Clinical Study Protocol

NCT Number: NCT04718779

Title: A Multicenter, Interventional, Retrospective and Prospective Study of Enzyme Replacement Therapy (VPRIV) Clinical Outcomes and Safety in Gaucher Disease Type 1 Patients Previously Treated With Substrate Reduction Therapy

Study Number: TAK-669-4017

Document Version and Date: Amendment 01 (03 January 2022)

Certain information within this document has been redacted (i.e., specific content is masked irreversibly from view) to protect either personally identifiable information or company confidential information.

TAKEDA PHARMACEUTICALS

PROTOCOL

A Multicenter, Interventional, Retrospective and Prospective study of Enzyme Replacement Therapy (VPRIV) Clinical Outcomes and Safety in Gaucher Disease Type 1 Patients Previously Treated with Substrate Reduction Therapy

Sponsor:	Takeda Pharmaceuticals U.S.A., Inc. 95 Hayden Avenue Lexington, MA, 02421		
Study Number:	TAK-669-4017		
IND Number:	Not Applicable	**EudraCT Number:**	Not Applicable
Compound:	VPRIV		
Date:	03 January 22	**Amendment Number:**	01

Amendment History:

Date	Amendment Number:	Amendment Type (for Regional Europe purposes only)	Region
16 November 20	Initial Protocol	Not Applicable	US
03 January 22	01	Not Applicable	US

1.0 ADMINISTRATIVE INFORMATION

1.1 Contacts

A separate contact information list will be provided to each site.

General advice on protocol procedures should be obtained through the monitor assigned to the study site. Information on service providers is given in Section 3.1 and relevant guidelines provided to the site.

Contact Type/Role	Contact
Serious adverse event reporting	E-mail: drugsafety@shire.com Fax Number: +1-484-595-8155
Medical Monitor (medical advice on protocol)	[redacted], MD, PhD [redacted] Rare Diseases U.S. Medical
Responsible Medical Officer (carries overall responsibility for the conduct of the study)	[redacted], MD, PhD [redacted] Rare Diseases U.S. Medical

1.2 Approval

REPRESENTATIVES OF TAKEDA

This study will be conducted with the highest respect for the individual participants in accordance with the requirements of this study protocol and also in accordance with the following:

- The ethical principles that have their origin in the Declaration of Helsinki.
- International Conference on Harmonization E6 Good Clinical Practice: Consolidated Guideline.
- All applicable laws and regulations, including, without limitation, data privacy laws, clinical trial disclosure laws, and regulations.

SIGNATURES

The signature of the responsible Takeda medical officer and other signatories, as applicable can be found on the signature page.

Electronic Signatures are provided on the last page of this document

[redacted], MD, PhD
Rare Diseases, US Medical

Date

[redacted], Statistics, US Medical

01/13/2022
Date

[redacted], MS, RD
[redacted], Clinical Research, US Medical

01/13/202
Date

[redacted], MBA
[redacted], Clinical Research US Medical

1/13/2022
Date

INVESTIGATOR AGREEMENT

I confirm that I have read and that I understand this protocol, package insert and any other product information provided by the sponsor. I agree to conduct this study in accordance with the requirements of this protocol and also to protect the rights, safety, privacy, and well-being of study subjects in accordance with the following:

- The ethical principles that have their origin in the Declaration of Helsinki.
- International Conference on Harmonization, E6 Good Clinical Practice: Consolidated Guideline.
- All applicable laws and regulations, including, without limitation, data privacy laws and regulations.
- Regulatory requirements for reporting serious adverse events defined in Section 9.2 of this protocol.
- Terms outlined in the study site agreement.
- Responsibilities of the Investigator. (Appendix B)

I further authorize that my personal information may be processed and transferred in accordance with the uses contemplated in Appendix E of this protocol.

Signature of Investigator Date

Investigator Name (print or type)

Investigator's Title

Location of Facility (City, State/Provence)

Location of Facility (Country)

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2.0 STUDY SUMMARY

Name of Sponsor: Takeda Pharmaceuticals U.S.A., Inc.	**Compound:** VPRIV	
Title of Protocol: A multicenter, interventional, retrospective and prospective study of Enzyme Replacement Therapy (ERT) (VPRIV) clinical outcomes and safety in Gaucher Disease type 1 (GD1) Patients Previously Treated with Substrate Reduction Therapy (SRT)	**IND No.:** Not applicable	**EudraCT No.:** Not applicable
Study Number: TAK-669-4017	**Phase:** 4	

Study Design:

This is a multicenter, interventional, retrospective/prospective, non-controlled, non-comparative study conducted with an observational period of ERT velaglucerase alfa (VPRIV) for 12 months. Patients will be included into two arms (Arm A: retrospective/prospective and Arm B: retrospective only) studied by observing standard patient care. Data will be collected as per the data collection schedule, depending on the availability of the data based on the frequency of visits, after the patient has been transitioned from SRTs to ERT (VPRIV) or from ERT to SRT and then to ERT (VPRIV). For patients who have already transitioned from SRTs to VPRIV the data will be collected retrospectively from the time of transition until the point at which the patient enters the study as per data collection schedule in Table 6.a, 6.b. For patients in Arm B relevant information will be abstracted from medical records to complete the required forms. For Arm A additional clinical data will be collected prospectively for all patients on VPRIV for 12 months as per data collection schedule in Table 6.a. **For Arm A** the patient reported outcomes (PRO) data and glucosylsphingosine (Lyso-Gb1) data will be collected starting at the point at which the patient enters the study for 12 months. **For Arm B**, "Baseline" will refer to the time of the switch to VPRIV, and this date will be used to plan study visits. For Arm B the patient reported outcomes (PRO) data will not be collected and glucosylsphingosine (Lyso-Gb1) data will be collected retrospectively from the patients' charts and subject to availability. The patients from Arm B will be assessed retrospectively for up to 12 months before they switched from SRT to VPRIV and then followed by retrospective assessments for 12 months post-switch.

Primary Objectives:

- The primary objective is to describe the treatment outcomes of VPRIV in patients with GD1 transitioning from SRTs to VPRIV or ERT to SRT and then to ERT (VPRIV) in a real-world setting among adults.

Secondary Objectives:

- The secondary objective is to describe the safety of VPRIV in patients with GD1 transitioning from SRT to ERT (VPRIV) or ERT to SRT and then to ERT (VPRIV) in real-world setting among adults.

Exploratory/Additional Objective(s):

- To describe the change in treatment effect on Glucosylsphingosine (Lyso-Gb1) following the transition from SRTs to ERT (VPRIV) or ERT to SRT and then to ERT (VPRIV).
- To describe the change in treatment effect on PROs with the use of a digital tool (to evaluate patient clinical engagement, shared decision making, emotional wellbeing, activities of daily living, goal attainment and Gaucher Disease specific measures.
- Remote qualitative assessments will be conducted to better understand the patient journey and to assess patients' perceptions of and reactions to the mobile application to inform further development of a digital tool in GD.

Subject Population: The study will enroll approximately 20 patients with GD 1, aged 18 and older with confirmed diagnosis of GD type I (biochemically and/or genetically), who meet the eligibility criteria into two (2) Arms:
Arm A (Retrospective/Prospective) will include approximately 10 patients who have switched from SRT to ERT

(VPRIV) or ERT to SRT and then to ERT (VPRIV) and will be followed prospectively for 12 months.

Arm B (Retrospective) will include approximately 10 patients who have switched from SRT to ERT (VPRIV) or ERT to SRT and then to ERT (VPRIV) previously (within the past 5 years at the time of enrollment). These patients will be assessed retrospectively after switch to ERT for up to12 months.

Number of Subjects:	**Number of Sites:**
Approximately 20	5
Dose Level(s):	**Route of Administration:**
Not applicable	Not applicable
Duration of Treatment:	**Period of Evaluation:**
Not applicable	Retrospective 12 months Prospective 12 months

Criteria for Inclusion for Arm A and Arm B:

1. In the opinion of the investigator, the subject is capable of understanding and complying with protocol requirements.
2. The subject either signs and dates a written, informed consent form or completes an e-consent process prior to the initiation of any study procedures.
3. The subject has been diagnosed with GD type 1, diagnosis was confirmed biochemically and/or genetically.
4. The subject has been treated with an SRT for at least 3 months prior to switch to VPRIV.
5. The subject has been treated with VPRIV at least 3 months prior to enrollment (Baseline Day 0).
6. The subject is aged 18 or older.
7. Arm A (retrospective/prospective): The subject is able to use mobile application based on clinician's judgment, (e.g., owns an iPhone version 5 or later or smartphones with Android operating systems, have an active data plan or regular Wi-Fi access).
8. Arm A (retrospective/prospective): The subject's primary language is English

Criteria for Exclusion for Arm A and Arm B:

1. The subject is an immediate family member, study site employee, or is in a dependent relationship with a study site employee who is involved in conduct of this study (e.g., spouse, parent, child, sibling) or may consent under duress.
2. The subject is judged by the investigator as being ineligible for any other reason.
3. The subject has L444P/L444P GBA1 genotype (c.1448T>C).
4. The subject has Parkinson's disease, a history of CNS manifestations, or any other neurological disorder (e.g., Lewy Body Disease, Alzheimer's Disease, Amyotrophic Lateral Sclerosis, Multiple sclerosis).

Criteria for Evaluation and Analyses:

Primary endpoint: stability in clinical parameters (composite of spleen and liver volume, hemoglobin level, and platelet count based on changes between baseline and 12 months of observational period.

Prespecified threshold of changes:

- hemoglobin level <1.5 g/dl decrease.
- platelet count < 25% decrease.
- liver volume <20% increase.
- spleen volume <25% increase.

Secondary endpoint: The number and proportion of patients experiencing AEs.

Exploratory endpoints: % Change in Glucosylsphingosine (lyso-Gb1). Additionally, absolute and % change in mobile application assessments of patient activation (PAM-13), shared decision making (CollaboRATE), activities of daily living/function (WSAS), mood (PHQ-4), emotional wellbeing (WHO-5), medication

adherence and goal attainment (GAS-D). GD specific patient reported measures to be evaluated.
Statistical Considerations: The statistical evaluation will be descriptive. No statistical hypotheses will be tested. All continuous variables will be summarized using standard measures (i.e. number of observations, mean, standard deviation, median, interquartile range, minimum and maximum). All categorical variables will be summarized in frequency tables. The primary endpoints will be presented descriptively with 95% CIs. The number and percentage of patients within threshold along with 95% CI will also be reported. There will be no imputation of missing values. Results will be presented in tables and graphs. Exploratory outcomes will be described and will be compared between baseline and end of Study. Change in these outcomes overtime will also be explored.
Sample Size Justification: This is a feasibility study in which no sample size estimation was performed. It is expected that 20 patients are sufficient to better understand clinical and real-world patient reported and safety outcomes in GD1 patients transitioning from SRTs to ERT (VPRIV) and ERT to SRT and then to ERT (VPRIV) and will inform future, larger-scale studies and the clinical utility of the mobile application.

3.0 STUDY REFERENCE INFORMATION

3.1 Study-Related Responsibilities

The sponsor will perform all study-related activities with the exception of those identified in the Clinical Study Supplier List Template. The vendors identified in the template for specific study-related activities will perform these activities in full or in partnership with the sponsor.

3.2 Coordinating Investigator

Takeda will select a Signatory Coordinating Investigator from the investigators who participate in the study. Selection criteria for this investigator will include significant knowledge of the study protocol, the study drug, their expertise in the therapeutic area and the conduct of clinical research as well as study participation. The Signatory Coordinating Investigator will be required to review and sign the clinical study report and by doing so agrees that it accurately describes the results of the study.

3.3 List of Abbreviations

AE	adverse event
eCRF	case report form (electronic or paper)
CRO	contract research organization
CSR	clinical study report
EDC	electronic data capture
ERT	enzyme replacement therapy
FDA	Food and Drug Administration
GAS	Goal Attainment Scale
Gb1	glucosylceramides
GCP	Good Clinical Practice
GD1	Gaucher Disease Type 1
ICH	International Conference on Harmonization
IRB	institutional review board
Lyso-Gb1	Glucosylsphingosine
MedDRA	Medical Dictionary for Regulatory Activities
PDQ	Perceived Deficits Questionnaire
PAM	Patient Activated Measure
PHQ	Patient Health Questionnaire
PRO	patient reported outcomes
SAE	serious adverse event
SAP	statistical analysis plan
SOC	standard of care
SOP	standard operating procedure
SRT	substrate reduction therapy
WHO	World Health Organization
WSAS	Work and Social Adjustment Scale

4.0 INTRODUCTION

4.1 Background

Gaucher disease is an autosomal recessive disorder due to mutations in both alleles of *GBA1* resulting in deficient activity of the lysosomal enzyme, acid β-glucosidase (glucocerebrosidase, EC3.2.1.45) [1-2]. The consequent accumulation of its substrates, notably glucosylceramides (Gb1) and glucosylsphingosines (Lyso-Gb1), primarily in the spleen, liver, and bone marrow can lead to progressive and debilitating manifestations, including spleen and liver enlargement, anemia, thrombocytopenia, pulmonary disease, immune dysfunction, bone pain, osteoporosis, avascular necrosis (osteonecrosis), osteolytic lesions and destruction of joints [1,3-6]. GD is categorized into three clinical types: type 1 (GD1), type 2 and type 3. GD1 makes up 94% of cases in the Western World and is termed non-neuronopathic, since it does not manifest early onset CNS involvement. GD1 is the most common form in the United States and Northwestern European populations, affecting an estimated 1 in 40,000 to 1 in 60,000 individuals. Gaucher disease types 2 and 3 have early onset primary CNS disease [7].

Two different types of treatment are available for GD1: the intravenous supplementation of the deficient protein acid β-glucosidase (ERT), or the oral administration of a drug that slows down the production of Gb1s (SRT). Administration of recombinant human acid β-glucosidase augments the endogenous enzyme activity in the patient to enhance the breakdown of accumulated Gb1s in the lysosomal compartment of macrophages. SRT inhibits the enzyme glucosylceramide synthase, thereby slowing the over-production of Gb1s relative to their rate of recycling in the lysosomal compartment [8].

Overall, ERT as a modality is very safe: safety has been documented in clinical trials, by pharmacovigilance of each of the manufacturers, and via disease registries. Depending upon the testing sensitivity and specificity, anti-drug antibodies were reported in 1% to 53% of patients, but were rarely associated with anaphylactic reactions or with suppressed response to ERT and their overall clinical significance remained to be determined [9]. Long-term AEs related to ERT include primarily weight gain (~10% of patients have an increase in body weight (BW) by >10% from baseline), metabolic syndrome (particularly fatty liver) and overt diabetes (up to 8% of the patients) [10]. However, untreated GD1 patients have on average about a 50% increase in BMR that leads to untreated patients consuming increases in calories to maintain BW. This "habit" continues after ERT or splenectomy leading to increase BW (Barton DJ et al 1989). This has not been documented in SRT. ERT returns BMR to normal and "exposes" the patients underlying predisposition to hyperlipidemias, diabetes and metabolic syndrome.

Some SRTs are oral therapies and are non-inferior to ERTs with regard to several clinical measures and health-related quality of life instruments [11-15]. Miglustat is inferior to ERT and second line for GD1 treatment. It is taken three times per day and adjusted for renal creatinine clearance. Eliglustat is dosed according to CYP2D6 genotype and taken once or twice daily depending on metabolizer status with adjustments for patients taking other CYP2D6 inhibitors. Eliglustat and miglustat have well established, but differing, side effect profiles [11,12]. Safety of eliglustat was documented in the clinical trials with a certain percentage of cardiac AEs [16]

and issues of drug-drug interactions. This therapy has a higher incidence of adverse effects than ERT, and long-term reduction of Gb1 may affect several different cell functions. Some patients are unable to tolerate SRT or may experience other adverse reactions. Gastrointestinal side effects (dyspepsia, nausea, diarrhea, gastritis, etc.) are more common with the oral treatments eliglustat, and particularly miglustat, than with ERT. Cardiac electrophysiology was monitored extensively during the eliglustat clinical trials via continuous ECG and Holter monitoring. SRTs also should be avoided in pregnant women, and in men and women attempting to conceive [17]. Even though both substrate reduction therapies are Pregnancy Category C medications, there are limited data to support safety in pregnancy. SRT require evaluation of patient-specific variables (e.g., genotype evaluation, renal function) and consideration of adverse effect and dosing profiles.

Some patients are switched to ERT, because they cannot tolerate SRT with eliglustat because of its complex cytochrome P450 metabolism that complicates the use of some medications and because of potential nontrivial cardiotoxicity. ERT is preferred for the management of Gaucher disease [18]. Similarly, the peripheral neuropathy that occurs in many miglustat treated patients leads to institution of ERT to avoid this adverse effect. It should be noted that miglustat is used very rarely for GD1 SRT in the USA.

Treatment of GD, as described above, is now an area beset with choices: choice of the treatment modality, choice of specific treatment, choice of treatment goals. Ensuring the patients voice is central to clinical decision making is key to delivering, evaluating and understanding the efficacy of therapeutic interventions. Patient reported outcome (PRO) measures are used to capture the patient's views about their health status and facilitate our understanding of the impact of these diseases and their treatments on patient's quality of life and symptoms. To that end, health-related information and communication technology solutions that utilize mobile phones, known as mobile health applications (apps), are well situated to provide these benefits for both patients and providers.

In rare diseases particularly, digital tools are used by patients, caregivers to increase engagement, patient advocacy, and access to care. A recent study by Ernst&Young [19] examined the digital capabilities of 14 leading companies in the rare disease space and noted that those with the strongest social media presence and those leading innovation in unique methods of communication, such as chatbots and mobile apps, had higher patient and physician engagement. Digital capabilities are critical for continued success.

However, disease-specific apps for metabolic diseases have typically focused on patient symptom tracking rather than working as a tool in support of the patient-clinician relationship and decision making. For example, a 2019 study by Donald et al [20] looked at correlating GD disease activity and patient experience using a symptom tracking app and wearable accelerometer. The pilot data are encouraging, but the underlying app technology did not allow the patient's provider real-time access to data or to use it to assist with decisions in patient care. Other apps for metabolic diseases are typically utilized as patient networks or disease awareness and education.

Arm A of this study will explore the use of a mobile app to facilitate shared decision making and patient-clinician engagement. The app will capture comprehensive measures of patient experience including fatigue, depression, anxiety, activities of daily living, functional status, goal attainment and GD-specific symptoms and outcomes. The goal of this study is to provide real-world insight into the role of mobile apps in health and how they may benefit patient outcomes in GD. Patient input throughout the evaluation of a mobile app including qualitative research is essential to ensure that outcomes that matter to people living with rare disease are appropriately captured.

There is limited real-world data available for patients changing from SRTs to ERTs, therefore Arms A and B of the study intend to assess the limited clinical and real-world evidence and describe the experience for patients with GD1 transitioning from SRTs to velaglucerase alfa (VPRIV) treatment. This study also seeks to provide insights on the use of a biomarker, Glucosylsphingosine (lyso-Gb1), with 100% specificity for Gaucher disease.

Rationale for the Proposed Study

These study Arms intend to augment the limited clinical and real-world safety and patient outcomes data for VPRIV in GD1 patients transitioning from SRT to ERT with VPRIV or ERT to SRT and then to ERT (VPRIV). These Arms will explore the effect of change in treatment on the Lyso-Gb1 biomarker after the switch from SRT to ERT with VRPIV or ERT to SRT and then to ERT (VPRIV). Arm A of the study will also explore the use of a digital tool (Smart phone mobile application with a conversational text interface) to evaluate patient-clinician engagement and shared decision making. Patient reported outcomes (PROs) including, but not limited to, activities of daily living, goal attainment and key GD patient reported outcome measure questions will be evaluated.

VPRIV, supplied as a powder for reconstitution for injection (400 U/vial), is produced by gene activation technology in a human cell line. VPRIV is a glycoprotein with the same amino acid sequence as the naturally occurring human enzyme, acid β-glucosidase. VPRIV catalyzes the hydrolysis of the glycolipid glucosylceramide (glucocerebroside) to glucose and ceramide in the lysosome [21].

VPRIV is indicated for long-term ERT for pediatric and adult patients with GD1 and associated with fewer hypersensitivity reactions and fewer antibodies than the other enzymes.

5.0 STUDY OBJECTIVES AND ENDPOINTS

5.1 Objectives

5.1.1 Primary Objective

- The primary objective is to describe the treatment outcomes of VPRIV in adult patients with GD1 transitioning from SRTs to VPRIV or ERT to SRT and then to ERT (VPRIV) in a real-world setting among adults.

5.1.2 Secondary Objective

- The secondary objective is to describe the safety of VPRIV in adult patients with GD1 transitioning from SRTs to VPRIV or ERT to SRT and then to ERT (VPRIV) in real-world setting.

5.1.3 Additional Objectives

- To describe the change in treatment effect on glucosylsphingosine (Lyso-Gb1) following the transition from SRTs to ERT (VPRIV) or ERT to SRT and then to ERT (VPRIV).
- To describe the change in treatment effect on PROs with the use of a digital tool (to evaluate patient clinician engagement, shared decision making, fatigue, depression, anxiety, emotional wellbeing, activities of daily living, goal attainment and Gaucher Disease specific measures).
- Remote qualitative assessments will be conducted to better understand the patient journey and to assess patients' perceptions of and reactions to the mobile application to inform further development of a digital tool in GD.
- Remote qualitative assessments will be conducted to assess HCP reactions to the mobile application to inform further development of a digital tool in GD.

5.2 Endpoints

5.2.1 Primary Endpoint

Primary endpoint: stability in clinical parameters (composite of spleen and liver volume, hemoglobin level, and platelet count) based on changes between baseline and 12 month of observational period.

Prespecified threshold of changes:

- hemoglobin level <1.5 g/dl decrease
- platelet count <25% decrease
- liver volume <20% increase
- spleen volume <25% increase

5.2.2 Secondary Endpoint

The number and proportion of patients experiencing AEs.

5.2.3 Additional Endpoints

% Change in Lyso-Gb1. Additionally, absolute and % change in mobile application assessments of patient activation (PAM-13), shared decision making (CollaboRATE), activities of daily living/function (WSAS), mood (PHQ-4), emotional wellbeing (WHO-5), medication adherence and goal attainment (GAS-D). GD specific patient report measures to be evaluated.

6.0 STUDY DESIGN AND DESCRIPTION

6.1 Study Design

This is a Phase 4, interventional, retrospective/prospective, non-controlled, non-comparative, multicenter study conducted with a 12 month observational period of ERT (VPRIV). Patients will be included into one of two arms (Arm A: retrospective/prospective and Arm B: retrospective only) studied by observing standard patient care. For Arm A, clinical data will be collected prospectively for all patients on VPRIV for up to12 months as per data collection schedule in Table 6.a. For patients in Arm B, relevant information will be abstracted from medical records to complete the required forms. For Arm B, "Baseline" will refer to the time of the switch to VPRIV, and this date will be used to plan study visits. For Arm B, the patient reported outcomes (PRO) data will not be collected and glucosylsphingosine (Lyso-Gb1) data will be collected retrospectively from the patients charts and subject to availability. The patients from Arm B will be assessed retrospectively for up to 12 months before they switched from SRT to VPRIV and then followed by retrospective assessments for 12 month post-switch. Patients who enter in Arm A will be followed prospectively for up to12 months after entering the study.

Table 6.a Study Schematic: ARM A

	Retrospective Period		Prospective Period			
	SRT Baseline	ERT Baseline				
	≥3 months prior to ERT start	≥3 months prior to study enrollment	Month 1	Month 3 (±1 week)	Month 6 (±1 week)	Month 12 (±1 week)
Data Capture Time Point*	1	2	3	4	5	6
Informed consent			X			
Inclusion/Exclusion criteria			X			
Demographics			X			
Medical history			X			
Medication History	X	X	X	X	X	X
Concomitant Medication	X	X	X	X	X	X
Height and Weight	X	X	X	X	X	X
Pregnancy Status	X	X	X	X	X	X
Adverse Event	X	X	X	X	X	X
Clinical parameters (Hb, Platelet count, BMD, spleen add liver volume)	X	X	X	X	X	X
BMD Z-scores and T-scores	X					X

Biomarker Chart Review (Chitotriosidase, CCL18, Lyso-Gb1)	X	X	X	X	X	X
Mobile App Data Collection			X	X	X	X
Remote Qualitative Assessment			X			X
Biomarker Collection Lyso-Gb1			X	X	X	X

Hb=Hemoglobin; BMD=Bone Mineral Density; CCL18=CC-chemokine ligand18; Lyso-Gb1=Glucosylsphingosine
* time point of data capture for across sample comparisons within period of observation

For Arm A, Patients will be studied by observing standard patient care. Data will be collected as per the data collection schedule in Table 6.a depending on the availability of the data based on the frequency of visits, after the patient has been transitioned from SRTs to ERT (VPRIV) or ERT to SRT and then to ERT (VPRIV).

Patients with GD1 who were treated with SRT for GD1 for at least 3 months before baseline enrollment will be eligible. For patients who have already transitioned from 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 be collected starting at the point at which the patient enters the study.

There are no requirements for run-in or washout of medication (SRT). Reason for switch will be documented in the case report form.

Data will be collected for each patient for at least 3 months of SRT before switch to ERT (baseline data), then ≥ 3 months of ERT (up to12 months of retrospective data before study enrollment in total) and 12 months prospective data ±1 week. 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 enrolled into the study.

Should the infusions have been taken outside the physician's office (e.g., 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. Study will continue until last subject/last visit occurs.

Patients will be treated in accordance with physician treatment plan (standard clinical practice). VPRIV is a hydrolytic lysosomal Gb1-specific enzyme indicated for long-term ERT for patients with GD1. The recommended VPRIV dosage is 60 Units/kg administered every other week as a 60-minute intravenous infusion.

Data collected during any consultations during the retrospective period of up to12 months and observational prospective of up to 12 months will be reported in the study eCRF. Data will be collected prospectively for Months 1, 3, 6 and 12 (±1 week) (for total duration of VPRIV treatment) as shown in Table 6.a. All prospective visits can be virtual or in person, as applicable.

Table 6.b Study Schematic: ARM B

	Up to 12 months SRT data PRIOR switch to VPRIV	12 months data collection POST switch to VPRIV
Informed consent *	X	X
Inclusion/Exclusion criteria	X	X
Demographics	X	X
Medical history	X	X
Medication History	X	X
Concomitant Medication	X	X
Height and Weight	X	X
Pregnancy Status	X	X
Adverse Event	X	X
Clinical parameters (Hb, Platelet count, BMD, spleen add liver volume)	X	X
BMD Z-scores and T-scores	X	X
Biomarker Chart Review (Chitotriosidase, CCL18, Lyso-Gb1)	X	X

Hb=Hemoglobin; BMD=Bone Mineral Density; CCL18=CC-chemokine ligand18; Lyso-Gb1=Glucosylsphingosine, ICF is subjective to site requirement

For Arm B, patient data will be collected as per the data collection schedule in Table 6.b depending on the availability of the data based on the frequency of visits documented in the patients' medical notes. Data collected during any consultations of patients on SRT, within the range of 12 months prior to switching to VPRIV, are to be reported in the study eCRF. Data collected during any consultations of patients POST switch to VPRIV, for up to 12 months, are also to be reported in the study eCRF.

A schedule of assessments for arm A and arm B is listed in Appendix A.

This is non-controlled, non-comparative study.

6.2 Justification for Study Design, Dose, and Endpoints

- The study aims to collect data from 20 patients. As there will be no statistical testing of hypotheses in the study, this sample size was chosen based on site feasibility. Study is designed in accordance with a standard GD management algorithm.
- The study will be performed in USA at up to 5 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.
- There is no formal screening procedure for suitable study patients.

6.3 Premature Termination or Suspension of Study or Study Site

6.3.1 Criteria for Premature Termination or Suspension of the Study

The study will be completed as planned unless 1 or more of the following criteria are satisfied that require temporary suspension or early termination of the study.

- New information or other evaluation, such that the risk is no longer acceptable for subjects participating in the study.
- Significant violation of Good Clinical Practice (GCP) that compromises the ability to achieve the primary study objectives or compromises subject safety.

6.3.2 Criteria for Premature Termination or Suspension of Study Sites

A study site may be terminated prematurely or suspended if the site (including the investigator) is found in significant violation of GCP, protocol, or contractual agreement, is unable to ensure adequate performance of the study, or as otherwise permitted by the contractual agreement.

6.3.3 Procedures for Premature Termination or Suspension of the Study or the Participation of Study Site(s)

In the event that the sponsor, an institutional review board (IRB) or regulatory authority elects to terminate or suspend the study or the participation of a study site, a study-specific procedure for early termination or suspension will be provided by the sponsor; the procedure will be followed by applicable study sites during the course of termination or study suspension.

7.0 SELECTION AND DISCONTINUATION/WITHDRAWAL OF SUBJECTS

All entry criteria, including test results, need to be confirmed prior to enrollment.

7.1 Inclusion Criteria for Arm A and Arm B:

Subject eligibility is determined according to the following criteria prior to entry into the study:

1. In the opinion of the investigator, the subject is capable of understanding and complying with protocol requirements.
2. The subject either signs and dates a written, informed consent form, or completes an e-consent process prior to the initiation of any study procedures.
3. The subject has been diagnosed with GD type 1; diagnosis was confirmed biochemically and/or genetically.
4. The subject has been treated with SRT for at least 3 months prior to switch to VPRIV.
5. The subject has been treated with VPRIV at least 3 months prior to enrollment (Baseline Day 0).
6. The subject is aged 18 years or older.
7. Arm A: The subject is able to use mobile application based on clinician's judgment, (e.g. owns an iPhone version 5 or later or smartphones with Android operating systems, have an active data plan or regular Wi-Fi access).
8. Arm A: The subject's primary language is English.

7.2 Exclusion Criteria for Arm A and Arm B:

Any subject who meets any of the following criteria will not qualify for entry into the study:

1. The subject is an immediate family member, study site employee, or is in a dependent relationship with a study site employee who is involved in conduct of this study (e.g., spouse, parent, child, sibling) or may consent under duress.
2. The subject is judged by the investigator as being ineligible for any other reason.
3. The subject has L444P/L444P *GBA1* genotype (c.1448T>C).
4. The subject has Parkinson's disease, a history of CNS manifestations, or any other neurological disorder (e.g. Lewy Body Disease, Alzheimer's Disease, Amyotrophic Lateral Sclerosis, Multiple sclerosis).

7.3 Criteria for Discontinuation or Withdrawal of a Subject

The primary reason for discontinuation or withdrawal of the subject from the study or study drug should be recorded in the case report form (eCRF) using the following categories. For screen failure subjects, refer to Section 8.1.9.

1. Adverse event (AE). The subject has experienced an AE that requires early termination because continued participation imposes an unacceptable risk to the subject's health or the subject is unwilling to continue because of the AE.

2. Significant protocol deviation. The discovery that the subject failed to meet protocol entry criteria or did not adhere to protocol requirements, and continued participation poses an unacceptable risk to the subject's health.
3. Lost to follow-up. The subject did not return to the clinic and attempts to contact the subject were unsuccessful. Attempts to contact the subject must be documented in the subject's source documents.
4. Voluntary withdrawal. The subject (or subject's legally acceptable representative) wishes to withdraw from the study. The reason for withdrawal, if provided, should be recorded in the eCRF.

   Note: All attempts should be made to determine the underlying reason for the withdrawal and, where possible, the primary underlying reason should be recorded (i.e., withdrawal due to an AE should not be recorded in the "voluntary withdrawal" category).
5. Study termination. The sponsor, IRB, IEC or regulatory agency terminates the study.
6. Other.

   Note: The specific reasons should be recorded in the "specify" field of the eCRF.

7.4 Procedures for Discontinuation or Withdrawal of a Subject

The investigator may discontinue a subject's study participation at any time during the study when the subject meets the study termination criteria described in Section 3. In addition, a subject may discontinue his or her participation without giving a reason at any time during the study. Should a subject's participation be discontinued, the primary criterion for termination must be recorded by the investigator. In addition, efforts should be made to perform all procedures scheduled for the Early Termination Visit. Discontinued or withdrawn subjects may be replaced on a case by case basis.

8.0 STUDY PLAN

8.1 Study Procedures

The following sections describe the study procedures and data to be collected. For each procedure, subjects are to be assessed by the same investigator or site personnel whenever possible. The Schedule of Study Procedures is in Appendix A. Visits may be conducted virtually or in- person, as applicable.

8.1.1 Informed Consent Procedure

The requirements of the informed consent are described in Section 14.2.

Informed consent must be obtained prior to the subject entering into the study, and before any protocol-directed procedures are performed.

A unique subject identification number (subject number) will be generated by the eCRF and assigned to each subject at the time that informed consent is obtained; this subject number will be used throughout the study.

eConsent may be offered for this study. There are three options for how this may be conducted:

- Site invites patient: which will require the Investigator to enter some high-level patient details (to be defined during CRF preparation) into the eCRF and then to enter the patient's email address for access to be provided to the patient to give consent. The email address is stored logically separate from the patient record in the database and will not at any time be linked to the patient's eCRF.
- Patient consents at site: which will usually require the site to agree to provide access to an existing electronic device (computer or tablet) owned by the site for use by the attending patients for consent. In the absence of the site owning such a device, arrangements can be made for the hire of a computer or tablet for the purpose of patient consent. Any such device will be returned to its origin upon site close-out. The patient completes the process at the site.
- Patient self-registers: the patient is given a letter containing an access code and instructions for how to access the e-consent portal.

After the patient has provided e-consent, the Investigator will be able to view this on their dashboard on the EDC to verify that consent has been given and to begin the study data entry.

Should it be necessary to collect the HIPAA authorization separately from the e-consent, as required by some IRBs, it will be possible to ask the Investigator to confirm completion of the authorization as part of the 'screening criteria' to ensure that the consent process has been fully accounted for before commencing data entry.

8.1.2 Demographics, Medical History, and Medication History Procedure

Demographic information to be obtained will include date of birth, sex, Hispanic ethnicity, race as described by the subject, height, weight, and smoking status of the subject at Screening

Medical history to be obtained will include determining whether the subject has any significant conditions or diseases relevant to the disease under study that resolved at or prior to signing of informed consent. Ongoing conditions are considered concurrent medical conditions (see Section 8.1.4).

Medication history information to be obtained includes any medication relevant to eligibility criteria stopped at or within 12 months prior to signing of informed consent.

GD medication history will be collected at or within 12 months prior to signing of informed consent, and should include any use of ambroxol.

8.1.3 Documentation of Concomitant Medications

Current GD medication use will be collected. Concomitant medication is any drug prescribed by a physician or obtained by the subject over the counter. Concomitant medication is not provided by the sponsor. At each study visit, subjects will be asked whether they have taken any medication, and all medication including vitamin supplements, over-the-counter medications, and oral herbal preparations, must be recorded in the eCRF.

8.1.4 Documentation of Concurrent Medical Conditions

Concurrent medical conditions are those significant ongoing conditions or diseases that are present at signing of informed consent. The condition (i.e., diagnosis) should be described and recorded in the eCRF.

8.1.5 Procedures for Clinical Laboratory Samples

8.1.6 Lyso-Gb1 Biomarker Testing

All samples will be collected in accordance with acceptable laboratory procedures. The maximum volume of blood at any single visit, and the approximate total volume of blood for the study is 2-8 mL. If a visit is done virtually, all efforts should be made to collect the Lyso-Gb1 blood sample through standard site procedures.

Appendix E describes procedures for specimen collection, handling and shipment.

Table 8.a lists the tests that will be obtained for each laboratory specimen.

Table 8.a Clinical Laboratory Test

Dried Blood Spot
Glucosylsphingosine (Lyso-Gb1)

The central laboratory will perform laboratory tests for LysoGb-1 (for Arm A only). The results will be returned to the investigator, who is responsible for reviewing and filing these results.

The investigator is responsible for transcribing or attaching laboratory results to the eCRF. The investigator will maintain a copy of the laboratory accreditation and the reference ranges for the laboratory used.

In some cases, laboratory results can be sent directly to the EDC. This will be explored as part of the study set up phase.

8.1.7 Contraception and Pregnancy Avoidance Procedure

There are no requirements for contraception or pregnancy avoidance.

8.1.8 Pregnancy

There are no requirements for contraception or pregnancy avoidance.

Available data on VPRIV on pregnancy and contraception can be found in the VPRIV package insert [21]. Pregnancies that occur during the study will be recorded on the eCRF.

8.1.9 Documentation of Screen Failure

Investigators must account for all subjects who sign informed consent.

The primary reason for screen failure is recorded in the eCRF using the following categories:

- Adverse Event (AE).
- Did not meet inclusion criteria or did meet exclusion criteria. <specify reason>
- Significant protocol deviation.
- Lost to follow-up.
- Voluntary withdrawal <specify reason>.
- Study termination.
- Other <specify reason>.

Subject identification numbers assigned to subjects who fail screening should not be reused.

8.1.10 Documentation of Study Entrance

Only subjects who meet all the inclusion criteria and none of the exclusion criteria are eligible for enrollment into the study.

If the subject is found to be not eligible for enrollment, the investigator should record the primary reason for failure on the applicable eCRF.

8.1.11 Patient Engagement

8.1.11.1 Mobile Application (Arm A only)

This study will utilize a digital mobile health app specifically customized by Takeda for the study and powered by Fora Health. The Smart phone mobile app has a conversational interface to evaluate patient clinician engagement, shared decision making and will be the primary source for goal setting, progress tracking, and immersive medical education and support related to goal attainment. PROs related to fatigue, depression, anxiety, emotional wellbeing, activities of daily living, quality of life, goal attainment and GD specific patient reported outcome measure questions will be evaluated. Remote qualitative assessments will be conducted to better understand the patient journey and to assess patients' perceptions of and reactions to the mobile application to inform further development of a digital tool in GD.

The mobile app will also contain visit-specific modules for the patient to complete prior to the scheduled visit date. The information reported by the patient in the mobile application will be available in the Fora Health Web portal for review by the clinical study team members at the site as applicable.

8.1.11.2 Patient Activation Measure-PAM-13

PAM-13 is a 13-item measure that was developed to measure a patient's engagement and confidence in self-management of disease [22].

PAM-13 will be collected at Baseline and Final Visit.

8.1.11.3 CollaboRATE

CollaboRATE2 was developed as a process measure of shared decision making between patients and clinicians [23]. CollaboRATE consists of three brief questions, each on a 0-4 scale, suitable for use both in research and in routine health care delivery. CollaboRATE has previously been validated in a simulation sample5 and included significant end-user input in its development.

CollaboRATE will be collected at Baseline, Month 6, and Final Visit.

8.1.11.4 Work and Social Adjustment Scale-WSAS

The WSAS is a patient reported outcome that assesses functioning including ability to work, ability for home management, ability for social and private leisure activities and ability to maintain close relationships. WSAS is a 5-item scale where each item is rated on a 9-point scale ranging from 0 (not at all a problem) to 8 (very severely impaired). The total score ranges from 0 to 40 with a high score indicating high dysfunction [24].

WSAS will be collected at Baseline, Month 6, and Final Visit.

8.1.11.5 Patient Health Questionnaire-PHQ-4

The PHQ-4 is a patient reported outcome aiming at screening, diagnosing, monitoring and measuring the severity of depression. Total score is determined by adding together the scores of each of the 4 items. Scores are rated as normal (0-2), mild (3-5), moderate (6-8), and severe (9-12). [25]

PHQ-4 will be collected every month from Baseline through Final Visit.

8.1.11.6 World Health Organization-WHO-5

The WHO-5 is a short, self-administered questionnaire covering 5 positively worded items, related to positive mood (good spirits, relaxation), vitality (being active and waking up fresh and rested), and general interests (being interested in things) [26].

WHO-5 will be collected every month from Baseline through Final Visit.

8.1.11.7 GD-Goal Attainment

The Goal Attainment Scale, previously adapted by Takeda for depression, is a tool to measure the progress each subject has towards achieving their individualized goals [27-29]. While the outcome measure is unique to each subject, standardized scoring is applied to allow for statistical analysis.

At baseline, each patient will create up to (3) goals, highlighting the aspect(s) of treatment, care, and life goals that are most important to the patient. Goals may focus on particular symptoms, improvement in quality of life, social participation, or early detection of long-term complications or associated diseases. Patients will be able to set goals that matter most to them and will also have a list of goals to select from to make the goal setting process easier when possible.

All goals will follow the SMART framework, and outcomes will be unique to each goal. Goal attainment levels or progress is measured against equidistant benchmarks ranging from -2 to +2. The progress of goals will be evaluated by the patient and the HCP during the study.

GD-Goal Attainment will be collected at Baseline and assessed based on individual goals through Final Visit.

8.1.11.8 GD Patient Reported Measures

The GD-specific PRO was developed to provide quantitative measurements of GD-specific symptoms and concerns not typically assessed in generic health-related quality of life questionnaires [30]. This study will use a modified clinical version consisting of questions assessing impact of GD on activities of daily living, functional status, emotional wellbeing, and impression of GD-related health over the past month. Specific questions assessing severity of fatigue and bone pain and specific questions related to their current GD- treatment over the last 12 weeks.

GD Reported Measures will be collected at Baseline, Month 6, and Final Visit.

8.1.11.9 Side Effects, Tolerability, and Medication Adherence

Side Effects and Tolerability questions may be entered at any time using the mobile app.

Medication adherence will be prompted weekly.

8.1.11.10 Remote Qualitative Assessment

Remote Qualitative data collection around app usage and patient-provider engagement will be collected following the Baseline and Final Visit (i.e. within 1 week of visit). Following the baseline visit, patients will be invited to participate in a remote interview. The interview will be approximately 60 minutes. The post baseline interview will focus on the patient's management of GD, gather information to better understand the patient treatment journey over the last 12 months as well as gather feedback regarding the mobile application functionality. Patients will be asked to voluntarily participate in the qualitative interview. Following the end of study visit the patient and care team members will complete a remote interview. The interview will be approximately 60 minutes. The post end of study interview will focus on the following:

- How the mobile app functionality impacts the patient-provider engagement in the management of GD;
- The appropriate level of information provided through the app, and how it can be made most accessible to patients and physicians; and

- How the app affects patient's self-management, physician's methods of care and the clinical care pathway.

The interview will allow patients to reflect on the process and identify higher level causes behind any difficulties or challenges, explore any suggested changes and to gather general feedback regarding the patients experience during the study.

Additionally, an interview post end of study will be conducted with the HCP(s) to understand from them which elements of the patient web portal were useful in their provision of care, and where there might be opportunities for improvement.

A remote research tool called Lookback will be used to conduct all interviews.

Lookback allows the interviewer to observe and talk to interviewees as they look at features on their own device, record the interview (including the participant interactions) and capture time stamped notes. Interviewees will be sent a live-link to the Lookback app, which can be downloaded onto mobile devices and computers.

8.2 Schedule of Observations and Procedures

The schedule for all study-related procedures for all evaluations is shown in Appendix A. Assessments should be completed at the designated visit/time points.

8.2.1 Study Entrance Prospective Baseline Visit

Subjects will be screened and evaluated within 30 days prior to enrollment. Subjects will be screened in accordance with predefined inclusion and exclusion criteria as described in Section 7.0. See Section 8.1.9 for procedures for documenting screening failures.

Procedures to be completed at Screening Visit include:

- Informed consent.
- Inclusion/Exclusion criteria.
- Demographics.
- Medical history.
- GD specific Medical History, (splenectomy, medullary bone infarcts, avascular necrosis).
- Medication history.
- GD Medication history.
- Concomitant medications.
- Concurrent medical conditions.
- Height and weight.
- Pregnancy status.

- Adverse event assessment.
- Chart Review of the following clinical parameters: hemoglobin, platelet count, bone mineral density, spleen volume, liver volume. Bone mineral density Z scores and T scores if available.
- Chart review of the following biomarkers: chitotriosidase and CCL 18.
- Chart review of antidrug antibodies.
- Lyso-Gb1 biomarker sample collection.
- Study ID assigned in Mobile App.
- Mobile App Onboarding.
- Goal setting and mobile app assessments.
- Collection of Reason for Switch.
- Remote qualitative assessment.

8.2.2 Retrospective Chart Review

A retrospective chart review will be done looking at data 12 months prior to Study Enrollment for Arm A and Arm B. The patients from Arm B will be assessed retrospectively for 12 months post Switch date.

- Chart review of medical history, medication history, height, weight, pregnancy status, and adverse events.
- Chart review of GD related medical conditions including but not limited to: Type 2 Diabetes Mellitus, obesity (BMI≥30), hypercholesterolemia, Sickle trait or Thal minor, any attendant autoimmune disease (Rheumatoid arthritis, Systemic Lupus Erythematosus, Inflammatory Bowel Disease) [31].
- Chart Review of the following clinical parameters: hemoglobin, platelet count, bone mineral density, spleen volume, liver volume.
- Chart review of the following biomarkers: chitotriosidase, CCL 18, and Lyso-Gb1.
- Chart review of antidrug antibodies.

8.2.3 Prospective Follow-up Period (Arm A only)

Follow-up will begin the first day after the Prospective Baseline Visit and will continue for up to 12 months. Visits will take place at Months 3, 6 and 12 during the Follow-up Period.

The following procedures will be performed and documented during each Follow-Up visit:

- Adverse event assessment.
- Height and weight.

- Pregnancy status.
- Chart Review of the following clinical parameters: hemoglobin, platelet count, bone mineral density, spleen volume, liver volume. Bone mineral density Z scores and T scores if available.
- Chart review of the following biomarkers: chitotriosidase and CCL 18.
- Chart review of antidrug antibodies.
- Concomitant medications.
- Concurrent medical conditions.
- Lyso-Gb1 biomarker sample collection.
- Goal tracking and mobile app assessments.
- Remote qualitative assessment, patient journey and patient satisfaction with app (Month 12).

9.0 PRETREATMENT EVENTS AND ADVERSE EVENTS

9.1 Definitions

9.1.1 Adverse Events

An AE is defined as any untoward medical occurrence in a clinical investigation subject administered with a drug; it does not necessarily have to have a causal relationship with this treatment.

An AE can therefore be any unfavorable and unintended sign (e.g., a clinically significant abnormal laboratory value), symptom, or disease temporally associated with the use of a drug whether or not it is considered related to the drug.

9.1.2 Additional Points to Consider for AEs

An untoward finding generally may:

- Indicate a new diagnosis or unexpected worsening of a pre-existing condition. (Intermittent events for pre-existing conditions or underlying disease should not be considered AEs.)
- Necessitate therapeutic intervention.
- Require an invasive diagnostic procedure.
- Require discontinuation or a change in dose of study drug or a concomitant medication.
- Be considered unfavorable by the investigator for any reason.

AEs caused by a study procedure (e.g., a bruise after blood draw) should be recorded as an AE.

Diagnoses vs. signs and symptoms:

- Each event should be recorded to represent a single diagnosis. Accompanying signs (including abnormal laboratory values or ECG findings) or symptoms should NOT be recorded as additional AEs. If a diagnosis is unknown, sign(s) or symptom(s) should be recorded appropriately as AE(s).

Laboratory values and ECG findings:

- Changes in laboratory values or ECG findings are only considered to be AEs if they are judged to be clinically significant (i.e., if some action or intervention is required or if the investigator judges the change to be beyond the range of normal physiologic fluctuation). A laboratory or ECG re-test and/or continued monitoring of an abnormal value or finding are not considered an intervention. In addition, repeated or additional noninvasive testing for verification, evaluation or monitoring of an abnormality is not considered an intervention.
- If abnormal laboratory values or ECG findings are the result of pathology for which there is an overall diagnosis (e.g., increased creatinine in renal failure), the diagnosis only should be reported appropriately as an AE.

Pre-existing conditions:

- Pre-existing conditions (present at the time of signing of informed consent) are considered concurrent medical conditions and should NOT be recorded as AEs. Baseline evaluations (e.g., laboratory tests, ECG, X-rays etc.) should NOT be recorded as AEs unless related to study procedures. However, if the subject experiences a worsening or complication of such a concurrent medical condition, or an AE (worsening or complication occurs after start). Investigators should ensure that the event term recorded captures the change in the condition (e.g., "worsening of…").
- If a subject has a pre-existing episodic concurrent medical condition (e.g., asthma, epilepsy) any occurrence of an episode should only be captured as an AE if the condition becomes more frequent, serious or severe in nature. Investigators should ensure that the AE term recorded captures the change in the condition from Baseline (e.g. "worsening of…").
- If a subject has a degenerative concurrent medical condition (e.g., cataracts, rheumatoid arthritis), worsening of the condition should only be recorded as an AE if occurring to a greater extent to that which would be expected. Investigators should ensure that the AE term recorded captures the change in the condition (e.g., "worsening of…").

Worsening of AEs:

- If the subject experiences a worsening or complication of an AE, the worsening or complication should be recorded as a new AE. Investigators should ensure that the AE term recorded captures the change in the condition (e.g., "worsening of…").

Changes in intensity of AEs:

- If the subject experiences changes in intensity of an AE, the event should be captured once with the maximum intensity recorded.

Preplanned procedures (surgeries or interventions):

- Preplanned procedures (surgeries or therapies) that were scheduled prior to signing of informed consent are not considered AEs. However, if a preplanned procedure is performed early (e.g., as an emergency) due to a worsening of the pre-existing condition, the worsening of the condition should be recorded as an AE. Complications resulting from any planned surgery should be reported as AEs.

Elective surgeries or procedures:

- Elective procedures performed where there is no change in the subject's medical condition should not be recorded as AEs, but should be documented in the subject's source documents. Complications resulting from an elective surgery should be reported as AEs.

Insufficient clinical response (lack of efficacy):

- Insufficient clinical response, efficacy, or pharmacologic action, should NOT be recorded as an AE. The investigator must make the distinction between exacerbation of pre-existing illness and lack of therapeutic efficacy.

Overdose:

- Cases of overdose with any medication without manifested side effects are NOT considered AEs, but instead will be documented on an Overdose page of the (e)CRF. Any manifested side effects will be considered AEs/SAEs and will be recorded on the AE page of the (e)CRF.

9.1.3 SAEs

An SAE is defined as any untoward medical occurrence that at any dose:

1. Results in DEATH.
2. Is LIFE THREATENING.
   - The term "life threatening" 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 that hypothetically might have caused death if it were more severe.
3. Requires inpatient HOSPITALIZATION or prolongation of existing hospitalization.
4. Results in persistent or significant DISABILITY/INCAPACITY.
5. Leads to a CONGENITAL ANOMALY/BIRTH DEFECT.
6. Is an IMPORTANT MEDICAL EVENT that satisfies any of the following:
   - May require intervention to prevent items 1 through 5 above.

- May expose the subject to danger, even though the event is not immediately life threatening or fatal or does not result in hospitalization.
- Includes any event or synonym described in the Takeda Medically Significant AE List (Table 9.a).

Table 9.a Takeda Medically Significant AE List

Term	
Acute respiratory failure/acute respiratory distress syndrome	Hepatic necrosis
Torsade de pointes / ventricular fibrillation / ventricular tachycardia	Acute liver failure
	Anaphylactic shock
Malignant hypertension	Acute renal failure
Convulsive seizure	Pulmonary hypertension
Agranulocytosis	Pulmonary fibrosis
Aplastic anemia	Confirmed or suspected endotoxin shock
Toxic epidermal necrolysis/Stevens-Johnson syndrome	Confirmed or suspected transmission of infectious agent by a medicinal product
	Neuroleptic malignant syndrome / malignant hyperthermia
	Spontaneous abortion / stillbirth and fetal death

Note: Terms identified on the Medically Significant AE List represent the broad medical concepts to be considered as "Important Medical Events" satisfying SAE reporting requirements.

9.1.4 Intensity of AEs

The different categories of intensity (severity) are characterized as follows:

Mild:	The event is transient and easily tolerated by the subject.
Moderate:	The event causes the subject discomfort and interrupts the subject's usual activities.
Severe:	The event causes considerable interference with the subject's usual activities.

9.1.5 Causality of AEs

The relationship of each AE to study drug(s) will be assessed using the following categories:

Related:	An AE that follows a reasonable temporal sequence from administration of a drug (including the course after withdrawal of the drug), or for which possible involvement of the drug cannot be ruled out, although factors other than the drug, such as underlying diseases, complications, concomitant medications and concurrent treatments, may also be responsible.
Not Related:	An AE that does not follow a reasonable temporal sequence from administration of a drug and/or that can reasonably be explained by other factors, such as underlying diseases, complications, concomitant medications and concurrent treatments.

9.1.6 Relationship to Study Procedures

Relationship (causality) to study procedures should be determined for all AEs.

The relationship should be assessed as Related if the investigator considers that there is reasonable possibility that an event is due to a study procedure. Otherwise, the relationship should be assessed as Not Related.

9.1.7 Start Date

The start date of the AE is the date that the first signs/symptoms were noted by the subject and/or investigator.

9.1.8 Stop Date

The stop date of the AE is the date at which the subject recovered, the event resolved but with sequelae or the subject died.

9.1.9 Frequency

Episodic AEs (e.g., vomiting) or those which occur repeatedly over a period of consecutive days are intermittent. All other events are continuous.

9.1.10 Outcome

- Recovered/Resolved – Subject returned to first assessment status with respect to the AE.
- Recovering/Resolving – the intensity is lowered by 1 or more stages: the diagnosis or signs/symptoms has almost disappeared; the abnormal laboratory value improved, but has not returned to the normal range or to baseline; the subject died from a cause other than the particular AE with the condition remaining "recovering/resolving".
- Not recovered/not resolved – there is no change in the diagnosis, signs or symptoms; the intensity of the diagnosis, signs/ symptoms or laboratory value on the last day of the observed study period has got worse than when it started; is an irreversible congenital anomaly; the subject died from another cause with the particular AE state remaining "Not recovered/not resolved".
- Resolved with sequelae – the subject recovered from an acute AE-but was left with permanent/significant impairment (e.g., recovered from a cardiovascular accident but with some persisting paresis.
- Fatal – the AEs which are considered as the cause of death.
- Unknown – the course of the AE cannot be followed up due to hospital change or residence change at the end of the subject's participation in the study.

9.2 Procedures

9.2.1 Collection and Reporting of AEs

9.2.1.1 AE Collection Period

Collection of AEs will commence from the time that the subject signs informed consent at the Prospective Baseline Visit. Routine collection of AEs will continue until Month 12 Final Study Visit or Early Termination.

9.2.1.2 AE Reporting

At each study visit, the investigator will assess whether any subjective AEs have occurred. A neutral question, such as "How have you been feeling since your last visit?" may be asked. Subjects may report AEs occurring at any other time during the study.

All subjects experiencing AEs, whether considered associated with the use of the study drug or not, must be monitored until the symptoms subside and any clinically relevant changes in laboratory values have returned to baseline or until there is a satisfactory explanation for the changes observed. All AEs will be documented in the AE page of the eCRF, whether or not the investigator concludes that the event is related to the drug treatment. The following information will be documented for each event:

1. Event term.
2. Start and stop date.
3. Frequency.
4. Intensity.
5. Investigator's opinion of the causal relationship between the event and administration of study drug(s) (related or not related).
6. Investigator's opinion of the causal relationship to study procedure(s), including the details of the suspected procedure.
7. Action concerning study drug.
8. Outcome of event.
9. Seriousness.

PROs will not be used as a primary means to collect AEs. However, should the investigator become aware of a potential AE through the information collected with this instrument, proper follow-up with the patient for medical evaluation should be undertaken. Through this follow-up if it is determined that an AE not previously reported has been identified, normal reporting requirements should be applied.

The EDC system has an AE reporting module, which includes a prompt from the system if data is entered that suggests an AE has occurred (the Investigator can either state that there was no

AE, report the AE at that point, or confirm that it was reported). The EDC automatically sends a report for each AE as they are reported to the designated safety officer, who will manually code and submit them to the safety authority. In addition, a report can be set up for the client (automatic or on-demand) to summarize reported AEs during the study.

9.2.2 Collection and Reporting of SAEs

When an SAE occurs through the AE collection period it should be reported according to the following procedure:

A Takeda SAE form must be completed, in English, and signed by the investigator immediately or within 24 hours of first onset or notification of the event. The information should be completed as fully as possible but contain, at a minimum:

A short description of the event and the reason why the event is categorized as serious.

- Subject identification number.
- Investigator's name.
- Name of the study drug(s)
- Causality assessment.

The SAE form should be transmitted within 24 hours to the attention of the contact listed in Section 1.1. If for some reason international phone or fax is unavailable, please submit the completed SAE reports within 24 hours of Investigator's awareness by email. Please add the following information to the email´s subject line: Takeda Clinical Study#: xxx, Site#: xxx / and Subject#: xx-xxxx. The SAE should also be entered on the EDC under the AE reporting module.

Any SAE spontaneously reported to the investigator following the AE collection period should be reported to the sponsor if considered related to study participation.

9.3 Follow-up of SAEs

If information is not available at the time of the first report becomes available at a later date, the investigator should complete a follow-up SAE form or provide other written documentation and fax it immediately within 24 hours of receipt. Copies of any relevant data from the hospital notes (e.g., ECGs, laboratory tests, discharge summary, postmortem results) should be sent to the addressee, if requested.

All SAEs should be followed up until resolution or permanent outcome of the event. The timelines and procedure for follow-up reports are the same as those for the initial report.

9.3.1 Safety Reporting to Investigators, IRBs, and Regulatory Authorities

The sponsor will be responsible for reporting all suspected unexpected serious adverse reactions (SUSARs) and any other applicable SAEs to regulatory authorities, investigators and IRBs. Relative to the first awareness of the event by/or further provision to the sponsor or sponsor's designee, SUSARs will be submitted to the regulatory authorities as expedited report within 7

days for fatal and life-threatening events and 15 days for other serious events, unless otherwise required by national regulations. The sponsor will also prepare an expedited report for other safety issues where these might materially alter the current benefit-risk assessment of a study drug/sponsor supplied drug or that would be sufficient to consider changes in the study drug/sponsor supplied drug administration or in the overall conduct of the trial. The study site also will forward a copy of all expedited reports to his or her IRB or IECs, as applicable.

10.0 STUDY-SPECIFIC COMMITTEES

No steering committee, data safety monitoring committee, or clinical endpoint committee will be used in this study.

11.0 DATA HANDLING AND RECORDKEEPING

The full details of procedures for data handling will be documented in the Data Management Plan. AEs, medical history, and concurrent medical conditions will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Drugs will be coded using the World Health Organization (WHO) Drug Dictionary.

11.1 eCRFs

Completed eCRFs are required for each subject.

The sponsor or its designee will supply study sites with access to eCRFs. These forms are used to transmit the information collected in the performance of this study to the sponsor and regulatory authorities. eCRFs must be completed in English.

After completion of the entry process, computer logic checks will be run to identify items, such as inconsistent dates, missing data, and questionable values. Queries may be issued by Takeda personnel (or designees) and will be answered by the site.

The principal investigator must review the eCRFs for completeness and accuracy and must e-sign the appropriate eCRFs as indicated. Furthermore, the investigator must retain full responsibility for the accuracy and authenticity of all data entered on the eCRFs.

eCRFs will be reviewed for completeness and acceptability at the study site during periodic monitoring by the sponsor or its designee. The sponsor or its designee will be permitted to review the subject's medical and hospital records pertinent to the study to ensure accuracy of the eCRFs. The completed eCRFs are the sole property of the sponsor and should not be made available in any form to third parties, except for authorized representatives of appropriate governmental health or regulatory authorities, without written permission of the sponsor.

11.2 Record Retention

The investigator agrees to keep the records stipulated in Section 11.1 and those documents that include (but are not limited to) the study-specific documents, the identification log of all participating subjects, medical records, temporary media such as thermal sensitive paper, source worksheets, all original signed and dated informed consent forms, subject authorization forms

regarding the use of personal health information (if separate from the informed consent forms), electronic copy of eCRFs, including the audit trail, and detailed records of drug disposition to enable evaluations or audits from regulatory authorities, the sponsor or its designees. Any source documentation printed on degradable thermal sensitive paper should be photocopied by the site and filed with the original in the subject's chart to ensure long term legibility. Furthermore, International Conference on Harmonization (ICH) E6 Section 4.9.5 requires the investigator to retain essential documents specified in ICH E6 (Section 8) until at least 2 years after the last approval of a marketing application for a specified drug indication being investigated or, if an application is not approved, until at least 2 years after the investigation is discontinued and regulatory authorities are notified. In addition, ICH E6 Section 4.9.5 states that the study records should be retained until an amount of time specified by applicable regulatory requirements or for a time specified in the study site agreement between the investigator and sponsor.

Refer to the study site agreement for the sponsor's requirements on record retention. The investigator should contact and receive written approval from the sponsor before disposing of any such documents.

12.0 STATISTICAL METHODS

12.1 Statistical and Analytical Plans

This study is descriptive in nature and is not designed to test or refute pre-defined hypotheses. All statistical analyses will be performed using Stata 16 (Stata Corp. 2019. Stata Statistical Software: Release 16. College Station, TX: Stata Corp LLC.).

Statistical analyses will be descriptive in nature. A statistical analysis plan (SAP) will be developed and finalized prior to any data analyses being performed and will define all analytic populations and sub-populations and definitions of derived variables.

12.1.1 Analysis Sets

No formal analyses sets will be defined due to small size of the study. All available data will be included in the analysis.

12.1.2 Analysis of Demographics and Other Baseline Characteristics

All demographic and baseline characteristics data will be analyzed descriptively. Details of the analyses variables will be described and finalized in SAP before the database lock.

Baseline characteristics will be reported for the full cohort. There will be no substitution of missing data. Incomplete (i.e., missing) data will be reported, for all study variables. If applicable, tests may be performed to identify the patterns and type of missing data. Full details of the handling of missing data will be specified in the SAP.

12.1.3 Primary, Secondary and Exploratory Analyses

Study endpoints will be analyzed for those subjects with available data. All variables will be summarized using descriptive statistics. Categorical variables will be presented as frequencies

and percentages. Continuous variables will be presented as mean with standard deviation (SD) or standard error (SE) and range for normally distributed variables, and as mean and SD as well as median, interquartile range (IQR) and range for non-normally distributed. 95% confidence intervals will be presented, in addition to the number and percentage of patients within threshold along with 95% CI.

The SAP will provide a detailed description of analyses to be performed and will describe methods to deal with missing data and censoring (if applicable). The final SAP will inform the interim analysis and the final data analysis. Any known deviations from the planned analyses, the reason for such deviations and all alternative / additional statistical analyses that may be performed as well as the final statistical analysis will be described in a revised SAP before completion of data collection. All later deviations and / or alterations will be summarized in the final study report.

12.1.4 Remote Qualitative Assessment Analyses

The output from the following sources will be analyzed:

- Post Baseline visit interviews.
- App analytics.
- Patient reports.
- Post End of Study Remote Patient Qualitative Interview.
- Post Study Remote HCP Qualitative Interview.

Interpretative Phenomenological Analysis will be used to analyze the qualitative data. Analysis will involve 2 stages:

1. Data management, which will include:
   a) Familiarization with the data, reading notes, and/or listening to the audio dialogue in order to extract main themes and ideas.
   b) Thematic framework development, identifying the key issues and concepts present in the data and creating themes both inductively, based on the data, and deductively, based on the research questions.
2. Interpretation stage, which will include focused defining the main concepts and mapping the ways in which different parts of the data are related to each other.

12.1.5 Safety Analysis

All AEs will be coded using MedDRA. Data will be summarized using preferred term and primary system organ class.

12.2 Interim Analysis and Criteria for Early Termination

An interim analysis is planned when approximately 50% of enrolled subjects complete the study.

12.3 Determination of Sample Size

The target sample size for this study is 20 to 22 patients in total. This sample size was chosen based on site feasibility. The study is designed in accordance with a standard GD management algorithm.

The study is descriptive in nature, is designed in accordance with a standard GD management algorithm and employs a convenient sampling procedure to maximize the enrolment of patients who meet the study eligibility criteria. The determination of the target sample size was not based on statistical considerations.

13.0 QUALITY CONTROL AND QUALITY ASSURANCE

13.1 Study-Site Monitoring Visits

Monitoring will be done periodically during the study to ensure that all aspects of the protocol are followed. Source documents will be reviewed for verification of data recorded on the eCRFs. Source documents are defined as original documents, data, and records. The investigator guarantee access to source documents by the sponsor or its designee (CRO) and by the IRB or IEC.

All aspects of the study and its documentation will be subject to review by the sponsor or sponsor's designee, including but not limited to the Investigator's Binder, subject medical records, informed consent documentation, documentation of subject authorization to use personal health information, and review of eCRFs and associated source documents. It is important that the investigator and other study personnel are available during the monitoring visits and that sufficient time is devoted to the process.

13.2 Protocol Deviations

The investigator should not deviate from the protocol, except where necessary to eliminate an immediate hazard to study subjects. Should other unexpected circumstances arise that will require deviation from protocol-specified procedures, the investigator should consult with the sponsor or designee (and IRB, as required) to determine the appropriate course of action. There will be no exemptions (a prospectively approved deviation) from the inclusion or exclusion criteria.

The site should document all protocol deviations in the subject's source documents. In the event of a significant deviation, the site should notify the sponsor or its designee (and IRB, as required). Significant deviations include, but are not limited to, those that involve fraud or misconduct, increase the health risk to the subject, or confound interpretation of primary study assessment. A Protocol Deviation Form should be completed by the site and signed by the sponsor or designee for any significant deviation from the protocol.

13.3 Quality Assurance Audits and Regulatory Agency Inspections

The study site also may be subject to quality assurance audits by the sponsor or designees. In this circumstance, the sponsor-designated auditor will contact the site in advance to arrange an

auditing visit. The auditor may ask to visit the facilities where laboratory samples are collected, where the medication is stored and prepared, and any other facility used during the study. In addition, there is the possibility that this study may be inspected by regulatory agencies, including those of foreign governments (e.g., the FDA, the United Kingdom Medicines and Healthcare products Regulatory Agency, the Pharmaceuticals and Medical Devices Agency of Japan). If the study site is contacted for an inspection by a regulatory body, the sponsor should be notified immediately. The investigator and the study site guarantee access for quality assurance auditors to all study documents as described in Section 13.1.

14.0 ETHICAL ASPECTS OF THE STUDY

This study will be conducted with the highest respect for the individual participants (i.e., subjects) according to the protocol, the ethical principles that have their origin in the Declaration of Helsinki, and the ICH Harmonized Tripartite Guideline for GCP. Each investigator will conduct the study according to applicable local or regional regulatory requirements and align his or her conduct in accordance with the "Responsibilities of the Investigator" that are listed in Appendix B. The principles of Helsinki are addressed through the protocol and through appendices containing requirements for informed consent and investigator responsibilities.

14.1 IRB

IRBs must be constituted according to the applicable state and federal/local requirements of each participating region. The sponsor or designee will require documentation noting all names and titles of members who make up the respective IRB. If any member of the IRB has direct participation in this study, written notification regarding his or her abstinence from voting must also be obtained. Those Americas sites unwilling to provide names and titles of all members due to privacy and conflict of interest concerns should instead provide a Federal Wide Assurance Number or comparable number assigned by the Department of Health and Human Services.

The sponsor or designee will supply relevant documents for submission to the respective IRB for the protocol's review and approval. This protocol, the Investigator's Brochure, a copy of the informed consent form, and, if applicable, subject recruitment materials and/or advertisements and other documents required by all applicable laws and regulations, must be submitted to a central or local IRB for approval. The IRB's written approval of the protocol and subject informed consent must be obtained and submitted to the sponsor or designee before commencement of the study (i.e., before study specific screening activity). The IRB approval must refer to the study by exact protocol title, number, and version date; identify versions of other documents (e.g., informed consent form) reviewed; and state the approval date. The sponsor will notify site once the sponsor has confirmed the adequacy of site regulatory documentation and, when applicable, the sponsor has received permission from competent authority to begin the study. Until the site receives notification no protocol activities, including screening may occur.

Study sites must adhere to all requirements stipulated by their respective IRB. This may include notification to the IRB regarding protocol amendments, updates to the informed consent form, recruitment materials intended for viewing by subjects, local safety reporting requirements,

reports and updates regarding the ongoing review of the study at intervals specified by the respective IRB, and submission of the investigator's final status report to IRB. All IRB approvals and relevant documentation for these items must be provided to the sponsor or its designee.

Subject incentives should not exert undue influence for participation. Payments to subjects must be approved by the IRB and sponsor.

14.2 Subject Information, Informed Consent, and Subject Authorization

Written consent documents will embody the elements of informed consent as described in the Declaration of Helsinki and the ICH Guidelines for GCP and will be in accordance with all applicable laws and regulations. The informed consent form, subject authorization form (if applicable), and subject information sheet (if applicable) describe the planned and permitted uses, transfers, and disclosures of the subject's personal and personal health information for purposes of conducting the study. The informed consent form and the subject information sheet (if applicable) further explain the nature of the study, its objectives, and potential risks and benefits, as well as the date informed consent is given. The informed consent form will detail the requirements of the participant and the fact that he or she is free to withdraw at any time without giving a reason and without prejudice to his or her further medical care.

The investigator is responsible for the preparation, content, and IRB approval of the informed consent form and if applicable, the subject authorization form. The informed consent form, subject authorization form (if applicable), and subject information sheet (if applicable) must be approved by both the IRB and the sponsor prior to use.

The informed consent form, subject authorization form (if applicable), and subject information sheet (if applicable) must be written in a language fully comprehensible to the prospective subject. It is the responsibility of the investigator to explain the detailed elements of the informed consent form, subject authorization form (if applicable), and subject information sheet (if applicable) to the subject. Information should be given in both oral and written form whenever possible and in the manner deemed appropriate by the IRB.

The subject, must be given ample opportunity to: (1) inquire about details of the study and (2) decide whether or not to participate in the study. If the subject determines they will participate in the study, then the informed consent form and subject authorization form (if applicable) must be signed and dated by the subject, at the time of consent and prior to the subject entering into the study. The subject should be instructed to sign using their legal names, not nicknames, using blue or black ballpoint ink, or electronically as applicable. The investigator must also sign and date the informed consent form and subject authorization (if applicable) at the time of consent and prior to subject entering into the study.

Once signed, the original informed consent form, subject authorization form (if applicable), and subject information sheet (if applicable) will be stored in the investigator's site file. The investigator must document the date the subject signs the informed consent in the subject's medical record. Copies of the signed informed consent form, the signed subject authorization form (if applicable), and subject information sheet (if applicable) shall be given to the subject.

All revised informed consent forms must be reviewed and signed by relevant subjects or the relevant subject's legally acceptable representative in the same manner as the original informed consent. The date the revised consent was obtained should be recorded in the subject's medical record, and the subject should receive a copy of the revised informed consent form.

14.3 Subject Confidentiality

The sponsor and designees affirm and uphold the principle of the subject's right to protection against invasion of privacy. Throughout this study, a subject's source data will only be linked to the sponsor's clinical trial database or documentation via a subject identification number. As permitted by all applicable laws and regulations, limited subject attributes, such as sex, age, or date of birth, and subject initials may be used to verify the subject and accuracy of the subject's unique identification number.

To comply with ICH Guidelines for GCP and to verify compliance with this protocol, the sponsor requires the investigator to permit the monitor or the sponsor's designee, representatives from any regulatory authority (e.g., FDA, Medicines and Healthcare products Regulatory Agency, Pharmaceuticals and Medical Devices Agency), the sponsor's designated auditors, and the appropriate IRBs to review the subject's original medical records (source data or documents), including, but not limited to, laboratory test result reports, ECG reports, admission and discharge summaries for hospital admissions occurring during a subject's study participation, and autopsy reports. Access to a subject's original medical records requires the specific authorization of the subject as part of the informed consent process (see Section 14.2).

Copies of any subject source documents that are provided to the sponsor must have certain personally identifiable information removed (i.e., subject name, address, and other identifier fields not collected on the subject's eCRF).

14.4 Publication, Disclosure, and Clinical Trial Registration Policy

14.4.1 Publication and Disclosure

The investigator is obliged to provide the sponsor with complete test results and all data derived by the investigator from the study. During and after the study, only the sponsor may make study information available to other study investigators or to regulatory agencies, except as required by law or regulation. Except as otherwise allowable in the study site agreement, any public disclosure (including publicly accessible websites) related to the protocol or study results, is the sole responsibility of the sponsor.

14.4.2 Clinical Trial Registration

In order to ensure that information on clinical trials reaches the public in a timely manner and to comply with applicable laws, regulations and guidance, Takeda will, at a minimum register all interventional clinical trials it sponsors anywhere in the world on ClinicalTrials.gov and/or other publicly accessible websites before start of study, as defined in Takeda Policy/Standard. Takeda

contact information, along with investigator's city, state (for Americas investigators), country, and recruiting status will be registered and available for public viewing.

For some registries, Takeda will assist callers in locating study sites closest to their homes by providing the investigator name, address, and phone number to the callers requesting trial information. Once subjects receive investigator contact information, they may call the site requesting enrollment into the trial. The investigative sites are encouraged to handle the trial inquiries according to their established subject screening process. If the caller asks additional questions beyond the topic of trial enrollment, they should be referred to the sponsor.

Any investigator who objects to the sponsor providing this information to callers must provide the sponsor with a written notice requesting that their information not be listed on the registry site.

14.4.3 Clinical Trial Results Disclosure

Takeda will post the results of clinical trials on ClinicalTrials.gov and/or other publicly accessible websites, as required by Takeda Policy/Standard, applicable laws and/or regulations.

14.5 Insurance and Compensation for Injury

Each subject in the study must be insured in accordance with the regulations applicable to the site where the subject is participating. If a local underwriter is required, then the sponsor or sponsor's designee will obtain clinical study insurance against the risk of injury to study subjects. Refer to the study site agreement regarding the sponsor's policy on subject compensation and treatment for injury. If the investigator has questions regarding this policy, he or she should contact the sponsor or sponsor's designee.

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Appendix A: Schedule of Study Procedures (Arm A)

Schedule of Activities	Retrospective Period		Prospective Period			
	SRT Baseline	ERT Baseline	Month 1 Prospective Baseline	Month 3	Month 6	Month 12 Final Visit or Early Term Visit
Study Week/Days:	≥ 3 months prior to ERT start	≥ 3 months prior to study enrollment	Day 0	Day 90	Day 180	Day 365
Visit Windows (Days):				±7 days	±7 days	±7 days
Prospective Data Collection						
Informed consent			X			
Inclusion/exclusion criteria			X			
Demographics			X			
Study ID assignment and Onboarding of App*			X			
Mobile App data collection-						
• PAM-13			X			X
• CollaboRATE**			X		X	X
• WSAS			X		X	X
• GD-Goal Attainment			----X-----	----	---	----X-----
• PHQ-4 (monthly)			----X-----	----	---	----X-----
• WHO-5 (monthly)			----X-----	----	----	----X-----
• Side effects and tolerability questions			----X-----	----	-----	----X-----
• Medication Adherence			X	----	----	X
• GD-specific questions			X	X	X	X
Reason for switch and patient satisfaction questions related to the mobile application use			X			X
Remote Qualitative assessment			X			X
AE assessment			X	X	X	X
Biomarker collection- Lyso-Gb1			X	X	X	X

*App onboarding will occur as soon as the subject has provided informed consent; ** to be completed following baseline visit

Appendix A: Schedule of Study Procedures (Arm A) Continued….

Retrospective/ Prospective Chart review	SRT Baseline	ERT Baseline	Month 1 Prospective Baseline	Month 3	Month 6	Month 12 Final Visit or Early Term Visit
Medical history	X	X	X	X	X	X
Medication history	X	X	X	X	X	X
Concurrent medical conditions	X	X	X	X	X	X
Concomitant medication	X	X	X	X	X	X
Height and Weight	X	X	X	X	X	X
Pregnancy Status	X	X	X	X	X	X
Adverse Event	X	X	X	X	X	X
Clinical parameters						
• Hemoglobin	X	X	X	X	X	X
• Platelet Count	X	X	X	X	X	X
• Bone Mineral Density %	X	X	X	X	X	X
• Bone Mineral Density Z-score and T-score	X					X
• Spleen volume	X	X	X	X	X	X
• Liver volume	X	X	X	X	X	X
Biomarkers						
• Chitotriosidase	X	X	X	X	X	X
• CCL 18	X	X	X	X	X	X
• Lyso-Gb1	X	X				
Antidrug Antibodies	X	X	X	X	X	X

Appendix A: Schedule of study procedures Arm B

Retrospective Chart review	Up to 12 months SRT data PRIOR switch to VPRIV	12 months data collection POST switch to VPRIV
Demographic information	X	
Medical history	X	X
Medication history	X	X
Concurrent medical conditions	X	X
Concomitant medication	X	X
Height and Weight	X	X
Pregnancy Status	X	X
Adverse Event	X	X
Clinical parameters		
• Hemoglobin	X	X
• Platelet Count	X	X
• Bone Mineral Density %	X	X
• Bone Mineral Density Z-score and T-score	X	X
• Spleen volume	X	X
• Liver volume	X	X
Biomarkers		
• Chitotriosidase	X	X
• CCL 18	X	X
• Lyso-Gb1	X	X
Antidrug Antibodies	X	X

Data to be captured where possible

Appendix B Responsibilities of the Investigator

Clinical research studies sponsored by the sponsor are subject to ICH GCP and all the applicable local laws and regulations.

The investigator agrees to assume the following responsibilities:

1. Conduct the study in accordance with the protocol.
2. Personally conduct or supervise the staff who will assist in the protocol.
3. Ensure that study related procedures, including study specific (non-routine/non-standard panel) screening assessments are NOT performed on potential subjects, prior to the receipt of written approval from relevant governing bodies/authorities.
4. Ensure that all colleagues and employees assisting in the conduct of the study are informed of these obligations.
5. Secure prior approval of the study and any changes by an appropriate IRB that conform to ICH, and local regulatory requirements.
6. Ensure that the IRB will be responsible for initial review, continuing review, and approval of the protocol. Promptly report to the IRB all changes in research activity and all anticipated risks to subjects. Make at least yearly reports on the progress of the study to the IRB, and issue a final report within 3 months of study completion.
7. Ensure that requirements for informed consent, as outlined in ICH and local regulations, are met.
8. Obtain valid informed consent from each subject who participates in the study, and document the date of consent in the subject's medical chart. Valid informed consent is the most current version approved by the IRB. Each informed consent form should contain a subject authorization section that describes the uses and disclosures of a subject's personal information (including personal health information) that will take place in connection with the study. If an informed consent form does not include such a subject authorization, then the investigator must obtain a separate subject authorization form from each subject.
9. Prepare and maintain adequate case histories of all persons entered into the study, including eCRFs, hospital records, laboratory results, etc., and maintain these data for a minimum of 2 years following notification by the sponsor that all investigations have been discontinued or that the regulatory authority has approved the marketing application. The investigator should contact and receive written approval from the sponsor before disposing of any such documents.
10. Allow possible inspection and copying by the regulatory authority of GCP-specified essential documents.
11. Report adverse reactions to the sponsor promptly. In the event of an SAE, notify the sponsor within 24 hours.

Appendix C Elements of the Subject Informed Consent

In seeking informed consent, the following information shall be provided to each subject:

1. A statement that the study involves research.
2. An explanation of the purposes of the research.
3. The expected duration of the subject's participation.
4. A description of the procedures to be followed, including invasive procedures.
5. The identification of any procedures that are experimental.
6. The estimated number of subjects involved in the study.
7. A description of the subject's responsibilities.
8. A description of the conduct of the study.
9. A description of any benefits to the subject or to others that reasonably may be expected from the research. When there is no intended clinical benefit to the subject, the subject should be made aware of this.
10. A statement describing the extent to which confidentiality of records identifying the subject will be maintained, and a note of the possibility that regulatory agencies, auditor(s), IRB/IEC, and the monitor may inspect the records. By signing a written informed consent form, the subject or the subject's legally acceptable representative is authorizing such access.
11. For research involving more than minimal risk, an explanation as to whether any compensation and an explanation as to whether any medical treatments are available if injury occurs and, if so, what they consist of or where further information may be obtained.
12. The anticipated prorated payment(s), if any, to the subject for participating in the study.
13. The anticipated expenses, if any, to the subject for participating in the study.
14. An explanation of whom to contact for answers to pertinent questions about the research (investigator), subject's rights, and IRB and whom to contact in the event of a research-related injury to the subject.
15. A statement that participation is voluntary, that refusal to participate will involve no penalty or loss of benefits to which the subject otherwise is entitled, and that the subject may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled.
16. The consequences of a subject's decision to withdraw from the research and procedures for orderly termination of participation by the subject.
17. A statement that the subject will be informed in a timely manner if information becomes available that may be relevant to the subject's willingness to continue participation in the study.

18. The foreseeable circumstances or reasons under which the subject's participation in the study may be terminated.

19. A written subject authorization (either contained within the informed consent form or provided as a separate document) describing to the subject the contemplated and permissible uses and disclosures of the subject's personal information (including personal health information) for purposes of conducting the study. The subject authorization must contain the following statements regarding the uses and disclosures of the subject's personal information:

    c) that personal information (including personal health information) may be processed by or transferred to other parties in other countries for clinical research and safety reporting purposes, including, without limitation, to the following: (1) Takeda, its affiliates, and licensing partners; (2) business partners assisting Takeda, its affiliates, and licensing partners; (3) regulatory agencies and other health authorities; and (4) IRBs;

    d) it is possible that personal information (including personal health information) may be processed and transferred to countries that do not have data protection laws that offer subjects the same level of protection as the data protection laws within this country; however, Takeda will make every effort to keep your personal information confidential, and your name will not be disclosed outside the clinic unless required by law;

    e) that personal information (including personal health information) may be added to Takeda's research databases for purposes of developing a better understanding of the safety and effectiveness of the study drug(s), studying other therapies for patients, developing a better understanding of disease, and improving the efficiency of future clinical studies;

    f) that subjects agree not to restrict the use and disclosure of their personal information (including personal health information) upon withdrawal from the study to the extent that the restricted use or disclosure of such information may impact the scientific integrity of the research; and

    g) that the subject's identity will remain confidential in the event that study results are published.

20. A statement that clinical trial information from this trial will be publicly disclosed in a publicly accessible website, such as ClinicalTrials.gov.

Appendix D Investigator Consent to Use of Personal Information

Takeda will collect and retain personal information of investigator, including his or her name, address, and other personally identifiable information. In addition, investigator's personal information may be transferred to other parties located in countries throughout the world (e.g., the United Kingdom, United States, and Japan), including the following:

- Takeda, its affiliates, and licensing partners.
- Business partners assisting Takeda, its affiliates, and licensing partners.
- Regulatory agencies and other health authorities.
- IRBs and IECs.

Investigator's personal information may be retained, processed, and transferred by Takeda and these other parties for research purposes including the following:

- Assessment of the suitability of investigator for the study and/or other clinical studies.
- Management, monitoring, inspection, and audit of the study.
- Analysis, review, and verification of the study results.
- Safety reporting and pharmacovigilance relating to the study.
- Preparation and submission of regulatory filings, correspondence, and communications to regulatory agencies relating to the study.
- Preparation and submission of regulatory filings, correspondence, and communications to regulatory agencies relating to other medications used in other clinical studies that may contain the same chemical compound present in the study drug.
- Inspections and investigations by regulatory authorities relating to the study.
- Self-inspection and internal audit within Takeda, its affiliates, and licensing partners.
- Archiving and audit of study records.
- Posting investigator site contact information, study details and results on publicly accessible clinical trial registries, databases, and websites.

Investigator's personal information may be transferred to other countries that do not have data protection laws that offer the same level of protection as data protection laws in investigator's own country.

Investigator acknowledges and consents to the use of his or her personal information by Takeda and other parties for the purposes described above.

Appendix E LysoGB-1 Biomarker Sample Collection and Processing (Arm A only)

Collection Container is a dried blood spot card.

Collection and Processing Instructions: Follow kit instructions to fill all spots. Briefly, allow blood to saturate card until indicated areas are filled and blood has soaked through card. Air dry card at ambient temperature for at least 3 hours.

Preferred Sample Condition: Follow kit instructions. Store at ambient temperature. Shipping Instructions: Follow kit instructions. Double bag and ship overnight at ambient temperature.

Samples should be shipped to: PerkinElmer Genomics 250 Industry Dr. Suite 400 Pittsburgh, PA 15275.

For general questions on the collection and return of sample results, please call: PerkinElmer Genomics at +1 (866) 354-2910 (Monday-Friday, 8:00AM - 5:00PM EST) or by emailing Genomics@perkinelmer.com.