Statistical Analysis Plan

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: 1.0 (02 November 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.

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

Version: 1.0

Prepared by

[redacted]

CONFIDENTIAL

In preparation for:

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Table of Contents

List of Tables

List of Figures

List of Abbreviations

AE	Adverse Event
BMI	Body Mass Index
CNS	Central nervous system
CRF	Case Report Form
EDC	Electronic Data Capture
ERT	Enzyme replacement therapy
GAS	Goal Attainment Scale
Gb1	Glucosylceramides
GD	Gaucher disease
PAM	Patient activation measure
PHQ	Patient Health Questionnaire
PRO	Patient reported outcome
SAEs	Serious adverse events
SAP	Statistical analysis plan
SRT	Substrate reduction therapy
WHO	World Health Organization
WSAS	Work and Social Adjustment Scale

APPROVAL

REPRESENTATIVES OF TAKEDA

This study will be conducted with the highest respect for the individual participants in accordance with the requirements of this statistical analyses plan.

SIGNATURES

By: _____ [redacted] _____

Name: _ _____

Title: __ _____

1. Introduction

Disease context

Gaucher disease (GD) 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 central nervous system (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. GD types 2 and 3 have early onset primary CNS disease (7).

Treatments

Two different types of treatment are available for GD1: the intravenous supplementation of the deficient protein acid β-glucosidase (enzyme replacement therapy [ERT]), or the oral administration of a drug that slows down the production of Gb1s (substrate reduction therapy [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). Some SRTs are oral therapies and are non-inferior to ERTs with regard to several clinical measures and health-related quality of life instruments (10–14). Miglustat is inferior to ERT and second line for GD1 treatment (10,11). Some patients are switched to ERT, because they cannot tolerate SRT with eliglustat because of it's complex cytochrome P450 metabolism that complicates the use of some medications and because of potential nontrivial cardiotoxicity. ERT is preferred for the management of GD (15). 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. 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 (16). 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.

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 and caregivers to increase engagement, patient advocacy, and access to care. Digital capabilities are critical for continued success. However, disease-specific apps for metabolic diseases have typically focused on patient's symptom tracking rather than working as a tool in support of the patient-clinician relationship and decision making. 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 realworld 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 are 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 GD. The 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.

2. Aims and Objectives

Primary Objective(s)

1. 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 realworld setting among adults.

Secondary Objective(s)

1. 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.

Exploratory/Additional Objective(s)

1. To describe the change in treatment effect on glucosylsphingosine (Lyso-Gb1), CCL18, and Chitotrio-sidase following the transition from SRTs to ERT (VPRIV) or ERT to SRT and then to ERT (VPRIV).

2. 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 GD specific measures).

The following two exploratory objectives will be addressed using qualitative methods. Please see **Section 7** for further information about the specific methods, endpoints and results that will be derived.

3. 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.

4. Remote qualitative assessments will be conducted to assess HCP reactions to the mobile application to inform further development of a digital tool in GD.

3. Methods

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 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.

Patients with GD1 standard of care will be observed both prospectively and retrospectively to assess treatment outcomes associated with a treatment switch from SRT to ERT (VPRIV). Patient will be enrolled into one of two study arms:

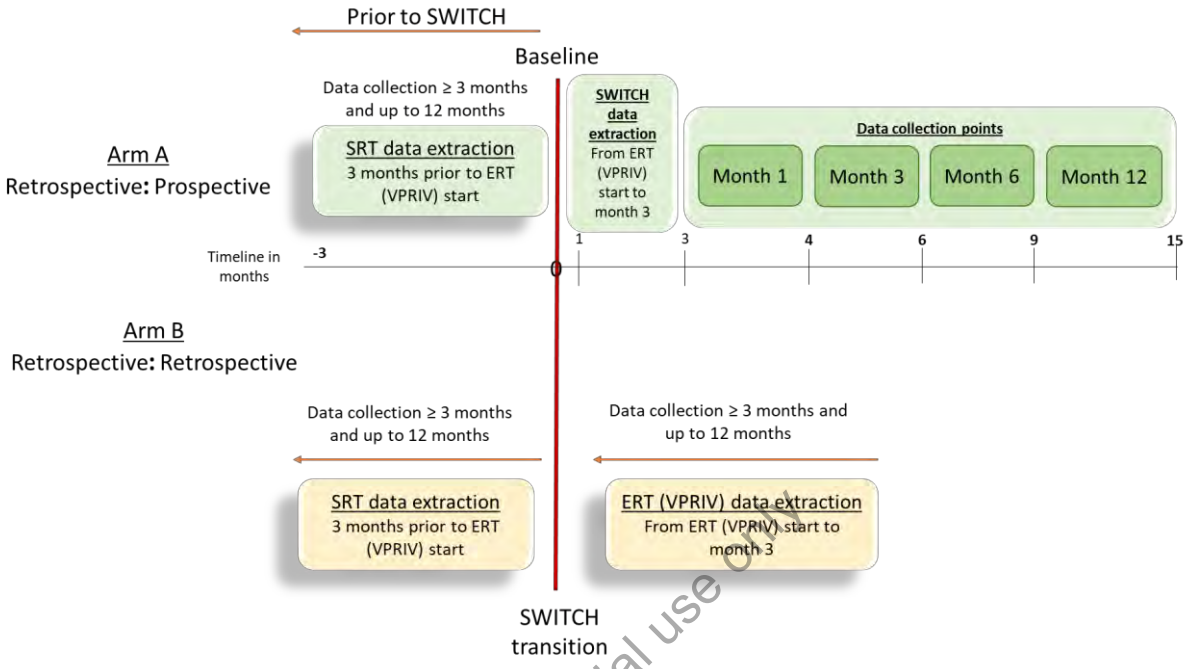
Patients will be included into one of two arms:

- Arm A: retrospective and prospective; or
- Arm B: retrospective only

Patients are eligble for Arm A and B if they have been diagnosed with GD1. Patients enrolled into Arm A must have been treated with SRT for at least 3 months before being switched to ERT (VPRIV) (baseline). Patients in Arm A are then followed-up prospectively for 12 months from baseline (switch from SRT to VPRIV). Follow-up begins on the first day after the prospective baseline visit (month 0) and will continue for up to 12 months. Visits (virtual or in person, as applicable) will take place at months 3, 6 and 12 during the follow-up period. Patients in Arm B will be assessed retrospectively for up to 12 months before being switched from SRT to VPRIV. Once on VPRIV, patients will be followed-up for the subsequent 12 months post-switch. All patients (enrolled in Arms A and B) will be treated in accordance with physician treatment plan (standard clinical practice). SRT cannot be prescribed to pregnant women, (therefore if patients on SRT becomes pregnant, they are switched immediately to ERT (VPRIV). **Figure 1** illustrates the study design for Arms A and B of this study.

A schematic study design and patient flow diagram is presented in **Figure** 1.

Figure 1: Study Design – Patient Flow Diagram



Abbrevations: ERT;enzyme replacement therapy, SRT;substrate reduction therapy, VPRIV;Velaglucerase alfa

Patient Population

Patient Inclusion criteria

Subject's eligibility for Arm A and B 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 econsent 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.

Patient Exclusion Criteria

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).

Data collection

Table 1 and Table 2 reports the type of data that will be collected for Arms A and B of this study, respectively. Data will be collected as per these 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 ERT to SRT and then to ERT (VPRIV). For restrospective part of the study (for both Arm A and B), data will be extracted 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. 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.

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.

For Arm A, data including demographics, clinical, and PROs, will be collected prospectively for all patients on VPRIV for at least 3 months and up to12 months. PRO data and Lyso-Gb1 data will be collected starting at the point at which the patient enters the study. 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 to 12 months of retrospective data before study enrollment in total) and 12 months prospective data ±1 week. Data collected during any consultations during the retrospective period of up to 12 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 1**.

For patients in Arm B, glucosylsphingosine (Lyso-Gb1) data will be collected retrospectively from the patientsmedical records, subject to availability. Due to the nature of the study, it will not be possible to collect PROs for patients in Arm B as these are not routinely collected and entered into patient medical records.

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

Table 1. Study Schematic: Arm A (Retrospective / Prospective)

	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 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			X	X	X	X

Collection Lyso-Gb1						

Abbreviations: Hb=Hemoglobin; BMD=Bone Mineral Density; CCL18=CC-chemokine ligand18; Lyso-Gb1=Glucosylsphingosin

Table 2. Study Schematic: Arm B (Retrospective only)

	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

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

4. Endpoints

This section describes the endpoints that will be reported for each objective.

Primary Objective Endpoint(s)

Stability in clinical parameters including composite of spleen and liver volume, hemoglobin level, and platelet count, overtime from baseline and up to 12 months. Instability of clinical parameters are those that meet and surpass pre-specficed thresholds mentioned below, used by Kishnani et al., (17) and Cox et al., (18):

- Hemoglobin level <1.5 g/dl decrease
- Liver volume <20% increase
- Spleen volume <25% increase
- Platelet count < 25% decrease

Secondary Objective Endpoint(s)

The number and proportion (%) of patients experiencing adverse events (AEs) (such as dizziness, headache, bone pain, etc) or / serious adverse events (SAEs) with levels of severity measured as mild, moderate or severe. For full list of AEs/SAEs please refer to **Appendix 3**: Extracted Variables: Secondary Objectives **(Table** 7**).**

Exploratory Objective endpoints

Exploratory objective 1 (quantitative)

Percentage change in Lyso-Gb1, CCL18, and chitotrio-sidase overtime from baseline and up to 12 months.

Exploratory objective 2 (quantitative)

Data for patient reported outcomes (PROs) will be collected at month 1, 3, 6 and 12. The absolute and percentage change in mobile application assessments will be reported for the following PROs:

- Patient activation measure (PAM-13): PAM consists of 13 questions to assess the knowledge, skills and confidence of patients to manage their health by selecting options like 'disagree strongly', 'disagree', 'agree', 'agree strongly' to answer each question.

- Shared decision making (CollaboRATE): CollaboRATE is a brief patient survey focused on shared decision making and consists of questions such as:

    - (i) How much effort was made to help you understand your health issues?
    - (ii) How much effort was made to listen to what matters most to you about your health issues?
    - (iii) How much effort was made to include what matters most to you in choosing what to do next?

  CollaboRATE survey data needs responses to the three questions, each on a 0-9 scale, along with each respondent's age, gender and clinician.

- Activities of daily living/function (Work and Social Adjustment Scale [WSAS]): The Work and Social Adjustment Scale ("WSAS") is a simple and reliable measure for impairment in functioning. The WSAS assesses the impact of a person's mental health difficulties on their ability to function in terms of work, home management, social leisure, private leisure and personal or family relationships. This instrument is 5 questions long, and is a sensitive and useful outcome measure with correlations to severity of depression and some anxiety symptoms.

- Mood (Patient Health Questionnaire-4 [PHQ-4]): This is a 4-item inventory rated on a 4-point Likert-type scale. Its items are drawn from the first two items of the 'Generalized Anxiety Disorder–7 scale' (GAD–7) and the 'Patient Health Questionnaire-8' (PHQ-8). Its purpose is to allow for very brief and accurate measurement of depression and anxiety. Scores are rated as normal (0-2), mild (3-5), moderate (6-8), and severe (9-12).

- Emotional wellbeing (World Health Organization Well-Being Index [WHO-5]): The 5-item WHO-5 is a short and generic global rating scale measuring subjective well-being, contains 5 positively phrased statements/items. The respondent is asked to rate how well each of the 5 statements applies to him or her when considering the last 14 days. Each of the 5 items is scored from 5 (all of the time) to 0 (none of the time).

- Medication adherence and goal attainment (GAS-D): Goal attainment scaling (GAS) is a method of setting and evaluating goal achievement across different patient groups. This scale uses a semiquantitative approach incorporating a patient's individual expectations from treatment by assessing outcomes against specific, measurable, attainable, relevant, and time-bound (SMART) goals allowing for acceptable inter-rater reliability.

5. Data Analysis

This section described the how the data will be analysed for each objective that required quantitative synthesis. Due to the small sample size, a descriptive analysis will be conducted to describe treatment outcomes and adverse events of a treatment switch from SRT to ERT (VPRIV). No formal statistical hypothesis tests will be applied. All results will be dependant on the availability of the variables in the final sample and reported per patient.

Overview of the sample

The expected sample size for this study is 20 patients. Due to possible enrollement issues, the study may be completed before the target sample size is reached. The limited sample size requires that all data are summarised with descriptive statistics and and within-cohort comparisons are limited.

Continuous variables will be summarized as the number of observations (n), mean, SD, median (Q1 and Q3 percentiles), and minimum and maximum values. Categorical variables will be summarized as numbers and percentages of patients as described above. Endpoints and variables will be reported for baseline, Month 1, Month 3, and Month 12, depending on the objective. The final analysis may include the evaluation of exploratory objectives depending on data availability and as permitted by sample size and will be performed at the end of the data collection period once all data management procedures have been completed. The analyses will be undertaken using packages for statistical analysis STATA 16 (StataCorp. 2019. Stata Statistical Software: Release 16. College Station, TX: StataCorp LLC.).

Patient sociodemographic characteristics and clinical characteristics will be described at baseline. Variables for these are listed in **Table 3**, **Table 4** and **Table 5**, respectively. Overview of the sample will be reported for the overall population only.

Key demographics includes (full table in Appendix):

- Sex
- Age, years

- Height, cm
- Weight, kg
- BMI
- Ethnicity
- Smoking History, yes/no

Pregnancies details:

- Pregnancy status per time period (number of pregnancies)
- Number of treatment switches due to pregnancy

Key clinical variables at baseline (full table in Appendix as above):

- Medical history (including Splenectomy, Medullary bone infarcts, and Avascular necrosis)
- Diagnosis of GD (including methods used, genotype)
- Medication history:
    - SRT / ERT – drug name, duration of treatment, dose (IU/Kg; mg), frequency, reason for switch
    - Concomitant, and concurrent medication

Primary Objectives

Primary Objective 1: *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.*

All variables for Primary Objective 1 will be extracted as presented in **Table 6.** For each clinical parameter, a descriptive analysis of the following will be reported:

- The number and percentage of patients who meet and exceed pre-specified thresholds per clinical parameter overtime given treatment used (SRT or VPRIV) (see Section 4)
- The average percentage change per clinical parameter presented numerically and graphically overtime for:
    - The whole sample
    - For patients who exceed the threshold only

Specifically for BMD, Z-scores and T-scores will be reported at 3 months and up to 12 months; for lumbar spine and femur neck.

Secondary Objectives

Secondary Objective 1: *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.*

All variables for secondary objective 1 will be extracted as presented in **Table 7** and reported descriptively for:

- The number and percentage of patients experiencing AEs/SAEs (mild/moderate/severe)
    - In total
    - Overtime (baseline through to 12 months)
- The number and percentage of patients hospitalized
    - In total
    - Overtime (baseline through to 12 months)
- The number and percentage of deaths

Exploratory/Additional Analyses

Exploratory Objective 1: *Describe the change in treatment effect on glucosylsphingosine (Lyso-Gb1), CCL18, and Chitotrio-sidase following the transition from SRTs to ERT (VPRIV) or ERT to SRT and then to ERT (VPRIV).*

All variables for exploratory objective 1 will be extracted as presented in **Table 8.** For each clinical parameter, a descriptive analysis of the following will be reported:

- The average percentage change of the following clinical parameters presented numerically and graphically overtime (3 monthsand up to 12 months):
    - Glucosyl sphingosine (Lyso-Gb1)
    - CCL18
    - Chitotrio-sidase

Exploratory Objective 2: *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 GD specific measures).*

For each PRO, the following descriptive statistics will be reported:

- The number of patients who have completed each PRO
- The mean result of each PRO for the sample
- The change in PRO results overtime (baseline and up to 12 months) presented numerically and graphically

Exploratory Objective 3 and 4: Please see **Section 7** for the qualitative analysis methods.

6. Data Management

Missing Data

Exhaustive attempts will be made to ensure that data for the core variables is retrieved from the sites for entry into the Electronic Data Capture (EDC). Incomplete (i.e., missing) data will be reported, for all study variables. Baseline characteristics will be reported for the full cohort. Study endpoints will be analysed for those subjects with complete data. If applicable, a feasibility analysis may be conducted on the sample with missing responses and may inform sensitivity analyses. No imputation of missing responses will be conducted on the data.

Quality Control

Quality control of the data will be undertaken by the statistician assigned to the project. The statistician will undertake the analysis in accordance with the statistical analysis plan (SAP). Once each step in the SAP has been completed – the statistician will undertake a complete code review and quality check. This will ensure:

- Check adherence to requirements and specifications as per the SAP.
- Test and check the entire code including review of any errors in the log.

This step-wise is to ensure an on-going quality control rather than a complete code review being conducted at the end of the project. This process ensures that any changes or adjustments that need to be made to the code can be completed at an early stage and maintain a controlled development process.

7. Qualitative Analyses

Following the completion of the 'Post End of Study Remote Patient Qualitative Interviews' and the 'Post Study Remote HCP Qualitative Interview', the following 'Interpretative Phenomenological Analysis' analysis will take place across the following 2 stages:

1. Data coding stage, which will include:
    a. Familiarization with the data, reading transcriptions and notes, and/or listening to the audio dialogue in order to extract the main themes and ideas from the interviews.
    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. DeDoose software will be used to manage the creation of these top down and bottom up codes.

2. Data interpretation stage, which will include focused definition of the main concepts and mapping the ways in which different parts of the data are related to each other.

Following the completion of these stages a qualitative interview research report will be created and shared alongside the qualitative research interview transcripts.

8. References

1. Grabowski GA, Andria G, Baldellou A, Campbell PE, Charrow J, Cohen IJ, et al. Pediatric non-neuronopathic Gaucher disease: presentation, diagnosis and assessment. Consensus statements. Eur J Pediatr. 2004 Feb;163(2):58–66.

2. Grabowski GA, Petsko GA, Kolodny EH. The Online Metabolic and Molecular Bases of Inherited Disease. Gaucher Disease. 2013.

3. Charrow J, Esplin JA, Gribble TJ, Kaplan P, Kolodny EH, Pastores GM, et al. Gaucher disease: recommendations on diagnosis, evaluation, and monitoring. Arch Intern Med. 1998 Sep 14;158(16):1754–60.

4. Pastores GM, Weinreb NJ, Aerts H, Andria G, Cox TM, Giralt M, et al. Therapeutic goals in the treatment of Gaucher disease. Semin Hematol. 2004 Oct;41(4 Suppl 5):4–14.

5. Mistry PK, Weinreb NJ, Kaplan P, Cole JA, Gwosdow AR, Hangartner T. Osteopenia in Gaucher disease develops early in life: response to imiglucerase enzyme therapy in children, adolescents and adults. Blood Cells Mol Dis. 2011 Jan 15;46(1):66–72.

6. Goker-Alpan O. Therapeutic approaches to bone pathology in Gaucher disease: past, present and future. Mol Genet Metab. 2011 Dec;104(4):438–47.

7. Mistry PK, Weinthal JA, Weinreb NJ. Disease state awareness in Gaucher disease: a Q&A expert roundtable discussion. Clin Adv Hematol Oncol. 2012 Jun;10(6 Suppl 8):1–16.

8. Belmatoug N, Di Rocco M, Fraga C, Giraldo P, Hughes D, Lukina E, et al. Management and monitoring recommendations for the use of eliglustat in adults with type 1 Gaucher disease in Europe. Eur J Intern Med. 2017 Jan;37:25–32.

9. Revel-Vilk S, Szer J, Mehta A, Zimran A. How we manage Gaucher Disease in the era of choices. Br J Haematol. 2018 Aug;182(4):467–80.

10. Cox TM, Drelichman G, Cravo R, Balwani M, Burrow TA, Martins AM, et al. Eliglustat compared with imiglucerase in patients with Gaucher's disease type 1 stabilised on enzyme replacement therapy: a phase 3, randomised, open-label, non-inferiority trial. Lancet. 2015 Jun 13;385(9985):2355–62.

11. Elstein D, Dweck A, Attias D, Hadas-Halpern I, Zevin S, Altarescu G, et al. Oral maintenance clinical trial with miglustat for type I Gaucher disease: switch from or combination with intravenous enzyme replacement. Blood. 2007 Oct 1;110(7):2296–301.

12. Lukina E, Watman N, Dragosky M, Pastores GM, Arreguin EA, Rosenbaum H, et al. Eliglustat, an investigational oral therapy for Gaucher disease type 1: Phase 2 trial results after 4 years of treatment. Blood Cells Mol Dis. 2014 Dec;53(4):274–6.

13. Mistry PK, Lukina E, Ben Turkia H, Amato D, Baris H, Dasouki M, et al. Effect of oral eliglustat on splenomegaly in patients with Gaucher disease type 1: the ENGAGE randomized clinical trial. JAMA. 2015 Feb 17;313(7):695–706.

14. Pastores GM, Barnett NL, Kolodny EH. An open-label, noncomparative study of miglustat in type I Gaucher disease: efficacy and tolerability over 24 months of treatment. Clin Ther. 2005 Aug;27(8):1215–27.

15. Van Rossum A, Holsopple M. Enzyme Replacement or Substrate Reduction? A Review of Gaucher Disease Treatment Options. Hosp Pharm. 2016 Jul;51(7):553–63.

16. Vpriv (velaglucerase alfa for injection). 2010.

17. Kishnani PS, DiRocco M, Kaplan P, et al.. A randomized trial comparing the efficacy and safety of imiglucerase (Cerezyme) infusions every 4 weeks versus every 2 weeks in the maintenance therapy of adult patients with Gaucher disease type 1. *Mol Genet Metab*. 2009;96(4):164-17

18. Cox TM, Drelichman G, Cravo R, Balwani M, Burrow TA, Martins AM, Lukina E, Rosenbloom B, Goker-Alpan O, Watman N, El-Beshlawy A, Kishnani PS, Pedroso ML, Gaemers SJM, Tayag R, Peterschmitt MJ. Eliglustat maintains long-term clinical stability in patients with Gaucher disease type 1 stabilized on enzyme therapy. Blood. 2017 Apr 27;129(17):2375-2383. doi: 10.1182/blood-2016-12-758409. Epub 2017 Feb 6. PMID: 28167660; PMCID: PMC5409450.

9. Appendices:

Appendix 1: Extracted Variables: Demographic and Other Baseline Characteristics

The following variables will be collected for all patients:

Demographics and other baseline characteristics will be collected for all patients. The following will be collected: patient sociodemographic characteristics, pregnancy status, and clinical characteristics at baseline shown in **Table 3**, **Table 4**Table 4, and **Table** 5, respectively.

Table 3: Participant Sociodemographic Characteristics

Category/Variable	Variable definition	Type	Values of category/variable
Gender	Participant gender	Categorical	Male Female Unknown Other please specify:
Age	Participant age (years)	Continuous	-
Age	Participant age (years)	Categorical	18-29 30-44 45-64 ≥ 65
Height	Participant Height (feet and inch[es])	Continuous	-
Weight	Participant weight (lbs)	Continuous	-
BMI	Participant BMI Index	Categorical	
BMI	BMI will be calculated automatically by the EDC by using the following formula: $BMI = \frac{kg}{m^2}$ Where kg is patient weight in kilograms and m2 is the squared patient height in meters.	Categorical	Underweight: below 18.5 Healthy: 18.5 – 24.9 Overweight: 25 – 29.9 Obesity class I: 30 and above Obesity class II: 35.0 – 39.9 Obesity class III: Above 40

Category/Variable	Variable definition	Type	Values of category/variable
Race	Participant's race	Categorical	American Indian or Alaska Native Asian Black or African American Native Hawaiian or Other Pacific Islander White
Ethnicity	Participant's ethnicity	Categorical	Hispanic or Latino Not Hispanic or Latino
Smoking History	Participant smoking history	Categorical	Yes No

Table 4: Participant Pregnancy Status

Category/ Variable	Variable definition	Type of variable	Value of category/variable
Pregnancy Status (SRT baseline)	Participant's pregnancy status during their most recent SRT treatment phase	Categorical	Yes No No (Using birth control) Unknown
Pregnancy Status (ERT baseline)	Participant's pregnancy status during their transition to velaglucerase alfa (VPRIV)	Categorical	Yes No Unknown
Current pregnancy Status (Month 1)	Participant's current pregnancy status	Categorical	Yes No Unknown
Pregnancy Status during the past 12 months	Was the patient pregnant at any time in the last 12 months?	Categorical	Yes No Unknown
Pregnancy Details (SRT pregnancy or ERT pregnancy or at Month 1):	If participant was pregnant at any time during the past 12 months	Categorical	Currently pregnant Now post-partum: live birth Now post-partum: still birth

Category/ Variable	Variable definition	Type of variable	Value of category/variable
			Miscarriage Induced abortion Other
Pregnancy Status (Month 3, Month 6, Month 12)	Has the patient become pregnant since the last visit?	Categorical	Yes No Unknown
Pregnancy Progressing Status (Month 3, Month 6, Month 12)	Is the patient's pregnancy progressing normally?	Categorical	Pregnancy is progressing Miscarriage Induced abortion Now post-partum: live birth Now post-partum: Still birth

Table 5: Participant Clinical Characteristics at Baseline

Category/ Variable	Variable definition	Type of variable	Values of category/variable
Medical history			
Time since diagnoses	Time since diagnosis will be expressed in years and will be calculated by taking the difference between diagnosis year and quarter (mid-point+1) and the year and quarter (mid-point+1) of the event of interest.	Continuous	
Diagnosis Method	The method of Gaucher disease diagnosis used for the participant	Categorical	Deficient glucocerebrosidase (GCB) activity in leukocytes (whole blood only) DNA testing: GBA mutation analysis

			Enzyme activity Don't know Other
Genotype		Categorical	L444P / L483P (exclusion criterion – needs a hard check) F2131 F2521 R496H R535H D409H D488H N370S N409S Unknown Other
Splenectomy history	Has the patient ever had a splenectomy?	Categorical	Yes No
Medullary bone infarcts	Has the patient experienced medullary bone infarcts?	Categorical	Yes No
Avascular necrosis	Participant's avascular necrosis history	Categorical	Yes No
Avascular necrosis time experienced	How long was the Avascular necrosis episode?	Continuous	Start date/ End date Ongoing
Medication history: SRT history (SRT baseline)			
Drug (product) used	SRT product	Categorical	Cerdelga (Eliglustat) Zavesca (Miglustat) Other
Treatment Duration	Number of days a patient is on the specified drug measured in days	Continuous	
Dose of SRT (mg)	Dose of drug used before the switch	Continuous	

Frequency of treatment	Frequency of drug administration	Categorical	Daily Twice per day Three times per day Other
Reason for treatment switch	Reason for the Participant's treatment switch	Categorical	Lack of efficacy/ poor half-life Product availability/ reimbursement Patient request Tolerability/ side effects Allergic reaction Thrombotic events Cardiac events Fatigue, bone pain Concomitant conditions that prohibit use of SRT Drug Interactions Other
ERT treatment use	Was ERT treatment used prior to most recent SRT treatment administration?	Categorical	Yes No
Treatment gap	Treatment gap between ERT and SRT initiation	Categorical	Immediately After 2 weeks After 1 month Other
ERT Drug (product) used	ERT	Categorical	Cerezyme (Imiglucerase) Elelyso (Taliglucerase alfa) Other
Treatment Duration	Number of days a patient is on the specified drug measured in days	Continuous	
Dose	Dose of ERT drug used prior to SRT (mg)	Continuous	
Frequency of treatment	Frequency of drug administration	Categorical	Daily Twice per day

			Three times per day Other
ERT anti-drug antibodies	Participant's history of developing anti-drug antibody	Categorical	Yes No
Reason for treatment switch	Reason for the Participant's treatment switch	Categorical	Lack of efficacy/ poor half-life Product availability/ reimbursement Patient request Tolerability/ side effects Allergic reaction Thrombotic events Cardiac events Fatigue, bone pain Concomitant conditions that prohibit use of SRT Drug Interactions Other
Medication history: ERT history (ERT baseline)			
Treatment Dose (Velaglucerase alfa - VPRIV)	Dose of VPRIV used (IU/Kg)	Continuous	
Frequency of treatment (VPRIV)	Frequency of drug administration	Categorical	Weekly Every other week Daily Other
Place of drug administration (VPRIV)	Where does the patient usually receive infusions?	Categorical	At clinic At home Other
Ongoing Velaglucerase alfa (Month 3, Month 6, Month 12)			
Treatment Duration (VPRIV)	Number of days a patient is on the specified drug measured in days	Continuous	
Treatment Dose (VPRIV)	Dose of VPRIVused (IU/Kg)	Continuous	

Frequency of treatment (VPRIV)	Frequency of VPRIV administration	Categorical	Every other week Other
Current use of VPRIV	Participant's currently on VPRIV	Categorical	Yes No
Missed Dose	Participant missed dose of VPRIV	Categorical	Yes No
Number of missed dose	Missed dose since last visit	Continuous	
Change in dose	Change in dose	Categorical	Yes No
Change in frequency	Change in frequency	Categorical	Yes No
Anti-drug antibody collection	Anti-drug antibody collection status	Categorical	Yes No
Details of anti-drug antibody collection	Details of anti-drug antibody collection	Continuous	Lab name Lab city Lab state unknown
Anti-drug antibody Parameters			
Concomitant / Concurrent* Medication (Month 1)			
Concomitant medication (during SRT)	Participant received any concomitant medication *(during their most recent SRT treatment phase)*	Categorical	Yes No
Concomitant medication (during VPRIV)	Participant received any concomitant medication *(during their most recent VPRIV treatment phase)*	Categorical	Yes No

Concomitant medication (Current)	Participant receiving any concomitant medication currently	Categorical	Yes No
Concomitant medication details	Additional medication details taken		• Indication • Diagnosis date • SRT or ERT use • Drug name • Start and end date • Dose • Administration method • Frequency
Concomitant / Concurrent* Medication (Month 3, Month 6, and Month 12)			
Concomitant medication (since last visit)	Participant received any concomitant medication since last visit	Categorical	Yes No
Concomitant medication details	Additional medication details taken		• Indication • Diagnosis date • SRT or ERT use • Drug name • Start and end date • Dose • Administration method • Frequency

*Ongoing conditions are considered concurrent medical conditions

Appendix 2: Extracted Variables: Primary Objective

Primary Objective 1: *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 realworld setting among adults.*

The variables listed in **Table 6** will be extracted to address the Primary Objective 1.

Table 6: Variables extracted for Primary Objective 1: Spleen and liver volume, hemoglobin level, and platelet count at baseline and 12 month of observational period

Category/ Variable	Variable definition	Type of variable	Values of category/variable
Hematology/Chemistry			
Hemoglobin test done	Hemoglobin test was done	Categorical	Yes No
Hemoglobin level	Hemoglobin level (g/L)	Continuous	
Hemoglobin result	Hemoglobin test was abnormal	Categorical	Yes No
Hemoglobin result significance	Hemoglobin abnormality was clinically significant	Categorical	Yes No
Platelet test done	Platelet test was done	Categorical	Yes No
Platelet count	Platelet level (*10^9/L)	Continuous	
Platelet count result	Platelet test was abnormal	Categorical	Yes No
Platelet count result significance	Platelet abnormality was clinically significant	Categorical	Yes No
BMD, Liver, and Spleen Volume			
BMD test done	BD test was done	Categorical	Yes No
BMD	BMD (g/cm^2)	Continuous	
BMD result	BMD was abnormal	Categorical	Yes No

BMD result significance	BMD abnormality was clinically significant	Categorical	Yes No
BMD test method	BMD test method	Categorical	DEXA Other
Liver volume test done	Liver volume test was done	Categorical	Yes No
Liver volume	Liver volume (cm^3)	Continuous	
Liver volume result	Liver volume was abnormal	Categorical	Yes No
Liver volume significance	Liver volume abnormality was clinically significant	Categorical	Yes No
Liver volume test method	Liver volume test method	Categorical	MRI Other
Spleen volume test done	Spleen volume test was done	Categorical	Yes No
Spleen volume	Spleen volume (cm^3)	Continuous	
Spleen volume result	Spleen volume was abnormal	Categorical	Yes No
Spleen volume significance	Spleen volume abnormality was clinically significant	Categorical	Yes No
Spleen volume test method	Spleen volume test method	Categorical	MRI Other
BMD Z-scores and T-scores (SRT baseline, Month 12)			
Lumbar Spine			
T-score test done	T-score test was done	Categorical	Yes No
T-score	T-score	Continuous	
T-score result	T-score was abnormal	Categorical	Yes No

T-score result significance	T-score abnormality was clinically significant	Categorical	Yes No
Z-score test done	Z-score test was done	Categorical	Yes No
Z-score	Z-score	Continuous	
Z-score result	Z-score was abnormal	Categorical	Yes No
Z-score result significance	Z-score abnormality was clinically significant	Categorical	Yes No
BMD done	BMD test was done	Categorical	Yes No
BMD	BMD (g/cm^2)	Continuous	
BMD result	BMD was abnormal	Categorical	Yes No
BMD result significance	BMD abnormality was clinically significant	Categorical	Yes No
Femur Neck			
T-score test done	T-score test was done	Categorical	Yes No
T-score	T-score	Continuous	
T-score result	T-score was abnormal	Categorical	Yes No
T-score result significance	T-score abnormality was clinically significant	Categorical	Yes No
Z-score test done	Z-score test was done	Categorical	Yes No
Z-score	Z-score	Continuous	
Z-score result	Z-score was abnormal	Categorical	Yes No
Z-score result significance	Z-score abnormality	Categorical	Yes No

	was clinically significant		
BMD done	BMD test was done	Categorical	Yes No
BMD	BMD (g/cm^2)	Continuous	
BMD result	BMD was abnormal	Categorical	Yes No
BMD result significance	BMD abnormality was clinically significant	Categorical	Yes No

Appendix 3: Extracted Variables: Secondary Objectives

The following variables will be extracted for all patients to address the secondary objectives:

Secondary Objective 1: *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.*

Table 7 list the variables that will be extracted to analyse and report adverse events.

Table 7: Variables extracted for adverse events.

Category/ Variable	Variable definition	Type of variable	Values of category/variable
Event category	Event category	Categorical	Adverse Event Serious Adverse Event
Event name	Event name	Categorical	Dizziness Headache Abdominal pain Nausea Arthralgia Back pain Bone pain Upper respiratory tract infections Activated partial thromboplastin time prolonged Neutralizing antibody positive

			Asthenia/fatigue Infusion-related headache Infusion-related dizziness Infusion-related hypotension Infusion-related hypertension Infusion-related nausea Infusion-related fatigue/asthenia Infusion-related pyrexia/body temperature increased Infusion-related chest discomfort Infusion-related dyspnea Infusion-related pruritis Pyrexia/body temperature increased Flushing Hypertension Hypotension Tachycardia Rash Urticaria Hypersensitivity reactions: Dermatitis Hypersensitivity reactions: Anaphylaxis Other
Event Status	Event Status - Ongoing?	Categorical	Yes No
Event Severity	Event Severity	Categorical	Mild Moderate Severe
Event duration	Event duration (days)	Continuous	
Disability status	Participant experienced persistent or significant disability or	Categorical	Yes No

	incapacity as a result of the adverse event?		
Death	Participant died?	Categorical	Yes No
Hospitalisation	Initial or Prolonged Hospitalisation due to this event?	Categorical	Yes No
Hospitalisation duration	Hospitalisation duration (days)	Continuous	Number of days or ongoing
Life threatening event	The event was life threatening?	Categorical	Yes No
Treatment for the event	Treatment given for the event	Categorical	None Medication Non-medication Both medication and non-medication
Relationship to standard of care treatment	Relationship to standard of care treatment	Categorical	Related Possible Probable Unlikely Unknown/ unassessable Not related Not reported
Action taken with standard of care drug	Action taken with standard of care drug	Categorical	Dose Increased Dose Not Changed Dose Reduced Drug interrupted Drug Withdrawn Drug replaced with another ERT Not applicable Unknown
If treatment was interrupted: Duration of time off-treatment	Duration of time off-treatment (says)	Continuous	

Outcome of the adverse event	Outcome of the adverse event	Categorical	Fatal Not Recovered/ Not Resolved Recovered/ Resolved Recovered/ Resolved with Sequelae Recovering/ Resolving Unknown

Appendix 4: Extracted Variables: Exploratory Objectives

Exploratory Objective 1: *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).*

Variables listed in **Table 8** will be extracted to address this objective.

Table 8: Variables extracted for exploratory objective 1

Category/ Variable	Variable definition	Type of variable	Values of category/variable
Glucosyl sphingosine (Lyso-Gb1) test done	Glucosyl sphingosine (Lyso-Gb1) test was done	Categorical	Yes No
Glucosyl sphingosine (Lyso-Gb1) value	Glucosyl sphingosine (Lyso-Gb1) plasma value (ng/ml)	Continuous	
Glucosyl sphingosine (Lyso-Gb1) result	Glucosyl sphingosine (Lyso-Gb1) was abnormal	Categorical	Yes No
Glucosyl sphingosine (Lyso-Gb1) result significance	Glucosyl sphingosine (Lyso-Gb1) abnormality was clinically significant	Categorical	Yes No
Lab name	Lab name	Continuous	
Lab's normal range	Lab's normal range for this test	Continuous	
CCL18 test done	CCL18 test was done	Categorical	Yes No
CCL18 value	CCL18 value (ng/ml)	Continuous	
CCL18 result	CCL18 was abnormal	Categorical	Yes No
CCL18 result significance	CCL18 abnormality was clinically significant	Categorical	Yes No

Lab name	Lab name	Categorical	Takeda Lab Services PerkinElmer Genomics Lab Corp Quest Diagnostics Bio-Reference Laboratories Genoptix Medical Laboratory ARUP Laboratories Clarient Inc. (NeoGenomics) Other
Lab's normal range	Lab's normal range for this test	Continuous	
Chitotrio-sidase test done	Chitotrio-sidase test was done	Categorical	Yes No
Chitotrio-sidase value	Chitotrio-sidase value (ng/ml)	Continuous	
Chitotrio-sidase result	Chitotrio-sidase was abnormal	Categorical	Yes No
Chitotrio-sidase result significance	Chitotrio-sidase abnormality was clinically significant	Categorical	Yes No
Lab name	Lab name	Categorical	Takeda Lab Services PerkinElmer Genomics Lab Corp Quest Diagnostics Bio-Reference Laboratories Genoptix Medical Laboratory ARUP Laboratories Clarient Inc. (NeoGenomics) Other
Lab's normal range	Lab's normal range for this test	Continuous	

Lyso-Gb1 FP-DBS lab results (Month 1, Month 3, Month 6, Month 12)			
Glucosyl sphingosine (Lyso-Gb1) test done	Glucosyl sphingosine (Lyso-Gb1) test was done	Categorical	Yes No
Glucosyl sphingosine (Lyso-Gb1) value	Glucosyl sphingosine (Lyso-Gb1) plasma value **(ng/ml)**	Continuous	
Glucosyl sphingosine (Lyso-Gb1) result	Glucosyl sphingosine (Lyso-Gb1) was abnormal	Categorical	Yes No
Glucosyl sphingosine (Lyso-Gb1) result significance	Glucosyl sphingosine (Lyso-Gb1) abnormality was clinically significant	Categorical	Yes No

Exploratory Objective 2: *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 GD specific measures).*

Table 9: Variables extracted for exploratory objective 2

Category/ Variable	Variable definition	Type of variable	Values of category/variable

Exploratory Objective 3: *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.*

Exploratory Objective 4: *Remote qualitative assessments will be conducted to assess HCP reactions to the mobile application to inform further development of a digital tool in GD.*