Study Title:
A Multicenter, Safety and Efficacy Study of Taliglucerase Alfa in Subjects With Type 3 Gaucher Disease

NCT Number:
NCT04002830

Protocol Date:
10 December 2021

CLINICAL STUDY PROTOCOL

Protocol Title: A Multicenter, Safety and Efficacy Study of Taliglucerase Alfa in Subjects with Type 3 Gaucher Disease

Study Product:	Taliglucerase alfa (plant cell expressed recombinant human glucocerebrosidase)
Indication:	Type 3 Gaucher Disease
Phase:	3B
Version and Date:	Version: 5.0 Date: December 10 2021
Name and Affiliation of Principal Investigators	A list of the Principal Investigators is maintained in the trial master file
Name and Address of Sponsor	Prof. Ari Zimran, MD Shaare Zedek Medical Center Jerusalem Israel
Good Clinical Compliance (GCP) Statement	This study will be performed in compliance with GCP, including the archiving of essential documents.

1. SYNOPSIS

TITLE: A Multicenter, Safety and Efficacy Study of Taliglucerase Alfa in Subjects with Type 3 Gaucher Disease

INVESTIGATIONAL PRODUCT: Taliglucerase alfa (plant cell expressed recombinant human glucocerebrosidase)

INDICATION: Gaucher Disease (GD)

PHASE OF DEVELOPMENT: 3B

INVESTIGATIONAL SITES/LOCATIONS: Multicenter, (Israel, India, and Turkey)

INTERNAL PFIZER STUDY NUMBER: WI224302

OBJECTIVES: To assess the safety and efficacy of taliglucerase alfa in untreated subjects (any age) with symptoms and clinical manifestations of Type 3 GD.

STUDY DESIGN: This is a multicenter study to assess the safety and efficacy of taliglucerase alfa (60 units/kg) in previously untreated subjects of any age with Type 3 GD. Subjects will receive an infusion of taliglucerase alfa every 2 weeks for 12 months. Subjects who tolerate the infusions well, and who are treated in centers where home therapy is the SOC will be allowed to switch from site to home treatment at the discretion of the PI but after no less than 3 uneventful infusions at the site.

NUMBER OF SUBJECTS (PLANNED): up to 15

DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION:

Key inclusion criteria

Eligible subjects must fulfill the following inclusion criteria:

1. Male or female of any age; however, if female:
   - must be using contraception if of childbearing potential or must be surgically sterile
   - must not be lactating
2. Diagnosis of Type 3 GD by enzyme and sequence analysis; and confirmed by the Medical Monitor.
3. Splenomegaly at least 5 x multiples of normal (MN).
4. Treatment-naïve.

Key exclusion criteria

Eligible subjects may not have any of the following exclusion criteria:

1. Type 2 GD.
2. Presence of myoclonic seizures.
3. At least one allele of:
   - N370S (N409S in recent nomenclature)
   - R496H (R535H in recent nomenclature)
4. Presence of calcification in heart valves or arteries in echocardiography.
5. Presence of untreated iron, folic acid, vitamin B_{12} deficiency and/or hypothyroidism. (Resolved anemia is not an exclusion criterion.)
6. Presence of human immunodeficiency virus (HIV), hepatitis B surface antigen (HBsAg), and/or hepatitis C infections.
7. Splenectomy and bone marrow transplantation.
8. Presence of any medical, emotional, behavioural, or psychological condition that in the judgment of the Investigator would interfere with the subject's compliance with the requirements of the study.
9. Any other disorder that may interfere with the results of the efficacy endpoints.
10. Pregnancy or breastfeeding.
11. Currently taking another investigational drug for any condition or any therapeutic drug for Gaucher disease.
12. The subject and/or subject's parent(s) or legal guardian(s) are unable to understand the nature, scope, and possible consequences of the study.
13. Medical history of any food/drugs allergy.

TEST PRODUCT(S), DOSE AND MODE OF ADMINISTRATION: Taliglucerase alfa, 60 units/kg, intravenously, every 2 weeks

DURATION OF TREATMENT: 12 months

DISCONTINUATION FROM THE STUDY:

Reasons for permanent discontinuation include the following:

- The subject experiences two or more Grade 3 toxicities or one or more Grade 4 toxicity considered by the Investigator associated with taliglucerase alfa treatment
- A subject who experiences progressive hypersensitivity or severe hypersensitivity will be treated appropriately and may be withdrawn from the study, at the discretion of the treating Investigator and/or Medical Monitor

- The subject, or subject's parent or guardian, requests to discontinue treatment
- Investigator feels that it is not in the best interest of the subject to continue treatment and/or the Investigator believes that the subject can no longer be compliant with the requirements of the study
- Deteriorating clinical condition, for which the Investigator decides additional treatments would be needed

EFFICACY VARIABLES:

Primary efficacy variable is:

- Percent change in spleen volume (expressed in MN) from baseline to Month 12

Secondary efficacy variables are:

- Percent change in liver volume (expressed in MN) from baseline to Month 12
- Percent change in hemoglobin from baseline to Months 3, 6, 9, and 12
- Percent change in platelet count from baseline to Months 3, 6, 9, and 12
- Percent change in Lyso-Gb1 from baseline to Months 3, 6, 9, and 12
- Percent change in Chitotriosidase from baseline to Months 3, 6, 9, and 12

Other efficacy variables are:

- Change in height SDS (standard deviation score) from baseline to Months 3, 6, 9, and 12
- Change in weight SDS from baseline to Months 3, 6, 9, and 12
- Change in Tanner Stage from baseline to Month 12
- Change in bone age (by X-ray of left hand and wrist) from baseline to Month 12
- Change in bone mineral density (DEXA) from baseline to Month 12

Exploratory endpoints:

- Change in mSST from screening, Month 6 and 12.

SAFETY ENDPOINTS:

- Adverse events
- Clinical laboratory tests
- Vital signs
- Physical examinations

IMMUNOGENICITY:

- Anti-taliglucerase alfa antibodies

STATISTICAL ANALYSIS:

A sample size of 9 subjects is chosen to evaluate the efficacy and safety of taliglucerase alfa in subjects with this orphan disease in which recruitment in clinical trials is difficult. This sample size of 9 evaluable subjects will provide a power of 80.9% to detect a responder rate of 0.91 for reduction in spleen volume from baseline to Month 12, with an actual significant level of 0.04. Up to 15 subjects will be enrolled in order to yield at least 9 subject who will complete the study.

The primary endpoint is the percent change in spleen volume (expressed in MN) from baseline to Month 12. The Wilcoxon signed rank test at 2-sided significance level of 0.05 will be performed to analyse this primary efficacy endpoint. The Wilcox signed rank test will be applied for the secondary efficacy endpoints: percent change from baseline to Month 12 in liver volume MN, hemoglobin, platelet count, chitotriosidase and Lyso-Gb1 separately.

The other efficacy endpoints will be primarily summarized using descriptive statistics by visit. For example, change in growth and development assessment from baseline to each visit will be summarized using descriptive statistics by visit. Descriptive statistics will also be reported for change in Tanner Stage, bone assessment (bone age, bone mineral density and Z-score) and modified severity score (mSST) from screening to Month 12.

The immunogenicity status will be tabulated by frequency and percentage. Safety data will be descriptively summarized.

DOCUMENT APPROVAL

This study will be conducted in compliance with the protocol, Good Clinical Practice (GCP) and applicable regulatory requirements.

PRINCIPAL INVESTIGATOR

Signature: _____ **Date**: _____

Name (print): _Ari Zimran_____

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2. ABBREVIATIONS

Abbreviation or Specialist Term	Definition/Description
AE(s)	Adverse Event(s)
β-GCD	β-Glucocerebrosidase
CCL18	Pulmonary and activation-regulated chemokine
CDC	Centers for Disease Control and Prevention
CRF	Case Report Form
CRO	Contract Research Organization
DEXA	Dual-emission X-ray Absorptiometry
EC	Ethics Committee
ERT	Enzyme Replacement Therapy
GBA	Glucoside Beta Acid
GCP	Good Clinical Practice
GD	Gaucher Disease
HBsAg	Hepatitis B Surface Antigen
HCG	Human Chorionic Gonadotropin
HCV	Hepatitis C Virus
hGCD	Human Glucocerebrosidase
HIV	Human Immunodeficiency Virus
ICH	International Conference on Harmonization
IR	Infusion Rate
IRB	Institutional Review Board
IV	Intravenous
Lyso-Gb1	Lyso-glucosylsphingosine
MedDRA	Medical Dictionary for Regulatory Activities
MN	Multiples of Normal
MRI	Magnetic Resonance Imaging
mSST	Modified severity scoring tool
PK	Pharmacokinetic
SAE(s)	Serious Adverse Event(s)

Abbreviation or Specialist Term	Definition/Description
SAP	Statistical Analysis Plan
SBP	Systolic Blood Pressure
Taliglucerase alfa	Plant Cell Expressed Recombinant Human Glucocerebrosidase
TEAE	Treatment-emergent Adverse Event
T4	Free Thyroxine
TSH	Thyroid Stimulating Hormone
WHO	World Health Organization

3. ETHICAL CONDUCT OF THE STUDY AND REGULATORY REQUIREMENTS

3.1 Institutional Review Board (IRB)

An Institutional Review Board (IRB) or Ethics Committee (EC) will review the study protocol and any amendments. The IRB or EC will also review the informed consent form, their updates (if any), and any written materials given to the subjects. A list of all IRBs and ECs and contact information will be included in the study report.

3.2 Ethical Conduct of the Study

This study will be conducted in accordance with the ethical principles that have their origins in the Declaration of Helsinki, in compliance with the approved protocol, GCP and applicable regulatory requirements.

3.3 Subject Information and Consent

The Investigator will obtain a freely given written consent or assent from each subject or parent or guardian after an appropriate explanation of the aims, methods, anticipated benefits, potential hazards, and any other aspects of the study that are relevant to the subject's decision to participate. The consent form must be signed and dated by the subject or parent or guardian before the subject is exposed to any protocol-specific procedure.

The Investigator will explain that the subjects are completely free to refuse to enter the study or to withdraw from it at any time, without any consequences for their further care and without the need to justify.

The subject or parent or guardian will receive a copy of the subject information and the signed informed consent.

The subject or parent or guardian will be informed if information becomes available that may be relevant to his/her willingness to continue participation in the study.

Each subject or parent or guardian will be informed that a monitor or a health authority inspector, in accordance with applicable regulatory requirements, may review the portions of their source records and source data related to the study. Data protection and confidentiality will be handled in compliance with local laws.

4. INTRODUCTION

4.1 Gaucher Disease (GD)

Gaucher disease is a rare genetic disorder of lipid metabolism and is the most common inherited lysosomal storage disorder, thought to affect around 10,000 people globally [1,2]. The disease affects persons of all ages and both sexes and is the result of mutations that affect the GBA gene that encodes β-glucocerebrosidase (β-GCD) [3, 4]. The defect results in a deficiency in β-GCD, which consequently leads to the build-up of glucocerebroside in macrophages, mostly in the spleen, liver, lungs, and bone marrow [5].

Gaucher disease is classified into 3 major phenotypic subcategories based on the absence (Type 1) or presence and severity (Types 2 and 3) of primary central nervous system involvement [6]. Gaucher disease Type 3, the population under study in this current protocol, affects approximately 5% of documented GD cases [6]. Type 3 GD is associated with progressive neurodegenerative disease, with symptom onset usually between infancy and adolescence [7]. Manifestations of Type 3 GD vary among patients, ranging from visceral and bone disease, cytopenia, hearing impairment, supranuclear gaze palsy, developmental delay, and cardiac calcification to myoclonic encephalopathy with seizures and eventual death [8, 9]. Overall life expectancy is usually dramatically shortened, although there are some documented patients now alive in their sixth decade [10].

4.2 Taliglucerase Alfa

Taliglucerase alfa, a hydrolytic lysosomal glucocerebroside-specific enzyme for intravenous infusion, is a recombinant active form of the lysosomal enzyme, β-GCD. In contrast to other β-GCD products for GD therapy, which are produced in mammalian cell culture [11, 12] taliglucerase alfa is produced using transgenic [13] carrot plant root cells [14] grown in suspension culture with a modified gene sequence encoding human β-GCD [13]. Taliglucerase alfa is a glycosylated protein with mannose-terminated oligosaccharide chains that are specifically recognized by endocytic carbohydrate receptors on macrophages [14], enabling uptake into Gaucher cells [13].

Taliglucerase alfa is currently an approved therapy in the United States and many other countries for adults and children with a confirmed diagnosis of Type 1 GD [14], and is also approved for use in Type 3 GD in a small number of countries.

4.3 Overview of Clinical Data

4.3.1 Study PB-06-001 in Adult GD Patients

Study PB-06-001 was a Phase 3, multicenter (11 centers worldwide), double-blind trial in which 32 adult patients with Type 1 GD randomly received either 30 units/kg or 60 units/kg of taliglucerase alfa intravenously every 2 weeks for 38 weeks (20 infusions). At the end of the study, eligible patients were offered enrollment in an open-label extension study (PB-06-003).

The primary efficacy analysis demonstrated that taliglucerase alfa treatment significantly reduced spleen volume from screening to Month 9 (taliglucerase alfa 30 units/kg, 26.91%, p<0.0001; taliglucerase alfa 60 units/kg, 38.01%, p<0.0001) and Month 6 (taliglucerase alfa 30 units/kg, 22.21%, p<0.0001; taliglucerase alfa 60 units/kg, 29.94%, p<0.0001).

The secondary efficacy analysis demonstrated that taliglucerase alfa treatment significantly increased hemoglobin level from baseline to Month 9 (taliglucerase alfa 30 units/kg, 1.6 g/dL, p<0.0001; taliglucerase alfa 60 units/kg, 2.2 g/dL, p<0.0001). A significant reduction in liver volume from screening was also observed in both taliglucerase alfa dose groups at the end of the study (taliglucerase alfa 30 units/kg, 10.48%, p=0.0041; taliglucerase alfa 60 units/kg, 11.11%, p<0.0001). In addition, a significant increase in platelet count from baseline was observed in the 60 units/kg dose group at Month 9 (41,494/mm^3, p=0.0031) and an increase in platelet count at Month 9 was also observed for the taliglucerase alfa 30 units/kg dose group (11,427/mm^3, p=0.0460). Improvements were also observed at the Month 6 visit.

Overall, 23 patients experienced 137 adverse events (AEs) (12 in the 30 units/kg had 65 AEs and 11 in the 60 units/kg had 72 AEs). Eight patients (3 in the 30 units/kg group and 5 in the 60 units/kg group) experienced 28 events that were considered by the respective investigators to be treatment-related. Of the treatment-related events, none were seen in more than one patient in each group. All AEs were mild or moderate in intensity and the majority of the events resolved by the end of the study. No deaths or serious adverse events (SAEs) occurred during the study. Two patients (1 per dose group) discontinued from the study due to a hypersensitivity reaction.

Pharmacokinetic (PK) analyses showed no tendency for accumulation or change in PK parameters with repeated doses of taliglucerase alfa.

4.3.2 Study PB-06-002 in Adult and Pediatric GD Patients Previously Treated with Imiglucerase

Study PB-06-002 was a Phase 3, multicenter (11 centers worldwide), open-label study that assessed the safety and efficacy of taliglucerase alfa in adult (n=25) and pediatric (n=5) patients with Type 1 GD who were switched from treatment with Cerezyme® (imiglucerase) (note: 1 pediatric patient was subsequently diagnosed with Type 3 GD). The initial dose of taliglucerase alfa was equivalent to the patient's imiglucerase dose, with subsequent dosage increases allowed up to a maximum of 60 units/kg. Taliglucerase alfa was administered intravenously every 2 weeks for 9 months. At the end of the study, eligible patients were offered enrollment in open-label extension studies (PB-06-003 for adults, PB-06-006 for pediatric patients).

At the end of 9 months of treatment, all patients main disease parameters remained clinically stable. Mean platelet counts and hemoglobin values were within expected parameters in both adult and pediatric patients, and there was also a mean reduction in spleen and liver volumes.

There was no evidence of increased safety concerns in patients after switching from imiglucerase to taliglucerase alfa.

Comparison between Type 1 GD and Type 3 GD Pediatric Patients

Pediatric patients showed improvement in the systemic symptoms of Gaucher disease, regardless of disease variant. The absolute mean reductions observed in spleen volume and liver volume in the single pediatric patient with Type 3 GD were qualitatively similar, yet quantitatively greater

than the change observed in the 4 pediatric patients with Type 1 GD: spleen volume -1.9 MN (-9.5%) *vs*. -0.5 (-23.7%) MN; liver volume 0.1 MN (-6.3%) *vs*. 0 MN (-3.5%).

4.3.3 Study PB-06-005 in Pediatric Patients with Type 1 GD or Type 3 GD

Study PB-06-005 was a multicenter (11 centers in Israel, Paraguay, and South Africa), double-blind trial in which 11 untreated pediatric patients (2 to <18 years of age) with a diagnosis of Type 1 or Type 3 GD (excluding acute neuropathic GD) were randomized to receive 30 units/kg (n=6) or 60 units/kg (n=5) of taliglucerase alfa intravenously every 2 weeks for 12 months. At the end of the study (Month 12) both treatment doses demonstrated the therapeutic efficacy of taliglucerase alfa in this pediatric population. Patients had an increase from baseline in median hemoglobin level, decrease in chitotriosidase and CCL18 levels, mean reduction in spleen and liver volumes, and mean increase in platelet count, height and weight, and bone age. Additionally, the Child Health Questionnaire scores showed that the quality of life of both the children and their parents/guardians improved after 12 months of taliglucerase alfa treatment. The efficacy results and the observed safety profile in these pediatric patients are consistent with previous data of taliglucerase alfa from clinical trials conducted in adult patients. No new safety signals were observed in this study.

Comparison between Type 1 GD and Type 3 GD in Pediatric Patients

The 9 patients with Type 1 GD receiving either 30 units/kg or 60 units/kg of taliglucerase alfa had improvements in hemoglobin concentration of +2.1 g/dL (20.8%) and 1.6 g/dL (15.8%), respectively, from baseline to Month 12, whereas the 2 patients with Type 3 GD had no meaningful change in hemoglobin. The changes from baseline to Month 12 in liver volume, spleen volume, and platelet count in the patients with Type 3 GD were qualitatively similar, but quantitatively less than the changes observed in patients with Type 1 GD.

4.3.4 Long-term Studies in Adult GD Patients

4.3.4.1 Extension Study PB-06-003

This study extended treatment for adult patients who were treatment-naïve (n=26) or previously treated with imiglucerase (n=18) and had completed studies PB-06-001 PB-06-002, respectively. Thirty-seven patients completed this long-term extension study.

Long-term data from treatment-naïve adult patients with Type 1 GD who were treated for a total of 36 months (9 months in PB-06-001 and 27 months in extension study PB-06-003) support a conclusion of continued improvement with both doses of taliglucerase alfa. After 36 months, reductions in spleen volume of 50.1% and 64.6% were observed in the 30 units/kg and 60 units/kg dose groups, respectively.

Patients from study PB-06-002 who were switched from imiglucerase to taliglucerase alfa maintained stability across efficacy measures, with a reduction in spleen volume of 19.8% after 36 months of treatment.

Overall, long-term treatment with taliglucerase alfa was well tolerated and there was no evidence of increased safety concerns in patients switched from imiglucerase to taliglucerase alfa.

4.3.4.2 Extension Study PB-06-007

This study extended treatment for 17 treatment-naïve adult patients (8 at 30 units/kg and 9 at 60 units/kg) who completed studies PB-06-001 and PB-06-003. Patients demonstrated tolerability and efficacy as determined by organ volume size, hematologic parameters, and biomarker measurements. Taligulcerase alfa was well tolerated during administration for up to 60 months.

4.3.5 Long-Term Extension Study in Pediatric GD Patients

Study PB-06-006 extended treatment for pediatric patients who were previously treated with imiglucerase (n=10) or were treatment-naïve (n=5) and had completed studies PB-06-002 or PB-06-005, respectively. Eleven patients completed this long-term extension study.

After a total of 36 months of treatment with taliglucerase alfa, treatment-naïve patients showed improvements from baseline in organ volumes, hematologic parameters, and biomarkers. Patients receiving 60 units/kg of taliglucerase alfa showed greater improvement in most of these parameters compared with patients receiving 30 units/kg. In patients previously treated with imiglucerase, disease parameters (spleen volume, liver volume, platelet counts, and hemoglobin levels) remained stable through 33 months of treatment.

Overall, taliglucerase alfa was well tolerated and there was no evidence of increased safety concerns in pediatric patients with up to 36 months of treatment.

Type 3 GD Pediatric Patients

Two patients with Type 3 GD continued into the PB-06-006 extension study: 1 treatment-naïve patient and the 1 previously treated with imiglucerase.

At 36 months, the treatment-naïve patient showed improvement in hemoglobin (4.9%) and platelet count (5.5%), both less than changes observed in patients with Type 1 GD. For the Type 3 GD patient previously treated with imiglucerase, changes in spleen volume and platelet count were greater than changes observed in patients with Type 1 GD, whereas changes in liver volume and hemoglobin were less in the Type 3 GD patient than in Type 1 GD patients.

4.4 Rationale for Study

Patients with Type 3 GD exhibit both visceral and neurologic manifestations. In addition to the progressive neurologic involvement, somatic disease manifestations, especially splenomegaly and resulting cytopenia, contribute to significant mortality and morbidity [15]. The effects of enzyme replacement therapy (ERT) on patients with Type 1 GD have been clearly documented and have a beneficial effect on visceral and hematologic disease parameters [16]. It is known that recombinant enzyme does not pass the blood-brain barrier and has no effect on neurologic involvement [17]. Probably due to the rarity of Type 3 GD, information on the somatic effects of ERT is largely limited to case reports or single-center series [18]. There are also few reviews of cohorts but the clinical subtype, age, genotype, ERT dosage, accompanying therapies, and treatment response vary widely among patients in these cohorts [19]. This prospective study aims to objectively evaluate the hematologic and visceral effects of ERT with taliglucerase alfa on a rather clinically and genetically homogenous group of treatment-naïve patients with Type 3 GD. For the purposes of this study, subjects receiving no Gaucher-specific medications for at

least 12 months will be considered “untreated”. The results of this study are expected to provide a more objective view of the degree of response of this patient type, and potentially create new areas of research.

5. STUDY OBJECTIVES

The efficacy objectives of this study are to assess the efficacy of taliglucerase alfa in subjects with Type 3 GD, as measured by percent change from baseline in spleen and liver volume evaluated by magnetic resonance imaging (MRI), hemoglobin, platelet count, and Lyso-Glucosylsphingosine (Lyso-Gb1); bone mineral density evaluated by dual-emission X-ray absorptiometry (DEXA) in all children 9 years of age and above, and evaluation of modified severity.

For children, change from baseline in growth and development (height, weight, sexual development by Tanner classification, and bone age by X-ray of left hand and wrist) will be measured,

The safety of taliglucerase alfa will be assessed by adverse events, clinical laboratory tests, vital signs, and physical examinations. Anti-taliglucerase alfa antibodies will also be assessed.

6. INVESTIGATIONAL PLAN

6.1 Overall Study Design and Plan – Description

This is a multicenter study to assess the efficacy and safety of taliglucerase alfa (60 units/kg) in previously untreated subjects of any age with Type 3 GD. For the purposes of this study, subjects receiving no Gaucher-specific medications for at least 12 months will be considered “untreated”. Subjects will receive an IV infusion of taliglucerase alfa every 2 weeks for 12 months. Subjects who are treated in centers where home therapy is the SOC will be allowed to switch from site to home treatment at the discretion of the PI but after no less than 3 uneventful infusions at the site. At the end of the 12-month treatment period, eligible subjects will be offered enrollment in an open-label extension study if taliglucerase alfa is not commercially available.

6.2 Discussion of Study Design and Choice of Control Group(s)

Type 3 GD is a very rare genetic orphan disease. This study will not have a placebo control group because it would be unethical to deny patients the possibility to improve their symptomology with an ERT that has been proved efficacious and safe, not only for Type 1 GD in many countries but also for Type 3 GD in a small number of countries. Thus, all subjects will receive the investigational product in this study.

The parameters chosen as endpoints for this study are the most relevant parameters to GD and allow a significant and relevant evaluation of improvement as a result of treatment for 12 months. Improvement in the clinical manifestations of the disease leads to the achievement of the therapeutic goals of GD treatment in the medical community, which are improved fatigue and decreased risk for morbidities.

6.3 Selection of Study Population

6.3.1 Inclusion Criteria

For inclusion into the trial, subjects are required to fulfill all of the following criteria:

1. Male or female of any age; however, if female:
   - must be using contraception if of childbearing potential or must be surgically sterile
   - must not be lactating
2. Diagnosis of Type 3 GD by enzyme and sequence analysis; and confirmed by the Medical Monitor.
3. Splenomegaly at least 5 x multiples of normal (MN).
4. Treatment-naïve.

6.3.2 Exclusion Criteria

Any of the following is regarded as a criterion for exclusion from the trial:

1. Type 2 GD.
2. Presence of myoclonic seizures.
3. At least one allele of:
   - N370S (N409S in recent nomenclature)
   - R496H (R535H in recent nomenclature)
4. Presence of calcification in heart valves or arteries in echocardiography.
5. Presence of untreated iron, folic acid, vitamin B_{12} deficiency and/or hypothyroidism. (Resolved anemia is not an exclusion criterion.)
6. Presence of human immunodeficiency virus (HIV), hepatitis B surface antigen (HBsAg), and/or hepatitis C virus (HCV) infections.
7. Splenectomy and bone marrow transplantation.
8. Presence of any medical, emotional, behavioural, or psychological condition that in the judgment of the Investigator would interfere with the subject's compliance with the requirements of the study.
9. Any other disorder that may interfere with the results of the efficacy endpoints.
10. Pregnancy or breastfeeding.
11. Currently taking another investigational drug for any condition or any therapeutic drug for Gaucher disease.
12. The subject and/or subject's parent(s) or legal guardian(s) are unable to understand the nature, scope, and possible consequences of the study.
13. Any medical history of food/drugs allergy.

6.3.3 Removal of Subjects from Study

Reasons for permanent discontinuation include the following:

1. The subject experiences two or more Grade 3 toxicities or one or more Grade 4 toxicity considered by the Investigator associated with taliglucerase alfa treatment (see Section 8.2.1: Adverse Events; and Appendix 14.5: WHO Common Toxicity Criteria)

2. The subject experiences progressive hypersensitivity or severe hypersensitivity will be treated appropriately and may be withdrawn from the study, at the discretion of the treating Investigator and/or Medical Monitor (see Appendix 14.2: Infusion Rate Algorithm; and Appendix 14.3: Taliglucerase Alfa Hypersensitivity Evaluation and Treatment Algorithm)

3. The subject, or subject's parent or guardian, requests to discontinue treatment

4. Investigator feels that it is not in the best interest of the subject to continue treatment and/or the Investigator believes that the subject can no longer be compliant with the requirements of the study

5. Deteriorating clinical condition, which the Investigator decides additional treatments would be needed

For any discontinuation, the Investigator will obtain all required details and document the date and the main reason for the premature discontinuation. If the reason for discontinuation is an adverse event, the specific event or the main laboratory abnormality will be recorded in the case report form (CRF). The Investigator will make thorough efforts to document the outcome. The Investigator will attempt to continue to follow the subject for the full duration of the study or at least for 30 days following discontinuation. If circumstances prevent the subject from completing all visits, every attempt will be made to complete all procedures listed in Section 9.2.11 for Visit 27.

6.3.4 Replacement Policy

Withdrawn subjects will not be replaced.

7. STUDY PRODUCT

7.1 Study Medication Supply

Reconstitution of each taliglucerase alfa vial (212 units) with sterile water for injection (5.1 mL) yields a final volume of 5.3 mL human taliglucerase alfa (40 U/mL), which provides a withdrawal volume of 5.0 mL (200 units). The solution must be mixed gently until clear.

7.2 Description of Study Product

Human taliglucerase alfa is a purified recombinant, plant cell-expressed glucocerebrosidase, which is described in detail in the taliglucerase alfa Prescribing Information (Appendix 14.1).

Each 200 unit vial contains the following lyophilized ingredients:

- 212 units of taliglucerase alfa

- 195 mg mannitol
- 35 mg sodium citrate
- 0.53 mg polysorbate 80, NF

7.3 Description of Comparator Product

Not applicable.

7.4 Study Drug Administration

Taliglucerase alfa will be administered over 1 to 2 hours (the total volume to be prepared and infused is 100-120 mL + 20 mL saline flushing of the system) for initial infusions in all subjects. Tolerability will be determined by vital signs taken 30 minutes after starting the infusion and symptoms during the infusion and for one hour after the infusion in the clinic and also by telephone contact the day after the first infusion. If this initial rate of infusion is well tolerated, the infusion rate may be increased up to 2.0 mL/min (120 mL/hr) to deliver the volume of reconstituted enzyme plus 20 mL saline flush over 1 to 2 hours for all subsequent dose administrations (see Appendix 14.2: Infusion Rate Algorithm).

7.5 Packaging and Labeling

Lyophilized drug powder is stored in 13.5 mL borosilicate glass (Type 1) bottles (Forma Vitrum AG, Hungary). Lyophilization stoppers (Helvoet Pharma, Belgium) composed of two-leg brombutyl rubber are sealed with aluminum Snap Caps and polypropylene discs (Helvoet Pharma, Belgium).

7.6 Conditions for Storage and Use

The study product is to be stored at 2°C to 8°C (36°F to 46°F) before reconstitution.

7.7 Method of Assigning Subjects to Treatment Groups

Not applicable.

7.8 Dispensing, Compliance, and Accountability

The Sponsor will provide drug accountability forms to assist the pharmacist in maintaining current and accurate inventory records covering receipt, dispensing, and the return of investigational drug supplies. When a shipment is received, the pharmacist will verify the quantities received and return the acknowledgment to the study monitor or designee. The pharmacist investigational drug accountability record includes the identification of the person to whom the drug is dispensed, the quantity and the date of dispensing and any returned or unused drug. This record is in addition to any drug accountability information recorded on the CRF. These records will be readily available for inspection by a monitor or Sponsor audits and are open to regulatory authority inspection at any time.

7.9 Prior and Concomitant Therapy

Medications having the potential to interfere with the evaluation of efficacy are excluded throughout the trial.

The following medications are strictly prohibited during the study:

- Zavesca® (miglustat)
- Ceredase® (algucerase)
- Cerezyme® (imiglucerase)
- Vpriv® (velaglucerase alfa)
- Cerdelga® (eliglustat)

The following medications are allowed and expected during the study:

- Treatments for hypersensitivity, anaphylaxis, or anaphylactoid reactions, e.g., epinephrine, norepinephrine, glucagon, albuterol
- Treatments for anemia, e.g., iron, folic acid, vitamin B_{12}
- Treatments for bone disease, e.g., bisphosphonates
- Analgesics, e.g., nonsteroidal anti-inflammatory drugs (note: aspirin may be contraindicated due to its effects on platelets and risk for bleeding)

8. EFFICACY AND SAFETY ASSESSMENTS

8.1 Efficacy Variables

Spleen and liver volumes will be measured by MRI using a standardized protocol (see Appendix 14.4). Hemoglobin and platelet counts will be measured locally by standard laboratory procedures, and biomarkers will be analyzed at a central laboratory

Primary efficacy variable is:

- Percent change in spleen volume (expressed in MN) from baseline to Month 12

Secondary efficacy variables are:

- Percent change in liver volume (expressed in MN) from baseline to Month 12
- Percent change in hemoglobin from baseline to Months 3, 6, 9, and 12
- Percent change in platelet count from baseline to Months 3, 6, 9, and 12
- Percent change in Lyso-Gb1 from baseline to Months 3, 6, 9, and 12
- Percent change in Chitotriosidase from baseline to Months 3, 6, 9, and 12

Other efficacy variables are:

- Change in height SDS from baseline to Months 3, 6, 9, and 12
- Change in weight SDS from baseline to Months 3, 6, 9, and 12
- Change in Tanner Stage from baseline to Month 12
- Change in bone age (by X-ray of left hand and wrist) from baseline to Month 12

- Change in bone mineral density (DEXA) from baseline to Month 12
- Change in mSST from screening Month 6 and 12

8.2 Safety Variables

8.2.1 Adverse Events

8.2.1.1 Adverse Events (AE) and Serious Adverse Events (SAE)

An adverse event is any untoward medical occurrence in a subject participating in a clinical trial. An adverse event can be any unfavorable and unintended sign, symptom or disease temporally associated with the use of the study medication, whether or not considered related to the study medication. Adverse events will be collected from the start of treatment until 30 days following the final visit dose. Any events occurring prior to treatment will be recorded on the medical history page with the event name and onset date and end date if not continuing. Pre-existing, known clinically significant conditions observed at screening should be recorded as medical history.

This definition also includes accidental injuries, reasons for any change in medication (drug and/or dose) other than planned titration, reasons for admission to a hospital, or reasons for surgical procedures (unless for minor elective surgery for a pre-existing condition). It also includes adverse events commonly observed and adverse events anticipated based on the pharmacological effect of the study medication. Any laboratory abnormality assessed as clinically significant by the Investigator must be recorded as an adverse event.

A treatment-emergent adverse event (TEAE) is any adverse event occurring after start of study medication and within the time of residual drug effect, or a pre-treatment adverse event or pre-existing medical condition that worsens in intensity after start of study medication and within the time of residual drug effect.

Adverse events should be recorded as diagnoses, if available. If not, separate sign(s) and symptom(s) are to be recorded. One diagnosis/symptom should be entered per record.

Note that death is not an event, but the cause of death is. An exception is the event of sudden death of unknown cause. Note that hospitalization is not an event; however, the reason for hospitalization is. Procedures are not events; the reasons for conducting the procedures are. In general, only the reason for conducting the procedure will be captured as an adverse event. However, if deemed necessary by the Investigator, a procedure can be captured along with the reason for conducting the procedure.

An overdose or medication error is not an adverse event unless it is temporally associated with an unfavorable or unintended sign or symptom.

Each adverse event is to be classified by the Investigator as serious or non-serious. A serious adverse event (SAE) is any untoward medical occurrence or effect that occurs at any dose:

- Results in death
- Is life-threatening (i.e., an immediate risk of death)
- Requires in-patient hospitalization or prolongation of existing hospitalization

- Results in persistent or significant disability/incapacity
- Is associated with a congenital anomaly/birth defect
- Is an important medical event

An adverse event caused by an overdose or medication error is considered serious if a criterion listed in the definition above is fulfilled.

Important adverse events that may not result in death, may not be life-threatening, or do not require hospitalization may be considered serious when, based on appropriate medical judgment, they may jeopardize the subject's safety or may require medical or surgical intervention to prevent one of the outcomes listed above.

Serious adverse events also include any other event that the Investigator or Sponsor judges to be serious or which is defined as serious by the regulatory agency.

The Investigator is to report all directly observed adverse events and all adverse events spontaneously reported by the trial subject using concise medical terminology. In addition, each trial subject will be questioned about adverse events. The question asked will be "Since you began taking the study medication, have you had any health problems?"

8.2.1.2 Procedures for Assessing, Recording, and Reporting Adverse Events and Serious Adverse Events

Throughout the duration of the study, the Investigator will closely monitor each subject for evidence of drug intolerance and for the development of clinical or laboratory evidence of adverse events. All adverse events (expected or unexpected) that occur during the course of the study, whether observed by the Investigator or by the subject, and whether or not thought to be drug-related, will be reported and followed until resolution or until they become stable.

The description of the adverse event will include description of event, start date, stop date, intensity, if it was serious, relationship to test drug, change in test drug dosage, if the subject died, and if treatment was required.

Adverse events will be coded to one of the following intensity categories below:

Severity	Definition
Mild	Awareness of signs or symptoms, but no disruption of usual activity
Moderate	Event sufficient to affect usual activity (disturbing)
Severe	Event causes inability to work or perform usual activities (unacceptable)

Adverse events will be coded into one of the following causality categories as defined below:

Category	Definition
Unrelated	Clearly and incontrovertibly due only to extraneous causes, and does not meet criteria listed under possible or probable.
Unlikely	Does not follow a reasonable temporal sequence from administration. May have been produced by the subject's clinical state or by environmental factors or other therapies administered.
Possible	Follows a reasonable temporal sequence from administration, but may have been also produced by the subject's clinical state, environmental factors, or other therapies administered.
Probable	Clear-cut temporal association with administration with improvement on cessation of investigational medicinal product or reduction in dose. Reappears upon rechallenge. Follows a known pattern of response to the investigational medicinal product.

Adverse events with the causality assessed as unrelated or unlikely are categorized as not related to study medication.

Adverse events with the causality assessed as possible or probable are categorized as related to study medication and are called adverse drug reactions.

All SAEs must be reported **immediately (no more than 24 hours after becoming aware of the event)**. The Investigator must complete the eCRF SAE Report according to the Serious Adverse Event Report Form Instructions.

8.2.2 Clinical Laboratory

The following laboratory tests will be analyzed locally by standard laboratory procedures:

- Hematology: complete blood count, total white blood cell count, differential count (neutrophils, lymphocytes, monocytes, eosinophils and basophils), red blood cells (hemoglobin, hematocrit, mean corpuscular volume, mean corpuscular hemoglobin and mean corpuscular hemoglobin concentration), platelets and reticulocytes.
- Biochemistry: sodium, potassium, glucose, blood urea nitrogen, creatinine, calcium, phosphate (inorganic), uric acid, total protein, albumin, bilirubin (total), alkaline phosphatase, aspartate transaminase, alanine transaminase, gamma-glutamyl transferase, and lactate dehydrogenase, iron, activated AST (GOT), activated ALT(GPT), LDH, cholesterol,HDL cholesterol, C-reactive protein, TIBC.
- Endocrynology: Ferritin, Vitamin D.
- Urinalysis: presence of glucose, ketones, protein, and leukocytes

8.2.3 Vital Signs

Vital signs measurements will include systolic/diastolic blood pressure, pulse rate, temperature, and respiratory rate.

8.2.4 Physical Examination

Physical examination will include assessment of standard body systems.

8.3 Immunogenicity

Anti-taliglucerase alfa antibodies, including neutralizing antibodies in subjects having a positive antibody response, will be assessed using a validated analytical method by a central laboratory.

9. STUDY PROCEDURES AND FLOW CHART

9.1 Study Flow Chart

Table 1: Study Flow Chart

Activity	Visit 0 Screening Day -50 ±10	Visit 1 Baseline Day 1	Visits 2-5 Weeks 2, 4, 6, 8, (±3 days)	Visit 6 Week 10 (±3 days)	Visit 7 Month 3 Week 12 (±7 days)	Visits 8-13 Weeks 14, 16, 18, 20, 22, 24 (±3 days)	Visit 14 Month 6 Week 26 (±7 days)	Visits 15-19 Weeks 28, 30, 32, 34, 36 (±3 days)	Visit 20 Month 9 Week 38 (±7 days)	Visits 21-26 Weeks 40, 42, 44, 46, 48, 50 (±3 days)	Visit 27 Month 12 Week 52[d] (±7 days)
Sign informed consent	X										
Review inclusion/exclusion criteria	X										
Demographics	X										
Medical history	X										
Current/concomitant medications	X	X	X	X	X	X	X	X	X	X	X
Weight/height	X	X			X		X		X		X
Physical examination	X	X			X		X		X		X
Neurologic assessment	X						X				X
Hematology	X	X			X		X		X		X
Biochemistry[f,g]	X	X			X		X		X		X
Urinalysis	X	X			X		X		X		X
Serology (HIV, HBsAg, HCV)	X										
TSH, free T4, transferrin, B_{12} and folic acid	X										
Beta HCG (post-menarcheal girls)	X										
Vital signs[h]	X	X	X	X	X	X	X	X	X	X	X
Anti-taliglucerase alfa antibodies		X					X				X
Organ volumes (MRI)	X										X
Ultrasound (liver and spleen)	X						X				X
Echocardiography	X										
Tanner Stage		X									X
X-ray of left hand and wrist		X									X
DEXA		X									X
mSST	X						X				X
Molecular analysis[e]	X										
Lyso-Gb1 biomarker		X			X		X		X		X
Chitotriosidase		X			X		X		X		X
IV infusion of taliglucerase alfa		X[a]	X[b]	X	X[c]	X	X[c]	X	X[c]	X	X[c]
Observe subject clinically		X	X		X		X		X		X
Evaluate injection site		X	X		X		X		X		X
Adverse events		X	X	X	X	X	X	X	X	X	X

DEXA = dual-emission X-ray absorptiometry; HBsAg = hepatitis B surface antigen; HCG = human chorionic gonadotropin; HCV = hepatitis C virus; HIV = human immunodeficiency virus, IV = intravenous; MRI = magnetic resonance imaging; T4 = thyroxine; TSH = thyroid stimulating hormone

[a] A follow-up telephone call with the subject and/or parent or guardian will be held the day after the infusion.
[b] Subjects who tolerate the infusions will be eligible for transfer to home or infusion center treatment after this visit at the discretion of the Investigator and Medical Monitor.
[c] Taliglucerase alfa infusion must be done at the subject's selected medical center.
[d] All Month 12 (Week 52) procedures/assessments are to be done for any subject who withdraws or is discontinued from the study before completion.
[e] Molecular analysis will be done localy (if not done before), and a confirmation from Central Laboratory (Centogene) will be done using the CentoCard.
[f] HDL, Phosphate inorganic and cholesterol assessments, which are taken at screening, should not be repeated at baseline, if done within a period of 1 month.
[g] ALT and AST assessments are enough if activated ALT and activated AST are done on site (or the way around).
[h] Vital signs to be done once on screening visit, from baseline till visit 27; to be done only pre and post infusion, and as needed if an AE occurs during infusion.

9.2 Study Visits

9.2.1 Screening (Visit 0, Day -50 ± 10)

The following procedures will be performed:

1. Obtain written informed consent from the subject and/or parent or guardian
2. Assign screening number
3. Record demographic data
4. Medical history
5. Current medications
6. Physical examination, including body weight and height
7. Neurologic assessment
8. mSST evaluation
9. Molecular Analysis; Done locally (if not done before), and a confirmation from Central Laboratory (Centogene) will be done using the CentoCard)
10. Vital signs (systolic/diastolic blood pressure, pulse rate, temperature, and respiration rate)
11. MRI for spleen and liver volume
12. Ultrasound for spleen and liver volume.
13. Clinical laboratory tests:
    - Hematology
    - Biochemistry
    - Urinalysis
    - Thyroid stimulating hormone (TSH)
    - Free thyroxine (free T4)
    - Transferrin
    - Folic acid
    - Vitamin B_{12}
    - Blood pregnancy test (beta-HCG) for females of childbearing potential
    - Serology for HIV, HBsAg, HCV
14. Review all inclusion and exclusion criteria and determine subject's eligibility
15. Request for subject and/or parent or guardian approval

9.2.2 Visit 1 (Baseline, Day 1)

The following procedures will be performed:

1. Concomitant medications
2. Physical examination including body weight and height
3. Clinical laboratory tests:
    - Hematology
    - Biochemistry;
        - (HDL, Phosphate inorganic and cholesterol assessments, which are taken at screening, should not be repeated at baseline, if done within a period of 1 month).
        - ALT and AST assessments are enough if activated ALT and activated AST are done on site (or the way around).
    - Urinalysis
    - Anti-taliglucerase alfa antibody test
    - Biomarkers: Lyso-Gb1 and Chitotriosidase
4. Left hand and wrist X-ray for bone age
5. Tanner Stage
6. DEXA
7. Taliglucerase alfa infusion
8. Adverse event evaluation

The following procedures will be performed after taliglucerase alfa dosing:

1. Observe the subject clinically for a minimum of 1 hour post-dosing.
2. Evaluate vital signs pre and post infusion, and as needed if an AE occurs during infusion. Evaluate the injection site.
3. A follow up telephone call with the subject and/or parent or guardian will be held the day after the infusion.

The subject and/or parent or guardian will be reminded of the date of the next visit.

9.2.3 Visits 2 – 5 (Weeks 2, 4, 6, and 8 ± 3 Days)

Subjects will receive their taliglucerase alfa infusion at their selected medical center. The following procedures will be performed post-dosing:

1. Observe the subject clinically for a minimum of 1 hour post-dosing.
2. Evaluate vital signs pre and post infusion, and as needed if an AE occurs during infusion.
3. Evaluate the injection site.

Adverse events and concomitant medications will be recorded at each visit.

Subjects will only receive transfusions at the medical center where they will be followed up and treated. The procedures to be followed will depend on local standards of care and procedures established at the medical center Minimally, safety data (vital signs, adverse events, concomitant medications) will be recorded at each bi-weekly treatment with taliglucerase alfa administered at the medical center.

The subject and/or parent or guardian will be reminded of the date of the next visit.

9.2.4 Visit 6 (Week 10 ± 3 Days)

Subjects will receive their taliglucerase alfa infusion at their selected medical center. The following procedures will be performed post-dosing:

1. Adverse event evaluation.
2. Concomitant medications.
3. Vital signs pre and post infusion, and as needed if an AE occurs during infusion.

The subject and/or parent or guardian will be reminded of the date of the next infusion/visit.

9.2.5 Visit 7 (Month 3 [Week 12] ± 7 Days)

All subjects will receive their taliglucerase alfa infusion at their selected medical center and have the following evaluations:

1. Adverse event evaluation.
2. Concomitant medications.
3. Physical examination including body weight and height.
4. Clinical laboratory tests:
    - Hematology
    - Biochemistry
    - Urinalysis
    - Biomarkers: Lyso-Gb1 and Chitotriosidase

The following procedures will be performed post-dosing:

1. Observe subjects clinically for 1 hour post-dosing
2. Evaluate vital signs pre and post infusion, and as needed if an AE occurs during infusion.
3. Evaluate the injection site.

The subject and/or parent or guardian will be reminded of the date of the next visit.

9.2.6 Visits 8 – 13 (Weeks 14, 16, 18, 20, 22, and 24 ± 3 Days)

Subjects will receive their Taliglucerase alfa infusion at their selected medical center. The following procedures will be performed post-dosing:

4. Adverse event evaluation.

5. Concomitant medications.
6. Vital signs pre and post infusion, and as needed if an AE occurs during infusion.

The subject and/or parent or guardian will be reminded of the date of the next infusion/visit.

9.2.7 Visit 14 (Month 6 [Week 26] ± 7 Days)

All subjects are required to return to their selected medical center to receive their taliglucerase alfa infusion and have the following evaluations:

1. Adverse event evaluation
2. Concomitant medications
3. Physical examination including body weight and height
4. Neurologic assessment
5. Ultrasound for spleen and liver volume.
6. mSST evaluation.
7. Clinical laboratory tests:
   - Hematology
   - Biochemistry
   - Urinalysis
   - Biomarkers: Lyso-Gb1 and Chitotriosidase
   - Anti-taliglucerase alfa antibody test

The following procedures will be performed post-dosing:

1. Observe the subject clinically for 1 hour post-dosing
2. Evaluate vital signs pre and post infusion, and as needed if an AE occurs during infusion.
3. Evaluate the injection site.

The subject and/or parent or guardian will be reminded of the date of the next visit.

9.2.8 Visits 15 – 19 (Weeks 28, 30, 32, 34, and 36 ± 3 Days)

Subjects will receive their taliglucerase alfa infusion at their selected medical center. The following procedures will be performed post-dosing:

1. Adverse event evaluation.
2. Concomitant medications.
3. Vital signs pre and post infusion, and as needed beforehence

The subject and/or parent or guardian will be reminded of the date of the next infusion/visit.

9.2.9 Visit 20 (Month 9 [Week 38] ± 7 Days)

All subjects are required to return to their selected medical center to receive their taliglucerase alfa infusion and have the following evaluations:

1. Adverse event evaluation.
2. Concomitant medications.
3. Physical examination including body weight and height.
4. Clinical laboratory tests:
    - Hematology
    - Biochemistry
    - Urinalysis
    - Biomarkers: Lyso-Gb1 and Chitotriosidase

The following procedures will be performed post-dosing:

1. Observe the subject clinically for 1 hour post-dosing.
2. Evaluate vital signs pre and post infusion, and as needed if an AE occurs during infusion.
3. Evaluate the injection site.

The subject and/or parent or guardian will be reminded of the date of the next infusion/visit.

9.2.10 Visits 21 – 26 (Weeks 40, 42, 44, 46, 48, and 50 ± 3 Days)

Subjects will receive their aliglucerase alfa infusion at their selected medical center. The following procedures will be performed post-dosing:

1. Adverse event evaluation.
2. Concomitant medications.
3. Vital signs pre and post infusion, and as needed if an AE occurs during infusion.

The subject and/or parent or guardian will be reminded of the date of their next infusion/visit.

9.2.11 Visit 27 (Month 12 [Week 52] ± 7 Days)

All subjects are required to return to their selected medical center to receive their taliglucerase alfa infusion and have the following evaluations:

1. Physical examination including body weight and height.
2. Neurologic assessment.
3. MRI for spleen and liver volume.
4. Ultrasound for spleen and liver volume.
5. Clinical laboratory tests

- Hematology
- Biochemistry
- Urinalysis
- Biomarkers: Lyso-Gb1 and Chitotriosidase
- Anti-taliglucerase antibody test

6. Left hand and wrist X-ray for bone age
7. Tanner Stage
8. DEXA
9. mSST evaluation
10. Adverse event evaluation
11. Concomitant medications

The following procedures will be performed post-dosing:

1. Observe the subject clinically for 1 hour post-dosing.
2. Evaluate vital signs pre and post infusion, and as needed if an AE occurs during infusion
3. Evaluate the injection site.

9.2.12 Early Termination Visit

If the subject withdraws or is discontinued from the study before completion, the reason for discontinuation must be documented in the subject's CRF. Whenever a subject is discontinued, the procedures/assessments listed in Section 9.2.11 should be conducted, unless advised otherwise by the Medical Monitor.

10. STATISTICAL METHODS PLANNED AND SAMPLE SIZE

Detailed methodology for the summary and statistical analysis of the data collected in this study will be documented in a Statistical Analysis Plan (SAP), which will be prepared and finalized prior to database lock.

10.1 Determination of Sample Size

It is assumed that the Type 3 GD patients and Type 1 GD patients will have similar efficacy response to taliglucerase alfa 60 units/kg. Given the fact that Type 3 GD usually develops at younger age and 60 units/kg is the recommended dose, data from the 5 treatment-naïve pediatric patients (Type 1 GD) treated with taliglucerase alfa 60 units/kg in Study PB-06-005 are used to calculate sample size. Since the available data are limited and the data distribution is unknown, a responder rate is calculated from the percent change from baseline in spleen volume MN in these 5 patients as a reference. A subject is considered a responder if the subject has a reduction from baseline in spleen volume MN greater than 20%.

The sample size and power calculation are then estimated using the exact computation from a 2-sided sign test for the null hypothesis that the responder rate is equal to 0.5 for this single-group design. This null hypothesis is corresponding to a median reduction of 20% in spleen volume at Month 12. A sample size of 9 evaluable subjects will provide a power of 80.9% to detect a responder rate of 0.91 with an actual significant level of 0.04. An actual significant level of 0.05 is not available when the data are discrete and the sample size is small.

10.2 Analysis Populations

Full analysis population is defined as all subjects who receive at least one complete dose (or partial dose if adverse events prevent complete infusion dose) of study medication.

Per protocol population is defined as subjects who have the primary efficacy data collected at Month 12 and baseline, and receive at least one complete dose (or partial dose if adverse events prevent complete infusion dose) of study medication.

The safety analysis population is equivalent to the full analysis population.

10.3 Analysis

10.3.1 Demographics

Continuous variables will be summarized with descriptive statistics (number, mean, standard deviation, median, minimum, and maximum). For categorical variables, frequency counts and percentages will be presented.

10.3.2 Medical History

Frequency counts will be provided for each body system.

10.3.3 Medications

Data listings of the prior, concomitant medication, and class of medication will be provided.

10.3.4 Efficacy Analysis

Efficacy variables are listed in Section 8.1.

Analysis for the primary efficacy endpoint

The primary efficacy evaluation will be the median percent change in spleen volume (expressed in MN) from baseline to Month 12 measured by MRI. For the primary efficacy endpoint, a Wilcoxon signed rank test at 2-sided significance level of 0.05 will be applied to test the null hypothesis that the median percent change from baseline to Month 12 in spleen volume MN is equal to -20%. The median percent change from baseline and the corresponding p-value will be reported.

Frequency and percentage of the responders who have the reduction greater than 20% in spleen volume MN will be provided. The 95% confidence interval for the responder rate will be provided using Clopper-Pearson method.

Analysis for the secondary efficacy endpoints

The percent change from baseline (Visit 1 or Screening) to each assessment time point will be calculated and summarized by visit with descriptive statistics (number, mean, median, standard deviation, minimum, and maximum) for spleen and liver volume (MN), hemoglobin, platelet count, chitotriosidase and Lyso-Gb1.

The Wilcoxon signed rank test will be applied for the secondary efficacy endpoints: percent change from baseline to Month 12 in liver volume MN measured by MRI, hemoglobin, platelet count, and chitotriosidase and Lyso-Gb1 separately. Though hemoglobin, platelet counts, chitotriosidase and Lyso-Gb1 will be collected at Month 3, 6 and 9 as well, no adjustment will be made for multiple comparisons, as the changes from baseline to Month 3, 6 and 9 will be descriptively summarized only.

Analysis for other efficacy variables

For change in growth and development, the height and weight will be assigned to a SDS-scores using the World Health Organization (WHO) Child Growth Standards. The Centers for Disease Control and Prevention (CDC) reference standards will be used for the age categories where the WHO reference standards are not available. Change in growth and development assessment from baseline to each visit will be summarized using descriptive statistics by visit.

Descriptive statistics will also be reported for change in Tanner Stage, bone assessment (including bone age, bone mineral density and Z-score for each bone area), and mSST from screening to Month 6, Month 12.

10.3.5 Safety Analysis

10.3.5.1 Adverse Events

The Medical Dictionary for Regulatory Activities (MedDRA) (latest version) will be used to classify all adverse events to system organ class and preferred term. All adverse events occurring after the initiation of the study treatment (TEAEs) will be reported, including events present at baseline that worsened during the study.

Adverse events will be summarized by overall incidence (the number of subjects reporting at least one episode of a specific adverse event), incidence of adverse events by severity within system organ class, incidence of adverse events by attribution within system organ class, and incidence of adverse events causing discontinuation, and incidence of serious adverse events. Regarding severity and attribution summaries, the most extreme outcome (highest severity and closest to study drug related) will be used for those subjects who experience the same adverse event on more than one occasion.

Written narratives will be provided for all serious, unexpected, or other significant adverse events that are judged to be of special interest because of their clinical importance.

10.3.5.2 Clinical Laboratory

Lab data will be presented for the value and abnormality of each of the clinical laboratory results by visit.

10.3.5.3 Vital Signs

Descriptive statistics will be presented for vital signs (systolic/diastolic blood pressure, pulse, temperature, and respiratory rate) at baseline (Visit 1) and Month 3, 6, 9 and 12 visits, including absolute values, change from baseline and percent change from baseline.

10.3.5.4 Physical Examinations

The physical examination data collected at screening and all post-treatment visits will be tabulated by frequency count and percentage of normal or abnormal findings for each body system.

10.3.6 Immunogenicity

Antibody status (Positive / Negative) determined at baseline (Visit 1), Month 6, and Month 12 will be tabulated by frequency count and percentage.

11. QUALITY CONTROL AND QUALITY ASSURANCE

11.1 Source Data Records

Source data are all the information in original records and certified copies of original records of clinical findings, observations, laboratory reports, data sheets provided by the Sponsor or other activities in the study, which are necessary for the reconstruction and evaluation of the study. The Investigator will permit study-related monitoring, audit(s), IRB review(s), and regulatory inspection(s), with direct access to all the required source records.

All study records will be retained for a period of time as defined by the regulatory authority for the country in which the investigation is conducted. Generally, this means at least 2 years following the date on which the drug is approved by the regulatory authority for marketing for the purposes that were the subject of the investigation. In other situations (e.g., where the investigation is not in support of or as part of an application for a research or marketing permit), a period of 2 years following the date on which the entire clinical program is completed, terminated or discontinued or the investigational application under which the investigation is being conducted is terminated or withdrawn by the regulatory authorities.

In the event the Investigator retires, relocates, or for any other reason withdraws from the responsibility for maintaining records for the period of time required, custody of the records may be transferred to any other person who will accept responsibility for the records. Notice of such a transfer must be given in writing to the Sponsor. The Investigator must contact the Sponsor before disposal of any records related to this study.

11.2 Reporting of Results

The CRF is an integral part of the study and subsequent reports. The CRF must be used to capture all study data recorded in the subject's medical record. The CRF must be kept current to reflect subject status during the course of the study. Only a subject screening number and subject initials will be used to identify the subject. A CRF will be provided for each screened subject.

The monitor is responsible for performing on-site monitoring at regular intervals throughout the study to verify adherence to the protocol; verify adherence to local regulations on the conduct of

clinical research; and ensure completeness, accuracy, and consistency of the data entered in the CRF.

All protocol-required information collected during the study must be entered by the Investigator, or designated representative, in the Target e*CRF™, an Internet-based electronic data collection system. All details of the CRF completion and correction will be explained to the investigator. The management module of Target e*CRF™ includes edit check and query systems that seamlessly integrate with the data entry system. All modifications to the data in the eCRF are tracked by an electronic audit trail (date and identity of the person making the change are instantaneously recorded). Target e*CRF™ is 21CFR Part 11 compliant.

If the Investigator authorizes other persons to make entries in the CRF, the names, positions, and signatures of these persons must be supplied to the Sponsor.

The Investigator, or designated representative, should complete the eCRF as soon as possible after information is collected, preferably on the same day that a study subject is seen for an examination, treatment, or any other study procedure. Any outstanding entries must be completed immediately after the final examination. By design, an explanation must be provided for all missing data, altered data, and/or out of range data.

The completed CRF must be reviewed and signed by the Investigator named in the study protocol or by a designated sub-investigator.

Final monitored and audited eCRFs will be provided by the Sponsor to the sites at the end of the study in the format of a PDF file.

11.3 Confidentiality of Subject Data

The Investigator will ensure that the confidentiality of the subjects' data will be preserved. In the CRF or any other documents submitted to the Sponsor, the subjects will not be identified by their names, but by an identification system, which consists of their initials and number in the study. The Investigator will maintain documents not meant for submission to the Sponsor, e.g., the confidential subject identification code and the signed informed consent forms, in strict confidence.

12. REPORTING AND PUBLICATION

12.1 Confidentiality of Subject Data

Any information relating to the study product or the study, including any data and results from the study, will be the exclusive property of the Sponsor. The Investigator and any other persons involved in the study will protect the confidentiality of this proprietary information belonging to the Sponsor.

12.2 Publication Policy

The Sponsor agrees to make the report of the multicenter study results available to Investigators for preparing a publication of the results in meeting abstract or medical journal form. The Sponsor will have 30 days to review any proposed publication of the data for accuracy and proprietary information.

13. REFERENCES

1. Jmoudiak M, Futerman AH. Gaucher disease: pathological mechanisms and modern management. Br J Haematol 2005;129(2):178-188.

2. Zeller JL, Burke AE, Glass RM. JAMA patient page. Gaucher Disease. JAMA 2007;298(11):1358.

3. Amato D, Stachiw T, Clarke JT, Rivard GE. Gaucher disease: variability in phenotype among siblings. J Inherit Metab Dis 2004;27(5):659-669.

4. Sidransky E. Gaucher disease: complexity in a "simple" disorder. Mol Genet Metab 2004;83(1-2):6-15.

5. Baris HN, Cohen IJ, Mistry PK. Gaucher disease: the metabolic defect, pathophysiology, phenotypes and natural history. Pediatr Endocrinol Rev 2014;12(Suppl 1):72-81.

6. Charrow J, Andersson HC, Kaplan P, Kolodny EH, Mistry P, Pastores G, et al. The Gaucher registry: demographics and disease characteristics of 1698 patients with Gaucher disease. Arch Intern Med 2000;160(18):2835-2843.

7. Biegstraaten M, van Schaik IN, Aerts JM, Hollak CE. "Non-neuronopathic" Gaucher disease reconsidered. Prevalence of neurological manifestations in a Dutch cohort of type I Gaucher disease patients and a systematic review of the literature. J Inherit Metab Dis 2008;31(3):337-349.

8. Lim-Melia ER, Kronn DF. Current enzyme replacement therapy for the treatment of lysosomal storage diseases. Pediatric Ann 2009;38(8):448-455.

9. Cox TM. Gaucher disease: clinical profile and therapeutic developments. Biologics 2010;4:299-313.

10. Rosenbloom BE, Weinreb NJ. Bone disease in patients with Gaucher disease. Expert Review of Endocrinology & Metabolism 2014;9(2):153-162.

11. Cerezyme (imiglucerase for injection). Prescribing information. Cambridge, MA: Genzyme Corporation; 2009.

12. VPRIV (velaglucerase alfa for injection). Prescribing information. Cambridge, MA: Shire Human Genetic Therapies, Inc.; 2010.

13. Shaaltiel Y, Bartfeld D, Hashmueli S, et al. Production of glucocerebrosidase with terminal mannose glycans for enzyme replacement therapy of Gaucher's disease using a plant cell system. Plant Biotechnol J 2007;5:579-590.

14. Taliglucerase alfa for injection. Prescribing Information. New York, NY: Pfizer, Inc.; 2016.

15. Lee NC, Chien YH, Wong SL, Sheen JM, Tsai FJ, Peng SF, et al. Outcome of early-treated type III Gaucher disease patients. Blood Cells Mol Dis 2014;53(3):105-109.

16. Deegan P, Fernandez-Sasso D, Giraldo P, Lau H, Panahloo Z, Zimran A. Blood Cells Mol Dis 2016;S1079-9796(16):30213-3.

17. Zimran A, Elstein D. Management of Gaucher disease: enzyme replacement therapy. Pediatr Endocrinol Rev 2014;12(Suppl 1):82-87.

18. Kraoua I, Sedel F, Caillaud C, Froissart R, Stirnemann J, Chaurand G, et al. A French experience of type 3 Gaucher disease: phenotypic diversity and neurological outcome of 10 patients. Brain Dev 2011;33(2):131–139.

19. El-Beshlawy A, Tylki-Szymanska A, Vellodi A, Belmatoug N, Grabowski GA, Kolodny EH, et al. Long-term hematological, visceral, and growth outcomes in children with Gaucher disease type 3 treated with imiglucerase in the International Collaborative Gaucher Group Gaucher Registry. Mol Genet Metab 2017;120 (1-2):47–56.

14. APPENDICES

14.1 Appendix 1: ELELYSO® Prescribing Information (US)

HIGHLIGHTS OF PRESCRIBING INFORMATION

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

ELELYSO® (taliglucerase alfa) for injection, for intravenous use

Initial US Approval: 2012

----------INDICATIONS AND USAGE----------

ELELYSO is a hydrolytic lysosomal glucocerebroside-specific enzyme indicated for the treatment of patients with a confirmed diagnosis of Type 1 Gaucher disease (1).

----------DOSAGE AND ADMINISTRATION----------

Recommended Dosage in Patients 4 Years and Older (2.1)

- Treatment-naïve: 60 units/kg administered every other week as a 60 to 120 minute intravenous infusion
- Patients switching from imiglucerase: Begin ELELYSO at the same unit/kg dose as the patient's previous imiglucerase dose. Administer ELELYSO every other week as a 60 to 120 minute intravenous infusion. Dosage adjustments can be based on achievement and maintenance of each patient's therapeutic goals.

Preparation and Administration (2.2, 2.3)

- Reconstitute, dilute and administer under the supervision of a healthcare professional.
- See Full Prescribing Information for complete instructions.

----------DOSAGE FORMS AND STRENGTHS----------

For injection: 200 units, lyophilized powder in single-use vials for reconstitution (3)

----------CONTRAINDICATIONS----------

None (4)

----------WARNINGS AND PRECAUTIONS----------

- Hypersensitivity Reactions Including Anaphylaxis: Observe patients during and after the infusion; immediately discontinue infusion if anaphylaxis occurs and initiate appropriate treatment. Reduction in the infusion rate and/or pre-medication may prevent subsequent reactions (5.1, 6.3).

----------ADVERSE REACTIONS----------

The most common adverse reactions are:

- Treatment-Naïve Adults (≥5%): headache, arthralgia, fatigue, nausea, dizziness, abdominal pain, pruritus, flushing, vomiting, urticaria (6.1).
- Patients Switched from Imiglucerase, after 9 Months on Treatment (≥10%): arthralgia, headache, pain in extremity (6.1).

To report SUSPECTED ADVERSE REACTIONS, contact Pfizer Inc. at 1-800-438-1985 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 12/2016

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

ELELYSO is indicated for the treatment of patients with a confirmed diagnosis of Type 1 Gaucher disease.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosage in Patients 4 Years and Older

Treatment-naïve patients: The recommended dosage of ELELYSO for long-term treatment is 60 units/kg of body weight administered every other week as a 60 to 120 minute intravenous infusion.

Patients switching from imiglucerase: Patients currently being treated with imiglucerase for Type 1 Gaucher disease can be switched to ELELYSO. Patients previously treated on a stable dosage of imiglucerase are recommended to begin treatment with ELELYSO at that same units/kg dosage when they switch from imiglucerase to ELELYSO. Administer ELELYSO for long-term treatment every other week as a 60 to 120 minute intravenous infusion. Dosage adjustments can be made based on achievement and maintenance of each patient's therapeutic goals *[see Clinical Studies (14.2)]*.

2.2 Preparation Instructions

ELELYSO should be reconstituted, diluted, and administered under the supervision of a healthcare professional.

Each vial of ELELYSO provides 200 units of taliglucerase alfa and is intended for single use only. Do not use the vial more than one time. The reconstitution and dilution steps must be completed using aseptic technique.

ELELYSO should be reconstituted with Sterile Water for Injection and diluted with 0.9% Sodium Chloride Injection, USP, to a final volume of 100 mL to 200 mL, and delivered by intravenous infusion.

Prepare ELELYSO according to the following steps. Use aseptic technique.

a. Determine the number of vials to be reconstituted based on the patient's weight and the recommended dose of 60 units/kg, using the following calculations (1-3):
   (1) Total dose in units = Patient's weight (kg) x dose (units/kg)
   (2) Total number of vials = Total dose in units divided by 200 units/vial
   (3) Round up to the next whole vial.
b. Remove the required number of vials from the refrigerator. Do not leave these vials at room temperature longer than 24 hours prior to reconstitution. Do not heat or microwave these vials.
c. Reconstitute each vial of ELELYSO with 5.1 mL of Sterile Water for Injection to yield a reconstituted product with a concentration of 40 units/mL and an extractable volume of 5 mL. Upon reconstitution, mix vials gently. DO NOT SHAKE. Prior to further dilution, visually inspect the solution in the vials; the solution should be clear and colorless. Do not use if the solution is discolored or if foreign particulate matter is present.
d. Withdraw the calculated dose of drug from the appropriate number of vials and dilute with 0.9% Sodium Chloride Injection, USP, to a final volume of 100 to 200 mL.
   i. For pediatric patients, a final volume of 100 to 120 mL should be used.
   ii. For adult patients, a final volume of 130 to 150 mL may be used. However, if the volume of reconstituted product alone is equal to or greater than 130 to 150 mL, then the final volume should not exceed 200 mL.
e. Mix gently. DO NOT SHAKE. Since this is a protein solution, slight flocculation (described as translucent fibers) occurs occasionally after dilution.

2.3 Administration Instructions

After reconstitution and dilution, the preparation should be administered via intravenous infusion and filtered through an in-line low protein-binding 0.2 µm filter.

- For pediatric patients: An initial infusion rate of 1 mL/minute should be used. After tolerability to ELELYSO is established, the infusion rate may be increased, but should not exceed the maximum recommended infusion rate of 2 mL/minute. The total volume of the infusion should be delivered over a minimum of 60 minutes.
- For adult patients: An initial infusion rate of 1.2 mL/minute should be used. After tolerability to ELELYSO is established, the infusion rate may be increased, but should not exceed the maximum recommended infusion rate of 2.2 mL/minute. The total volume of the infusion should be delivered over a minimum of 60 minutes.

As ELELYSO contains no preservative, the product should be used immediately once reconstituted. If immediate use is not possible, the reconstituted product may be stored for up to 24 hours at 2 to 8 °C (36 to 46 °F) under protection from light or up to 4 hours at 20 to 25 °C (68 to 77 °F) without protection from light. The diluted product may be stored for up to 24 hours at 2 to 8 °C (36 to 46 °F) under protection from light. Storage of the reconstituted product and the diluted product should not exceed a total of 24 hours. Do not freeze. Discard any unused product.

3 DOSAGE FORMS AND STRENGTHS

For injection: 200 units, lyophilized powder in single-use vials for reconstitution.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Hypersensitivity Reactions Including Anaphylaxis

Serious hypersensitivity reactions, including anaphylaxis, have occurred in some patients treated with ELELYSO. In clinical trials, 2 of 72 (3%) patients treated with ELELYSO experienced signs and symptoms consistent with anaphylaxis. Signs and symptoms of these patients included urticaria, hypotension, flushing, wheezing, chest tightness, nausea, vomiting, and dizziness. These reactions occurred during ELELYSO infusion.

In clinical trials with ELELYSO, 21 of 72 (29%) patients experienced hypersensitivity reactions, including anaphylaxis. Signs and symptoms of hypersensitivity reactions included pruritus, angioedema, flushing, erythema, rash, nausea, vomiting, cough, chest tightness, and throat irritation. These reactions have occurred up to 3 hours after the start of infusion *[see Adverse Reactions (6.1)]*.

Due to the potential for anaphylaxis, appropriate medical support should be readily available when ELELYSO is administered. Observe patients closely for an appropriate period of time after administration of ELELYSO, taking into account the time to onset of anaphylaxis seen in clinical trials. Inform patients of the signs and symptoms of anaphylaxis, and instruct them to seek immediate medical care should signs and symptoms occur. If anaphylaxis occurs, ELELYSO should be immediately discontinued, and appropriate medical treatment should be initiated.

Management of hypersensitivity reactions should be based on the severity of the reaction and include slowing or temporary interruption of the infusion and/or administration of antihistamines, antipyretics, and/or corticosteroids for mild reactions. Pretreatment with antihistamines and/or corticosteroids may prevent subsequent hypersensitivity reactions. Patients were not routinely premedicated prior to infusion of ELELYSO during clinical studies. If severe hypersensitivity reactions occur, immediately stop the infusion of ELELYSO and initiate appropriate treatment.

Consider the risks and benefits of re-administering ELELYSO in patients who have experienced a severe reaction associated with ELELYSO. Caution should be exercised upon rechallenge, and appropriate medical support should be readily available *[see Adverse Reactions (6.3)]*.

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

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

Clinical Trials of ELELYSO as Initial Therapy

- Clinical Trial in Patients 19 Years and Older

The safety of ELELYSO at dosages of either 30 units/kg (n=16) or 60 units/kg (n=16) every other week was assessed in 32 adult treatment-naïve patients (aged 19 to 74 years) with Type 1 Gaucher disease in a 9-month double-blind, randomized clinical trial.

Table 1: Adverse Reactions in ≥5% of Treatment-Naïve Adult Patients Treated with ELELYSO

Preferred Term	Treatment-Naïve Adults (N=32) n (%)
Headache	6 (19)
Arthralgia	4 (13)
Fatigue	3 (9)
Nausea	3 (9)
Dizziness	3 (9)
Abdominal pain	2 (6)
Pruritus	2 (6)
Flushing	2 (6)
Vomiting	2 (6)
Urticaria	2 (6)

- Clinical Trial in Patients 16 Years and Younger

The safety of ELELYSO at dosages of either 30 units/kg (n=4) or 60 units/kg (n=5) every other week was assessed in 9 pediatric treatment-naïve patients (aged 2 to 13 years) with Type 1 Gaucher disease in a 12-month randomized clinical trial.

The most common adverse reaction (≥10%) was vomiting, which occurred in 4 of 9 patients. Two patients developed hypersensitivity reactions; one patient experienced severe vomiting and gastrointestinal inflammation, and 1 experienced mild throat irritation and chest discomfort. Both patients responded to treatment with antihistamines and continued ELELYSO treatment.

Clinical Trial in Patients Switching from Imiglucerase Treatment to ELELYSO

The safety of ELELYSO was assessed in 31 patients (26 adult and 5 pediatric patients), ages 6 to 66 years old, with Type 1 Gaucher disease who had previously been receiving treatment with imiglucerase for a minimum of 2 years. ELELYSO was administered for 9 months at the same number of units as each patient's previous imiglucerase dose.

Table 2: Adverse Reactions in ≥10% of Patients Switched from Imiglucerase to ELELYSO (after 9 months on treatment)

Preferred Term	Patients Switched from Imiglucerase (N=31; 26 adults and 5 children) n (%)
Arthralgia	4 (13)
Headache	4 (13)
Pain in extremity	3 (10)

6.2 Immunogenicity

As with all therapeutic proteins, patients may develop anti-drug antibodies (ADA) to ELELYSO.

In clinical trials of treatment-naïve adults, 17 (53%) of 32 patients developed ADA during treatment with ELELYSO, and 2 (6%) of 32 patients tested positive for ADA at baseline prior to ELELYSO treatment. Of the 17 patients who developed ADA during ELELYSO treatment, 6 patients (35%) developed hypersensitivity reactions, 2 of whom met criteria for anaphylaxis. Two of the 17 patients who developed ADA during ELELYSO treatment discontinued treatment due to hypersensitivity reactions, one of whom had met criteria for anaphylaxis. Of the 2 patients who tested positive for ADA prior to initiation of ELELYSO treatment, one patient developed a hypersensitivity reaction during the first dose of ELELYSO and withdrew from the study. The second patient did not experience a hypersensitivity reaction.

In a clinical trial of treatment-naïve pediatric patients, 2 (22%) of 9 patients developed ADA during treatment with ELELYSO, and one of 9 patients was ADA-positive prior to initiation of ELELYSO. Two of these 3 patients experienced hypersensitivity reactions (1 who developed ADA during treatment and became negative after Week 12 and 1 who was ADA-positive at baseline and became ADA negative after Week 8) and continued treatment with ELELYSO. The third patient who developed ADA during treatment and continued to be ADA-positive until study completion at Week 52 did not experience a hypersensitivity reaction.

In clinical trials of 31 patients (26 adult and 5 pediatric patients) who switched from imiglucerase to ELELYSO treatment, 5 adults (16% of patients) developed ADA during treatment with ELELYSO. Four additional patients (13%, 2 adults and 2 children) tested positive for ADA at baseline but became ADA-negative after the switch to ELELYSO; one of these adult patients subsequently developed ADA to ELELYSO. Two adult patients (1 patient who developed ADA after the switch and 1 who was ADA positive at baseline) experienced hypersensitivity reactions. Both patients continued treatment with ELELYSO.

The relationship between ADA and hypersensitivity reactions is not fully understood. Monitoring for ADA to ELELYSO may be useful in ADA positive patients or in patients who have experienced hypersensitivity reactions to ELELYSO or other enzyme replacement therapies.

Twenty-nine of the 30 adult and pediatric patients who tested positive for ADA were tested for neutralizing antibodies capable of inhibiting the enzymatic activity of ELELYSO. Neutralizing antibodies were detected in 5 (17.2%) of 29 patients, 3 treatment-naïve adult patients, 1 treatment-naïve pediatric patient, and 1 adult patient who switched from imiglucerase. Due to limited available data, it is not possible to determine a relationship between the presence of neutralizing antibodies and therapeutic response with ELELYSO.

Immunogenicity assay results are highly dependent on the sensitivity and specificity of the assay and may be influenced by several factors such as: assay methodology, sample handling, timing of sample collection, concomitant medication, and underlying disease. For these reasons, comparison of the incidence of antibodies to ELELYSO with the incidence of antibodies to other products may be misleading.

6.3 Postmarketing Experience

The following adverse reactions have been identified during post-approval use of ELELYSO in countries where it is marketed. Because these reactions include those reported voluntarily from a population of uncertain size in addition to those from postmarketing studies, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Gastrointestinal disorders: Vomiting, diarrhea

General disorders and administration site conditions: Fatigue

Immune system disorders: Anaphylaxis *[see Warning and Precautions (5.1)]*, Type III immune-mediated fixed drug eruption

Musculoskeletal and connective tissue disorders: Back pain

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

The limited available data on ELELYSO use in pregnant women are not sufficient to inform a drug-associated risk. However, there are clinical considerations *[see Clinical Considerations]*. In animal reproduction studies when pregnant rats and rabbits were administered taliglucerase alfa at intravenous doses up to 5 times the recommended human dose (RHD), there was no evidence of embryo-fetal toxicity *[see Data]*. The estimated background risk of major birth defects and miscarriage for the indicated population(s) are unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively.

Clinical Considerations

Disease-Associated Maternal and/or Embryo/Fetal Risk

Women with Type 1 Gaucher disease have an increased risk of spontaneous abortion if disease symptoms are not treated and controlled pre-conception and during a pregnancy. Pregnancy may exacerbate existing Type 1 Gaucher disease symptoms or result in new disease manifestations. Type 1 Gaucher disease manifestations may lead to adverse pregnancy outcomes, including hepatosplenomegaly which can interfere with the normal growth of a fetus and thrombocytopenia which can lead to increased bleeding and possible postpartum hemorrhage requiring transfusion.

Data

Animal Data

Reproduction studies have been performed with taliglucerase alfa administered during the period of organogenesis in rats and rabbits. In rats, intravenous doses up to 55 mg/kg/day (about 5 times the RHD of 60 units/kg based on the body surface area) did not cause any adverse effects on embryo-fetal development. In rabbits, intravenous doses up to 27.8 mg/kg/day (about 5 times the RHD of 60 units/kg based on the body surface area) did not show any embryo-fetal toxicity.

8.2 Lactation

Risk Summary

There are no data on the presence of taliglucerase in human milk, the effects on the breast fed infant or the effects on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for ELELYSO and any potential adverse effects on the breastfed child from ELELYSO or from the underlying maternal condition.

8.4 Pediatric Use

The use of ELELYSO for treatment of pediatric patients with Type 1 Gaucher disease is supported by evidence of effectiveness from adequate and well-controlled trials of ELELYSO in adults, with additional pharmacodynamic data from 5 pediatric patients and pharmacokinetic data from 9 pediatric patients who participated in clinical trials *[see Clinical Studies (14.1, 14.2), Clinical Pharmacology (12.3)]*. Data from 14 pediatric patients were included in the safety evaluation *[see Adverse Reactions (6.1)]*. There are insufficient data to inform dosing in patients less than 4 years of age.

Pediatric patients experienced a higher frequency of vomiting during ELELYSO treatment (4 of 9 treatment-naïve patients) than adult patients, and this may be a symptom of hypersensitivity reaction. The frequencies of other adverse reactions were similar between pediatric and adult patients *[see Adverse Reactions (6.1)]*.

8.5 Geriatric Use

During clinical trials, 8 patients aged 65 or older were treated with ELELYSO. Clinical trials of ELELYSO did not include sufficient numbers of patients aged 65 and over to determine whether they respond differently from younger patients.

11 DESCRIPTION

Taliglucerase alfa, a hydrolytic lysosomal glucocerebroside-specific enzyme for intravenous infusion, is a recombinant active form of the lysosomal enzyme, β-glucocerebrosidase, which is expressed in genetically modified carrot plant root cells cultured in a disposable bioreactor system (ProCellEx®). β-Glucocerebrosidase (β-D-glucosyl-N-acylsphingosine glucohydrolase, E.C. 3.2.1.45) is a lysosomal glycoprotein enzyme that catalyzes the hydrolysis of the glycolipid glucocerebroside to glucose and ceramide.

ELELYSO is produced by recombinant DNA technology using plant cell culture (carrot). Purified taliglucerase alfa is a monomeric glycoprotein containing 4 N-linked glycosylation sites (Mr = 60,800). Taliglucerase alfa differs from native human glucocerebrosidase by two amino acids at the N terminal and up to 7 amino acids at the C terminal. Taliglucerase alfa is a glycosylated protein with oligosaccharide chains at the glycosylation sites having terminal mannose sugars. These mannose-terminated oligosaccharide chains of taliglucerase alfa are specifically recognized by endocytic carbohydrate receptors on macrophages, the cells that accumulate lipid in Gaucher disease.

ELELYSO is supplied as a sterile, non-pyrogenic, lyophilized product. The quantitative composition of each 200 unit vial is D-mannitol (206.7 mg), polysorbate 80 (0.56 mg), sodium citrate (30.4 mg), and taliglucerase alfa (212 units). Citric acid may be added to adjust the pH at the time of manufacture.

A Unit is the amount of enzyme that catalyzes the hydrolysis of 1 micromole of the synthetic substrate para-nitrophenyl-β-D-glucopyranoside (*p*NP-Glc) per minute at 37°C. After reconstitution with Sterile Water for Injection, taliglucerase alfa concentration is 40 units/mL *[see Dosage and Administration (2)]*. Reconstituted solutions have a pH of approximately 6.0.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Gaucher disease is an autosomal recessive disorder caused by mutations in the human glucocerebrosidase gene, which results in a reduced activity of the lysosomal enzyme glucocerebrosidase. Glucocerebrosidase catalyzes the conversion of the sphingolipid glucocerebroside into glucose and ceramide. The enzymatic deficiency results in accumulation of substrate glucocerebroside primarily in the lysosomal compartment of macrophages, giving rise to foam cells or "Gaucher cells," which accumulate in the liver, spleen and bone marrow.

ELELYSO, a long term enzyme replacement therapy, is a recombinant analog of human lysosomal glucocerebrosidase that catalyzes the hydrolysis of glucocerebroside to glucose and ceramide, reducing the amount of accumulated glucocerebroside. ELELYSO uptake into cellular lysosomes is mediated by binding of ELELYSO mannose oligosaccharide chains to specific mannose receptors on the cell surface leading to internalization and subsequent transport to the lysosomes.

12.3 Pharmacokinetics

Pharmacokinetics of taliglucerase alfa were evaluated in 38 patients (29 adult and 9 pediatric patients) who received intravenous infusions of ELELYSO 30 units/kg or 60 units/kg every other week. ELELYSO 30 units/kg is not a recommended dose in treatment-naïve Gaucher disease patients *[see Dosage and Administration (2.1)]*. The pharmacokinetic parameters in adult and pediatric patients are summarized in Table 3.

In adult Type 1 Gaucher disease patients treated with ELELYSO 30 units/kg or 60 units/kg (N=29) every other week as initial therapy, pharmacokinetics were determined with the first dose and at Week 38 of treatment. The pharmacokinetics of taliglucerase alfa appeared to be nonlinear with a greater than dose-proportional increase in exposure at the doses studied.

No significant accumulation or change in taliglucerase alfa pharmacokinetics over time from Weeks 1 to 38 was observed with repeated dosages of 30 units/kg or 60 units/kg every other week. Based on the limited data, there were no significant pharmacokinetic differences between male and female patients in this study.

The pharmacokinetics of taliglucerase alfa were evaluated in 9 pediatric patients 4 to 17 years of age with Type 1 Gaucher disease who were treated with ELELYSO for 10 to 27 months. Six of the 9 patients were treatment-naïve, and 3 patients were switched from imiglucerase. In both the 30 units/kg and 60 units/kg dose groups, clearance values in pediatric patients were similar to those in adult patients. AUC values in pediatric patients were lower than AUC values in adult patients, due to weight-based dosing of taliglucerase alfa and lower body weights in pediatric patients.

Table 3: Taliglucerase Alfa Pharmacokinetic Parameters after Repeated Dosing in Adult and Pediatric Patients with Type 1 Gaucher Disease

	Pediatric Patients (N=9) Median (Range)		Adult Patients at Week 38 (N=29) Median (Range)	
	30 units/kg n = 5	60 units/kg n = 4	30 units/kg n = 14	60 units/kg n = 15
Age (years)	15 (10, 17)	11 (4, 16)	35 (19, 74)	33 (19, 58)
Weight (kg)	44.3 (22.8, 71.0)	28.6 (16.5, 50.4)	72.5 (51.5, 99.5)	73.5 (58.5, 87.0)[a]
$AUC_{0-\infty}$ (ng*h/mL)[b]	1416 (535, 1969)	2984 (1606, 4273)	2007 (1007, 10092)	6459 (2548, 21020)[a]
$T_{1/2}$ (min)	37.1 (22.5, 56.8)	32.5 (18.0, 42.9)	18.9 (9.20, 57.9)	28.7 (11.3, 104)[a]
CL (L/h)	30.5 (17.4, 37.8)	15.8 (11.7, 24.9)	30.5 (6.79, 68.0)	18.5 (6.20, 37.9)[a]
V_{ss} (L)	14.9 (10.1, 35.6)	8.80 (3.75, 21.4)	11.7 (2.3, 22.7)	10.7 (1.4, 18.5)[a]

[a] n = 14

[b] Values were derived from concentration data expressed in ng/mL

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term studies in animals to evaluate carcinogenic potential or studies to evaluate mutagenic potential have not been performed with taliglucerase alfa. In a male and female fertility study in rats, taliglucerase alfa did not cause any significant adverse effect on male or female fertility parameters up to a maximum dose of 55 mg/kg/day (about 5 times the recommended human dose of 60 units/kg based on the body surface area).

14 CLINICAL STUDIES

14.1 Clinical Trials of ELELYSO as Initial Therapy

Clinical Trial in Patients 19 Years and Older

The safety and efficacy of ELELYSO were assessed in 31 adult patients with Type 1 Gaucher disease. The trial was a 9-month, multi-center, double-blind, randomized trial in patients with Gaucher disease-related enlarged spleens (>8 times normal) and thrombocytopenia (<120,000 /mm³). Sixteen patients had enlarged livers and ten patients had anemia at baseline. All patients were naïve to ERT. Patients with severe neurological symptoms were excluded from the trial. Patients were 19 to 74 years of age (mean age 36 years), and 48% were male. Patients were randomized to receive ELELYSO at a dosage of either 30 units/kg (n=15) or 60 units/kg (n=16) every other week. The recommended dosage in treatment-naïve adult patients is 60 units/kg every other week. ELELYSO 30 units/kg every other week is not a recommended dosage *[see Dosage and Administration (2.1)]*.

Table 4 shows the baseline values and mean (SD) changes in clinical parameters (spleen volume, liver volume, platelet count, and hemoglobin) after 9 months of treatment with ELELYSO. For all clinical trials, liver and spleen volumes were measured by MRI and are reported as percentage of body weight (%BW) and multiples of normal (MN). The observed change from baseline in the primary endpoint, reduction in spleen volume, was considered to be clinically meaningful in light of the natural history of untreated Gaucher disease.

Table 4: Mean (SD) Changes in Clinical Parameters from Baseline to 9 Months in Treatment-Naïve Adults with Type 1 Gaucher Disease Initiating Therapy with ELELYSO (N=31)**

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

*The recommended ELELYSO dosage in treatment-naïve adult patients is 60 units/kg every other week. ELELYSO 30 units/kg every other week is not a recommended dosage. *[see Dosage and Administration (2.1)]*

** *SD = standard deviation*

‡ *%BW = percentage of body weight*

MN = multiples of normal

Twenty-six of the 31 patients in this 9-month clinical trial continued blinded treatment with ELELYSO in an extension trial for a total treatment duration of 24 months. The following data are the changes in clinical parameters from baseline to Month 24 for the 30 units/kg (n=12) and 60 units/kg (n=14) dose groups, respectively: mean (SD) spleen volume (%BW) decreased by 1.4 (0.6) and 2.0 (2.0), in MN by 6.8 (3.0) and 10.2 (9.8); hemoglobin increased by 1.3 (1.7) g/dL and 2.4 (2.3) g/dL; liver volume (%BW) decreased by 1.1 (0.5) and 1.0 (0.7), in MN by 0.4 (0.2) and 0.4 (0.3 and platelet count increased 28,433 (31,996)/mm^3 and 72,029 (68,157)/mm^3. Twenty-three of the 26 patients who continued open-label treatment with ELELYSO for additional 12 months demonstrated stability in these clinical parameters.

Clinical Trial in Patients 16 years and Younger

The safety and efficacy of ELELYSO were assessed in 9 pediatric patients with Type 1 Gaucher disease. The trial was a 12-month, multi-center, double-blind, randomized study in treatment-naïve patients. Patients were 2 to 13 years of age (mean age 8.1 years), and 67% were male. Patients were randomized to receive ELELYSO at a dosage of either 30 units/kg (n=4) or 60 units/kg (n=5) every other week. The recommended ELELYSO dosage in treatment-naïve pediatric patients is 60 units/kg every other week. ELELYSO 30 units/kg every other week is not a recommended dosage *[see Dosage and Administration (2.1)]*.

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

Nine pediatric patients in the 12-month clinical trial continued blinded treatment with ELELYSO in an extension trial for a total treatment duration of 24 months. The following data are the changes [median (Q1, Q3)] in clinical parameters from baseline to Month 24 for the 60 units/kg dose group (n=5): spleen volume decreased by 19.0 (8.3, 41.2) MN; hemoglobin increased by 2.5 (1.9, 3.0) g/dL; liver volume decreased by 0.8 (0.6, 1.1) MN; and platelet count increased by 76,000 (67,000, 100,000)/mm^3.

14.2 Clinical Trial in Patients Switching from Imiglucerase Treatment to ELELYSO

The safety and efficacy of ELELYSO were assessed in 31 patients (26 adult and 5 pediatric patients) with Type 1 Gaucher disease who were switched from imiglucerase to ELELYSO. The trial was a 9-month, multi-center, open-label, single arm study in patients who had been receiving treatment with imiglucerase at dosages ranging from 9.5 units/kg to 60 units/kg every other week for a minimum of 2 years. Patients were required to be clinically stable and have a stable biweekly dose of imiglucerase for at least 6 months prior to enrollment. Patients were 6 to 66 years of age (mean age 42 years, including pediatric patients), and 55% were male. Imiglucerase therapy was stopped, and treatment with ELELYSO was administered every other week at the same number of units as each patient's previous imiglucerase dose. If needed, adjustment of dosage was allowed during the study in order to maintain stability of clinical parameters (i.e., spleen volume, liver volume, platelet count, and hemoglobin).

Mean (SD) organ volumes and hematologic values remained stable through 9 months of ELELYSO treatment. At baseline, spleen volume was 5.2 (4.5) MN, liver volume was 1.0 (0.3) MN, platelet count was 161,137 (73,387)/mm^3, and hemoglobin was 13.5 (1.4) g/dL. After 9 months of ELELYSO treatment, spleen volume was 4.8 (4.6) MN, liver volume was 1.0 (0.2) MN, platelet count was 161,167 (80,820)/mm^3, and hemoglobin was 13.4 (1.5) g/dL. ELELYSO dose remained unchanged in 30 of 31 patients. One patient required a dose increase at Week 24 (from 9.5 units/kg to 19 units/kg) for a platelet count of 92,000/mm^3 at Week 22, which subsequently increased to 170,000/mm^3 at Month 9.

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

Five pediatric patients in the 9-month clinical trial who continued open-label treatment with ELELYSO for additional 24 months demonstrated stability in these clinical parameters.

16 HOW SUPPLIED/STORAGE AND HANDLING

ELELYSO is supplied as a lyophilized powder in single use vials. Each vial contains 200 units of ELELYSO.

NDC 0069-0106-01, 200 units per vial

Store ELELYSO under refrigeration at 2°C to 8°C (36°F to 46°F). Do not freeze. Protect vials from light.

As ELELYSO contains no preservative, the product should be used immediately once reconstituted. If immediate use is not possible, the reconstituted product may be stored for up to 24 hours at 2 to 8 °C (36 to 46 °F) under protection from light or up to 4 hours at 20 to 25 °C (68 to 77 °F) without protection from light. The diluted product may be stored for up to 24 hours at 2 to 8 °C (36 to 46 °F) under protection from light. Storage of the reconstituted product and the diluted product should not exceed a total of 24 hours. Do not freeze. Discard any unused product.

17 PATIENT COUNSELING INFORMATION

Hypersensitivity Reactions Including Anaphylaxis

Advise patients and caregivers that reactions related to administration and infusion may occur during and after ELELYSO treatment, including life-threatening anaphylaxis and severe hypersensitivity reactions. Inform patients of the signs and symptoms of anaphylaxis and hypersensitivity reactions, and have them seek medical care should signs and symptoms occur. Inform patients that they should be carefully re-evaluated for treatment with ELELYSO if serious hypersensitivity reactions, including anaphylaxis, occur. Reduction of the infusion rate and/or pre-treatment with antihistamines, antipyretics and/or corticosteroids may prevent subsequent reactions *[see Warnings and Precautions (5.1)]*.

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14.2 Appendix 2: Infusion Rate Algorithm

The infusion rate (IR) may be adjusted according to individual subject symptoms and signs. The assumptions with respect to adverse experiences to the infusion are:

1. Most of the subjects will tolerate the infusion without any special symptom or event. The infusion rate may be increased over time to the maximal rate 2.0 mL/minute (or 120 mL/hour) only after discussion with the Medical Monitor (an infusion duration of 1 hour).

2. Subjects presenting symptoms and signs of **severe** hypersensitivity will be evaluated according to the WHO Drug Toxicity criteria and there may be a discontinuation of treatment according to the protocol.

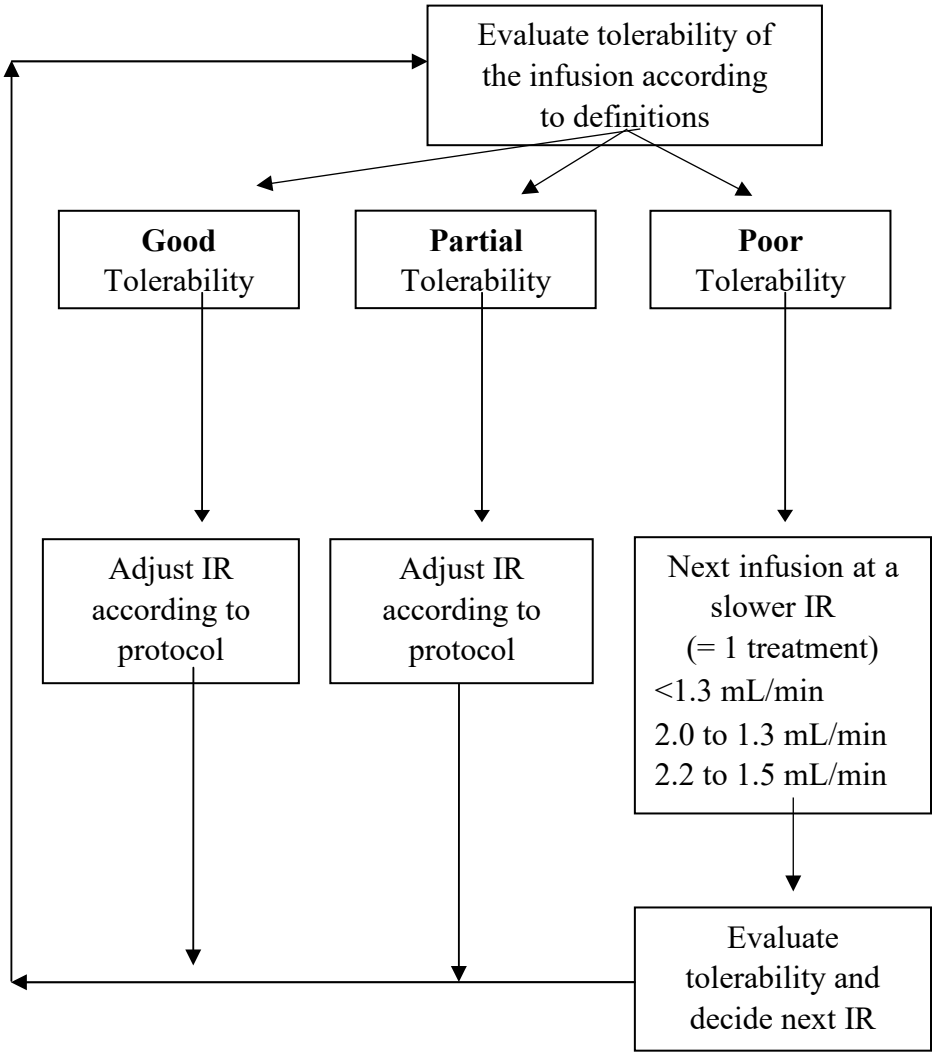
3. Subjects may present signs and symptoms that will respond to reducing of the infusion rate and may not appear at the next infusion.

4. Tolerability and the subject specific infusion rate will be assessed and decided by the Investigator according to vital signs and clinical status of the subject.

Definitions to be applied regarding tolerability of infusions are as follows:

Good Tolerability	**Partial Tolerability**	**Poor Tolerability**
Infusion was performed without signs and symptoms (such as burning, pruritus, flushing, discomfort, or change in vital signs).	Signs and symptoms appeared during the infusion **and resolved after slowing infusion rate** or at the end of the infusion.	Signs and symptoms meeting the definitions of WHO Grade 1 or 2 toxicity responding to reduction of infusion rate or responding to treatment (example, antihistamine for urticaria).

The specific algorithm to be followed is below.


Evaluate tolerability of the infusion according to definitions
Good Tolerability
Partial Tolerability
Poor Tolerability
Adjust IR according to protocol
Adjust IR according to protocol
Next infusion at a slower IR (= 1 treatment)
<1.3 mL/min
2.0 to 1.3 mL/min
2.2 to 1.5 mL/min
Evaluate tolerability and decide next IR

14.3 Appendix 3: Taliglucerase Alfa Hypersensitivity Evaluation and Treatment Algorithm

During and after infusion of taliglucerase alfa, the following algorithm will be followed to monitor and manage the occurrence of hypersensitivity, anaphylaxis, or anaphylactoid reactions.

Clinical Signs

Early

- Sensations of warmth and itching
- Feelings of anxiety or panic

Moderate

- Pruritus
- Flushing
- Urticaria
- Chest discomfort
- Mild hypotension

Progressive

- Erythematous or massive urticarial rash
- Edema of face, neck, soft tissues

Severe

- Hypotension
- Bronchospasm (wheezing)
- Laryngeal edema (dyspnea, stridor, aphonia, drooling)
- Arrhythmias

Treatment Algorithm

With the onset of any of the above clinical signs, immediately discontinue study medication administration and initiate the following monitoring:

- Continuous electrocardiographic monitoring
- Continuous pulse oximetry
- Measure blood pressure every 5 minutes
- Perform chest auscultation every 5 minutes

- Blood samples need to be collected for Tryptase (29-33) and antibodies. Tryptase samples need to be withdrawn at:
  - 1st sample taken 0.25-3 hours after onset of symptoms
  - 2nd sample taken between 3-6 hours
  - 3rd sample taken 24-48 hours to verify the return to baseline

In the case of progressive or severe hypersensitivity, treat appropriately and withdraw the subject from the study. Treat as detailed below.

Urticaria or edema of the face, neck, or soft tissues

- Epinephrine 1:1000 solution, 0.5 mL subcutaneously, repeat as needed every 5-10 minutes
- Antihistamines
- Corticosteroids

Hypotension (systolic blood pressure (SBP) ≤90 mmHg)

- Isotonic sodium chloride solution, 1 L every 30 minutes as needed to maintain SBP >90 mmHg
- Epinephrine 1:10,000 solution given IV at 1 µg/minute initially, then 2-10 µg/minute to maintain SBP >90 mmHg
- Norepinephrine 4 mg in 1 L 5% dextrose in water given IV at 2-12 µg/minute to maintain SBP >90 mmHg
- Glucagon 1 mg in 1 L 5% dextrose in water given IV at 5-15 µg/minute for refractory hypotension

Bronchospasm

- Oxygen by face mask at 6-8 L/minute to maintain oxygen saturation at >90%
- Epinephrine 1:1000 solution, 0.5 mL subcutaneously
- Albuterol 0.5 mL of 0.5% solution in 2.5 mL of sterile saline every 15 minutes up to three doses
- Inhaled beta-agonists
- Corticosteroids

Laryngeal edema

- Epinephrine 1:1000 solution, 0.5 mL subcutaneously, repeat as needed every 5 to 10 minutes
- Corticosteroids

Premedication

Premedication for subsequent taliglucerase alfa infusions may be considered at the discretion of the Investigator and Medical Monitor for subjects experiencing early clinical signs of hypersensitivity or rash/urticaria that responds promptly to oral antihistamine administration (see also Appendix 14.2 for adjustment of infusion rate). The premedication will be applied according to the following steps as needed to prevent progressive hypersensitivity:

- Antihistamine (H1 blocker: diphenhydramine, hydroxyzine, cetrizine, loratadine, desloratidine) at a standard dose 12 hours and 2 hours before the start of the infusion
- H1 blocker plus H2 blocker (ranitidine, cimetidine, famotidine) at standard doses 12 hours and 2 hours before the start of the infusion
- H1 blocker plus H2 blocker plus prednisone up to 50 mg administered 12 hours and 2 hours before the start of the infusion

14.4 Appendix 4: Magnetic Resonance Imaging (MRI)

14.4.1 Subject and Sites

Nine subjects will be enrolled in this study by 5 to 10 sites worldwide.

14.4.2 MRI Data

Each subject enrolled in this study will have 2 MRI time points during the course of the trial at Baseline and Month 12 (or early termination). For each time point, the same set of T1 and T2-weighted MRI sequences will be acquired. An imaging manual will be shared with sites to outline the scanning protocol. The exact sequence parameters will be defined based on site's equipment and abilities to provide sufficient image quality and contrast for organ (spleen and liver) detection and quantification, and full spleen and liver coverage in GD subjects. No contrast agent will be used.

An MRI of the abdomen containing the entire spleen and liver will be collected at the Screening visit (Day -25 ± 10) and Week 52 Visit (± 7 days). Volumes of liver and spleen will be evaluated centrally by an independent radiologist. All scans should be submitted within 2 days of acquisition to allow quality review by the central radiologist. . The MRI site must confirm the scan is acceptable prior to sending images for central review. The inspection by the site will include complete anatomic coverage of the liver and spleen. Scans that are not accepted by the central radiologist may result in rescan requests. The method of evaluation used for each patient at baseline should remain consistent for the duration of the study. In instances when the scan must be repeated (ie, if upon submission to the central radiologist, quality control issues are identified and communicated to the site) the repeated scan must be evaluated.

14.4.3 MRI Evaluation Parameters

The following MRI parameters will be evaluated during this study:

- Volume of spleen (in cm^3)
- Volume of liver (in cm^3)

14.4.3.1 Standardization of Image Acquisition, Initial Site Qualification

The image acquisition procedure will be provided to sites in a separate image acquisition manual. The same image acquisition and management procedure will be used by all sites. All images will be anonymized by the sites (in order to remove any subject-related nominative information) and provided in digital format (DICOM). Only digital images will be centrally processed by the central radiologist.

14.4.3.2 Subject Sedation

Pediatric subjects may require sedation in order to obtain the high quality images required. Sites may use standard sedation protocols approved by the institution.

14.4.3.3 Quality Control of Image Data and Site Quality Assurance During the Course of the Study

The image data will be collected and quality inspected by the central radiologist for checking the technical adequacy, the compliance of data acquisition with the imaging guidelines and the

diagnostic quality of the images (their appropriateness for centralized evaluations). If any quality-related issue is detected by the central reviewer this will be communicated to the site.

14.5 Appendix 5: WHO Common Toxicity Criteria

Category	Toxicity	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
Hematology	WBC ($x10^3$/L)	4	3.0 - 3.9	2.0 - 2.9	1.0 - 1.9	< 1.0
Hematology	Platelets ($x10^3$/L)	WNL	75.0 - normal	50.0 - 74.9	25.0 - 49.9	< 25.0
Hematology	Hemoglobin (g/dL)	WNL	10.0 - normal	8.0 - 9.9	6.5 - 7.9	< 6.5
Hematology	Granulocytes/ Bands	2	1.5 - 1.9	1.0 - 1.4	0.5 - 0.9	< 0.5
Hematology	Lymphocytes ($x10^3$/L)	2	1.5 - 1.9	1.0 - 1.4	0.5 - 0.9	< 0.5
Hematology	Hemorrhage	none	mild, no	gross, 1 - 2 units transfusion per episode	gross, 3 - 4 units transfusion per episode	massive, > 4 units transfusion per episode
Coagulation	Fibrinogen	WNL	0.99 - 0.75 x N	0.74 - 0.50 x N	0.49 - 0.25 x N	< 0.25 x N
Coagulation	Prothrombin time(Quick)	WNL	1.01 - 1.25 x N	1.26 - 1.50 x N	1.51 - 2.00 x N	> 2.00 x N
Coagulation	Partial thrombo-plastin time	WNL	1.01 - 1.66 x N	1.67 - 2.33 x N	2.34 - 3.00 x N	> 3.00 x N
Metabolic	Hyperglycemia (mg/dL)	< 116	116 - 160	161 - 250	251 - 500	> 500 or ketoacidosis
Metabolic	Hypoglycemia (mg/dL)	> 64	55 – 64	40 - 54	30 - 39	< 30
Metabolic	Amylase	WNL	< 1.5 x N	1.5 - 2.0 x N	2.1 - 5.0 N	> 5.0 x N
Metabolic	Hypercalcemia (mg/dL)	< 10.6	10.6 - 11.5	11.6 - 12.5	12.6 - 13.4	13.5
Metabolic	Hypocalcemia (mg/dL)	> 8.4	8.4 - 7.8	7.7 - 7.0	6.9 - 6.1	6
Metabolic	Hypomagnesemia (mg/dK)	> 1.4	1.4 - 1.2	1.1 - 0.9	0.8 - 0.6	0.5

Category	Toxicity	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
Gastrointestinal	Nausea	none	able to eat reasonable intake	intake significantly decreased but can eat	no significant intake	-----
Gastrointestinal	Vomiting	none	1 episode in 24 hrs	2 - 5 episodes in 24 hrs	6 - 10 episodes in 24 hrs	> 10 episodes in 24 hrs or requiring parenteral support
Gastrointestinal	Diarrhea	none	increase of 2 - 3 stools / day over pre-Rx	increase of 4 - 6 stools / day, or nocturnal stools, or moderate cramping	increase of 7 - 9 stools / day, or incontinence, or severe cramping	increase of > 10 stools / day or grossly bloody diarrhea, or need for parenteral support
Gastrointestinal	Stomatitis	none	painless ulcers, erythema, or mild soreness	painful erythema, edema, or ulcers but can eat solids	painful erythema, edema, or ulcers and cannot eat solids	requires parenteral or enteral support for alimentation
Liver	Bilirubin (N = 17 µmol/L)	WNL	-----	< 1.5 x N	1.5 - 3.0 x N	> 3.0 x N
Liver	Transaminase (SGOT, SGPT)	WNL	2.5 x N	2.6 - 5.0 x N	5.1 - 20.0 x N	> 20.0 x N
Liver	Alk phos or 5 nucleotidase	WNL	< 2.5 x N	2.6 - 5.0 x N	5.1 - 20.0 x N	> 20.0 x N
Liver	Liver- clinical	No change from baseline	-----	-----	precoma	hepatic coma
Kidney, bladder	Creatinine	WNL	< 1.5 x N	1.5 - 3.0 x N	3.1 - 6.0 x N	> 6.0 x N
Kidney, bladder	Proteinuria	No change	1 (+) or < 0.3 g% or 3 g/L	2 - 3 (+) or 0.3 - 1.0 g% or 3 - 10 g/L	4 (+) or > 1.0 g% or > 10g/L	nephrotic syndrome
Kidney, bladder	Hematuria	Negative	microscopic only	gross, no clots no Rx needed	gross and clots bladder irrigation	requires trans fusion or cystectomy
Kidney, bladder	Weight gain/ loss	< 5.0 %	5.0 - 9.9 %	10.0 - 19.9 %	20.00%	-----
Pulmonary	Pulmonary	none or no change	asymptomatic, with abnormality in PFTs	dyspnea on significant exertion	dyspnea at normal level of activity	dyspnea at rest

Category	Toxicity	Grade 0	Grade1	Grade2	Grade3	Grade4
Cardiac	Cardiac arrhythmias	none	asymptomatic, transient, requiring no therapy	recurrent or persistent, no therapy required	requires treatment	requires monitoring; or hypotension, or ventricular tachycardia or fibrillation
Cardiac	Cardiac function	none	asymptomatic, decline of resting ejection fraction by less than 20 % of baseline value	asymptomatic, decline of resting ejection fraction by more than 20 % of baseline value	mild CHF, responsive to therapy	severe of refractory CHF
Cardiac	Cardiac ischemia	none	non-specific T- wave flattening	asymptomatic, ST and T wave changes suggesting ischemia	angina without evidence of infraction	acute myocardial infarction
Cardiac	Cardiac-pericardial	none	asymptomatic effusion, no intervention required	pericarditis (rub, chest pain, ECG changes)	symptomatic effusion; drainage required	tamponade; drainage urgently required
Cardiac	Hypertension	none or no change	asymptomatic, transient increase by greater than 20 mm Hg (D) or to > 150 / 100 if previously WNL. No treatment required.	recurrent or persistent increase by greater than 20 mm HG (D) or to > 150 / 100 if previously WNL. No treatment required.	requires therapy	hypertensive crisis
Cardiac	Hypotension	none or no change	changes requiring no therapy (including transient orthostatic hypotension)	requires fluid replacement or other therapy but not hospitalization	requires therapy and hospitalization; resolves within 48 hours of stopping the agent	requires therapy and hospitalization for > 48 hrs after stopping the agent
Neurologic	Neuro: sensory	none or no change	mild paresthesia; loss of deep tendon reflexes	mild or moderate objective sensory loss moderate paresthesia	severe objective sensory loss or paresthesia that interfere with function	-----
Neurologic	Neuro: motor	none or no change	subjective weakness; no objective findings	mild objective weakness without significant impairment of function	objective weakness with impairment of function	paralysis

Category	Toxicity	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
Neurologic	Neuro: cortical	none	mild somnolence or agitation	moderate somnolence or agitation	severe somnolence, (>50% waking hours), agitation, confusion, disorientation or hallucinations	coma, seizures, toxic psychosis
Neurologic	Neuro: cerebellar	none	slight incoordination, dysdiadochokinesia	intention tremor, dysmetria, slurred speech, nystagmus	locomotor ataxia	cerebellar necrosis
Neurologic	Neuro: mood	no change	mild anxiety or depression	moderate anxiety or depression	severe anxiety or depression	suicidal ideation
Neurologic	Neuro: headache	none	mild	moderate or severe but transient	unrelenting and severe	-----
Neurologic	Neuro: constipation	none or no change	mild	moderate	severe	ileus > 96 hrs
Neurologic	Neuro: hearing	none or no change	asymptomatic, hearing loss on audiometry only	tinnitus	hearing loss interfering with function but correctable with hearing aid	deafness not correctable
Neurologic	Neuro: vision	none or no change	-----	-----	symptomatic subtotal loss of vision	blindness
Pain	Pain	none	mild	moderate	severe	requires narcotics
Skin	Skin	none or no change	scattered macular or papular eruption or erythema that is asymptomatic	scattered macular or papular eruption or erythema with pruritus or other associated symptoms	generalized symptomatic macular, papular or vesicular eruption	exfoliative dermatitis or ulcerating dermatitis
Alopecia	Alopecia	no loss	mild hair loss	pronounced or total hair loss	-----	-----

Category	Toxicity	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
Allergy	Allergy	none	transient rash, drug fever < 38°C (100.4°F)	urticaria, drug fever 38°C (100.4°F), mild bronchospasm	serum sickness, bronchospasm requiring parenteral medication	anaphylaxis
Local	Local	none	pain	pain and swelling with inflammation or phlebitis	ulceration	plastic surgery indicated
Fever of unknown origin	Fever of unknown origin	none	37.1 - 38.0°C 98.7° - 100.4°F	38.1 - 40.0°C 100.5 - 104°F	> 40.0°C > 104.0°F for less than 24hrs	> 40.0°C (>104°F) for more than 24 hrs or accompanied by hypotension
Infection	Infection	none	mild	moderate	severe	life-threatening
Additional events	Asthenia	analogous to Karnofsky index (WHO grading)				
Additional events	Chills	Analogous to fever				
Additional events	Peripheral edema	analogous to weight gain				
Additional events	Anorexia	analogous to weight loss				