SANOFI GENZYME

AMENDED NON-INTERVENTIONAL POST AUTHORIZATION SAFETY STUDY (PASS) PROTOCOL NO. 04

COMPOUND: eliglustat

A prospective multicenter observational post authorization safety sub-registry to characterize the long-term safety profile of commercial use of eliglustat (Cerdelga®) in adult patients with Gaucher disease

STUDY NUMBER: OBS14099

STUDY NAME: ELISAFE

VERSION DATE/STATUS: 03-Dec-2020/Approved

The Study is conducted by Sanofi Genzyme hereinafter referred also as “MAH/MAH representative”.

Version Number:	1	EudraCT IND Number(s) WHO universal trial number:	not applicable not applicable not applicable
Date:	03-Dec-2020	Total number of pages:	58

PROTOCOL AMENDMENT SUMMARY OF CHANGES

DOCUMENT HISTORY

Document	Country/countries impacted by amendment	Date, version
Amended PASS Protocol 04	All	03-Dec-2020, version 1 (electronic 7.0)
Amended PASS Protocol 04	All	31-Jul-2020, version 1 (electronic 6.0) for review
Amended PASS Protocol 03	All	19-Dec-2019, version 1 (electronic 5.0)
Amended PASS Protocol 02	All	11-Sep-2018, version 1 (electronic 4.0)
Amended PASS Protocol 01	All	27-Mar-2017, version 1 (electronic 3.0)
Protocol Amendment 01	All	27-Mar-2017, version 1 (electronic 1.0)
Clinical Trial Protocol		18-Jan-2017, version 1 (electronic 2.0)

Amended protocol 04 (03 December 2020)

This amended protocol (amendment 04) is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

OVERALL RATIONALE FOR THE AMENDMENT

Amended protocol 03 and amended protocol 04 (version 1 [electronic 6.0] for review) submitted to the European Medicines Agency via the procedure EMEA/H/C/PSA/S/0054 were not endorsed by the Pharmacovigilance Risk Assessment Committee (PRAC). Marketing Authorization Holder (MAH) was requested to revise the amended protocol 03 and amended protocol 04 (version 1 [electronic 6.0] for review) in line with the PRAC Assessment Report dated 11 June 2020 and 29 October 2020, respectively.

Amended protocol 04 (version 1 [electronic 7.0]), dated 03-Dec-2020 includes the revised proposal for data collection:

- Revised proposal for end of data collection: data collection will be concluded four years after the last Cerdelga patient has been enrolled in the study, at which time the analysis will be performed. An interim analysis will be performed two years after the last Cerdelga patient has been enrolled in the study and an interim report of study results will be submitted subsequently.

- Revised proposal for annual evaluation of the number of patients: The number of patients from both of the groups who continue their observation in the safety sub-registry will be evaluated annually after the end of the recruitment period to determine the need to replace patients who dropped out of the study for any reason. The need to continue this requirement will be reassessed two years after the last Cerdelga patient has been enrolled in the study in the interim report.

Additionally, a secondary analysis/endpoint of change from the initial clinically significant abnormal laboratory results proposed in the amended protocol 03 has been removed for the current revised protocol.

Protocol amendment summary of changes table

Section # and Name	Description of Change	Brief Rationale
Section 4, Abstract, Variables, Analysis of endpoint; Section 8.2.3, Analysis population(s); Section 8.8, Data Analysis	Revised text (replacement of "adjusted for" by "considering") to specify that the main analysis of interest will be the incidence rate of any AE report for Cerdelga treated patients during participation in the sub-registry, **considering** treatment status at sub-registry enrollment (if applicable).	Clarification ("adjustment" was a statistical term dedicated to comparisons).
Section 4, Abstract, Analysis of endpoint	Revised text to specify that the primary endpoint will be the incidence rate of any AE report for Cerdelga treated patients during participation in the sub-registry, considering treatment status at sub-registry enrollment (if applicable).	To align with Section 8.8, Data analysis.
Section 4, Abstract, Data analysis, Analysis of endpoint; Section 8.8.2, Secondary Analysis	Removal of secondary analysis/endpoint: change from the initial clinically significant abnormal laboratory results.	As noted by the PRAC, the analysis is part of the ICGG Gaucher Registry.
Section 4, Abstract, Data analysis; Section 5, Milestones; Section 8.8.4, Interim Analysis	Revised text to specify that interim analysis is planned two years after the last Cerdelga patient has been enrolled in the study.	To reflect amendment specific changes - to align with the revised proposal for end of data collection.
Section 4, Abstract, Milestones; Section 5, Milestones; Section 8.2, Setting; Section 8.2.1, Duration of the study	Revised proposal for end of data collection: Data collection will be concluded four years after the last Cerdelga patient has been enrolled into the study.	Extension of enrollment period by approximately one year to enroll more Cerdelga patients than originally planned and duration of safety follow up ranging from 4 years to up to 6.5 years will provide long-term safety data on Cerdelga for a sufficient number of patients.

Section # and Name	Description of Change	Brief Rationale
Section 4, Abstract, Milestones; Section 5, Milestones; Section 8.2, Setting; Section 8.2.1, Duration of the study; 8.10, Limitations of the research methods	The following text was revised to: The number of patients from both of the groups who continue their observation in the safety sub-registry will be evaluated annually after the end of recruitment period to determine the need to replace patients who dropped out of the study for any reason. The need to continue with this requirement will be reassessed two years after the last Cerdelga patient has been enrolled in the study in the interim report.	To reflect amendment-specific changes.
Section 5, Milestones	Updated recruitment duration to 32 months and expected date of the end of date collection to Q1 2025. Updated the expected date of final report of study results to Q3 2025.	To reflect amendment specific changes - to align with the revised proposal for end of data collection.
Section 8.2, Setting; Section 8.2.3, Analysis population(s); Section 8.8, Data analysis	Text specifying that additional patients will be recruited for patients who switch from the Cerdelga to the Cerezyme group was removed.	To reflect the amendment-specific changes.
Section 8.3 Variables; Section 8.4, Statistical Analysis	Removed text regarding “change from the initial” abnormal laboratory results.	Consistency with removal of secondary analysis/endpoint.
Section 8.6.1, Determination of sample size	Revised text to specify true “cumulative” rate as follows: “With 100 patients on Cerdelga, there is more than 95% of probability of observing at least one patient with an AE if the true **cumulative** rate of such an event is 5%.”	Precision.
Section 10.1.3.2, Adverse Event reporting to MAH/MAH representative	Updated text to specify that copies of medical records may be requested by the Sponsor. In such case the photocopy of requested documents should be sent (by fax or email) to MAH/MAH representative.	Consistency with current Sponsor process (simplification and standardization to the current clinical safety data flow).
Throughout	Typos have been corrected where necessary.	Clarifications.
Throughout	Minor editorial and document formatting revisions.	Minor, therefore have not been summarized.

NAMES AND ADDRESSES OF

STUDY MANAGEMENT	Name: Address: Tel: Fax: E-mail:	
COUNTRY TEAM'S REPRESENTATIVE	Name: Address: Tel: Fax: E-mail:	
PHARMACOVIGILANCE	QPPV Name: Address: Tel: Fax: E-mail:	[redacted]
SCIENTIFIC COMMITTEE CHAIR PERSON	Name: Address: Tel: Fax: E-mail:	No Scientific Committee is planned for this study.
MAH/MAH REPRESENTATIVE	MAH/MAH representative: Address: Tel: Fax:	NA

PASS Information

Title	A prospective multicenter observational post authorization safety sub-registry to characterize the long-term safety profile of commercial use of eliglustat (Cerdelga) in adult patients with Gaucher disease.
Protocol version identifier	4
Date of last version of protocol	11 Sep 2018
EU PAS register number	ENCEPP/SDPP/11998
Active substance	Eliglustat, ATC code: A16AX10
Medicinal product	eliglustat (Cerdelga)
Product reference	EU/1/14/974/001 -003
Procedure number	EMEA/H/C/003724
Marketing authorization holder(s)	Genzyme Europe B.V. Paasheuvelweg 25 - 1105 BP AMSTERDAM - The Netherlands
Joint PASS	"No"
Research question and objectives	Primary objectives: 1. To evaluate the long-term safety of Cerdelga in real-world clinical practice 2. To describe the utilization of Cerdelga: - To assess compliance/adherence of Health Care Providers (HCP) to the labelling with regard to CYP2D6 (Cytochrome P450 2D6) genotyping prior to initiation of Cerdelga - To assess compliance/adherence of HCPs to the Cerdelga label with regard to patients' CYP2D6 predicted phenotype - To assess compliance/adherence of HCPs to the Cerdelga label with regard to use in Gaucher disease (GD) type 1.
Country(-ies) of study	Patients will be recruited from sites in countries where Cerdelga is already on the market or will become available on the market during the sub-registry enrollment period.
Author	[redacted]

Marketing authorization holder(s)

Marketing authorization holder(s)	Genzyme Europe B.V. Paasheuvelweg 25 - 1105 BP AMSTERDAM - The Netherlands
MAH/MAH representative contact person	[redacted]

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2 LIST OF ABBREVIATIONS

AE:	Adverse Event
AESI:	Adverse event of special interest
ADR:	Adverse Drug Reaction
CRF:	Case Report Form
e-CRF:	Electronic Case Report Form
EM:	Extensive Metabolizer
EMA:	European Medicines Agency
ENCePP:	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
ERT:	Enzyme Replacement Therapy
EU:	European Union
GD:	Gaucher Disease
GPV:	Global Pharmacovigilance
CYP2D6:	Cytochrome P450 2D6
CYP3A:	Cytochrome P450 3A
HCP:	Health Care Provider
ICGG:	International Collaborative Gaucher Group
IEC:	Independent Ethics Committee
IM:	Intermediate Metabolizer
IRB:	Institutional Review Board
MAH:	Marketing Authorization Holder
PASS:	Post Authorization Safety Study
PM:	Poor Metabolizer
PSUR:	Periodic Safety Update Report
RMP:	Risk Management Plan
P-gp:	P-glycoprotein
PRAC:	Pharmacovigilance Risk Assessment Committee
SAE:	Serious Adverse Event
SRT:	Substrate Reduction Therapy
URM:	Ultra-rapid metabolizer

3 RESPONSIBLE PARTIES

Genzyme Europe B.V. is the holder of the market authorization for Cerdelga and Cerezyme. This safety sub-registry is a sub-registry of the ICGG (International Collaborative Gaucher Group) Gaucher Registry (DIREGC07009). The governance and scientific direction of the ICGG Gaucher Registry is provided by International and Regional Boards of Advisors. The ICGG Gaucher Registry and sub-registry are sponsored logistically and financially by Sanofi Genzyme.

The role of the ICGG Board is:

- Review and provide feedback on the Protocol proposal, as per European Medicines Agency (EMA) request
- Endorse and support sub-registry implementation

Investigators for the safety sub-registry will be chosen among sites within the ICGG Gaucher Registry and in countries where Cerdelga will be available on the market.

4 ABSTRACT

Title: A prospective multicenter observational post authorization safety sub-registry to characterize the long-term safety profile of commercial use of eliglustat (Cerdelga) in adult patients with Gaucher disease.

Rationale and background

This sub-registry is set up to complement the ICGG Gaucher Registry, a multi-center, international, longitudinal, observational program for patients with Gaucher disease (GD) designed to track the natural history of the disease, and outcomes of patients on GD treatments. Similarly, using the same ICGG technology platform, the sub-registry is designed to follow patients on Cerdelga and Cerezyme and in particular assess the long-term safety profile of Cerdelga and descriptively compare it with Cerezyme by collecting real-world safety data as part of a post approval commitment.

Though the studies supporting the registration of Cerdelga have continued to collect data for multiple years (up to 8 years for the Phase 2 study), an extended follow-up of patients treated in real-world clinical practice will support the longer-term safety of Cerdelga.

Clinical studies with Cerdelga have demonstrated a favorable benefit-risk profile, with robust efficacy results and a treatment that was generally well-tolerated across the clinical program. However, safety concerns were identified and include important potential risks and missing information.

Important potential risks:

- Drug-drug interactions:
  - Use with CYP2D6 (Cytochrome P450 2D6) and/or CYP3A (Cytochrome P450 3A) inhibitors
  - Use with strong CYP3A inducers
  - Use with P-glycoprotein (P-gp) or CYP2D6 substrates
- Use of Cerdelga in patients who are CYP2D6 indeterminate metabolizers or non-genotyped patients
- Cardiac conduction disorders and arrhythmias

Missing information:

- Use in patients with a history of or current cardiac ischemia or heart failure, clinically significant arrhythmias or conduction findings
- Use during pregnancy and lactation
- Safety in long-term treatment use
- Use in patients who are CYP2D6 ultra-rapid metabolizers (URMs)

Available published and unpublished data related to gaps in knowledge reflect the current information presented above and in the European Union (EU) Risk Management Plan (RMP).

The sub-registry will allow assessment of clinical practice and prescribing patterns, the adherence of prescribing Health Care Provider (HCPs) to Cerdelga key label (prescribing information) requirements, and will provide data to assess the effectiveness of risk minimization measures.

As the sub-registry is a voluntary program, the total number of patients who will participate and the total number of person-years of follow-up are not pre-defined, as not all patients have been identified, nor will all patients who could meet the study criteria wish to participate. The sub-registry database has been designed to collect a variety of baseline and follow-up data obtained through routine clinical and laboratory assessments in the ICGG Gaucher Registry database. In contrast with the ICGG Gaucher Registry where only Adverse Drug Reactions (ADRs, ie, adverse events (AEs) considered drug-related) to be reported by the treating physician, all AEs that occur during sub-registry participation, regardless of relationship to treatment, should be collected and reported in this safety sub-registry.

Research question and objectives

Primary objectives:

1. To evaluate the long-term safety of Cerdelga in real-world clinical practice
2. To describe the utilization of Cerdelga:
    - To assess compliance/adherence of HCPs to the labelling with regard to CYP2D6 genotyping prior to initiation of Cerdelga
    - To assess compliance/adherence of HCPs to the Cerdelga label with regard to patients' CYP2D6 predicted phenotype
    - To assess compliance/adherence of HCPs to the Cerdelga label with regard to use in GD type 1.

Study design

This is a safety sub-registry of the ICGG Gaucher Registry (DIREGC07009).

This is a non-interventional, international, multicenter, prospective Post Authorization Safety Study (PASS) of Cerdelga, a treatment approved in many countries for adult patients with GD1 who have a CYP2D6 Poor Metabolizer (PM), Intermediate Metabolizer (IM), or Extensive Metabolizer (EM) phenotype. The study will enroll patients who will be receiving Cerdelga or Cerezyme for the first time or as part of ongoing treatment of their GD. At least 100 patients enrolled will be on Cerdelga. Patients will receive treatment as determined by the patient's HCP and guided by the provisions of the prevailing locally approved product labelling and educational materials, and the ICGG Gaucher Registry recommendations for patient monitoring.

Population

The target study population will include adult patients who are treated with, or plan to be treated with Cerdelga or Cerezyme as part of routine management of their GD.

Inclusion Criteria:

I 01. Male or female patient aged 18 years or older;

I 02. The patient must be enrolled in the ICGG Gaucher Registry prior to safety sub-registry enrollment;

I 03. The patient is willing and able to provide written informed consent for the safety sub-registry;

I 04. The patient must have a confirmed diagnosis of GD, as defined in the protocol of the ICGG Gaucher Registry (documented acid ß-glucosidase deficiency and/or mutations in the acid ß-glucosidase gene);

I 05. The patient must either initiate or continue treatment with Cerdelga or Cerezyme at the time of safety sub-registry enrollment.

Exclusion Criteria:

E 01. The patient is concurrently enrolled in another clinical study; or participates in the compassionate use program with Cerdelga.

E 02. The patient is treated with both Cerezyme and Cerdelga at the time of enrollment, or investigator consider treating patient with both therapies concurrently at any time during participation in the safety sub-registry.

Variables

The outcome variable will be a report of an AE, exposure will be duration (in months or years) of time of exposure to Cerdelga while enrolled in the sub-registry, grouping factors will include category of Treatment Status (defined below), duration of GD treatment (including Cerdelga or other GD treatments) prior to enrolling in the sub-registry, selected demographic and baseline characteristics such as age, sex, and genotype as listed in Section 8.7.5.

Patients treatment status will be defined at the time of sub-registry enrollment in three categories:

a) Patients naive to any GD treatment (Enzyme Replacement Therapy [ERT] or Substrate Reduction Therapy [SRT]). This category will include, for example, newly diagnosed patients.

b) Patients naive to the product of interest (Cerdelga in the Cerdelga group and Cerezyme in the comparator group) but experienced to any other treatment for GD (ERT or SRT). This category will include, for example, patients who will switch from any one therapy to the product of interest.

c) Patients experienced to the product of interest. This category will include patients who were on treatment with the product of interest at the entry in the sub-registry and then continue this therapy.

The main analysis of interest will be the incidence rate of any AE report for Cerdelga-treated patients during participation in the sub-registry, considering treatment status at sub-registry enrollment (if applicable). Similar calculations will be performed for the Cerezyme-treated patients. Summaries will also be presented for three treatment status categories within each of the Cerdelga and Cerezyme groups (if applicable).

Frequencies and percentages of timing of CYP2D6 genotyping, CYP2D6 predicted phenotypes and GD subtype among Cerdelga-treated patients will be presented.

For all AEs summary statistics, frequencies, cumulative incidence, and incidence rates per person-time will be calculated as appropriate.

All summaries will be descriptive. No formal hypothesis testing will be performed.

When available, AEs reported by the patient and in the opinion of investigator related to Cerdelga intake and Cerezyme administration (prior to enrollment into the safety sub-registry) will be collected as part of the patient enrollment characteristics (medical history).

Data Sources

Data will be collected from enrolled patients by participating HCPs at the time of all patient office visits occurring as per local practice visit schedule or following the recommended schedule of assessments of the ICGG Gaucher Registry. If a patient temporarily stops (for any reason) the treatment with Cerdelga or Cerezyme and the treating physician considers that the treatment can be potentially restarted, the patient can stay in the sub-registry as long as the sub-registry is open, the patient is willing to participate and is available for follow-up assessments. Collection of all AEs will be continued for the duration of 30 days after stopping Cerdelga or Cerezyme, and after that period only new Serious Adverse Events (SAEs) will be collected and follow-up of ongoing AEs will be performed. Collection of all AEs in ELISAFE will be resumed when the patient restarts treatment with Cerdelga or Cerezyme. Information that is shared by the Registry and sub-registry will be collected only once. Information specific to the sub-registry will be collected in specifically designed case report forms (CRFs). Data collected by sub-registry HCPs or their designees will be submitted to the sub-registry for central processing and evaluation.

Study size

The sample size of at least 100 patients on Cerdelga was chosen to provide a sufficient number of patients to describe the real-world safety profile of Cerdelga and was not empirically derived. It is a similar size (n=106) to the number of Cerdelga patients treated in the primary analysis period of the ENCORE registration study (1) which was a direct comparison of Cerdelga to Cerezyme and should then confirm the safety profile experienced in a real-world setting. Accordingly, a control group of safety sub-registry to descriptively compare the safety profile of Cerdelga to that of Cerezyme will include approximately 50 patients on Cerezyme.

Based on the treatment experienced patients in the ENCORE study, the risk ratio of any AE comparing Cerdelga to Cerezyme is expected to be approximately 1.2.

Data analysis

Analysis will be performed on the Safety Set, defined as all patients enrolled in the sub-registry who have received at least one dose of Cerdelga or Cerezyme following enrollment. The analysis will be performed for each treatment group and overall (where appropriate) by treatment status (if applicable).

Primary analysis

- Incidence rate of any AE.
- Frequencies and percentages of timing of CYP2D6 genotyping (prior to or following) initiation of Cerdelga.
- Frequencies and percentages of CYP2D6 predicted phenotype among Cerdelga-treated patients.
- Frequencies and percentages of types of GD among Cerdelga-treated patients.

Secondary analysis

- Incidence rate of any SAE.

Exploratory analysis

- Frequencies and percentages of AEs related to risks defined in RMP as important potential risks (if available).

Interim analysis

One interim analysis is planned two years after the last Cerdelga patient has been enrolled in the study.

Analysis of endpoint:

The main analysis of interest will be the incidence rate of any AE report for Cerdelga-treated patients during participation in the sub-registry, considering treatment status at sub-registry enrollment (if applicable). Similar calculations will be performed for the Cerezyme-treated patients.

Primary endpoint: The incidence rate of any AE report for Cerdelga-treated patients during participation in the sub-registry, considering treatment status at sub-registry enrollment (if applicable).

Secondary endpoints: SAEs will be summarized as above.

Exploratory endpoints: Adverse events related to risks defined in the RMP as important potential risks.

Milestones

There is no set duration of participation in the study. Patients can remain in the sub-registry as long as they receive Cerezyme or Cerdelga and as long as the sub-registry remains open. The number of patients for both of the groups who continue their observation in the safety sub-registry will be evaluated annually after the end of the recruitment period to determine the need to replace patients who dropped out for any reason. The need to continue this requirement will be reassessed two years after the last Cerdelga patient has been enrolled in the study in the interim report. Data collection will be concluded four years after the last Cerdelga patient has been enrolled in the study, at which time the analysis will be performed.

5 MILESTONES

The milestones have been tied to events instead of date because the milestones are very much dependent on activities outside the control of the Marketing Authorization Holder (MAH)/MAH representative and it is difficult to assign specific dates.

- It is the aim of the Sanofi Genzyme to start the study approximately 6 months after Pharmacovigilance Risk Assessment Committee (PRAC) protocol approval has been obtained. The study start date is, however, also dependent on when physicians will input data into the study, which is outside of Sanofi Genzyme's control.
- There is no set duration of participation in the study; patients can remain in the sub-registry as long as they receive Cerezyme or Cerdelga and as long as the sub-registry remains open.
- The number of patients for both of the groups who continue their observation in the safety sub-registry will be evaluated annually after the end of the recruitment period to determine the need to replace patients who dropped out of the study for any reason. The need to continue with this requirement will be reassessed two years after the last Cerdelga patient has been enrolled in the study in the interim report.
- The AEs reported for the patients enrolled in the ICGG sub-registry will be reported in the Periodic Safety Update Reports (PSURs) in the EU regional annex.
- An interim analysis will be performed two years after the last Cerdelga patient has been enrolled in the study and an interim report of study results will be submitted subsequently.

Event	**Expected date**
Start of data collection	Q2 2018
Interim report(s) of study results	Adverse events collected for the patients enrolled in the ICGG sub-registry will be reported in the PSURs in the EU regional annex. Progress report will be included in PSUR in the EU regional annex. An interim analysis will be performed two years after the last Cerdelga patient has been enrolled in the study, and an interim report of study results will be submitted subsequently.
First Cerdelga patient reaches 5 year (RMP)	Q2 2023
End of data collections (four years after the last Cerdelga patient has been enrolled in the study.)	Based on the actual start of data collection date and recruitment of 32 months, the expected date of the end of data collection would be Q1 2025. Data collection completed and analysis performed.
Final report of study results	Q3 2025

6 RATIONALE AND BACKGROUND

6.1 BACKGROUND

Characterization of the long-term safety profile of Cerdelga in patients with GD has been identified as a mandatory (EU) pharmacovigilance activity, beyond routine pharmacovigilance. The objective is to collect these data from a less controlled environment than that of the clinical studies conducted so far. For this purpose, and to enable comparison of the Cerdelga safety profile to that of Cerezyme (which has been well established), a prospective ICGG safety sub-registry to collect long-term safety data in patients treated with Cerdelga or Cerezyme will be created. These long-term data should provide valuable information on the potential risks of Cerdelga, and may clarify whether certain AEs observed in the clinical studies are due to the underlying disease, to Cerdelga or to another cause. The sub-registry will also be used to describe patient characteristics and utilization patterns of Cerdelga by HCPs as a means to assess the effectiveness of the risk minimization measures (eg, local labelling and educational materials).

6.2 RATIONALE

This registry is set up as a sub-registry to complement the ICGG Gaucher Registry, a multi-center, international, longitudinal, observational program for patients with GD designed to track the natural history of the disease, and outcomes of patients on GD treatments. Similarly, using the same ICGG technology platform, the sub-registry is designed to follow patients on Cerdelga and Cerezyme and in particular assess the long-term safety profile of Cerdelga and descriptively compare it with Cerezyme by collecting real-world safety data as part of a post approval commitment.

Enzyme Replacement Therapies, such as Cerezyme, and SRTs, such as Cerdelga, are substitutive or corrective treatments that ameliorate disease manifestations, but do not eliminate the root cause of the disease. Therefore, it is assumed that long-term maintenance therapy with ERT or SRT is required for reaching or maintaining therapeutic goals. Though the studies supporting the registration of Cerdelga have continued to collect data for multiple years (up to 8 years for the Phase 2 study), an extended follow-up of patients treated in real-world clinical practice will support the longer-term safety of Cerdelga.

Clinical studies with Cerdelga have demonstrated a favorable benefit-risk profile, with robust efficacy results and a treatment that was generally well-tolerated across the clinical program. However, safety concerns were identified and include important potential risks and missing information.

Important potential risks:

- Drug-drug interactions:
  - Use with CYP2D6 and/or CYP3A inhibitors
  - Use with strong CYP3A inducers
  - Use with P-gp or CYP2D6 substrates

- Use of Cerdelga in patients who are CYP2D6 indeterminate metabolizers or non-genotyped patients
- Cardiac conduction disorders and arrhythmias

Missing information:

- Use in patients with a history of or current cardiac ischemia or heart failure, clinically significant arrhythmias or conduction findings
- Use during pregnancy and lactation
- Safety in long-term treatment use
- Use in patients who are CYP2D6 URMs

Available published and unpublished data related to gaps in knowledge reflect the current information presented above and in the EU RMP.

Additional pharmacovigilance activities beyond routine to gather long-term safety data are needed to explore and further characterize this missing information. As European Authorities have identified the limited number of exposed patients, particularly in real-world experience and in the long-term, as a major concerned area of research given that Cerdelga is intended to be a chronic treatment, long-term data will provide a better understanding of the potential risks that were identified in clinical studies and may clarify whether these risks are due to Cerdelga treatment, the underlying GD, or another cause.

Finally, the sub-registry will allow assessment of clinical practice and prescribing patterns, and the adherence of prescribing HCPs to Cerdelga key label (prescribing information) requirements, and will provide data to assess the effectiveness of risk minimization measures. Key prescribing information requirements include testing the genotype and predicting the phenotype of the key metabolic pathway, CYP2D6, in each patient before starting treatment to guide dosing; excluding CYP2D6 indeterminate and URMs from treatment; and prescribing Cerdelga only to patients with type 1 GD.

As the sub-registry is a voluntary program, the total number of patients who will participate and the total number of person-years of follow-up are not pre-defined, as not all patients have been identified, nor will all patients who could meet the study criteria may wish to participate. The sub-registry database has been designed to collect a variety of baseline and follow-up data obtained through routine clinical and laboratory assessments in the ICGG Gaucher Registry database. Each participating HCP is solely responsible for determining the appropriate clinical care for each patient. All data submissions are voluntary and there are no pre-determined follow-up periods. Participating sites will be encouraged to enter comprehensive baseline data at patient enrollment and to perform follow-up assessments at regular intervals, as described in the Recommended Schedule of Assessments of the ICGG Gaucher Registry. However, since this is a registry where data will be derived from routine clinical practice and not an interventional study, there will be no predefined diagnostic or monitoring procedures. Health Care Providers will decide what assessments to perform and when for each patient. Interviews, questionnaires and blood samples will be performed as in routine clinical practice.

In the sub-registry HCP's will be instructed to collect and report all AEs that occur during sub-registry participation, regardless of relationship to treatment.

The aim is to enroll as many patients on Cerdelga as possible.

Therefore, the only inclusion criteria for patients are:

I 01. Male or female patient aged 18 years or older;

I 02. The patient must be enrolled in the ICGG Gaucher Registry prior to safety sub-registry enrollment;

I 03. The patient is willing and able to provide written informed consent for the safety sub-registry;

I 04. The patient must have a confirmed diagnosis of GD, as defined in the protocol of the ICGG Gaucher Registry (documented acid ß-glucosidase deficiency and/or mutations in the acid ß-glucosidase gene);

I 05. The patient must either initiate or continue treatment with Cerdelga or Cerezyme at the time of safety sub-registry enrollment.

The only exclusion criteria for patients are:

E 01. The patient is concurrently enrolled in another clinical study; or participates in the compassionate use program with Cerdelga.

E 02. The patient is treated with both Cerezyme and Cerdelga at the time of enrollment, or investigator consider treating patient with both therapies concurrently at any time during participation in the safety sub-registry.

Patients on Cerezyme will provide a control group to descriptively compare the safety profile of Cerdelga to that of Cerezyme.

Both Cerdelga and Cerezyme are currently first line treatment for GD1 and thus expectedly both will be prescribed as such to GD1 patients. Miglustat is approved as second line SRT, for patients for whom ERT is unsuitable. Comparison of Cerdelga with miglustat would create a bias when trying to use miglustat as the comparator, since Cerdelga does not have the limitation of only to be prescribed to patients for whom ERT is not a therapeutic option. Thus, the underlying patient population will be different for those eligible to receive Cerdelga versus miglustat, and any subsequent analyses will be biased by design. In the real clinical practice the number of patients on miglustat would be insufficient to provide a viable comparison group due to the reduced current use of miglustat, which is expected to continue decreasing. For these reasons, Cerezyme and not miglustat has been chosen as comparator group.

7 RESEARCH QUESTION AND OBJECTIVES

7.1 PRIMARY OBJECTIVE

The primary objectives:

1. To evaluate the long-term safety of Cerdelga in real-world clinical practice.
2. To describe the utilization of Cerdelga.

The long-term safety of Cerdelga will be evaluated by the incidence rate of any AE during sub-registry participation, whether considered related or unrelated to Cerdelga by the treating HCP. The risk of an AE compared to Cerezyme will be evaluated in terms of the risk ratio (ratio of incidence rates).

Evaluation of utilization patterns of Cerdelga includes:

- To assess compliance/adherence of HCPs to the labelling with regard to CYP2D6 genotyping prior to initiation of Cerdelga
- To assess compliance/adherence of HCPs to the Cerdelga label with regard to patients' CYP2D6 predicted phenotype
- To assess compliance/adherence of HCPs to the Cerdelga label with regard to use in GD type 1.

In order to avoid the introduction of an element of positive or negative bias into the safety reporting from the ICGG Gaucher Registry physicians by providing a specific list of safety issues to be collected (and subsequently recorded in the CRFs) in protocol, there will be no suggested areas of safety data collection. Rather all safety data will be collected and subsequently assessed in relation to the important potential risks in the RMP. All AEs for Cerdelga and Cerezyme, regardless of their relation to treatment will be collected. However, when the safety analysis will be performed, specific exploratory analyses of the potential risks listed in RMP and any new safety concern that could arise from the sub-registry, will be included and reported in the PSUR in the EU regional annex.

8 RESEARCH METHODS

8.1 STUDY DESIGN

This is a safety sub-registry of the ICGG Gaucher Registry (DIREGC07009).

This is a non-interventional, multicenter, prospective PASS of Cerdelga, a treatment approved in many countries for adult patients with GD1 who have a CYP2D6 PM, IM, or EM phenotype. Participating HCPs will enroll eligible patients after the decision to treat with Cerdelga or Cerezyme. The study will enroll patients who will be receiving Cerdelga or Cerezyme for the first time or as part of ongoing treatment of their GD.

Patients will receive treatment as determined by the patient's HCP and guided by the provisions of the prevailing locally approved product labelling and educational materials, and the ICGG Gaucher Registry recommendations for monitoring. All treatment decisions and medical assessments are at the discretion of the HCPs and are not mandated by study design or protocol.

No experimental intervention is involved. Participating patients will undergo clinical assessments and receive the standard of-care treatment for GD, as determined by their treating HCPs, who may want to use the Gaucher registry Recommended Schedule of Assessments as a guideline. The observational nature of this study design will allow for an estimate of 'real world' safety experience of Cerdelga among patients who receive Cerdelga in a commercial versus clinical study setting.

Patients will complete and sign a patient written Informed Consent Form specific to this safety sub-registry before participating.

Selected data from the sub-registry CRFs will be monitored periodically against source documents at the treating HCP's site by a representative of Sanofi Genzyme (or its designee) to ensure data completeness and accuracy. Refer to Section 8.7.2 for further details.

Study baseline will be defined as the time of entry into the sub-registry.

8.2 SETTING

This is a non-interventional, international, multicenter, prospective PASS of Cerdelga, a treatment approved in many countries for adult patients with GD1. The aim of the study is to collect long-term safety data from the ICGG Gaucher Registry for patients treated with Cerdelga and Cerezyme. HCPs will enroll eligible patients after the decision to treat with Cerdelga or Cerezyme. As Cerdelga is not approved for pediatric patients, only adult patients are included in this study. There is no set duration for this study. The number of patients for both of the groups who continue their observation in the sub-registry will be evaluated annually after the end of the recruitment period to determine the need to replace patients who dropped out of the study for any reason. The need to continue with this requirement will be reassessed two years after the last Cerdelga patient has been enrolled in the study in the interim report. Data collection will be concluded four years after the last Cerdelga patient has been enrolled in the study. The sub-registry study patients will be recruited from sites in countries where Cerdelga is already on

the market or will become available on the market during the sub-registry enrollment period. Both ICGG Gaucher Registry sites and new sites, which could potentially become ICGG Gaucher Registry sites, will be considered for the study. Health Care Providers at these sites who manage patients with GD1 will be invited to participate in the sub-registry.

At least 100 patients on Cerdelga will be representative of the entire population of GD1 adult patients treated with Cerdelga in countries where Cerdelga is on the market or is expected to become available on the market within the enrollment period of the study (the sample size justification is further discussed in Section 8.6.1). The ratio of Cerdelga versus Cerezyme patients recruited for the study is planned to be approximately 2:1.

There is no predefined number of sites which are planned to be opened for this sub-registry, nor is there a predefined number of patients to be enrolled per site. The final number of sites will ensure achievement of enrollment goals for the set duration of the recruitment. The patient recruitment will be EU focused to represent GD1 patients treated with Cerdelga in the EU. Depending on study enrollment during the recruitment period, other countries and regions where Cerdelga has a marketing authorization (eg, USA, Israel) will also be considered.

List of countries where data will be collected may depend on the actual dates when Cerdelga will become available on the market in particular country. Potential countries for safety sub-registry could include Germany, Denmark, France, United Kingdom, Italy, the Netherlands, Belgium, Portugal, Sweden, Spain, Czech Republic, and Romania. There is no limit of patients or sites per country. However, every effort will be made to ensure equal representation of patients per country to represent the real-world safety profile of Cerdelga with the majority of patients recruited in the EU. Data collection in the sub-registry is planned to start approximately 6 months after PRAC protocol approval has been obtained.

Inclusion criteria (see Section 8.2.2.1) for the study are very wide to enable HCP's to enroll as many adult patients treated or to be treated with Cerdelga or Cerezyme as possible in order to collect data in as many patients as possible. The exclusion criteria are limited only to patients currently enrolled in another clinical study (especially any receiving Cerdelga as part of that study) and patients treated with Cerezyme and Cerdelga in combination at the time of enrollment.

Patients who have been exposed to Cerdelga in clinical studies prior to their enrollment in the sub-registry can be enrolled in any group of the sub-registry and will be considered as experienced to Cerdelga. Their previous exposure to Cerdelga in clinical studies will be considered and described, notwithstanding the group of treatment these patients belong to during the safety sub-registry.

The data for enrolled patients who switch treatment from Cerdelga to Cerezyme or vice-versa during the follow-up will be evaluated to and from the point of switch in the therapy (if applicable).

8.2.1 Duration of the study

There is no set duration of participation. Patients can remain in the safety sub-registry as long as they receive Cerezyme or Cerdelga and the sub-registry is open. The number of patients for both of the groups who continue their observation in the safety sub-registry will be evaluated annually after the end of the recruitment period to determine the need to replace patients who dropped out of the study for any reason. The need to continue with this requirement will be reassessed two years after the last Cerdelga patient has been enrolled in the study in the interim report.

Data collection will be concluded four years after the last Cerdelga patient has been enrolled in the study, at which time analysis will be performed.

8.2.2 Eligibility criteria

8.2.2.1 Inclusion criteria

Patients must meet the following criteria to be eligible to participate in the safety sub-registry:

I 01. Male or female patient aged 18 years or older;

I 02. The patient must be enrolled in the ICGG Gaucher Registry prior to safety sub-registry enrollment;

I 03. The patient is willing and able to provide written informed consent for the safety sub-registry;

I 04. The patient must have a confirmed diagnosis of GD, as defined in the protocol of the ICGG Gaucher Registry (documented acid ß-glucosidase deficiency and/or mutations in the acid ß-glucosidase gene);

I 05. The patient must either initiate or continue treatment with Cerdelga or Cerezyme at the time of safety sub-registry enrollment.

8.2.2.2 Exclusion criteria

A patient who meets any of the following criteria will be excluded from this sub-registry:

E 01. The patient is concurrently enrolled in another clinical study; or participates in the compassionate use program with Cerdelga.

E 02. The patient is treated with both Cerezyme and Cerdelga at the time of enrollment, or investigator consider treating patient with both therapies concurrently at any time during participation in the safety sub-registry.

8.2.3 Analysis population(s)

Analysis will be performed on the Safety Set, defined as all patients enrolled in the sub-registry who have received at least one dose of Cerdelga or Cerezyme following enrollment.

Category of treatment status at the time of sub-registry enrollment will be defined as:

a) Patients naive to any GD treatment (ERT or SRT). This category will include, for example, newly diagnosed patients.
b) Patients naive to the product of interest (Cerdelga in the Cerdelga group and Cerezyme in the comparator group) but experienced to any other treatment for GD (ERT or SRT). This category will include, for example, patients who will switch from any one therapy to the product of interest.
c) Patients experienced to the treatment of interest. This category will include patients who were on treatment with the product of interest at entry into the sub-registry and then continue this therapy.

Note:

- Patients whose first GD treatment is commercial Cerdelga or Cerezyme, and who enroll in the sub-registry within 3 months of the first dose will be considered treatment naive for the purposes of analysis. Regardless of prior treatment, these patients must receive either Cerdelga or Cerezyme during their participation in the sub-registry.
- Previous exposure to Cerdelga in clinical studies will be considered for any patient of the sub-registry, notwithstanding the group of treatment they belong to during sub-registry participation.
- The data for enrolled patients who switch treatment from Cerdelga to Cerezyme or vice-versa during follow-up will be evaluated to and from the point of switch in the therapy (if applicable).
- A subset of treatment experienced patients will be patients who will switch from any one therapy to any other therapy.
- When available, AEs reported by the patient and in the opinion of investigator related to Cerdelga intake and Cerezyme administration (prior to enrollment into the safety sub-registry) will be collected as part of the patient enrollment characteristics (medical history).

Analysis of endpoint: The main analysis of interest will be the incidence rate of any AE report for Cerdelga-treated patients during their participation in the sub-registry, considering treatment status at sub-registry enrollment (if applicable). Similar calculations will be performed for the Cerezyme-treated patients. Summaries will also be presented for three categories of treatment status within each of the Cerdelga and Cerezyme groups (if applicable). Data will be analyzed as available, missing data will not be imputed. All summaries will be descriptive; no formal hypothesis testing will be performed.

8.2.4 Modalities of recruitment

8.2.4.1 Investigator selection

The sub-registry study patients will be recruited from sites in countries where Cerdelga is already on the market or will become available on the market during the sub-registry enrollment period. Both ICGG Gaucher Registry sites and new sites, which could potentially become ICGG Gaucher

Registry sites, will be considered for the study. Health Care Providers at these sites who manage patients with GD1 will be invited to participate in the sub-registry.

8.2.4.2 Patient selection

The patients who will be enrolled in the study will be selected among the patients who are enrolled or agree to enroll in the ICGG Gaucher Registry and either initiate or continue treatment with Cerdelga or Cerezyme while enrolled in the sub-registry.

Each participating HCP is solely responsible for determining the appropriate clinical care for each patient. The Investigator/HCP should refer to the locally approved prescribing information for any information on the treatment being administered.

8.3 VARIABLES

The main analysis of interest will be the incidence rate of any AE report for Cerdelga-treated patients during participation in the sub-registry.

The outcome variable will be a report of an AE, exposure will be duration (in months or years) of time of exposure to Cerdelga while enrolled in the sub-registry, grouping factors will include category of Treatment Status (defined below), duration of GD treatment (including Cerdelga or other GD treatments) prior to enrolling in the sub-registry, selected demographic and baseline characteristics such as age, sex, and genotype as listed in Section 8.7.5.

Category of treatment status at the time of sub-registry enrollment will be defined as:

a) Patients naive to any GD treatment (ERT or SRT). This category will include, for example, newly diagnosed patients.
b) Patients naive to the product of interest (Cerdelga in the Cerdelga group and Cerezyme in the comparator group) but experienced to any other treatment for GD (ERT or SRT). This category will include, for example, patients who will switch from any one therapy to the product of interest.
c) Patients experienced to the treatment of interest. This category will include patients who were on treatment with the product of interest at entry into the sub-registry and then continue this therapy.

Note:

- Patients whose first GD treatment is commercial Cerdelga or Cerezyme, and who enroll in the sub-registry within 3 months of the first dose will be considered treatment naive for the purposes of analysis. Regardless of prior treatment, these patients must receive either Cerdelga or Cerezyme during their participation in the sub-registry.
- Previous exposure to Cerdelga in clinical studies will be considered for any patient of the sub-registry, notwithstanding the group of treatment they belong to during sub-registry participation.
- The data for enrolled patients who switch treatment from the Cerdelga to the Cerezyme or vice-versa during follow-up will be evaluated to and from the point of switch in the therapy.

- A subset of treatment experienced patients will be patients who will switch from any one therapy to any other therapy.
- When available, AEs reported by the patient and in the opinion of investigator related to Cerdelga intake and Cerezyme administration (prior to enrollment into the safety sub-registry) will be collected as part of the patient enrollment characteristics (medical history).

Other outcome variables include SAEs, events of interest, reported values of the clinically significant abnormal laboratory result in the course of AE follow-up, and frequencies and percentages of timing of CYP2D6 genotyping, and CYP2D6 predicted phenotypes and GD subtype among Cerdelga-treated patients will be presented.

8.4 STATISTICAL ANALYSIS

Adverse events, SAEs, and events of interests will be summarized by treatment group, and by the three categories of treatment status and treatment group using percentage and frequency. For abnormal laboratory results assessed as AEs (clinically significant abnormal laboratory results), reported values of laboratory results in the course of AE follow-up will be summarized descriptively, including mean, standard deviation (SD), median, minimum and maximum. Categorical or qualitative variables will be summarized using percentages and frequency distributions. Timing of CYP2D6 genotyping and prevalence of CYP2D6 predicted phenotypes and GD subtype among Cerdelga-treated patients will be summarized using percentages and frequency.

In addition, the 95% confidence interval of incidence rates will be provided by treatment group. The risk of any AE in the Cerdelga group compared to Cerezyme will be evaluated in terms of the risk ratio with associated 95% confidence interval.

Data will be analyzed as available, missing data will not be imputed. For all AEs summary statistics, frequencies, cumulative incidence, and incidence rates per person-time will be calculated as appropriate. All summaries will be descriptive; no formal hypothesis testing will be performed.

8.5 DATA SOURCES

The data source for the ICGG sub-registry study is all patients enrolled in the ICGG Gaucher registry who are Cerdelga or Cerezyme treatment naive or continue treatment with Cerdelga or Cerezyme. The ICGG Gaucher Registry is a multi-center, international, longitudinal, observational program for patients with GD designed to track the natural history and outcomes of patients. The ICGG Gaucher Registry database has been designed to collect a variety of baseline and follow-up data obtained through routine clinical and laboratory assessments.

Data in the ICGG sub-registry study will be collected from enrolled patients by participating HCPs at the time of all patient office visits occurring as per local practice visit schedule or following the recommended schedule of assessments of the ICGG Gaucher Registry. Information that is shared by the Registry and sub-registry will be collected only once. Information specific to

the sub-registry will be collected in specifically designed CRFs. Data collected by sub-registry HCPs or their designees will be submitted to the sub-registry for central processing and evaluation. A primary contact person located at the participating site should be designated as the individual responsible for completing and entering CRFs into the sub-registry database.

8.6 STUDY SIZE

8.6.1 Determination of sample size

The sample size determination was not based on power consideration. The sample size of at least 100 patients on Cerdelga was chosen to provide a sufficient number of patients to describe the real-world safety profile of Cerdelga. With 100 patients on Cerdelga, there is more than 95% of probability of observing at least one patient with an AE if the true cumulative rate of such an event is 5%. In addition, it is a similar size (n=106) to the number of Cerdelga patients treated in the primary analysis period of the ENCORE registration study (1) which was a direct comparison of Cerdelga to Cerezyme and should then confirm the safety profile experienced in a real-world setting. Accordingly, a control group of safety sub-registry to descriptively compare the safety profile of Cerdelga to that of Cerezyme will include approximately 50 patients on Cerezyme.

Based on the treatment experienced patients in the ENCORE study, the risk ratio of any AE comparing Cerdelga to Cerezyme is expected to be approximately 1.2.

8.6.2 Sample size

In countries where Cerdelga will be available on the market at least 100 Cerdelga patients will be recruited in the study and approximately 50 Cerezyme patients will be included in the control group of safety sub-registry to descriptively compare the safety profile of Cerdelga to that of Cerezyme.

8.7 DATA MANAGEMENT

8.7.1 Data collection schedule

Data will be collected from enrolled patients by participating HCPs at the time of all patient office visits occurring as per local practice visit schedule or following the recommended schedule of assessments of the ICGG Gaucher Registry. Adverse events should be collected from patients at least every 6 months. If the period of time between the last ELISAFE sub-registry assessment and the next planned ICGG Gaucher Registry assessment is expected to be more than 6 months, a phone call to inquire about new/ongoing AEs is recommended.

If a patient temporarily stops (for any reason) treatment with Cerdelga or Cerezyme and the treating physician considers that the treatment can be potentially restarted, the patient can stay in the sub-registry as long as the sub-registry is open, the patient is willing to participate and is available for follow-up assessments. Collection of all AEs will be continued for the duration of 30 days after stopping Cerdelga or Cerezyme, and after that period only new SAEs will be collected and follow-up of ongoing AEs will be performed. Collection of all AEs in ELISAFE will be resumed when the patient restarts treatment with Cerdelga or Cerezyme.

8.7.2 Data collected

See Section 8.7.5.

Information specific to the sub-registry will be collected in specifically designed CRFs. Data collected by sub-registry HCPs or their designees will be submitted to the sub-registry for central processing and evaluation. A primary contact person located at the participating site should be designated as the individual responsible for completing and entering CRFs into the sub-registry database.

Selected data from the sub-registry CRFs will be monitored periodically against source documents at the treating HCP's site by a representative of Sanofi Genzyme (or its designee) to ensure data completeness and accuracy.

8.7.3 Site/Investigators questionnaire

Not applicable.

Since this is a registry where data will be derived from routine clinical practice, there will be no predefined diagnostic or monitoring procedures. Interviews or questionnaires will be performed as in routine clinical practice.

8.7.4 Patient/Subject tracking log

The patient/subject tracking log will be used to document the reason for non-inclusion. Data collected on this log will be fully anonymous (patient # [1, 2,…], included: Yes/No, reason for non-inclusion).

8.7.5 Patient data

Note: The observational study operates under real-world clinical practice conditions. It collects only available data. There are no imposed protocol visits or procedures.

Evaluation	At enrollment	Study follow-up assessments [a,c]	End of study
Informed Consent Form	x		
Inclusion criteria/Exclusion criteria	x		
Demographics *	x		
CYP2D6 predicted phenotype*	x		
GD history*	x		
Clinically significant medical history with assessment of relationship to Cerdelga or Cerezyme before enrollment	x		
GD treatment history*	x		
Current GD treatment*	x [b]	x [b]	x [b]
All adverse events		x	x
Concomitant medications for particular cases only [d]	x	x	x

* Information collected as a part of ICGG Gaucher registry assessments

a Frequency of the follow-up visits will be as per local practice visit schedule, or following the recommended schedule of events of the ICGG Gaucher Registry. Study assessments will be performed during office visits. In exceptional cases, follow-up information (including treatment status and AEs) could be collected by phone. Adverse events should be collected from patients at least every 6 months. If the period of time between the last ELISAFE sub-registry assessment and the next planned ICGG Gaucher Registry assessment is expected to be more than 6 months, a phone call to inquire about new/ongoing AEs is recommended.

b Any data that are already entered in the ICGG Gaucher registry will not need to be entered in the sub-registry.

c If a patient temporarily stops (for any reason) treatment with Cerdelga or Cerezyme and the treating physician considers that the treatment can be potentially restarted, the patient can stay in the sub-registry as long as the sub-registry is open, the patient is willing to participate and is available for follow-up assessments. Collection of all AEs will be continued for the duration of 30 days after stopping Cerdelga or Cerezyme, and after that period only new SAEs will be collected and follow-up of ongoing AEs will be performed. Collection of all AEs in ELISAFE will be resumed when the patient restarts treatment with Cerdelga or Cerezyme.

d Any corrective treatment prescribed following the occurrence of an AE. Any concomitant medication that caused an overdose. In case of relationship of the AE/overdose/pregnancy to other concomitant medication.

Data collected in the ICGG Gaucher Registry and sub-registry to be used in this study include:

Upon enrollment into the sub-registry:

- Demographics
  - Gender and date of birth
  - CYP2D6 genotype testing result and date of blood sample collection, if available
- GD history
  - GD diagnosis confirmation
  - Date of diagnosis
  - GD type
- Primary GD treatment history:
  - Date and type of first primary GD treatment
  - Date, dose and type of all past primary GD treatments
  - Start date and dose of Cerdelga or Cerezyme treatment at sub-registry enrollment
- Date of sub-registry enrollment
- Clinically significant medical history (including AEs reported by patient and in opinion of investigator related to Cerdelga intake and Cerezyme administration which occurred prior to enrollment into the safety sub-registry).

At follow-up visits:

No experimental intervention is involved. Participating patients will undergo clinical assessments and receive treatment for GD, as determined by their treating HCPs and using the ICGG Gaucher Registry Recommended Schedule of Assessments as a guideline.

At each follow-up visit the following will be collected:

- Dosing information: including Cerdelga or Cerezyme regimen at the time of follow-up and treatment interruptions for ≥1 month or regimen changes since last visit with reasons for treatment interruptions or regimen changes.
- Adverse events: information on all AEs ongoing and occurring since the last visit, regardless of seriousness or relationship to Cerdelga or Cerezyme. Adverse events should be collected from patients at least every 6 months. If the period of time between the last ELISAFE sub-registry assessment and the next planned ICGG Gaucher Registry assessment is expected to be more than 6 months, a phone call to inquire about new/ongoing AEs is recommended.

8.7.6 Procedure for withdrawal of patients from study follow-up schedule

The participating Investigator/HCP should make every effort to re-contact the patient to determine his/her health status, including at least his/her vital status.

There is no minimum duration of participation for patients.

Any patient is free to withdraw authorization and discontinue his/her participation in the sub-registry at any time, without prejudice to further treatment. The patient's participation in the sub-registry may be discontinued at any time at the discretion of the treating HCP. The following may be justifiable (but not exhaustive) reasons for the treating HCP to remove a patient from the sub-registry:

- The patient was erroneously included in the sub-registry;
- The patient is taking an investigational product during participation in the sub-registry;
- The sub-registry is terminated by Sanofi Genzyme.

Patients who withdraw, or are withdrawn, from this safety sub-registry are still permitted to participate in the ICGG Gaucher Registry.

8.7.7 Logistic aspects

Not applicable.

8.8 DATA ANALYSIS

Analysis will be performed on the Safety Set, defined as all patients enrolled in the sub-registry who have received at least one dose of Cerdelga or Cerezyme following enrollment. The analysis will be performed for each treatment group and overall (where appropriate) by treatment status (if applicable).

Patient's treatment status at the time of sub-registry enrollment will be defined in three categories:

a) Patients naive to any GD treatment (ERT or SRT). This category will include, for example, new diagnosed patients.
b) Patients naive to the product of interest (Cerdelga in the Cerdelga group and Cerezyme in the comparator group) but experienced to any other treatment for GD (ERT or SRT). This category will include, for example, patients who will switch from any one therapy to the product of interest.
c) Patients experienced to the treatment of interest. This category will include patients who were on treatment with the product of interest at entry into the sub-registry and then continue this therapy.

Note:

- Patients whose first GD treatment is commercial Cerdelga or Cerezyme, and who enroll in the sub-registry within 3 months of the first dose will be considered treatment naive for the purposes of analysis. Regardless of prior treatment, these patients must receive either Cerdelga or Cerezyme during their participation in the sub-registry.
- Exposure to Cerdelga in clinical studies will be considered for any patient of the sub-registry, notwithstanding the group of treatment they belong to during sub-registry participation.
- The data for enrolled patients who switch treatment from Cerdelga to Cerezyme or vice-versa during follow-up will be evaluated to and from the point of switch in the therapy.
- A subset of treatment experienced patients will be patients who will switch from any one therapy to any other therapy.
- When available, AEs reported by the patient and in the opinion of investigator related to Cerdelga intake and Cerezyme administration (prior to enrollment into the safety sub-registry) will be collected as part of the patient enrollment characteristics (medical history).

Analysis of endpoint: The main analysis of interest will be the incidence rate of any AE report for Cerdelga-treated patients during their participation in the sub-registry, considering treatment status at sub-registry enrollment (if applicable). If sufficient data within each treatment status category are collected, incidence rates within treatment status category will be estimated. Similar calculations will be performed for the Cerezyme-treated patients. Summaries will also be presented for three categories of treatment status within each of the Cerdelga and Cerezyme groups (if applicable). The implicit assumption of constant incidence rates over time will be evaluated.

Data will be analyzed as available, missing data will not be imputed. All summaries will be descriptive; no formal hypothesis testing will be performed.

As a part of exploratory analysis, specific analyses of the potential risks in the RMP and any new safety concern that could arise from the sub-registry will be conducted.

8.8.1 Primary analysis

- Incidence rate of any AE.
- Frequencies and percentages of timing of CYP2D6 genotyping (prior to or following) initiation of Cerdelga.
- Frequencies and percentages of CYP2D6 predicted phenotype among Cerdelga-treated patients.
- Frequencies and percentages of types of GD among Cerdelga-treated patients.

8.8.2 Secondary analysis

- Incidence rate of any SAE.

8.8.3 Exploratory analysis

- Frequencies and percentages of AEs related to risks defined in the RMP as important potential risks (if available).

8.8.4 Interim analysis

One interim analysis is planned two years after the last Cerdelga patient has been enrolled in the study.

8.9 QUALITY CONTROL

8.9.1 Data collection, validation and data quality control at MAH/MAH representative level

Data will be collected using an electronic case record form (e-CRF).

The computerized handling of the data by the MAH/MAH representative may generate additional requests to which the participating Investigator/HCP is obliged to respond by confirming or modifying the data questioned.

Data collection and validation procedures will be detailed in appropriate operational documents.

The purpose of this sub-registry is to collect uniform clinical data on patients with GD on treatment with Cerdelga or Cerezyme.

Data will be collected from enrolled patients by participating HCPs at the time of all patient office visits occurring as per local practice visit schedule or following the recommended schedule of

events of the ICGG Gaucher Registry. A set of CRFs designed for this sub-registry will be used by participating sites. Data collected by sub-registry HCPs or their designees will be submitted to the sub-registry for central processing and evaluation. A primary contact person located at the participating site should be designated as the individual responsible for completing and entering CRFs into the sub-registry database.

8.9.2 Data quality control at site level

Data collected through the sub-registry will be entered into a database and analyzed. Sub-registry staff working with the ICGG Gaucher registry staff will review the data for missing data points, incomplete information, and discrepancies with previously submitted data. If necessary, issues will be resolved with the site by telephone, fax, e-mail, or site visit, as appropriate. Sanofi Genzyme and/or its designee may conduct site visits to review the quality of the sub-registry data, as well as documentation related to institutional review board (IRB)/independent ethics committee (IEC) approvals, informed consent, and any patient authorization documents required by local law.

A clinical monitor from Sanofi Genzyme (or its designee) will manually review data in the CRFs for this safety sub-registry against source documents at the treating HCPs site for validity and completeness. All data captured in the CRFs will be made available to Sanofi Genzyme (or its designee) for data management and analysis. If necessary, the site will be contacted for corrections and/or clarification of the data.

All data management and analysis will occur in a validated computing environment.

Data quality control (site monitoring and/or phone QC) will be performed for 100% of the active sites (which have enrolled at least one patient).

8.10 LIMITATIONS OF THE RESEARCH METHODS

During the clinical studies the frequency of AEs had a tendency to decrease over time. To control for a possible relation between the frequency of AEs and the duration of treatment, AEs will also be analyzed after stratification of patients between three categories of treatment status.

For the sub-registry to meet its goal of providing real-world information on Cerdelga safety, the design of the study must ensure that HCPs report all AEs without preconceived ideas on the safety profile of Cerdelga. To this end no AESI have been specified.

To determine if there are any differences between patients who accept to enroll in the sub-registry and those who do not and, if these differences have any impact on the generalizability of the results, baseline characteristics (including age, sex, genotype, GD history, GD treatment history, current GD treatment and CYPD phenotype) of patients who were enrolled in the safety sub-registry will be compared based on provisions of ICGG Gaucher registry ICF with baseline characteristics of ICGG Gaucher registry patients who did not accept to enroll into safety sub-registry, if this information can be obtained.

Baseline characteristics of subjects who discontinue the study and subjects who complete the study will be summarized in the clinical study report. In addition, number and percent of subjects who discontinue the study will be provided.

The patients enrolled in the ICGG safety sub-registry are not expected to have an extra burden of physician visits or out of the standard of care procedures/tests to comply with, thus any drop out would be mostly expected for reasons not related to the safety sub-registry or for patients who transfer from either Cerdelga and Cerezyme to another GD treatment.

The number of patients for both of the groups who continue their observation in the safety sub-registry will be evaluated annually after the end of the recruitment period to determine the need to replace patients who dropped out of the study for any reason. The need to continue with this requirement will be reassessed two years after the last Cerdelga patient has been enrolled in the study in the interim report.

8.11 OTHER ASPECTS

Not applicable

9 PROTECTION OF HUMAN SUBJECTS

9.1 RESPONSIBILITIES OF THE INVESTIGATOR/HEALTH CARE PROVIDERS

The Investigator/HCP will perform the study in accordance with this protocol, applicable local regulations and international guidelines.

It is the Investigator/HCP's responsibility to obtain written informed consent from patients prior to inclusion in the study, to fill in the CRF and to record all data pertinent to the investigation. She/he will ensure that the information reported in the CRF is precise and accurate.

Investigator/HCP, and under the HCP's responsibility, should fully inform the Patient of all pertinent aspects of the study including the written information. All patients should be informed to the fullest extent possible about the study, in language and terms they are able to understand.

Prior to a patient's participation in the study, the written Informed Consent Form should be signed, name filled in and personally dated by the patient or by the patient's legally acceptable representative, and by the person who conducted the informed consent discussion. A copy of the signed and dated written Informed Consent Form will be provided to the patient.

The Informed Consent Form and the Information Sheet used by the Investigator/HCP for obtaining the Patient's Informed Consent must be reviewed and approved by the MAH/MAH representative prior to submission to the appropriate Ethics Committee (IRB/IEC) for approval/favorable opinion.

9.2 RESPONSIBILITIES OF MAH/MAH REPRESENTATIVE

The MAH/MAH representative is responsible for taking all reasonable steps and providing adequate resources to ensure the proper conduct of the study.

The MAH/MAH representative is responsible for:

- Local submission(s) complying with data protection rules,
- Any other local submission(s).

9.3 ETHICAL, REGULATORY AND ADMINISTRATIVE RULES

9.3.1 Ethical principles

This study will be conducted in accordance with the principles laid by the 18th World Medical Assembly (Helsinki, 1964) and all subsequent amendments.

9.3.2 Laws and regulations

This study will be conducted in accordance with the guidelines for Good Epidemiology Practice (International Society for Pharmacoepidemiology, 2015 [2]; International Epidemiological Association (IEA) European Federation, 2007 [3]).

Each participating country should locally ensure all necessary regulatory submissions (eg, IRB/IEC) are performed in accordance with local regulations including local data protection regulations.

9.3.3 Data protection

The patient's personal data and Investigator's personal data which may be included in the MAH/MAH representative database shall be treated in compliance with all local applicable laws and regulations.

When archiving or processing personal data pertaining to the Investigator and/or to the patients, the MAH/MAH representative shall take all appropriate measures to safeguard and prevent access to this data by any unauthorized third party.

9.3.4 Insurance

Participating countries may contract insurance according to local specific requirements.

9.3.5 Secrecy agreement

All material, information (oral or written) and unpublished documentation provided to the Investigator (or any action carried out by the MAH/MAH representative on their behalf), including the present protocol and the CRF, are exclusive property of the MAH/MAH representative.

These materials or information (both global and partial) cannot be given or disclosed by the Investigators or by any person of her/his group to unauthorized persons without the prior formal written consent of the MAH/MAH representative.

The Investigator shall consider as confidential all the information received, acquired or deduced during the study and will take all necessary steps to ensure that there is no break of confidentiality, other than for information to be disclosed by law.

9.3.6 Record retention

The Investigator shall arrange for the retention of study documentation until the end of the study. In addition, the Investigator will comply with specific local regulations/recommendations with regards to patient record retention.

It is recommended that the Investigator retains the study documents at least five (5) years after the completion or discontinuation of the study, unless otherwise specified in the Investigator Agreement in line with additional standards and/or local laws.

However, applicable regulatory requirements should be taken into account in the event that a longer period is required.

9.3.7 Discontinuation of the study

The MAH/MAH representative can decide at any time and for any reason to discontinue the study; the decision will be communicated in writing to the participating Investigator.

Similarly, should the Investigator decide to withdraw from the study, she/he will have to inform the MAH/MAH representative in writing.

If appropriate, according to local regulations, Ethic Committee(s) (IRB/IEC) and Competent Authorities should be informed.

9.3.8 MAH/MAH representative audits and inspections by competent authorities

The Investigator agrees to allow the MAH/MAH representative auditors/Competent Authorities inspectors to have direct access to his/her study records for review, being understood that these personnel are bound by professional secrecy, and as such will not disclose any personal identity or personal medical information.

The Investigator will make every effort to help with the performance of the audits and inspections, giving access to all necessary facilities, data, and documents.

The confidentiality of the data verified and the protection of the patients should be respected during these inspections.

Any result and information arising from the inspections by the competent authorities will be communicated by the Investigator to the MAH/MAH representative.

The Investigator shall take appropriate measures required by the MAH/MAH representative to take corrective actions for all problems found during the audit or inspections.

10 MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

All AEs regardless of seriousness or relationship to Cerdelga or Cerezyme, spanning from the signature of the informed consent form until the end of the study as defined by the protocol for each patient, are to be collected by the Investigator and reported to the MAH/MAH representative with an appropriate causality assessment in relation to Cerdelga or Cerezyme treatment within expedited time frame.

10.1 SAFETY INSTRUCTIONS

All events will be managed and reported in compliance with all applicable regulations.

10.1.1 Definitions of Adverse Event and Serious Adverse Event

An **AE** is any untoward medical occurrence in a patient or clinical investigation patient administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment.
Adverse events may include, but are not limited to:

- Subjective or objective symptoms spontaneously offered by the patient or subject and/or observed by the Investigator or medical staff;
- Findings at physical examinations;
- Laboratory abnormalities of clinical significance.

An **SAE** is any untoward medical occurrence that at any dose:

- Results in death, or;
- Is life-threatening, or;

  Note: The term "life-threatening" in the definition of "serious" refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.
- Requires inpatient hospitalization or prolongation of existing hospitalization, or;
- Results in persistent or significant disability/incapacity, or;
- Is a congenital anomaly/birth defect, or;
- Is a medically important event, or;
- Suspected transmission of infectious agent; is any suspected transmission of an infectious agent via a medicinal product (eg, product contamination).

Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above.

10.1.2 Collection of Overdose and Pregnancy

Overdose: Administration of a quantity of a medicinal product given per administration or cumulatively which is above the maximum recommended dose according to the authorized product information. Clinical judgment should always be applied.

Any case of accidental or intentional overdose, even in the absence of an AE (asymptomatic), is to be reported to the representative of MAH/MAH representative (within 30 days) and recorded accordingly on the corresponding page(s) of in the CRF as explained below. In case of overdose the patient should remain under observation for as long as it is considered appropriate by the Investigator. Appropriate symptomatic measures should be taken.

Pregnancy occurring in the patient or the female partner of a male patient exposed to Cerdelga and/or Cerezyme is to be reported to the MAH/MAH representative (within 24 hours of awareness) and recorded immediately on the corresponding page(s) in the CRF of the ELISAFE safety sub-registry and ICGG Gaucher registry. A pregnancy data collection form will be provided to ensure collection of additional information regarding the pregnancy (eg, outcome). If the exposed female refuses to provide any information regarding the pregnancy and its outcome, this information will be captured on the pregnancy data collection form. Investigators are encouraged to propose pregnant patients to enroll into Gaucher Disease Registry Pregnancy Sub-Registry. The Pregnancy Sub-Registry will be associated with a separate form (or forms) reflecting informed consent to participate and authorization to disclose health information to this sub-registry for the mother and infant.

10.1.3 Obligations of the Investigator regarding safety reporting

10.1.3.1 Adverse Events collection

All AEs regardless of relationship to Cerdelga or Cerezyme, spanning from the signature of the informed consent form until the end of the collection period for each patient (the last follow-up assessment of the particular patient), are to be recorded **immediately** (within 24 hours of awareness) for SAE and within 30 days of awareness for non-serious AE on the corresponding page(s) of the paper CRF or e-CRF, as explained below.

10.1.3.2 Adverse event reporting to MAH/MAH representative

- **All AEs (serious and non-serious)**
  - Are to be transmitted to the MAH including an appropriate causality assessment in relation to Cerdelga or Cerezyme.
  - Per the ICGG Gaucher Registry protocol ADRs are expected to be reported directly to Global Pharmacovigilance (GPV). However, for patients who are enrolled in the sub-registry, AE reporting should be done only in the sub-registry database (AE CRF) and not directly to GPV. If a patient leaves the sub-registry and remains in the ICGG Gaucher registry, ADR reporting should resume per the ICGG Gaucher Registry protocol.

- **In the case of an SAE** the Investigator must immediately:
  - ENTER (within 24 hours) the information related to the SAE in the appropriate screens of the e-CRF; the system will automatically send the notification to the MAH after approval of the Investigator within the e-CRF or automatically after a pre-set delay.
  - Copies of medical records for certain cases may be requested by the Sponsor. In such case, SEND (preferably by fax or e-mail) the photocopy of all examinations carried out and the dates on which these examinations were performed to MAH's GPV:

Global Pharmacovigilance
Fax: + 33 1 60 49 70 70 Email: CL-CPV-receipt@sanofi.com

  - Care should be taken to ensure that the patient's identity is protected and the patient's identifiers in the Study are properly mentioned on any copy of source document provided to MAH/MAH representative. For laboratory results, include the laboratory normal ranges.
  - All further data updates should be recorded in the e-CRF as appropriate, and further requested documentation should be sent (by fax or e-mail) to MAH/MAH representative within 24 hours of knowledge. In addition, any effort should be made to further document each SAE that is fatal or life threatening within the week (7 days) following initial notification.

A back-up plan is used (using paper flow) in case the e-CRF system does not work.

- **In case of Non-Serious AEs**
  - ENTER (within 30 days) the information related to the AE in the appropriate screens of the e-CRF; the system will automatically send the notification to MAH/MAH representative after approval of the Investigator within the e-CRF or automatically after a pre-set delay.

10.2 SAFETY OBSERVATIONS

- The Investigator should take all appropriate measures to ensure the safety of the patients as per normal practice.
- In case of any SAE, the patient must be followed up until clinical recovery is complete and laboratory results have returned to normal, or until progression has been stabilized. This may imply that follow-up will continue after the patient has left the study;
- In case of any SAE brought to the attention of the Investigator at any time after cessation of the Cerdelga or Cerezyme, and considered by him/her to be caused by Cerdelga or Cerezyme with a reasonable possibility, this should be reported to the MAH/MAH representative.

10.3 ADVERSE EVENTS OF SPECIAL INTEREST

There are no adverse event of special interests (AESIs) defined in this sub-registry. All AEs, regardless of their relation to treatment will be collected.

As a part of safety analysis, specific analyses of the potential risks and new safety concerns that could arise from the sub-registry will be conducted.

10.4 OBLIGATIONS OF MAH/MAH REPRESENTATIVE

During the course of the study, the MAH/MAH representative will report safety data to health authorities according to Directive 2001/83/EC and in accordance with all applicable local and global regulations (eg, All serious ADRs within 15 days (calendar) from the date of receipt of the reports to the health Authorities; All non-serious ADRs within 90 days (calendar) from the date of receipt of the reports to the health Authorities for some European countries).

The MAH will report all safety observations made during the conduct of the study in the final study report.

11 PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

11.1 OWNERSHIP AND USE OF DATA AND STUDY RESULTS

No use of the data will be possible without the authorization of the MAH/MAH representative conducting the study.

The Scientific Committee will have full access to the final data allowing for appropriate academic analysis and reporting of the study results.

11.2 PUBLICATIONS

The protocol and final report of results will be submitted to the EMA and other appropriate regulatory bodies according to the guidelines for post authorization safety studies (4). The AEs reported for the patients enrolled in the ICGG sub-registry will be reported in the PSUR in the EU regional annex. The PSUR will include a report about the progress of the study. An interim report of study results will be submitted when the 100th patient on Cerdelga has completed 2 years of follow-up.

Scientific Publication Committee is responsible for presentations and/or publications. The study results must be submitted to the review of the Scientific Publication Committee before publication.

All study Investigators give full authority to the Scientific Publication Committee for primary presentation and/or primary publication of results. No other publication is allowed before the primary publication. Any subsequent presentation or publication by a study participant (including for substudies) must be approved by the Scientific Publication Committee and make reference to the study and the primary publication.

The final decision to publish any manuscript/abstract/presentation will be made by the Scientific Publication Committee after prior notice to the MAH/MAH representative allowing for its internal review and comments. All manuscript/abstract/presentation must be submitted to the internal review of the MAH/MAH representative at least forty-five (45) calendar days in advance of submission. The MAH/MAH representative may request that the MAH/MAH representative's name and/or names of one or several of its employees appear or do not appear in such publication.

The MAH/MAH representative can delay publication or communication for a limited time in order to protect the confidentiality or proprietary nature of any information contained therein.

Any publication has to be disclosed onto the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) site within 2 weeks of acceptation by a Journal.

12 REFERENCES

1. 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. The Lancet. Published online March 26, 2015 http://dx.doi.org/10.1016/S0140-6736(14)61841-9. ClinicalTrials.gov, number NCT00943111.

2. International Society for Pharmocoepidemiology, June 2015. Guidelines for Good Pharmacoepidemiology Practices, (rev. 3) 2015. Available at URL: https://www.pharmacoepi.org/resources/guidelines_08027.cfm.

3. IEA European Federation. Good Epidemiological Practice (CEP) IEA Guidelines for proper conduct in epidemiologic research, November 2007.

4. Guideline on good pharmacovigilance practices (GVP), Module VIII – Post-authorisation safety studies; EMA/813938/2011, 19 Apr 2013.

ANNEXES

Annex 1 List of stand-alone documents

None

Annex 2 ENCePP checklist for study protocols

None

Annex 3 Country-specific requirements

Not applicable

Annex 4 Protocol amendment history

The protocol amendment summary of changes for the current amended protocol 04 (approved; 03-Dec-2020) is located after the title page of this document.

Amended protocol 04 (draft for review; 31 July 2020)

Amended protocol 03 submitted to the European Medicines Agency via the procedure EMEA/H/C/PSA/S/0054 was not endorsed by the Pharmacovigilance Risk Assessment Committee (PRAC). Marketing Authorization Holder (MAH) was requested to revise the protocol in line with the PRAC Assessment Report dated 11 June 2020.

Amended protocol 04 includes the revised proposal for data collection:

- Revised proposal for end of data collection: data collection will be concluded four years after the last Cerdelga patient has been enrolled in the study, at which time the analysis will be performed. An interim analysis will be performed two years after the last Cerdelga patient has been enrolled in the study and an interim report of study results will be submitted subsequently.
- Removal of the proposal that the number of patients from both of the groups who continue their observation in the safety sub-registry will be evaluated annually after the end of the recruitment period to determine the need to replace patients who dropped out of the study for any reason prior to completion of their 4-year observation period, and that the utility/effectiveness of the sub-registry to provide longer term safety data will be re-evaluated at 5 years after the first Cerdelga patient has been enrolled.

Additionally a secondary analysis/endpoint of change from the initial clinically significant abnormal laboratory results proposed in the amended protocol 03 has been removed for the current revised protocol.

Protocol amendment summary of changes table

Section # and Name	Description of Change	Brief Rationale
Abstract, Variables, Analysis of endpoint; Section 8.2.3, Analysis population(s); Section 8.8, Data Analysis	Revised text (replacement of "adjusted for" by "considering") to specify that the main analysis of interest will be the incidence rate of any AE report for Cerdelga treated patients during participation in the sub-registry, **considering** treatment status at sub-registry enrollment (if applicable).	Clarification ("adjustment" was a statistical term dedicated to comparisons).
Abstract, Analysis of endpoint	Revised text to specify that the primary endpoint will be the incidence rate of any AE report for Cerdelga treated patients during participation in the sub-registry, considering treatment status at sub-registry enrollment (if applicable).	To align with Section 8.8, Data analysis.
Abstract, Data analysis, Analysis of endpoint; Section 8.8.2, Secondary Analysis	Removal of secondary analysis/endpoint: change from the initial clinically significant abnormal laboratory results.	As noted by the PRAC, the analysis is part of the ICGG Gaucher Registry.
Abstract, Data analysis; Section 5, Milestones; Section 8.8.4, Interim Analysis	Revised text to specify that interim analysis is planned two years after the last Cerdelga patient has been enrolled in the study.	To reflect amendment specific changes - to align with the revised proposal for end of data collection.
Abstract, Milestones; Section 5, Milestones; Section 8.2, Setting; Section 8.2.1, Duration of the study	Revised proposal for end of data collection: Data collection will be concluded four years after the last Cerdelga patient has been enrolled into the study.	Extension of enrollment period by approximately one year to enroll more Cerdelga patients than originally planned and duration of safety follow up ranging from 4 years to up to 6.5 years will provide long-term safety data on Cerdelga for a sufficient number of patients.
Abstract, Milestones; Section 5, Milestones; Section 8.2, Setting; Section 8.2.1, Duration of the study	The following text was removed: The number of patients from both of the groups who continue their observation in the safety sub-registry will be evaluated annually after the end of recruitment period to determine the need to replace patients who dropped out of the study for any reason prior to completion of their 4-year observation period. The utility/effectiveness of the sub-registry to provide longer term safety data will be re-evaluated at 5 years after the first Cerdelga patient has been enrolled.	Extension of enrollment period by approximately one year to enroll more Cerdelga patients than originally planned to account for the anticipated attrition of patients. Duration of safety follow up ranging from 4 years to up to 6.5 years. Overall, data will provide long-term safety information on Cerdelga for a sufficient number of patients without further replacement of Cerdelga patients who have dropped out during the course of sub-registry.
Section 5, Milestones	Updated recruitment duration to 32 months and expected date of the end of date collection to Q1 2025. Updated the expected date of final report of study results to Q3 2025.	To reflect amendment specific changes - to align with the revised proposal for end of data collection.

Section # and Name	Description of Change	Brief Rationale
Section 8.2, Settings; Section 8.2.3, Analysis populations; Section 8.8, Data analysis; Section 8.10, Limitations of the research methods	Removed text specifying that additional patients will be recruited for patients who switch from the Cerdelga to the Cerezyme group during the 4-year observation period, or for patients who dropped out for any reason in the Cerdelga group.	Extension of enrollment period by approximately one year to enroll more Cerdelga patients than originally planned to account for the anticipated attrition of patients will provide long-term safety data on Cerdelga for a sufficient number of patients without further replacement of Cerdelga patients who have dropped out during the course of sub-registry.
Section 8.2, Setting; Section 8.2.3, Analysis population(s); Section 8.3, Variables	Removed text stating that data for enrolled patients who switch from Cerdelga to Cerezyme or vice-versa during follow-up will be evaluated to and from the point of switch in therapy.	Text removed from sections other than Section 8.8. Data analysis to avoid duplication.
Section 8.3 Variables; Section 8.4, Statistical Analysis	Removed text regarding "change from the initial" abnormal laboratory results.	Consistency with removal of secondary analysis/endpoint.
Section 8.6.1, Determination of sample size	Revised text to specify true "cumulative" rate as follows: "With 100 patients on Cerdelga, there is more than 95% of probability of observing at least one patient with an AE if the true **cumulative** rate of such an event is 5%."	Precision.
Section 10.1.3.2, Adverse Event reporting to MAH/MAH representative	Updated text to specify that copies of medical records may be requested by the Sponsor. In such case the photocopy of requested documents should be sent (by fax or email) to MAH/MAH representative.	Consistency with current Sponsor process (simplification and standardization to the current clinical safety data flow).
Throughout	Typos have been corrected where necessary.	Clarifications.
Throughout	Minor editorial and document formatting revisions.	Minor, therefore have not been summarized.

Amended protocol 03 (19 December 2019)

Amended protocol 03 was submitted to the European Medicines Agency via procedure EMEA/H/C/PSA/S/0054 but was not endorsed by the PRAC; therefore amended protocol 03 was not implemented. MAH was requested to revise the protocol in line with the PRAC Assessment Report dated 11 June 2020, which was completed with amended protocol 04 of 31-Jul-2020, version 1 (electronic 6.0) for review.

This amended protocol (amendment 03) is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

Overall Rationale For The Amendment

- Changes in study milestones, updates to sections referring to the Risk Management Plan in line with recent changes in EU RMP for Cerdelga, and correction of typographical errors and further clarifications, as required.

- To propose a more realistic objective of reaching about 400 patient-years (which may require enrolling more than 100 patients to compensate for premature study discontinuations) instead of at least 100 Cerdelga patients have exactly 4 years of follow-up (as, for instance, some can be lost to follow-up or initiate another treatment before 4 years).

Protocol amendment summary of changes table

Section # and Name	Description of Change	Brief Rationale
Throughout	MAH name and address updated.	Administrative update.
PASS information	Name of author and contact details updated.	Administrative update.
Section 4 (Abstract; Rationale and background) and Section 6.2 (Rationale)	Important potential risks: "Vasovagal syncope" and "Off-label use in GD Type 2 and 3" were deleted from important potential risks list. Missing information: "Use in children" was removed from the missing information list.	To align with latest EU RMP V 6.1 (dated 28-Mar-2019).
Section 4 (Abstract, Study design)	Additional text was added to clarify the adult patient population with GD1 as "who have a CYP2D6 Poor Metabolizer (PM), IM, or Extensive Metabolizer (EM) phenotype".	For consistency with body text.
Section 4 (Abstract; Variables)	The following text was added: "The outcome variable will be a report of an AE, exposure will be duration (in months or years) of time of exposure to Cerdelga while enrolled in the sub-registry, grouping factors will include category of Treatment Status (defined below), duration of GD treatment (including Cerdelga or other GD treatments) prior to enrolling in the sub-registry, selected demographic and baseline characteristics such as age, sex, and genotype as listed in Section 8.7.5".	Clarification.
	Text regarding main analysis of interest was updated to reflect the amendment-specific changes.	Based on the preliminary data surveillance results, analysis by treatment status subgroup may not be possible due to insufficient numbers of patients within subgroups.
	The following text was added: "All summaries will be descriptive. No formal hypothesis testing will be performed."	Clarification
Section 4 (Abstract; Data analysis) and Section 8.8 (Data analysis)	The following text was added under analysis populations: "The analysis will be performed for each treatment group and overall by treatment status (if applicable)."	To complete the description of data analysis.

Section # and Name	Description of Change	Brief Rationale
Section 4 (Abstract; Data analysis), Section 8.8.1 (Primary analysis), Section 8.8.2 (Secondary analysis), and Section 8.8.3 (Exploratory analysis)	Primary analysis: "Incidence rate of AEs related to risks defined in RMP as important potential risks" was moved to exploratory analysis.	Moved to exploratory analysis as they are not part of the primary objectives of the study. However, the Sponsor acknowledges any safety concerns, potential risks, and selected missing information as per RMP and commits to present any AEs observed in the concerned group of patients (if available).
	"Summary of timing of CYP2D6 genotyping (prior to or following) initiation of Cerdelga" was updated to "Frequencies and percentages of timing of CYP2D6 genotyping (prior to or following) initiation of Cerdelga".	To clarify statistics in data analysis.
	"Summary of CYP2D6 predicted phenotype among Cerdelga-treated patients" was updated to "Frequencies and percentages of CYP2D6 predicted phenotype among Cerdelga-treated patients".	To clarify statistics in data analysis.
	"Frequency of types of GD among Cerdelga-treated patients" was updated to "Frequencies and percentages of types of GD among Cerdelga-treated patients".	To clarify statistics in data analysis.
	Secondary analysis: The following endpoint was added: "Change from the initial clinically significant abnormal laboratory results will be summarized descriptively by time points (as available)."	To complete secondary analysis.
	Exploratory analysis: New subsection and corresponding endpoint was added: "Frequencies and percentages of AEs related to risks defined in the RMP as important potential risks (if available)."	Moved from primary analysis to exploratory analysis as not part of primary objectives of the study. However, the Sponsor acknowledges any safety concerns, potential risks, and selected missing information as per RMP and commits to present any AEs observed in the concerned group of patients (if available).
Section 4 (Abstract, Data analysis) and Section 8.8.4	The following text was added: "Interim analysis" (heading added to Abstract only). "One interim analysis is planned in this study when patients treated with Cerdelga will collectively contribute to the study long-term follow up with about 200 patient-years."	To complete the description of interim analysis.

Section # and Name	Description of Change	Brief Rationale
Section 4 (Abstract; Analysis of endpoint)	Primary endpoint was updated to: "Incidence rate of any AE after 4 years of follow-up, adjusted for treatment status at enrollment (if applicable)". Exploratory endpoint new subsection and corresponding endpoint was added: "Adverse events related to risks defined in the RMP as important potential risks."	Clarification
Section 4 (Abstract; Milestones)	Text was updated to: "The utility/effectiveness of the sub-registry to provide longer-term safety data will be re-evaluated at 5 years after the first Cerdelga patient has been enrolled. Data collection will be concluded when all patients treated with Cerdelga will collectively contribute to the study long-term follow-up with 400 patient-years, at which time the analysis will be performed".	To propose a more realistic objective of reaching about 400 patient-years (which may require enrolling more than 100 patients to compensate for premature study discontinuations) instead of at least 100 Cerdelga patients have exactly 4 years of follow-up (as, for instance, some can be lost to follow-up or initiate another treatment before 4 years).
Section 5 (Amendments and updates)	This section and corresponding table were deleted.	To align with CPT template and to avoid duplication. Note: Document history is appropriately documented in Annex 4. Also, subsequent sections were re-numbered accordingly.
Section 5 (Milestones)	The following bullet points were updated to reflect the amendment-specific changes: "The utility/effectiveness of the sub-registry to provide longer-term safety data will be re-evaluated at 5 years after the first Cerdelga patient has been enrolled." "Data analysis will be performed after all patients treated with Cerdelga will collectively contribute to the study long-term follow-up with about 400 patient-years." "The AEs reported for the patients enrolled in the ICGG sub-registry will be reported in the Periodic Safety Update Reports (PSURs) in the EU regional annex". "An interim report of study results will be submitted when patients treated with Cerdelga will collectively contribute to the study long-term follow-up with about 200 patient-years". The study milestones summary table was updated.	To reflect amendment-specific changes.

Section # and Name	Description of Change	Brief Rationale
Section 8.2 (Setting)	Text was updated to: "Data collection will be concluded when all patients treated with Cerdelga will collectively contribute to the study long-term follow-up with about 400 patient-years at which time analysis will be performed". Sentence of potential countries for safety sub-registry was updated to include the Czech Republic and Romania. Text was updated to: "For patients who switch from the Cerdelga to the Cerezyme group during the 4-year observation period, additional patients will be recruited into the Cerdelga group to ensure about 400 patient-years is collectively achieved by patients treated with Cerdelga." "If appropriate, similar actions will be considered for patients who dropped out for any reason (including switch from Cerezyme to Cerdelga) in the Cerezyme group in order to keep the ratio of Cerdelga versus Cerezyme patients recruited for the sub-registry approximately 2:1."	To reflect the amendment-specific changes.
Section 8.2.1 (Duration of the study)	Text was updated to: "The number of patients for both of the groups who continue their observation in the safety sub-registry will be evaluated annually after the end of the recruitment period to determine the need to replace patients who dropped out of the study for any reason prior to completion of their 4-year observation period." "Data collection will be concluded when all patients treated with Cerdelga will collectively contribute to the study long-term follow-up with about 400 patient-years, at which time analysis will be performed."	To reflect the amendment-specific changes.
Section 8.2.3 (Analysis population[s])	Text was updated to: "For patients who switch from the Cerdelga to the Cerezyme group during the 4-year observation period, additional patients will be recruited into the Cerdelga group to ensure about 400 patient-years is collectively achieved by patients treated with Cerdelga." "If appropriate, similar actions will be considered for patients who dropped out for any reason (including switch from Cerezyme to Cerdelga) in the Cerezyme in order to keep the ratio of Cerdelga versus Cerezyme patients recruited for the sub-registry approximately 2:1."	To reflect the amendment-specific changes.

Section # and Name	Description of Change	Brief Rationale
Section 8.3 (Variables)	Text was updated to: "Other outcome variables include SAEs, events of interest, reported values and change from the initial clinically significant abnormal laboratory result in the course of AE follow-up, and frequencies and percentages of timing of CYP2D6 genotyping, and CYP2D6 predicted phenotypes and GD subtype among Cerdelga-treated patients will be presented."	To reflect the amendment-specific changes.
Section 8.4 (Statistical analysis)	The following sentence was added: "The risk of any AE in the Cerdelga group compared to Cerezyme will be evaluated in terms of the risk ratio with associated 95% confidence interval."	To clarify statistics in data analysis.
Section 8.6.1 (Determination of sample size)	Text was updated to: "Accordingly, a control group of safety sub-registry to descriptively compare the safety profile of Cerdelga to that of Cerezyme will include approximately 50 patients on Cerezyme." The following text was added "Based on the treatment experienced patients in the ENCORE study, the risk ratio of any AE comparing Cerdelga to Cerezyme is expected to be approximately 1.2."	To reflect the amendment-specific changes.
Section 8.7.5 (Patient data)	A row for "Concomitant medications for particular cases only" and the respective footnote were added to the in-text table.	To reflect the amendment-specific changes.
Section 8.8 (Data analysis)	The following text was added: "The analysis will be performed for each treatment group and overall (where appropriate) by treatment status (if applicable)."	To reflect the amendment-specific changes.
	The following text was updated: "For patients who switch from the Cerdelga to the Cerezyme group during 4-year observation period, additional patients will be recruited into the Cerdelga group to ensure about 400 patient-years is achieved collectively by patients treated with Cerdelga."	To reflect the amendment-specific changes.
	"If appropriate, similar actions will be considered for patients who dropped out for any reason (including switch from Cerezyme to Cerdelga) in the Cerezyme group in order to keep the ratio of Cerdelga versus Cerezyme patients recruited for the sub-registry approximately 2:1."	To reflect the amendment-specific changes.
	"Summaries will also be presented for three categories of treatment status within each of the Cerdelga and Cerezyme groups (if applicable). The implicit assumption of constant incidence rates over time will be evaluated."	To check the assumption of primary analysis.
	"As a part of exploratory analysis, specific analyses of the potential risks in the RMP and any new safety concern that could arise from the sub-registry will be conducted."	To check the assumption of primary analysis.

Section # and Name	Description of Change	Brief Rationale
Section 8.10 (Limitations of the research methods)	Text was updated to: "To determine if there are any differences between patients who accept to enroll in the sub-registry and those who do not and, if these differences have any impact on the generalizability of the results, baseline characteristics (including age, sex, genotype, GD history, GD treatment history, current GD treatment and CYPD phenotype) of patients who were enrolled in the safety sub-registry will be compared based on provisions of ICGG Gaucher registry ICF with baseline characteristics of ICGG Gaucher registry patients who did not accept to enroll into safety sub-registry, if this information can be obtained." "When patients on Cerdelga who drop out for any reason, additional patients will be recruited into the Cerdelga group to ensure about 400 patient-years is achieved collectively by patients treated with Cerdelga. Duration of data collection for patients enrolled into the Cerdelga group in place of patients who dropped out for any reason (including switch from Cerezyme to Cerdelga) will be determined at the time of re-evaluation of the sub-registry effectiveness to provide long-term safety data (at 5 years after the first Cerdelga patient has been enrolled)."	To reflect the amendment-specific changes.
Section 10.1.3.2 (Adverse event reporting to MAH/MAH representative)	Text was updated to: "However, for patients who are enrolled in the sub-registry, AE reporting should be done only in the sub-registry database (AE CRF) and not directly to GPV".	To clarify that "AE reporting" is required, not "ADR reporting.
Annex 3: Country-specific requirements	New Annex 3 (Country-specific requirements) heading was added.	Administrative update.
Throughout	Typos have been corrected where necessary.	Clarifications.
Throughout	Minor editorial and document formatting revisions.	Minor, therefore have not been summarized.

Amended protocol 02: (11-Sep-2018)

This amended protocol (Amendment 02) is considered to be nonsubstantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union because it neither significantly impacts the safety or physical/mental integrity of participants nor the scientific value of the study.

Overall Rationale for the Amendment

According to EMA post-authorization procedural advice for users of the centralized procedure, changes in the milestones affecting the timelines for the submission of the final study reports

should be considered as substantial amendments to the protocol and should consequently be submitted for assessment to the PRAC according to the Article 107o of Directive 2001/83/EC.

Protocol amendment summary of changes table

Section # and Name	Description of Change	Brief Rationale
4. Abstract 7.1 Background 7.2 Rationale	'Peripheral neuropathy' was removed from section 'Rationale and background'.	Peripheral neuropathy was lifted as an important potential risk from the EU RMP V4.0 (dated 13-Apr-2017).
4. Abstract 7.2 Rationale	'Use in patients with hepatic impairment' was removed from section 'Rationale and background'.	Use in patients with hepatic impairment was lifted as Missing information from the EU RMP V5.1 (dated 19-Mar-2018).
4. Abstract 7.2 Rationale	'Use in patients with renal impairment' was removed from section 'Rationale and background'.	Use in patients with renal impairment was lifted as Missing information from the EU RMP V5.1 (dated 19-Mar-2018).
4. Abstract. Study design. 9.1 Study design. 9.2 Settings.	'… Cerdelga, a treatment approved in ~~some~~ countries for adult patients with GD 1.' was changed to '… Cerdelga, a treatment approved in many countries for adult patients with GD 1.	Number of countries where Cerdelga is approved increased since the time of protocol amendment 01 release.
6. Milestones	Updated start of data collection. Subsequent milestones/events (including planned date of CSR) were updated accordingly.	Change in the start of data collection.
11.1.3.2 Adverse event reporting to MAH/MAH representative	Global Pharmacovigilance & Epidemiology (GPE) changed to Global Pharmacovigilance (GPV)	Administrative change

Amended protocol 01: (27-Mar-2017)

This amended protocol (Amendment 01) is considered to be nonsubstantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union because it neither significantly impacts the safety or physical/mental integrity of participants nor the scientific value of the study.

Overall Rationale for the Amendment

Introduction of the option to temporarily stop the treatment with Cerdelga or Cerezyme with the description of collection of AEs during the period when a patient temporarily stops the treatment.

Protocol amendment summary of changes table[a]

Section # and Name	Description of Change	Brief Rationale
Abstract (data sources), 9.7.1, 9.7.5	If a patient temporarily stops the treatment with Cerdelga or Cerezyme, collection of all AEs will be continued for the duration of 30 days and after that period only new SAEs will be collected and follow-up of ongoing AEs will be performed. Collection of all AEs in ELISAFE will be resumed when the patient restarts treatment with Cerdelga or Cerezyme.	To describe collection of AEs in situation when patient temporarily stops the treatment.

a Protocol Amendment 01 (prior to the start of data collection) - table includes only major change.

Annex 5 Additional information

None

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