PROTOCOL: SHP669-405

TITLE:	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 2.0, 26 Mar 2021
EU PAS REGISTER NO.:	Study not yet 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, and Shire is now part of Takeda
JOINT STUDY:	No
RESEARCH QUESTION AND OBJECTIVES:	**Primary Objective** • To describe the safety in patients with GD1 transitioning from other Enzyme Replacement Therapies (ERTs)/Substrate Reduction Therapies (SRTs) to velaglucerase alfa (VPRIV) across all age groups

	Secondary Objectives • To describe VPRIV treatment dosing and administration patterns for patients with GD1 of all ages transitioning from other ERTs/SRTs • To describe the effect of treatment change on a novel biomarker for GD1, namely glucosylspingosine (Lyso-Gb1) • To describe the effect of treatment change on the patient reported outcome (PRO) of health-related quality of life (for adults ≥local age of majority)
COUNTRY(-IES) OF STUDY:	Canada, Israel and around 6 European countries
AUTHOR:	[redacted], [redacted] Takeda AS Drammensveien 852,1383 Asker [redacted] [redacted]
CONTACT PERSON:	[redacted], PhD [redacted] Global Development Office DC Tower 1, Donau-City-Str. 7 A-1220 Vienna, Austria [redacted] [redacted]

PROTOCOL SIGNATURE PAGE – SHIRE

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

Study number: SHP669-405

Version number: 2.0, 26 Mar 2021

[redacted]	**Date:** 30-Mar-2021 | 23:03 JST
	Date: 31-Mar-2021 | 00:22 JST

PROTOCOL SIGNATURE PAGE – INVESTIGATOR

Investigator's Acknowledgement

I have read this protocol for Shire Study SHP669-405 Version 2.0 dated 26 March 2021.

Title: 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 a severe adverse event (SAE), the investigator must e-mail the Clinical Trial Adverse Event Form within 1 business day to the Takeda Pharmacovigilance[1].

Email: [redacted]

For protocol-related issues, the investigator must contact the medical monitor

[redacted]

[redacted],

Takeda AS Drammensveien 852,1383 Asker

[redacted]

[1] Shire is now part of Takeda

1. TABLE OF CONTENTS

1.1 List of Tables

1.2 List of Figures

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2. ABBREVIATIONS

ADR	adverse drug reaction
AE	adverse event
BMD	bone mineral density
CCL18	cc-chemokine ligand18
CI	confidence interval
CRO	contract research organization
DEXA	dual-energy X-ray absorptiometry
EAP	early access program
EC	ethics committee
eCRF	electronic case report form
EDC	electronic data collection
EMA	European Medicines Agency
ERT	enzyme replacement therapy
EU	European Union
GD1	gaucher disease Type 1
GPP	good pharmacoepidemiology practices
GVP	good pharmacovigilance practices
Hb	haemoglobin
IRB	institutional review board
Lyso-Gb1	glucosylspingosine
MAH	marketing authorisation holder
PAS	post authorisation study
PASS	post authorisation safety study
PRO	patient reported outcome
PQI	product quality issue
QPPV	qualified person responsible for pharmacovigilance
SAE	serious adverse event
SAP	statistical analysis plan
SRT	substrate reduction therapy
SSR	special situation report
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 (eg, Hb, platelet count, BMD, spleen and liver volume, vitamin D, vitamin B12)	✔	✔	✔	✔	✔
Biomarkers (chitotriosidase, CCL18, & Lyso-Gb1)	✔	✔	✔	✔	✔
VPRIV dosing information	✔	✔	✔	✔	✔
Antidrug antibodies	✔	✔	✔	✔	✔
Concomitant medication	✔	✔	✔	✔	✔
Adverse events / adverse reactions		✔	✔	✔	✔
Gaucher disease questionnaire (PRO) (≥local age of majority)	✔				✔

HB=Hemoglobin; BMD=Bone Mineral Density; CCL18=CC-chemokine ligand 18; Lyso-Gb1=Glucosylspingosine

4. RESPONSIBLE PARTIES

Protocol Author(s): [redacted]

[redacted],

Takeda AS Drammensveien 852,1383 Asker

[redacted]

EU QPPV [redacted]

5. ABSTRACT

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

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 to describe the experience for patients with Gaucher disease type 1 (GD1) transitioning from other 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 in patients with GD1 transitioning from other ERTs/SRTs to VPRIV across all age groups.

The secondary objectives of the study are to:

- describe VPRIV treatment dosing and administration patterns for patients with GD1 of all ages transitioning from other ERTs/SRTs
- describe the effect of treatment change on a novel biomarker for GD1, namely glucosylspingosine (Lyso-Gb1)
- describe the effect of treatment change on the patient reported outcome (PRO) of health-related quality of life (for adults ≥local age of majority)

Study Design:

This is a retrospective/prospective non-interventional study. Patients will be studied by observing routine patient care. Data will be collected as per the data collection schedule in Table 1, depending on the availability of the data and based on the frequency of visits according to routine clinical practice, 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 begins participation in the study and then followed prospectively until 12 months of observation is completed. Neither the PRO, nor the Lyso-Gb1 data will be collected, unless it is routinely available within the standard of care.

Population:

This study aims to collect data from approximately 24 patients across 6-8 countries.

Patients included in the study will have a diagnosis of Type 1 GD and be in enzyme/substrate replacement therapy other than VPRIV, for at least 6 months prior to enrolment in the study,

or will have been previously treated with an ERT/SRT other than VPRIV for a minimum of 6 months prior to transitioning to VPRIV. The patient or legally authorized representative must provide written informed consent to be included in this study. Patients will be excluded if they are at high risk of non-compliance or are, in the investigator's opinion, unsuitable in any other way to participate in this study.

Variables:

Where available, the following will be collected during the study:

- Demographics (age, sex)
- Height and weight
- Medical history
- Clinical parameters (haemoglobin (Hb), platelet count, bone mineral density (BMD), spleen and liver volume)
- Biomarkers (chitotriosidase, CCL18, & Lyso-Gb1)
- VPRIV dosing information
- Antidrug antibodies
- Concomitant medications
- Adverse events
- The Gaucher disease questionnaire (PRO), only completed by patients ≥ local age of majority
- Patient's pregnancy status

Data will be collected as per the data collection schedule illustrated in Table 1. No data will be imputed. Because this is an observational study, routine care visits may not follow the study's data collection schedule; thus, data routinely collected by the treating physician nearest to the data collection timepoints will be used.

Data Sources:

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

Study Size:

Data will be collected for approximately 24 patients. No formal sample size calculation has been, nor will be, performed. The sample size was determined based on a feasibility assessment of the study's rare disease population.

Data Analysis:

The statistical analysis will be descriptive and there will be no hypothesis testing. 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.

6. AMENDMENTS AND UPDATES

Protocol Amendment 1 (26 Mar 2021)

Amendment Rationale

The purpose of this amendment is to expand the study to include up to 8 countries.

Number	Date	Section of study protocol	Amendment or update	Reason
1	26 March 2021	Throughout	Addition of approximately 6 European countries and Israel as locations for the study	To increase the scope of the study and to allow for recruitment of 24 patients in the study
		Throughout	Language tweaks and updates to medical writing style	To improve protocol clarity and consistency
		Title page, Sections 5 and 9	Minor updates to wording of objectives	To improve objective clarity and consistency while preserving objective aims
		Sections 1 and 2	Table of Contents and Abbreviation Table updated	To reflect current protocol text
		Sections 10 and 12	Safety Reporting requirements removed from section 10 and completely updated in section 12	Section 12 was updated to align with current processes for the Management and Reporting of Adverse Events/Adverse Reactions

7. MILESTONES

Milestone	**Planned Date (Estimated)**
Start of data collection:	First Patient First Visit September 2019 (Canada)
End of data collection:	Last Patient Last Visit May 2023
Study progress report(s):	Monthly
Interim report(s), where applicable:	Not planned
Final report:	February 2024
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 (Stirnemann et al., 2017).

There is limited real world data available on patients changing from one ERT to another and even less when it comes to changes from SRTs to ERTs. A previously reported 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 of 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.

Plasma levels of glucosylsphingosine (Lyso-Gb1), the deacylated form of glucosylceramide, are elevated in patients with symptomatic GD1 and act as a sensitive and specific biomarker of the disease (Rolfs et al., 2013). Importantly, plasma Lyso-Gb1 is produced by Gaucher cells (Dekker et al., 2011), thereby reflecting underlying disease, and making it a useful tool for the monitoring of disease progression and treatment response (Elstein et al., 2017).

This study intends to augment the limited clinical and real world safety and patient outcomes for VPRIV in patients with GD1 transitioning from ERTs/SRTs to VPRIV treatment. The study will also explore the effect of change in treatment on Lyso-Gb1 biomarker levels and the patient reported outcome (PRO) on health-related quality of life for adults.

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; Israeli VPRIV Summary of Product Characteristics and EMA VPRIV Summary of Product Characteristics).

In Canada, Israel, and Europe, Velaglucerase alfa is indicated as a long-term ERT for pediatric and adult patients with type 1 Gaucher disease (Canadian VPRIV Product Monograph; Israeli VPRIV Summary of Product Characteristics and EMA VPRIV Summary of Product Characteristics).

9. RESEARCH QUESTION AND OBJECTIVES

Research Question

What are the safety profiles, treatment patterns, effects on biomarker levels and patient reported outcomes of VPRIV treatment in patients with GD1 transitioning from other ERTs/SRTs to VPRIV in a routine clinical practice setting?

Primary Objective

The primary objective is to describe the safety in patients with GD1 transitioning from other ERTs/SRTs to VPRIV across all age groups.

Secondary Objectives

The secondary objectives of the study are to:

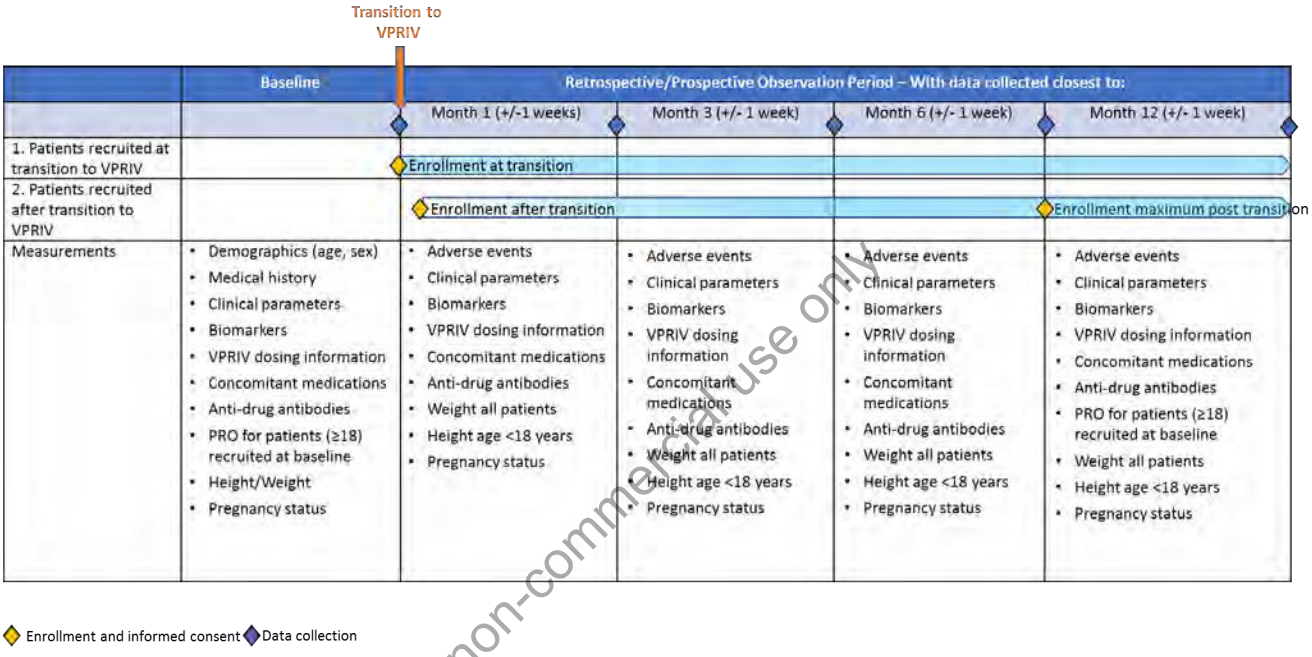
- describe VPRIV treatment dosing and administration patterns for patients with GD1 of all ages transitioning from other ERTs/SRTs
- describe the effect of treatment change on a novel biomarker for GD1, namely glucosylspingosine (Lyso-Gb1)
- describe the effect of treatment change on the patient reported outcome (PRO) of health-related quality of life (for adults ≥local age of majority)

10. RESEARCH METHODS

10.1 Study Design

This is a Phase 4, observational, retrospective/prospective, non-controlled, non-comparative, multi-center 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 previously transitioned to VPRIV, the data from the start of VPRIV treatment will be collected retrospectively from the patient charts until the time the patient is recruited into the study and then followed prospectively until 12 months of observation is complete.

Should VPRIV infusions have taken place outside the physician's office (eg, home infusion), the data will be transferred by the healthcare professional to the patient's medical records to ensure they 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 ≥local age of majority, with the assistance of the physician or physician's delegate, and the data will be entered into the eCRF by the site staff.

10.1.1.2 Consultations

Data collected during any consultation during the 12-month study period will be recorded in the study eCRF. The aim is to collect data from visits occurring nearest to months 1, 3, 6 and 12, as shown in Table 1, because routine care visits in the real world may not follow the study's data collection schedule.

10.1.1.3 Final Observation

Data will be collected at 12 months (Table 1).

10.1.2 Setting for Non-interventional Clinical Studies

10.1.2.1 Number and Type of Patients

The study aims to collect data from approximately 24 patients with GD1 across approximately 6-8 countries. As there will be no statistical testing of hypotheses in the study, this sample size was chosen based on a feasibility assessment of the study's rare disease population.

10.1.2.2 Sites and Regions

The study will be performed in in approximately 20 sites in up to 8 countries, including Canada, Israel and approximately 6 European countries. 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 of their patients transitioning to VPRIV from other ERTs/SRTs for inclusion in the study, in accordance with the inclusion and exclusion criteria set forth below.

10.1.2.4 Inclusion Criteria

1. Patient with GD1 currently being treated with an ERT/SRT other than VPRIV for at least 6 months before baseline enrolment; or patient previously treated with another ERT/SRT for at least 6 months prior to transitioning to VPRIV.
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. In the opinion of the investigator, patient is at high risk of non-compliance.
2. In the opinion of the investigator, patient is unsuitable in any other way to participate in this study.
3. Patient is pregnant.

10.1.2.6 Discontinuation of Patients

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 in 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 in 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 is observational and will rely on retrospective and prospective data collection. Information will be extracted from patient medical records, charts, or other source data for the data the timepoints in illustrated in Figure 1 and recorded in an eCRF using an EDC platform.

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 (eg, Hb, platelet count, BMD, spleen and liver volume, vitamin D, vitamin B12)
- Biomarkers (chitotriosidase, CCL18, & Lyso-Gb1, where possible)
- VPRIV dosing information
- Concomitant medications
- Antidrug antibodies
- PRO for patients ≥local age of majority enrolled prior to transition to VPRIV (where possible)

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

- Informed consent
- Exclusion criteria

- Height for patients aged <18 years
- Weight
- Adverse events
- Clinical parameters (eg, Hb, platelet count, BMD, spleen and liver volume, vitamin D, vitamin B12)
- Biomarkers (chitotriosidase, CCL18, & Lyso-Gb1, where possible)
- VPRIV dosing information
- Concomitant medications
- Antidrug antibodies

10.2.1.3 Month 12 (+/- 1 week)

- Informed consent
- Exclusion criteria
- Height for patients aged <18 years
- Weight
- Adverse events
- Clinical parameters (eg, Hb, platelet count, BMD, spleen and liver volume, vitamin D, vitamin B12)
- Biomarkers (chitotriosidase, CCL18, & Lyso-Gb1, where possible)
- VPRIV dosing information
- Concomitant medications
- Antidrug antibodies
- PRO for patients ≥local age of majority enrolled prior to transition to VPRIV (where possible)

10.2.2 Risk Factors

This is a non-interventional study that will observe patients treated in accordance with the standard physician treatment plan. This protocol does not recommend the use of any specific treatments and all treatment decisions are made independent of the study.

10.2.3 Demographic and Other Baseline Characteristics

The following patient-level information will be collected at baseline (where available):

- Age (years)
- Sex (male/female/unknown)

- VPRIV dosing information
- Concomitant medications
- Height and weight
- Medical history
- Clinical parameters (eg, Hb, platelet count, BMD, spleen and liver volume, vitamin D, vitamin B12)
- Biomarkers (chitotriosidase, CCL18 and Lyso-Gb1, where possible)
- The Gaucher disease questionnaire (PRO) completed by patients ≥local age of majority
- Antidrug antibodies
- Patient's pregnancy status

10.2.3.1 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.

The patient's current medical history will be collected at their first visit and will include all comorbidities that the patient has at the time of the inclusion visit. All medications taken concomitantly, and concomitant therapeutic procedures received will be recorded in the concomitant medications and concomitant therapeutic procedures pages of the eCRF. If deemed medically relevant, other medications, including supportive therapy, will also be recorded.

10.2.3.2 Vital Signs

Not applicable.

10.2.3.3 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, where available:

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

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

- Chitotriosidase
- CCL18
- Lyso-Gb1

No clinical laboratory assays or diagnostic tests are mandated as part of this study; they will be performed according to standard of care. 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 whether they are or are not clinically significant.

10.2.4 Efficacy

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

10.2.5 Health-related Quality of Life Assessments

The Gaucher disease questionnaire (PRO) will be used to collect health-related quality of life outcome data from patients.

10.3 Data Sources

As per the 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, which are necessary for the reconstruction and evaluation of the study. 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 that GD1 is a rare disease. As such, data from approximately 24 patients from across 6-8 countries will be collected.

10.5 Data Management

For non-interventional studies, the investigator's authorized site personnel must enter the information requested by the protocol in the eCRF, using the electronic data capture platform.

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

Patient-level data will be anonymized, while site information (investigator addresses and user roles) will be stored nonanonymized. The investigator is responsible for the collection the and for the quality of the 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.

For patients who are enrolled prior to transition to VPRIV, PRO data (for patients ≥local age of majority) will be collected at the first visit (baseline) and at 12 months. Patients who transitioned to study VPRIV prior to enrolment will not be required to complete the PRO. The completed PROs will be entered into the EDC by the site staff.

10.6 Data Analysis

The study will be analyzed by IQVIA.

Detailed methodology for descriptive 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%) CIs will be calculated when applicable. There will be no imputation of missing values.

10.6.1 Planned Interim Analysis

There is no interim analysis planned for this study.

10.6.2 Study Population

All patients who meet the enrolment eligibility (ie, meeting all inclusion criteria and none of the exclusion criteria) will be included in the analysis. This study will either enroll patients who transition to VPRIV at study enrolment or collect retrospective data until the point of enrolment for patients who have previously transitioned to VPRIV.

10.6.3 Safety Analyses

Adverse events (AEs) of interest will be coded using the most recent version of the Medical Dictionary for Regulatory Activities (MedDRA). 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 by subgroups. AEs will be further summarized by severity and relationship to study product. AEs related to study product, AEs leading to withdrawal, severe adverse events (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

Gaucher disease questionnaire PRO scores will be calculated for each adult (≥local age of majority) patient at baseline and when the last data is collected based on the patients' visit scheduled nearest to the 12 month timepoint. 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 data entry into the eCRF within approximately five (5) business days of the patient's consultation/observation.

Data are to be entered into the EDC 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.

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

10.7.4 Vendor Certification/Qualification

IBM eClinical will be used as the EDC platform for this study. It has been qualified by Shire.

10.8 Limitations of the Research Methods

This study intends to expand available clinical and real world safety and patient outcomes data of VPRIV, in patients with GD1 transitioning from ERTs/SRTs to VPRIV. This is a Phase 4, observational, retrospective/prospective, noncontrolled, noncomparative multi-center 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, Israel, and the included European countries. As a result, they may not be generalizable to studies conducted elsewhere, due to differences in clinical practice and patient characteristics.

Lastly, caution is required when interpreting results of observational studies. This could be due to the challenge of establishing a cause-and-effect relationship in this type of study design.

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 (PASS), 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 in the eCRFs, 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. Subinvestigators or other appropriate study personnel are eligible to sign for the investigator on designated eCRFs.

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 patients 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 the investigators 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 patients 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 multi-center 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 and/or CRO will write the amendments in a standard format and provide them to the investigator for submission to the IRB/EC.

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 into eCRFs that 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 by the site delegation log.

All key data must be recorded in the patient's medical records from which the eCRF will be populated; no new data will be recorded directly into the eCRF.

The clinical research assistant/study monitor will verify the contents against the source data, as 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 patient'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 eCRF entries against the source documents. The consent form includes a statement whereby the patient 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, patient's medical file, appointment books, original laboratory reports, X-rays, etc.). Nonstudy 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 patients. All consent and assent documentation must be in accordance with applicable regulations. Each patient or the patient's legally-authorized representative, as applicable, is requested to sign and date the patient informed consent form or a certified translation if applicable, after the patient has received and read (or been read) the written patient information and received an explanation of what the study involves, including but not limited to:

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

The investigator provides the sponsor/CRO with a copy of the consent form and assent form template which was reviewed by the IRB/EC and received favorable opinion/approval. A copy of the IRB/EC's written favorable opinion/approval of these documents must be provided to the sponsor/CRO, 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 patient 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 (ie, CRO), relevant supporting information and all types of patient recruitment information to the IRB/EC for review, and all must be approved prior to site initiation.

For sites within the EU, the applicant for an EC opinion can be the sponsor, the investigator, or for multi-center studies the coordinating investigator or sponsor, according to national provisions.

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 patient 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. For sites within the EU, this can be done by the sponsor, the CRO, the investigator or for multi-center studies the coordinating investigator, according to national provisions. 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 patients will be protected in accordance with applicable laws, regulations, and guidelines of participating countries.

After patients have consented to take part in the study, the sponsor and/or its representatives (ie, CRO) will review their medical records and data collected during the study. These records and data may, in addition, be reviewed by others including , but not limited to, 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 patients' identities.

Patients are assigned a unique identifying number (2 digit study site number (eg, 02) to be provided by the Marketing Authorisation Holder, and 2 digit patient numbers (eg, 03) reflecting the sequential 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 patient).

The study results – containing patients' unique identifying number, relevant medical records, and possibly year of birth – will be recorded. They may be transferred to and used outside of their country of origin 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, multi-center Phase 2-4 and certain other studies as determined by Shire. The purpose of the publication steering committee is to act as a noncommercial 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 multi-center study, the first publication of the study results shall be made by the sponsor in conjunction with the sponsor's presentation of a joint, multi-center publication of the compiled and analyzed study results. If such a multi-center 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 multi-center 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 Definitions

Adverse Events

An adverse event (AE) is any untoward medical occurrence in a subject administered a medicinal product and which does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, a new disease or worsening in severity or frequency of a concomitant disease, temporally associated with the use of a medicinal product, whether or not the event is considered causally related to the use of the product.

Although abnormal laboratory values are typically not considered AEs, the following considerations may result in an abnormal laboratory value being considered an AE:

- A laboratory test result that meets the criteria for an SAE
- A laboratory test result that requires the subject/patient to receive specific corrective therapy
- A laboratory abnormality that leads to discontinuation of therapy
- A laboratory abnormality that the health care provider considers to be clinically significant

Serious Adverse Events

A Serious Adverse Event (SAE) is any untoward medical occurrence that at any dose:

- Results in death. Note that death is an outcome of an event. The event(s) causing death should be recorded.
- In the view of the health care provider, places the subject/patient at immediate risk of death (a life-threatening event); however, this does not include an event that, had it occurred in a more severe form, might have caused death.
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Results in a congenital anomaly/birth defect
- An SAE may also be any other medically important event that, in the opinion of the Health care provider, may jeopardize the subject/patient or may require intervention to prevent one of the other outcomes listed in the definition above. (Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or convulsions occurring at home that do not require an inpatient hospitalization).

Adverse Drug Reactions

An adverse drug reaction (ADR) is an AE for which there is at least a reasonable suspicion of a causal relationship between an AE and a suspected medicinal product.

Product Quality Issues

A product quality issue (PQI) refers to defects related to the safety, identity, strength, quality, or purity of the product or with the physical characteristics, packaging, labeling, or design of the product.

Special Situation Reports

A Special Situation Report (SSR) includes any of the following events:

- Pregnancy: Any case in which a pregnancy patient is exposed to a Shire product or in which a female patient or female partner of a male patient becomes pregnant following treatment with Shire product. Exposure is considered either through maternal exposure or via semen following paternal exposure.
- Breastfeeding: Infant exposure from breast milk
- Overdose: All information of any accidental or intentional overdose
- Drug abuse, misuse or medication error: All information on medicinal product abuse, misuse or medication error (potential or actual)
- Suspected transmission of an infectious agent: Suspected (in the sense of confirmed or potential) transmission of an infectious agent by a medicinal product
- Lack of efficacy of Shire Product
- Accidental/Occupational exposure
- Use outside the terms of the marketing authorization, also known as "off-label"
- Use of falsified medicinal product
- Use of counterfeit medicinal product
- Drug-drug interactions and drug-food interactions
- Inadvertent or accidental exposure with or without an AE
- Unintended benefit

An SSR should be reported even if there is no associated AE.

Relationship of an AE to studied drug(s)

The investigator is required to provide an assessment of the relationship of an AE to the studied drug(s), based on the consideration of all available information about the event, including temporal relationship to drug administration, recognized association with drug product/class, pharmacological plausibility, and alternative etiology (eg, underlying illness, concurrent conditions, concomitant treatments).

- Related (Yes): An AE that follows a reasonable temporal sequence from administration of the medication (including the course after withdrawal of the medication), and for which a causal relationship is at least a reasonable possibility, ie, the relationship cannot be ruled out, although factors other than the medication, such as underlying diseases, complications, concomitant drugs and concurrent treatments, may also have contributed.

- Not related (No): An AE that does not follow a reasonable temporal sequence from administration of the medication, and/or that can reasonably be explained by other factors, such as underlying disease, complications, concomitant drugs and concurrent treatments.

12.2 Retrospective Data

Collection and notifying of adverse events, special situation reports and product quality issues to Takeda pharmacovigilance.

SAEs, AEs, ADRs, SSRs and PQIs in the healthcare record or other applicable source data that are part of the study objectives or endpoints:

- Events/issues which are part of the study objectives or endpoints will be systematically identified and collected from healthcare records or other applicable source records and summarized as part of any analysis and in the final study report. Such events do not need to be notified as individual reports to Takeda pharmacovigilance.

SAEs, AEs, SSRs and PQIs in the healthcare records or other applicable source data that are not part of the study objectives and endpoints:

- Events/Issues which are not part of the study objectives and endpoints will not be abstracted or collected from healthcare records or other applicable source records.

SAEs, AEs, ADRs, SSRs and PQIs spontaneously reported to the investigator(s) or research team:

If during the conduct of the study the investigator(s) or a member of the research team is spontaneously informed by a healthcare professional or patient of an SAE, AE, ADR, SSR or PQI where the event/issue pertains to a Shire product (or unbranded generic), such information should be forwarded to the relevant Takeda pharmacovigilance department within 1 working day for fatal or life-threatening SAEs, within 4 calendar days for other SAEs, and within 7 calendar days for all other events. This includes events spontaneously notified to the investigator(s) or research team which are study endpoints and also events spontaneously notified which are not study endpoints. As such reports are spontaneously notified, causality of any adverse events should be assumed unless there is evidence to the contrary.

12.3 Prospective Data

Collection and Recording of Adverse Events, Special Situation Reports and Product Quality Issues

Collection and recording of SAEs, AEs, SSRs and PQI will commence once the study participant has provided informed consent.

The investigator should notify Takeda[2] within 1 working day of becoming aware of a fatal or life-threatening SAE, and within 4 calendar days other SAEs, and within 7 calendar days for all other events/issues. This is typically achieved by the investigator completing the adverse event report pages of an electronic CRF or by submitting an AE Report Form to Takeda.

The investigator may be contacted by Takeda to obtain additional information on the event or for data clarification. The investigator shall make best effort to obtain the requested additional information and will notify Takeda within 1 working day of obtaining the additional information for a fatal or life-threatening SAE, within 4 calendar days for other SAEs, and within 7 calendar days for all other events/issues.

Adverse event reports and SSRs shall be reported to [redacted]

Product and Quality Complaints shall be sent to [redacted]

12.4 Reporting of Adverse Drug Reactions to Regulatory Agencies and IRB/EC

Takeda is responsible for reporting serious and nonserious adverse drug reactions suspected of being related to Shire products to regulatory authorities. The investigator is responsible for reporting adverse drug reactions to the IRB/EC, if required by national law or regulation, within the timelines required by such law or regulation. The investigator shall maintain records of all such submissions.

[2] Shire is now part of Takeda

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 nonpediatric studies as per guidance.

14. REFERENCES

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15. APPENDICES

APPENDIX 1 PROTOCOL HISTORY

Document	Date	Global/Country/Site Specific
Original Protocol	14 Jan 2019	
Amendment 1	26 Mar 2021	