NON-INTERVENTIONAL (NI) STUDY PROTOCOL

Study information

Title	A MULTICENTER, MULTICOUNTRY, POSTMARKETING ACTIVE SURVEILLANCE TALIGLUCERASE ALFA REGISTRY IN PATIENTS WITH GAUCHER DISEASE
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2. ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation	Definition
ACE	Angiotensin Converting Enzyme
ADA	Anti-Drug Antibody
AE	Adverse Event
AEM	Adverse Event Monitoring report form
ALT	Alanine Aminotransferase
ATC	Anatomical Therapeutic Chemical
aPTT	Activated Partial Thromboplastin Time
ART	Assisted Reproductive Technology
CCL18	Chemokine (C-C motif) Ligand 18
CIOMS	Council for International Organizations of Medical Sciences
CRF	Case Report Form
CT	Computed Tomography
DMP	Data Management Plan
DRL	Drug Reference List
eCRF	Electronic Case Report Form
EDP	Exposure during Pregnancy
EMA	European Medicines Agency
ENCePP	European Networks for Centres for Pharmacoepidemiology and Pharmacovigilance
ERT	Enzyme Replacement Therapy
FDA	United States Food and Drug Administration
GBA	Glucocerebrosidase
GGT	Gamma-glutamyltransferase
GOS	Gaucher Outcome Survey
GPP	Good Pharmacoepidemiology Practices
ICGG	International Collaborative Gaucher Group
ICU	Intensive Care Unit
IRB/IEC	Institutional Review Board/Independent Ethics Committee
IEA	International Epidemiological Association
ISPE	International Society for Pharmacoepidemiology
ISPOR	International Society for Pharmacoeconomics and Outcomes Research
LMP	Last Menstrual Period
MedDRA	Medical Dictionary for Regulatory Activities
MGUS	Monoclonal Gammopathy of Unknown Significance
MRI	Magnet Resonance Imaging
NI	Non-Interventional
NIS	Non-Interventional Study
NORD	National Organization for Rare Disorders

PASS	Post-Authorization Safety Study
PMR	Post-Marketing Requirement
PT	Prothrombin Time
PTT	Partial Thromboplastin Time
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SRT	Substrate Reduction Therapy
TIBC	Total Iron Binding Capacity
TRAP	Tartrate Resistant Acid Phosphatase
TSH	Thyroid Stimulating Hormone
US	Ultrasound
VPRIV	Velaglucerse alfa for injection
WHO	World Health Organization

3. RESPONSIBLE PARTIES

Principal Investigator(s) of the Protocol

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4. ABSTRACT

Title

A MULTICENTER, MULTICOUNTRY, POSTMARKETING ACTIVE SURVEILLANCE TALIGLUCERASE ALFA REGISTRY IN PATIENTS WITH GAUCHER DISEASE

Version and Date of Protocol

Protocol Amendment 5, 07 August 2017

Names and Affiliations of Principal Investigators of the Protocol

Lina Titievsky, Pfizer Inc.

Rationale and Background

Taliglucerase alfa for injection is a hydrolytic lysosomal glucocerebroside-specific enzyme indicated for long-term enzyme replacement therapy (ERT) for adult and pediatric patients with a confirmed diagnosis of Type 1 Gaucher disease. In the United States Taliglucerase alfa received approval in adult patients in 2012 and in pediatric patients in 2014. This taliglucerase alfa exposure registry is being conducted as Post-Marketing Requirement (PMR) to the United States Food and Drug Administration (FDA), and has been designated

as a Post-Authorization Safety Study (PASS) by the sponsor. The purpose of the registry is to evaluate the long-term safety and effectiveness of taliglucerase alfa for Gaucher disease patients being treated with taliglucerase alfa.

As part of this PMR, a pregnancy and lactation exposure-related sub-study will be conducted to follow all female patients who are/get pregnant and/or breastfeed while in the Drug Registry and their infants up to the child's first birthday, regardless of the treatment they receive for their Gaucher Disease during that time but with the primary exposure of interest being taliglucerase alfa.

Research Question and Objectives

- The primary objective of the registry is to characterize the safety profile of taliglucerase alfa through the solicited collection and summary of non-serious and serious adverse event data;

- The secondary objective of the registry is to characterize the effectiveness of taliglucerase alfa through the collection and analysis of Gaucher disease measures, including hematologic (hemoglobin and platelet count) and organ volume (spleen and liver) assessments.

The primary objectives of the pregnancy and lactation exposure-related sub-study are:

- To assess pregnancy outcomes of female Drug Registry participants exposed to taliglucerase alfa at any time during pregnancy;

- To assess clinical outcomes of newborns of female Drug Registry participants potentially exposed to taliglucerase alfa in utero;

- To assess clinical outcomes of infants potentially exposed to taliglucerase alfa through breast milk or in utero, up to the child's first birthday.

Sample size permitting, exploratory objectives of the pregnancy and lactation exposure related sub-study are provided in section 9.15.1.

Study Design

To gather data on the long term safety and effectiveness of taliglucerase alfa in the real world post-marketing setting, Pfizer will conduct a prospective non-interventional active surveillance drug registry of patients with Gaucher disease undergoing taliglucerase alfa treatment (referred to as the "**Drug Registry**"). The registry will be open for at least ten years.

The pregnancy and lactation exposure-related sub-study will be **nested** within the Drug Registry (and is referred to as the "**Pregnancy/Lactation Sub-Study**"). The Pregnancy/Lactation Sub-Study will be open for the maximum of 11 years (i.e.,

approximately 1 year beyond the end of data collection in the Drug Registry in an instance if a woman becomes pregnant during the last 9 months of the Drug Registry).

Drug Registry:

- **Study Population**

  The study population eligible for the Drug Registry includes any patient with Gaucher disease who is initiating or is currently receiving taliglucerase alfa treatment and meets inclusion criteria. Drug Registry patients may potentially be recruited from countries where Pfizer has made taliglucerase alfa commercially available, including the United States. Pfizer will make the registry participation available to non-Pfizer entities commercializing taliglucerase alfa. However, such registry participation will be at the non-Pfizer entities' discretion.

- **Variables**

  Demographic, medical history including obstetrics history in female patients, treatment history, clinical measures, safety, clinical effectiveness, and anti-taliglucerase alfa antibody status variables will be collected.

- **Data Sources**

  The primary data sources for the Drug Registry and the Pregnancy/Lactation Sub-Study will be the patient medical record and patient interview, if relevant. All study data will be captured in an electronic case report form (eCRF).

- **Study Size**

  Given the rarity of Gaucher disease, and the fact that, in the United States there are two ongoing Gaucher disease registries, the number of participants is expected to be small. For this reason, no hypotheses have been pre-specified and sample size calculations are not applicable.

- **Data Analysis**

  Data will be analyzed using descriptive statistics. For outcomes of interest, summary statistics, frequencies, crude cumulative incidence proportion, and crude incidence rates per person-time will be calculated as appropriate. Further exploratory analyses will be developed as necessary.

Pregnancy/Lactation Sub-Study:

- **Population**

  The study population eligible for this sub-study are all female Drug Registry participants who are or become pregnant during the Drug Registry and/or all female Drug Registry participants who breastfeed during the course of the

Drug Registry. All pregnant and/or breastfeeding women enrolled in the Drug Registry will be approached for participation in the sub-study regardless of whether they are receiving taliglucerase alfa for their Gaucher Disease at the time of their pregnancy/breastfeeding. This is because during the 10 years of the Drug Registry duration and in particular, during the pregnancy/breastfeeding time period, women may switch and/or discontinue their treatment with taliglucerase alfa for various reasons.

- **Variables**

  In addition to all the variables collected as part of the Drug Registry, specific variables to the Pregnancy/Lactation Sub-Study include information on the course of pregnancy, pregnancy outcomes in the mother and offspring, and infant outcomes.

- **Data Sources**

  The primary data sources for the Pregnancy/Lactation Sub-Study will be the patient medical record and patient interview, if relevant. All study data will be captured in an electronic case report form (eCRF).

- **Sample Size**

  Since a small number of patients are expected to participate in the Drug Registry, few female patients are expected to get pregnant and/or breastfeed, and even fewer will be exposed to taliglucerase alfa in utero or during breastfeeding. For this reason, no hypotheses have been pre-specified and sample size calculations are not applicable.

- **Data Analysis**

  Data will be summarized using descriptive statistics. For outcomes of interest, summary statistics, frequencies, crude cumulative incidence proportion, and crude incidence rates per person-time will be calculated as appropriate.

Milestones

Milestone	Planned date
Completion of feasibility assessment	September 2012
Final protocol	June 2013
Start of data collection	October 2013
Interim report	July 2019
End of data collection	October 2023
Final study report	July 2024

5. AMENDMENTS AND UPDATES

Amendment number	Date	Substantial or administrative amendment	Protocol section(s) changed	Summary of amendment(s)	Reason
1	01 August 2013	Administrative	9.12.5, 9.12.6 and 9.12.7	The section was revised to include that the frequency of assessments in an infant potentially exposed to taliglucerase alfa in utero and/or during breastfeeding will be more than once per year, i.e., three or more times in the first year of life such as at 0 months (i.e., birth and shortly after), 4 months and 12 months 9.4, footnote 12 in Table 1 and footnote 8 in Table 2 Clarification has been added that the collection of samples for antibody testing be done prior to the administration of taliglucerase alfa, when the drug concentration is low.	FDA request

2	13 August 2013	Administrative	9.4 Table 1 • Clarification of pediatric baseline assessments. • Clarification of biomarkers as separate assessment category. • Clarification of testing if abnormal liver enzymes detected. • Reiteration of sampling time for ADA obtained to assess infusion reaction. 9.4 Table 2 • Clarification of biomarkers as separate assessment category. • Clarification of testing if abnormal liver enzymes detected. • Addition of tryptase sampling and timing of sampling. 9.5 • Correction that recommended study assessments are in Section 9.4.. • Addition of tryptase sampling if immune/infusion reaction (footnote 6 Table 2). 9.15.9 Table 3 • Clarification of footnotes	FDA request and clarifications
3	11 October 2013	Administrative	9.4 Table 1 • Clarification of footnote 12. 9.4 Table 2 • Clarification of footnote 7. 9.5 • Further clarification and elaboration on the antibody testing due to adverse reactions and the type adverse reactions. 9.12.4 • Addition of text to clarify that the eligibility for the sub-study differs from requirements for reporting exposure-in-utero. For the purposes of management and reporting of adverse events/adverse reactions as per Pfizer's processes and reporting obligations (see Section 11) both maternal and paternal exposures are reportable. However, the sub-study only includes women and their potentially exposed offspring if the woman is directly exposed to taliglucerase alfa (i.e., via maternal exposure) and enrolled in the Drug Registry. That is, women and their	FDA IRB communication

			potentially exposed offspring are not eligible for the sub-study if exposed through paternal exposure to taliglucerase alfa only. 11.0, page 33 • Addition of text that outlines new adverse event reporting requirements for non-interventional studies in respect to the reports of overdose, misuse and extravasation associated with the use of a Pfizer product as well as the occupational exposure to a Pfizer product.	Change in AEM01-POL 1.0 Adverse Event Monitoring System (Pfizer SOP) effective 28-Oct-2013
4	20 March 2015	Substantial	Updated language/editorial changes to Section 9.13 DRUG REGISTRY: MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS and addition of Section 9.15.13 Pregnancy/lactation sub-study: management and reporting of adverse events/adverse reactions. Additional language has been added to clarify the differences associated with safety reporting and collection of exposure during pregnancy (EDP) and exposure during breastfeeding between the participants in Drug Registry only vs. Drug Registry and pregnancy/lactation sub-study. Specifically: • The two sections within 9.13, specific to exposure during pregnancy (EDP) 9.13.4.1 and to exposure during breastfeeding 9.13.4.2, apply only to those female patients **who do not consent** to be part of the pregnancy/lactation sub-study and to pregnant female partners of male study participants. • For those female patients **who meet the eligibility of the pregnancy/lactation sub-study and consent to be part of the pregnancy/lactation sub-study**, the safety reporting criteria specified in section 9.15.13 should be followed for reporting EDP and/or exposure during breastfeeding.	Clarification

			Editorial changes to Section 9.15.4 Inclusion Criteria in the Pregnancy/Lactation Sub-Study, Section 9.15.5 Exclusion Criteria in the Pregnancy Lactation Sub-Study and inclusion of Figure 3 to further clarify eligibility criteria into the Pregnancy/lactation sub-study, i.e. the pregnancy/lactation sub-study only includes women and their potentially exposed offspring if the woman is directly exposed to taliglucerase alfa (i.e. via maternal exposure) and enrolled in the Drug Registry and/or if she is exposed to taliglucerase alfa at any time during the first year of breastfeeding and enrolled in the Drug Registry. Women and their potentially exposed offspring are not eligible for this sub-study if exposed through paternal exposure to taliglucerase alfa. Editorial and formatting changes to Section 4 ABSTRACT Editorial changes to Section 9.7 with the intent to clarify that the eCRF is the primary data collection used in the study.	
5	07 August 2017	Substantial	Changes to Section 4 ABSTRACT to align with subsequent changes in Section 9.15 Addition of exploratory objectives to Sections 9.15.1 Update of Figure 2 in Section 9.15.2 Changes to Sections 9.15.3, 9.15.4 and 9.15.5 to reflect broadening of an inclusion criterion to all pregnant and/or breastfeeding women enrolled in the Drug Registry regardless of their exposure to taliglucerase alfa at the time of the pregnancy and/or breastfeeding. This change was necessary given the long duration of the Drug Registry study and in particular, the pregnancy/breastfeeding time period, there is the potential for switch to other Gaucher disease treatments and/or discontinuation from taliglucerase alfa treatment, the Pregnancy/Lactation Sub-Study will include all pregnant and /or breastfeeding women regardless of whether they are taking the taliglucerase alfa during the time of their index pregnancy and/or breastfeeding.	

			Minor editorial changes in Section 9.4, Tables 1 and 2, to align with the content of electronic case report forms (eCRFs) and minor editorial changes throughout Section 9.15	

6. MILESTONES

Milestone	Planned date
Completion of feasibility assessment	September 2012
Final protocol	June 2013
Start of data collection	October 2013
Interim report	July 2019
End of data collection	October 2023
Final study report	July 2024

7. RATIONALE AND BACKGROUND

7.1. Drug Registry

Gaucher disease, the most prevalent lysosomal storage disorder [1,2] is caused by mutations in the human glucocerebrosidase gene *GBA* which has been mapped to chromosome 1 q21-q31.[1,2] β-glucocerebrosidase (β-D-glucosyl-N-acylsphingosine glucohydrolase, E.C. 3.2.1.45) is a lysosomal glycoprotein enzyme that catalyses the hydrolysis of the glycolipid glucocerebroside to glucose and ceramide. The absence or reduced activity of this enzyme leads to the accumulation of glucocerebroside in the cells of the monocyte-macrophage system producing the visceral manifestations of hepatosplenomegaly, anemia, thrombocytopenia, skeletal effects and less frequently lung disease.[3]

Gaucher disease is traditionally classified into three broad phenotypic categories: type 1 (non-neuronopathic disease); type 2, fulminant neuronopathic disease that is fatal during infancy; and type 3, chronic neuronopathic disease.[4] Type 1 Gaucher disease is the most prevalent and accounts for more than 90% of all Gaucher disease patients.[4] According, to the National Organization for Rare Disorders (NORD)[5] there are approximately 6,000 individuals with Gaucher disease in the United States. Gaucher disease is the most common genetic disorder of persons of Ashkenazic Jewish ancestry, where the incidence may be as high as 1 in 450 births.[5]

The identification of human glucocerebrosidase deficiency as the etiology of Gaucher disease corresponded with the development of enzyme replacement therapy (ERT) as a therapeutic strategy for this disorder. ERT has been established as safe and effective over the past 19 years, in over 4000 patients worldwide using either natural (placental-derived) or recombinant human glucocerebrosidase derived from mammalian tissue culture production systems.[6, 7, 8, 9] In Gaucher disease, the affected cells are macrophages which play an important role in scavenging waste material such as red and white blood cells. Enzyme replacement, in turn, is aimed at reducing the accumulated waste material within these macrophages by augmenting the activity of the enzyme and attempting to restore the cell

back to normality.[10] With the marketing of taliglucerase alfa, there are now three enzyme replacement therapies including velaglucerase alfa for injection (VPRIV)[11] which is a hydrolytic lysosomal glucocerebroside-specific enzyme and imiglucerase for injection (Cerezyme), an analogue of the human enzyme β-glucocerebrosidase, produced by recombinant DNA technology.[12]

Taliglucerase alfa is a recombinant active form of the human lysosomal enzyme, β-glucocerebrosidase, expressed in genetically modified carrot plant root cells which are produced in a disposable bioreactor system. Taliglucerase alfa for injection is indicated for long-term enzyme replacement therapy (ERT) for adult and pediatric patients with a confirmed diagnosis of Type 1 (non-neuronopathic) Gaucher disease. In the United States, taliglucerase alfa for injection received initial approval for treatment of adults in 2012 and subsequent approval for treatment of children in 2014.

As of 01 May 2012, a total of 132 patients were treated with taliglucerase alfa in clinical studies, representing a total exposure of 230 person-years. Overall safety results from the clinical program indicate that taliglucerase was generally well-tolerated with non-serious adverse events (AEs) being self-limited and resolving without specific treatment. In clinical studies, none of the serious adverse events (SAEs) reported by adult subjects were considered treatment- related and the majority of subjects recovered. One pediatric subject who experienced a treatment related SAE of gastrointestinal inflammation, recovered and remained on treatment.

There were no unexpected AEs except for alanine aminotransferase (ALT) elevations in some patients who showed a slight trend by dose, however, the hepatic enzyme elevations were not considered to be clinically significant. For class effect infusion-related reactions and allergic reactions, the safety profile of taliglucerase alfa appears to be similar to that of other approved ERTs. Comparison of the incidence of immunogenicity to other ERT is not possible given assay differences. Clinical program data do not suggest an association between anti-taliglucerase antibodies and efficacy. The number of treatment-emergent adverse events from the clinical program in various patient subgroups, by previous ERT and antibody status, is small, which precludes the ability to make conclusions about immunogenicity and its relevance to safety events; additional data are needed.

Real world data on the natural history of Gaucher disease and effectiveness of various treatments for Gaucher disease, including the ERT, have been evaluated as part of two ongoing Gaucher disease registries: the International Collaborative Gaucher Group (ICGG) Gaucher Registry sponsored by Genzyme[13] and Gaucher Outcome Survey (GOS) sponsored by Shire.[14] Both registries are global, multi-center, long-term, observational studies, which are open to all patients diagnosed with Gaucher disease. ICGG was launched in 1991[14] and has information on over 6,000 Gaucher disease patients world-wide.[15]

This taliglucerase alfa exposure registry is being conducted as a Post-Marketing Requirement (PMR) to the United States Food and Drug Administration (FDA), and has been designated as a Post-Authorization Safety Study (PASS) by the sponsor. The purpose of the registry (referred to as the "Drug Registry") is to specifically evaluate the long-term safety and

effectiveness of taliglucerase alfa for Gaucher disease patients being treated with taliglucerase alfa. Detailed clinical status information will be collected for these patients.

7.2. Pregnancy/Lactation Sub-Study

Taliglucerase alfa has been investigated in reproduction studies in pregnant rats and rabbits and there are several human cases reported from both the clinical, compassionate use and post-marketing programs. However, to date, there are no adequate and well controlled taliglucerase alfa studies in pregnant women.

Animal studies were conducted at intravenous doses giving exposures of about 5 times the recommended human dose of 60 Units/kg based on the body surface area. These studies did not reveal any evidence of impaired fertility or harm to the fetus due to taliglucerase alfa.

Six pregnancy cases in 4 patients and the spouse of 1 male patient were reported in the ongoing and completed clinical studies as of 01 February 2013. Four pregnancies resulted in live, healthy births; there was one elective pregnancy termination and one spontaneous abortion. In addition to the clinical trial cases there have been 7 cases (including 5 pregnancies, 2 of which were linked maternal/fetal cases) reported to the Pfizer safety database. Four of these were from the Compassionate Use Program and 1 from the post-marketing program. Two of these pregnancies resulted in spontaneous abortion, 1 case resulted in a successful birth and the outcome of 2 others is as yet unknown.

These limited data do not allow assessment of the effect of taliglucerase alfa on pregnancy outcomes. Taliglucerase alfa is currently classified as FDA Pregnancy Category B.

No studies on the appearance of taliglucerase alfa in breast milk have been conducted and there have been no post-marketing reports of exposure during breastfeeding. Thus, it is not known if taliglucerase alfa is excreted in human milk. Because many drugs are excreted in human milk, it might be assumed that taliglucerase alfa is excreted as well.

The clinical course of Gaucher disease during pregnancy is heterogeneous and depends mainly on the severity of the disease at the beginning of the pregnancy.[16] Pregnancy in Gaucher disease has the potential to exacerbate the existing disease, or result in new disease manifestations.[17] Anemia and thrombocytopenia may worsen above what is normally expected to occur during pregnancy, and excessive bleeding may complicate pregnancy, delivery and the postpartum period.[16] In fact, in patients previously undiagnosed, the physiologic stress of pregnancy may cause complications that lead to the diagnosis of Gaucher disease.[16] Although there are limited data on the use of ERT during pregnancy, the available published data supports the use of ERT during pregnancy, as it does not appear to have a negative impact on the pregnancy or the fetus.[18]

Gaucher disease does not appear to lead to an increase in infertility and organomegaly, which may manifest in patients with Gaucher disease, and rarely restricts fetal growth.[16] Enzyme replacement therapy use before and during pregnancy has demonstrated benefits in reducing the risk of spontaneous abortion, and of Gaucher disease-related complications, notably, bleeding during delivery and postpartum. The rate of spontaneous abortions for pregnant women with Gaucher disease and on ERT does not appear to appreciably differ from that of the general population.[18] However, among women who are not treated with ERT, the

incidence rate of abortions is appreciably higher compared to women who are treated with ERT.[18]

In light of the limited data, this Drug Registry includes a Pregnancy/Lactation Sub-Study which will be nested within the Drug Registry, and conducted with the primary goal to further characterize the potential impact of taliglucerase alfa exposure in utero on pregnancy outcomes and on the newborn, or the potential impact of taliglucerase alfa exposure through breast milk, on infant outcomes.

This Sub-Study is described in detail in Section 9.15 Other Aspects: Pregnancy/Lactation Sub-study. The remaining sections below (Section 8 to Section 9.14) pertain to the overall Drug Registry.

8. DRUG REGISTRY: RESEARCH QUESTION AND OBJECTIVES

The purpose of this active surveillance Drug Registry is to further characterize the long-term safety and effectiveness of taliglucerase alfa in the real world post-marketing setting. No hypotheses have been pre-specified and all Drug Registry data will be analyzed using descriptive statistics.

The primary objective of the Drug Registry is to characterize the safety profile of taliglucerase alfa through the solicited collection and summary of non-serious and serious adverse event data.

The secondary objective of the Drug Registry is to characterize the effectiveness of taliglucerase alfa through the collection and analysis of Gaucher disease measures, including hematologic (hemoglobin and platelet count) and organ volume (spleen and liver) assessments.

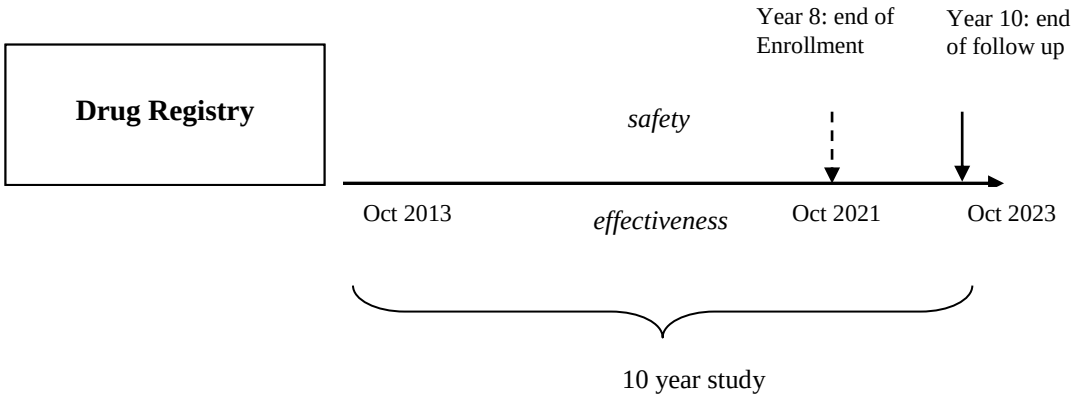
9. DRUG REGISTRY: RESEARCH METHODS

9.1. Study Design

To gather safety and effectiveness data of taliglucerase alfa in the real world post-marketing setting, Pfizer will conduct a prospective non-interventional drug registry specific for Gaucher disease patients undergoing taliglucerase alfa treatment. The Drug Registry will be operational for at least ten years. All information collected for each patient will be per standard of care, as determined by his/her enrolling physician.

A schedule of assessments is provided, however no assessment is required if considered by the enrolling physician to be outside standard clinical practice for Gaucher disease treatment. It is anticipated that each patient in the Drug Registry will be seen at least on an annual basis. Treatment and dose will correspond to the recommendations in the local Health Authority approved product label and at the discretion of the treating physician.

Figure 1. Drug Registry



9.1.1. Safety Endpoints

Any patient who receives at least one dose of taliglucerase alfa will be included in the evaluation for safety. Given that this is an active surveillance study, no a priori specified safety endpoints were chosen for the Drug Registry. To meet the primary objective, reports of all serious adverse events (SAEs) and non-serious adverse events (AEs) that occur during follow-up will be summarized using descriptive statistics.

9.1.2. Effectiveness Endpoints

To meet the secondary objective, Gaucher disease measures including hematologic (hemoglobin and platelet count) and organ volume (spleen and liver) assessments will be summarized using descriptive statistics.

Other relevant endpoints listed in Table 1 and 2 will also be summarized.

9.2. Setting

9.2.1. Study Population

The study population eligible for the Drug Registry includes any patient with Gaucher disease who is initiating or is currently receiving taliglucerase alfa treatment and meets inclusion criteria. Drug Registry patients may potentially be recruited from countries where Pfizer has made taliglucerase alfa commercially available, including the United States. Pfizer will make the registry participation available to non-Pfizer entities commercializing taliglucerase alfa. However, such registry participation will be at the non-Pfizer entities' discretion.

9.2.2. Inclusion Criteria

Patients must meet all of the following inclusion criteria to be eligible for enrollment in the Registry:

1. A confirmed diagnosis of Gaucher disease.
2. New or current treatment with taliglucerase alfa.
3. Evidence of a personally signed and dated informed consent document indicating that the patient (or a legally acceptable representative) has been informed of all pertinent aspects of the Drug Registry.

9.2.3. Exclusion Criteria

There are no exclusion criteria; all patients who meet the inclusion criteria are eligible for enrollment.

9.2.4. Patient Enrollment and Follow up

Duration of follow-up will depend on time of enrollment; enrollment will occur during the first eight years of the Drug Registry, i.e., the first eight years after the start of data collection. See

Figure 1. Patients enrolled earlier during this time period will have a longer follow-up period (up to 10 years) than those enrolled later, and the minimum duration of follow up will be two years. This minimum duration of follow-up was established to allow assessment of long term safety and effectiveness for all enrolled patients. As this Drug Registry is observational, treatment switches and discontinuations are allowed and patients will continue to be followed for the duration of the Drug Registry regardless of taliglucerase alfa discontinuation and/or treatment switches. In light of the possibility of dropout/loss to follow-up in an observational study, the end of the follow-up will be defined as the date of the last visit or the date of drop out/loss to follow or the end of the study period, whichever is the earliest.

9.3. Data Sources

The primary data source for the Drug Registry will be the patient medical record and patient interview. All data will be captured in an electronic case report form (eCRF).

9.4. Variables in the Drug Registry

For the Drug Registry, demographic, medical history including obstetrics history in female patients, treatment history, clinical measures, safety, clinical effectiveness, and anti-taliglucerase alfa antibody status variables will be collected. All study assessments will be recorded according to the schedule of recommended assessments as outlined in Table 1 and Table 2. However, completion of a particular assessment will be at the discretion of the participating investigator (i.e., the enrolling physician), and dependent on local standards of care and individual physician practice patterns. It is anticipated that each patient in the Drug Registry will be seen at least on an annual basis.

Variables highlighted in Table 1 reflect information that will be collected at the Baseline Visit. Variables highlighted in Table 2 reflect information that will be collected during the nine anticipated Annual Visits, Final Visit (at year 10) and at any Unscheduled Visit. The

participating investigator should prospectively follow all study patients as per routine clinical care and record the study data, as relevant and applicable, according to Table 1 and Table 2.

A complete description of variables, including operational definitions, will be detailed in a Statistical Analysis Plan (SAP), which will be dated, filed, and maintained by the sponsor.

Table 1. Schedule of Recommended Assessments at Baseline for Drug Registry Enrolled Patients

Assessment	Variables
Informed consent	
Patient demographics	Date of birth; gender; race; ethnicity; proportion Ashkenazi Jewish descent (via number of grandparents); country of residence; current occupation
Medical/surgical history[1]	
Physical examination & vital signs	Date of visit; vital signs; height; weight
Childbearing potential	
Concomitant medications	
Obstetric and pregnancy history for female subjects[2] (information excludes current pregnancy)	Number of pregnancies; history of assisted reproductive technology (ART); number of live births; number of losses; reasons for losses; pregnancy related complications;[3] mode of delivery; post-partum complications;[4] multiple births; fetal/neonatal congenital anomalies; birth weight and gestational age of her children; recreational drug use during pregnancy;[5] use of ERT during pregnancy and/or breastfeeding; menopausal status including hysterectomy
Gaucher disease diagnosis history	Diagnostic confirmation of Gaucher disease results (enzyme activity; bone marrow; genotype); age of initial Gaucher disease diagnosis; age to onset of initial symptoms of Gaucher disease; Presenting Gaucher disease symptoms (anemia; thrombocytopenia; splenomegaly; hepatomegaly; fatigue); Gaucher disease type
Family history of Gaucher disease	Description of affected family members (first degree relatives or other)
Historical antibody assessment	Prior antibody assay results to Elelyso or another Gaucher disease ERT.
Historical enzyme replacement therapy for Gaucher disease	Previous treatment with an ERT[6]
Historical substrate therapy for Gaucher disease	Previous treatment with an Substrate Reduction Therapy (SRT[7])
Taliglucerase alfa dose record	Taliglucerase alfa dose[8], frequency, dose changes, discontinuation
Visceral assessments	Spleen volume and method of ascertainment[9]; lesions; Liver volume and method of ascertainment[9]
Skeletal assessments	Bone fractures and location; bone pain and bone crises;[10] kyphosis; osteonecrosis; pectus carinatum
Pediatric: physical development assessment	Height and weight, Bone Age, Pubertal staging (Testicular volume, Breast, Genitalia, Pubic Hair, Parent's height, Age at menarche, Thyroid stimulating hormone, Cognitive development)
Laboratory data including abnormal liver function work up[11] and biomarkers	Platelet count; hemoglobin; white blood cell count (total) Viral hepatitis screen, Gamma-glutamyl transferase (GGT), Albumin, Prothrombin time (PT)/Partial Thromboplastin Time (PTT), Total bilirubin, Direct bilirubin, chitotriosidase, Chemokine (C-C motif) Ligand 18 (CCL18), Tartrate Resistant Acid Phosphatase (TRAP), and ACE
Pregnancy status	Current pregnancy status
Breastfeeding status	Current breastfeeding status

Adverse event/serious adverse event reporting	Any non-serious or serious adverse event including, but not limited to potential drug-drug interactions; prolonged aPTT; potential hepatotoxicity; suspected loss of efficacy
Anti-taliglucerase alfa antibody assessments (Anti-Drug Antibody-ADA)[12]	IgG antibodies to taliglucerase alfa; IgE antibodies to taliglucerase alfa; in vitro enzymatic activity neutralizing antibodies; cellular uptake neutralizing antibodies to taliglucerase alfa

1. Medical and surgery history may include splenectomy, cholecystectomy, joint replacement, osteoporosis, bleeding, fractures, myeloma/MGUS, polyclonal gammopathy, hepatocellular carcinoma, history of pre-existing hepatic impairment, cardiovascular disease, renal impairment, diabetes, Parkinson's disease, pulmonary hypertension, interstitial lung disease, seizures, eye movement abnormality, mandibular problems, asthma and other relevant medical conditions.
2. Information excludes current pregnancy. Data on the current pregnancy (i.e. active pregnancy among Drug Registry enrollees) would be collected as per Table 3.
3. If a patient reports pregnancy- related complications, if relevant and reported, information recorded will include gestational diabetes, peri-partum bleeding and pregnancy induced hemorrhage.
4. If a patient reports postpartum complications, if relevant and reported, information recorded will include bleeding, anemia, infections, bone crisis and other relevant complications.
5. If a patient reports recreational drug use during pregnancy, information recorded will include tobacco, alcohol and illicit drugs
6. If a patient reports or has a history of being treated with an ERT, if available and/or reported, information on the specific ERT(s) including duration, prior history of hypersensitivity reaction and infusion related reactions to an ERT and history of carrot allergy will be recorded.
7. If a patient reports or has a history of being treated with an SRT, if available and/or reported, information on the specific SRT(s) including duration will be recorded.
8. For patients new to Taliglucerase alfa, the dosing information should be recorded in the dose record. For patients not new to Taliglucerase alfa, the current dosing information should be recorded in the dose record.
9. Method of ascertainment includes magnet resonance imaging (MRI), ultrasound (US), computed tomography (CT) and palpation.
10. If a patient reports experiencing bone and/or bone crisis then additional information, if available, will be recorded, including site, precipitating/alleviating factors, drug use, treatment/analgesics, intensity and duration.
11. If relevant and available.
12. Samples for antibody testing should be obtained at taliglucerase alfa trough concentration, i.e., prior to infusion; this minimizes the likelihood of taliglucerase alfa interference with the detection of antibodies Please refer to Section 9.5

Table 2. Schedule of Recommended Assessments during Follow- Up Visits for Drug Registry Enrolled Patients

Assessment	Variables	Anticipated Annual Visit ± 2 months: Year 1-9	Anticipated Final Visit ± 2 months: Year 10	Unanticipated Visit
Physical examination & vital signs[1]	date of visit; vital signs; height; weight	X	X	X
Concomitant medications[1]		X	X	X
Visceral assessments[1]	spleen volume and method of ascertainment;[3] lesions; liver volume and method of ascertainment[3]	X	X	X
Skeletal assessments[1]	bone fractures and location;[4] bone pain and bone crises[5] kyphosis; osteonecrosis; pectus carinatum	X	X	X
Laboratory data including Abnormal liver function work-up[1] and biomarkers	platelet count; hemoglobin; white blood cell count (total)[2] viral hepatitis screen,, Gamma-glutamyl transferase (GGT), Albumin, Prothrombin time (PT)/Partial Thromboplastin Time (PTT), Total bilirubin, Direct bilirubin as available and appropriate chitotriosidase, CCL18, TRAP, and ACE if available	X	X	X
Pregnancy status[1]	current pregnancy status	X	X	X
Breastfeeding status[1]	current breastfeeding status	X	X	X
Adverse event/serious adverse event reporting	any non-serious or serious adverse event including, but not limited to potential drug-drug interactions, prolonged aPTT, potential hepatotoxicity, suspected loss of efficacy, immune or infusion reactions[6]	X (throughout the entire study period)		
Taliglucerase alfa dose [1]	frequency, dose changes, discontinuation	X	X	X

Anti-taliglucerase alfa antibody assessments[1, 7]	IgG antibodies to taliglucerase alfa; IgE antibodies to taliglucerase alfa; in vitro enzymatic activity neutralizing antibodies; cellular uptake neutralizing antibodies to taliglucerase alfa	X	X	X
Pediatric: physical development assessment (if relevant)[1]	height and weight; bone age; pubertal staging; age at menarche; TSH; cognitive development	X	X	X

1. If relevant and available.
2. If relevant and available, information on iron and related studies (Total Iron Binding Capacity (TIBC)), folate, B12, and ferritin will be collected.
3. Method of ascertainment includes MRI, US, CT and palpation.
4. If relevant and available, information on X-ray (lytic or sclerotic lesions (including region)), fractures, MRI, bone mineral density, vitamin D, and bone marrow biopsy will be collected.
5. If a patient previously experienced bone pain and/or bone crisis then additional information will be collected, if available, including anatomic site, precipitating/alleviating factors, treatment/analgesics, intensity and duration.
6. Tryptase samples are optimally obtained at 0.25-3 hours after onset of symptoms, between 3-6 hours and between 24-48 hours to verify the return to baseline.
7. The recommended schedule of routine anti-taliglucerase alfa antibody assessments is detailed in the Study Assessments (Section 9.5). Samples for antibody testing should be obtained at taliglucerase alfa trough concentration, i.e., prior to infusion; this minimizes the likelihood of drug interference for the detection of antibodies as with any antibody testing. Consideration to tryptase analysis should be given (see footnote 6 for timing of sample collection). Please refer to Section 9.5.

9.5. Study Assessments

Recommended study assessments are contained in Section 9.4.

The collection of blood samples for anti-taliglucerase alfa antibody testing is recommended and antibody kits[1] are currently provided by the Sponsor to all taliglucerase alfa prescribers as part of routine care in the US regardless of Drug Registry participation and may become part of routine care in other countries during the duration of the study period,.

Anti-taliglucerase antibody testing will be done at baseline, 6 months, 12 months and 24 months and additionally at the discretion of the investigator when considered to be clinically appropriate (e.g., for patients experiencing lack or loss of efficacy, or for patients with apparent hypersensitivity or infusion-related reactions).

When Anti-drug antibody (ADA) testing is performed as part of routine care, the samples for antibody testing should be obtained at taliglucerase alfa trough concentration, i.e., prior to infusion; as with any antibody testing, this minimizes the likelihood of drug interference in the detection of antibodies. Adverse reactions due to anti-drug antibodies may occur minutes to hours after taliglucerase alfa infusion or days to 3 weeks after infusion. The reactions that occur soon after infusion are likely mediated by IgE ADA that produce Type 1 (immediate) hypersensitivity reactions (symptoms include hypotension, rash, urticaria, respiratory distress). The delayed reactions produced by ADA are likely mediated by IgG and IgM ADA that produce Type 3 (immune complex or serum sickness) hypersensitivity reactions (symptoms include rash, fever, arthralgia, lymphadenopathy). If antibody testing is being performed because of an adverse reaction as part of routine care, after Type 1-like reactions, the blood samples should be collected at least 48 hours after infusion so that taliglucerase alfa would have been cleared and not interfere with the analysis for IgE ADA. Consideration should also be given to obtaining tryptase samples (see Table 2 for recommended sampling timeline) in the event of a Type 1 reaction. After Type 3-like reactions, blood samples should be collected 2 to 4 weeks after the adverse reaction to allow for the clearance of immune complexes which may interfere with the measurement of IgG ADA.

9.6. Study Size

Given the rarity of Gaucher disease, and that in the United States there are two ongoing Gaucher disease registries, the number of participants is expected to be small. For this reason, no hypotheses have been pre-specified and sample size calculations are not applicable. All willing patients meeting the study inclusion criteria will be included in the Drug Registry. The total number of taliglucerase alfa-treated patients that will enroll in the Drug Registry is unknown and will depend on patient and enrolling physician participation, and taliglucerase alfa market authorizations.

[1] The kits include collection instructions and materials, the recommended schedule and timing of blood sample collection and pre-paid return shipping to a central laboratory.

9.7. Data Collection and Data Management

9.7.1. Data Collection

Electronic case report form (e-CRF) will be administered through Electronic Data Capturing (EDC) system in this study. After a patient or a legally acceptable representative agrees to participate in this study by signing a written and dated informed consent/assent document, the treating physician or an authorized staff member will complete the patient baseline e-CRF at enrollment. The follow-up e-CRF will be completed when a patient returns to an office visit close to each study visit as per routine clinical practice. Data should be entered in e-CRF within 5 business days of each visit.

9.7.2. Electronic Case Report Forms

An e-CRF should be completed for each subject. The completed e-CRFs are the sole property of Pfizer and should not be made available in any form to third parties, except for authorized representatives of Pfizer or appropriate regulatory authorities, without written permission from Pfizer.

Each study investigator has ultimate responsibility for the timely collection and reporting of all clinical and safety data entered on the e-CRFs and any other data collection forms (source documents) and ensuring that they are accurate, authentic / original, attributable, complete, consistent, legible, timely (contemporaneous), enduring and available when required. The e-CRFs must be signed or approved by the study investigator or by an authorized staff member to attest that the data contained on the e-CRFs is true.

In most cases, the source documents are the patient's medical chart. In these cases data collected on the e-CRFs must match the data in those charts. For any corrections to entries made in the e-CRFs, source documents must be dated, initialed and explained (if necessary) and should not obscure the original entry. In some instances (e.g., patient interview) may also serve as source documents. In these situations a document should be available at the investigator's site and clearly identify those data that will be recorded in the e-CRF.

9.7.3. Data Management

Detailed methodology for data management software programs to be used in the study will be documented in the Data Management Plan (DMP), which will be dated, filed, and maintained by the sponsor. This document will include details about which data (e.g., Previous and Concomitant Medications; Adverse Events) are coded using the World Health Organization (WHO) Drug Reference List (DRL), which employ the Anatomical Therapeutic Chemical (ATC) classification System, or the Medical dictionary for regulatory activities (MedDRA) terminology. The specific versions of the coding dictionaries used will be documented within the DMP.

In addition, Statistical Analysis System (SAS) software may be used to create listings for data review purposes. Such listings will be described in the Data Validation Specifications component of the DMP.

9.7.4. Data Cleaning

Data cleaning specifications will be developed during study start-up before the initiation phase of the study (i.e., before enrollment). The specifications will include consistency and plausibility checks on data, as well as rules for data handling (i.e., process for query creation/closure and categorization, process for listing data review, process for missing and non-conformant data review, process for flagging data in the clinical data management system, process for SAE reconciliation, process for data handling and validation of electronic records; process for medical coding of data and application of coding conventions (if applicable), process for collection of investigator signature, process for transferring a patient from one site to another, process for freeze/lock of the clinical database). A data cleaning specifications document will be dated, filed, and maintained by the sponsor.

9.8. Data Analysis

Data will be analyzed using descriptive statistics. For outcomes of interest, summary statistics, including counts and frequencies will be calculated. Crude cumulative incidence and crude incidence rates per person-time will be calculated as appropriate. Depending on the outcome of interest, stratified analyses may be performed. Further exploratory analyses will be developed as necessary.

Detailed methodology for the summary and statistical analyses of data collected in this study will be documented in a Statistical Analysis Plan (SAP), which will be dated, filed, and maintained by the sponsor. The SAP may modify the plans outlined in the protocol; any major modifications of primary endpoint definitions or their analyses will be reflected in a protocol amendment.

9.9. Quality Control

During study conduct, Pfizer (or their designee) will perform routine remote oversight of the sites' data collection activities and may also conduct periodic on-site monitoring visits of sites to ensure that the protocol is being followed. During on-site visits the monitors may review source documents to confirm that the data recorded is accurate. All information recorded on the CRFs for this study must be consistent with the patients' source documentation (i.e., medical records).

Data entered into the clinical database and some integrated data from third parties (if applicable), will be verified/validated as documented in components of the DMP, which will be dated, filed, and maintained by the sponsor. After completion of these activities, the investigator will be required to sign off the CRFs electronically.

9.10. Record Retention

All analytical datasets and statistical programs owned by Pfizer will be available for audit and inspection purposes.

To enable evaluations and/or audits from regulatory authorities or Pfizer, the investigators will agree to keep records, including the identity of all participating patients (sufficient information to link records, e.g., hospital records), all original signed informed consent forms, serious adverse event forms, source documents, and detailed records of treatment disposition, and adequate documentation of relevant correspondence (e.g., letters, meeting minutes, telephone calls reports). The records should be retained by the investigator according to local regulations, or as specified in the Clinical Study Agreement, whichever is longer.

If an investigator becomes unable for any reason to continue to retain study records for the required period (e.g., retirement, relocation), Pfizer should be prospectively notified. The study records must be transferred to a designee acceptable to Pfizer, such as another investigator, another institution, or to an independent third party arranged by Pfizer. An investigator must obtain Pfizer's written permission before disposing of any records, even if retention requirements have been met.

9.11. Strengths of the Research Methods

The Drug Registry will enable Pfizer to prospectively monitor and characterize the long-term safety and effectiveness of taliglucerase in the real-world setting. Although the active surveillance approach used in this study is not intended to be used for hypothesis testing, it permits to identify large safety signals for further refinement.

Given the anticipated small number of participants, the Drug Registry was designed to minimize the burden on participating investigators and patients in an effort to increase enrollment and minimize withdrawal from the registry. These design considerations include: recruitment of taliglucerase alfa exposed patients only, capture of only critical variables, and only yearly recommended reporting for many variables.

9.12. Limitations of the Research Methods

Because the Drug Registry will only enroll taliglucerase alfa-treated patients, the lack of an internal comparator group may pose a challenge for the interpretation of the data. Without the same data collected among Gaucher disease patients eligible for ERT but not treated with taliglucerase alfa (i.e., treated with one of the other ERTs), comparative analyses will not be possible and it may be challenging to contextualize the safety and effectiveness findings in this study. Furthermore, this Drug Registry is being initiated in the US several years after other existing Gaucher disease registries, which may likely result in the competition for the small numbers of patients with this rare disease.

9.13. DRUG REGISTRY: MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

The safety reporting criteria below apply to all male and female patients. All of the sections below within 9.13 are applicable to all participants except for those subjects that meet eligibility criteria for the pregnancy/lactation sub-study and consent to be part of the sub-study.

*The two sections within 9.13, specific to exposure during pregnancy (EDP) 9.13.4.1 and to exposure during breastfeeding 9.13.4.2, apply only to those female patients **who do not consent** to be part of the pregnancy/lactation sub-study and to pregnant female partners of male study participants.*

*For those female patients **who meet the eligibility of the pregnancy/lactation sub-study and consent to be part of the pregnancy/lactation sub-study**, the safety reporting criteria specified in section 9.15.13 should be followed for reporting EDP and/or exposure during breastfeeding.*

The table below summarizes the requirements for recording safety events on the e-CRF and for reporting safety events on the non-interventional study (NIS) adverse event monitoring (AEM) Report Form to Pfizer Safety. These requirements are delineated for three types of events: (1) serious adverse events (SAEs); (2) non-serious AEs (as applicable); and (3) Scenarios involving drug exposure, including exposure during pregnancy, exposure during breast feeding, medication error, overdose, misuse, extravasation, and occupational exposure. These events are defined in the section "Definitions of safety events".

Safety event	Recorded on the eCRF	Reported on the NIS AEM Report Form to Pfizer Safety within 24 hours of awareness
SAE	All	All
Non-serious AE	All	None
Scenarios involving exposure to a drug under study, including exposure during pregnancy, exposure during breast feeding, medication error, overdose, misuse, extravasation; lack of efficacy; and occupational exposure	All (regardless of whether associated with an AE), **except occupational exposure**	All (regardless of whether associated with an AE)

For each AE, the investigator must pursue and obtain information adequate both to determine the outcome of the adverse event and to assess whether it meets the criteria for classification as a SAE (see section "Serious Adverse Events" below)

Safety events listed in the table above must be reported to Pfizer within 24 hours of awareness of the event by the investigator **regardless of whether the event is determined by the investigator to be related to a drug under study**. In particular, if the SAE is fatal or life-threatening, notification to Pfizer must be made immediately, irrespective of the extent of available event information. This timeframe also applies to additional new (follow-up) information on previously forwarded safety event reports. In the rare situation that the investigator does not become immediately aware of the occurrence of a safety event, the investigator must report the event within 24 hours after learning of it and document the time of his/her first awareness of the events.

For safety events that are considered serious or that are identified in the far right column of the table above that are reportable to Pfizer within 24 hours of awareness, the investigator is obligated to pursue and to provide any additional information to Pfizer in accordance with this 24-hour timeframe. In addition, an investigator may be requested by Pfizer to obtain specific follow-up information in an expedited fashion. This information is more detailed than that recorded on the eCRF. In general, this will include a description of the adverse event in sufficient detail to allow for a complete medical assessment of the case and independent determination of possible causality. Any information relevant to the event, such as concomitant medications and illnesses must be provided. In the case of a patient death, a summary of available autopsy findings must be submitted as soon as possible to Pfizer or its designated representative.

9.13.1. Reporting period

For each patient, the safety event reporting period begins at the time of the patient's first dose of taliglucerase alfa or the time of the patient's informed consent if s/he is already exposed to *taliglucerase alfa*, and lasts through the end of the observation period of the study, which must include at least 28 calendar days following the last administration of a drug under study; a report must be submitted to Pfizer Safety (or its designated representative) for any of the types of safety events listed in the table above occurring during this period. If a patient was administered a drug under study on the last day of the observation period, then the reporting period should be extended for 28 calendar days following the end of observation. Most often, the date of informed consent is the same as the date of enrollment. In some situations, there may be a lag between the dates of informed consent and enrollment. In these instances, if a patient provides informed consent but is never enrolled in the study (e.g., patient changes his/her mind about participation, the reporting period ends on the date of the decision to not enroll the patient.
If the investigator becomes aware of a SAE occurring at any time after completion of the study and s/he considers the SAE to be related to *taliglucerase alfa,* the SAE also must be reported to Pfizer Safety.

9.13.2. Causality assessment

The investigator is required to assess and record the causal relationship. For all AEs, sufficient information should be obtained by the investigator to determine the causality of each adverse event. For AEs with a causal relationship to *taliglucerase alfa*, follow-up by the investigator is required until the event and/or its sequelae resolve or stabilize at a level acceptable to the investigator, and Pfizer concurs with that assessment.

An investigator's causality assessment is the determination of whether there exists a reasonable possibility that *taliglucerase alfa* caused or contributed to an adverse event. If the investigator's final determination of causality is "unknown" and s/he cannot determine whether *taliglucerase alfa* caused the event, the safety event must be reported within 24 hours.

If the investigator cannot determine the etiology of the event but s/he determines that *taliglucerase alfa* did not cause the event, this should be clearly documented on the *eCRF* and the NIS AEM Report Form.

9.13.3. DEFINITIONS OF SAFETY EVENTS

9.13.3.1. Adverse events

An AE is any untoward medical occurrence in a patient administered a medicinal product. The event need not necessarily have a causal relationship with the product treatment or usage. Examples of adverse events include but are not limited to:

- Abnormal test findings (see below for circumstances in which an abnormal test finding constitutes an adverse event);
- Clinically significant symptoms and signs;
- Changes in physical examination findings;
- Hypersensitivity;
- Progression/worsening of underlying disease;
- Lack of efficacy;
- Drug abuse;
- Drug dependency.

Additionally, for medicinal products, they may include the signs or symptoms resulting from:

- Drug overdose;
- Drug withdrawal;
- Drug misuse;
- Off-label use;
- Drug interactions;
- Extravasation;
- Exposure during pregnancy;
- Exposure during breast feeding;
- Medication error;

- Occupational exposure.

9.13.3.2. Abnormal test findings

The criteria for determining whether an abnormal objective test finding should be reported as an adverse event are as follows:

- Test result is associated with accompanying symptoms, and/or
- Test result requires additional diagnostic testing or medical/surgical intervention, and/or
- Test result leads to a change in study dosing or discontinuation from the study, significant additional concomitant drug treatment, or other therapy, and/or
- Test result is considered to be an adverse event by the investigator or sponsor.

Merely repeating an abnormal test, in the absence of any of the above conditions, does not constitute an adverse event. Any abnormal test result that is determined to be an error does not require reporting as an adverse event.

9.13.3.3. Serious adverse events

A serious adverse event is any untoward medical occurrence in a patient administered a medicinal or nutritional product (including pediatric formulas) at any dose that:

- Results in death;
- Is life-threatening;
- Requires inpatient hospitalization or prolongation of hospitalization (see below for circumstances that do not constitute adverse events);
- Results in persistent or significant disability/incapacity (substantial disruption of the ability to conduct normal life functions);
- Results in congenital anomaly/birth defect.

Medical and scientific judgment is exercised in determining whether an event is an important medical event. An important medical event may not be immediately life-threatening and/or result in death or hospitalization. However, if it is determined that the event may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above, the important medical event should be reported as serious.

Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse.

Additionally, any suspected transmission via a Pfizer product of an infectious agent, pathogenic or non-pathogenic, is considered serious. The event may be suspected from clinical symptoms or laboratory findings indicating an infection in a patient exposed to a Pfizer product. The terms "suspected transmission" and "transmission" are considered synonymous. These cases are considered unexpected and handled as serious expedited cases by PV personnel. Such cases are also considered for reporting as product defects, if appropriate.

9.13.3.4. Hospitalization

Hospitalization is defined as any initial admission (even if less than 24 hours) to a hospital or equivalent healthcare facility or any prolongation to an existing admission. Admission also includes transfer within the hospital to an acute/intensive care unit (e.g., from the psychiatric wing to a medical floor, medical floor to a coronary care unit, neurological floor to a tuberculosis unit). An emergency room visit does not necessarily constitute a hospitalization; however, an event leading to an emergency room visit should be assessed for medical importance.

Hospitalization in the absence of a medical AE is not in itself an AE and is not reportable. For example, the following reports of hospitalization without a medical AE are not to be reported.

- Social admission (e.g., patient has no place to sleep)
- Administrative admission (e.g., for yearly exam)
- Optional admission not associated with a precipitating medical AE (e.g., for elective cosmetic surgery)
- Hospitalization for observation without a medical AE
- Admission for treatment of a pre-existing condition not associated with the development of a new AE or with a worsening of the pre-existing condition (e.g., for work-up of persistent pre-treatment lab abnormality)
- Protocol-specified admission during clinical study (e.g., for a procedure required by the study protocol)

9.13.4. Scenarios necessitating reporting to Pfizer Safety within 24 hours

Scenarios involving exposure during pregnancy, exposure during breastfeeding, medication error, overdose, misuse, extravasation, lack of efficacy, and occupational exposure are described below.

9.13.4.1. Exposure during pregnancy

An exposure during pregnancy (EDP) occurs if:

1. A female becomes, or is found to be, pregnant either while receiving or having been exposed to (e.g., environmental) *taliglucerase alfa*, or the female becomes, or is found to be, pregnant after discontinuing and/or being exposed to *taliglucerase alfa* (maternal exposure).

   An example of environmental exposure would be a case involving direct contact with a Pfizer product in a pregnant woman (e.g., a nurse reports that she is pregnant and has been exposed to chemotherapeutic products).

2. A male has been exposed, either due to treatment or environmental exposure to *taliglucerase alfa* prior to or around the time of conception and/or is exposed during the partner pregnancy (paternal exposure).

As a general rule, prospective and retrospective exposure during pregnancy reports from any source are reportable irrespective of the presence of an associated AE and the procedures for SAE reporting should be followed.

If a study participant or study participant's partner becomes, or is found to be, pregnant during the study participant's treatment with *taliglucerase alfa*, this information must be submitted to Pfizer, irrespective of whether an adverse event has occurred using the NIS AEM Report Form and the EDP Supplemental Form.

In addition, information regarding environmental exposure to *taliglucerase alfa* in a pregnant woman (e.g., a subject reports that she is pregnant and has been exposed to a cytotoxic product by inhalation or spillage) must be submitted using the NIS AEM Report Form and the EDP supplemental form. This must be done irrespective of whether an AE has occurred.

Information submitted should include the anticipated date of delivery (see below for information related to termination of pregnancy).

Follow-up is conducted to obtain general information on the pregnancy; in addition, follow-up is conducted to obtain information on EDP outcome for all EDP reports with pregnancy outcome unknown. A pregnancy is followed until completion or until pregnancy termination (e.g., induced abortion) and Pfizer is notified of the outcome. This information is provided as a follow up to the initial EDP report. In the case of a live birth, the structural integrity of the neonate can be assessed at the time of birth. In the event of a termination, the reason(s) for termination should be specified and, if clinically possible, the structural integrity of the terminated fetus should be assessed by gross visual inspection (unless pre-procedure test findings are conclusive for a congenital anomaly and the findings are reported).

If the outcome of the pregnancy meets the criteria for an SAE (e.g., ectopic pregnancy, spontaneous abortion, intrauterine fetal demise, neonatal death, or congenital anomaly [in a live born, a terminated fetus, an intrauterine fetal demise, or a neonatal death]), the procedures for reporting SAEs should be followed.

Additional information about pregnancy outcomes that are reported as SAEs follows:

- Spontaneous abortion includes miscarriage and missed abortion;

- Neonatal deaths that occur within 1 month of birth should be reported, without regard to causality, as SAEs. In addition, infant deaths after 1 month should be reported as SAEs when the investigator assesses the infant death as related or possibly related to exposure to investigational product

Additional information regarding the exposure during pregnancy may be requested. Further follow-up of birth outcomes will be handled on a case-by-case basis (e.g., follow-up on preterm infants to identify developmental delays).

In the case of paternal exposure, the study participant will be provided with the Pregnant Partner Release of Information Form to deliver to his partner. It must be documented that the study participant was given this letter to provide to his partner.

9.13.4.2. Exposure during breastfeeding

Scenarios of exposure during breastfeeding must be reported, irrespective of the presence of an associated AE. An exposure during breastfeeding report is not created when a Pfizer drug specifically approved for use in breastfeeding women (e.g., vitamins) is administered in accord with authorized use. However, if the infant experiences an AE associated with such a drug's administration, the AE is reported together with the exposure during breastfeeding.

9.13.4.3. Medication error

A medication error is any unintentional error in the prescribing, dispensing or administration of a medicinal product that may cause or lead to inappropriate medication use or patient harm while in the control of the health care professional, patient, or consumer. Such events may be related to professional practice, health care products, procedures, and systems including: prescribing; order communication; product labeling, packaging, and nomenclature; compounding; dispensing; distribution; administration; education; monitoring; and use.

Medication errors include:

- Near misses, involving or not involving a patient directly (e.g., inadvertent/erroneous administration, which is the accidental use of a product outside of labeling or prescription on the part of the healthcare provider or the patient/consumer);

- Confusion with regard to invented name (e.g., trade name, brand name).

The investigator must submit the following medication errors to Pfizer, irrespective of the presence of an associated AE/SAE:

- Medication errors involving patient exposure to the product, whether or not the medication error is accompanied by an AE.

- Medication errors that do not involve a patient directly (e.g., potential medication errors or near misses). When a medication error does not involve patient exposure to the product the following minimum criteria constitute a medication error report:

  - An identifiable reporter;

  - A suspect product;

  - The event medication error.

9.13.4.4. Overdose, Misuse, Extravasation

Reports of overdose, misuse, and extravasation associated with the use of a Pfizer product are reported to Pfizer by the investigator, irrespective of the presence of an associated AE/SAE.

9.13.4.5. Lack of Efficacy

Reports of lack of efficacy to a Pfizer product are reported to Pfizer by the investigator, irrespective of the presence of an associated AE/SAE or the indication for use of the Pfizer product.

9.13.4.6. Occupational Exposure

Reports of occupational exposure to a Pfizer product are reported to Pfizer by the investigator, irrespective of the presence of an associated AE/SAE.

9.14. Single Reference Safety Document

Complete information for taliglucerase alfa may be found in the Single Reference Safety Document, which for this study is the current Core Data Sheet.

9.15. Other Aspects: Pregnancy/Lactation Sub-study

9.15.1. Research Question and Objective

The primary objectives of the Pregnancy/Lactation Sub-Study are:

1. To assess pregnancy outcomes of female Drug Registry participants exposed to taliglucerase alfa at any time during pregnancy.

2. To assess clinical outcomes of newborns of female Drug Registry participants potentially exposed to taliglucerase alfa in utero.

3. To assess clinical outcomes of infants potentially exposed to taliglucerase alfa through breast milk or in utero, up to the child's first birthday.

The exploratory objectives of the Pregnancy/Lactation Sub-Study are:

1. To assess pregnancy outcomes of female Drug Registry participants not exposed to taliglucerase alfa at any time during pregnancy *(this includes every woman who does*

not meet the definition of exposure to talgilcuerase alfa during pregnancy in primary objective 1 above).

2. To assess clinical outcomes of newborns of female Drug Registry participants not exposed to taliglucerase alfa in utero.

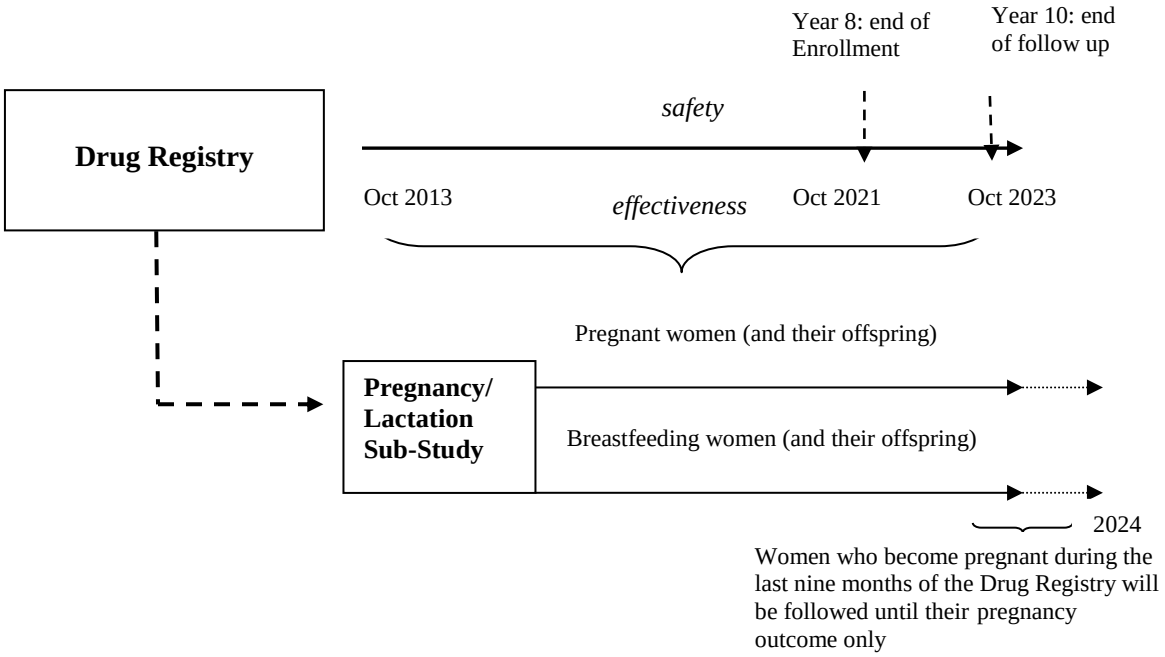
3. To assess clinical outcomes of infants not exposed to taliglucerase alfa through breast milk or in utero, up to the child's first birthday.

Not exposed to taliglucerase alfa includes those not receiving any treatment or receiving treatment other than taliglucerase alfa during pregnancy and lactation.

9.15.2. Study Design

The Pregnancy/Lactation Sub-Study will be nested within the Drug Registry in order to obtain information on taliglucerase alfa exposure in utero on pregnancy outcomes and newborns and/or through breast milk exposure on infant outcomes as shown in Figure 2.

Figure 2. Pregnancy/ Lactation Sub Study nested within the Drug Registry



9.15.3. Study Population in the Pregnancy/Lactation Sub-Study

The study population eligible for this sub-study are all female Drug Registry participants who are or become pregnant during the Drug Registry and/or all female Drug Registry participants who breastfeed during the course of the Drug Registry. All pregnant and breastfeeding women enrolled in the Drug Registry will be approached for participation in the sub-study regardless of whether they are receiving taliglucerase alfa for their Gaucher Disease at the time of their pregnancy/breastfeeding. This is because during the 10 years of the Drug Registry duration, and in particular during the pregnancy/breastfeeding time period,

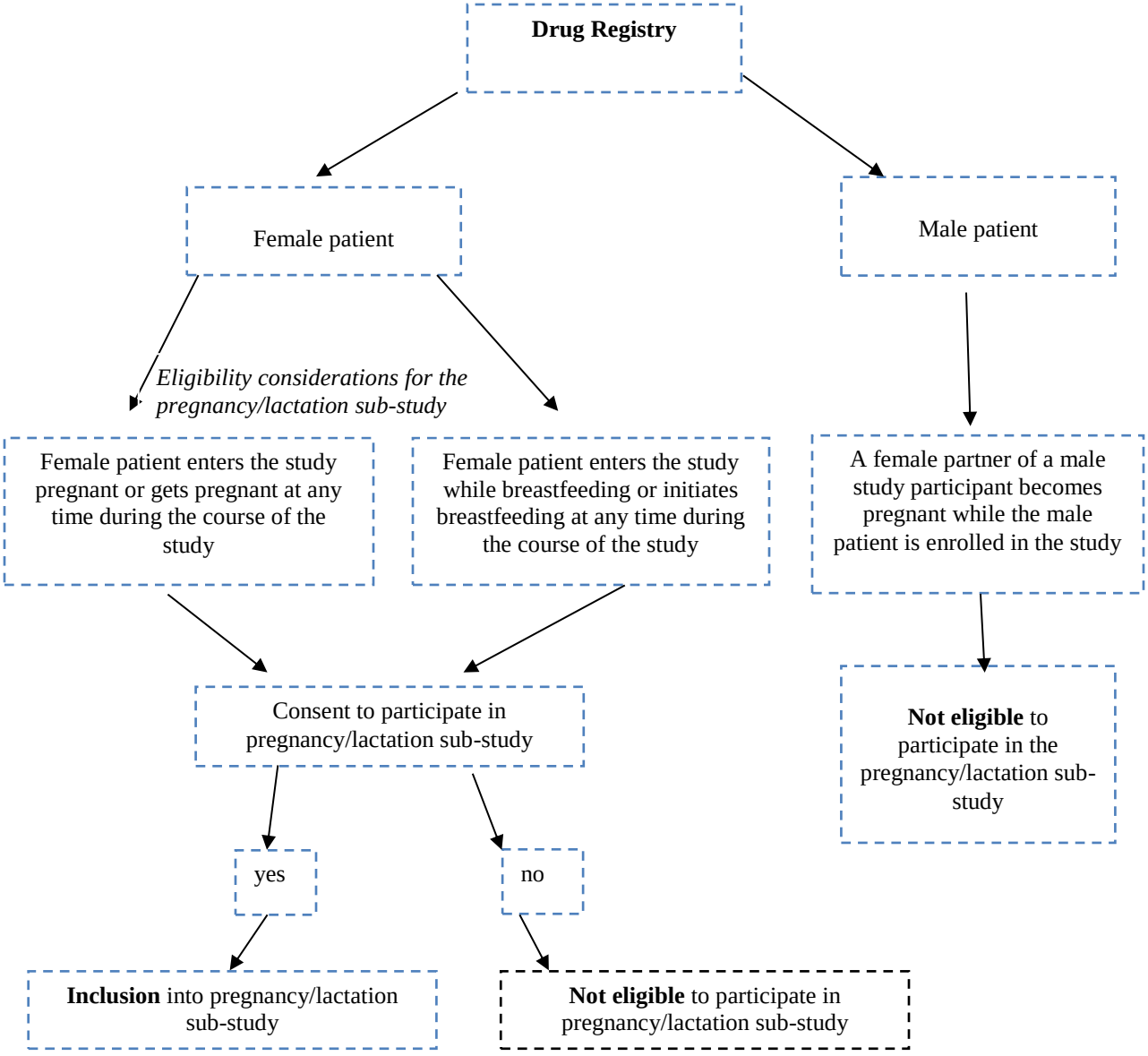
women may switch and/or discontinue their treatment with taliglucerase alfa for various reasons.

9.15.4. Inclusion Criteria in the Pregnancy/Lactation Sub-Study

A woman and her potentially exposed offspring will be eligible for the sub-study if the woman meets the following criteria:

- Currently enrolled in the Drug Registry (Section 9.2.2);
- Pregnant and/or breastfeeding
- Evidence of a personally signed and dated informed consent document indicating that the patient has been informed of all pertinent aspects of the Pregnancy/Lactation Sub-Study.

Figure 3. Inclusion Criteria for Pregnancy/Lactation Sub-Study



The pregnancy/lactation sub-study includes only those women and their offspring if the woman is herself enrolled in the Drug Registry and is pregnant and/or actively breastfeeding and consents to participate in the Pregnancy/Lactation sub-study (Figure 3). Women and their offspring who are not enrolled in the Drug Registry are not eligible for this sub-study which includes female partners of male study participants who become pregnant while the male patient is enrolled in the study, i.e.paternal exposure to taliglucerase alfa, which is further elaborated in Section 9.13.4.1.

If eligibility criteria above are met, information on the women's pregnancies and their offspring will be collected on the eCRF and stored as part of the study database (i.e. the

clinical database). If there is an SAE, the EDP associated with that SAE also needs to be reported to the Company's safety database (i.e., Pfizer Safety) as per 9.15.13.

9.15.5. Exclusion Criteria in the Pregnancy/Lactation Sub-Study

A woman and her potentially exposed offspring will not be eligible for the sub-study if the woman meets either of the following criteria:

1) Enrolled in the Drug Registry and is pregnant and/or breastfeeding, but does not consent to be part of the Pregnancy/Lactation Sub-Study (maternal exposure), or

2) Pregnant partners of male patients who are found to be pregnant during their male partner's study participation and treatment with taliglucerase alfa, at the time of the study (paternal exposure), and are themselves not enrolled in the Drug Registry

Reports relating to pregnancies where the fetus (from pre-embryo to birth) may have been exposed at any time during pregnancy to taliglucerase alfa, either through maternal or paternal exposure are to be forwarded to Pfizer as per Section 9.13.4.1 .

9.15.6. Patient Enrollment and Follow up Period in the Pregnancy/Lactation Sub-Study

As the Drug Registry is observational, treatment switches and discontinuations are allowed. It is possible that a woman may switch or discontinue her taliglucerase alfa treatment during her pregnancy or during breastfeeding. However, women participating in the Sub-Study will continue to be followed regardless of taliglucerase alfa discontinuation and/or treatment switches.

A woman's pregnancy status will be queried and reported by the participating investigator at any contact over the course of the Drug Registry (Anticipated and Unanticipated Visits). Once a woman's pregnancy status becomes known, she will continue to participate in the Drug Registry but will also provide additional information specific to her pregnancy and/or breastfeeding to the Pregnancy/Lactation Sub-Study[2] as depicted in Figure 2. A woman will be enrolled in the Pregnancy/Lactation Sub-Study prospectively, i.e., prior to her delivery or pregnancy termination. Women who may have knowledge of the prenatal test will still be enrolled but will be analyzed separately as discussed in Section 9.15.10.

As part of the Pregnancy/Lactation Sub-Study, additional information will be collected over the course of the pregnancy (see Table 3) by obtaining medical records from the woman's obstetrician/gynecologist and/or other relevant prenatal specialist monitoring the woman's pregnancy. The information on the course of pregnancy will be collected during each trimester after the pregnancy is reported to the participating investigator. This will be done through a participating investigator/site establishing a contact with a woman's physicians and

[2] Those women who do not become pregnant during the course of the Drug Registry or whose pregnancy outcomes are known (ie, live birth or pregnancy termination) at the time of their follow up visits will contribute to the Drug Registry only.

thereby proactively ascertaining information on the course of pregnancy and pregnancy outcomes. Following the birth of a child, the information on the newborn and infant outcomes including information on whether an infant is being breastfed will be collected following the child being seen by his pediatrician three or more times in the first year of life such as at 0 months (i.e., birth and shortly after), ~4 months and ~12 months. The exposure period from the time of delivery until 12 months of age was chosen based on the breastfeeding recommendations from the American Academy of Pediatrics.

For the Pregnancy/Lactation Sub-Study, among women who become pregnant during the last nine months of the Drug Registry, the Sub-Study will end at the time that their pregnancy outcomes are reported. Consequently, information on these women will be collected until their first post-pregnancy visit or contact with the participating investigator. In the case of the mothers who give birth and/or initiate breastfeeding at any time during the last year of the Drug Registry, October 2022 to October 2023, the Pregnancy/Lactation Sub-Study will end at the same time as the Drug Registry. Accordingly, exposure period for the offspring exposed to taliglucerase in utero or through breast milk will extend from the time of delivery until the age of the infant at the time of his mother's final visit in the Drug Registry.

9.15.7. Data Sources

The primary data source for the Pregnancy/Lactation Sub-Study will be the patient medical records including her obstetric/gynecologic medical records and her offspring's pediatric medical records. During the course of her pregnancy and after birth, a pregnant enrolled woman in the Pregnancy/Lactation Sub-Study will be asked by her participating investigator to release her obstetric medical records and the pediatric medical records for her child. In those instances where access to the medical records is available, information provided by a woman will be verified with the information recorded in the medical records by her obstetrician and her child's pediatrician as appropriate. All data will be captured in an electronic case report form (eCRF).

9.15.8. Variables in the Pregnancy/Lactation Sub-Study

For the Pregnancy/Lactation Sub-Study, all study assessments will be conducted according to the recommended schedule of assessments as outlined in Table 3. However, completion of a particular assessment will be at the discretion of the participating investigator, and dependent on local standards of care and individual physician practice patterns.

Given that this is an active surveillance study, all reported pregnancy, neonatal and infant outcomes will be collected, if available and reported. Table 3 describes information that will be collected during each visit and the timing during which outcomes will be assessed. In addition, to all the variables collected as part of the Drug Registry, specific variables to the Pregnancy/Lactation Sub-Study include information on the course of pregnancy, pregnancy outcomes in the mother and offspring, and infant outcomes. The information collected includes but not limited to the information on fetal/neonatal congenital anomalies detected shortly post-delivery and information on relevant physical and developmental milestones until the infant is 12 months old. Information on whether the child is being breastfed will be ascertained through the review of pediatric records.

9.15.9. Study Size of the Pregnancy/Lactation Sub-Study

Since a small number of patients is expected to participate in the Drug Registry, few female patients are expected to get pregnant and/or breastfeed and even fewer in utero and breast feeding exposures to taliglucerase alfa are anticipated. For this reason, no hypotheses have been pre-specified and sample size calculations are not applicable. All pregnant and/or breast feeding female patients will be included in the Pregnancy/Lactation Sub-Study.

Table 3. Schedule of Recommended Assessments for Pregnancy/Lactation Sub -Study Participation

Assessment	Timing of assessment	Data elements to be collected	During Pregnancy Visit	First Post-Pregnancy Visit	Additional Post-Pregnancy Visits
Course of pregnancy	**Following report of pregnancy to Gaucher Disease participating investigator**	Pregnancy status; date of last menstrual period; due date; history of assisted reproductive technology; number of attempts to get pregnant; current pregnancy complications; prenatal testing and results; use of recreational drugs (tobacco, alcohol, illicit drugs)	X		
Pregnancy outcomes: mother	**Following delivery and postpartum**	Delivery complications; method of delivery (vaginal or Cesarean); number of births, pregnancy outcome (live birth, elective termination, spontaneous abortion, stillborn, gestational age at delivery; date of pregnancy outcome; post-partum complications (bleeding, anemia, infections, bone crisis)		X	
Pregnancy outcomes: live births and non-live births/fetal losses	**Following delivery (live births and non-live births)**	Sex; birth weight; gestational age; Apgar score at minute 1 and minute 4; admission to ICU; complications experienced by an fetus/infant; fetal/neonatal congenital anomalies detected at birth and shortly post-delivery		X	
Infant outcomes until the 1st birthday[1]	**Following delivery and/or initiation of breastfeeding**	Breast feeding attempted and/or whether the child is currently being breastfed;[2] age of infant; physical and developmental milestones		X	X

1. In those instances where a woman becomes pregnant during the last 9 months of the Drug Registry and/or initiates breastfeeding prior to the end of the 10 year Drug Registry, collection of data on infant outcomes will stop at the time that the Drug Registry is concluded.
2. If breastfeeding was attempted then additional questions may include duration of breastfeeding, baby's weight gain during breastfeeding, supplemental feeding, difficulties/complications in breastfeeding and difficulty for infant to nurse. If breastfeeding was not attempted then reason(s) may be ascertained.

9.15.10. Data Analysis

Data will be summarized using descriptive statistics. For outcomes of interest, summary statistics, including counts and frequencies for categorical variables and N, mean, standard deviation, median, range for continuous variables will be calculated. Crude cumulative incidence and crude incidence rates per person-time will be calculated only if statistically appropriate.

A woman is considered to be exposed to taliglucerase alfa or to another treatment (including the lack of treatment) for her Gaucher Disease during her pregnancy if she receives that treatment at any time following two weeks post last menstrual period (LMP), i.e. conception, until the end of the pregnancy. Treatment switches during the course of the pregnancy and/or breastfeeding will be further defined in the Pregnancy/Lactation sub-study statistical analysis plan.

When describing pregnancy and infant outcomes, the following variables will be considered whenever possible:

- A prenatal diagnosis of a birth defect prior to being enrolled in the Pregnancy/ Lactation Sub-Study;
- Any prior exposure, at any time to substrate reduction therapy.

9.15.11. Limitations of the Research Methods

Given the very small number of anticipated pregnancies and live births in this sub-study, the sample size may be too small to rule out risks potentially indicative of reproductive toxicity.

While every effort will be made to obtain pregnancy-related and newborn/infant medical records, it is anticipated that the medial release consent rate will be appreciably less than 100%. Some women may not provide medical release consent for her obstetrician and/or her child's pediatrician may not comply with such a request. Moreover, women who provide such consent may differ from those women who do not.

9.15.12. Discontinuation of the Pregnancy/Lactation Sub-Study will be Considered at Such Time as:

- Sufficient information has accumulated to meet the scientific objectives of the Pregnancy/Lactation Sub-Study;
- Other methods of gathering appropriate information become achievable or are deemed preferable;
- The feasibility of collecting sufficient information diminishes to unacceptable levels because of low exposure rates, poor enrollment, or losses to follow up or
- The Drug Registry is stopped.

These considerations are documented in the FDA Guidance document.[19] The Sponsor will continuously monitor taliglucerase alfa rates and enrollment.

9.15.13. Pregnancy/Lactation Sub-Study: Management and reporting of adverse events/adverse reactions

The requirements for recording safety events on the e-CRF and for reporting safety events on the non-interventional study (NIS) adverse event monitoring (AEM) Report Form to Pfizer Safety are the same as those in Section 9.13 with the exception of Exposure during Pregnancy and exposure during breastfeeding cases. This is because this Pregnancy/Lactation Sub-Study is considered to be a non-interventional study conducted in pregnant and breastfeeding women (i.e. infant exposure during breastfeeding) and as such, data on the pregnancy and breastfeeding outcomes and non-serious AEs are expected to be collected and analyzed in the study database. In these instances, only EDPs associated with an SAE and/or infant exposure during breastfeeding associated with an SAE are to be reported to Pfizer Safety using the NIS AEM Report Form and the EDP Supplemental Form.

If the outcome of the pregnancy meets the criteria for an SAE (e.g., ectopic pregnancy, spontaneous abortion, intrauterine fetal demise, neonatal death, or congenital anomaly [in a live born, a terminated fetus, an intrauterine fetal demise, or a neonatal death]), the procedures for reporting SAEs should be followed. Additional information about pregnancy outcomes that are reported as SAEs follows:

- Spontaneous abortion includes miscarriage and missed abortion;
- Neonatal deaths that occur within 1 month of birth should be reported, without regard to causality, as SAEs. In addition, infant deaths after 1 month should be reported as SAEs when the investigator assesses the infant death as related or possibly related to exposure to investigational product

Additional information regarding the exposure during pregnancy may be requested. Further follow-up of birth outcomes will be handled on a case-by-case basis (e.g., follow-up on preterm infants to identify developmental delays).

9.16. Description of Oversight Committee with External Members

A Scientific Steering Committee consisting of membership external to Pfizer will be convened and will serve to provide guidance on the study conduct, monitor study progress, and advise on study analyses. The committee will be comprised of experts in epidemiology, Gaucher disease treatment, and treatment of pregnant women with Gaucher disease. The committee may recommend changes to the study conduct with respect to the data acquisition and patient safety.

10. PROTECTION OF HUMAN SUBJECTS

10.1. Patient Information and Consent

All parties will ensure protection of patient personal data and will not include patients' names on any sponsor forms, reports, publications, or in any other disclosures, except where required by laws. In case of data transfer, Pfizer will maintain high standards of confidentiality and protection of patient personal data.

The informed consent form must be in compliance with local regulatory requirements and legal requirements.

The informed consent form used in this study, and any changes made during the course of the study, must be prospectively approved by both the Institutional Review Board (IRB)/Independent Ethics Committee (IEC) and Pfizer before use.

The investigator must ensure that each study patient, or his/her legally acceptable representative, is fully informed about the nature and objectives of the study and possible risks associated with participation. The investigator, or a person designated by the investigator, will obtain written informed consent from each patient or the patient's legally acceptable representative before any study-specific activity is performed. The investigator will retain the original of each patient's signed consent form.

10.2. Patient Withdrawal

Patients may withdraw from the study at any time at their own request, or they may be withdrawn at any time at the discretion of the investigator or sponsor for safety, behavioral, or administrative reasons. In any circumstance, every effort should be made to document patient outcome, if possible. An investigator should inquire about the reason for withdrawal and follow-up with the patient regarding any unresolved adverse events.

If the patient withdraws from the study, and also withdraws consent for disclosure of future information, no further evaluations should be performed, and no additional data should be collected. The sponsor may retain and continue to use any data collected before such withdrawal of consent.

Distinction should be made between discontinuation of taliglucerase alfa treatment and discontinuation of study participation. Study participants discontinuing taliglucerase alfa treatment will continue to be followed to the end of the ten year study period from enrollment, voluntary withdrawal from the study, withdrawal at the discretion of the treating physician or sponsor, or loss to follow-up due to other reasons (e.g., cannot be located through alternative contact), whichever is soonest.

10.2.1. Institutional Review Board (IRB)/Independent Ethics Committee (IEC)

It is the responsibility of investigators to have prospective approval of the study protocol, protocol amendments, informed consent forms, and other relevant documents,

(e.g., recruitment advertisements), if applicable, from the IRB/IEC. All correspondence with the IRB/IEC will be retained in the Investigator File. Copies of IRB/IEC approvals will be forwarded to Pfizer.

10.2.2. Ethical Conduct of the Study

The study will be conducted in accordance with legal and regulatory requirements, as well as with scientific purpose, value and rigor and follow generally accepted research practices described in Good Pharmacoepidemiology Practices (GPP) issued by the International Society for Pharmacoepidemiology (ISPE), Good Epidemiological Practice (GEP) guidelines issued by the International Epidemiological Association (IEA), Good Outcomes Research Practices issued by the International Society for Pharmacoeconomics and Outcomes Research (ISPOR), International Ethical Guidelines for Epidemiological Research issued by the Council for International Organizations of Medical Sciences (CIOMS), and the European Medicines Agency (EMA) European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) Guide on Methodological Standards in Pharmacoepidemiology.

11. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

Pfizer has no objection to publications by participating investigators of any information collected or generated by investigator, whether or not the results are favorable to taliglucerase alfa. However, to ensure against inadvertent disclosure of confidential information or unprotected inventions, participating investigators will be required to provide Pfizer an opportunity to review any proposed publication or other type of disclosure before it is submitted or otherwise disclosed. Investigators will also be required to provide manuscripts, abstracts, or the full text of any other intended disclosure (e.g., poster presentation, invited speaker or guest lecturer presentation, etc.) to Pfizer at least 30 days before they are submitted for publication or otherwise disclosed. If any patent action is required to protect intellectual property rights, the investigator will agree to delay the disclosure for a period not to exceed an additional 60 days. Investigators will, on request, remove any previously undisclosed confidential information (other than the Study results themselves) before disclosure.

Investigators will agree that the first publication is to be a joint publication covering all study sites. However, if a joint manuscript has not been submitted for publication within 12 months of completion or termination of the study at all participating sites, investigators are free to publish separately, subject to the other requirements of this Section.

For all publications relating to the study, the institution will comply with recognized ethical standards concerning publications and authorship, including Section II - “Ethical Considerations in the Conduct and Reporting of Research” of the Uniform Requirements for Manuscripts Submitted to Biomedical Journals, (http://www.icmje.org/index.html#authorship), established by the International Committee of

Medical Journal Editors. Publication of study results will also provided for in the Clinical Study Agreement between Pfizer and institutions.

COMMUNICATION OF ISSUES

In the event of any prohibition or restriction imposed (e.g., clinical hold) by an applicable Competent Authority in any area of the world, or if the investigator is aware of any new information which might influence the evaluation of the benefits and risks of taliglucerase alfa, Pfizer should be informed immediately.

In addition, the investigator will inform Pfizer immediately of any urgent safety measures taken by the investigator to protect the study patients against any immediate hazard, and of any serious breaches of this non-interventional (NI) study protocol that the investigator becomes aware of.

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