TITLE PAGE

NON-INTERVENTIONAL POST-AUTHORISATION SAFETY STUDY (PASS) PROTOCOL

Protocol Title:	Drug utilisation study of eliglustat for the treatment of Gaucher Disease Type 1 in Europe using electronic healthcare records
Protocol Number:	ELIGLC06913
Protocol Version:	3.0
Protocol Date:	23 June 2023
Date and Version of Previous Protocol:	17 Nov 2015; Version 2.0
European Union (EU) Post-authorisation Study (PAS) Register Number:	EUPAS34611
Active Substance:	A16AX10 (eliglustat)
Medicinal Product:	Eliglustat (Cerdelga®)
Product Reference:	EMEA/H/C/003724
Procedure Number:	EMEA/H/C/003724
Date of Authorisation for Marketing in Europe	19 January 2015
Marketing Authorisation Holder	Sanofi B.V. Paasheuvelweg 25 1105 BP Amsterdam The Netherlands

Joint Post-authorisation Safety Study (PASS):	No
Clinical Research Organisation:	Parexel International
Research Question and Objectives:	The main objective is to estimate the dose and duration of eliglustat therapy as well as the proportion, therapeutic class, and duration of past and concomitant medication use in patients with Gaucher Disease Type 1, treated with eliglustat. The concomitant medications of interest (CMI) are strong and moderate CYP2D6 inhibitors, strong and moderate CYP3A inhibitors, strong CYP3A inducers, P-gp substrates and CYP2D6 substrates. Simultaneous use of strong or moderate CYP2D6 inhibitors with strong or moderate CYP3A inhibitors concomitantly with eliglustat will be explored, if feasible.
Countries of Study:	France, Denmark, Germany and Israel Data sources of these countries accepted to participate but not all research agreements have been signed yet.

SPONSOR

Sponsor:

Sanofi B.V.

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The Netherlands

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SIGNATURE PAGE

Declaration of Qualified Person Responsible for Pharmacovigilance (QPPV) or Sponsor's Responsible Medical Officer

Title: Drug utilisation study of eliglustat for the treatment of Gaucher Disease Type 1 in Europe using electronic healthcare records

This study protocol was subjected to critical review. The information it contains is consistent with the International Society for Pharmacoepidemiology Guidelines on Good Pharmacoepidemiology Practices.

_____ _____

[redacted]

Date

Declaration of the Investigator

Title: Drug utilisation study of eliglustat for the treatment of Gaucher Disease Type 1 in Europe using electronic healthcare records

All documentation for this study that is supplied to me and that has not been previously published will be kept in the strictest confidence. This documentation includes this study protocol and other scientific data.

The study will not be commenced without the prior written approval of a properly constituted Independent Ethics Committee (IEC). No changes will be made to the study protocol without the prior written approval of the Sponsor.

I have read and understood and agree to abide by all the conditions and instructions contained in this protocol.

Responsible investigator of the local study centre

_____ _____

Date

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Figures in Text

2 LIST OF ABBREVIATIONS

Abbreviation	Definition
ADS	Analytical dataset specification
ATC	Anatomical Therapeutic Chemical
BIPS	Leibniz Institute for Prevention Research and Epidemiology
CépiDc	Centre d'épidémiologie sur les causes médicales de Décès (epidemiological Centre on medical causes of Death)
CESREES	Comité éthique et scientifique pour les recherches, les études et les évaluations dans le domaine de la santé (Ethical and Scientific Committee for Research, Studies and Evaluations in the Health Field)
CMI	Concomitant medication(s) of interest
CNIL	Commission Nationale de l'Informatique et des Libertés (National Commission on Informatics and Liberty)
CNS	Central nervous system
DUS	Drug utilisation study
EMA	European Medicines Agency
ERT	Enzyme replacement therapy
EU	European Union
GD	Gaucher disease
GD1	Gaucher disease type 1
GePaRD	German Pharmacoepidemiological Research Database
GP	General practitioner
HCP	Health care provider
ICD-10	International Classification of Diseases and related health problems, 10t^{h} edition
IEC	Independent Ethics Committee
LSD	Lysosomal storage disease
NHS	National Health Service
NPR	National Prescription Registry
PRAC	Pharmacovigilance Risk Assessment Committee
SAP	Statistical analysis plan
SmPC	Summary of products characteristic
SNDS	Système National des Données de Santé (National Health Data System)
SRT	Substrate reduction therapy

3 RESPONSIBLE PARTIES

Sponsor	Sanofi B.V. Paasheuvelweg 25 1105 BP Amsterdam The Netherlands
Principal Investigator	[redacted]
Contract Research Organisation	Parexel International One Kilmainham Square Inchicore Rd. Dublin 8, Ireland +3531 473 9500

Note that formal participation of each data source to the study will be dependent on Ethics Committee approval. Also, these data sources accepted to participate but not all research agreements have been signed yet.

4 ABSTRACT

Protocol Title:	**Error! Reference source not found.**
Protocol Number:	**Error! Reference source not found.**
Protocol Version:	**Error! Reference source not found.**
Protocol Date:	**Error! Reference source not found.**
Author (of version 3.0):	Etsuko Amano on behalf of Sanofi Medical Writing Services Parexel International
Sponsor:	**Error! Reference source not found.**
Study Centres:	France, Denmark, Germany and Israel
Rationale and Background:	Eliglustat (Cerdelga®) is an oral treatment indicated in Europe for the long-term treatment of adult patients with Gaucher Disease Type 1 (GD1) who are CYP2D6 poor metabolisers, intermediate metabolisers or extensive metabolisers. Eliglustat is metabolised primarily by the cytochrome P450 enzyme CYP2D6, and to a lesser extent by the cytochrome P450 enzyme CYP3A. The ability to metabolise drugs through the CYP2D6 pathway may vary between individuals, leading to intervariable plasma concentrations of eliglustat depending on the individual's CYP2D6 metaboliser phenotype. The concomitant use of drugs inhibiting the CYP2D6 and the CYP3A enzyme activity may lead to substantially elevated eliglustat plasma concentrations. On the other hand, concomitant use of strong CYP3A inducers, may decrease eliglustat plasma concentrations. Conversely, eliglustat is a P-gp and CYP2D6 inhibitor; concomitant administration of eliglustat may increase plasma concentrations of P-gp and CYP2D6 substrate substances.
Research Question and Objectives:	The primary objective of this Drug Utilisation Study (DUS) is to estimate the dose and duration of eliglustat therapy as well as the proportion, therapeutic class, and duration of past and concomitant medication use in GD1 patients treated with eliglustat. The concomitant medications of interest (CMI) are strong and moderate CYP2D6 inhibitors, strong and moderate CYP3A inhibitors, strong CYP3A inducers, P-gp substrates and CYP2D6 substrates. Simultaneous use of strong or moderate CYP2D6 inhibitors with strong or moderate CYP3A inhibitors concomitantly with eliglustat will be explored, if feasible. The secondary objective of the DUS is to describe the healthcare service pattern (i.e., prescriber's specialty and types of patient visit) for the prescriptions of concomitant medications in patients treated with eliglustat.
Study Design:	This is a drug utilisation study based on the follow-up of a cohort of GD1 patients treated with eliglustat. The study period will be from one year before the first prescription of eliglustat in each data source to the study end (i.e., data extraction date) planned on Q3 2024.

Population: Gaucher Disease Type 1 patients in France, Denmark, Germany and Israel who are prescribed eliglustat after approval of the drug in each country.

Variables: Data will be collected on dose and duration of eliglustat as well as on therapeutic class and duration of drugs used concomitantly with eliglustat that are susceptible to significantly interfere with eliglustat metabolism or whose plasma concentration might be altered by eliglustat intake. These drugs are strong and moderate CYP2D6 inhibitors, strong and moderate CYP3A inhibitors, strong CYP3A inducers, P-gp substrates and CYP2D6 substrates. Data will also be collected on the age, sex and death date of GD1 patients, as well as (whenever feasible) on prescriber's specialty and type of patient visit.

Data Sources: Use of secondary data from prescription databases running in the four selected countries. Of note, there is generally a time-lag (different for each selected country) between data collection and availability of complete set of data in prescription databases.

Study Size: All GD1 patients with an eliglustat prescription in the prescription databases will be included. A minimum number of 128 GD1 patients treated with eliglustat is expected.

Data Analysis: Descriptive analysis of eliglustat therapy in terms of duration and dose.

Descriptive analysis of the past medication use (one year prior to the exposure period) and concomitant medication use (i.e., during the exposure period) in terms of proportion, therapeutic class and duration.

Descriptive analysis of the healthcare service pattern (i.e., prescriber's specialty and types of patient visit) for the use of concomitant medications.

Milestones: A final report will be submitted at the latest in Q4 2024.

Milestone	**Planned Date**
Start of data collection	Q3 2022
End of data collection	Q3 2024
Final report of study results	Q4 2024

5 AMENDMENTS AND UPDATES

This protocol was first written and submitted to Pharmacovigilance Risk Assessment Committee (PRAC) as version 1.0 in 2015. Due to the comments received from PRAC during the assessment procedure, the protocol was updated and finalised as version 2.0 and approved by PRAC. The protocol was then updated several times as internal draft versions (not finalised due to feasibility issues in relation to the access to the data in the different countries) and this last final version was updated in June 2023.

Version	Date	Section of study protocol	Amendment or update	Reason
3.0	23 June 2023	Throughout the protocol	Update	1. Information was updated due to the change of CRO. 2. The protocol was transferred from the previous CRO's template to Parexel template. 3. The sources of data were updated. Initially, this study was planned to be conducted in Belgium, Italy, Norway and Scotland. In 2020, Italy, Norway and Scotland were removed and replaced by France, Germany and Denmark. In 2021, Israel was also added to the DUS. Israel is considered as a European country since several agreements are in place between the European Union and Israel, including EMA agreements. In January 2023, Belgium was removed. 4. Some missing information was added from the SAP, including endpoints.

Abbreviation: CRO = Contract Research Organisation; DUS = Drug Utilisation Study; EMA = European Medicines Agency; SAP = statistical analysis plan

6 MILESTONES

Milestone	Planned Date
Registration in the EU PAS register	Q2 2020
Start of data collection*	Q3 2022
End of data collection*	Q3 2024
Final report of study results	Q4 2024

* Definition according to the GVP Module VIII - Post-authorisation safety studies (Rev 3) (accessible at: https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-good-pharmacovigilance-practices-gvp-module-viii-post-authorisation-safety-studies-rev-3_en.pdf)

Abbreviations: EU = European Union, GVP = Good pharmacovigilance practices, PAS = Post authorisation Study, Q = quarter

This Drug Utilisation Study (DUS) has been registered in the European Union (EU) PAS register in April 2020. Its registration number is EUPAS34611.

Data collection corresponds to the data extraction from each database and started in Q3 2022 (Germany). At this date, data spanning from one year before the first prescription of eliglustat to the date of last available data in each database will be extracted.

The end of data collection may be adjusted according to the date of last database update in each data source.

A final report will be submitted to the European Medicines Agency (EMA) at the latest in Q4 2024.

7 BACKGROUND AND RATIONALE

7.1 Background

Eliglustat, an oral substrate reduction therapy (SRT) for the treatment of Gaucher Disease Type 1 (GD1), is metabolised mainly by CYP2D6 and to a lesser extent by CYP3A4. Concomitant administration of substances affecting CYP2D6 or CYP3A4 activity may alter eliglustat plasma concentrations. Eliglustat is an inhibitor of P-gp and CYP2D6; concomitant administration of eliglustat with P-gp or CYP2D6 substrate substances may increase the plasma concentration of those substances. Therefore, it is important that the use of strong and moderate CYP2D6 inhibitors, strong and moderate CYP3A inhibitors, strong CYP3A inducers, P-gp substrates and CYP2D6 substrates as concomitant medications among patients treated with eliglustat be carefully monitored.

CYP2D6, a member of the cytochrome P450 mixed-function oxidase system, is one of the most important enzymes involved in the metabolism of xenobiotics in the body. CYP2D6 is responsible for the metabolism and elimination of approximately 25% of all clinically used drugs. For drugs that are metabolised by CYP2D6 (i.e., CYP2D6 substrates), certain individuals will eliminate these drugs very quickly (ultra-rapid metabolisers) while others will metabolise slowly (poor metabolisers). If a drug dose is metabolised too quickly, this may not achieve adequate plasma concentrations to achieve therapeutic effects. If a drug dose is metabolised too slowly, elevated plasma concentrations may occur, that potentially may lead to side effects. CYP2D6 metaboliser phenotype indicates the speed at which a drug is metabolised by CYP2D6. It can often be predicted, using genotyping, and is classified into four categories: poor (slow), intermediate, extensive, and ultra-rapid (fastest). Patients for whom no phenotype can be predicted based on genotyping are considered indeterminate metabolisers. Hence the patient's dose of a drug may have to be adjusted considering the patient's CYP2D6 metaboliser phenotype.

Certain drugs may function as inhibitors of CYP2D6 activity; decreased CYP2D6 enzyme activity could lead to increased plasma concentrations of CYP2D6 substrates. When administered concomitantly with CYP2D6 substrates, CYP2D6 inhibitor drugs might contribute to the occurrence of side effects. CYP2D6 inhibitor drugs can be classified as strong, moderate or weak inhibitors.

CYP3A is the most abundant cytochrome P450 enzyme in the body (mainly found in the liver and intestine) and is responsible for the metabolism of nearly 50% of therapeutic compounds. Certain drugs may function as inhibitors of CYP3A activity and can be classified as strong, moderate or weak inhibitors. Decreased CYP3A enzyme activity could lead to increased plasma concentrations of CYP3A substrates when administered concomitantly, and, in some cases, result in side effects.

Some drugs may function as inducers of CYP3A activity; increased CYP3A enzyme activity could lead to decreased plasma concentrations of CYP3A substrates.

Eliglustat is indicated in the EU for the long-term treatment of adult patients with GD1, who are CYP2D6 poor metabolisers, intermediate metabolisers or extensive metabolisers. Eliglustat is an inhibitor of P-gp and CYP2D6 in vitro; concomitant administration of eliglustat with P-gp or CYP2D6 substances may increase the plasma concentration of those substances. Eliglustat is contraindicated in patients who are CYP2D6 intermediate metabolisers or extensive metabolisers taking a strong or moderate CYP2D6 inhibitor concomitantly with a strong or moderate CYP3A inhibitor, and patients who are CYP2D6 poor metabolisers taking a strong CYP3A inhibitor. Use of eliglustat under these conditions results in substantially elevated eliglustat plasma concentrations.

Further details are available in the eliglustat (Cerdelga®) Summary of Product Characteristics (SmPC)[1].

7.2 Rationale for Study

It is clear from the pilot study conducted in Regione Lombardia in 2015 (Appendix 3 [Section 14.3]) that there is a significant prescription of concomitant medications among patients treated for GD in Europe, including CYP2D6 inhibitors and CYP3A inhibitors.

A study on the use of eliglustat and concomitant medications needs to provide a valid reflect of usage patterns prevailing in European countries. To this end, such study will be based on the collection and analysis of secondary data gathered in healthcare databases. These data provide exhaustive information on usage patterns of GD1 patients who are treated with eliglustat. However, a time-lag exists between the time of prescription and the time when this prescription appears in the database; this time-lag varies between data sources and can be several years. This time-lag needs to be considered for the conduct and reporting of a DUS on eliglustat. The pilot study conducted in Regione Lombardia in 2015 (Appendix 3 [Section 14.3]) showed the feasibility of using regional/national prescription databases for drug utilisation evaluation of concomitant medications.

Collection and assessment of concomitant drug use data cannot be determined in a short timeframe from one database or using a limited group of resources. A DUS of eliglustat should be undertaken in a series of prescription databases. Prescription databases must cover large populations to provide useful and reliable investigations of drug usage patterns in diseases as rare as GD. The DUS of eliglustat will be performed using existing databases including those of France, Denmark,

Germany and Israel. This will provide a total population of approximately 100 million to identify GD patients from.

7.3 Risk Management Measures

The safety concerns relevant for eliglustat are primarily managed through routine risk minimisation activities: labelling recommendations and prescription status of the product, to be initiated and supervised by a physician knowledgeable in the management of GD.

Moreover, the following educational materials have been developed to reinforce knowledge and adherence of the prescribers and patients to the risks associated with the use of eliglustat, including:

- A guide for prescriber: targeted to specialists initiating and supervising eliglustat treatment including a checklist of steps to be performed prior to initiation of eliglustat.
- A patient alert card: targeted to Health Care Providers (HCP) who do not prescribe eliglustat regarding important drug-drug interactions with eliglustat and to ensure that the patient's risk for drug-drug interactions reach the relevant HCP. It is also targeted to patients who will be educated regarding self-medication, and to present the card to all other HCP at each visit.

Also, recommendations and precautions to be followed by healthcare professionals and patients for the safe and effective use of eliglustat have also been included in the summary of product characteristics and in the package leaflet of eliglustat.

This DUS will allow to assess the effectiveness of risk minimisation measures that have been put in place and also to improve them.

8 RESEARCH QUESTION AND OBJECTIVES

As part of pharmacovigilance activities of eliglustat risk management plan, this DUS will allow to assess the effectiveness of risk minimisation measures (EU labelling, guide for prescribers and patient alert card) regarding understanding and implementing avoidance of significant drug-drug interactions.

8.1 Primary Objective

The primary objective of the DUS is to estimate the dose and duration of eliglustat therapy as well as the proportion, therapeutic class, and duration of past and concomitant medication use in patients treated with eliglustat. The concomitant medications of interest (CMI) are strong and moderate CYP2D6 inhibitors, strong and moderate CYP3A inhibitors, strong CYP3A inducers, P-gp substrates and CYP2D6 substrates (Appendix 1 in Section 14.1). Simultaneous use of strong or moderate CYP2D6 inhibitors with strong or moderate CYP3A inhibitors concomitantly with eliglustat will be explored, if feasible.

8.2 Secondary Objective

The secondary objective of the DUS is to describe the healthcare service pattern (i.e., prescriber's specialty and types of patient visit) for the prescriptions of concomitant medications in patients treated with eliglustat. The relevance of prescriber's specialty and types of patient visit is to inform whether prescriptions to GD1 patients are made in hospital or in outpatients services, and to inform on the number of health professionals taking care of these patients.

8.3 Exploratory Objective

There are no exploratory objectives planned for this study. However, CMI use will be described in greater detail and by drug therapeutic class which could improve the understanding of eliglustat usage patterns in the four included European countries. The prescriber specialty and the type of patient visit will also be analysed for eliglustat deliveries.

9 RESEARCH METHODS

9.1 Study Design

The DUS of eliglustat will be undertaken in a series of prescription databases covering large populations to provide useful and reliable investigations of diseases as rare as Gaucher Disease. This DUS will be based on secondary use of data. This DUS is descriptive only with no comparative elements.

The study shall take the form of a cohort study using electronic health records. Gaucher Disease Type 1 patients identified in each prescription database who are being prescribed eliglustat will be followed from one year before their first prescription of eliglustat to the end of the study in Q3 2024. During this period, all prescriptions of past and CMI will be recorded (Appendix 1 in Section 14.1). The study will rely entirely on analysis of secondary data as described in the initial study synopsis submitted in the Risk Management Plan (RMP).

9.1.1 Primary Endpoints

The primary outcomes of interest include the dose of eliglustat, the duration of eliglustat use, and the use of specific CMI one year before the first delivery of eliglustat and during the use of eliglustat.

Similarly to eliglustat, the CMI use will be identified through the Anatomical Therapeutic Chemical Code (ATC), country-specific coding system or through the mention of the CMI in the patient's chart. The list of medications of interest is described in Appendix 1 in Section 14.1).

9.1.2 Secondary Endpoints

The secondary endpoints include prescriber's specialty corresponding to the delivered drugs (general practitioner [GP], haematologist, oncologist, ophthalmologist, rheumatologist, surgeon, etc.) and visit type corresponding to the delivered drug (e.g., in city, in hospital, in specialised care centres, etc.).

9.1.3 Exploratory Endpoints

The exploratory endpoints include drug therapeutic class of CMI used to prior to and during the use of eliglustat, as well as prescriber speciality and type of visit for the eliglustat deliveries.

9.1.4 Rationale for the Study Design

A pilot study conducted in Regione Lombardia in 2015 has demonstrated the feasibility of using high-quality, population-based regional/national prescription databases for drug utilisation evaluation of concomitant medications (Appendix 3 [Section 14.3]). This study took the form of a twelve-month retrospective study of the drug prescriptions in GD1 patients before eliglustat became available.

9.2 Setting

9.2.1 Study Period

The study period will begin from one year before the first prescription of eliglustat in each data source to the end of the study.

The date of the first prescription of eliglustat will vary between data sources since the launching/reimbursement of eliglustat is different in each country (see Section 9.4). In any case, the first prescription will be after the date of approval of eliglustat by the EMA that is 19 January 2015.

The exposure period for one patient will be defined as the period between the exposure start date (date of the first record of eliglustat prescription) and the exposure end date, i.e., the date of the last eliglustat prescription plus the duration of eliglustat use according to the last prescription or the end of the study or the death of the patient if it occurs before the end of the study.

The end date of the study period will also vary between data sources since different time-lag exist between the time of prescription/delivery of drugs and availability of these data in databases. Consequently, in case of a two-year time-lag, data extracted in 2022 will have been collected until 2020 thus, the study period will end in 2020.

9.2.2 Inclusion Criteria

The study population will include all GD1 patients, of all ages, with at least one recorded prescription of eliglustat over the study period in the selected databases.

Since eliglustat is indicated for GD1 only and there are no specific diagnostic/International Classification of Diseases and related health problems, 10^{h} edition (ICD-10) codes for this condition, all patients with at least one recorded prescription of eliglustat during the study period will be considered to have GD1 diagnosis.

9.2.3 Exclusion Criteria

Not applicable.

9.2.4 Patient Enrolment

This DUS is a European, multi-centric retrospective cohort study. The study is based on the secondary use of data of GD1 patients treated with eliglustat that have been prospectively and consecutively enrolled in healthcare databases of four European countries (France, Germany, Denmark and Israel).

9.2.5 Patient Withdrawal and Replacement

Not applicable.

9.2.6 Patient Identification Numbers

Each patient will be identified by an identification (ID) variable defined as follows:

- Patient ID: The unique patient identifier in the study database. This identifier must be different from the unique identifier routinely used in the data source (e.g., the national number, or ID number in medical charts).

9.3 Variables

A more detailed description of the variables described in this section can be found in the statistical analysis plan (SAP) and country-specific analytical dataset specification (ADS) documents.

Variables in the study will be identified using ICD-10 and ATC codes, where applicable.

9.3.1 Exposure Assessment

The exposure of interest is the eliglustat use characterised by its dose and duration of use. Any GD1 patient with at least one prescription of eliglustat will be included in the exposure assessment.

During the exposure period, a patient taking eliglustat might be at risk for undesirable effect due to concomitant drug use (Appendix 1 in Section 14.1) with potentiation or inhibition of the therapeutic effects of eliglustat or potentiation or inhibition of therapeutic effects of concomitant drugs.

9.3.2 Outcomes of Interest

Outcomes of interest include concomitant medication use in terms of therapeutic class and duration. The CMI are strong and moderate CYP2D6 inhibitors, strong and moderate CYP3A inhibitors, strong CYP3A inducers, P-gp substrates and CYP2D6 substrates. Simultaneous use of strong or moderate CYP2D6 inhibitors with strong or moderate CYP3A inhibitors concomitantly with eliglustat will be explored, if feasible. Other outcomes will be the prescriber's specialty and the type of patient visit (e.g., hospital or in outpatient settings).

Concomitant medication use will be identified using ATC codes available in each database.

The duration of drug use will be defined with a continuous variable (number of days) and also with a categorical variable. The categorical variables will be defined as follows: 1. Total use of concomitant medication will be defined as any prescription whatever the duration; 2. Chronic use of concomitant medication will be defined as total duration of single or consecutive prescriptions of 15 days or over.

Where information is available, and subject to Ethics Committee approval, data on prescriber's specialty will be defined as the specialty of doctors prescribing concomitant medications to GD1 patients (e.g., GPs, haematologists, neurologists, etc.). These data will enable to define the number and profile of health professionals managing these patients. Data on the type of patient's visit is intended to capture whether prescriptions of concomitant drugs to GD1 patients are written in hospital or in outpatient settings.

9.3.3 Covariates

The only important covariates required are age and sex. Also, the death date of patients will be necessary to compute duration of drug use.

9.4 Data Sources

This DUS is planned to take place in France, Denmark, Germany and Israel. Data sources of these countries accepted to participate but not all research agreements have been signed yet. In each of these countries, there are effective, population-based databases which provide a large coverage of the country. Also, national death registers are in place in all of these countries to ascertain the vital status of patients. Passive follow-up can be accomplished in all data sources thanks to a unique personal ID number which can be used to link together the information from several population-based registries.

Data from these databases will be used to identify GD1 patients treated with eliglustat. These databases cover a total population of approximately 100 million inhabitants.

These data sources can provide detailed data on eliglustat prescription and duration of use, and also on concomitant therapies listed in Appendix 1 in Section 14.1, provided that these drugs are marketed in the country.

In all data sources, data on the prescriber's specialty of eliglustat is available. However, there may be variability in the availability of these data, depending on decision of local competent authorities. In any event, the data from all data sources can address all DUS objectives. The data recorded in these data sources are considered to be valid for the information included in this study by the data holders.

Databases have been selected in European countries where eliglustat is approved and have been launched. Israel is considered as a European country since several agreements are in place between EU and Israel, including EMA agreements.

France

In France, the launching/reimbursement of eliglustat is effective since 09 November 2016.

France has a high-quality national healthcare database which covers around 99% of the French population. This database is one of the most important healthcare databases in the world. Since 01 April 2017, the "Système National des Données de Santé" or national health data system (SNDS) gathers various health-related databases in France, including the social security database ("Système National d'Information Inter Régimes de l'Assurance Maladie" or national health insurance information system [SNIIRAM], main database set up in 2003) and the hospital records ("Programme de Médicalisation des Systèmes d'Information" or Medicalisation Programme of Information Systems [PMSI]). Since June 2018, the cause of death collected by the CépiDc ("Centre d'épidémiologie sur les causes médicales de décès" or epidemiological centre on medical cause of death) are progressively integrated to the SNDS. In the future, disability data and data from private health insurances will be available.

The French database contains outpatient data (i.e., expenses and reimbursements of medical visits and drugs, type and number of drugs delivered, date and nature of paramedical interventions, etc.) and hospitalisation data (i.e., admission date, duration of stay, main and associated diagnosis, medical acts, etc) through a unique personal identification number (NIR). All diagnoses are based on the ICD-10. Also, patient characteristics (i.e., sex, year of birth, place of residence and death data) and healthcare professional characteristics (i.e., speciality and type of practice) are available in the database. The main limitation of this database is the absence of data regarding clinical

information, biological results and risk factor, and few social data. Another limitation concerns hospitalised patients for whom no details on the drugs used during hospitalisation are available (except for some expensive drugs). Moreover, drug data available in this database concern drugs actually delivered to patients, which means that patients have actually taken the prescribed drugs from pharmacies. However, this does not guarantee that patients actually took their treatment, but this information is more accurate than when prescriptions only are considered.

This database is increasingly made accessible to researchers and to studies on drug safety and effectiveness in recent years. Of note, data for year N are usually fully available in year N + 1 (updated in summer each year). Regarding the cause of death data, a time-lag of two years is observed.

Access to the SNDS database is supervised by the Health Data Hub (HDH) which is in charge to transmit the applications to the CESREES ("Comité éthique et scientifique pour les recherches, les études et les évaluations dans le domaine de la santé" or Ethical and Scientific Committee for Research, Studies and Evaluations in the Health Field). The CESREES evaluates the methodology of the study and approves (or refuses) the project within one month. The final step consists in submitting the application to the CNIL ("Commission Nationale de l'Informatique et des Libertés" or National Commission on Informatics and Liberty), the governmental body in charge of personal data protection. The CNIL needs to give its green light for accessing and using the data. The CNIL has two to four months for approving (or refusing) the application.

Denmark

In Denmark, the launching/reimbursement of eliglustat is effective since April 2015.

In Denmark, there are two centres for patients with rare diseases: one in Copenhagen and one in Aarhus. Patients with GD are all followed in Copenhagen University Hospital, which allowed to establish a GD registry. This registry includes data recorded in Excel files (demographic data of patients) and also in electronic medical charts (REDCap system). Therefore, the creation of a unique database gathering both types of data will be needed.

In Denmark, eliglustat is prescribed by a paediatrician who takes care of all Danish GD patients. Patients have to go fill their eliglustat prescription in a hospital pharmacy. Therefore, both prescription and delivery dates are recorded in the GD registry. Also, this registry contains all data related to the management of GD patients including vital status. Of note, the completeness of information extracted from medical charts is not guaranteed, and information on the speciality of the prescriber of concomitant medications is not always available. Data on common over-the-counter medications such as Paracetamol, are not registered anywhere.

Even though the completeness of data is not guaranteed, it is not planned to use the National Prescription Registry (NPR) to complete data from the GD registry because the process of getting NPR applications approved is known to be very long. Moreover, the NPR application would be useless for a small number of patients (the expected number of patients treated with eliglustat in Denmark is ten).

The advantage of this registry is the absence of time-lag between the prescription/delivery of drugs and availability of these data in the registry since data are routinely collected in medical charts. Therefore, if the data extraction occurs in December 2022, all data recorded until this date will be available for the study. Also, patients in the GD registry have already consented to share their data for research purposes; thus, there is no need for a validation from an Ethics Committee. Furthermore, the small cell will not be an issue.

Germany

In Germany, the launching/reimbursement of eliglustat is effective since 15 April 2015.

Since 2004, the Leibniz Institute for Prevention Research and Epidemiology (BIPS) has been working on the establishment and maintenance of the project-based German Pharmacoepidemiological Research Database (GePaRD). This database contains claims data from four statutory health insurance providers and covers about 25 million insured German since 2004 which represents approximately 20% of the general population of Germany.

GePaRD includes demographic characteristics for each person (sex, birth year, nationality, etc.), information on drug prescriptions, outpatient and inpatient services and diagnoses starting with the year 2004. Hospital data include the period of hospitalisation with the entry date and exit date, the reasons for admission and discharge, and the diagnostic and therapeutic procedures. Claims of outpatient physician visits contain diagnoses, treatments, and procedures. Prescription data are limited to reimbursable drugs and include dates of prescription and delivery, the amount of drug prescribed, and details on the prescriber such as his/her specialty. All diagnoses (inpatient and outpatient) are based on the German Modification of the International Classification of Diseases, 10th revision (ICD-10-GM). A linkage to the central pharmaceutical reference database adds information on the prescribed drug such as the ATC code, the packaging size and the defined daily dose. One limitation of this database is that in-hospital medications are not included in GePaRD (except expensive medications).

This database is updated on an annual basis (i.e., at the end of each year) with anonymised and validated data. Of note, the entire process from data delivery to availability for studies can take up to two years.

Access to the database is granted only to BIPS employees within the framework of officially approved research projects. It is not permitted to give third parties access to the data. However, BIPS can be commissioned to carry out drug utilisation or drug safety studies that are requested by health authorities (e.g., EMA).

Israel

In Israel, the launching/reimbursement of eliglustat is effective since 12 January 2017.

Maccabi Healthcare Services is the second health provider in Israel which counts 2.5 million members (about 27% of the Israel population). It is a state mandated organisation with medical records fully computerised since 1993. Membership is accessible to everyone; it is free and independent of status of employment, occupation and location. This healthcare database gathers data going back 30 years on demographic characteristics, mortality and emigration, all physician diagnoses, medical visits records, hospitalisation, laboratory results, prescribed and dispensed medications, and other services delivered to patients (e.g., scans and images). Due to the high cost of eliglustat, all GD patients treated with this medication are fully compensated by the government.

Of note, there is no time-lag between the prescription/delivery of drugs and availability of these data in the database. Therefore, if the data extraction occurs in December 2022, all data recorded until this date will be available for the study.

9.5 Study Size

Gaucher Disease is a rare disease, therefore no restriction on the number of participants will be made. In other words, all patients with GD1 and taking eliglustat will be included in the analysis. This will allow to maximise the statistical power and to minimise the small cell/identifiability issue. Indeed, this problem may arise due to the small number of patients with GD1.

Knowing that the SNDS covers 99% of the French population, the Danish GD registry covers all the Danish population, the GePaRD database covers about 25 million of Germans and the Maccabi database covers approximately 2.5 million Israelis, the DUS will cover approximately 100 million people.

According to estimated number of patients taking eliglustat in each data source, the expected minimum number of participants in the DUS is 128 (87 in the SNDS, 10 in Danish GD registry, 11 in GePaRD and 20 in Maccabi database).

9.6 Data Management

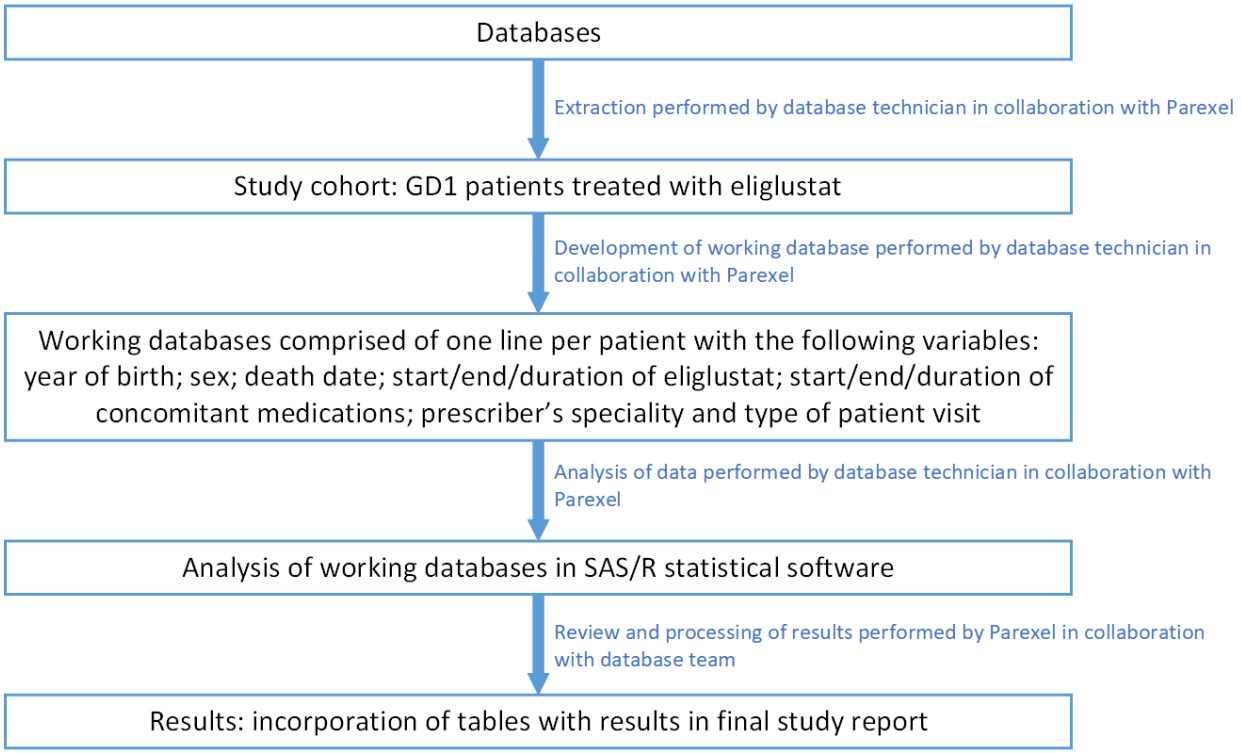
The selected registries have already participated in other DUS or post-authorisation safety studies (PASS), required by EMA or by the national or local health authorities.

The data management process is depicted in Figure 1.

In each data source, GD1 patients treated with eliglustat will be extracted into a working database whose format is adapted to receive raw prescription data. In the working database, variables will be re-coded and aligned in order to have one line of data per patient. The creation and re-working of variables will follow locally defined procedures and requirements (e.g., access to non-anonymised data limited to database personnel). Then, the working database will be pseudo-anonymised according to local requirements and the European Directive of personal data protection. This pseudo-anonymised database will become the analysis database with all needed variables for data analyses according to the objectives of the DUS. This database will be in a SAS- or R-compatible format.

Due to data protection issue, data from the selected data sources cannot be gathered in a single place and analysed by a single team. Therefore, a statistical programme in SAS or R will be written by (or in close collaboration with) the Parexel statisticians or statistical programmers and applied on their analysis database. Where Parexel is responsible for writing the programmes, the programmes may be transferred to each data source to be applied on their database. For the French data, after approval of the study by the regulatory authority, the analyses will be directly conducted by the statisticians from RCTs, subcontractor from Parexel, on data posted in a dedicated server of the SNDS. For the Danish and Israelian data, since there is no statistician in these data sources, Parexel statisticians will conduct analyses either on-site or through a secured virtual private network (VPN) access. Finally, statistical results obtained in each data source will be transferred to Parexel, assembled in tables and included in the final report.

Figure 1 Data flow



Abbreviations: GD1 = Gaucher Disease Type 1

9.7 Data Analysis

A separate SAP and country-specific ADS documents will be produced, providing detailed methods for the analyses outlined below.

Any deviations from the planned analyses will be described and justified in the final study report.

9.7.1 General Considerations

The exposure period for one patient corresponds to the period of eliglustat use. This period will be defined as the period between the exposure start date (the first record of eliglustat prescription) and the exposure end date (end of study or date of the last eliglustat prescription plus the duration of eliglustat use according to the last prescription or death date).

The statistical analyses will be only descriptive and will include the following:

- Descriptive analysis of eliglustat therapy in terms of duration and dose.

- Descriptive analysis of the past medication use (one year prior to the exposure period) in terms of proportion, therapeutic class and duration. The treatments of interest will be (details in Appendix 1 in Section 14.1):
    - Strong and moderate CYP2D6 inhibitors (CMI1 and CMI2)
    - Strong and moderate CYP3A inhibitors (CMI3 and CMI4)
    - Simultaneous use of strong or moderate CYP3A inhibitors with strong or moderate CYP2D6 inhibitors (CMI1 + CMI2 + CMI3 + CMI4)
    - Strong CYP3A inducers (CMI5)
    - P-gp substrates (CMI6)
    - CYP2D6 substrates (CMI7)

The proportions will be computed taking into account all treatments of interest and also by type of treatments and by duration. Proportions for the group CYP inhibitors will be also computed. The duration will be treated as a continuous variable and also as a categorical variable. The categorical variable will be defined as follow: 1. Total use will be defined as any prescription whatever the duration; 2. Chronic use will be defined as total duration of single or consecutive prescriptions of 15 days or over.

If the number of GD1 patients allows it, stratified analyses based on gender and age groups will be performed as well as analyses by year.

- Descriptive analysis of the concomitant medication use (i.e., during the exposure period) in terms of proportion, therapeutic class and duration. The treatments of interest will be the same as for the past medication use. The proportions will be computed as for the past medication use that is considering all treatments and also by therapeutic class and duration.
- Descriptive analysis of the health care service pattern (i.e., prescriber's specialty and types of patient visit) for the use of concomitant medications.

Analyses will be conducted on the whole period of study for each data source separately for data protection reasons. This will allow to compare the drug availability and prescribing patterns between European countries.

If the number of GD1 patients taking eliglustat allows it, stratification analyses based on sex and age will be performed as well as analyses by year with trends in proportions over time.

9.7.2 Control of Bias and Confounding

This DUS is a descriptive study, therefore confounding will not be examined. Only age and sex will be considered and used for stratification if sufficient participants are included in the study (i.e., in absence of small cell).

9.7.3 Analysis of Primary Endpoint

9.7.3.1 Dose of Eliglustat

The dose of eliglustat will be reported as a categorical variable since only two dosages exist: one capsule per day (i.e., 84 mg/day) and two capsules per day (i.e., 168 mg/day). A third category, other, will be created for patients that would not fit in the two previous categories for any reasons. Number and percentage of patients in each category will be reported.

9.7.3.2 Duration of Eliglustat

Using the duration of eliglustat use of all GD1 patients, a mean duration will be computed together with dispersion.

Patients will be also classified in three categories according to their eliglustat duration: <1 year, 1-<2 years and ≥2 years. Number and percentage of patients in each category will be reported. These categories may change depending on results in each data source.

9.7.3.3 Concomitant Medications

To analyse the use of concomitant medications, two study periods will be determined:

1. The one-year period before the first delivery of eliglustat.
2. The period during eliglustat use which will span from the first delivery of eliglustat to the last delivery of eliglustat plus the duration of supply.

The analyses described in the following sections will be conducted separately for each of the two periods.

9.7.3.3.1 Proportion of Patients with CMI

Proportion of patients with CMI will be computed considering all CMI, by therapeutic class of CMI (CMI1 to CMI7), and separately for the group of CYP inhibitors (CMI1 to CMI4). Also, proportion of patients that have taken a strong or moderate CYP2D6 inhibitor simultaneously with a strong or moderate CYP3A inhibitor will be explored, if feasible.

9.7.3.3.2 Duration of Concomitant Medications

The duration of use of a CMI will be expressed in days.

The duration of concomitant medication use will be computed considering all CMI, by therapeutic class of CMI (CMI1 to CMI7), and for the group of CYP inhibitors (CMI1 to CMI4). Also, for patients that have taken a strong or moderate CYP2D6 inhibitor simultaneously with a strong or moderate CYP3A inhibitor, the duration of CMI overlap will be explored, if feasible.

For each CMI, the duration of CMI use will be computed in two steps. First, a total duration will be computed for each patient taking into account all deliveries belonging to the CMI category. Second, the average of the total duration for all patients will be computed together with its dispersion.

9.7.4 Analysis of Secondary Endpoints

The secondary endpoints will be assessed considering the two study periods separately, as in Section 9.7.3.3.

9.7.4.1 Type of Prescribers for Concomitant Medications

Prescribers of CMI will depend on the data source and could include general practitioner, haematologist, oncologist, ophthalmologist, rheumatologist, surgeon, etc. A list of prescriber specialties will be identified. For each prescriber, numbers and proportion of patients having had at least one CMI delivery realised by this prescriber will be computed considering all CMI, by therapeutic class of CMI (CMI1 to CMI7) and for the group of CYP inhibitors (CMI1 to CMI4).

9.7.4.2 Type of Visit for Concomitant Medications

The visit types will depend on the data source and could include in city, in hospital, in specialised care centres, etc. A list of visit types will be identified. For each type of visit, numbers and proportion of patients having had at least one CMI delivery realised during this type of visit will be computed considering all CMI deliveries, by therapeutic class of CMI and for the group of CYP inhibitors (CMI1, CMI2, CMI3 and CMI4).

9.7.5 Analysis of Exploratory Endpoints

9.7.5.1 Description of Concomitant Medications by Individual Drugs

To better understand the therapeutic classes of CMI used prior to and during the use of eliglustat, a description will be conducted by drug. For each drug taken before and during eliglustat, the

number of patients having had this drug will be counted. Numbers will be reported by period of study, one year before eliglustat and during eliglustat.

9.7.5.2 Healthcare Service Patterns for Eliglustat

The prescriber specialty and the type of patient visit will also be analysed for eliglustat deliveries.

For each prescriber, the number of patients who had at least one eliglustat delivery realised by prescriber will be counted.

9.8 Quality Control

In France, the national prescription database (SNDS) has been in place for more than 15 years. These databases are based on mandatory information provided by health care professionals and hospitals in order to obtain reimbursement of medical activities. In this regard, each database has locally defined procedures for data quality and integrity, including accuracy and legibility of collected data and original documents, extent of source data verification, storage of records and archiving of statistical programmes.

In the Danish GD registry, only confirmed cases of GD are included. Furthermore, the small number of patients treated with eliglustat will allow to check the quality of individual data manually.

In Germany and Israel, the GePaRD and Maccabi databases, respectively, have been in place for more than 20 years (since 2004 for GePaRD and since 1993 for Maccabi) and have been used for several epidemiological studies in the past. Therefore, their long experience as well as locally defined quality procedures ensure the quality and integrity of their data.

9.8.1 Data Quality Assurance

Quality assessment will be performed as a series of systematic checks of the data and at several timepoints. The main objectives of the quality assessment include the identification of missing data and incomplete dates; detecting inconsistencies and outliers; verification of database linkages and variable transformations. No imputation of missing data will be conducted. Further information will be described in the SAP.

9.9 Limitations of the Research Methods

Biases relative to missing data or non-reporting of prescribed drugs should be minimal since registered data are mandatory for the payment or reimbursement of drugs by social security offices.

Nonetheless, the prescription databases involved in this study have the known limitation of the administrative data provided by health services and health professionals for reimbursement purposes or because of legal obligation. The type of collected data and the logic of data collection have not been primarily devised for being used for scientific purposes. Moreover, the protection of data privacy and confidentiality of medical records imposes strict boundaries on the type of data that can be registered in prescription databases. Hence, for a number of activities recorded in the database, the result of that activity is not recorded. However, in the light of the specific objectives of this study, this limitation should not impact the results.

There are no confounders and other sources of bias that could impact the DUS results. However, underreporting of information and misclassification of the study variables can occur due to missing information in the data. Selection bias is less likely to occur since all included data sources are nationally representative. The results of the study will be interpreted in context of the limitations.

9.10 Other Aspects

9.10.1 Establishment of Study Scientific and Steering Committees

The eliglustat study scientific and steering committee will comprise the country-specific principal investigators, the Parexel principal investigator and one or several representatives of the marketing authorisation holder (MAH). This committee will meet regularly throughout the study period, will be responsible for the day-to-day decisions about study progress arriving at decisions in a consensual mode.

10 PROTECTION OF HUMAN SUBJECTS

10.1 Ethical Considerations

The procedures set out in this study protocol are designed to ensure that the Sponsor and investigator abide by the principles of the International Society for Pharmacoepidemiology Guidelines for good pharmacoepidemiology practices (GPP) guidelines[2]. The study will also be carried out in compliance with local legal requirements.

10.2 Informed Consent

In each participating country, all necessary regulatory/ethics submissions will be performed in accordance with local regulations including local data protection regulations, if required.

For Denmark, patients in the GD registry have already consented to share their data for research purposes.

For administrative data from France and Germany, explicit consent is not required due to secondary use of anonymised data.

For Israel, patient consent is carried out at the local level. The lead principal investigator for the study will apply to the Ethic Committee for approval.

10.3 Protocol Approval and Amendment

Before the start of the study, the study protocol and/or other relevant documents will be approved by the IEC or relevant authorities, in accordance with local legal requirements. The Sponsor must ensure that all ethical and legal requirements have been met before the first patient is enrolled in the study.

To alter the protocol, amendments must be written, receive approval from the appropriate personnel, and receive IEC approval prior to implementation.

Administrative changes (not affecting patient risk) may be made without the need for a formal amendment. All amendments will be distributed to all protocol recipients, with appropriate instructions.

10.4 Confidentiality

All data collected for this study are secondary and retrospective.

The national prescription databases participating in the study have operated for 15 years or more and all have implemented rules for data protection complying with legal and European requirements on data protection. The pseudo-anonymisation of personal identifiers is performed by each database according to locally defined rules. For each database, a limited number of technicians are allowed to handle these personal identifiers. Data are stored electronically on computers/servers installed in dedicated premises and equipped with a comprehensive range of protections against external and internal intrusions.

As described in Section 9.6, the database technician of each data source will prepare an analysis database with fully pseudo-anonymised data containing all needed variables for the statistical analyses. There is thus no data on personal identifiers that will be part at any stage of the statistical analysis procedures. However, as GD is a rare disease it is possible that the so-called "small cell" issue arises due to the small number of participants. Indeed, patient identifiability could be possible in a data source where the age and sex are known for a single or few patients taking a highly specific treatment. For the sake of preserving the confidentiality of reported data, if less than X patients have specific characteristics, the label "<X" will be reported in tables to prevent identification of patients (the value of X will depend on country-specific regulations). In any case, the way the DUS will be conducted in each data source will follow the rules imposed by owners of the relevant health data.

10.5 Duration of the Study

Refer to Section 9.2.1.

10.6 Premature Termination of the Study

Not applicable.

11 MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE DRUG REACTIONS

11.1 Collection and Reporting of Adverse Events/Adverse Reactions

This study is a non-interventional post-authorisation study based on secondary use of data. According to Module VI – Management and reporting of adverse reactions to medicinal products (Rev 1), the reporting of suspected adverse reactions in the form of individual case safety reports is not required.

12 PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

A final report with results is scheduled in Q4 2024. After final approval of the final report by the EMA, this report will enter in the public domain and be accessible via the EMA website. In addition, main results may be published in peer-reviewed journals and presented at scientific meetings specialised in rare diseases, pharmacology and haematologic/neurologic diseases.

13 REFERENCES

1 Eliglustat (Cerdelga®) SmPC. https://www.ema.europa.eu/en/documents/product-information/cerdelga-epar-product-information_en.pdf. Accessed on 30 May 2023.

2 International Society for Pharmacoepidemiology (ISPE). Guidelines for good pharmacoepidemiology practices (GPP). Pharmacoepidemiol Drug Saf. 2008;17(2):200-8.

14 APPENDICES

14.1 Appendix 1: Concomitant Medications of Interest

This appendix is adapted from the University of Washington Drug Interaction Database (DIDB®): https://www.druginteractionsolutions.org/.

The concomitant medications of interest (CMI) include:

- Strong CYP2D6 inhibitors (detailed in Table 1)
- Moderate CYP2D6 inhibitors (detailed in Table 1)
- Strong CYP3A inhibitors (detailed in Table 2)
- Moderate CYP3A inhibitors (detailed in Table 2)
- Strong CYP3A inducers (detailed in Table 3)
- P-gp substrates (detailed in Table 4)
- CYP2D6 substrates (detailed in Table 5)

Table 1 Strong and Moderate CYP2D6 Inhibitors

Strong inhibitors	Moderate inhibitors
Drug (INN)	**Drug (INN)**
bupropion	abiraterone acetate
dacomitinib	asunaprevir
fluoxetine	berotralstat
paroxetine	cinacalcet
quinidine	dronedarone
	duloxetine
	escitalopram
	lorcaserin
	mirabegron
	moclobemide
	quinine
	rolapitant
	terbinafine
	tipranavir and ritonavir

Adapted from the University of Washington Drug Interaction Database (DIDB®): https://www.druginteractionsolutions.org/

Table 2 Strong and Moderate CYP3A Inhibitors

Strong inhibitors	Moderate inhibitors
Drug (INN)	**Drug (INN)**
boceprevir	amprenavir
ceritinib	aprepitant
clarithromycin	atazanavir
cobicistat	atazanavir and ritonavir
conivaptan	berotralstat
dasabuvir, ombitasvir, paritaprevir and ritonavir	casopitant
idelalisib	cimetidine
indinavir	ciprofloxacin
itraconazole	clofazimine
josamycin	crizotinib
ketoconazole	darunavir
lonafarnib	darunavir and ritonavir
lopinavir and ritonavir	diltiazem
mibefradil	dronedarone
mifepristone	duvelisib
nefazodone	erythromycin
nelfinavir	faldaprevir
posaconazole	fedratinib
ribociclib	fluconazole
ritonavir	imatinib
saquinavir	isavuconazole
telaprevir	istradefylline
telithromycin	lefamulin
tipranavir	letermovir
troleandomycin	nilotinib
tucatinib	tofisopam
voriconazole	treosulfan
	verapamil
	voxelotor

Adapted from the University of Washington Drug Interaction Databuase (DIDB®):
https://www.druginteractionsolutions.org/

Table 3 Strong CYP3A Inducers

Drug (INN)
apalutamide

Drug (INN)
carbamazepine
enzalutamide
ivosidenib
lumacaftor
mitotane
phenytoin
rifampicin
rifapentine

Adapted from the University of Washington Drug Interaction Database (DIDB®):
https://www.druginteractionsolutions.org/

Table 4 P-gp Substrates

Drug (INN)	Drug (INN)	Drug (INN)
aliskiren	ethinylestradiol	ranolazine
atorvastatin	etoposide	rifampicin
celiprolol	everolimus	risperidone
cimetidine	fexofenadine	ritonavir
ciprofloxacin	idarubicin	saquinavir
colchicine	indinavir	simvastatin
ciclosporin	irinotecan	sirolimus
dabigatran etexilate	loperamide	tacrolimus
daunorubicin	methylprednisolone	talinolol
dexamethasone	morphine	telaprevir
digoxin	nadolol	temsirolimus
docetaxel	nelfinavir	teniposide
domperidone	paclitaxel	topotecan
doxorubicin	phenytoin	verapamil
edoxaban	quinidine	vinblastine
erythromycin	ranitidine	vincristine

Adapted from the University of Washington Drug Interaction Database (DIDB®):
https://www.druginteractionsolutions.org/

Table 5 CYP2D6 Substrates

Drug (INN)	Drug (INN)	Drug (INN)
aripiprazole	haloperidol	primaquine
atomoxetine	iloperidone	propafenone
brexpiprazole	imipramine	propranolol
carvedilol	loratadine	risperidone

Drug (INN)	Drug (INN)	Drug (INN)
chlorpheniramine	maprotiline	sparteine
codeine	methoxyphenamine	tamoxifen
cyclizine	metoclopramide	tamsulosin
dapoxetine	metoprolol	thioridazine
darifenacin	mexiletine	timolol
debrisoquine	nebivolol	tipepidine
desipramine	nicergoline	tolperisone
deutetrabenazine	nortriptyline	tolterodine
dextromethorphan	oliceridine	tramadol
dimemorfan	paroxetine	trimipramine
doxepin	perhexiline	tropisetron
encainide	perphenazine	venlafaxine
ethylmorphine	pimozide	vernakalant
fluoxetine	pitolisant	vortioxetine
fluvoxamine	prajmaline	yohimbine
gefitinib		

Adapted from the University of Washington Drug Interaction Database (DIDB®):
https://www.druginteractionsolutions.org/

14.2 Appendix 2: ENCePP Checklist for Study Protocols

ENCePP Checklist for Study Protocols (Revision 4)

Adopted by the ENCePP Steering Group on 15/10/2018

The European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) welcomes innovative designs and new methods of research. This Checklist has been developed by ENCePP to stimulate consideration of important principles when designing and writing a pharmacoepidemiological or pharmacovigilance study protocol. The Checklist is intended to promote the quality of such studies, not their uniformity. The user is also referred to the ENCePP Guide on Methodological Standards in Pharmacoepidemiology, which reviews and gives direct electronic access to guidance for research in pharmacoepidemiology and pharmacovigilance.

For each question of the Checklist, the investigator should indicate whether or not it has been addressed in the study protocol. If the answer is "Yes", the section number of the protocol where this issue has been discussed should be specified. It is possible that some questions do not apply to a particular study (for example, in the case of an innovative study design). In this case, the answer 'N/A' (Not Applicable) can be checked and the "Comments" field included for each section should be used to explain why. The "Comments" field can also be used to elaborate on a "No" answer.

This Checklist should be included as an Annex by marketing authorisation holders when submitting the protocol of a non-interventional post-authorisation safety study (PASS) to a regulatory authority (see the Guidance on the format and content of the protocol of non-interventional post-authorisation safety studies). The Checklist is a supporting document and does not replace the format of the protocol for PASS presented in the Guidance and Module VIII of the Good pharmacovigilance practices (GVP).

Study title:
Drug utilisation study of eliglustat for the treatment of Gaucher Disease Type 1 in Europe using electronic healthcare records

EU PAS Register® number: EUPAS34611
Study reference number (if applicable): ELIGLC06913

Section 1: Milestones	**Yes**	**No**	**N/A**	**Section Number**
1.1 Does the protocol specify timelines for				
1.1.1 Start of data collection[1]	☒	☐	☐	6
1.1.2 End of data collection[2]	☒	☐	☐	6
1.1.3 Progress report(s)	☐	☐	☒	6
1.1.4 Interim report(s)	☐	☐	☒	6
1.1.5 Registration in the EU PAS Register®	☒	☐	☐	6
1.1.6 Final report of study results.	☒	☐	☐	6

[1] Date from which information on the first study is first recorded in the study dataset or, in the case of secondary use of data, the date from which data extraction starts.
[2] Date from which the analytical dataset is completely available.

Comments:

Section 2: Research question		**Yes**	**No**	**N/A**	**Section Number**
2.1	Does the formulation of the research question and objectives clearly explain:	☒	☐	☐	
	2.1.1 Why the study is conducted? (e.g. to address an important public health concern, a risk identified in the risk management plan, an emerging safety issue)	☒	☐	☐	7.2
	2.1.2 The objective(s) of the study?	☒	☐	☐	8
	2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised)	☒	☐	☐	9.2.2
	2.1.4 Which hypothesis(-es) is (are) to be tested?	☐	☐	☒	
	2.1.5 If applicable, that there is no *a priori* hypothesis?	☐	☐	☒	

Comments:

Section 3: Study design		**Yes**	**No**	**N/A**	**Section Number**
3.1	Is the study design described? (e.g. cohort, case-control, cross-sectional, other design)	☒	☐	☐	9.1
3.2	Does the protocol specify whether the study is based on primary, secondary or combined data collection?	☒	☐	☐	9.1
3.3	Does the protocol specify measures of occurrence? (e.g., rate, risk, prevalence)	☒	☐	☐	9.7
3.4	Does the protocol specify measure(s) of association? (e.g. risk, odds ratio, excess risk, rate ratio, hazard ratio, risk/rate difference, number needed to harm (NNH))	☒	☐	☐	9.7
3.5	Does the protocol describe the approach for the collection and reporting of adverse events/adverse reactions? (e.g. adverse events that will not be collected in case of primary data collection)	☒	☐	☐	11.1

Comments:

Section 4: Source and study populations		**Yes**	**No**	**N/A**	**Section Number**
4.1	Is the source population described?	☒	☐	☐	9.4
4.2	Is the planned study population defined in terms of:				

Section 4: Source and study populations	**Yes**	**No**	**N/A**	**Section Number**
4.2.1 Study time period	☒	☐	☐	9.2.1
4.2.2 Age and sex	☒	☐	☐	9.2.2
4.2.3 Country of origin	☒	☐	☐	9.2.4
4.2.4 Disease/indication	☒	☐	☐	9.2
4.2.5 Duration of follow-up	☒	☐	☐	9.1
4.3 Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria)	☒	☐	☐	9.2.2 9.2.3

Comments:

Section 5: Exposure definition and measurement	**Yes**	**No**	**N/A**	**Section Number**
5.1 Does the protocol describe how the study exposure is defined and measured? (e.g. operational details for defining and categorising exposure, measurement of dose and duration of drug exposure)	☒	☐	☐	9.3.1
5.2 Does the protocol address the validity of the exposure measurement? (e.g. precision, accuracy, use of validation sub-study)	☒	☐	☐	9.4
5.3 Is exposure categorised according to time windows?	☒	☐	☐	9.7.3.2
5.4 Is intensity of exposure addressed? (e.g. dose, duration)	☒	☐	☐	9.2.2
5.5 Is exposure categorised based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☒	☐	☐	9.7.3.1
5.6 Is (are) (an) appropriate comparator(s) identified?	☐	☐	☒	

Comments:

Section 6: Outcome definition and measurement	**Yes**	**No**	**N/A**	**Section Number**
6.1 Does the protocol specify the primary and secondary (if applicable) outcome(s) to be investigated?	☒	☐	☐	9.1.1 9.1.2
6.2 Does the protocol describe how the outcomes are defined and measured?	☒	☐	☐	9.3
6.3 Does the protocol address the validity of outcome measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, use of validation sub-study)	☒	☐	☐	9.4

Section 6: Outcome definition and measurement	**Yes**	**No**	**N/A**	**Section Number**
6.4 Does the protocol describe specific outcomes relevant for Health Technology Assessment? (e.g. HRQoL, QALYs, DALYS, health care services utilisation, burden of disease or treatment, compliance, disease management)	☐	☐	☒	

Comments:

Section 7: Bias	**Yes**	**No**	**N/A**	**Section Number**
7.1 Does the protocol address ways to measure confounding? (e.g. confounding by indication)	☐	☐	☒	9.7.2 9.9
7.2 Does the protocol address selection bias? (e.g. healthy user/adherer bias)	☒	☐	☐	9.9
7.3 Does the protocol address information bias? (e.g. misclassification of exposure and outcomes, time-related bias)	☒	☐	☐	9.9

Comments:

Section 8: Effect measure modification	**Yes**	**No**	**N/A**	**Section Number**
8.1 Does the protocol address effect modifiers? (e.g. collection of data on known effect modifiers, subgroup analyses, anticipated direction of effect)	☐	☐	☒	

Comments:

Section 9: Data sources	**Yes**	**No**	**N/A**	**Section Number**
9.1 Does the protocol describe the data source(s) used in the study for the ascertainment of:				
9.1.1 Exposure? (e.g. pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview)	☒	☐	☐	9.4
9.1.2 Outcomes? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics)	☒	☐	☐	9.4
9.1.3 Covariates and other characteristics?	☒	☐	☐	9.4
9.2 Does the protocol describe the information available from the data source(s) on:				
9.2.1 Exposure? (e.g. date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☒	☐	☐	9.4

Section 9: Data sources	**Yes**	**No**	**N/A**	**Section Number**
9.2.2 Outcomes? (e.g. date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	9.4
9.2.3 Covariates and other characteristics? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, lifestyle)	☒	☐	☐	9.4
9.3 Is a coding system described for:				
9.3.1 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC) Classification System)	☒	☐	☐	9.3
9.3.2 Outcomes? (e.g. International Classification of Diseases (ICD), Medical Dictionary for Regulatory Activities (MedDRA))	☒	☐	☐	9.3
9.3.3 Covariates and other characteristics?	☒	☐	☐	9.3
9.4 Is a linkage method between data sources described? (e.g. based on a unique identifier or other)	☒	☐	☐	9.4

Comments:

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Section Number**
10.1 Are the statistical methods and the reason for their choice described?	☒	☐	☐	9.7.1
10.2 Is study size and/or statistical precision estimated?	☐	☒	☐	9.5
10.3 Are descriptive analyses included?	☒	☐	☐	9.7
10.4 Are stratified analyses included?	☒	☐	☐	9.7
10.5 Does the plan describe methods for analytic control of confounding?	☐	☐	☒	
10.6 Does the plan describe methods for analytic control of outcome misclassification?	☐	☐	☒	
10.7 Does the plan describe methods for handling missing data?	☒	☐	☐	9.8.1
10.8 Are relevant sensitivity analyses described?	☐	☐	☒	

Comments:

Section 11: Data management and quality control	**Yes**	**No**	**N/A**	**Section Number**
11.1 Does the protocol provide information on data storage? (e.g. software and IT environment, database maintenance and anti-fraud protection, archiving)	☒	☐	☐	9.6
11.2 Are methods of quality assurance described?	☒	☐	☐	9.8.1
11.3 Is there a system in place for independent review of study results?	☒	☐	☐	9.10.1

Comments:

Section 12: Limitations	**Yes**	**No**	**N/A**	**Section Number**
12.1 Does the protocol discuss the impact on the study results of:				
12.1.1 Selection bias?	☒	☐	☐	9.9
12.1.2 Information bias?	☒	☐	☐	9.9
12.1.3 Residual/unmeasured confounding? (e.g. anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods).	☐	☐	☒	9.9
12.2 Does the protocol discuss study feasibility? (e.g. study size, anticipated exposure uptake, duration of follow-up in a cohort study, patient recruitment, precision of the estimates)	☐	☐	☒	

Comments:

Section 13: Ethical/data protection issues	**Yes**	**No**	**N/A**	**Section Number**
13.1 Have requirements of Ethics Committee/ Institutional Review Board been described?	☒	☐	☐	10.3
13.2 Has any outcome of an ethical review procedure been addressed?	☐	☐	☒	
13.3 Have data protection requirements been described?	☒	☐	☐	9.6

Comments:

Section 14: Amendments and deviations	**Yes**	**No**	**N/A**	**Section Number**
14.1 Does the protocol include a section to document amendments and deviations?	☒	☐	☐	5

Comments:

Section 15: Plans for communication of study results	**Yes**	**No**	**N/A**	**Section Number**
15.1 Are plans described for communicating study results (e.g. to regulatory authorities)?	☒	☐	☐	12
15.2 Are plans described for disseminating study results externally, including publication?	☒	☐	☐	12

Comments:

Name of the main author of the protocol: [redacted] for Sanofi B.V.

Date: 23/Jun/2023

Signature: _____

14.3 Appendix 3: Results of the Pilot Study on Patterns of Concomitant Drug Use in Patients with Gaucher Disease in Regione Lombardia (Northern Italy)

Treatment Patterns of Gaucher Disease in Europe

Report of Pilot Study

[redacted]

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March, 2015

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I Preliminary Information

Gaucher Disease is a rare metabolic disorder due to deficiency of acid β-glucosidase (β glucocerebrosidase, GBA1; D-glucosyl-N-acylsphingosine glucohydrolase, EC 3.2.1.45). Bi-weekly infusions of enzyme replacement therapy (ERT) with recombinant human acid β-glucosidase is the standard of care for Gaucher Disease Type 1. SRT is an alternative that seeks to balance glucosylceramide production with its impaired rate of degradation by partly inhibiting glucosylceramide synthase, the rate limiting step for glycosphingolipid biosynthesis. Miglustat is an approved SRT for adults with Gaucher Disease, but because of its less favourable efficacy, safety, and tolerability profiles than ERT, it has been licensed only for patients who are not suitable candidates for ERT.

Criteria for access to prescription databases has been tightened recently. In particular, it is now no longer straightforward to get access to such data unless there is evidence of a direct benefit to patients. This has been brought in as a response to pharmaceutical companies wishing to use such prescription databases in order to obtain marketing information. For requests which could be considered as such, it is necessary to make a full declaration in a submission outlining the patient benefit. This process causes delays.

The submission regarding the Pilot Study of Gaucher Disease has been considered in this light and has had to be reviewed by administrative authorities for authorisation of access. This has been a longer process than anticipated and has led to delays.

Initially, it was planned to undertake this Pilot Study in Norway but it is limited in its size and the scope of the prescription database. In view of these constraints, a database covering a larger population and with more comprehensive prescription information available was sought. It has been possible to obtain data from the databases of Regione Lombardia, in Northern Italy, for the period 2008-2012.

Prescription databases have been created to monitor drug use and associated costs. They generally do not contain information about the diagnosis for which a prescription has been issued. In Regione Lombardia, in Northern Italy and with Milan at its centre, several databases exist which can be linked to provide some more detailed information on diagnosis and prescriptions.

Gaucher Disease does not have a specific code in the revision of the ICD currently in use. It is contained within the rubric lipidosis. Patients with Gaucher Disease can only be identified by having a diagnosis of lipidosis and having been treated with drugs specific for the treatment of Gaucher Disease.

We have identified three specific treatments for Gaucher Disease used in Regione Lombardia.

- Cerezyme® (Imiglucerase for injection) is indicated for long-term enzyme replacement therapy for paediatric and adult patients with a confirmed diagnosis of Type 1 Gaucher Disease that results in one or more of the following conditions: anaemia (low red blood cell count), thrombocytopenia (low blood platelet count), bone disease, or hepatomegaly or splenomegaly (enlarged liver or spleen). In addition, it can be prescribed for Type 3 Gaucher Disease, where there is neurologic involvement (but not as severe as that seen in Gaucher Type 2). Cerezyme® is available as 200 U for injection (AIC: 034088017; ATC: A16AB02) or 400 U for injection (AIC: 034088031; ATC: A16AB02). The drug was authorised for use in Italy on 17th November 1997 and was last renewed on 17th September 2007.
- Velaglucerase alfa (Vpriv) (Shire Italia S.p.A.) is indicated for long-term replacement therapy (terapia enzimatica sostitutiva [TES]) among patients diagnosed with Gaucher Disease Type 1. It is available as 400 U for injection (AIC: 040424020; ATC: A16AB10). It was first authorised for use in Italy on 26th August 2010.
- Miglustat (OGT 918, N-butyl-deoxynojirimycin) is a drug developed by Oxford GlycoSciences and marketed by Actelion. It is used primarily to treat Type 1 Gaucher Disease. It is marketed under the trade name Zavesca. Miglustat (ATC: A16AX06) is used to treat adults with mild-to-moderate Type 1 Gaucher Disease for whom enzyme replacement therapy is unsuitable. It was approved in Europe in 2002 and by the US Food and Drug Administration (FDA) in 2003.

Gaucher Disease is an orphan condition and as such rare, treatment patterns are not systematically understood. In particular, there is no systematic information regarding the use of important concomitant therapies, members of the CYP2D6 and CYP3A families. The list of the CYP2D6 inhibitors and CYP3A inhibitors used concomitantly in patients with Gaucher Disease medications creates several problems since these drugs are used for a wide variety of common indications other than for Gaucher Disease.

CYP2D6 a member of the cytochrome P450 mixed-function oxidase system, is one of the most important enzymes involved in the metabolism of xenobiotics in the body. CYP2D6 is responsible for the metabolism and elimination of approximately 25% of all clinically used drugs. There is considerable variation in the efficiency and amount of CYP2D6 enzyme produced between individuals (i.e., CYP2D6 metaboliser phenotype). For drugs that are metabolised by CYP2D6 (i.e., CYP2D6 substrates), certain individuals will eliminate these drugs fast (ultra-rapid metabolisers) while others metabolise slowly (poor metabolisers). If a drug dose is metabolised too fast, this may not achieve adequate concentrations to achieve a therapeutic effect, while if a drug dose is metabolised too slow, elevated drug plasma

concentrations may occur, that potentially may lead to toxicity. Hence the patient's dose of the drug may have to be adjusted to take into account the speed at which it is metabolised by CYP2D6. Other drugs may function as inhibitors of CYP2D6 activity and can be classified as strong, moderate or weak inhibitors, potentially leading to decreased CYP2D6 activity and therefore to increased plasma concentrations of CYP2D6 substrates, and, in some cases, adverse outcomes may occur.

Members of the cytochrome P450 3A family are responsible for the metabolism of a vast array of therapeutic compounds. In humans, several members of the 3A family have been identified, but CYP3A is the most abundant P450 in the body (mainly found in the liver and in the intestine) and is responsible for the metabolism of nearly 50% of therapeutic compounds. Other drugs may function as inhibitors of CYP3A activity and can be classified as strong, moderate or weak inhibitors. This could lead to decreased CYP3A activity and therefore to increased plasma concentrations of CYP3A substrates, and, in some cases, adverse outcomes may occur. Some drugs may also function as inducers of CYP3A activity and lead to decreased plasma concentrations of CYP3A substrates.

II Detailed Findings

II.1 Data sources

Regione Lombardia is in Northern Italy centred around its capital, Milan. With a population of 10 million, Lombardia represents one fifth of the population of Italy and is renowned for the quality of its medical services and has been developing comprehensive databases relating to the health of its population. Using the data currently available in Regione Lombardia, an indication of use of specific Gaucher Disease treatments and the concomitant use of CYP2D6 inhibitors or CYP3A inhibitors can be determined.

In Italy, the population is covered by the National Health Service (NHS), and in Lombardia (Regione Lombardia) this has been associated with an automated system of databases to collect a variety of information since 1997. These databases, which have been created for administrative purposes, have also been used for research.

Two regional health administrative databases were employed in this study. The first source of data is the File F. This database includes drug prescriptions administered directly in the outpatient setting and in the day hospital, reimbursed by the NHS. The second source of data is the regional outpatient drug prescription database, which stores all drug prescriptions reimbursed by the NHS and dispensed by pharmacies in Lombardia. All databases include the unique

anonymous identification code of the patient receiving the drug, the Anatomical Therapeutic Chemical (ATC) code, the date of administration/collection and drug dosage.

II.2 Numbers of patients treated for Gaucher Disease (Regione Lombardia, 2008-2012)

Of the 61 patients treated for Gaucher Disease during the period 2008-2012, there were 37 men (61.7%) and 23 women (38.3%). There were 10 patients less than 18 years of age; 20 patients between 18-39 years old; 21 patients between 40 and 59 and 10 patients over the age of 60 (Table 1).

Table 1. Demographic characteristics of 61 subjects treated for Gaucher Disease

	No. (%)
Gender[a]	
Male	37 (61.7)
Female	23 (38.3)
Age[b]	
<18	10 (16.4)
18-39	20 (32.8)
40-59	21 (34.4)
60-90	10 (16.4)
TOTAL	61 (100.0)

[a] One subject with missing data on gender
[b] Age calculated at first drug prescription

Fifty subjects were prescribed Imiglucerase recorded in the databases of the Regione Lombardia between 2008 and 2012. A total of 3,553 prescriptions for Imiglucerase were issued during this period. Imiglucerase was the commonest of the three products prescribed for the treatment of Gaucher Disease (Table 2).

Fourteen subjects were prescribed Miglustat with a total of 204 prescriptions issued (Table 2). Prescriptions of Miglustat may be underestimated[3].

[3] In Italy, Miglustat can be dispensed by both hospital pharmacies and local pharmacies. In the first case, prescriptions are recorded on the so-called “File F” registry. In the second case, they are recorded on the outpatient drug prescription database. Data available in the File F registry only, since in the outpatient drug prescription database there are no data available on drugs with ATC code ‘A16’.

Two subjects were prescribed Velaglucerase alfa with a total of 56 prescriptions over the period (Table 2).

Note that some subjects had been prescribed more than one of these compounds over the period investigated.

II.3 CYP2D6 inhibitors and CYP3A inhibitors prescribed for any cause (Regione Lombardia, 2000-2012)

In particular, details were sought of the concomitant prescription of CYP2D6 inhibitors and CYP3A inhibitors among patients being treated for Gaucher Disease. Table 3 contains details of prescriptions for CYP2D6 inhibitors and CYP3A inhibitors issued annually in Regione Lombardia between 2000 and 2012.

CYP2D6 inhibitors and CYP3A inhibitors are widely prescribed in the general population and are not specific for patients also receiving medications for Gaucher Disease treatment.

Table 2. Drug prescriptions of Imiglucerase, Velaglucerase alfa and Miglustat in File F registry of Regione Lombardia (2008-2012)

	Imiglucerase (Genzyme)			Velaglucerase alfa (Vpriv)			Miglustat (Zavesca)[b]		
Year	**No. prescriptions**	**No. incident users**	**No. prevalent users**	**No. prescriptions**	**No. incident users**	**No. prevalent users**	**No. prescriptions**	**No. incident users**	**No. prevalent users**
2008[a]	724	36	36	N/A	-	-	23	6	6
2009	731	4	39	N/A	-	-	33	2	6
2010	647	5	40	0	0	0	43	1	6
2011	726	2	40	14	1	1	42	2	7
2012	725	3	39	42	1	2	63	3	9
TOTAL	3,553	50	-	56	2	-	204	14	-

Total number of Imiglucerase, Velaglucerase alfa and Miglustat users: 61 subjects

[a] First year for which data are available – likely includes prevalent cases.

[b] Prescriptions of Miglustat could be underestimated. In Italy, Miglustat can be dispensed by both hospital pharmacies and local pharmacies. In the first case, prescriptions are recorded on the so-called "File F" registry. In the second case, they are recorded on the outpatient drug prescription database. We have data available in the File F registry only, since in the outpatient drug prescription database we do not have data available on drugs with ATC code 'A16'.

Table 3. CYP2D6 inhibitors and CYP3A inhibitors drug prescriptions (Regione Lombardia, 2000-2012)

	CYP2D6 inhibitors							CYP3A inhibitors					
	Strong					Moderate							
Year	**Fluoxetine N06AB03**	**Paroxetine N06AB05**	**Bupropion N06AX12**	**Quinidine C01BA01**	**Cinacalcet H05BX01**	**Sertraline N06AB06**	**Duloxetine N06AX21**	**Ritonavir J05AR10**	**Indinavir J05AE02**	**Nelfinavir J05AE04**	**Saquinavir J05AE01**	**Clarithromycin J01FA09**	**Telithromycin J01FA15**
2000	62,154	166,735	0	3,612	0	67,366	0	0	0	0	0	532,258	1
2001	150,731	364,876	0	3,148	0	187,475	0	0	0	0	0	592,386	3
2002	143,055	386,100	0	2,820	0	264,314	0	0	0	0	0	599,403	20,225
2003	122,915	355,367	0	2,330	0	322,525	0	0	0	0	0	568,318	30,167
2004	114,407	368,486	0	1,941	0	304,698	0	0	0	0	0	566,301	31,720
2005	96,819	347,411	0	1,486	0	270,259	0	0	0	0	0	566,436	30,135
2006	96,384	370,944	0	1,084	0	298,529	36,836	0	0	0	0	550,891	24,039
2007	95,439	402,245	0	443	480	314,097	69,228	0	0	0	0	596,088	277
2008	93,851	427,537	9,089	214	2,150	320,043	92,730	28,157	275	56	2,479	647,292	3,183
2009	91,103	430,870	18,055	177	3,327	319,426	129,283	47,798	187	81	2,265	673,435	1,987
2010	89,777	422,713	23,721	191	4,293	325,529	184,432	50,566	134	77	1,765	641,224	1,235
2011	0	0	0	132	0	0	0	68,859	92	83	1,295	637,930	1,027
2012	0	0	0	0	0	0	0	76,602	78	75	1,078	580,697	787
TOTAL	**1,156,635**	**4,043,284**	**50,865**	**17,578**	**10,250**	**2,994,261**	**512,509**	**271,982**	**766**	**372**	**8,882**	**7,752,659**	**153,786**

II.4 CYP2D6 inhibitors and CYP3A inhibitors prescribed concomitantly with Gaucher Disease Therapies (Regione Lombardia, 2008-2009)

Table 4 contains details of the concomitant prescription of CYP2D6 inhibitors and CYP3A inhibitors in patients being treated for Gaucher Disease. The cohort of patients treated for Gaucher Disease (Imiglucerase, Velaglucerase alpha and Miglustat) in the years 2008 and 2009 were assessed for concomitant drug use. There were no prescriptions for Velaglucerase for these years.

Only four medications identified as either CYP2D6 inhibitors or CYP3A inhibitors were prescribed (Clarithromycin, Duloxetine, Paroxetine and Sertraline) among 48 subjects with Gaucher Disease who used Imiglucerase or Miglustat during the period 2008-2009.

Ten out of 48 patients (20.8%) treated for Gaucher Disease were also prescribed either a CYP2D6 or a CYP3A inhibitor (Table 4).

Among patients who were treated with Imiglucerase, nine patients out of 40 (22.7%) received concomitant therapy with either a CYP2D6 or a CYP3A inhibitor (Table 4). Seven of these 9 patients received the (strong) CYP3A inhibitor Clarithromycin. Two patients of the nine were prescribed the (moderate) CYP2D6 inhibitor Sertraline. One patient was prescribed the (strong) CYP2D6 inhibitor Paroxetine and one patient was prescribed the (moderate) CYP2D6 inhibitor Duloxetine. One patient was also prescribed Duloxetine, Paroxetine and Sertraline in the period covered by the study.

Of eight patients treated with Miglustat, one patient received concomitant therapy with either a CYP2D6 or a CYP3A inhibitor. One patient receiving Miglustat was also prescribed the (strong) CYP3A inhibitor Clarithromycin (Table 4).

Table 4. Concomitant medications among 48 subjects who used Imiglucerase or Miglustat (Regione Lombardia, 2008-2009[a]).

Concomitant medications	Gaucher disease treatments	
	Imiglucerase (N=40)	Miglustat (N=8)
Clarithromycin	7 (17.5)	1 (12.5)
Duloxetine	1 (2.5)	0 (0.0)
Paroxetine	1 (2.5)	0 (0.0)
Sertraline	2 (5.0)	0 (0.0)
No. of subjects[a]	9 (22.5)	1 (12.5)

[a] The cohort of patients treated for the Gaucher Disease (Imiglucerase, Velaglucerase alpha and Miglustat) in the years 2008 and 2009 was assessed for concomitant drug use in the whole period 2008-2012. There were no prescriptions for Velaglucerase for these years.
[b] One subject with missing data on gender One Imiglucerase user used both Duloxetine, Paroxetine and Sertraline

III Implications for Drug Utilisation Study of Eliglustat in Europe

In these comprehensive datasets from a large population, it is clear that Gaucher Disease is indeed a rare disease. In Europe, the birth prevalence of Gaucher Disease Type 1 is estimated to range from 0.8 to 2.5 per 100,000 (1 in 125,000 to 1 in 40,000) (Dionisi-Vici et al, 2002; Pinto et al, 2004; Poorthuis et al, 1999). Moreover, there is no unique rubric in the ICD for Gaucher Disease which is classified under the broader rubric lipidosis. Patients with Gaucher Disease are identified in the prescription databases according to the prescription of specific pharmaceutical compounds.

In addition to treatment with Imiglucerase or Miglustat, ten out of 48 patients (20.8%) with Gaucher Disease received concomitant therapy with either a CYP2D6 or a CYP3A inhibitor.

Eliglustat (Cerdelga®) is a (recently approved) glucosylceramide synthase inhibitor indicated for the long-term treatment of adult patients with Gaucher Disease Type 1 who are CYP2D6 extensive, intermediate, or poor metabolisers as detected by an FDA-cleared test. CYP2D6 ultra-rapid metabolisers taking 84 mg Eliglustat twice daily may not achieve adequate concentrations to achieve a therapeutic effect. A specific dose cannot be recommended for CYP2D6 ultra-rapid and indeterminate metabolisers.

While the mainstay of treatment for Gaucher Disease Type 1 currently is bi-weekly infusion via ERT, it has been shown recently that patients stable on such ERT treatment remain so after switching to oral Eliglustat (Cox et al, 2015).

Eliglustat, an oral SRT, is metabolised, mainly by CYP2D6 and to a lesser extent CYP3A4. Therefore, it is important that the use of CYP2D6 inhibitors and CYP3A inhibitors as concomitant medications among patients treated with Eliglustat be carefully monitored to investigate the extent of use.

It is essential that the study relies on collection and analysis of secondary data. The time-lag between having prescription data available and corrected for a complete year is variable and can be a number of years. This has implications for the conduct and reporting of the prospective study of Eliglustat.

The pilot study conducted in Regione Lombardia shows the feasibility of using regional/national prescription databases for drug utilisation evaluation of concomitant medication.

It is clear that this cannot be determined in a short timeframe using data from one database or using a limited group of resources. The prospective study of Eliglustat should be undertaken in a series of prescription databases. Prescription databases must cover large populations to provide useful and reliable investigations of diseases as rare as Gaucher Disease.

The prospective study of Eliglustat will be performed in existing databases including those of Regione Lombardia, Belgium and Israel. This will provide a total population of 28 million. We will also seek to utilise Nordic and other population-based prescription databases to get a larger total population.

IV Annex 1: Treatment Patterns of Gaucher Disease in Europe: Proposal for Pilot Study

Treatment Patterns of Gaucher Disease in Europe

Proposal for Pilot Study

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July, 2013
(revised) December 2013

I Introduction

Gaucher Disease is a rare autosomal recessive disease due to a deficit of an enzyme, acid β-glucosidase that is involved in the metabolism of lipid components of cell membranes. In 1882, Philippe Gaucher described a 32-year-old woman with massive splenomegaly and unusually large cells in the spleen, which he called a “primary epithelioma of the spleen” (Gaucher, 1882). The systemic nature of this disease, its inheritance, and variants that involve the viscera and central nervous system (CNS) were described over the next century (Desnick, 1982; Mandelbaum et al, 1916). The delineation of the causal enzymatic, genetic, and molecular pathology and genomics have provided pathologic insights into the phenotypic spectrum and bases for the development of specific therapies for what is now known as Gaucher Disease.

Gaucher Disease was the first lysosomal storage disease (LSD) described and has become a prototype for the clinical description and phenotypic variability of more than 50 LSDs. These LSDs include several variants of Gaucher, Fabry, Pompe, and Niemann-Pick diseases, as well as several mucopolysaccharidoses and other disorders caused by defective function of more than 300 lysosomal enzymes or lysosomal membrane proteins. These diseases manifest as a variety of visceral and CNS diseases. In aggregate, they occur with a frequency of 1 in 7,000 to 1 in 3,000 live births. Herein, the focus will be on Gaucher Disease because of its principal involvement of hematopoietic-derived cellular systems and because it is a prototype for other similar diseases, including Niemann-Pick disease type A and B, the lysosomal acid lipase deficiency disorders, Wolman disease, and cholesteryl ester storage disease. The phenotypic variation and the importance of specific hematopoietic cell type involvement will be emphasised as the basis for the development specific enzyme replacement therapy (ERT) and other approaches to the treatment of these disorders. Finally, the impact on the disruptions that these diseases cause on the lysosomal/autophagy systems and proteostasis will be extrapolated to more common disorders and to the role of these systems in neurodegenerative and haematologic malignancies.

A guiding principle in the understanding of LSDs, and Gaucher Disease in particular, has been the identification of specific primary cell types that are involved in the disease process. In the visceral variants of Gaucher Disease, the major organs involved include the spleen, liver, lungs and the cortical and bone marrow compartments (Grabowski et al, 2001). These organs are involved specifically because the principally affected cells are macrophage derived. The primary enzyme defect leads to the accumulation of an excess indigestible substrate, glucosylceramide, in organs that contain significant numbers of macrophage-lineage cells. Recent studies have also shown the involvement of most myeloid- and lymphoid-derived cells and their elaboration of numerous cytokines and chemokines (Pandey et al, 2012). The primary source for the accumulated glucosylceramide in visceral organs is the turnover of senescent blood-formed

element membranes that contain glycosphingolipids, including leukocytes, erythrocytes, and platelets (Kattlove et al, 1969).

With the development of hepatomegaly, splenomegaly, and bone marrow expansion, the disease process becomes an accelerating vicious cycle of accumulating material that activates macrophages and leads to the production of additional macrophages and accumulating Gaucher cells in the various tissues. Although the primary storage material, glucosylceramide, leads to classical and alternatively activated macrophages, the exact mechanism by which this activation and the subsequent production of numerous cytokines and chemokines has not been defined clearly. Therefore, the tissues involved in the visceral Gaucher Disease variant called Type 1 or non-neuronopathic disease have accumulations of Gaucher cells with inflammation, production of IFNs and IL-4 pathway–mediated cytokines and chemokines, the development of fibrotic changes, and changes in the space occupying the lesion caused by the progressive accumulated Gaucher cells. The pro- and anti-inflammatory effects lead to irreversible tissue damage and the variably progressive clinical course of the disease.

II Therapies[4]

Gaucher Disease is the prototype for ERT for LSDs and several other disorders. The initial studies conducted at the National Institutes of Health by Dr Roscoe Brady's group indicated that specific modifications of the oligosaccharide chains of the purified natural enzyme would be required for targeting to specific tissues and for therapeutic effect (Grabowski, 2012). These studies demonstrated the essential need for specific cellular targeting and dosing to provide significant therapeutic effects.

For newly synthesized acid β-glucosidase inside the cell, LIMP2 is the receptor for lysosomal targeting; this is not true for delivery of enzyme from outside of the cell to the lysosome. Because of the presence on macrophages of a specific mannose receptor, first natural placental and then recombinant acid β-glucosidases were modified to expose terminal mannosyl residues of the oligosaccharide chains. This led to the preferential uptake of IV-administered acid β-glucosidase into the affected macrophages and the degradation of the stored glucosylceramide. The concept of specific tissue targeting has been applied to ERT for the other LSDs and indicates the need for such preferential targeting, because misdirection of the enzyme to alternative tissues can lead to a blunting or absence of the therapeutic response.

[4] Note that Eliglustat was not approved and the randomised trial of Eliglustat (Cox et al, 2015) was not available when this proposal was written.

Using the macrophage mannose receptor as a “Trojan horse” for the delivery of the enzyme to the lysosomes, 3 ERTs have been developed for Gaucher Disease. Two of these, Imiglucerase (Genzyme) and Velaglucerase alfa (Shire HGT) are currently approved worldwide for the treatment of significantly involved patients with Gaucher Disease Type 1. Another product, Taliglucerase alfa (Protalix/Pfizer), was approved for the treatment of adults (> 18 years of age) by the United States Food and Drug Administration (FDA) on May 3, 2012. Each of these enzymes has different oligosaccharide modifications that may affect their interactions, uptake, and delivery to different cell types. This has been studied thoroughly with Imiglucerase and Velaglucerase alfa in mouse models of Gaucher Disease, and the essential equivalency of these 2 enzymes has been demonstrated (Xu et al, 2010). Clinical trials in which equal doses of either enzyme are used have also shown high clinical similarity. Based on limited data, Taliglucerase appears to have some similarity to the other 2 enzymes. Therefore, ERT by the IV administration of recombinant-produced enzymes that are macrophage- preferentially targeted has become the standard of care for Gaucher Disease Type 1.

Intravenous administered ERT has similar effectiveness for the visceral manifestations of Gaucher Disease Types 2 and 3, but does not have effects on the neuronopathic involvement. Overall, the results of ERT have been rather remarkable and, in many cases, lifesaving.

Miglustat (Zavesca®, by Actelion) is a pharmacological treatment of Gaucher Disease based on the reduction of chemical substrate necessary for the synthesis of glucosylceramide. Miglustat inhibits the enzyme glucosylceramide synthase that catalyses the first step in the biosynthesis of glucosylceramide. This drug may be used only in the treatment of patients for whom enzyme replacement therapy is unsuitable.

Newer agents have been developed including Eliglustat (Genzyme) which is a glucosylceramide synthase inhibitor for the long-term treatment of adult patients with Gaucher Disease Type 1.

A third approach to therapy for Gaucher Disease was termed pharmacologic chaperone therapy, but the term enzyme enhancement therapy (EET) is preferable because it more accurately reflects the mechanistic bases. This approach is based on the counterintuitive notion that highly potent and specific competitive inhibitors would bind to mutant enzymes in the endoplasmic reticulum or other parts of the protein synthesis system and reconform or conform enzymes to a more active state by improving either their stability or their fundamental kinetic properties or both.

III Study Questions

Due to the rarity of the condition, treatment patterns of Gaucher Disease are not well understood.

The purpose of this study is to obtain a better understanding of treatment patterns and the prescription of concomitant medications. Before launching into a major study, a pilot study will be conducted in the prescription database of Norway[5] which has been active at national level since 2004.

This was successfully used in the "Northern European Database Study of Insulin and Cancer Risk". The data are of a high-quality and are accessible for linkage, when needed.

IV Design of Pilot Study

It is proposed to assess this database to obtain the total number of patients treated with at least one of the drugs used for Gaucher Disease. For each patient identified, their entire prescription history in the database, from its start until the present, will be obtained. Fully anonymised basic patient's characteristics will be collected, such as year of birth and gender.

Patients will be identified who have been prescribed one of the medications listed in Table 1. Each compound listed will be identified by its ATC and these terms will be searched in the database.

A Scientific Committee of three external experts oversees the study and add guidance to the investigators as required. They will meet once at the beginning of the study and once to finalise the final report.

V Deliverables

The final report will contain the following information:

1. Numbers of patients treated with at least one of the drugs used for Gaucher Disease treatment.
2. A listing of concomitant medications prescribed.
3. Concomitant medications prescribed detailed by class of medications prescribed and with some interpretation.
4. Recommendations regarding the feasibility and calculations of the sample size (power) of a larger study.

[5] Initially it was planned to undertake this Pilot Study in Norway but it is limited in its size and the scope of the prescription database. In view of these constraints and the rarity of Gaucher Disease, a database covering a larger population and with more comprehensive prescription information available was sought. It has been possible to obtain data from the databases of Regione Lombardia, in Northern Italy, for the period 2008-2012.

Table 1. Medications of interest

The list of drugs considered for the pilot is not an exhaustive list of CYP2D6 or CYP3A inhibitors.

CYP2D6 inhibitors		**CYP3A inhibitors**
Strong	**Moderate**	**Strong**
SSRI fluoxetine paroxetine bupropoin quinidine cinacalcet ritonavir	sertraline duloxetine terbinafine	protease inhibitors ritonavir indinavir nelfinavir saquinavir macrolide antibiotics clarithromycin telithromycin chloramphhenicol azole antifungals ketonazole itraconazole nefazodone

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