PROTOCOL: SHP669-405

TITLE:	Canadian VPRIV® Non-Interventional Study in Patients Previously Treated with Other Enzyme Replacement Therapies (ERTs)/Substrate Reduction Therapies (SRTs)
PROTOCOL VERSION AND DATE:	SHP669-405, Version 1.0, 14 Jan 2019
EU PAS REGISTER NO.:	Study not registered
ACTIVE SUBSTANCE:	velaglucerase alfa
MEDICINAL PRODUCT:	velaglucerase alfa powder for solution for injection 400 U/vial
PRODUCT REFERENCE:	A16AB10
PROCEDURE NUMBER:	Not applicable
SPONSOR/MAH:	USA: Shire Human Genetic Therapies, Inc.*, 300 Shire Way, Lexington, MA 02421 USA EU: Baxalta Innovations GmbH*, Industriestrasse 67, A-1221 Vienna, Austria * Baxalta is now part of Shire
JOINT STUDY:	No

RESEARCH QUESTION AND OBJECTIVES:	**Primary Objective** • To describe the safety in patients transitioning from other Enzyme Replacement Therapies (ERTs)/Substrate Reduction Therapies (SRTs) to velaglucerase alfa (VPRIV) across all age groups **Secondary Objectives** • To describe the treatment of patients transitioning from other ERTs/SRTs to velaglucerase alfa (VPRIV) across all age groups • To describe the effect of the change in treatment on glucosylspingosine (also called Lyso-Gl1/Lyso-Gb1) following the transition from other ERTs/SRTs to velaglucerase alfa (VPRIV) • To describe the effect of the change in treatment on Patient Reported Outcomes (PRO) tool
COUNTRY(-IES) OF STUDY:	Canada
AUTHOR:	
CONTACT PERSON:	[redacted] PhD [redacted] Global Clinical Development Operations, Shire Vienna DC Tower 1, Donau-City-Str. 7 A-1220 Vienna, Austria [redacted] [redacted]

PROTOCOL SIGNATURE PAGE – SHIRE

Shire Approval

Signature:	[redacted]	**Date:**	[redacted]

PROTOCOL SIGNATURE PAGE – INVESTIGATOR

Investigator's Acknowledgement

I have read this protocol for Shire Study SHP669-405.

Title: Canadian VPRIV® Non-Interventional Study in Patients Previously Treated with Other Enzyme Replacement Therapies (ERTs)/Substrate Reduction Therapies (SRTs)

I have fully discussed the objective(s) of this study and the contents of this protocol with the sponsor's representative.

I understand that the information in this protocol is confidential and should not be disclosed, other than to those directly involved in the execution or the scientific/ethical review of the study, without written authorization from the sponsor. It is, however, permissible to provide the information contained herein to a subject in order to obtain their consent to participate.

I agree to conduct this study according to this protocol and to comply with its requirements, subject to ethical and safety considerations and guidelines, and to conduct the study in accordance with the principles of the Guideline on Good Pharmacovigilance Practices (GVP) Module VIII – Post Authorization Safety Studies, and the Guidelines for Good Pharmacoepidemiology Practice (GPP), together with any applicable regulatory requirements.

I understand that failure to comply with the requirements of the protocol may lead to the termination of my participation as an investigator for this study.

I understand that the sponsor may decide to suspend or prematurely terminate the study at any time for whatever reason; such a decision will be communicated to me in writing. Conversely, should I decide to withdraw from execution of the study I will communicate my intention immediately in writing to the sponsor.

Investigator Name and Address: (please hand print or type)	

Signature: _____ **Date:** _____

CONTACT INFORMATION

In the event of an SAE, the investigator must e-mail the Shire Clinical Trial Adverse Event Form within 1 business day to the Shire GDS Department or log the SAE using Electronic Data Capture (EDC), via the appropriate URL. Applicable e-mail address can be found on the form (sent under separate cover).

[redacted]

For protocol-related issues, the investigator must contact the Shire Medical Monitor:

[redacted] Global Medical Affairs

300 Shire Way

Lexington, MA

02421, USA

[redacted]

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2. ABBREVIATIONS

AE	adverse event
BMD	bone mineral density
CRA	clinical research associate
CRF	case report form
CRO	contract research organization
DMC	data monitoring committee
EC	ethics committee
EDC	electronic data collection
ERT	enzyme replacement therapy
GDS	global drug safety
GD1	Gaucher disease Type 1
GPP	good pharmacoepidemiology practices
GVP	good pharmacovigilance practices
Hb	haemoglobin
hCG	human chorionic gonadotropin
HEOR	health economics and outcome research
HIPAA	Health Insurance Portability and Accountability Act
ICH	International Council on Harmonisation
IRB	institutional review board
MAH	marketing authorisation holder
ORE	outcomes research and epidemiology
PAES	post-authorisation efficacy study
PAS	post-authorisation study
PASS	post-authorisation safety study
PMC	post marketing commitment
PRAC	pharmacovigilance risk assessment committee
PRO	patient reported outcome
QPPV	qualified person responsible for pharmacovigilance
RMP	risk management plan
SAE	serious adverse event
SAP	statistical analysis plan
SOC	system organ class
SRT	substrate reduction therapy
URL	uniform resource locator
US	United States
VPRIV	velaglucerase alfa

3. DATA COLLECTION SCHEDULE

Table 1 Data Collection Schedule

		Retrospective/Prospective Observation Period –With data collected closest to:			
	Transition to VPRIV	**Month 1 (+/- 1 week)**	**Month 3 (+/- 1 week)**	**Month 6 (+/- 1 week)**	**Month 12 (+/- 1 week)**
Data Capture Point	**1**	**2**	**3**	**4**	**5**
Months on Therapy	**0**	**1**	**3**	**6**	**12**
Informed consent (At point of recruitment into the study)	✔				
Inclusion criteria	✔				
Exclusion criteria	✔	✔	✔	✔	✔
Demographic data (Age, sex)	✔				
Height age ≥18	✔				
Height age <18	✔	✔	✔	✔	✔
Weight	✔	✔	✔	✔	✔
Medical history	✔				
Clinical parameters (Hb, Platelet count, BMD, spleen and liver volume)	✔	✔	✔	✔	✔
Biomarker (Chitotriosidase, CCL18, & Lyso-Gb1)	✔	✔	✔	✔	✔
VPRIV dosing information	✔	✔	✔	✔	✔
Anti-drug antibodies	✔	✔	✔	✔	✔
Concomitant medication	✔	✔	✔	✔	✔
Adverse events / adverse reactions		✔	✔	✔	✔
Gaucher Disease Questionnaire (PRO) ≥ 18	✔				✔

HB=Hemoglobin; BMD=Bone Mineral Density; CCL18=CC-chemokine ligand18; Lyso-Gb1=Glucosylspingosine

4. RESPONSIBLE PARTIES

Protocol Author(s): [redacted],
[redacted], Global Medical Affairs

300 Shire Way

Lexington, MA, 02421, USA

EU QPPV Not applicable

5. ABSTRACT

Title of the Study: Canadian VPRIV® Non-Interventional Study in Patients Previously Treated with Other Enzyme Replacement Therapies (ERTs)/Substrate Reduction Therapies (SRTs)

SHP669-405, V1.0, 14 Jan 2019

Main author:

[redacted] *MD, PhD*

[redacted], *Global Medical Affairs*

300 Shire Way

Lexington, MA

02421, USA

Rationale and Background:

There is limited real-world data available for patients with Gaucher disease changing from one enzyme replacement therapy (ERT) to another and even less so when it comes to changes from substrate reduction therapy (SRT) to ERTs. This study intends to augment the limited clinical and real-world evidence and describe the experience for patients with type 1 Gaucher disease (GD1) transitioning from ERTs/SRTs to VPRIV (velaglucerase alfa) treatment. This study also seeks to provide insights on the use of a biomarker, Glucosylspingosine (Lyso-Gb1), with 100% specificity for Gaucher disease.

Research Question and Objectives:

The primary objective is to describe the safety of VPRIV in patients with GD1 transitioning from other ERTs/SRTs to VPRIV in a Canadian real-world setting across all age groups.

The secondary objective is to describe the treatment of VPRIV in patients affected with GD1 transitioning from other ERTs/SRTs to VPRIV in a Canadian real-world setting across all age groups.

Additional secondary objectives include evaluating the effect of the change in treatment on:

- The Lyso-Gb1 biomarker
- Patient reported outcomes (PRO) for adults

Study Design:

This is a retrospective/prospective non-interventional study. Patients will be studied by observing patient care. Data will be collected as per the data collection schedule in Table 1, depending on the availability of the data based on the frequency of visits, after the patient has been transitioned from ERTs/SRTs to VPRIV.

For patients who have already transitioned from ERTs/SRTs to VPRIV the data will be collected retrospectively from the time of transition until the point at which the patient enters the study. The PRO data and Lyso-Gb1 data will not be collected.

Population:

It is anticipated to collect the data from 12 to 24 patients, who are being treated at up to 6 sites across Canada.

Patients included have a diagnosis of GD1 and are currently being treated with another ERT/SRT for at least 6 months before the transition to VPRIV, and the patient or legally authorized representative has provided written informed consent. Patients will be excluded if they are at high risk of non-compliance or are unsuitable in any other way to participate in this study in the Investigator's opinion.

Variables:

The following will be collected during the study:

- Demographics (Age, Sex)
- Height and weight
- Medical history
- Clinical parameters (Hb, Platelet count, BMD, spleen and liver volume)
- Biomarkers (Chitotriosidase, CCL18, & Lyso-Gb1)
- VPRIV Dosing information
- Anti-drug antibodies
- Concomitant medications
- Adverse events
- The Gaucher Disease Questionnaire (PRO) completed by patients ≥ 18 years
- Pregnancy status

The data will be collected as per the data collection schedule (Table 1). No data will be imputed. As patients may not follow the data collection frequency with their visit schedules, the values collected by the treating physician nearest to the collection date will be used.

Data Sources:

The data will be obtained from the medical records and entered without identifiers into a validated electronic data collection (EDC) platform. Data will also be collected from the patient reported outcomes questionnaire.

Study Size:

The data will be collected for 12 to 24 patients. No formal sample size calculation has been performed. The sample size was determined by a feasibility assessment.

Data Analysis:

The statistical evaluation will be descriptive. No statistical hypotheses will be tested. Continuous numeric variables will be summarized as mean, standard deviation, median, interquartile range, minimum and maximum. For categorical variables, frequency counts will be applied (absolute and relative frequencies). For estimated frequencies, and if applicable for other parameters, 95% confidence intervals will be calculated. There will be no imputation of missing values. Results will be presented in tables and graphs.

Milestones

Milestone	Planned Date
Start of data collection:	First Patient First Visit March 2019
End of data collection:	Last Patient Last visit June 2020
Study progress report(s):	Monthly
Interim report(s), where applicable:	Not planned
Final report:	October 2020
Any other important milestones:	N/A

6. AMENDMENTS AND UPDATES

Not applicable.

7. MILESTONES

Milestone	Planned Date
Start of data collection:	First Patient First Visit March 2019
End of data collection:	Last Patient Last visit June 2020
Study progress report(s):	Monthly
Interim report(s), where applicable:	Not planned
Final report:	October 2020
Any other important milestones:	N/A

8. RATIONALE AND BACKGROUND

Gaucher disease is an autosomal recessive disorder characterized by mutations in the glucocerebrosidase gene and is categorized into three subtypes: type 1 (GD1), type 2 and type 3. GD1 makes up 94% of cases and is traditionally considered to be non-neuronopathic. Enzyme replacement therapy (ERT) is the treatment of choice in these patients, and SRTs are typically reserved for second line treatment in Canada (Amato et al., 2018).

There is limited real-world data available on patients changing from one ERT to another and even less so when it comes to changes from SRTs to ERTs. One 12-month study evaluated the safety and efficacy of transitioning to velaglucerase alfa (VPRIV) in 40 patients previously treated with another ERT (imiglucerase) (Elstein et al., 2015). The authors concluded that adult and pediatric patients with GD1, previously treated with imiglucerase, successfully transitioned to VPRIV, which was generally well tolerated and demonstrated efficacy over 12 months' treatment consistent with that observed in the VPRIV Phase 3 clinical trials. Another paper reported on the safety and efficacy findings from an Early Access Program (EAP) with VPRIV in 71 patients 36 of whom completed 6, 9, or 12 months as intravenous VPRIV every other week (Elstein et al., 2012). The authors concluded that the switch-over from imiglucerase (10-24 months) was safe and in several patients VPRIV induced a booster-effect, primarily in the disease-specific parameters of platelet counts and splenic volume.

This study intends to augment the limited clinical and real-world safety and patient outcomes for VPRIV in GD1 patients transitioning from ERTs/SRTs to VPRIV. The study will also explore the effect of change in treatment on the use of a biomarker with 100% specificity for Gaucher disease, Lyso-Gb1, and PROs.

8.1 Description of VPRIV

Velaglucerase alfa, supplied as a powder for reconstitution for injection (400 U/vial), is produced by gene activation technology in a human cell line. Velaglucerase alfa is a glycoprotein with the same amino acid sequence as the naturally occurring human enzyme, glucocerebrosidase. Velaglucerase alfa catalyzes the hydrolysis of the glycolipid glucocerebroside to glucose and ceramide in the lysosome (Canadian VPRIV Product Monograph, 2010).

Velaglucerase alfa is indicated for long-term ERT for pediatric and adult patients with type 1 Gaucher disease (Canadian VPRIV Product Monograph, 2010).

9. RESEARCH QUESTION AND OBJECTIVES

Research Question

What is the real-world safety profile and patient outcomes of VPRIV in patients affected with GD1 transitioning from other ERTs/SRTs to VPRIV in a Canadian setting across all age groups?

Primary Objective

The primary objective is to describe the safety of VPRIV in patients affected with GD1 transitioning from other ERTs/SRTs to VPRIV in a Canadian real-world setting across all age groups.

Secondary Objectives

The secondary objective is to describe the treatment of VPRIV in patients affected with GD1 transitioning from other ERTs/SRTs to VPRIV in a Canadian real-world setting across all age groups.

Additional secondary objectives include evaluating the effect of the change in treatment on:

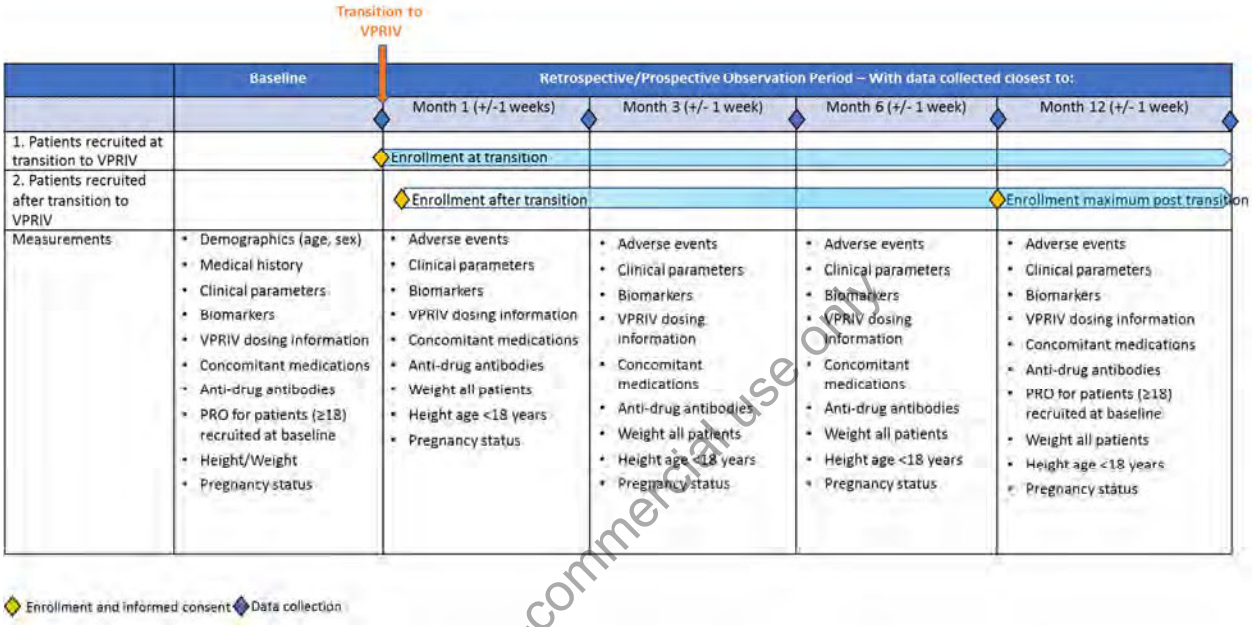
- The Lyso-Gb1 biomarker
- Patient reported outcomes (PROs) for adults

10. RESEARCH METHODS

10.1 Study Design

This is a Phase 4, observational, retrospective/prospective, non-controlled, non-comparative, multicenter study conducted with an observational period of 12 months (Figure 1).

Figure 1 Study Design Flow Chart



10.1.1 Data Collection

Data will be collected from the patients' medical records and entered into an electronic case report form (eCRF) throughout the study. For patients who have already transitioned to VPRIV, the data from the start of VPRIV treatment will be collected from the patient charts until the time the patient is recruited into the study.

Should the infusion have taken outside the physician's office (eg, home infusion) the data will need to be transferred by the healthcare professional to the patient's medical records to ensure those values are available for the study.

10.1.1.1 Start of Data Collection

Data collection will start at the time informed consent is obtained. Baseline observations and medical history will be collected at the first consultation as displayed in Figure 1. The PROs will be completed for adults aged ≥18 years with the physician, and the data will be collected in the eCRF.

10.1.1.2 Consultations

Data collected during any consultations during the 12-month study period will be reported in the study eCRF. Data will be collected +/-1 week for month 1, months 3, 6 and 12 as shown in Table 1.

10.1.1.3 Final Observation

Data will be collected at 12 months, +/-1 week (Table 1).

10.1.2 Setting for Non-interventional Clinical Studies

10.1.2.1 Number and Type of Subjects

The study aims to collect data from 12 to 24 patients. As there will be no statistical testing of hypotheses in the study, this sample size was chosen based on site feasibility.

10.1.2.2 Sites and Regions

The study will be performed in Canada at up to 6 study sites. Hospital- or office-based physicians are eligible for participation if they are experienced in the treatment of patients with GD1 and are responsible for the treatment of patients taking VPRIV.

10.1.2.3 Selection Criteria

There is no formal screening procedure for suitable study patients. Physicians are requested to consider suitability for inclusion in the study for their patients transitioning to VPRIV from other ERTs/SRTs in accordance with the inclusion and exclusion criteria set forth below.

10.1.2.4 Inclusion Criteria

1. Patients with GD1 and currently being treated with another ERT/SRT for at least 6 months before baseline enrolment.
2. Patient or legally authorized representative has provided written informed consent.

10.1.2.5 Exclusion Criteria

Patients are excluded from the study if any of the following criteria are met.

1. Patient is at high risk of non-compliance in the investigator's opinion.
2. Patient is in the opinion of the investigator, unsuitable in any other way to participate in this study.
3. Patient is pregnant.

10.1.2.6 Discontinuation of Subjects

A patient may withdraw from the study at any time, for any reason, without prejudice to their future medical care by the physician or at the institution. The investigator or sponsor may withdraw the patient at any time.

The reason for withdrawal must be determined by the investigator and recorded in the patient's medical record and on the eCRF. If a patient is withdrawn for more than one reason, each reason should be documented in the source document and the most clinically relevant reason should be entered on the eCRF.

Whenever possible, all data should be collected up to the time of withdrawal of consent. Comments (spontaneous or elicited) or complaints made by the patient must be recorded in the source documents.

10.2 Variables

The study will use available data and is observational. Information will be extracted from patient medical records at the indicated time-points as per Figure 1. Data will be extracted from the individual patient's chart or other sources of medical information and entered into an eCRF using EDC platform. Data extraction should follow visits of the patient to the site.

10.2.1 Study Periods

10.2.1.1 Baseline

- Informed consent
- Inclusion/exclusion criteria
- Demographics (age, sex)
- Height and weight
- Medical history
- Clinical parameters (Hb, Platelet count, BMD, spleen and liver volume)
- Biomarkers (Chitotriosidase, CCL18, & Lyso-Gb1)
- VPRIV dosing information
- Concomitant medications
- Anti-drug antibodies
- PRO for adult patients enrolled prior to transition to VPRIV

10.2.1.2 Month 1 (+/- 1 week), Month 3 (+/- 1 week) and Month 6 (+/-1 week)

- Informed consent
- Exclusion criteria
- Height age <18 years
- Weight
- Adverse events
- Clinical parameters (Hb, Platelet count, BMD, spleen and liver volume)

- Biomarkers (Chitotriosidase, CCL18, & Lyso-Gb1)
- VPRIV dosing information
- Concomitant medications
- Anti-drug antibodies

10.2.1.3 Month 12 (+/- 1 week)

- Informed consent
- Exclusion criteria
- Height age <18 years
- Weight
- Adverse events
- Clinical parameters (Hb, Platelet count, BMD, spleen and liver volume)
- Biomarkers (Chitotriosidase, CCL18, & Lyso-Gb1)
- VPRIV dosing information
- Concomitant medications
- Anti-drug antibodies
- PRO for adult patients enrolled prior to transition to VPRIV

10.2.2 Risk Factors

This is a non-interventional, observational study, during which patients will be treated in accordance with physician treatment plan.

10.2.3 Demographic and Other Baseline Characteristics

The following patient-level information will be collected at baseline:

a. Age (years)
b. Sex (male/female/unknown)
c. VPRIV dosing information
d. Concomitant medications
e. Height and weight
f. Medical history
g. Clinical parameters (Hb, Platelet count, BMD, spleen and liver volume)
h. Biomarkers (Chitotriosidase, CCL18 and Lyso-Gb1)
i. The Gaucher Disease Questionnaire (PRO) completed by patients ≥18 years
j. Anti-drug antibodies
k. Pregnancy status

10.2.4 Safety

10.2.4.1 Medical and Medication History

Medical and medication history will be collected at the start of data collection, from the patient's medical records and documented in the eCRF.

On the first visit, the patient's current medical history will be collected, and will include all comorbidities that the patient has at the time of the inclusion visit. All medications taken, and non-drug therapies received will be recorded on the concomitant medications and non-drug therapies page of the eCRF. Also, if deemed medically relevant, other medications, including supportive therapy, will also be recorded.

10.2.4.2 Adverse Events

Note: For this protocol, all SAEs and non-serious AEs will be collected. All SAEs (regardless of relationship to study) are collected from the time the subject signs the informed consent until the end of the study period and must be reported to the Shire Global Drug Safety Department [redacted] within 1 business day of the first awareness of the event. AEs of interest, including infections, will be collected per documentation schedule in the eCRF following visits of the subject to the study site.

Adverse events are collected from the time informed consent is signed until the end of the observational period. An AE is any untoward medical occurrence in a clinical investigation subject administered a pharmaceutical product and that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (study) product, whether or not related to the medicinal (study) product (ICH Guidance E2A 1995).

Events that do not necessarily meet the definition of AEs, regardless of causal association with commercial product, should be treated as AEs because they may be reportable to Regulatory Authorities according to AE reporting regulation; these include the following:

- Commercial product overdose, whether accidental or intentional
- Commercial product abuse
- An event occurring from commercial product withdrawal
- Any failure of expected pharmacological action
- Exposure to commercial product during pregnancy (refer to Section 12.2)
- Unexpected therapeutic or clinical benefit from the commercial product

Where possible, a diagnosis rather than a list of symptoms should be recorded. If a diagnosis has not been made, then each symptom should be listed individually. All AEs should be captured on the appropriate AE pages in the CRF and in source documents. In addition to AEs, unexpected benefits outside the investigational product indication should also be captured on the AE CRF.

All AEs must be followed to closure (the subject's health has returned to his/her baseline status or all variables have returned to normal), regardless of whether the subject is still participating in the study. Closure indicates that an outcome is reached, stabilization achieved (the investigator does not expect any further improvement or worsening of the event), or the event is otherwise explained. When appropriate, medical tests and examinations are performed so that resolution of event(s) can be documented.

Severity Categorization

The severity of AEs must be recorded during the course of the event including the start and stop dates for each change in severity. An event that changes in severity should be captured as a new event. Worsening of pre-treatment events, after initiation of study product, must be recorded as new AEs (for example, if a subject experiences mild intermittent dyspepsia prior to dosing of study product, but the dyspepsia becomes severe and more frequent after first dose of study product has been administered, a new AE of severe dyspepsia [with the appropriate date of onset] is recorded on the appropriate CRF).

The medical assessment of severity is determined by using the following definitions:

Mild: A type of AE that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.

Moderate: A type of AE that is usually alleviated with specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the research subject.

Severe: A type of AE that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention.

Causality Categorization

A physician/investigator must make the assessment of relationship to investigational product for each AE. The investigator should decide whether, in his or her medical judgment, there is a reasonable possibility that the event may have been caused by the investigational product. If there is no valid reason for suggesting a relationship, then the AE should be classified as "not related". Otherwise, if there is any valid reason, even if undetermined or untested, for suspecting a possible cause-and-effect relationship between the investigational product and the occurrence of the AE, then the AE should be considered "related". The causality assessment must be documented in the source.

The causality of AEs must be recorded during the course of the study on the CRF. Causality relationships are as follows:

- Related (The temporal relationship between the event and the administration of the investigational product is compelling enough and/or follows a known or suspected response pattern to that product, and the event cannot be explained by the subject's medical condition, other therapies, or accident.)

- Possible
- Probable
- Unlikely
- Unknown/unassessable
- Not related (The event can be readily explained by other factors such as the subject's underlying medical condition, concomitant therapy, or accident and no plausible temporal or biologic relationship exists between the investigational product and the event.)
- Not reported.

Outcome Categorization

The outcome of AEs must be recorded during the course of the study on the CRF. Outcomes are as follows:

- Fatal
- Not Recovered/Not Resolved
- Recovered/Resolved
- Recovered/Resolved with Sequelae
- Recovering/Resolving
- Unknown.

Symptoms of the Disease Under Study

Symptoms of the disease under study should not be classed as AEs as long as they are within the normal day-to-day fluctuation or expected progression of the disease and are part of the efficacy data to be collected in the study; however, significant worsening of the symptoms should be recorded as an AE.

Clinical Laboratory and Other Safety Evaluations

Any changes in clinical laboratory, vital sign, or other safety assessments observed as part of routine clinical practice can represent an AE. The investigator should decide, based on the clinical condition of a subject, whether these changes are clinically significant and therefore represent an AE.

Serious Adverse Events

A ***Serious Adverse Event*** **(SAE)** is any untoward medical occurrence (whether considered to be related to study product or not) that at any dose:

- Results in death

- Is life-threatening. Note: The term 'life-threatening' in the definition of "serious" refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it was more severe.
- Requires inpatient hospitalization or prolongation of existing hospitalization. Note: Hospitalizations, which are the result of elective or previously scheduled surgery for pre-existing conditions, which have not worsened after initiation of treatment, should not be classified as SAEs. For example, an admission for a previously scheduled ventral hernia repair would not be classified as an SAE; however, complication(s) resulting from a hospitalization for an elective or previously scheduled surgery that meet(s) serious criteria must be reported as SAE(s).
- Results in persistent or significant disability/incapacity
- Is a congenital abnormality/birth defect
- Is an important medical event. Note: Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered an SAE when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent 1 of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home; blood dyscrasias or convulsions that do not result in inpatient hospitalization; or the development of drug dependency or drug abuse.

10.2.4.3 Vital Signs

Not applicable.

10.2.4.4 Clinical Laboratory Evaluations

When measured as a part of clinical practice, the following clinical laboratory parameters and diagnostic test results will be captured in the eCRF:

- Haemoglobin (Hb)
- Spleen and liver volume
- Bone Mineral Density (BMD)
- Platelet counts
- VitB12
- VitD

When measured as a part of clinical practice, the following biomarkers will be captured in the eCRF if the data is available:

- Chitotriosidase
- CCL18
- Lyso-Gb1

All clinical laboratory assays and diagnostic test results will be performed according to the site's normal procedures. Reference ranges are to be supplied and will be used to assess the data for clinical significance and out-of-range changes. The investigator should assess out-of-range values for clinical significance, indicating if the value(s) is/are not clinically significant or clinically significant.

10.2.5 Efficacy

The study is not designed to measure the efficacy of VPRIV as it is a real-world study.

10.2.6 Health-related Quality of Life Assessments

The Gaucher Disease Questionnaire (PRO) will be used to collect information from patients.

10.3 Data Sources

As per International Council for Harmonization Good Clinical Practice, source data are defined as all information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical study which may be in paper and/or electronic format, that are necessary for the reconstruction and evaluation of the study. In addition, in this study we are going to collect data on a biomarker with 100% specificity for Gaucher disease, Lyso-Gb1. Source data for this observational study comprise, but are not limited to, the following: hospital records, medical records, clinical and office charts, laboratory notes, memoranda, patients' diaries or evaluation checklists, outcomes reported by patients, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate copies, microfiche, photographic negatives, microfilm or magnetic media, x-rays, Dual-energy X-ray absorptiometry (DEXA), patient files, and records kept at the pharmacy, at the laboratories, and/or at medico-technical departments involved in the clinical study.

Only such source data will be used as basis for any data to be entered into the eCRF.

10.4 Study Size

The sample size was determined by feasibility given GD1 is a rare disease. As such, 12 to 24 patients will be consecutively enrolled from up to 6 sites in Canada.

10.5 Data Management

For non-interventional clinical studies, the investigator's authorized site personnel must enter the information required by the protocol on the CRF, using the electronic data capture platform (eCRF).

The data will be collected and securely transferred to the host database. Data will be stored on secure servers by IQVIA (Kirkland, Quebec) until study end, after which the anonymized dataset will be securely transferred to Shire.

Patient-level data will be anonymized, while site information (investigator addresses and user roles) will be stored non-anonymized. The investigator is responsible for the collection of data and for the quality of data recorded in the eCRFs. Quality checks are undertaken by IQVIA using the data management system to detect irregularities, data cleaning and statistical checks (to detect outliers or clinically improbable values), and ongoing remote monitoring.

Data will be stored at secure servers by the IQVIA until study end, after which data are securely transferred to Shire. Each investigator will receive his/her own patient's data at study end, and/or according to local regulations.

Patients who enroll and are about to transition to VPRIV, PRO data (for patients age ≥18) will be collected at the first visit and at 12 months (+/- 1 week). Patients who transitioned prior to enrolment will not receive a PRO. Each participating site will be provided with the required number of questionnaires. For each enrolled patient, a unique code will be generated and linked to the questionnaires. Unique code generated by the eCRF will be used to identify the same patient's PROs.

10.6 Data Analysis

The study will be analyzed by IQVIA.

Detailed methodology for summary and statistical analyses of data collected in this study will be documented in the statistical analysis plan (SAP), which will be finalized prior to database lock for the final analysis. The SAP may modify the plans outlined in the protocol; any major modifications of primary endpoint definitions or their analyses would be reflected in a protocol amendment.

All statistical analyses will be performed using SAS version 9.2 or higher (SAS Institute, Cary, NC 27513).

The statistical evaluation of all collected data will be done on a descriptive basis. No statistical hypotheses will be tested.

Results will be presented in tables and graphs. Continuous numeric variables will be summarized as mean, standard deviation, median, interquartile range, minimum, and maximum. For categorical variables, frequency counts will be applied (absolute and relative frequencies). Ninety-five percent (95%) confidence intervals will be calculated when applicable. There will be no imputation of missing values. If groups of sufficient sample sizes are available, confidence intervals may accompany the point estimates.

To preserve the integrity of the statistical analysis and study conclusions, the SAP will be finalized prior to database lock.

10.6.1 Planned Interim Analysis

There is no planned interim analysis in this study.

10.6.2 Study Population

All patients with enrolment eligibility (ie, meeting all inclusion criteria and not fulfilling any exclusion criteria) and providing data on at least one VPRIV administration will be included in the analysis. In this study we enroll patients who transition to VPRIV at the study initiation or collect retrospective data until the point of enrolment for patients who have already transitioned to VPRIV previously.

10.6.3 Safety Analyses

AEs of interest will be coded using the Medical Dictionary for Regulatory Activities. The number of events, incidence, and percentage of patients or infusions with AEs will be calculated overall, by system organ class, by preferred term, and by cohorts and subgroups. AEs will be further summarized by severity and relationship to study product. AEs related to study product, AEs leading to withdrawal, SAEs, and deaths will be summarized/listed in a similar manner.

10.6.4 Efficacy Analyses

The study is not designed to measure the efficacy of VPRIV.

10.6.5 Health Outcomes

No other analyses are planned in this study.

10.6.5.1 Health-related Quality of Life Analyses

For the Gaucher Disease Questionnaire (PRO) scores will be calculated for each adult (≥18 years) patient at baseline and when the last data is collected based on the patients' visit schedules nearest to the 12 months. Descriptive statistics will be shown for each of the scores.

10.7 Quality Control

10.7.1 Data Quality and Integrity

Remote and on-site monitoring will occur in accordance with the monitoring plan. Data collection procedures will be discussed with the site at the site initiation visit and/or at the investigator's meeting. Once a patient is enrolled, it is expected that site personnel will complete the eCRF entry within approximately five (5) business days of the patient's consultation/observation.

Data are to be entered into the clinical database as specified in IQVIA's data management plan. Quality control and data validation procedures will be applied to ensure the validity and accuracy of the clinical database. Data are to be reviewed and checked for outliers and clinically improbable values requiring further clarification using statistical review. Data queries requiring clarification are to be communicated to the site for resolution via the IBM Clinical data management platform. Only authorized personnel will make corrections to the clinical database, and all corrections will be documented in an auditable manner.

10.7.2 Validation of Endpoints

Not applicable.

10.7.3 Storage of Records and Archiving

Essential documents must be maintained and may not be destroyed without written permission from the sponsor. Statistical programs will be archived in accordance with company policy.

The investigator will maintain all records pertaining to this study for a minimum of five (5) years after study end, or up to the maximum period required by local law and may not destroy records without written permission from the sponsor. Statistical programs will be archived in accordance with company policy.

As the investigator conducts the questionnaire portion of the study, copies of the completed questionnaires will be made by site staff, signed by the investigator, and stored at the corresponding site. Upon study completion, the original questionnaire will be archived by IQVIA Kirkland in a lockable cabinet for six (6) years. Once the archiving period has passed, all documents will be confidentially pulped and recycled or destroyed. Investigators are responsible for ensuring that questionnaires remain anonymous, and any accidental addition of patient identifiers are removed or blacked out before sending to the study team.

All the electronic data will be filed into the IQVIA file server. The files will be locked and protected from being updated or deleted for six (6) years.

10.7.4 Vendor Certification/Qualification

No third-party vendors are used.

10.8 Limitations of the Research Methods

This study intends to augment the limited clinical and real-world safety and patient outcomes of VPRIV in GD1 patients transitioning from ERTs/SRTs to VPRIV. This is a Phase 4, observational, retrospective/prospective, non-controlled, non-comparative multicenter study. Final study results might not reflect pivotal clinical trial results, in which patients are assigned to active or control group by chance (through randomization) to reduce errors or bias.

Patients' experience and data collected in this study will reflect clinical practice in Canada and may not be generalizable to studies conducted elsewhere due to differences in clinical practice and patient characteristics.

Last, a need for caution is required when interpreting results of observational studies due to their challenges in study design to establish cause-and-effect relationships.

10.9 Other Aspects

Not applicable.

11. PROTECTION OF HUMAN SUBJECTS

This study is conducted in accordance with current applicable regulations, and local ethical and legal requirements.

11.1 Sponsor's Responsibilities

11.1.1 Compliance with Relevant Guidelines

Shire will ensure that Local Regulatory Authority requirements are met before the start of the study. Shire (or a nominated designee) is responsible for the preparation, submission, and confirmation of receipt of any regulatory authority approvals required.

For a non-interventional post-authorisation safety study, Shire shall ensure that the study meets the requirements applicable to non-interventional post-authorisation safety studies set out in DIR Art 107m-q, REG Art 28b, IR Art 36-38 and the Guideline on Good Pharmacovigilance Practices (GVP) Module VIII – Post-Authorisation Safety Studies.

For a non-interventional post-authorisation efficacy study, Shire shall ensure that the study meets the requirements applicable to non-interventional PAES set out in Article 108a of Directive 2001/83/EC, in conjunction with Delegated Regulation (EU) No 357/2014, Regulation (EC) No 726/2004, Regulation (EC) No 1901/2006, Directive 2001/83/EC and Directive 2001/20/EC2.

Shire will ensure the fulfilment of its pharmacovigilance obligations in relation to the study and that this fulfilment can be audited, inspected and verified.

The sponsor and investigator must comply with all applicable regulations.

The sponsor will provide notification to the investigator of protocol and amendment approvals by regulatory authorities, if applicable.

The sponsor will select investigators on the basis of their expertise in the treatment of patients with ERTs/SRTs, and the study site's ability to conduct a study of this nature.

11.1.2 Study Suspension, Termination, and Completion

The sponsor may suspend or terminate the study, or part of the study, at any time for any reason.

If the study is suspended or terminated, the sponsor will ensure that applicable sites, and IRBs/ECs are notified as appropriate. Additionally, the discontinuation of a registered study which has been posted to a designated public website will be updated accordingly.

11.2 Investigator's Responsibilities

11.2.1 Compliance with Relevant Guidelines

Except where the investigator's signature is specifically required, it is understood that the term "investigator" as used in this observational protocol and on CRFs refers to the investigator or appropriate study personnel that the investigator designates to perform a certain duty.

The investigator is ultimately responsible for the conduct of all aspects of the surveillance. Sub-investigators or other appropriate study personnel are eligible to sign for the investigator on designated CRFs.

The investigator must undertake to perform the study in accordance with applicable regulatory requirements and guidelines.

It is the investigator's responsibility to ensure that adequate time and appropriately trained resources are available at the site prior to commitment to participate in this study. The investigator should also be able to estimate or demonstrate a potential for recruiting the required number of suitable subjects within the agreed recruitment period.

The investigator will maintain a list of appropriately qualified persons to whom the investigator has delegated significant study-related tasks, and shall, upon request of the sponsor, provide documented evidence of any licenses and certifications necessary to demonstrate such qualification. Curriculum vitae for these individuals as well as the investigator are provided to the study sponsor (or designee) before starting the study.

11.2.2 Protocol Adherence and Investigator Agreement

The investigator must adhere to the protocol as detailed in this document. The investigator is responsible for enrolling only those subjects who have met the protocol eligibility criteria. The investigator is required to sign the Protocol Signature Page (electronic signature is accepted) to confirm understanding, acceptance, and willingness to comply with the study protocol, and to send to the contract research organization (CRO)/site manager for filing in the study master file.

If the investigator suspends or terminates the study at their site, the investigator will promptly inform the sponsor and the institutional review board (IRB)/ethics committee (EC) and provide them with a written explanation. Upon study completion, the sponsor will provide the investigator, IRB/EC, and regulatory agency with final reports and summaries as required by (inter)national regulations.

Communication with local IRBs/ECs, to ensure accurate and timely information is provided at all phases during the study, may be done by the sponsor, applicable CRO, investigator, or for multicenter studies, the coordinating investigator according to national provisions and will be documented in the investigator agreement.

Should amendments to the protocol be required, the sponsor will write the amendments in a standard format and provide them to the investigator for submission to the IRB/IEC.

11.2.3 Documentation and Retention of Records

11.2.3.1 Case Report Forms

eCRFs are supplied by the CRO and should be handled in accordance with instructions from the sponsor.

The investigator is responsible for maintaining adequate and accurate medical records from which accurate information is recorded onto eCRFs, which have been designed to record all observations and other data pertinent to the clinical investigation. eCRFs must be completed by the investigator or designee as stated in the site delegation log.

All key data must be recorded in the subject's medical records from which the eCRF will be populated; no data will be recorded directly onto the CRF.

The clinical research assistant/study monitor will verify the contents against the source data per the monitoring plan. If the data are unclear or contradictory, queries are sent for corrections or verification of data.

11.2.3.2 Recording, Access, and Retention of Source Data and Study Documents

Original source data to be reviewed during this study will include, but are not limited to: subject's medical file, and original clinical laboratory reports.

The investigator must permit authorized representatives of the sponsor, the respective national, local, or foreign regulatory authorities, the IRB/EC, and auditors to inspect facilities and to have direct access to original source records relevant to this study, regardless of media.

The clinical research assistant/study monitor (and auditors, IRB/EC or regulatory inspectors) may check the CRF entries against the source documents. The consent form includes a statement whereby the subject agrees to the monitor/auditor from the sponsor or its representatives, national or local regulatory authorities, or the IRB/EC, having access to source data (eg, subject's medical file, appointment books, original laboratory reports, X-rays, etc.). Non-study site personnel will not disclose any personal information or personal medical information.

11.2.3.3 Audit/Inspection

To ensure compliance with relevant regulations, data generated by this study must be available for inspection and duplication upon request by representatives of, for example, the sponsor or its representatives, an auditor, and the IRB/EC for each site.

11.2.3.4 Financial Disclosure

Not applicable.

11.3 Ethical Considerations

11.3.1 Informed Consent

When applicable, it is the responsibility of the investigator to obtain written informed consent or assent from all study subjects. All consent and assent documentation must be in accordance with applicable regulations. Each subject or the subject's legally-authorized representative, as applicable, is requested to sign and date the subject informed consent form or a certified translation if applicable, after the subject has received and read (or been read) the written subject information and received an explanation of what the study involves, including but not limited to: the objectives, potential benefits and risk, inconveniences, and the subject's rights and responsibilities.

A copy of the informed consent or assent documentation (ie, a complete set of subject information sheets and fully executed signature pages) must be given to the subject or the subject's legally-authorized representative, as applicable. This document may require translation into the local language. Signed consent forms must remain in each subject's study file and must be available for verification at any time.

The investigator provides the sponsor with a copy of the consent form and assent form template which was reviewed by the IRB/EC and which received their favorable opinion/approval. A copy of the IRB/EC's written favorable opinion/approval of these documents must be provided to the sponsor, prior to the start of the study unless it is agreed to and documented (abiding by regulatory guidelines and national provisions) prior to study start that another party (ie, sponsor or coordinating investigator) is responsible for this action. Additionally, if the IRB/EC requires modification of the sample subject information and consent document provided by the sponsor, the documentation supporting this requirement must be provided to the sponsor.

11.3.2 Institutional Review Board or Ethics Committee

For non-interventional, clinical studies conducted at sites outside the EU, it is the responsibility of the investigator to submit this protocol, the informed consent document (approved by the sponsor or their designee), relevant supporting information and all types of subject recruitment information to the IRB/EC for review, and all must be approved prior to site initiation.

Prior to implementing changes in the study, the sponsor and the IRB/EC must approve any revisions of all informed consent documents and amendments to the protocol unless there is a subject safety issue.

For sites outside the EU, the investigator is responsible for keeping the IRB/EC appraised of the progress of the study and of any changes made to the protocol, but in any case, at least once a year. The investigator must also keep the local IRB/EC informed of any serious and significant AEs.

11.4 Privacy and Confidentiality

The confidentiality of records that may be able to identify subjects will be protected in accordance with applicable laws, regulations, and guidelines.

After subjects have consented to take part in the study, the sponsor and/or its representatives reviews their medical records and data collected during the study. These records and data may, in addition, be reviewed by others including the following: independent auditors who validate the data on behalf of the sponsor; third parties with whom the sponsor may develop, register, or market VPRIV; national or local regulatory authorities; and the IRBs/ECs which gave approval for the study to proceed. The sponsor and/or its representatives accessing the records and data will take all reasonable precautions in accordance with applicable laws, regulations, and guidelines to maintain the confidentiality of subjects' identities.

Subjects are assigned a unique identifying number (2 digit study site number (eg, 02) to be provided by the Marketing Authorisation Holder, and 2 digit subject numbers (eg, 03) reflecting the order of enrolment at each site); however, their year of birth may also be collected and used to assist the sponsor to verify the accuracy of the data (eg, to confirm that laboratory results have been assigned to the correct subject).

The results of studies – containing subjects' unique identifying number, relevant medical records, and possibly year of birth – will be recorded. They may be transferred to and used outside Canada which may not afford the same level of protection that applies within the countries where this study is conducted. The purpose of any such transfer would include: to support regulatory submissions, to conduct new data analyses to publish or present the study results, or to answer questions asked by regulatory or health authorities.

11.5 Study Results/Publication Policy

Shire will endeavor to publish the results of all qualifying, applicable, and covered studies according to external guidelines in a timely manner regardless of whether the outcomes are perceived as positive, neutral, or negative. Additionally, Shire adheres to external guidelines (eg, Good Publication Practices 3) when forming a publication steering committee, which is done for large, multicenter Phase 2-4 and certain other studies as determined by Shire. The purpose of the publication steering committee is to act as a non-commercial body that advises or decides on dissemination of scientific study data in accordance with the scope of this policy.

All publications relating to Shire products or projects must undergo appropriate technical and intellectual property review, with Shire agreement to publish prior to release of information. The review is aimed at protecting the sponsor's proprietary information existing either at the commencement of the study or generated during the study. To the extent permitted by the publisher and copyright law, the investigator will own (or share with other authors) the copyright on his/her publications. To the extent that the investigator has such sole, joint or shared rights, the investigator grants the sponsor a perpetual, irrevocable, royalty-free license to make and distribute copies of such publications.

The term "publication" refers to any public disclosure including original research articles, review articles, oral presentations, abstracts and posters at medical congresses, journal supplements, letters to the editor, invited lectures, opinion pieces, book chapters, electronic postings on medical/scientific websites, or other disclosure of the study results, in printed, electronic, oral or other form.

Subject to the terms of the paragraph below, the investigator shall have the right to publish the study results, and any background information provided by the sponsor that is necessary to include in any publication of study results, or necessary for other scholars to verify such study results. Notwithstanding the foregoing, no publication that incorporates the sponsor's confidential information shall be submitted for publication without the sponsor's prior written agreement to publish, and shall be given to the sponsor for review at least 60 days prior to submission for publication. If requested in writing by Shire, the institution and investigator shall withhold submission of such publication for up to an additional 60 days to allow for filing of a patent application.

If the study is part of a multicenter study, the first publication of the study results shall be made by the sponsor in conjunction with the sponsor's presentation of a joint, multicenter publication of the compiled and analyzed study results. If such a multicenter publication is not submitted to a journal for publication by the sponsor within an 18-month period after conclusion, abandonment, or termination of the study at all sites, or after the sponsor confirms there shall be no multicenter study publication of the study results, an investigator may individually publish the study results from the specific site in accordance with this section. The investigator must, however, acknowledge in the publication the limitations of the single-site data being presented.

Unless otherwise required by the journal in which the publication appears, or the forum in which it is made, authorship will comply with the International Committee of Medical Journal Editors (ICMJE) current standards. Participation as an investigator does not confer any rights to authorship of publications.

12. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

12.1 Serious Adverse Event Procedures

See Section 10.2.4.2 for definition of an SAE.

12.1.1 Reference Safety Information

The reference for safety information for this study is the VPRIV Product Monograph 01 Oct 2010, revised 2015.

12.1.2 Reporting Procedures

All initial and follow-up SAE reports must be reported by the investigator to the Shire Global Drug Safety Department ([redacted]) and the Shire Medical Monitor ([redacted]) within 1 business day of the first awareness of the event using the "Adverse Event Report Form." Note: The 1 business day reporting requirement for SAEs does not apply to reports of abuse, misuse, overdose, or medication errors unless they result in an SAE.

The investigator must log the SAE using the electronic data capture, via the appropriate uniform resource locator, and verify the accuracy of the information recorded with the corresponding source documents (Note: Source documents are not to be sent unless requested).

Any report of pregnancy for any female study participant must be reported within 1 business day to the Shire GDS Department ([redacted]) using the Shire "Pregnancy/Lactation Exposure Form."

12.1.3 Serious Adverse Event Collection Timeframe

All SAEs (regardless of relationship to study) are collected from the time the subject signs the informed consent until the end of the study period and must be reported to the Shire GDS Department ([redacted]) and the Shire Medical Monitor ([redacted]) within 1 business day of the first awareness of the event using the "Adverse Event Report Form." Non-serious AEs are preferably reported within 5 working days.

AEs of interest, including infections, will be collected per documentation schedule in the eCRF following routine visits of the patient to the study site.

12.1.4 Serious Adverse Event Onset and Resolution Dates

The onset date of the SAE is defined as the date the event meets serious criteria. The resolution date is the date the event no longer meets serious criteria, the date the symptoms resolve, or the event is considered chronic. In the case of hospitalizations, the hospital admission and discharge dates are considered the onset and resolution dates, respectively.

In addition, any signs or symptoms experienced by the subject after signing the informed consent form, or leading up to the onset date of the SAE, or following the resolution date of the SAE, must be recorded as an AE, if appropriate.

12.1.5 Fatal Outcome

Any SAE that results in the subject's death (ie,the SAE was noted as the primary cause of death) must have fatal checked as an outcome with the date of death recorded as the resolution date. For all other events ongoing at the time of death that did not contribute to the subject's death, the outcome should be considered not resolved, without a resolution date recorded.

For any SAE that results in the subject's death or any ongoing events at the time of death, the action taken with the study product should be recorded as "dose not changed" or "not applicable" (if the subject never received study product).

12.1.6 Regulatory Agency, Institutional Review Board, Ethics Committee, and Site Reporting

The investigator is responsible for notifying the local IRB, local EC, or the relevant local regulatory authority of all possibly related SAEs that occur at his or her site as required.

12.2 Pregnancy

All pregnancies are to be reported from the time informed consent is signed until the end of the observational period.

Any report of pregnancy for any female study participant must be reported within 1 business day to the Shire GDS Department using the Shire Pregnancy/Lactation Exposure Form. A copy of the Shire Pregnancy/Lactation Exposure Form (and any applicable follow-up reports) must also be sent to the Shire Medical Monitor ([redacted]) using the details specified in the emergency contact information section of the protocol. The pregnant female study participant must be withdrawn from the study.

Every effort should be made to gather information regarding the pregnancy outcome and condition of the infant. It is the responsibility of the investigator to obtain this information within 30 calendar days after the initial notification and approximately 30 calendar days post-partum.

Pregnancy complications, such as spontaneous abortion/miscarriage or congenital abnormality, are considered SAEs and must be reported using the Shire Clinical Trial Adverse Event Form within 1 business day. Note: An elective abortion is not considered an SAE.

In addition to the above, if the investigator determines that the pregnancy meets serious criteria, it must be reported as an SAE using the Shire Clinical Trial Adverse Event Form, as well as the Shire Investigational and Marketed Products Pregnancy Report Form. The test date of the first positive serum/urine beta human chorionic gonadotropin test or ultrasound result will determine the pregnancy onset date.

12.3 Abuse, Misuse, Overdose, and Medication Error

Please refer to the current VPRIV locally-applicable labeling for any case of overdose.

Abuse, misuse, overdose, or medication error (as defined below) must be reported to the sponsor according to the SAE reporting procedure whether or not they result in an AE/SAE. Note: The 1 business day reporting requirement for SAEs does not apply to reports of abuse, misuse, overdose, or medication errors unless these result in an SAE. Non-serious AEs are preferably reported within 5 working days.

The categories below are not mutually exclusive; the event can meet more than 1 category.

- **Abuse** – Persistent or sporadic intentional intake of study product when used for a non-medical purpose (e.g., to alter one's state of consciousness or get high) in a manner that may be detrimental to the individual and/or society
- **Misuse** – Intentional use of study product other than as directed or indicated at any dose (Note: this includes a situation where the study product is not used as directed at the dose prescribed by the treating physician)
- **Overdose** – Intentional or unintentional intake of a dose of study product exceeding the dosage described in the label for VPRIV
- **Medication Error** – An error made in prescribing, dispensing, administration, and/or use of study product. For studies, medication errors are reportable to the sponsor only as defined below.

Cases of patients missing doses of the study product are not considered reportable as medication errors.

Medication errors should be collected/reported for study product.

The administration and/or use of an expired study product should be considered as a reportable medication error.

13. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

13.1 Public Posting of Study Information

The sponsor is responsible for posting appropriate study information on applicable websites. Information included in clinical study registries may include participating investigators' names and contact information.

13.2 Submission of Summary of Final Study Report to Competent Authorities of Member States Concerned and Ethics Committees

The sponsor will provide a summary of the final study report to the competent authority of the member state(s) concerned as required by regulatory requirement(s) and to comply with the Community guideline on Good Clinical Practice or Good Pharmacovigilance Practices, as appropriate. This requirement will be fulfilled within 6 months of the end of data collection for pediatric studies and within 1 year for non-pediatric studies as per guidance.

14. REFERENCES

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Elstein, D., Altarescu, G., Maayan, H., Phillips, M., Abrahamov, A., Hadas-Halpern, I., et al. 2012. Booster-effect with velaglucerase alfa in patients with Gaucher disease switched from long-term imiglucerase therapy: Early Access Program results from Jerusalem. *Blood Cells, Molecules and Diseases,* 48, 45-50.

Elstein, D., Mehta, A., Hughes, D. A., Giraldo, P., Charrow, J., Smith, L., et al. 2015. Safety and efficacy results of switch from imiglucerase to velaglucerase alfa treatment in patients with type 1 Gaucher disease. *American Journal of Hematology,* 90, 592-597.

15. APPENDICES

APPENDIX 1 PROTOCOL HISTORY

Document	Date	Global/Country/Site Specific
Original Protocol	14 Jan 2019	