NON-INTERVENTIONAL POST AUTHORIZATION SAFETY STUDY (PASS) REPORT

COMPOUND: eliglustat

A prospective multicenter observational post-authorization safety sub-registry study (PASS) 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

The Study is conducted by Sanofi hereinafter referred also as the "MAH".

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PASS Information

Title	A prospective multicenter observational post-authorization safety sub-registry study (PASS) to characterize the long-term safety profile of commercial use of eliglustat (Cerdelga®) in adult patients with Gaucher disease
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EU PAS register number	EUPAS11998
Active substance	Eliglustat
Medicinal product	Cerdelga®
Product reference	EU/1/14/974/001-004
Procedure number	EMEA/H/C/003724
Marketing authorization holder(s)	Sanofi 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	Participants were recruited from sites in countries where Cerdelga® was already on the market or it would become available on the market during the sub-registry enrollment period (Belgium, Denmark, Greece, Italy, Portugal, Romania, Spain, and United Kingdom).
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Marketing authorization holder(s)

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1 ABSTRACT

Title

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

Date of the abstract: 24 Jun 2025

Main author (Name/affiliation): [redacted]

Keywords

Gaucher disease, International Collaborative Gaucher Group (ICGG) Gaucher Registry, Cerdelga (eliglustat), CYP2D6, Post-authorization safety study (PASS)

Rationale and background

This sub-registry is set up to complement the International Collaborative Gaucher Group (ICGG) Gaucher Registry, a multi-center, international, longitudinal, observational program for participants with Gaucher disease (GD) designed to track the natural history of the disease, and outcomes of participants on GD treatments.

Similarly, using the same ICGG technology platform, the sub-registry was designed to follow participants on Cerdelga and Cerezyme, and in particular to assess the long-term safety profile of Cerdelga, and descriptively compare it with Cerezyme[1] (imiglucerase) by collecting real-world safety data as part of a post approval commitment.

Though the studies supporting the registration of Cerdelga collected data for multiple years (up to 9.3 years for the Phase 2 study), an extended follow-up of participants 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 these include important potential risks and missing information.

<u>Important potential risks:</u>

- Drug-drug interactions:
  - Use with CYP2D6 (cytochrome P450 2D6) and/or CYP3A (cytochrome P450 3A) inhibitors.

[1] Cerezyme® is a registered trademark of Sanofi B.V.

  - Use with strong CYP3A inducers.
  - Use with P-glycoprotein (P-gp) or CYP2D6 substrates.
- Use of Cerdelga in participants who are CYP2D6 indeterminate metabolizers or non-genotyped participants.
- Cardiac conduction disorders and arrhythmias.

Missing information:

- Use in participants 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 participants 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).

This sub-registry will allow for the 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 participants and the total number of person-years of follow-up are not pre-defined, as not all participants have been identified, nor all participants who could meet the study criteria wished to participate. The sub-registry database was 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 adverse events (AE) are not reported by the HCPs, in the ELISAFE study safety sub-registry, all AEs occurring during the sub-registry participation, regardless of relationship to treatment, were collected and reported.

Research question and objectives

Primary objective

The overall primary goals of the ELISAFE study are:

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 participants' CYP2D6 predicted phenotype.

- To assess compliance/adherence of HCPs to the Cerdelga label with regard to use in Gaucher disease Type 1 (GD1).

Study design

This is a safety sub-registry of the ICGG Gaucher Registry (DIRECC07009), a non-interventional, multicenter, prospective PASS of Cerdelga, a treatment approved in many countries for adult participants with GD1 who have a CYP2D6 poor metabolizer (PM), intermediate metabolizer (IM), or extensive metabolizer (EM) phenotype. Participating Investigators enrolled eligible participants after the decision to treat with Cerdelga or Cerezyme. The study enrolled participants who received Cerdelga or Cerezyme, for the first time or as part of ongoing treatment of their GD.

Participants are receiving treatment as determined by their HCPs and guided by the provisions of the prevailing locally approved product labeling and educational materials. Study participants underwent clinical assessments, often as outlined in the ICGG Gaucher Registry Minimum Recommendations for Monitoring Patients with Gaucher disease Type 1 guidelines, and as determined by their treating HCP. All treatment decisions and medical assessments were at the discretion of the HCPs and were not mandated by study design or protocol. No experimental invention was involved.

The observational nature of this study design allowed for an estimate of "real-world" safety experience of Cerdelga, among participants who receive Cerdelga, in a commercial versus clinical study setting. Participants completed and signed a patient written informed consent form (ICF) specific to this safety sub-registry before participating.

Selected data from the sub-registry case report forms (CRF) were monitored periodically against source documents at the treating HCPs site by a representative of Sanofi (or its designee) to ensure data completeness and accuracy.

Setting

- Site and participant selection: No set duration was planned for this study. HCPs enrolled eligible participants after the decision to treat with Cerdelga or Cerezyme. Participants could remain in the safety sub-registry as long as they received Cerdelga or Cerezyme and the sub-registry remained open. The sub-registry study participants were recruited from sites in countries where Cerdelga was already on the market during the sub-registry enrollment period. Both existing ICGG Gaucher Registry sites and new sites, which could potentially become ICGG Gaucher Registry sites, were considered for the study. The HCPs at these sites, who already treated patients with GD1, were invited to participate and enroll eligible patients in the sub-registry.
- Overall participation status: Countries for safety sub-registry included Belgium, Denmark, Greece, Italy, Portugal, Romania, Spain and United Kingdom. There was no limit of participants or sites per country.
- Data collection: Information specific to the sub-registry was collected in specifically designed electronic case report forms (eCRFs). A primary contact person located at each participating site was designated as the individual responsible for completing and entering eCRFs into the sub-registry database.

- Safety data collection: Safety data were collected in specifically designed eCRFs. Data collected by sub-registry HCPs or their designees were submitted to the sub-registry for central processing and evaluation. Adverse events (AEs) and serious adverse everts (SAEs) were prospectively collected upon signing the ICF and on an ongoing basis including during scheduled visits (ie, participants were to report any AEs, or SAEs during the study period) as well as spontaneous AEs reported by the participants to the HCP following them at any time.

Participants and study size, including dropouts

Based on the countries where Cerdelga is available on the market, at least 100 participants on Cerdelga were planned to be recruited in the study and approximately 50 participants on Cerezyme were planned to be recruited in the control group of this safety sub-registry to descriptively compare the safety profile of Cerdelga to that of Cerezyme.

At the time of the data extraction for the final analysis a total of 166 participants were enrolled, however, 1 participant under Cerezyme was excluded from the safety population analyzed due to an error in enrollment (the participant did not meet all eligibility criteria). Out of the 165 eligible participants, 109 were enrolled under Cerdelga treatment and 56 were enrolled under Cerezyme treatment. A total of 20 participants (12.1%; 15 [13.8%] enrolled under Cerdelga and 5 [8.9%] enrolled under Cerezyme, respectively) had discontinued the study. Two participants prematurely ended the study (before the final cut-off date) because of site closure due to the site's non-compliance to Good Clinical Practice (GCP).

Variables and data sources

- **Data management, review, validation:** Data were collected from enrolled participants by participating HCPs at the time of participants' office visits, occurring as per local practice visit schedule or following the Minimum Recommendations for Monitoring Patients with Gaucher disease Type 1 guidelines of the ICGG Gaucher Registry. Adverse events were collected from participants at least every 6 months. If the time between the last ELISAFE sub-registry assessment and the next planned ICGG Gaucher Registry assessment was expected to be more than 6 months, a phone call to inquire about new/ongoing AEs was recommended. If a participant temporarily stopped (for any reason) treatment with Cerdelga or Cerezyme and the treating HCP considered that the treatment could be potentially restarted, the participant could stay in the sub-registry as long as the sub-registry was open, if the participant was willing to participate and was available for follow-up assessments. Collection of all AEs continued for the duration of 30 days after stopping Cerdelga or Cerezyme, and after that period only new SAEs were collected and follow-ups of ongoing AEs were performed. Collection of all AEs in ELISAFE study resumed when the participant restarted treatment with Cerdelga or Cerezyme. Data were collected using an eCRF. Information regarding the utilization of Cerdelga was collected at enrollment for those participants receiving Cerdelga or at the time of a change of treatment to Cerdelga as well as at each study follow-up assessment. The computerized handling of the data by the MAH/MAH representative may generate additional requests to which the participating HCP was obliged to respond by confirming or modifying the data questioned. Data collection and validation procedures were detailed in appropriate

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

- **Statistical considerations:** The main analysis of interest for the final report is the incidence rate of any AE report for Cerdelga and Cerezyme-treated participants during their participation in the sub-registry. Continuous variables were summarized using descriptive statistics (number of observations available [n], mean, median, 1st quartile, 3rd quartile, standard deviation [SD], minimum, and maximum); categorical variables were summarized using frequencies and percentages.
- **Variables and evaluation criteria:** The main variable of interest for this report is the incidence rate of any AE report for Cerdelga-treated participants during their participation in the sub-registry. Summaries are also presented for 3 categories of treatment status within the Cerdelga group (when applicable).

  The corresponding primary evaluation criterion was the IR of each AE (the number of participants with at least 1 AE divided by the total number of patient-years at risk of an event). Summaries are also presented for 3 categories of treatment (naïve to any GD treatment, naïve to Cerdelga, and experienced to Cerdelga) within the Cerdelga group, when applicable.

  Secondary evaluation criteria:

  - Occurrence of any SAE; corresponding evaluation criterion was the incidence rate (IR) of each SAE (the number of participants with at least 1 SAE divided by the total number of patient-years at risk of an event);
  - Occurrence of any related AE; corresponding evaluation criterion was the IR of each related AE (the number of participants with at least 1 related AE divided by the total number of patient-years at risk of an event);
  - Duration of exposure in patient-years and number of exposure episodes for Cerdelga and for Cerezyme treatment and treatment interruptions during ELISAFE.
- **Data analyses:**

  Primary and secondary analysis:

  - The main analyses include any AE reported for Cerdelga-treated patients during the index treatment period. AEs occurring out of the index treatment period were not taken into account in the main analyses.
  - Continuous variables are summarized using descriptive statistics (n, mean, median, 1st quartile, 3rd quartile, standard deviation [SD], minimum, and maximum); categorical variables are summarized using frequencies and percentages. The percentage of categorical variables are displayed at 1 decimal point. For descriptive statistics, mean and median are displayed at 2 decimal points; minimum and maximum are displayed at 1 decimal point; standard deviation is displayed at 3 decimal points.
  - Exposure-adjusted incidence rates were used to summarize the AE reported for cumulative Cerdelga treatment. The exposure-adjusted incidence rate is defined as the number of participants with a specific event divided by the Cerdelga patient-years at risk. For participants with the event, the Cerdelga exposure-time for the patient-years

at risk was calculated to the time of the event; if a participant has multiple occurrences of the event, it was calculated to the first occurrence. For participants without the event, the participant's total exposure-time to Cerdelga was used.

- Drug exposure in ELISAFE was computed as treated for the ELISAFE Cerdelga and Cerezyme treatments.
- For each participant, a treatment period (ie, exposure episode) is from the first day of administration of the treatment in ELISAFE to the last assessment date or date of study discontinuation or date of change of treatment (switch or permanent discontinuation of therapy).
- A patient with a switch in treatment (Cerdelga to Cerezyme or Cerezyme to Cerdelga) was included in treatment duration summaries for Cerdelga (patient's treatment period[s] for Cerdelga) and for Cerezyme (patient's treatment period[s] for Cerezyme).
- Duration of study treatment was summarized in units of months.
- The total treatment duration for Cerdelga and for Cerezyme was summarized in patient-year units with the number of participants with any exposure to each treatment.
- Years on Cerdelga and on Cerezyme treatment before ELISAFE enrollment were computed similarly to the above method, for each participant.

Results

- **Overall participation status:**

  The study enrollment period, for this report was from 18 April 2018 to 30 December 2020. There was no set duration of participation in the study. Participants could remain in the sub-registry as long as they received Cerdelga or Cerezyme and as long as the sub-registry remained open. Data collection was set to be concluded 4 years after the last Cerdelga participant had been enrolled in the study. There was no predefined number of sites which were planned to be opened for this sub-registry, nor there was a predefined number of participants to be enrolled per site. The ratio of Cerdelga versus Cerezyme recruited for the study was approximately 2:1.

  The final results as of the date of data extraction of 13 February 2025 are the following:

- **Descriptive data:**
  - The mean age of participants at enrollment was 42.7 ±14.1 years (Cerdelga 42.9 ±14.3, Cerezyme 42.1 ±13.9). There was an even distribution of males and females, 85 (51.5%) males, 80 (48.5%) females (56 [51.4%] males and 53 [48.6%] females for Cerdelga, 29 [51.8%] males and 27 [48.2%] females for Cerezyme).
  - The major medical history conditions of participants at enrollment included Musculoskeletal and connective tissue disorders in 63 (38.2%) participants (most commonly Arthralgia in 14 [8.5%], Osteoporosis in 11 [6.7%], Osteonecrosis in 10 [6.1%] and Osteopenia in 9 [5.5%] participants), followed by Metabolism and nutrition disorders in 32 (19.4%) participants (most commonly Hypercholesterolemia in 9 [5.5%] and Vitamin D deficiency in 5 [3.0%] participants).

- The median duration of GD from time of diagnosis was 18.91 ±11.49 years. The mean age at diagnosis was 23.18 ±14.98, and the majority of participants (163 [98.8%]) were classified by the Investigator as having a diagnosis of GD1.
- Mean duration (months) of exposure prior to first treatment administration was 15.20 ±12.69 for Cerdelga, 147.35 ±85.46 for Cerezyme, and 89.41 ±64.34 for other GD treatments

- **Participation per period of the study:**

  A total of 166 participants signed the ICF of whom all but one participant met the eligibility criteria. At the time of enrollment, 110 were receiving Cerdelga and 56 were receiving Cerezyme (later group including the non-eligible participant). Participants were enrolled from 29 sites in this study. Participating countries, at the time of the cut-off date, were: Belgium, Denmark, Greece, Italy, Portugal, Romania, Spain and United Kingdom. There was an even contribution to enrollment from most countries; highest recruiter was Spain (47 [28.3%]), followed by Italy (38 [22.3%]) and the United Kingdom (33 [19.9%]) participants. Regarding the rate of attrition, of the 166 participants enrolled in the study 20 (12.1%) participants (15 on Cerdelga and 5 on Cerezyme treatment) prematurely discontinued the study and 150 (90.9%) completed ≥4 years in the study.

- **Main Evaluation Variables:**

  The exposure-adjusted incidence rate of AEs for participants on Cerdelga treatment was 0.475 with 221.2 patient years at risk, and the most common AEs were those related to Gastrointestinal disorders reported in 45 participants (34.6% [IR: 0.100]). The most common SAEs by SOC were reported in the Infections and infestations in 4 participants (3.1% [IR: 0.007]). Exposure-adjusted incidence rate of SAEs for any Cerdelga treatment was for 28 events in 16 participants (IR: 0.030), and for any AEs related to treatment was for 51 events in 34 participants (IR: 0.072). Higher exposure-adjusted incidence rate for related AE was recorded for Gastrointestinal disorders (27 events in 23 participants [IR: 0.046]).

  For Cerezyme, the exposure adjusted incidence rate of any AE was 0.339 with 112.1 patient years at risk, the most common AE were those related to infections and infestations in 14 (20.9% [IR: 0.072]) participants. In terms of SAEs, neoplasms were reported in 2 (3.0%, 237.5 patient years at risk) participant. Exposure adjusted IR of SAE for any Cerezyme treatment was for 10 events in 6 participants (0.026) and for any AE related to treatment was 7 events in 2 participants (0.009).

- **Secondary Evaluation Variables:**

  Compliance to the Cerdelga label was over 98.2%. Cerdelga was administered to:

  - Adult participants,
  - Participants diagnosed with GD1.

  Majority (97.2%) of the participants receiving Cerdelga had a CYP2D6 genotype test performed prior to Cerdelga initiation to determine CYP2D6 metabolizer status.

  No participant with URM phenotype was administered Cerdelga.

Discussion and Conclusion

The main variables of interest for this report are the incidence rate of any AEs for Cerdelga-treated participants during their participation in the sub-registry and the compliance or adherence of HCPs as to the utilization of Cerdelga. Summaries are also presented for 3 categories of treatment status within the Cerdelga group (when applicable) in the appendices; all results presented in this report correspond to “any Cerdelga treatment” analysis.

Overall, Cerdelga showed a safety profile consistent with that observed during the clinical trials in adults with GD1 and market experience.

The data shows that the compliance/adherence of HCPs to the Cerdelga label was very high with regard to use in GD1 adults, CYP2D6 genotyping prior to initiation of Cerdelga, and use in the appropriate CYP2D6 metabolizer groups.

Marketing Authorization Holder(s)

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Study Personnel

The Coordinating Investigator’s and the Sponsor’s responsible medical officer’s signed approvals of the report are provided in Annex 2.

This report was prepared by

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The Company Internal Staff

The Company was responsible for providing adequate resources to ensure the proper conduct of the study.

The Company was responsible for local submission(s) complying with data protection rules and any other local submission(s) required.

Names and affiliations of Principal Investigators

See Section 3 “Investigators”.

National coordinators

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