"[Mesh] OR "gaucher disease" OR "gaucher's disease"

AND

((("alglucerase" [Supplementary Concept]) OR "imiglucerase" [Supplementary Concept]) OR "Velaglucerase alfa, human" [Supplementary Concept] OR alglucerase OR ceredase OR imiglucerase OR cerezyme OR velaglucerase OR "miglustat" [Supplementary Concept] OR miglustat OR zavesca

AND

("type 1" OR "type I") OR various study types (RCT, meta-analysis, comparative study)

AND

English language, humans

Results in PubMed =222

65 clinical studies identified in EMBASE = 4 appeared to be unique and possibly relevant

Cochrane search found 4 additional articles which were added.

#### Search 6 –

"Glycogen Storage Disease Type II"[Mesh] OR ("glycogen storage disease" AND ("type II" OR "type 2")) OR "pompe disease" OR "pompe's disease"

AND

"GAA protein, human" [Supplementary Concept] OR "alglucosidase alfa" OR myozyme

AND

English language, humans

Results in PubMed =99

41 clinical studies identified in EMBASE = 8 appeared to be unique and possibly relevant

Cochrane search found 2 trials – only 1 unique one – a meeting abstract – was added.

## Appendix B. Appendix Data Abstraction Tables

Clinical Trials of Enzyme Replacement Therapy for Lysosomal Storage Diseases

Disease/ERT	Author, Year, Country	Study Design	Comparator	No. of Patients	Disease Stage/Type	Mean Age at 1 <sup>st</sup> Infusion (range) yrs	Length of Follow-up (wks)	Outcomes Measured	Adverse Events
MPS I/ Aldurazyme® (α-L-ironidase) (laronidase)	Clarke, <sup>1</sup> 2009, international	open label extension to Wraith et al, 2004 <sup>2</sup>	none	40	attenuated	16 (6-43)	182	- urinary substrate levels - liver volume - 6-min walk test - pulmonary function - range of motion - mental development - visual acuity - sleep apnea - IgG	- infusion-associated reactions - IgG antibody development
	Giugliani, <sup>3</sup> 2009, international	dose optimization trial	0.58 mg/kg wkly vs 1.2 mg/kg EOW, 1.2 mg/kg wkly, and 1.8 mg/kg EOW	33	severe (n=10) and attenuated (n=23)	8.9 (1.4-20.7)	26	- urinary substrate levels - liver volume - 6-min walk test	- infusion-associated reactions - IgG antibody development - 1 death in pt w/ severe form, considered unlikely related to treatment
	Wraith, <sup>4</sup> 2007, international	open label trial for children <5 yrs of age	none	20	severe (n=16) and attenuated (n=4)	2.9 (0.5-5.1)	52	- urinary substrate levels - liver size - cardiac involvement - sleep apnea - growth - mental development	- infusion-associated reactions - IgG antibody development

Disease/ERT	Author, Year, Country	Study Design	Comparator	No. of Patients	Disease Stage/Type	Mean Age at 1 <sup>st</sup> Infusion (range) yrs	Length of Follow-up (wks)	Outcomes Measured	Adverse Events
	Wraith, <sup>2</sup> 2004, international	randomized, double-blind, placebo-controlled trial	placebo	laronidase: 22  placebo: 23	severe (n=1) and attenuated (n=44)	laronidase: 15.6 (7-43)  placebo: 15.4 (6-39)	26	- pulmonary function - 6-min walk test - urinary substrate levels - liver size - sleep apnea - range of motion	- infusion-associated reactions - IgG antibody development
MPS II/ Elaprase® (idursulfase)	Okuyama, <sup>5</sup> 2010, Japan	open label trial for adults	none	10	attenuated	30.1 (21.1-53.9)	52	- urinary substrate levels - liver size - 6-min walk test - pulmonary function - range of motion - cardiac involvement - sleep apnea - spleen volume	- infusion-associated reactions - IgG antibody development
	Muenzer, <sup>6</sup> 2011  N = 94	extension study of phase II/III randomized double-blind, placebo-controlled trial (Muenzer, 2006 <sup>7</sup> )	0.5 mg/kg weekly	treatment groups had same distribution baseline disease scores from 2-6	5-31			- 6-min walk test - pulmonary function - substrate level - liver volume - spleen volume - range of motion	

Disease/ERT	Author, Year, Country	Study Design	Comparator	No. of Patients	Disease Stage/Type	Mean Age at 1 <sup>st</sup> Infusion (range) yrs	Length of Follow-up (wks)	Outcomes Measured	Adverse Events
	Muenzer, <sup>8</sup> 2007, US	phase I/II, randomized, double-blind, placebo-controlled trial	3 treatment groups: 0.15, 0.5, and 1.5mg/kg EOW, and placebo	idursulfase : 9  placebo: 3	attenuated	overall: 14 (6-20)  0.15 mg/kg: 11 (9-14)  0.5 mg/kg: 20 (20)  1.5 mg/kg: 8 (6-10)  placebo: 17 (13-20)	double-blind trial: 24  open label extension : 26	- urinary substrate levels - liver and spleen volume - 6-min walk test - range of motion - pulmonary function - cardiac involvement - sleep apnea	- infusion-associated reactions - IgG antibody development
	Muenzer, <sup>7</sup> 2006, international	phase II/III, randomized double-blind, placebo-controlled trial	3 treatment groups: 1) 0.5 mg/kg wkly, 2) 0.5 mg/kg EOW, and 3) placebo	1) 32 2) 32 3) 32	each treatment grp had the same distribution of baseline disease scores ranging from 2-6	1) 15.1 (6.3-26.0)  2) 14.4 (5.4-30.9)  3) 13.1 (5.0-29.0)	53	- 6-min walk test - pulmonary function - substrate level - liver volume - spleen volume - range of motion	- infusion-associated reactions - IgG antibody development
MPS VI/ Naglazyme® (galsulfase )	Harmatz, <sup>9</sup> 2010, international	extension to phase I/II, II, III trials reporting results up to 48 wks, Harmatz 2004 <sup>10</sup>	1) 0.2 mg/kg or 1.0 mg/kg 2) 0.2 mg/kg 3) 0.2 mg/kg	1) 7 2) 10 3) 39	symptomatic	phase I/II: 12 (7-16) phase II: 12.1 (6-21) phase III: 13.7 (5-29)	up to 240 weeks	-pulmonary function -height	not reported
	Harmatz, <sup>43</sup> 2006, international	phase III, randomized double-blind, placebo-controlled trial	1) 1.0 mg/kg wkly  2) placebo	1) 19  2) 20	symptomatic	13.7 (5-29)	48 weeks	6 and 12 minute walks -3 minute stair climb - urinary substrate levels	not reported

Disease/ERT	Author, Year, Country	Study Design	Comparator	No. of Patients	Disease Stage/Type	Mean Age at 1 <sup>st</sup> Infusion (range) yrs	Length of Follow-up (wks)	Outcomes Measured	Adverse Events
	Harmatz, <sup>11</sup> 2005, international	open label	none	10	rapidly advancing disease	12.7 (6-22)	48	-mobility and physical function -6 and 12 minute walks -3 minute stair climb -oxygenation during sleep -ophthalmology evaluation -liver volume -spleen volume -height	-asthma attack - infusion-associated reactions - IgG antibody development
	Harmatz, <sup>44</sup> 2004 international	phase I/II randomized, two-dose, double-blind	1)0.2 mg/kg weekly 2)1.0 mg/kg weekly	1) 4 2) 3	entire severity spectrum	11 (7-16)	48	-mobility and physical function -6 minute walk -pain -urinary substrate levels	not reported
Fabry/ Fabrazyme® (agalsidase beta)	Wraith, <sup>12</sup> 2008, international	open label trial for children	none	16	no information provided	12.1 (8.5-11.7)	48	- skin and plasma substrate levels - renal function - cardiac function - growth - quality of life - school attendance - low, moderate, high energy level - general health	- infusion-associated reactions - IgG antibody development

Disease/ERT	Author, Year, Country	Study Design	Comparator	No. of Patients	Disease Stage/Type	Mean Age at 1 <sup>st</sup> Infusion (range) yrs	Length of Follow-up (wks)	Outcomes Measured	Adverse Events
	Banikazemi, <sup>13</sup> 2007, international	randomized double blind, placebo controlled trial	placebo	agalsidase β: 51  placebo: 31	no information provided	agalsidase β: 46.9 (SD: 9.8)  placebo: 44.3 (SD: 9.2)	mean: 74 up to 152	- renal function - cardiac function - cerebro-vascular events	- infusion-associated reactions
	Germain, <sup>14</sup> 2007, international	open label extension trial	none	58	no information provided	31.1 (17-62)	up to 234	- plasma substrate level - renal function - cardiac function - pain scores	- infusion-associated reactions - IgG antibody development  - 5 patients experienced stroke or TIA
	Eto, 2005, <sup>15</sup> Japan	open label phase 2 bridging study	none	13	no information provided	26.6 (16-34)	20	- renal function - kidney, urine, and plasma substrate levels	- infusion-associated reactions  - 1 pt hospitalized with malaise and limb pain
Fabry/ Fabrazyme® (agalsidase beta)	Vedder, <sup>16</sup> 2008, Netherlands	dose optimization trial	2 treatment groups: 1) 0.2 mg/kg beta 2) 1.0 mg/kg beta	1) 13  2) 21	no information provided	1) 47 (19-62)  2) 49 (25-73)  3) 48 (27-70)	52	- urinary substrate levels - renal function - cardiac function	- IgG antibody development
	Vedder, <sup>17</sup> 2007, Netherlands	open label randomized, controlled trial	0.2 mg/kg EOW beta	1) 18  2) 16	stratified within each grp by disease severity	1) 42 (19-60)  2) 48 (24-76)	52-104	- cardiac function - renal function - pain scores - urine and plasma substrate levels	in 1 beta pt: - sensorimotor polyneuropathy - oesophagitis



Disease/ERT	Author, Year, Country	Study Design	Comparator	No. of Patients	Disease Stage/Type	Mean Age at 1 <sup>st</sup> Infusion (range) yrs	Length of Follow-up (wks)	Outcomes Measured	Adverse Events
Gaucher/ Cerezyme® (imiglucerase)	Kishnani, <sup>18</sup> 2009, international	open label, randomized, phase IV, dose frequency trial	2 treatment groups: 1) monthly dose biwkly, 2) monthly dose every 4 wks	1) 33 2) 62	at least 2 yrs on imiglucerase	Age at 1 <sup>st</sup> imigluceras e infusion:  1) 35.9 (10- 74)  2) 41.9 (11- 75)	104	- anemia - hepato-megaly - spleno-megaly - skeletal pathology - physical score - mental score	- infusion- associated reactions
	Sims, <sup>19</sup> 2008, United States	open label, single cohort prospective	none	33	symptomatic	median 43.0 (12.0-70.0)	208	-splenomegaly -hepatomegaly -thrombocyto- penia -anemia -bone pain -bone crisis -bone mineral density -medullary infarction -osteoarticular Infarction -lytic lesions -fractures	-infusion- associated reactions
	de Fost, <sup>20</sup> 2007, Netherlands	randomized, controlled trial	2 treatment groups: 1) original dose (weekly or EOW) 2) dose every 4 weeks	1) 5 2) 6	symptomatic	overall 51 (34-75)	52	-splenomegaly -hepatomegaly -thrombocyto- penia -anemia -Chitotriosid-ase -Hexosamini- dase	not reported
Gaucher/ Cerezyme® (imiglucerase)	Grabowski, <sup>21</sup> 1995, United States	randomized, double-blind, parallel trial	2 treatment groups: 1) 60 U/kg EOW Ceredase 2) 60 U/kg EOW Cerezyme	1) 15 2) 15	symptomatic	1)28 (12-52) 2)39 (13-69)	39	-hepatic volume -splenic volume -thrombocyto- penia -anemia	- infusion- associated reactions - IgG antibody development

Disease/ERT	Author, Year, Country	Study Design	Comparator	No. of Patients	Disease Stage/Type	Mean Age at 1 <sup>st</sup> Infusion (range) yrs	Length of Follow-up (wks)	Outcomes Measured	Adverse Events
Gaucher/ Velaglucerase ® (velagluceras e alfa)	Elstein, <sup>22</sup> 2011, Israel (same study population as Zimran 2010)	open label, phase I/II study with extension	none	phase I/II: 11  extension (those who have data up to 208 wks): 8	symptomatic	extension: 39 (18-62)	phase I/II: 39  extension : up to 208	- anemia - thrombo- cytopenia - hepato-megaly - spleno-megaly - skeletal pathology	not reported
	Zimran, <sup>23</sup> 2010, Israel (same study population as Elstein 2010)	open label, phase I/II study with extension	none	phase I/II: 11  extension: 8	symptomatic	phase I/II: 41 (18-69)	phase I/II: 39  extension : up to 208	- anemia - hepato-megaly - spleno-megaly	- infusion- associated reactions - IgG antibody development - gastro-intestinal disorders - musculo- skeletal/connective tissue disorders
Pompe/ Myozyme® (alglucosidase alfa)	van der Ploeg, <sup>24</sup> 2010, international	randomized, double-blind, placebo controlled trial	placebo	Treatment: 60 Placebo: 30	juvenile/adult form	treatment: 45.3 (15.9- 70) placebo: 42.6 (11.6)	78	-6-minute walk test -predicted FVC -quantitative muscle testing, leg and arm -maximum inspiratory and expiratory pressure -SF-36 score	- infusion- associated reactions - IgG antibody development - nervous system disorders - skin and subcutaneous tissue disorders - gastro-intestinal disorders -musculoskeletal and connective tissue disorders -eye disorders -ear and labyrinth disorders -vascular disorders

Disease/ERT	Author, Year, Country	Study Design	Comparator	No. of Patients	Disease Stage/Type	Mean Age at 1 <sup>st</sup> Infusion (range) yrs	Length of Follow-up (wks)	Outcomes Measured	Adverse Events
	Strothotte, <sup>25</sup> 2010, Germany	open label	none	44	juvenile/adult form	48.9 (21-69)	52	-arm function test -Walton Gardner Medwin Scale -timed function tests -6 minute walk test -MRC sum score -PFT measured by FVC -SF-36 -liver enzyme and CK	-moderate allergic reactions -hand edema -acute hearing loss -herpes simplex infection -pollakisuria -prickling in the muscles
	Kishnani, <sup>26</sup> 2009, United States	open label randomized extension to Kishnani, 2006 <sup>27</sup>	1) 20 mg/kg EOW 2) 40 mg/kg EOW	16	infantile form	mean age at end of study: 2.8 (1.7-3.5)	60-150	-survival -ventilator use -cardiac parameters -motor development	- infusion-associated reactions - IgG antibody development
	Nicolino, <sup>28</sup> 2009, United States	open label	historical control group	21	infantile and juvenile form	mean age (in months): 15.7 (3.7-43.1)	up to 168	-survival -ventilator use -cardiac function -muscle GAA activity -motor development -functional independence -physical growth -cognitive function	- infusion-associated reactions -6 patients died, none attributed to treatment

Disease/ERT	Author, Year, Country	Study Design	Comparator	No. of Patients	Disease Stage/Type	Mean Age at 1 <sup>st</sup> Infusion (range) yrs	Length of Follow-up (wks)	Outcomes Measured	Adverse Events
	Levine, <sup>29</sup> 2008, international	open label, phase II trial for children, extension study to Kishnani 2006 <sup>27</sup>	none	8	infantile form	mean age (in months): 6.1 (2.7-14.6)	52	- cardiac function - pulmonary function	not reported
	McDowell, <sup>30</sup> 2008, international	retrospective study on patients who were in open label trial for children	1) patients with arrhythmias 2) patients without arrhythmias	1) 7 2) 31	infantile form	1) median (in months): 7 (6-13)  2) median (in months): 8 (1-43)	78	-cardiac function (QTc, LVMI, EF)	-arrhythmias
	Kishnani, <sup>27</sup> 2006, international	phase II, open label trial for children, same population as Kishnani 2009 <sup>26</sup>	none	8	infantile form	median age (in months) at first treatment: 4.7 (2.7-14.6)	up to 153	-survival -ventilator-free survival -cardiac response -motor response -mental and behavioral development -growth -hearing results -analysis of skeletal muscle	- infusion-associated reactions - IgG antibody development
	Orlikowski, <sup>31</sup> 2011, France	open label trial in adults	none	5	juvenile/adult form	48 (28-62)	52	-respiratory function -muscle strength -SF-36 -glucose tetrasaccharides	- infusion-associated reactions - IgG antibody development -1 patient died, not attributed to treatment

## Appendix C. Summaries of Published Registry Studies

**Appendix Table C1. Published Registry Study of ERT for Fabry Disease**

Author, Year, Country, Sample Size	ERT	Study Design	Inclusion Criteria	Treatment Groups	Mean Age at 1 <sup>st</sup> Infusion (range) yrs	Renal fFnction	IgG Antibody
Warnock, <sup>32, 33</sup> 2011, 2012 international  N=213 Q1: 53 Q2: 54 Q3: 54 Q4: 52	agalsidase beta	Observational, Fabry Registry	Patients in registry on ERT with baseline measure within 3 months before or after first infusion	Quartiles based on slope of estimated glomerular filtration rates (higher slope = more rapid renal disease progression)	Males: Q1: 35.3 (SD: 11.04) Q2: 40.7 (SD: 11.12) Q3: 37.0 (SD:10.91) Q4: 42.0 (SD: 9.22)  Females: Q1: 43.2 (SD: 11.30) Q2: 41.0 (SD: 11.83) Q3: 40.5 (SD:15.12) Q4: 47.4 (SD: 13.09)	•	
Wilcox, <sup>34</sup> 2012  N = 822	agalsidase beta	Observational, Fabry Registry	Patients in registry on ERT	The development of anti-alphaGAL IgG antibodies was evaluated in 571 men and 251 women from the Fabry Registry who were treated with agalsidase beta	NR		•

**Appendix Table C2. Published Registry Studies of ERT for Gaucher Disease**

Author, Year, Country, Sample Size	ERT	Study Design	Inclusion Criteria	Treatment Groups	Mean Age at 1 <sup>st</sup> Infusion (range) yrs	Anemia, Thrombocytopenia	Liver Size	Spleen Size	Skeletal Pathology
Weinreb, <sup>35</sup> 2008, international N=195	imiglucerase	Observational, International Collaborative Gaucher Group (ICGG)	patients in ICGG with 4 yrs followup and data on therapeutic goals	all who met inclusion criteria	27.7 (SD: 21.9)	•	•	•	•
Mistry, <sup>36</sup> 2011, international N=889 1) 156 2) 125 3) 185 4) 423		Observational, International Collaborative Gaucher Group (ICGG)	patients 5-50 yrs of age in ICGG with bone mineral density data	4 groups by age of ERT initiation: 1) 5-11 yrs 2) 12-19 yrs 3) 20-29 yrs 4) 30-50 yrs	not reported	•	•	•	•
Grabowski, <sup>37</sup> 2009, international N=366 1) 122 2) 122 3) 122		Observational, International Collaborative Gaucher Group (ICGG)	patients in ICGG with intact spleens	3 groups by every other wk dosage: 1) 5-28 U/kg 2) 29-47 U/kg 3) 48-74 U/kg	1) 22.1 (19.9) 2) 22.6 (SD: 19.9) 3) 23.1 (SD: 19.8)	•	•	•	
Weinreb, <sup>38</sup> 2002, international N=1028		Observational, International Collaborative Gaucher Group (ICGG)	patients in ICGG on ERT at least 6 mos and with at least one baseline outcome measure	all who met inclusion criteria	30 (SD: 19)	•	•	•	•

**Appendix Table C3. Published Registry Studies of ERT for MPS II**

Author, Year, Country, Sample Size	ERT	Study Design	Inclusion Criteria	Treatment Groups	Mean Age at 1 <sup>st</sup> Infusion (range) yrs	Substrate level	Liver Volume	Sleep Study	Spleen Size	Mental Function	Growth	Range of Motion	Pulmonary Function	Cardiac Symptoms	Discontinuation of Home tx
Muenzer, <sup>39</sup> 2011, international, N=124	idursulfase	observational, Hunter Outcome Survey (HOS)	patients in HOS who started ERT prior to 6 yrs of age	all who met inclusion criteria	3.6 (SD: 1.6)	•	•								
Alcalde-Martin, <sup>40</sup> 2010, international, N=6		observational, Hunter Outcome Survey	Spanish patients in HOS who started ERT prior to 5 yrs of age	all who met inclusion criteria	3.7 (2.8-4.7)	•	•	•	•	•	•	•	•	•	
Burton, <sup>41</sup> 2010, international, N=92		observational, Hunter Outcome Survey	patients in HOS who had received infusions at home or in nonhospital environment	all who met inclusion criteria	at 1 <sup>st</sup> infusion: median: 8.5 (3.4-17.9)  at time of transfer to home tx: median: 9.4 (3.9-21.3)										•

**Appendix Table C4. Published Registry Studies of ERT for MPS VI**

<b>Author, Year, Country, Sample Size</b>	<b>ERT</b>	<b>Study Design</b>	<b>Inclusion Criteria</b>	<b>Treatment Groups</b>	<b>Mean Age at 1<sup>st</sup> Infusion (range) yrs</b>	<b>Substrate Level</b>	<b>Liver Volume</b>	<b>Spleen Size</b>	<b>Cardiac Function</b>	<b>Growth</b>	<b>Range of Motion</b>	<b>Vision</b>
Hendriksz, <sup>42</sup> 2011 International, N = 123	galsulfase	Clinical Surveillance Program (CSP), a voluntary, multinational, observational program	all patients with a diagnosis of MPS VI	all who received galsulfase to treat MPS VI	1-59 years							



## Appendix D. Summaries of Unpublished Studies

**Appendix Table D1. Unpublished Studies From Manufacturer's Scientific Information Packet and Current Registered Clinical Trials**

Disease	Product	Manufacturer	Posters	Abstracts	Data on File With Manufacturer	Ongoing Studies
Fabry's Disease	Fabrazyme® (agalsidase beta)	Genzyme Corporation	Not reported	Not reported	Not reported	<p><b>2010:</b>  <b>NCT01196871:</b> Drug-Drug Interaction Study Between AT1001 and Agalsidase in Subjects With Fabry Disease</p> <p><b>NCT01218659:</b> Study to Compare the Efficacy and Safety of Oral AT1001 and Enzyme Replacement Therapy in Patients With Fabry Disease</p> <p><b>2007:</b>  <b>NCT00455104:</b> Canadian Fabry Disease Initiative (CFDI) Enzyme Replacement Therapy (ERT) Study</p> <p><i>(Status has not been verified in more than two years)</i>  <b>NCT00487630:</b> Evaluation of Efficacy and Safety of Agalsidase Beta in Heterozygous Females for Fabry Disease (HEART)</p> <p><b>2005:</b>  <b>NCT00196742:</b> Fabry Disease Registry</p> <p><b>NCT00230607:</b>  A Study of the Effects of Fabrazyme (Agalsidase Beta) on Mother's Lactation and on the Growth,</p>

						Development and Immunologic Response of Their Infants
Gaucher Disease Type I	Ceredase® (alglucerase)	Genzyme Corporation	Not reported	Not reported	Not reported	<b>2006:</b> <b>NCT00302146:</b> Positron Emission Tomography (PET) Imaging in People With Gaucher Mutations
	Cerezyme® (imiglucerase)	Genzyme Corporation	Not reported	Not reported	Not reported	<b>2011:</b> <b>NCT01344096:</b> Thrombocytopathy in Gaucher Disease Patients
	Velaglucerase® (velaglucerase alfa)	Shire Human Genetic Therapies Inc	<b>2008:</b> Zimram A, Altarescu G, Phillips M, Bhirang K, Mensah R, Elstein D. Velaglucerase alfa: a Phase I/II long-term study of enzyme replacement therapy (ERT) in patients with type 1 Gaucher disease [poster]. Presented at: Annual Meeting of the American Society of Human Genetics; November 11-15, 2008: Philadelphia, PA.	<b>2010:</b> Zimran A, Gonzalez D, Crombez E, et al. Enzyme replacement therapy with velaglucerase alfa improves key clinical parameters in a pediatric subgroup with type 1 Gaucher disease [abstract]. Presented at: World Symposium 2010; the Annual Meeting the Lysosomal Disease Network; February 10-12, 2010c; Miami, FL.  Zimram A, Gonzalez D, Lukina EA, et al. Enzyme replacement therapy with velaglucerase alfa significantly improves clinical parameters in type 1 Gaucher disease: positive results from a randomized, double-blind, global, phase III study [abstract]. Presented at: World Symposium 2010, the Annual Meeting of the Lysosomal Disease Network; February 10-12,	<b>2009:</b> A multicenter, randomized, double-blind, parallel-group, two-dose study of gene-activated human glucocerebrosidase (GA-GCB) enzyme replacement therapy in patients with type 1 Gaucher disease. Clinical Study Report: TKT032, Cambridge, MA; Shire Human Genetic Therapies; Jul 2009  A multicenter, randomized, double-blind, parallel-group study of gene-activated human glucocerebrosidase (GA-GCB) enzyme replacement therapy compared with imiglucerase in patients with type 1 Gaucher disease. Clinical Study	<b>2011:</b> <b>NCT01356537:</b> Home Therapy With VPRIV in Gaucher's Disease

				2010b; Miami, FL.	<p>Report: HGT-GCB-039, Cambridge, MA; Shire Human Genetic Therapies; Aug 2009.</p> <p>A multicenter open-label study of gene-activated human glucocerebrosidase (GA-GCB) enzyme replacement therapy in patients with type 1 Gaucher disease previously treated with imiglucerase.</p> <p>Clinical Study Report: TKT034, Cambridge, MA; Shire Human Genetic Therapies; Aug 2009.</p> <p><b>2006:</b></p> <p>A phase I/II safety study of velaglucerase alfa, a glucocerebrosidase replacement therapy in patients with type 1 Gaucher Disease.</p> <p>Clinical Study Report: TKT025, Final Version 1.0 Cambridge, MA; Shire Human Genetic Therapies; Jun 2006.</p>	
	Zavesca® (miglustat)	Actelion Pharmaceuticals	Not reported	Not reported	Not reported	<p><i>(Status has not been verified in more than two years)</i></p> <p><b>2007:</b></p> <p><b>NCT00418847:</b></p> <p>Pharmacokinetics and Tolerability of Zavesca® (Miglustat) In Patients With Juvenile GM2 Gangliosidosis</p>

Glycogen Storage Disease Type II (Pompe disease)	Myozyme® (alglucosidase alfa)	Genzyme Corporation	Not reported	Not reported	Not reported	<p><b>2011:</b> <b>NCT01288027:</b> Exploratory Muscle Biopsy Assessment Study in Patients With Late-Onset Pompe Disease Treated With Alglucosidase Alfa</p> <p><b>NCT01410890 :</b> Pharmacokinetics of Alglucosidase Alfa in Patients Aged 8-18 Years of Age (PAPAYA)</p> <p><b>2008:</b> <b>NCT00701701:</b> Immune Tolerance Induction Study</p> <p><b>2007:</b> <b>NCT00486889:</b> Growth and Development Study of Myozyme (Alglucosidase Alfa).</p> <p><b>NCT00566878:</b> Pompe Lactation Sub-Registry</p> <p><b>NCT00567073:</b> Pompe Pregnancy Sub-Registry</p>
MPS I (Hurler disease)	Aldurazyme® (laronidase)	Genzyme Corporation	Not reported	Not reported	Not reported	<p><b>2009:</b> <b>NCT00852358:</b> A Study of Intrathecal Enzyme Therapy for Cognitive Decline in MPS I</p> <p><b>2008:</b> <b>NCT00638547:</b> Intrathecal Enzyme Replacement for Hurler Syndrome</p> <p><b>NCT00741338:</b> Immune Tolerance Study With Aldurazyme®</p> <p><b>2007:</b></p>

						<p><b>NCT00418821:</b> A Study of the Effect of Aldurazyme® (Laronidase) Treatment on Lactation in Female Patients With Mucopolysaccharidosis I (MPS I) and Their Breastfed Infants</p> <p><b>2005:</b>  <b>NCT00144768:</b> A Study Investigating the Relationship Between the Development of Laronidase Antibody and Urinary GAG (Glycosaminoglycan) Levels in Aldurazyme® Treated Patients</p> <p><b>NCT00144794:</b>  Mucopolysaccharidosis I (MPS I) Registry</p>
MPS II (Hunter disease)	Elaprase® (idursulfase)	Shire Human Genetic Therapies Inc	Not reported	Not reported	Not reported	<p><b>2011:</b>  <b>NCT01330277:</b> Biomarker for Hunter Disease (BioHunt)</p> <p><b>NCT01506141:</b> An Extension Study of HGT-HIT-045 Evaluating Long-Term Safety and Clinical Outcomes of Idursulfase (Intrathecal) in Conjunction With Elaprase® in Pediatric Patients With Hunter Syndrome and Cognitive Impairment</p> <p><b>2009:</b>  <b>NCT00920647:</b> A Safety and Dose Ranging Study of Idursulfase (Intrathecal) Administration Via an Intrathecal Drug Delivery Device in Pediatric Patients</p>

					<p>With Hunter Syndrome Who Have Central Nervous System Involvement and Are Receiving Treatment With Elaprase®</p> <p><b>NCT00937794:</b> A Screening Study to Identify Pediatric Patients With Hunter Syndrome Who Demonstrate Evidence of Central Nervous System (CNS) Involvement and Who Are Currently Receiving Treatment With Elaprase®</p> <p><b>NCT01449240:</b> Collection and Study of Cerebrospinal Fluid in Patients With Hunter Syndrome</p>
MPS VI (Maroteaux-Lamy syndrome)	Naglazyme® (galsulfase)	BioMarin Pharmaceutical Inc	<p><b>2011:</b> Kim KH, Burton BK. Treatment with galsulfase results in improved endurance in a MPS VI patient with history of bone marrow transplantation in early childhood. 61st Annual Meeting of the American Society of Human Genetics (ASHG). Montreal, Canada. 11-15 October 2011. Poster.</p> <p>M. L. Raff. Galsulfase enzyme replacement therapy improves urine GAG excretion and clinical course in Maroteaux-Lamy syndrome (MPS type VI) after donor-engrafted bone marrow transplant. Genomics Institute,</p>	<p><b>2010:</b> Braunlin E, Howard R, Christoph K, et al. Long term cardiac effects of Naglazyme(galsulfase) therapy (NRx). 11th International Symposium on Mucopolysaccharide and Related Diseases. Adelaide, Australia: 23-27 June 2010. Abstract.</p> <p>Decker C, Devereaux D, Kim S, et al. Analysis of the clinical impact of immune response to enzyme replacement therapy with naglazyme. 11th International Symposium on Mucopolysaccharide and Related Diseases. Adelaide, Australia: 23-27 June 2010. Abstract.</p>	<p><b>2005:</b> <b>NCT00214773:</b> Mucopolysaccharidosis (MPS) VI Clinical Surveillance Program (CSP)</p>

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