EU-RISK MANAGEMENT PLAN FOR CERDELGA® (ELIGLUSTAT)

Data Lock Point (DLP)	**21-JUN-2023**
RMP Version number	**Version 8.3**
Date of final sign-off	**10-OCT-2024**

Table 1 - RMP version to be assessed as part of this application

Rationale for submitting an updated RMP	Risk management plan v8.3 has been updated to address PRAC Rapporteur comments on RMP v8.2 (submitted within procedure No. EMEA/H/C/003724/X/0036/G). RMP v8.2 has been updated to address CHMP Day 180 List of Outstanding Issues, on RMP v8.1 (submitted within procedure No. EMEA/H/C/003724/X/0036/G). RMP v8.1 was updated to address CHMP day 120 list of questions, dated 25-Apr-2024, on RMP v8.0 (submitted within procedure No. EMEA/H/C/003724/X/0036/G). RMP version 8.0 was updated in context of extension of indication application of Gaucher disease type 1 to paediatric patients (6 years and older with a minimum body weight of 15 kg).
Summary of significant changes in this RMP	In RMP v8.3, as per GVP, Module XVI Risk minimisation measures (Rev 3) (effective date 06-Aug-2024) the term "patient alert card" has been replaced by "patient card" throughout the document, including Annex 6. Annex 6 has been further amended to align with SmPC text. In RMP v8.2, proposed posology information for Paediatric population (from 6 to <18 years of age) weighing ≥15 kg (in RMP Part I) has been updated. Annex 6 has been updated in line with updated posology. In RMP v8.1, proposed indication (in RMP Part I, Part II Module SI and Part VI) has been updated as per CHMP day 120 list of questions. RMP Part II Module SII has been updated for clinical study EFC13738 (ELIKIDS). Annex 6 has been updated in line with updated indication. Risk management plan version 8.0 was updated to include data from the clinical study EFC13738 (ELIKIDS) for newly proposed extension of indication of Gaucher disease type 1 to paediatric patients (6 years and older with a minimum body weight of 15 kg). Risk management plan Part II Module SI, SIII and SIV were updated for clinical study EFC13738 (ELIKIDS) and newly proposed extension of indication. **Annexes:** Annex 2 was updated to include updated Interim report milestones of the prospective ICGG safety-sub registry (OBS14099-ELISAFE-category 1). Annex 5 was updated to remove Open label, 2 cohort (with and without imiglucerase), multicenter, historical controlled study to evaluate PK, safety, and efficacy of eliglustat in pediatric patients with GD1 and GD3. (EFC13738 ELIKIDS). Annex 6 was updated for newly proposed pediatric indication specific updates.

CHMP: Committee for Medicinal Products for Human Use; EMEA: European Medicines Agency; EU: European Union; GD1: Gaucher Disease Type 1; GD3: Gaucher Disease Type 3; GVP: Good Pharmacovigilance Practices; ICGG: International Collaborative Gaucher Group; PK: Pharmacokinetic; PRAC: Pharmacovigilance Risk Assessment Committee; RMP: Risk Management Plan; SmPC: Summary of Product Characteristics.

Table 2 - Other RMP versions under evaluation

RMP Version number	Submitted on	Submitted within
Not applicable	-	-

RMP Version number	Submitted on	Submitted within

RMP: Risk Management Plan.

Table 3 - Details of the currently approved RMP

Version number	7.1
Approved with procedure	Procedure EMEA/H/C/003724/IB/0033
Date of approval (opinion date)	18-Jul-2023 (CHMP date)

CHMP: Committee for Medicinal Products for Human Use; EMEA: European Medicines Agency; RMP: Risk Management Plan.

Table 4 - QPPV name and signature

QPPV name	Hadj Benzerdjeb[a], MD
QPPV signature	Electronic signature on file

a Deputy QPPV by delegation from Heike Schoepper, QPPV for Sanofi.
QPPV: Qualified Person Responsible for Pharmacovigilance.

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ABBREVIATIONS

ADR:	Adverse Drug Reaction
AE:	Adverse Event
ALT:	Alanine Aminotransferase
AST:	Aspartate Aminotransferase
ATC:	Anatomical Therapeutic Chemical
AV:	Atrioventricular
BID:	Twice Daily
BMD:	Bone Mineral Density
BMI:	Body Mass Index
CAD:	Coronary Artery Disease
CHF:	Coronary Heart Failure
CHMP:	Committee for Medicinal Products for Human Use
CI:	Confidence Interval
C_{max}:	Maximum Concentration
CMI:	Concomitant Medication of Interest
CNS:	Central Nervous System
COMP:	Committee for Orphan Medicinal Products
C_{trough}:	Trough Plasma Concentration
CYP:	Cytochrome P450
DALA:	Drug Abuse Liability Assessment
DDI:	Drug-Drug Interaction
DLP:	Data Lock Point
DUS:	Drug Utilization Study
ECG:	Electrocardiogram
e-CTD:	electronic-Common Technical Document
EEA:	European Economic Area
EM:	Extensive Metabolizer
EMEA:	European Medicines Agency
EPAR:	European Public Assessment Report
ERT:	Enzyme Replacement Therapy
EU:	European Union
FPI:	First Patient In
GBA:	Acid β-Glucosidase
GCS:	Glucosylceramide Synthase
GD:	Gaucher Disease
GD1:	Gaucher Disease Type 1
GD3:	Gaucher Disease Type 3
GI:	Gastrointestinal
GL-1:	Glucosylceramide
GVP:	Good Pharmacovigilance Practices
HCP:	Healthcare Professional
HDL-C:	High Density Lipoprotein Cholesterol
hERG:	Human Ether-a-go-go-related Gene

HI:	Hepatic Impairment
HIV:	Human Immunodeficiency Virus
HLT:	High Level Term
IC_{50}:	Concentration that Produces 50% Inhibition of the Target
ICGG:	International Collaborative Gaucher Group
IHD:	Ischemic Heart Disease
IM:	Intermediate Metabolizer
INN:	International Nonproprietary Name
ISS:	Integrated Safety Summary
IV:	Intravenous
LDL-C:	Low Density Lipoprotein Cholesterol
MedDRA:	Medical Dictionary for Regulatory Activities
MGUS:	Monoclonal Gammopathy of Undetermined Significance
MI:	Myocardial Infarction
MM:	Multiple Myeloma
MMSE:	Mini Mental State Examination
MN:	Multiples of Normal
MRI:	Magnetic Resonance Imaging
NA:	Not Applicable
NCV:	Nerve Conduction Velocity
NOAEL:	No Observed Adverse Effect Level
NOEL:	No Observed Effect Level
NSVT:	Non-Sustained Ventricular Tachycardia
p/P:	Probability
PBPK:	Physiologically Based Pharmacokinetic
PBRER:	Periodic Benefit Risk Evaluation Report
PD:	Pharmacodynamic
P-gp:	P-glycoprotein
PIL:	Patient Information Leaflet
PK:	Pharmacokinetic
PM:	Poor Metabolizer
PopPK:	Population Pharmacokinetic
PRAC:	Pharmacovigilance Risk Assessment Committee
PSUR:	Periodic Safety Update Report
PTC:	Product Technical Complaint
Q:	Quarter
Q2W:	Every Other Week
QD:	Once Daily
QOD:	Every Other Day
QPPV:	Qualified Person Responsible for Pharmacovigilance
QTc:	Corrected QT Interval
QTcF:	QT Interval Corrected with Fridericia's Formula
REE:	Resting Energy Expenditure Rate
RMP:	Risk Management Plan
SAE:	Serious Adverse Event
SD:	Standard Deviation
SmPC:	Summary of Product Characteristics

SRT:	Substrate Reduction Therapy
TEAE:	Treatment Emergent Adverse Event
ULN:	Upper Limit of Normal
URM:	Ultra-Rapid Metabolizer
US:	United States
VT:	Ventricular Tachycardia

RISK MANAGEMENT PLAN - PART I: PRODUCT (S) OVERVIEW

Table 5 - Product Overview

Active substance (INN or common name)	Eliglustat
Pharmacotherapeutic group (ATC Code)	A16AX10
Marketing Authorization Holder	Sanofi B.V. Paasheuvelweg 25 1105 BP Amsterdam The Netherlands
Medicinal products to which this RMP refers	1
Invented name in the EEA	CERDELGA
Marketing authorization procedure	Centralized procedure
Brief description of the product	Chemical Class: Eliglustat, a ceramide-based synthetic small molecule, is a potent and specific inhibitor of GCS, and acts as a SRT for GD1.
	Summary of mode action: Eliglustat is a SRT that reduces the synthesis of GL-1. Eliglustat is extensively metabolized by the CYP enzymes into inactive metabolites and has no or only a limited ability to cross the blood brain barrier with negligible exposure in the brain and has shown no propensity for eliciting any neurological effects in toxicology studies. Eliglustat is a highly selective inhibitor of GCS, and it is approximately 1000-fold more potent for its target than miglustat. In contrast, miglustat additionally non-specifically inhibits several glucosidases, including acid and neutral β-glucosidases, as well as intestinal disaccharidases, at concentrations similar to those that inhibit GCS. Miglustat's high frequency of AEs and poor tolerability are likely caused by these off-target effects, rather than a class effect of GCS inhibitors. Eliglustat mechanism of action (partial inhibition of the enzyme GCS) is distinct from that of the ERTs commonly used to treat GD1 which augment the deficient enzyme (acid β-glucosidase) activity in GD patients and catabolize stored GL-1 in lysosomes. While eliglustat and the approved SRT, miglustat, share the same target enzyme (GCS), their chemical structures are distinct: miglustat resembles the glucose moiety of GL-1, while eliglustat is similar in structure to the ceramide moiety. In addition to eliminating the need for life-long biweekly IV infusions, eliglustat provides a valuable first-line treatment alternative, and maintenance of disease control for adult GD1 patients, in particular for patients that continue to have residual bone disease despite treatment with ERT. Eliglustat also provides a valuable treatment alternative to previously treated paediatric GD1 patients with

<table>
<tr><td></td><td>ERT and met therapeutic goals. For these reasons, eliglustat is a valuable addition to the GD1 therapeutic armamentarium.</td></tr>
<tr><td></td><td>Important information about its composition:
The product contains lactose monohydrate as an excipient. The capsule shell contains gelatin.</td></tr>
<tr><td>Hyperlink to the product information</td><td>Refer to e-CTD sequence 0118, Module 1.3.1 English approved Product Information.</td></tr>
<tr><td>Indication in the EEA</td><td>Current:
CERDELGA is indicated for the long-term treatment of adult patients with GD1 who are CYP2D6 PMs, IMs or EMs.</td></tr>
<tr><td></td><td>Proposed:
Adults
CERDELGA is indicated for the long-term treatment of adult patients with GD1, who are CYP2D6 PMs, IMs or EMs.
Paediatric population (from 6 to ≤18 years) weighing ≥15 kg
CERDELGA is indicated for paediatric patients with GD1 who are 6 years and older with a minimum body weight of 15 kg, who are stable on enzyme replacement therapy (ERT), and who are CYP2D6 PMs, IMs or EMs.</td></tr>
<tr><td>Dosage in the EEA</td><td>Current:
Therapy with CERDELGA should be initiated and supervised by a physician knowledgeable in the management of Gaucher disease.
Posology: CERDELGA is to be taken orally twice daily in CYP2D6 IMs and EMs. The recommended dose is 84 mg eliglustat once daily in CYP2D6 PMs. If a dose is missed, the prescribed dose should be taken at the next scheduled time; the next dose should not be doubled.
The capsules should be swallowed whole, preferably with water, and should not be crushed, dissolved, or opened. The capsules may be taken with or without food. Consumption of grapefruit or its juice should be avoided.</td></tr>
<tr><td></td><td>Proposed:
Therapy with CERDELGA should be initiated and supervised by a physician knowledgeable in the management of Gaucher disease.
Patient selection
Before initiation of treatment with CERDELGA, patients should be genotyped for CYP2D6 to determine the CYP2D6 metaboliser status.
Eliglustat should not be used in patients who are CYP2D6 ultra-rapid metabolisers (URMs) or indeterminate metabolisers.
Posology
Adults
The recommended dose is 84 mg eliglustat twice daily in CYP2D6 IMs and EMs. The recommended dose is 84 mg eliglustat once daily in CYP2D6 PMs.
Paediatric population (from 6 to ≤18 years of age) weighing ≥15 kg
<table>
<tr><th>Weight</th><th>CYP2D6 EMs and IMs</th><th>CYP2D6 PMs</th></tr>
<tr><td>≥ 50 kg</td><td>84 mg twice daily</td><td>84 mg once daily</td></tr>
<tr><td>25 to < 50 kg</td><td>84 mg twice daily</td><td>42 mg once daily</td></tr>
<tr><td>15 to < 25 kg</td><td>42 mg twice daily</td><td>21 mg once daily</td></tr>
</table>
</td></tr>
</table>

Pharmaceutical form and strength	Current: CERDELGA is supplied as 84 mg of eliglustat (as tartrate) hard capsules. The 84 mg capsule has a pearl blue-green opaque cap and pearl white opaque body with “GZ02” printed in black on the capsule.
	Proposed: 21 mg hard capsule Capsules with a pearl white opaque cap and pearl white opaque body with "GZ04" printed in black on the capsule. The size of the capsule is “size 4” (dimensions 14 x 5 mm). 84 mg hard capsule Capsule with pearl blue-green opaque cap and pearl white opaque body with “GZ02” printed in black on the body of the capsule. The size of the capsule is “size 2” (dimensions 18 x 6.4 mm).
Is the product subject to additional monitoring in the EU?	Yes

AE: Adverse Event; ATC: Anatomical Therapeutic Chemical; CYP: Cytochrome P450; e-CTD: electronic-Common Technical Document; EEA: European Economic Area; EM: Extensive Metabolizer; ERT: Enzyme Replacement Therapy; EU: European Union; GL-1: Glucosylceramide; GCS: Glucosylceramide Synthase; GD1: Gaucher Disease type 1; IM: Intermediate Metabolizer; INN: International Nonproprietary Name; IV: Intravenous; PM: Poor Metabolizer; RMP: Risk Management Plan; SRT: Substrate Reduction Therapy; URM: Ultra-Rapid Metabolizer.

RISK MANAGEMENT PLAN - PART II MODULE SI: EPIDEMIOLOGY OF THE INDICATION(S) AND TARGET POPULATION(S)

Eliglustat (CERDELGA) is indicated for the long-term treatment of adult patients with GD1. The target population is patients who are CYP2D6 PMs, IMs or EMs. Eliglustat (CERDELGA) is proposed for paediatric patients with GD1 who are 6 years and older with a minimum body weight of 15 kg, who are stable on ERT, and who are CYP2D6 PMs, IMs or EMs.

Gaucher disease is a rare, pan-ethnic, multi-systemic and heterogeneous disorder that is often serious and chronically debilitating. Gaucher disease morbidity progresses over time in the majority of patients, and if untreated may lead to irreversible damage, such as bone infarcts and avascular necrosis. Systemic manifestations include visceromegaly, hematological abnormalities, and bone disease.

Gaucher disease is caused by a deficiency of lysosomal enzyme, acid β-glucosidase (glucocerebrosidase [GBA]), a glycosylated enzyme necessary for the catabolism of GL-1 into ceramide and glucose. This ubiquitous glycosphingolipid is the basic building block for the complex globosides and gangliosides that are important components of cell membranes, embedded receptors, and lipid rafts.

The 3 main clinical forms of Gaucher disease have traditionally been referred to as type 1 (non-neuronopathic), type 2 (acute neuronopathic), and type 3 (sub-acute neuronopathic), all of which are caused by allelic mutations in the GBA gene and are inherited in an autosomal recessive manner. Type 1 disease constitutes more than 90% of all cases of Gaucher disease currently known. Patients in all 3 types are deficient in GBA activity, but their clinical manifestations are heterogeneous, and the type and severity of symptoms vary by the presence or absence of neurological involvement, age at onset of clinical signs and symptoms, and disease progression.

The epidemiology of the disease is summarized in the following table.

Table 6 - Epidemiology of the Gaucher disease type 1

Indication	Gaucher disease type 1
Incidence	As Gaucher disease is an inherited genetic disorder present at birth, the true incidence of Gaucher disease cannot be computed. (1)(2) The burden of disease can be expressed more appropriately as birth prevalence, which is outlined in the next section.
Prevalence	Gaucher disease is an orphan disease, with an estimated frequency of approximately 1 in 100 000 births in the general population, (3)(4)(5)(6)(7), and approximately 1 in 30 000 to 1 in 100 000 in the EU (COMP Grounds for the Opinion on the Orphan Designation of eliglustat). (4)(5) Certain populations exhibit a higher birth prevalence. In populations from Western Europe or from Western European descent, birth prevalence rates of symptomatic Gaucher disease of between 1:57 000 and 1:111 000 have been reported, which translate into overall population prevalence rates in the order of 1 in 100 000. (3)(4)(5) In the Ashkenazi Jewish population, GD1 has a predicted prevalence of 1 in 850 births (8) but the actual prevalence estimates range from 1:400 and 1:2500. (9) A considerable proportion of Ashkenazi Jewish patients are homozygous for the most common *GBA* mutation, N370S (a missense mutation associated with a high amount of residual enzyme activity), and may not show clinically overt symptoms, or at least not until adulthood. (8)

Indication	Gaucher disease type 1

In most Caucasian countries, the neuronopathic variants of Gaucher disease (type 2 and 3) are much rarer than the type 1 variant and account for only 5% to 10% of Gaucher patients. In the Company-sponsored ICGG Gaucher Registry, approximately 94% of patients diagnosed with Gaucher disease are type 1, and the remaining cases are classified as neuronopathic Gaucher disease type 2 (1%), and type 3 (5%). (10)

Prevalence in the European Union:

Some EU countries for which there are published Gaucher disease birth prevalence data available include Italy, Portugal, and The Netherlands.

These data are summarized below. Based on the existing publications, the birth prevalence of GD1 is estimated to range from 0.8 to 2.5 per 100 000 (1 in 125 000 to 1 in 40 000).

Gaucher Disease Prevalence - Selected EU Countries

Country	Birth prevalence (per 100 000)		Reference
The Netherlands	1.16	(all types)	(4)
	0.9	(type 1)	
Portugal	1.35	(all types)	(5)
	0.8	(type 1)	
Italy[a]	2.5	(type 1)	(11)

a No Italian data are available for all types of GD.

EU: European Union; GD: Gaucher Disease.

It should however be noted that these data may not be representative of the overall European Community population. Historically, a considerable Jewish population existed in Portugal and in The Netherlands. Thus, part of the observed frequency in these countries may be due to founder effects which are not present throughout the rest of the EU. In addition, approximately 90% of patients with Gaucher disease were diagnosed with type 1. (10)

The prevalence estimates of Gaucher disease types 1, 2, and 3 were 0.94, 0.01 and 0.05 per 100 000, respectively. (5)

Among the population of Gaucher patients, the prevalence of genetic polymorphisms of CYP2D6 in the general population showed that approximately 90% of the US population is either a CYP2D6 IM or EM. (12)

In EU member states, the prevalence of CYP2D6 PMs and URMs, when available, is presented in the table below:

Prevalence of CYP2D6 PMs and URMs in EU

Country	PM (%)	URM (%)	Total (%)	Reference
Greece	3.18	6.01	9.19	(13)
Portugal	5.0	8.4	13.4	(14)
Spain	5.0	8.5	13.5	(15)(16)
Italian	3.4	8.3	11.7	(17)
Croatia	3	4	7	(18)
Germany	7.0	3.6	10.6	(19)
Sweden	8.5	1.5	10.0	(20)
Hungary	8.3	1.9	10.2	(21)

<table>
<tr><th>Indication</th><th>Gaucher disease type 1</th></tr>
<tr><td></td><td>
CYP: Cytochrome P450; EU: European Union; GD: Gaucher Disease; PM: Poor Metabolizer; URM: Ultra-Rapid Metabolizer.

Most recently, two literature reviews estimated the birth prevalence of GD1: 0.45-22.9/100 000 live births (Europe and North America) and GD3: 1.36/100 000 live births (Asia-Pacific only). Then, in the general population, GD type-specific prevalence estimates per 100 000 population were GD1: 0.26-0.63; GD2 and GD3: 0.02-0.08 (Europe only); estimates for GD type unspecified or overall ranged 0.11-139.0/100 000 inhabitants (17 studies), highest for North America. (22) Then, the second literature review provided the global birth prevalence of GD, estimated at 1.5 cases [95% CI: 1.0 to 2.0] per 100 000 live births, and the global prevalence of GD at 0.9 cases [95% CI: 0.7 to 1.1] per 100 000 inhabitants. (23)
</td></tr>
<tr><td>Demographics of the population in the authorized / proposed indication</td><td>
Gaucher disease is an autosomal recessive disease. There are no known gender-specific factors that affect the disease presentation. (8)

Gaucher disease type 1 may present at any age. An analysis of the frequency distribution of disease type by age of diagnosis for all patients in the ICGG Gaucher Registry (2008) is presented below. Approximately 50% of GD1 patients in the Registry were diagnosed before 18 years of age.

Age at Diagnosis of Gaucher Disease (ICGG Gaucher Registry, 2008)
<table>
<tr><th>Age at Diagnosis</th><th>Type 1
N = 4531
(n, %)</th><th>Type 2
N = 57
(n, %)</th><th>Type 3
N = 350
(n, %)</th><th>Not Reported
N = 172
(n, %)</th></tr>
<tr><td>Prenatal to <1 Year</td><td>150 (3)</td><td>38 (67)</td><td>48 (14)</td><td>0 (0)</td></tr>
<tr><td>1 - <2 Years</td><td>158 (3)</td><td>15 (26)</td><td>133 (38)</td><td>4 (2)</td></tr>
<tr><td>2 - <5 Years</td><td>607 (13)</td><td>1 (2)</td><td>87 (25)</td><td>8 (5)</td></tr>
<tr><td>5 - <12 Years</td><td>917 (20)</td><td>0 (0)</td><td>39 (11)</td><td>6 (3)</td></tr>
<tr><td>2 - <18 Years</td><td>436 (10)</td><td>0 (0)</td><td>14 (4)</td><td>5 (3)</td></tr>
<tr><td>≥18 Years</td><td>2073 (46)</td><td>1 (2)</td><td>17 (5)</td><td>13 (8)</td></tr>
<tr><td>Not Reported[a]</td><td>190 (4)</td><td>2 (4)</td><td>12 (3)</td><td>136 (79)</td></tr>
</table>
Based on N = 5110 patients. Disease type as reported by physician.
a Patients with no diagnosis date or with diagnosis date earlier than 1 year prior to their birth.
ICGG: International Collaborative Gaucher Group; N: Number.

Gaucher disease is inherited as an autosomal recessive disorder. The deficient enzyme, acid β-glucosidase, is encoded by the GBA gene located on chromosome 1q21. More than 300 GBA gene mutations are listed in the Human Gene Mutation database. More than 80% of these alleles are single nucleotide changes, whereas insertions, deletions, or other complex alleles account for the remainder. (24)
</td></tr>
<tr><td>Main existing treatment options</td><td>
Currently, there are 2 approved approaches for treating Gaucher disease by lowering GL-1 levels: ERT and SRT.

Most patients with GD1 are managed by IV-administered ERT using a glycan-modified, recombinant human acid β-glucosidase that targets mannose receptors on macrophages (imiglucerase - CEREZYME®). (25) Velaglucerase (VPRIV®) has also been approved as an ERT to treat GD1. Miglustat (ZAVESCA®), an N-alkyl aminosugar, was the first SRT approved for use in GD1. Because of its less favorable risk/benefit profile than ERT, the use of miglustat is restricted to adults with mild or moderate GD1 for whom ERT is not a therapeutic option.
</td></tr>
<tr><td>Natural history of the indicated condition in the untreated</td><td>
Mortality data on GD1 patients in the pre-ERT era are lacking. A study by Weinreb showed that GD1 patients taking ERT were found to have a reduced life expectancy of 68 years, compared
</td></tr>
</table>

Indication	Gaucher disease type 1
population including mortality and morbidity	to 77 years in the US population, with the most common causes of death being malignancy, cardiovascular, and cerebrovascular. (26) The prevalence of the most common clinically significant manifestations of Gaucher disease at diagnosis are presented in the following table. **Prevalences of Most Common Gaucher Disease Manifestations at the Time of Diagnosis[a] (All Disease Types)**

Patients enrolled in ICGG Gaucher Registry		**N = 5710**
Anaemia[b], n (%)		n = 2223
• *Present*		761 (34)
Thrombocytopaenia[c] (platelet count, x 10^3/mm^3), (non-splenectomized patients only), n (%)		n = 2098
• *Mild or None (≥120)*		873 (42)
• *Moderate (60 to <120)*		929 (44)
• *Severe (<60)*		296 (14)
Splenomegaly[d] (spleen volume in MN), n (%)		n = 839
• *Mild or None (≤5)*		128 (15)
• *Moderate (>5 to ≤15)*		389 (46)
• *Severe (>15)*		322 (38)
Hepatomegaly[d] (liver volume in MN), n (%)		n = 791
• *Mild or None (≤1.25)*		296 (37)
• *Moderate (>1.25 to ≤2.5)*		404 (51)
• *Severe (>2.5)*		91 (12)
Bone pain		n = 1548
• *Present*		517 (33)
Radiologic evidence of bone disease		n = 1150
• *Present*		948 (82)
Decreased BMD lumbar spine DXA Z-score		n = 307
• *Mild or None (>-1)*		159 (52)
• *Moderate (>-2.5 to ≤-1)*		114 (37)
• *Severe (≤-2.5)*		34 (11)
Type of bone disease reported	n	Present, n (%)
• *Marrow infiltration*	677	551 (81)
• *Erlenmeyer flask deformity*	691	405 (59)
• *Osteopaenia*	598	327 (55)
• *Infarction*	563	132 (23)
• *Lytic lesions*	479	88 (18)
• *Avascular necrosis*	592	99 (17)
• *Fractures*	465	34 (7)

Indication	Gaucher disease type 1
	a "At the time of diagnosis" is defined as the data point closest to the diagnosis date, no more than ± 2 years from diagnosis, and before any initiation of imiglucerase therapy. Patients with no diagnosis date or with diagnosis date earlier than 1 year prior to their birth and treated patients with no infusion date were excluded from the analysis for each assessment. *b* Anaemia is defined according to age and gender norms for haemoglobin as follows: <12 g/dL in males >12 years; <11 g/dL in females >12 years; <10.5 g/dL for ages >2 to 12 years; <9.5 g/dL for ages 6 months to 2 years; <10.1 g/dL for ages <6 months. *c* Among the 1221 partial or total splenectomy patients, thrombocytopaenia was classified as mild or none in 1157 (95%), moderate in 47 (4%), and severe in 17(1%). *d* Multiples of normal, where normal spleen volume is defined as 0.2% of body weight, and normal liver volume is defined as 2.5% of body weight. N is the number of patients in the Registry; n is the number of patients in the Registry with data. Source: ICGG Gaucher Registry Annual Report 2010; data on file. BMD: Bone Mineral Density; ICGG: International Collaborative Gaucher Group; MN: Multiples of Normal.
Important morbidities and co-morbidities	In addition to the characteristic features of Gaucher disease described in the table above, such as visceromegaly, bone disease, and hematologic abnormalities, less commonly observed co-morbidities include: an increased risk of malignancies; peripheral neuropathy; Parkinson's disease; and disease-specific metabolic abnormalities and associated lab findings. A DUS that covered the period between Jan-2003 and Jun-2012 has been conducted in the MarketScan® database in the US. There were 168 adult patients who were treated for Gaucher disease and retrospectively assessed for up to 6 months before treatment initiation to assess the frequency of comorbidities of interest (cardiac disease, arrhythmia, syncope, renal impairment, HI, depression and/or anxiety disorders and upper respiratory infection) (full report in [Annex 7]). In patients treated for Gaucher disease, about 7.1% had at least one claim of diagnosed upper respiratory infection and 3.6% of depression and/or anxiety disorders within 6 months prior to the initiation of Gaucher disease treatment. A few had arrhythmia (0.6%), syncope (0.6%), or renal impairment (0.6%) while no patient had HI and/or cardiac disease. **Epidemiology of visceral findings in Gaucher disease type 1** **Co-morbidity in the Indication/target population** / **Visceral findings** **Incidence/Prevalence** Many studies have shown that patients with GD present with increased size of the visceral organs (splenomegaly and hepatomegaly) as well as hematologic abnormalities (thrombocytopenia and anemia). (10)(27)(28)(29) A recent study published by Stirnemann et al utilizing the French Gaucher's disease registry reported that the most frequent initial manifestations leading to the diagnosis of GD were splenomegaly and thrombocytopenia in 562 patients. (28) At the time of diagnosis, 79.5% of the patients experienced hepatomegaly with the median liver size measured by ultrasound of 15 cm (range: 8.4-22). In addition, 98.9% of patients at the time of diagnosis experienced splenomegaly with a splenic size measured by ultrasound of 15.8 cm (range: 10-32). The results from the ICGG Gaucher Registry found that the mean spleen and liver volumes were 19.8 and 2.0 multiple of normal, respectively. (10) Splenectomy is only indicated if other measures fail to control life-threatening thrombocytopenia and associated high risk of bleeding. Other potential indications include unremitting abdominal

Indication	Gaucher disease type 1

	pain caused by recurrent splenic infarction, severe restrictive pulmonary disease, inferior vena cava syndrome, or inability to receive ERT. (29) Hepatobiliary complications can include the following: derangement of liver enzymes, parenchymal deposition of substrate, Gaucher cell infiltration, fibrosis, portal hypertension, and cirrhosis. Although case reports of liver failure reported in Gaucher disease patients have been published, liver failure is a rare complication that is usually associated with other intercurrent illnesses. (30)
Mortality	Splenic rupture, cirrhosis, and hepatocellular carcinoma have been reported in GD1 patients. Splenectomy has been associated with an increased risk of disease worsening, especially bone disease and the development of pulmonary hypertension, as well as an 8-year reduction in lifespan compared to non-splenectomized patients. (26)
Main co-prescribed medicinal products	None

ERT: Enzyme Replacement Therapy; GD: Gaucher Disease; GD1: Gaucher Disease Type 1; ICGG: International Collaborative Gaucher Group.

Epidemiology of skeletal abnormalities in Gaucher disease type 1

Co-morbidity in the Indication/target population	Skeletal abnormalities
Incidence/Prevalence	Patients with GD often experience skeletal manifestation that include abnormal bone remodeling, osteopenia, osteoporosis, lytic lesions, avascular necrosis of the humeral or femoral heads, and vertebral collapse. (31) An analysis from the results from the ICGG Gaucher Registry found that the most common signs and symptoms in children with non-neuropathic Gaucher disease were splenomegaly (95%), hepatomegaly (87%), radiologic bone disease (81%), thrombocytopenia (50%), anemia (40%), growth retardation (34%), bone pain (27%), and bone crisis (9%). (32) About 81% of children had at least one radiologic skeletal abnormality at the time of diagnosis with the 2 most common radiologic manifestations being Erlenmeyer flask deformity (49%) and bone marrow infiltration (38%). The heights of 34% of patients were in the 5th percentile, 28% were recorded in 5th to 25th percentile, and 39% were recorded as over 25th percentile in height. A study utilizing the French Gaucher's disease registry identified the major clinical complications in patients as bone events (including avascular necrosis, bone infarct, or pathological fracture), splenectomy, and Parkinson's disease. (28) Bone events occurred in 30.7% of patients with GD1. A study conducted by Khan and colleagues found that out of 5894 patients in the ICGG Gaucher Registry, 544 (9.2%) experienced at least one episode of avascular osteonecrosis and 319 (5.4%) experienced at least one fracture. Gaucher Disease type 1 patients with concurrent anemia are at an increased risk of avascular osteonecrosis. (33) Recent studies have also reported high prevalence of vitamin D deficiency among GD1 patients. (34)(35)(36)

Indication	Gaucher disease type 1

Mortality	An increase in hip fractures has been observed with increase in mortality. (37)
Main co-prescribed medicinal products	Vitamin D (if levels are low), calcium, bisphosphonates, non-steroidal anti-inflammatory medicinal products and narcotics.

GD: Gaucher Disease; GD1: Gaucher Disease type 1; ICGG: International Collaborative Gaucher Group.

Epidemiology of hematologic manifestation in Gaucher disease type 1

Indication/target population	Hematologic manifestations
Incidence/Prevalence	In untreated patients, thrombocytopenia and anemia are typically associated with increased cell destruction resulting from an enlarged spleen (hypersplenism), as well as decreased production caused by bone marrow infiltration by Gaucher disease cells. In a study published by Stirnemann that examined the characteristics, complications and treatment of 562 patients enrolled in the French Gaucher's disease registry, the first signs and symptoms leading to the diagnosis of Gaucher disease were splenomegaly in 37.6% of patients and thrombocytopenia in 26.3% of patients. (28) In addition, an ICGG Gaucher Registry study reported that at diagnosis, 40% of patients had mild thrombocytopenia, 45% had moderate thrombocytopenia, and 15% had severe thrombocytopenia. (38) Other hematologic manifestations including anemia and leucopenia also have been reported in GD patient populations. (38) Approximately 36% of patients were anemic at diagnosis. Leucopenia has been observed but at a lower frequency than for thrombocytopenia and/or anemia.
Mortality	Not available
Main co-prescribed medicinal products	Vitamin B12, folate

GD: Gaucher Disease; ICGG: International Collaborative Gaucher Group.

Epidemiology of malignancies in Gaucher disease type 1

Co-morbidity in the Indication/target population	Malignancies
Incidence/Prevalence	The association between GD and cancer has emerged through many individual case reports and more recently in well-conducted studies of large patient populations followed longitudinally. In a study conducted by Weinreb and Lee, 32.6% of deaths in a group of 175 patients with GD1 were attributable to malignant neoplasms. The proportional mortality ratio for all malignancies in GD1 patients was significantly increased when compared to the US reference population (1.57, p = 0.0002). (39) A study was conducted involving 2123 patients with GD1 to assess the incidence of hematological malignancies, gammopathies, and solid tumors in an international observational study, the International Cooperative Gaucher Group Gaucher Registry. Risk for cancer overall and for each type of malignancy was compared to the US population using the Surveillance, Epidemiology, and End Results database. Natural history of gammopathy was determined through assessing the

Indication	Gaucher disease type 1	
		progression from a diagnosis of MGUS to MM. Risk for hematological malignancies was more than four times higher than expected compared to the general population: non-Hodgkin lymphoma was approximately three times higher; MM was approximately nine times higher. Age-specific incidence rates of MGUS were unexpectedly high among younger patients. The 10-year cumulative incidence of MM after diagnosis of MGUS was 7.9%, comparable to the general population. Compared to the general US population, GD1 patients were at higher risk for solid malignancies of liver (2.9 times), kidney (2.8 times), melanoma (2.5 times), and breast (1.4 times). Colorectal, prostate, and lung cancer risks were lower than expected. Two other studies reported no increased overall risk of cancer in Gaucher patients as compared to non-Gaucher patients. (9)(40). De Fost et al. assessed the incidence and mortality of cancer in 131 patients with GD1 in Germany and The Netherlands. (41). A significantly increased risk was found for all types of cancer (2.5; 95% CI: 1.1-4.7), for hematological cancers as a whole (12.7; 95% CI: 2.6-37.0), for MM (51.1; 95% CI: 6.2-184) and for hepatocellular carcinoma (141.3; 95% CI: 17.1-510.5). Gaucher disease is associated with hyperimmunoglobulinemia and other manifestations of B cell stimulation. The prevalence of polyclonal gammopathies and MGUS in a cohort of 63 adult patients with GD1 was reported to be 41% and 19%, respectively. (42) The prevalence of MGUS in the general population is estimated to be 3.2% at age 50 and older and 5.3% in persons age 70 or older.(43) The risk of MGUS in adult patients with GD1 appears to increase with age and is not associated with disease severity. (42) Young age, however, does not preclude immunoglobulin disorders, and data suggest that the incidence of immunoglobulin abnormalities in pediatric patients is higher than in adult patients. The increased prevalence of MGUS in Gaucher disease patients corresponds to the observed increased risk of hematological malignancies in general, and MM in particular (see above). The mechanisms underlying the development of gammopathies remain to be elucidated but include a disturbance of cytokine levels involved in inflammation and B-cell function.
	Mortality	An increased standardized mortality ratio for all cancers in Gaucher disease patients (3.0; 95% CI: 0.96-6.9), and for specific cancers is described above. (41) Patients with GD1 were found to have a reduced life expectancy of 68 years, compared to 77 years in the US population, with the most common causes of death being malignancy, cardiovascular, and cerebrovascular. (26)
	Main co-prescribed medicinal products	Various chemotherapeutic agents depending on diagnosis.

CI: Confidence Interval; GD: Gaucher Disease; GD1: Gaucher Disease Type 1; ICGG: International Collaborative Gaucher Group; MGUS: Monoclonal Gammopathy of Undetermined Significance; MM: Multiple Myeloma; US: United States.

Epidemiology of neurological manifestations in Gaucher disease type 1

Co-morbidity in the Indication/target population	Neurological manifestations
Incidence/Prevalence	**Peripheral neuropathy** Emerging data suggest that neurological manifestations, including peripheral neuropathy, are infrequent manifestations of the GD1 phenotype. (44)(45)(46) A systematic review of the literature identified 86 reports in which patients with GD1, or carriers of a *GBA* gene mutation, were described with some form of neurological manifestation. In addition, a cohort of 75 GD1 patients was retrospectively investigated for the prevalence of neurological manifestations. Thirty-four neurological diagnoses were made and 45 patients reported at least one neurological symptom during the median follow-up time of 11 years. Paraesthesias were the most frequently mentioned complaint. (47) More recently, Biegstraaten et al. reported the results of a 2-year prospective cohort study in 103 GD1 patients, 14 of whom were untreated and the other 89 patients who received ERT. (48) At the study start, 11 patients (10.7%; 9 treated, 2 untreated) were diagnosed with sensory motor axonal polyneuropathy. Mononeuropathy of the ulnar nerve at the elbow was found in 2 patients (1.9%). The 2-year follow-up period revealed another 6 cases of polyneuropathy (2.9 per 100 person-years). Patients with polyneuropathy were older than those without (P<0.001). The 11 cases of polyneuropathy found at baseline were confirmed during follow-up. Enzyme replacement therapy use was not a risk factor for polyneuropathy. According to the literature, the prevalence of polyneuropathy in the general population was estimated to be between 0.09% and 1.3% and the incidence was estimated to be between 0.0046 and 0.015 per 100 person-years. It was concluded that the prevalence and incidence of polyneuropathy in patients with GD1 were increased compared with the general population. **Parkinson's disease** Gaucher disease type 1 is traditionally classified as non-neuronopathic but the medical literature contains increasing evidence of patients and carriers who have developed Parkinsonian symptomatology. (49) As of Jun-2010, the ICGG Gaucher Registry database included 68 patients with GD1 who were 18 years of age or older at last Registry assessment, and who had reports of Parkinsonism. (50) The incidence of Parkinsonism was 6 to 17 times higher in GD1 patients in the Registry database than in reference populations from Sweden and Russia. Similarly, a New York metropolitan area study estimated the adjusted lifetime relative risk of GD1 patients developing Parkinson's disease compared to the general population as 21.4. (51) Individuals heterozygous for *GBA* mutations have also been described with Parkinsonian phenotypes demonstrating that mutations in the *GBA* gene can be associated with a phenotype characterized by adult-onset progressive neurological deterioration and Parkinsonism. (52) In addition, a recent case-control study evaluating whether patients having Parkinson's disease with versus without *GBA* mutations differ in clinical phenotype or plasma protein expression found that in Parkinson patients with *GBA* mutations, the age at disease onset was earlier and cognitive

Indication	Gaucher disease type 1

	dysfunction was more common than patients without *GBA* mutations. (53) In most but not all accounts, Gaucher symptoms usually appear prior to the onset of Parkinsonian symptoms. The onset of Parkinsonism before diagnosis of Gaucher disease has also been reported. (54) In the reviewed literature, most Gaucher patients with Parkinsonian symptoms were diagnosed with Gaucher disease as adults, ranging in age from 17 to 68 years. (47) However, one patient exhibiting Parkinsonian symptoms was diagnosed with Gaucher disease at 9 years of age. (54) The range of Parkinsonian phenotypes reported in association with Gaucher disease includes more commonly adult-onset Parkinson's disease, mostly of the akinetic type, but also the less common phenotype of Lewy body dementia. There are also reports of early-onset, treatment-refractory Parkinsonism and atypical Parkinsonian findings such as electroencephalographic abnormalities and seizures. (49)(52)(54) Visceral, skeletal and hematological signs and symptoms among the group of Gaucher patients with Parkinsonian findings did not differ from those characteristic of GD1 patients, including hepatosplenomegaly, anemia, thrombocytopenia, and bone pain. (55)
Mortality	Increased risk of mortality in patients with Parkinson's disease. (56)(57)(58) In the study conducted using the French Gaucher Registry, 3 of the 38 deaths in GD1 patients were attributed to Parkinson's disease. (28)
Main co-prescribed medicinal products	Carbidopa-levodopa, dopamine agonist, monoamine-oxidase inhibitor, catechol O-methyltransferase inhibitors, anticholinergics, amantadine, gabapentin, topiramate, pregabalin, carbamazepine, phenytoin, amitriptyline, nortriptyline.

ERT: Enzyme Replacement Therapy; GD1: Gaucher Disease Type 1; GBA: Acid β-Glucosidase; ICGG: International Collaborative Gaucher Group.

Epidemiology of disease specific metabolic abnormalities and associated lab findings in Gaucher disease type 1

Co-morbidity in the Indication/target population	Disease specific metabolic abnormalities and associated lab findings
Incidence/Prevalence	**Altered lipid profiles** Lipid profiles are altered in Gaucher disease patients. Total plasma cholesterol, LDL-C and HDL-C have all been reported as being low in patients with Gaucher disease. (59) The reductions of LDL-C and HDL-C were associated with reduced levels of their respective major protein components apolipoprotein B 100 and apolipoprotein A1, while apolipoprotein E levels were reported to be high. (59) The levels of LDL-C and HDL-C were inversely correlated with parameters for disease severity, and splenectomy was associated with a subsequent increase of LDL-C and HDL-C. (59) In a study comparing 40 GD1 patients, 34 unaffected carriers of a *GBA* mutation, and 41 healthy normal subjects, no increased risk of cardiovascular disease was found in Gaucher patients despite the observed low HDL-C levels. (42) A review of the studies measuring plasma lipids in Gaucher disease patients are consistently associated with severely reduced HDL-C levels and poor non-HDL/HDL cholesterol ratios. (60) These lipid abnormalities have not been shown to

Indication	Gaucher disease type 1

	be associated with an increased cardiovascular risk in Gaucher disease patients but prospective data are lacking. **Metabolic abnormalities** Gaucher disease type 1 is associated with metabolic abnormalities such as high REE, increased glucose production and peripheral insulin resistance. (61) Resting energy expenditure in GD1 patients (measured by indirect calorimetry) was reported as being increased by 24% to 44% compared to healthy controls or to predicted values for the patient's age, sex, height, and weight. (62) Glucose production is also increased approximately 30% in GD1 patients compared to healthy controls. (62) A recent literature review shows in several small studies that GD1 is associated with insulin resistance irrespective of body weight and ERT/SRT. (60) It is unclear if this abnormality in glucose metabolism is associated with an increased risk for type II diabetes.
Mortality	Not known
Main co-prescribed medicinal products	Not applicable

ERT: Enzyme Replacement Therapy; GD1: Gaucher Disease Type 1; HDL-C: High Density Lipoprotein Cholesterol; LDL-C: Low Density Lipoprotein Cholesterol; REE: Resting Energy Expenditure Rate; SRT: Substrate Reduction Therapy.

Concomitant medications often used in this target population are those prescribed to treat co-morbidities listed above. A recent analysis of two national databases in the US and Germany found the most frequently prescribed co-medications in GD1 patients on ERT (imiglucerase or velaglucerase alfa) were analgesics, antibiotics and hypertension/cardiovascular drugs which is similar to general population. (63) For German patients, other commonly prescribed drugs included GI drugs (ie, pantoprazole and omeprazole) and glucocorticoids (ie, prednisolone). For the US patients, the other commonly prescribed medications included oral contraceptives (ie, ethinyl estradiol) (prescription of oral contraceptives which were not captured in the German prescription database), the corticosteroid prednisone, and the bronchodilator fluticasone. In Germany, approximately 20% of patients were co-prescribed a moderate/strong inhibitor of investigated CYP isoenzymes (CYP3A4, CYP1A2, CYP2C8, CYP2C9, CYP2C19, CYP2D6) while in the US, 57% of patients were co-prescribed a CYP isoenzyme inhibitor agent. In both countries, patients were rarely prescribed a CYP3A4 or CYP2C9 inducer. These databases analysis were limited in some aspects, since no information on dose scheduling and treatment duration of medications were provided, and polypharmacy was not taken in consideration in the analyses. In addition, the authors did not detail how they ascertained GD1 diagnosis in the databases used.

BMD: Bone Mineral Density; CI: Confidence Interval; COMP: Committee for Orphan Medicinal Products; CYP: Cytochrome P450; DUS: Drug Utilization Study; EM: Extensive Metabolizer; ERT: Enzyme Replacement Therapy; EU: European Union; GBA: Acid β-Glucosidase; GD: Gaucher Disease; GD1: Gaucher Disease Type 1; GD3: Gaucher Disease Type 3; GI: Gastrointestinal; GL-1: Glucosylceramide; HDL-C: High Density Lipoprotein Cholesterol; HI: Hepatic Impairment; ICGG: International Collaborative Gaucher Group; IM: Intermediate Metabolizer; IV: Intravenous; LDL-C: Low Density Lipoprotein Cholesterol; MGUS: Monoclonal Gammopathy of Undetermined Significance; MM: Multiple Myeloma; MN: Multiples of Normal; p/P: Probability; PM: Poor Metabolizer; REE: Resting Energy Expenditure Rate; SRT: Substrate Reduction Therapy; URM: Ultra-Rapid Metabolizer; US: United States.

RISK MANAGEMENT PLAN - PART II MODULE SII: NON-CLINICAL PART OF THE SAFETY SPECIFICATION

The drug substance, eliglustat tartrate (Genz-112638), is an L-tartaric acid salt, and exists in plasma as a free base, Genz-99067, which is the active moiety. Throughout this module, eliglustat is used when referring to the drug product administered in each clinical study, and Genz-99067 is used when referring to clinical drug exposure (ie, concentrations in plasma).

Acute dose safety pharmacology studies were conducted to evaluate the effects of eliglustat on cardiovascular, GI, renal, respiratory or central nervous system (CNS) functions. These studies were conducted according to the ICHS7 guideline (ICHS7A) and the current draft guidance on QT prolongation (ICHS7B). In safety pharmacology studies in the rat, eliglustat showed no effects on renal, respiratory or CNS function at the highest single dose of 400 mg/kg. Genz-99067 maximum concentration (C_{max}) values were measured or estimated to be as high as 1500 ng/mL, more than 30 times greater than the mean predicted steady-state C_{max} of 44.3 ng/mL in GD 1 patients based on the population pharmacokinetic (PopPK) model (SIM0124) for all predicted CYP450 2D6 phenotypes based on genotype represented in the patient populations in clinical trials at their recommended doses. Adverse effects were seen only in the cardiovascular and GI systems.

In safety pharmacology studies, the cardiac conduction system emerged as a potential target organ for effects of eliglustat. Cardiac conduction effects of eliglustat were observed in the in vitro human ether-a-go-go-related gene (hERG) (potassium channel), sodium and calcium cardiac ion channel assays (concentration that produces 50% inhibition of the target [IC_{50}] = 0.35, 5 and 12 μg/mL, respectively). Cardiovascular effects were observed in dogs at plasma eliglustat levels ≥300 ng/mL. In addition, in the Purkinje fibre assay, a small frequency-dependent effect (about 10% reduction in maximum rate of depolarization) was measured at 300 ng/mL. It is notable that while exposures at or above these levels were achieved in the repeat dose toxicology studies in dogs, no treatment-related effects on externally recorded electrocardiograms (ECG) were noted in any of these studies.

Toxicology studies demonstrated that eliglustat is generally well tolerated. The principal target organs for eliglustat pathology are the GI tract, the lymphoid organs, and, in the male rat only, the reproductive system. Effects in these target organs were evident only at the higher doses/exposures. Effects of eliglustat in toxicology studies were reversible and exhibited no evidence of delayed or recurring toxicity. Eliglustat is not genotoxic, and carcinogenicity studies in rat and mouse, at maximum tolerated doses, provided no evidence of any tumorigenic potential following 2 years of exposure.

Eliglustat is highly metabolized. All human systemic circulating metabolites identified by radioactivity were observed in preclinical species tested. Twenty-one metabolites were identified in human plasma. Nine of 10 metabolites with confirmed structures had steady-state exposure ratios of metabolite to total plasma radioactivity less than 10%. The other 11 metabolites with proposed structures were also each <10% of total drug-related exposure. Genz-399240, a 6-carboxy metabolite, was the only major metabolite with exposure exceeding 10% of total drug related exposure in plasma (15.9%). Steady-state exposure for Genz-399240 was 8.78-fold higher than parent drug exposure after repeated dosing of eliglustat 100 mg twice daily (BID), and tended to be higher in CYP2D6 URM compared to CYP2D6 PM.

The key non-clinical findings are presented in the following table.

Table 7 - Key safety findings from non-clinical studies and relevance to human usage

Key Safety Findings	Relevance to human usage
Toxicity	
Key issues identified from acute or repeat-dose toxicity studies: • Eliglustat metabolite toxicity: None of the 10 metabolites with confirmed structures showed any significant inhibition of GL-1 synthase activity (all IC_{50} values were >1 μM), indicating minimal contribution of metabolites to pharmacological activity of eliglustat, and in vitro IC_{50} values for inhibition of cardiac ion channels were well above the peak metabolite concentrations observed following repeat BID dosing of eliglustat in healthy subjects (GZGD02107, GZGD02407) and GD1 patients (Phase 2), indicating no cardiac safety signals from the metabolites. Genz 399240 is present at moderate levels in rabbits and monkeys. The former is one of the two species studied for potential effects on embryo-fetal development, and the latter is the species studied for potential effects on spermatogenesis. This disproportionate metabolite was not genotoxic. In a separate 13-week toxicology study in rats, the NOAEL for Genz-399240 was established as the highest dose tested (6 mg/kg/day) based on the absence of toxicity. • Lymphoid depletion: At a dose of 200 mg/kg/day for 2 weeks in rats, where significant systemic toxicity was evident, histopathology showed atrophy and lymphoid depletion in the thymus and spleen. In dogs, after 28 days of oral dosing, mild lymphoid depletion in the thymus and lymph nodes was observed upon microscopic examination in 1/3 female dogs at 10 mg/kg/day and 3/3 female dogs at 25 mg/kg/day. No effects were seen in males. At 13 weeks, mild lymphoid depletion in thymus was observed at 10 mg/kg/day; however, this also was seen in some control animals. No compound-related effect on lymphoid tissues was identified in a subsequent 52 week study at the same dose (10 mg/kg/day) and exposure. Where they were evident, these effects on lymphoid organs were not accompanied by correlating hematology changes and, thus, were difficult to clearly define as primary effects of eliglustat or secondary to stress associated with administration of the compound. There were no effects noted in other lymphoid organs or on clinical pathology parameters including lymphocyte counts and lymphocyte subsets.	Thorough evaluation of metabolites showed that they did not pose a safety concern at concentrations achieved in humans. Lymphoid depletion is a known stress response in dogs (these studies included daily dosing by oral gavage). In the total eliglustat clinical trial population, mean circulating lymphocyte values were observed to increase with treatment compared to baseline. Therefore, lymphoid depletion and potential decreases in circulating lymphocyte counts is not considered a safety risk in clinical use.

Reproductive/developmental toxicity studies: • Reproductive toxicity: Reproductive toxicity studies demonstrated no effects of eliglustat on reproductive function, and development effects were seen only in association with overt systemic toxicity. Eliglustat was evaluated in a full range of reproductive studies in the rat, including studies of fertility and reproductive function, developmental effects, and perinatal and neonatal effects. A developmental (teratology) study also was conducted in the rabbit. These studies all were negative for reproductive toxicity. In rats, the NOEL was 100 mg/kg/day for fertility and reproductive function and 30 mg/kg/day for pre- and post-natal development. The NOAEL in the F1 generation in rats was 100 mg/kg/day. In the teratology study in rats, the NOELs for maternotoxicity and embryo-fetal development were both 30 mg/kg/day. Thus, any developmental effects were seen only in association with overt maternal toxicity. In the rabbit, the NOEL for maternal toxicity was 30 mg/kg/day and the NOEL for embryo-fetal development was 100 mg/kg/day. Milk excretion of radioactivity after a single oral dose (30 mg/kg) of (14C)-eliglustat to lactating Sprague-Dawley rats showed that approximately 0.23% of the administered radioactivity was transferred to pups via milk during 24 hours pose dose on Day 11 post-partum, indicating milk excretion of (14C)-Genz-99067 and/or its related materials in rat. Placental transfer of radioactivity in female Sprague-Dawley rats following a single oral dose of (14C)-eliglustat at 30 mg/kg showed that approximately 0.034 % and 0.013 % of the administered radioactivity on Day 17 of gestation were detected in fetal tissues, at 2 and 24 hours post dose, respectively. Genz-99067 was identified, along with six metabolites of Genz-99067 detected, in rat fetus at 2 and 24 hours post dose. Placental transfer of (14)-Genz-99067 was confirmed in rat. Eliglustat has exhibited no effects on any reproductive function or developmental parameters, except for reversible inhibition of spermatogenesis at a systemically toxic dose in the rat, an effect that may relate to the unique role of the coagulating gland in that species. Similar effects on spermatogenesis were not seen in an investigational study in the monkey, with plasma concentrations at or above those measured in the Phase 2 and 3 clinical studies, where the male reproductive system more closely resembles that of humans. • Juvenile Toxicity: Eliglustat was well tolerated in a juvenile toxicology study in rats, with exposure levels and pharmacological activity (GL-1 reduction) similar to adult animals and no effect of treatment on growth or on physical or neurological development, immune function, or fertility assessment.	Animal studies do not indicate direct or indirect effects with respect to reproductive toxicity. Animal studies showed trace amount of milk excretion and placental transfer of eliglustat and/or its related materials in animals, but other than changes in fetal or neonatal body weight at maternally toxic doses, there were no embryo-fetal or effects on offspring. There are no data on the use of eliglustat in pregnant women. Therefore, its use during pregnancy is considered as missing information. There are no data on the use of eliglustat in lactating women. Therefore, the use of eliglustat in lactating women is considered as missing information. Effects on spermatogenesis were not evident in the monkey, where the male reproductive system more closely resembles that of humans, with plasma concentrations at or above those measured in phase 2 and 3 clinical trials. Eliglustat use does not appear to be a risk in humans. In ENGAGE clinical trial, out of 393 GD1 patients exposed to eliglustat safety set, 2 patients aged 16.6 and 16.9 years were enrolled and received eliglustat. In EFC13738 clinical trial, there were 57 pediatric patients (51 GD1 and 6 GD3) exposed to eliglustat. Overall, the safety profile in these 57

Key Safety Findings	Relevance to human usage
	paediatric patients was similar to that observed in the adult population. Use in children was considered as missing information initially. “Use in children” missing information is removed from EU-RMP version 6.1 as per the request of supplementary information following the assessment report on EU-RMP version 6.0).
Genotoxicity and carcinogenicity: Eliglustat is not genotoxic and was not carcinogenic in either mice or rats. After 2-year carcinogenicity studies at high doses of 75 mg/kg/day in mice and male rats and 50 mg/kg/day in female rats, no increases in tumor incidence were observed that were unequivocally attributed to treatment with eliglustat. Plasma samples were collected on Day 1 and after 13 weeks of treatment from satellite animals for toxicokinetic analysis. These data showed moderate to high inter-animal variability in systemic exposure to eliglustat in males and females after single and repeated administration. At the high dose, these represent about 4-fold and 3-fold multiples, respectively, of the mean predicted steady-state area under the curve at 12 hours of 307 ng.h/mL (SIM0124). Mouse exposure was confirmed by measuring levels of GL-1.	The risk of carcinogenicity and genotoxicity were not considered important in humans based on lack of non-clinical findings.
Safety pharmacology	
Gastrointestinal effects: Gastrointestinal effects, including emesis in dogs and hyper salivation and loud breathing in rats, were observed throughout the toxicology and safety pharmacology studies and these effects limited the maximum dose that was administered in repeat-dose studies. In rats, GI transit was completely inhibited at a single dose of 100 mg/kg and dogs vomited at doses of 25 mg/kg and higher. The NOEL for acute GI transit effects in the rat was 20 mg/kg, and the NOEL for emesis in the dog was 12.5 mg/kg. Safety pharmacology studies used single oral doses, covering a dose range of 20 to 400 mg/kg in rats and 1 to 80 mg/kg in dogs (cardiovascular), up to and exceeding the maximum tolerated dose.	The prediction of clinical correlates to these effects in laboratory animals is not straightforward, as dietary composition and feeding regimens are strictly controlled in the laboratory setting. Thus, the corresponding predicted GI effects of eliglustat treatment (eg, nausea, vomiting and constipation) based on decreased motility observed in animal studies may be quite different from the effects observed in humans. Eliglustat shows little or no inhibition of glycosidases, with no measurable inhibition of glucosidases and digestive disaccharidases. Diarrhea was more commonly a related treatment emergent AE in placebo patients (20%) than in eliglustat patients (10%) (ENGAGE clinical study report). Because of the nonspecific and transient GI symptoms ranging from diarrhea to constipation observed in humans, the inhibition of GI transit observed in animals is not considered relevant to human usage.
Cardiac electrophysiology: Cardiovascular effects of eliglustat were observed in the in vitro hERG (potassium channel), sodium and calcium cardiac ion channel assays (IC_{50} = 0.35, 5 and 12 μg/mL, respectively), the isolated Purkinje fibre assay, dog telemetry studies, and cardiac conduction studies in anesthetized dogs. The dog Purkinje fibre study suggested	A Phase 1 thorough QT study [Study GZGD01707] in healthy volunteers tested the effect of a single dose of 200 mg or 800 mg eliglustat on cardiac repolarization. QTcF, PR, and QRS intervals all increased from baseline in a concentration-dependent manner. The upper limit of the 95% CI of the QTcF change from baseline did not exceed 10 msec at any time point at the higher dose, therefore

Key Safety Findings	Relevance to human usage
a predominant effect on sodium channel currents, with NOEL defined as 0.1 μg/mL. The cardiac telemetry study in dogs showed a reversible dose related increase in QRS and PR durations at 30-60 minutes post dose, consistent with a predominant action of eliglustat on sodium channels and with recovery corresponding in time to clearance of the compound from plasma. The cardiovascular effects in dogs occurred at Genz-99067 plasma concentrations of ≥300 ng/mL.	showing no effect per ICH E14 guidance. The maximum C_{max} at the 200 mg dose was 142 ng/mL. The mean C_{max} at the 800-mg dose was 299 ng/mL. Based on PK/PD modeling, eliglustat plasma concentrations 11-fold (eg, 500 mg) above those expected at the indicated dose are predicted to cause mild increases in the PR, QRS, and QTc intervals of 20.4, 7.1, and 14.2 msec, respectively. Although these increases have not been observed in the therapeutic range of the clinical trials, if eliglustat exposure is substantially increased due to concomitant medication use, the positive changes in these intervals could lead to AEs of cardiac conduction as well as potential arrhythmias. These were also not observed in the clinical trials except for physiologic findings. Electrocardiogram effects following eliglustat treatment in GD1 patients are discussed in [Part II SVII]. The effect of eliglustat on cardiac depolarization, repolarization (and consequently, potential arrhythmias) and cardiac conduction in humans is considered an important potential risk.
CNS effects: Eliglustat was demonstrated to be a substrate of the drug transporter P-gp in in vitro studies conducted in the MDCKII-MDR1 cell model. Eliglustat was demonstrated as a substrate of the drug transporter P-gp and it was confirmed in in vivo studies of the P-gp knockout mice that this efflux transporter limited the brain penetration of eliglustat. In tissue distribution studies, no measurable radioactivity was observed in cerebellum, cerebrum and spinal cord in Long Evans rats following a single oral dose of 50 mg/kg of (14C)-eliglustat. Limited radioactivity was observed in brain tissue from Sprague-Dawley rats after administration of a single oral dose of 100 mg/kg (14C)-eliglustat or repeated dose of unlabeled eliglustat followed by a single dose of 100 mg/kg (14C)-eliglustat with 0 to 0.004% of dose in brain structures (of which the majority of radioactivity was associated with the pituitary gland). Based on these studies, it is projected that eliglustat penetration into the CNS human should be negligible. Furthermore, the Irwin assay (GT-157-TX-7), was negative at single oral doses as high as 400 mg/kg (C_{max} = 1500 ng/mL), and there were no neurological effects noted in chronic repeat- dose studies at doses as high as 50 mg/kg/day in rats (C_{max} was 1329 ng/mL [M] and 1521 ng/mL [F]) (GT-157-TX-17) and 10 mg/kg/day in dog (C_{max} about 1600 ng/mL (GT-157-TX-23).	Based on these studies it is projected that eliglustat penetration into the CNS in humans should be negligible. Although dizziness and headache were commonly observed as AEs in the eliglustat safety population, these AEs are not thought to be mediated by central effects of eliglustat, as eliglustat has no or only a limited ability to cross the blood-brain barrier with negligible exposure in brain. A drug abuse liability assessment study was not performed with eliglustat as the compound has no or only a limited ability to cross the blood-brain barrier with negligible exposure in brain and has shown no propensity for eliciting any neurological effects in toxicology studies. Eliglustat also has demonstrated no signal of dependence or abuse potential in clinical trials and has no structural similarities to known drugs of abuse. No risk to public health as a result of abuse is anticipated.
Other toxicity-related information or data Not applicable	

Key Safety Findings	Relevance to human usage

BID: Twice daily; CI: Confidence Interval; C_{max}: Maximum Concentration; CNS: Central nervous System; CYP: Cytochrome P450; DALA: Drug Abuse Liability Assessment; GD1: Gaucher disease type 1; GI: Gastrointestinal; GL-1: Glucosylceramide; hERG: Human Ether-a-go-go-related Gene; IC_{50}: Concentration that produces 50% inhibition of the target; NOAEL: No Observed Adverse Effect Level; NOEL: No Observed Effect Level; PD: Pharmacodynamic; P-gp: P-glycoprotein; QTc: Corrected QT Interval; QTcF: QT Interval Corrected with Fridericia's Formula.

No additional non-clinical data have been collected on the use of eliglustat in any special animal models.

RISK MANAGEMENT PLAN - PART II MODULE SIII: CLINICAL TRIAL EXPOSURE

The safety, tolerability, and PK profile of eliglustat in adults have been assessed in a total of 23 clinical studies. One study in pediatric patients is ongoing with an interim analysis performed in June 2023 to meet PIP requirements.

Table 8 - Studies

Studies	Number	Studies
Phase 1	18	GZGD00103, GZGD00204, GZGD00404, GZGD01707, GZGD01807, GZGD01907, GZGD02007, GZGD02107, GZGD02407, GZGD02707, GZGD03610, GZGD03811, GZGD04112, PKM14187, ACC14373, POP13777, POP13778, PKM14281.
Phase 2	1	GZGD00304.
Phase 3	5	GZGD02507 (ENGAGE), GZGD02607 (ENCORE), GZGD03109 (EDGE), EFC13781 (EXOSKEL), and EFC13738 (ELIKIDS).

An overview of the study design, key safety measures, and number of patients exposed to eliglustat in each of the Phase 2 and Phase 3 clinical studies conducted in patients with GD1 is provided in Table 9.

In the Phase 2 and Phase 3 clinical studies (ENGAGE, ENCORE and EDGE), patients initially received eliglustat 50 mg BID, with the potential for subsequent dose increases based on trough plasma concentrations (C_{trough}). In clinical practice, therapeutic monitoring would be complicated by the need for the repeat testing of Genz-99067 plasma levels in the setting of potentially large fluctuations in exposure. On the other hand, a PopPK analysis using data from healthy subjects and GD1 patients showed that CYP2D6 phenotype (PM, IM, EM or URM) was the most significant determinant of successful exposure to eliglustat. Therefore, a dosing regimen based on CYP2D6 phenotype is approved and implemented for postmarketing use.

During these studies, a limited number of URM patients (n = 11) with GD1 disease were treated with eliglustat. As a result, the amount of observed PK data available from URM patients in clinical studies that can be used to project exposures is currently limited. This is precluding a confident prediction of the full range of exposures that may occur in these subpopulations in the wider postmarketing setting, which in turn limits the ability to ensure that plasma levels will remain in the safe and efficacious range under conditions of commercial use. Additional PK, safety and efficacy data from URMs patients treated with eliglustat are necessary to provide adequate dosing guidance for a chronic treatment in these small subpopulations.

Table 9 - Company Sponsored Clinical Studies of Eliglustat in Gaucher Disease

Study Number Status	Study Phase, Design, and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Patients Exposed to Eliglustat	Key Safety Measures	Analysis Period
GZGD00304 Completed	Phase 2 open-label, uncontrolled study in patients with GD1 who were untreated or had not been treated in preceding 12 months.	Eliglustat oral capsule: 50 mg BID (initial dose) Adjustment[a] to 100 mg BID at Day 20 and 150 mg after 24 months	26	Adverse Events, SAEs, concomitant medications, pregnancies, ECGs, 24-hour Holter monitoring, echocardiograms, physical examinations, weight, BMI, vital signs, NCV, MMSE, and standard clinical laboratory tests.	52 weeks (1 year)[b], 96 months[c] (8 years)
ENGAGE (GZGD02507) Completed	Phase 3, randomized, double-blind, placebo-controlled study in patients with GD1 who were untreated or had not been treated in preceding 9 months.	Eliglustat oral capsule 50 mg BID (initial dose) or placebo Adjustment[a] to 100 mg BID at 4 weeks and 150 mg after 47 weeks	40	Adverse Events, SAEs, concomitant medications, pregnancies, ECGs, 24-hour Holter monitoring, echocardiograms, physical examinations, weight, BMI, vital signs, neurological examinations, MMSE, and standard clinical laboratory tests.	39 weeks[b] 54 months (4.5 years)[c]
ENCORE (GZGD02607) Completed	Phase 3, randomized, open-label, active comparator study in patients with GD1 who achieved therapeutic goals with ERT.	Eliglustat oral capsule: 50 mg BID (initial dose) Adjustment[a] to 100 mg at 4 weeks and 150 mg at 8 weeks or CEREZYME IV infusion, in an every 2-week regimen equivalent to the patient's dose prior to the study.	157	Adverse Events, SAEs, concomitant medications, pregnancies, ECGs, 24-hour Holter monitoring, echocardiograms, physical examinations, weight, vital signs, neurological examinations, MMSE, nerve conduction tests, and standard clinical laboratory tests.	52 weeks[b] 48 months (4 years)[c]
EDGE (GZGD03109) Completed	Phase 3 randomized, double-blind, study to evaluate QD versus BID dosing in patients with GD1 who demonstrate	Eliglustat oral capsule; Open-label Lead-in period: 50 mg BID (initial dose), adjustment[b] to 100 mg BID	170	Adverse Events, SAEs, concomitant medications, pregnancies, ECGs, 24-hour Holter monitoring, physical examinations, weight, vital signs, neurological examinations, and	Lead-in: 6-18 months Randomized treatment: 52 weeks[b] 42 months (3.5 years)[c]

Study Number Status	Study Phase, Design, and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Patients Exposed to Eliglustat	Key Safety Measures	Analysis Period
	clinical stability on BID dosing.	Randomized, blinded treatment period: BID or QD dosing at same dose as end of Lead-in period.		standard clinical laboratory tests.	
EXOSKEL (EFC13781) Completed	Phase 3b open-label study in patients who successfully completed the Phase 2 or Phase 3 studies (ENGAGE, ENCORE, EDGE).	Eliglustat oral capsule: 100 mg BID in Ims, EMs, and URMs; 100 mg QD in PMs	31	Adverse Events, SAEs, concomitant medications, physical examinations, pregnancy testing, clinical laboratory assessments (hematology).	The duration of study participation for individual participants was to be at least 2 years (unless early discontinuation occurred) and up to 4 years, or until commercial eliglustat was available to participants through reimbursement.
ELIKIDS	Phase 3 open label, two cohort (with and without imiglucerase), multicenter study to evaluate pharmacokinetics, safety, and efficacy of eliglustat in pediatric patients with GD Type 1 and Type 3	Eliglustat oral capsule and liquid formulation. Body weight, age, CYP2D6 phenotype adjusted dose regimen, including eliglustat 84 mg BID, 42 mg BID, 42 mg QD, 21 mg BID, 21 mg QD, 12.6 mg BID, 12.6 mg QD, and 8.4 mg QD. Cohort 1: eliglustat alone Cohort 2: eliglustat + imiglucerase combination.	57	Adverse Events, vital signs, physical and neurological examinations, Tanner stage, clinical laboratory tests, ECG, 24-hour Holter, echocardiogram, brain MRI, neuropsychological tests, electroencephalogram, NCV	At least 52-weeks (PAP)

a Dose increased based on trough plasma levels of eliglustat; patients with a Genz-99067 (the active moiety of eliglustat in plasma) trough concentration ≥5 ng/mL continued on same dose, while patients with a Genz-99067 trough concentration <5 ng/mL were adjusted to the next higher dose.

b Primary Analysis Period.

c Long-term treatment period (extension).

AE: Adverse Event; BID: Twice Daily; BMI: Body Mass Index; DLP: Data Lock Point; ECG: Electrocardiogram; EM: Extensive Metabolizer; ERT: Enzyme-Replacement Therapy; GD1: Gaucher Disease Type 1; IV: Intravenous; IM: Intermediate Metabolizer; MMSE: Mini Mental State Examination; NCV: Nerve Conduction Velocity; QD: Once Daily; RMP: Risk Management Plan; SAE: Serious Adverse Event; URM: Ultra-Rapid Metabolizer.

CLINICAL TRIAL EXPOSURE

Pediatric Population

- One study in patients aged ≥2 years to <18 years:
  - The ELIKIDS study (EFC13738) is open label, two cohort (with and without imiglucerase), multicenter study to evaluate PK, safety, and efficacy of eliglustat in pediatric patients with GD1 and GD3. The primary objective of the study was to evaluate the safety and PK of eliglustat in pediatric patients (≥2 to <18 years old). The secondary objective(s) was to evaluate the efficacy of eliglustat and quality of life in pediatric patients (≥2 to <18 years old). This study was conducted in Argentina, Canada, France, Italy, Japan, Russia, Spain, Sweden and Turkey. A total of 57 patients were randomized and received at least one dose of study medication.

Table 10 - Eliglustat Exposure by Dose and Duration Categories – Eliglustat Safety Set in Paediatric Patients

	21 mg BID (N=4)	42 mg BID (N=29)	42 mg QD (N=1)	84 mg BID (N=53)	126 mg BID (N=4)	126 mg QD (N=1)	Any dose (N=57)
Cumulative exposure to treatment (Participant years)	1.25	21.13	3.57	97.64	8.75	0.16	132.31
Duration of study treatment (Weeks)							
Number	4	29	1	53	4	1	57
Mean (SD)	16.3 (4.8)	38.0 (20.8)	186.4 (NC)	96.1 (57.9)	114.1 (67.6)	8.6 (NC)	121.1 (50.9)
Median	14.9	38.9	186.4	80.1	128.4	8.6	106.3
Min ; Max	13 ; 23	2 ; 77	186 ; 186	14 ; 209	29 ; 171	9 ; 9	39 ; 209
Duration of study treatment by category [n (%)]							
0 and ≤52 weeks	4 (100)	21 (72.4)	0	13 (24.5)	1 (25.0)	1 (100)	7 (12.3)
>52 and ≤104 weeks	0	8 (27.6)	0	18 (34.0)	1 (25.0)	0	12 (21.1)
>104 and ≤208 weeks	0	0	1 (100)	19 (35.8)	2 (50.0)	0	34 (59.6)
>208 and ≤312 weeks	0	0	0	3 (5.7)	0	0	4 (7.0)
>312 weeks	0	0	0	0	0	0	0
Cumulative duration of study treatment by category [n (%)]							
> 0 week	4 (100)	29 (100)	1 (100)	53 (100)	4 (100)	1 (100)	57 (100)
> 52 weeks	0	8 (27.6)	1 (100)	40 (75.5)	3 (75.0)	0	50 (87.7)
> 104 weeks	0	0	1 (100)	22 (41.5)	2 (50.0)	0	38 (66.7)
> 208 weeks	0	0	0	3 (5.7)	0	0	4 (7.0)

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N: Number; NC: Not Calculated; SD: Standard Deviation.

Table 11 - Eliglustat Exposure Duration by Dose and Gender – Eliglustat Safety Set in Paediatric Patients

Dose	Exposure	Male (N=29)	Female (N=28)	Overall (N=57)
21 / 42 / 84/ 126 mg BID	Cumulative exposure to treatment (Participant years)	65.25	63.49	128.74
	Duration of study treatment (Weeks)			
	Number	28	28	56
	Mean (SD)	121.6 (52.5)	118.3 (49.5)	120.0 (50.6)
	Median	106.0	113.9	106.1
	Min ; Max	39 ; 209	45 ; 208	39 ; 209
21 / 42 / 126 mg QD	Cumulative exposure to treatment (Participant years)	3.74		3.74
	Duration of study treatment (Weeks)			
	Number	2	0	2
	Mean (SD)	97.5 (125.8)		97.5 (125.8)
	Median	97.5		97.5
	Min ; Max	9 ; 186		9 ; 186
Overall	Cumulative exposure to treatment (Participant years)	68.82	63.49	132.31
	Duration of study treatment (Weeks)			
	Number	29	28	57
	Mean (SD)	123.8 (53.0)	118.3 (49.5)	121.1 (50.9)
	Median	106.3	113.9	106.3
	Min ; Max	39 ; 209	45 ; 208	39 ; 209

PGM=PRODOPS/GZ385660/EFC13738/CSR/EXPLO/PGM/dos_dur_bysex_rmp_s_t.sas
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BID: Twice Daily; N: Number; QD: Once Daily; SD: Standard Deviation.

Table 12 - Eliglustat Exposure Duration by Dose and Paediatric Age Group – Eliglustat Safety Set

Dose	Exposure	2-11 years old (N=21)	12-17 years old (N=36)
21 / 42 / 84/ 126 mg BID	Cumulative exposure to treatment (Participant years)	38.70	90.04
	Duration of study treatment (Weeks)		
	Number	21	35
	Mean (SD)	96.1 (32.5)	134.2 (54.4)
	Median	104.3	151.7
	Min ; Max	47 ; 157	39 ; 209
21 / 42 / 126 mg QD	Cumulative exposure to treatment (Participant years)	0.16	3.57
	Duration of study treatment (Weeks)		

Dose	Exposure	2-11 years old (N=21)	12-17 years old (N=36)
	Number	1	1
	Mean (SD)	8.6 (NC)	186.4 (NC)
	Median	8.6	186.4
	Min ; Max	9 ; 9	186 ; 186
Overall	Cumulative exposure to treatment (Participant years)	38.70	93.61
	Duration of study treatment (Weeks)		
	Number	21	36
	Mean (SD)	96.1 (32.5)	135.7 (54.3)
	Median	104.3	152.1
	Min ; Max	47 ; 157	39 ; 209

PGM=PRODOPS/GZ385660/EFC13738/CSR/EXPLO/PGM/dos_dur_byage_rmp_s_t.sas
OUT=EXPLO/OUTPUT/dos_dur_byage_rmp_s_t_i.rtf (20SEP2023 11:47)
BID: Twice Daily; N: Number; QD: Once Daily; SD: Standard Deviation.

Table 13 - Eliglustat Exposure Duration by Dose and Race – Eliglustat Safety Set in Paediatric Patients

Dose	Exposure	White (N=50)	Black or African American (N=0)	Asian (N=4)	Not reported (N=3)
21 / 42 / 84/ 126 mg BID	Cumulative exposure to treatment (Participant years)	116.62		7.32	4.80
	Duration of study treatment (Weeks)				
	Number	49	0	4	3
	Mean (SD)	124.2 (51.5)		95.5 (29.0)	83.5 (43.0)
	Median	106.3		92.9	76.3
	Min ; Max	39 ; 209		66 ; 131	45 ; 130
21 / 42 / 126 mg QD	Cumulative exposure to treatment (Participant years)	3.74			
	Duration of study treatment (Weeks)				
	Number	2	0	0	0
	Mean (SD)	97.5 (125.8)			
	Median	97.5			
	Min ; Max	9 ; 186			
Overall	Cumulative exposure to treatment	120.19		7.32	4.80

Dose	Exposure	White (N=50)	Black or African American (N=0)	Asian (N=4)	Not reported (N=3)
	(Participant years)				
	Duration of study treatment (Weeks)				
	Number	50	0	4	3
	Mean (SD)	125.4 (51.7)		95.5 (29.0)	83.5 (43.0)
	Median	106.5		92.9	76.3
	Min ; Max	39 ; 209		66 ; 131	45 ; 130

PGM=PRODOPS/GZ385660/EFC13738/CSR/EXPLO/PGM/dos_dur_byrace_rmp_s_t.sas
OUT=EXPLO/OUTPUT/dos_dur_byrace_rmp_s_t_i.rtf (20SEP2023 11:47)
BID: Twice Daily; N: Number; QD: Once Daily; SD: Standard Deviation.

Adult Population –

The total eliglustat safety population included 393 patients; 26 patients from the Phase 2 study, 40 patients from ENGAGE, 157 patients from ENCORE, and 170 patients from EDGE representing 1400.3 patient-years of eliglustat exposure. In addition, 462 healthy subjects were exposed to eliglustat while enrolled in completed Phase 1 clinical trials.

Table 14 summarizes number of healthy subjects who were exposed to eliglustat or placebo during phase 1 studies.

Table 15 summarizes overall treatment duration in the GZGD00304, ENGAGE (GZGD02507), ENCORE (GZGD02607), and EDGE (GZGD03109) studies.

Table 16 summarizes number of patients who did not have recent prior ERT exposure and the number of patients with recent prior ERT exposure. Within 393 patients, 134 patients did not have recent prior ERT exposure and 259 patients had recent prior ERT exposure. The patients who were treated with 100 mg eliglustat BID were exposed to eliglustat for a longer period of time.

Table 17 summarizes eliglustat exposure for all patients who received any eliglustat dose in the one Phase 2 and three Phase 3 studies, both overall and by treatment duration intervals. A total of 393 patients have been exposed to at least 1 dose of eliglustat in clinical studies. If a patient appears in more than 1 dose category for a given duration, he/she is counted only once in the total (any dose) column. Out of 393 patients exposed to eliglustat, 166 patients (42%) were exposed between ≥36 to <48 months and 93 patients (24%) were exposed between ≥48 to <60 months.

Table 14 - Estimates of cumulative healthy subject exposure to study drug, based upon actual Phase 1 exposure data from completed clinical trials

Treatment	Exposure in Healthy subjects[a]
Eliglustat	462
Placebo	37

a Data from completed trials as of 18-Sep-2018.

Treatment	Exposure in Healthy subjects[a]

Studies include: GZGD00103, GZGD00204, GZGD00404, GZGD01707, GZGD01807, GZGD01907, GZGD02007, GZGD02107, GZGD02407, GZGD02707, GZGD03610, GZGD03811, GZGD04112, PKM14187, ACC14373, POP13777, POP13778, PKM14281.

Table 15 - Eliglustat treatment duration in GZGD00304, ENGAGE, ENCORE, and EDGE studies

Exposure	GZGD00304 (N = 26)	GZGD02507 (N = 40)	GZGD02607 (N = 157)	GZGD03109 (N = 170)	Discontinued Patients (N = 162)	All Eliglustat Patients (N = 393)
Eliglustat Treatment Duration Categories (Years), n (%)						
n	26	40	157	170	162	393
Mean (SD)	6.5 (3.64)	3.9 (1.26)	3.3 (1.09)	3.3 (1.12)	2.6 (1.30)	3.6 (1.63)
Median	8.5	3.9	3.4	3.5	2.9	3.5
Min, Max	0.0, 9.3	0.5, 6.0	0.2, 5.3	0.1, 5.0	0.0, 4.9	0.0, 9.3
Total Duration	169.3	154.3	511.0	565.6	414.7	1400.3
>0 to <0.5 Years	3 (12)	1 (3)	3 (2)	7 (4)	14 (9)	14 (4)
≥0.5 to <1.0 Years	2 (8)	0	7 (4)	5 (3)	14 (9)	14 (4)
≥1.0 to <1.5 Years	1 (4)	1 (3)	4 (3)	8 (5)	14 (9)	14 (4)
≥1.5 to <2.0 Years	1 (4)	0	5 (3)	4 (2)	10 (6)	10 (3)
≥2.0 to <3.0 Years	0	8 (20)	31 (20)	14 (8)	38 (23)	53 (13)
≥3.0 to <4.0 Years	0	12 (30)	67 (43)	87 (51)	54 (33)	166 (42)
≥4.0 to <5.0 Years	0	10 (25)	38 (24)	45 (26)	18 (11)	93 (24)
≥5.0 to <6.0 Years	0	8 (20)	2 (1)	0	0	10 (3)
≥6.0 to <7.0 Years	0	0	0	0	0	0
≥7.0 to <8.0 Years	3 (12)	0	0	0	0	3 (1)
≥8.0 to <9.0 Years	11 (42)	0	0	0	0	11 (3)
≥9.0 to <10.0 Years	5 (19)	0	0	0	0	5 (1)

Note: Patient percentages are based on the total number of Eliglustat patients treated for each study.

Note: Duration of Eliglustat Treatment (Years) = (Date of Last Eliglustat dose [date of 1st Eliglustat dose] + 1 day)/365.25.

Names of input datasets: ADAM.ADEX and ADAM.ADSL

Output: texp_s.rtf

Program name: DEVOPS/GZ385660/OVERALL/POOL_2017/REPORT/PGM/texp.sas

Creation date of output 5.1: 10FEB2017 12:04

N: Number; SD: Standard Deviation.

Table 16 - Eliglustat Exposure Duration by Dose and Recent Prior ERT Exposure - Eliglustat Safety Set

Dose	Exposure	Recent Prior ERT Exposure - No (N = 134)	Recent Prior ERT Exposure - Yes (N = 259)
50 mg BID	**Duration of Eliglustat Treatment (Years)**		
	n	132	259
	Mean (SD)	0.6 (1.41)	0.6 (1.12)
	Median	0.1	0.1
	Min, Max	0.0, 8.5	0.0, 4.8
	Total Duration	81.9	160.2
100 mg BID	**Duration of Eliglustat Treatment (Years)**		
	n	114	208
	Mean (SD)	2.7 (2.66)	1.5 (1.45)
	Median	1.6	0.9
	Min, Max	0.1, 9.2	0.0, 4.7
	Total Duration	303.7	307.9
150 mg BID	**Duration of Eliglustat Treatment (Years)**		
	n	18	75
	Mean (SD)	3.0 (1.65)	3.1 (1.14)
	Median	3.3	3.2
	Min, Max	0.0, 5.1	0.0, 5.1
	Total Duration	53.6	229.4
50 mg QD	**Duration of Eliglustat Treatment (Years)**		
	n	48	20
	Mean (SD)	0.1 (0.39)	0.9 (1.22)
	Median	0.0	0.0
	Min, Max	0.0, 2.7	0.0, 3.4
	Total Duration	3.2	18.0
100 mg QD	**Duration of Eliglustat Treatment (Years)**		
	n	5	11
	Mean (SD)	0.9 (0.29)	0.9 (0.41)
	Median	1.1	1.1
	Min, Max	0.5, 1.1	0.1, 1.5
	Total Duration	4.4	10.4

Dose	Exposure	Recent Prior ERT Exposure - No (N = 134)	Recent Prior ERT Exposure - Yes (N = 259)
200 mg QD	**Duration of Eliglustat Treatment (Years)**		
	n	46	69
	Mean (SD)	2.0 (0.82)	1.9 (0.87)
	Median	2.0	1.9
	Min, Max	0.0, 3.3	0.1, 4.4
	Total Duration	90.1	132.1
Overall	**Duration of Eliglustat Treatment (Years)**		
	n	134	259
	Mean (SD)	4.0 (2.28)	3.3 (1.09)
	Median	3.6	3.5
	Min, Max	0.0, 9.3	0.2, 5.3
	Total Duration	538.9	861.4

Note: Recent prior ERT exposure = within 9 months prior to first dose of eliglustat in the study. Per protocol, patients who received ERT within 12 months prior to the study were excluded from the Phase 2 study and patients who received ERT within 9 months prior to the study were excluded from ENGAGE, while patients entering ENCORE were required to have had ERT for at least 3 years prior to the study.

Note: Patients' exposure at each eliglustat dose level is summarized separately.

Note: Dose regimens 50 mg QOD and 100 mg QOD are also included in "Overall".

Note: For each period of consecutive treatment at a particular dose level, Time on eliglustat treatment (years) = ((date of last eliglustat dose up to cut-off (date of 1st eliglustat dose) + 1 day)/365.25.

Note: Due to rounding, the minimum values of ranges of duration show 0.0 in cases where there were patients who received <0.1 year of eliglustat treatment.

Names of input datasets: ADAM.ADEX and ADAM.ADSL

Output: texp_ert_s.rtf

Program name: DEVOPS/GZ385660/OVERALL/POOL_2017/REPORT/PGM/texp_sub.sas

Creation date of output 5.3: 14FEB2017 15:28

BID: Twice Daily; ERT: Enzyme Replacement Therapy; SD: Standard Deviation; QD: Once Daily; QOD: Every Other Day.

Table 17 - Eliglustat Exposure by Dose and Duration Categories - Eliglustat Safety Set

Duration Category	50 mg BID (N = 391) n (%)	100 mg BID (N = 322) n (%)	150 mg BID (N = 93) n (%)	50 mg QD (N = 68) n (%)	100 mg QD (N = 16) n (%)	200 mg QD (N = 115) n (%)	Any Dose (N = 393) n (%)
>0 to <2 months	271 (69)	73 (19)	4 (1)	57 (15)	1 (0)	3 (1)	4 (1)
≥2 to <6 months	35 (9)	21 (5)	2 (1)	1 (0)	1 (0)	1 (0)	10 (3)
≥6 to <12 months	17 (4)	55 (14)	3 (1)	2 (1)	2 (1)	12 (3)	14 (4)
≥12 to <18 months	11 (3)	17 (4)	3 (1)	1 (0)	12 (3)	20 (5)	14 (4)
≥18 to <24 months	13 (3)	39 (10)	5 (1)	2 (1)	0	25 (6)	10 (3)
≥24 to <36 months	15 (4)	33 (8)	17 (4)	3 (1)	0	45 (11)	53 (13)
≥36 to <48 months	18 (5)	42 (11)	38 (10)	2 (1)	0	8 (2)	166 (42)

Duration Category	50 mg BID (N = 391) n (%)	100 mg BID (N = 322) n (%)	150 mg BID (N = 93) n (%)	50 mg QD (N = 68) n (%)	100 mg QD (N = 16) n (%)	200 mg QD (N = 115) n (%)	Any Dose (N = 393) n (%)
≥48 to <60 months	8 (2)	21 (5)	18 (5)	0	0	1 (0)	93 (24)
≥60 to <72 months	0	7 (2)	3 (1)	0	0	0	10 (3)
≥72 to <84 months	0	0	0	0	0	0	0
≥84 to <96 months	2 (1)	2 (1)	0	0	0	0	3 (1)
≥96 to <108 months	1 (0)	8 (2)	0	0	0	0	11 (3)
≥108 to <120 months	0	4 (1)	0	0	0	0	5 (1)
Total patients (any duration)	**391**	**322**	**93**	**68**	**16**	**115**	**393**
Patient-years of exposure	**242.1**	**611.7**	**283.0**	**21.3**	**14.8**	**222.2**	**1400.3**

Note: Patient percentages for each column are based on the total number of patients treated with eliglustat in the pooled studies: GZGD00304, GZGD02507, GZGD02607, and GZGD03109.
Note: Patients' exposure at each eliglustat dose level is summarized separately.
Note: Dose regimens 50 mg QOD and 100 mg QOD are also included in "Any Dose" Column.
Note: Duration of eliglustat treatment (months) = ([{date of last eliglustat dose up to cut-off (date of 1st eliglustat dose)} + 1 day]/365.25)*12.
Names of input datasets: ADAM.ADEX
Output: texp_dur_s.rtf
Program name: DEVOPS/GZ385660/OVERALL/POOL_2017/REPORT/PGM/texp_dur.sas
Creation date of output 5.4: 09FEB2017 19:37
BID: Twice Daily; N: Number; QD: Once Daily; QOD: Every Other Day.

Eliglustat exposure by gender, age and race is provided in Table 18, Table 19, and Table 20, respectively. In the total eliglustat population of 393 patients, 191 patients were male and 202 patients were female. Within this patient population, 157 patients were within 16 to 30 years of age, 226 patients were within >30 to 65 years of age, and 10 patients were more than 65 years of age. Two eliglustat-treated patients between the ages of 16 and 18 years were enrolled. The duration of eliglustat exposure was highest with the 100 mg BID dose and occurred mostly in the age group of >30 to 65 years. Most of the GD1 patients exposed to eliglustat in this clinical program were white.

Table 21 summarizes duration of eliglustat exposure by dose and CYP2D6 predicted phenotype based on genotype for the total population. Most of the patients were CYP2D6 EM and these patients were mostly exposed to 100 mg BID and for a longer duration.

Table 18 - Eliglustat Exposure Duration by Dose and Gender - Eliglustat Safety Set

Dose	Exposure	Male (N = 191)	Female (N = 202)	Overall (N = 393)
50 mg BID	**Duration of Eliglustat Treatment (Years)**			
	n	190	201	391
	Mean (SD)	0.6 (1.12)	0.7 (1.32)	0.6 (1.22)
	Median	0.1	0.1	0.1

Dose	Exposure	Male (N = 191)	Female (N = 202)	Overall (N = 393)
	Min, Max	0.0, 7.2	0.0, 8.5	0.0, 8.5
	Total Duration	106.8	135.3	242.1
100 mg BID	**Duration of Eliglustat Treatment (Years)**			
	n	155	167	322
	Mean (SD)	1.9 (2.11)	1.9 (1.98)	1.9 (2.04)
	Median	1.5	1.1	1.3
	Min, Max	0.1, 9.2	0.0, 9.1	0.0, 9.2
	Total Duration	301.8	309.8	611.7
150 mg BID	**Duration of Eliglustat Treatment (Years)**			
	n	42	51	93
	Mean (SD)	3.2 (1.19)	2.9 (1.29)	3.0 (1.25)
	Median	3.3	3.1	3.2
	Min, Max	0.0, 5.1	0.1, 4.9	0.0, 5.1
	Total Duration	135.0	148.0	283.0
50 mg QD	**Duration of Eliglustat Treatment (Years)**			
	n	31	37	68
	Mean (SD)	0.3 (0.78)	0.3 (0.86)	0.3 (0.82)
	Median	0.0	0.0	0.0
	Min, Max	0.0, 3.4	0.0, 3.1	0.0, 3.4
	Total Duration	9.2	12.1	21.3
100 mg QD	**Duration of Eliglustat Treatment (Years)**			
	n	8	8	16
	Mean (SD)	0.9 (0.42)	0.9 (0.33)	0.9 (0.37)
	Median	1.1	1.1	1.1
	Min, Max	0.1, 1.5	0.2, 1.1	0.1, 1.5
	Total Duration	7.5	7.3	14.8
200 mg QD	**Duration of Eliglustat Treatment (Years)**			
	n	67	48	115
	Mean (SD)	2.0 (0.82)	1.8 (0.87)	1.9 (0.84)
	Median	2.0	1.9	1.9
	Min, Max	0.2, 4.4	0.0, 3.3	0.0, 4.4
	Total Duration	134.1	88.1	222.2

Dose	Exposure	Male (N = 191)	Female (N = 202)	Overall (N = 393)
Overall	**Duration of Eliglustat Treatment (Years)**			
	n	191	202	393
	Mean (SD)	3.7 (1.63)	3.5 (1.64)	3.6 (1.63)
	Median	3.5	3.5	3.5
	Min, Max	0.0, 9.3	0.0, 9.2	0.0, 9.3
	Total Duration	698.4	701.8	1400.3

Note: Patients' exposure at each eliglustat dose level is summarized separately.
Note: Dose regimens 50 mg QOD and 100 mg QOD are also included in "Overall".
Note: For each period of consecutive treatment at a particular dose level, Time on eliglustat treatment (years) = (date of last eliglustat dose up to cut-off [date of 1st eliglustat dose] + 1 day)/365.25.
Note: Due to rounding, the minimum values of ranges of duration show 0.0 in cases where there were patients who received <0.1 year of eliglustat treatment.
Names of input datasets: ADAM.ADEX and ADAM.ADSL
Output: texp_gender_s.rtf
Program name: DEVOPS/GZ385660/OVERALL/POOL_2017/REPORT/PGM/texp_sub.sas
Creation date of output 5.5: 14FEB2017 15:28
BID: Twice Daily; N: Number; SD: Standard Deviation; QD: Once Daily; QOD: Every Other Day.

Table 19 - Eliglustat Exposure Duration by Dose and Age Group - Eliglustat Safety Set

Dose	Exposure	16-30 yrs (N = 157)	>30-65 yrs (N = 226)	>65 yrs (N = 10)
50 mg BID	**Duration of Eliglustat Treatment (Years)**			
	n	157	224	10
	Mean (SD)	0.7 (1.38)	0.6 (1.12)	0.6 (1.02)
	Median	0.1	0.1	0.1
	Min, Max	0.0, 8.5	0.0, 7.9	0.1, 3.3
	Total Duration	103.6	132.7	5.8
100 mg BID	**Duration of Eliglustat Treatment (Years)**			
	n	135	181	6
	Mean (SD)	2.0 (2.12)	1.8 (2.01)	1.7 (1.01)
	Median	1.5	1.1	1.7
	Min, Max	0.1, 9.2	0.0, 8.9	0.6, 3.2
	Total Duration	268.6	333.0	10.1
150 mg BID	**Duration of Eliglustat Treatment (Years)**			
	n	40	53	0
	Mean (SD)	3.1 (1.22)	3.0 (1.27)	
	Median	3.3	3.2	

Dose	Exposure	16-30 yrs (N = 157)	>30-65 yrs (N = 226)	>65 yrs (N = 10)
	Min, Max	0.0, 5.1	0.0, 5.1	
	Total Duration	125.0	158.0	
50 mg QD	**Duration of Eliglustat Treatment (Years)**			
	n	28	37	3
	Mean (SD)	0.3 (0.95)	0.3 (0.76)	0.0 (0.04)
	Median	0.0	0.0	0.0
	Min, Max	0.0, 3.4	0.0, 3.0	0.0, 0.1
	Total Duration	9.5	11.7	0.1
100 mg QD	**Duration of Eliglustat Treatment (Years)**			
	n	5	10	1
	Mean (SD)	1.0 (0.26)	0.9 (0.44)	1.1 (NA)
	Median	1.1	1.1	1.1
	Min, Max	0.5, 1.1	0.1, 1.5	1.1, 1.1
	Total Duration	4.8	8.9	1.1
200 mg QD	**Duration of Eliglustat Treatment (Years)**			
	n	42	67	6
	Mean (SD)	2.0 (0.78)	1.9 (0.88)	1.9 (0.93)
	Median	2.0	1.9	1.9
	Min, Max	0.1, 3.5	0.0, 4.4	0.9, 3.3
	Total Duration	85.9	124.7	11.7
Overall	**Duration of Eliglustat Treatment (Years)**			
	n	157	226	10
	Mean (SD)	3.8 (1.58)	3.4 (1.65)	2.9 (1.54)
	Median	3.6	3.5	3.3
	Min, Max	0.3, 9.3	0.0, 9.1	0.1, 4.8
	Total Duration	599.9	771.4	28.9

Note: Patients' exposure at each eliglustat dose level is summarized separately.
Note: Dose regimens 50 mg QOD and 100 mg QOD are also included in "Overall".
Note: For each period of consecutive treatment at a particular dose level, time on eliglustat treatment (years) = ([date of last eliglustat dose up to cut-off (date of 1st eliglustat dose)] + 1 day)/365.25.
Note: Due to rounding, the minimum values of ranges of duration show 0.0 in cases where there were patients who received <0.1 year of eliglustat treatment.
Names of input datasets: ADAM.ADEX and ADAM.ADSL
Output: texp_age_s.rtf
Program name: DEVOPS/GZ385660/OVERALL/POOL_2017/REPORT/PGM/texp_sub.sas
Creation date of output 5.6: 14FEB2017 15:28
BID: Twice Daily; NA: Not Applicable; N: Number; SD: Standard Deviation; QD: Once Daily; QOD: Every Other Day.

Table 20 - Eliglustat Exposure Duration by Dose and Race - Eliglustat Safety Set

Dose	Exposure	White (N = 323)	Black or African American (N = 17)	Asian (N = 42)	Other (N = 10)	Multiple (N = 1)
50 mg BID	**Duration of Eliglustat Treatment (Years)**					
	n	323	17	42	8	1
	Mean (SD)	0.6 (1.25)	0.7 (1.18)	0.7 (1.08)	0.7 (1.08)	0.1 (NA)
	Median	0.1	0.1	0.2	0.1	0.1
	Min, Max	0.0, 8.5	0.0, 3.4	0.0, 4.0	0.1, 2.8	0.1, 0.1
	Total Duration	196.5	11.8	28.3	5.4	0.1
100 mg BID	**Duration of Eliglustat Treatment (Years)**					
	n	266	12	37	6	1
	Mean (SD)	1.8 (2.01)	1.8 (1.24)	1.9 (1.27)	6.5 (3.27)	3.8 (NA)
	Median	1.0	1.8	1.7	8.2	3.8
	Min, Max	0.0, 9.2	0.1, 3.6	0.1, 4.3	0.4, 8.7	3.8, 3.8
	Total Duration	477.2	21.9	69.5	39.3	3.8
150 mg BID	**Duration of Eliglustat Treatment (Years)**					
	n	87	3	2	0	1
	Mean (SD)	3.1 (1.18)	2.0 (2.11)	2.7 (0.96)		0.1 (NA)
	Median	3.3	1.6	2.7		0.1
	Min, Max	0.0, 5.1	0.0, 4.2	2.0, 3.4		0.1, 0.1
	Total Duration	271.6	5.9	5.4		0.1
50 mg QD	**Duration of Eliglustat Treatment (Years)**					
	n	46	1	11	10	0
	Mean (SD)	0.4 (0.97)	0.7 (NA)	0.0 (0.00)	0.0 (0.00)	
	Median	0.0	0.7	0.0	0.0	
	Min, Max	0.0, 3.4	0.7, 0.7	0.0, 0.0	0.0, 0.0	
	Total Duration	20.5	0.7	0.0	0.0	
100 mg QD	**Duration of Eliglustat Treatment (Years)**					
	n	11	1	4	0	0
	Mean (SD)	0.9 (0.43)	1.1 (NA)	1.1 (0.03)		
	Median	1.1	1.1	1.1		
	Min, Max	0.1, 1.5	1.1, 1.1	1.1, 1.1		
	Total Duration	9.4	1.1	4.3		

Dose	Exposure	White (N = 323)	Black or African American (N = 17)	Asian (N = 42)	Other (N = 10)	Multiple (N = 1)
200 mg QD	**Duration of Eliglustat Treatment (Years)**					
	n	83	6	26	0	0
	Mean (SD)	2.0 (0.89)	1.8 (0.52)	1.9 (0.79)		
	Median	2.0	1.7	1.9		
	Min, Max	0.0, 4.4	1.3, 2.8	0.1, 3.1		
	Total Duration	162.0	11.1	49.2		
Overall	**Duration of Eliglustat Treatment (Years)**					
	n	323	17	42	10	1
	Mean (SD)	3.5 (1.58)	3.1 (1.08)	3.8 (1.11)	4.5 (4.16)	4.0 (NA)
	Median	3.5	3.4	4.0	5.0	4.0
	Min, Max	0.1, 9.3	0.3, 4.7	0.4, 5.0	0.0, 8.8	4.0, 4.0
	Total Duration	1141.5	52.5	157.6	44.7	4.0

Note: Patients' exposure at each eliglustat dose level is summarized separately.
Note: Dose regimens 50 mg QOD and 100 mg QOD are also included in "Overall".
Note: For each period of consecutive treatment at a particular dose level, time on eliglustat treatment (years) = ([date of last eliglustat dose up to cut-off (date of 1st eliglustat dose)] + 1 day)/365.25.
Note: Due to rounding, the minimum values of ranges of duration show 0.0 in cases where there were patients who received <0.1 year of eliglustat treatment.
Names of input datasets: ADAM.ADEX and ADAM.ADSL
Output: texp_race_s.rtf
Program name: DEVOPS/GZ385660/OVERALL/POOL_2017/REPORT/PGM/texp_sub.sas
Creation date of output 5.7: 14FEB2017 15:28
BID: Twice Daily; NA: Not Applicable; N: Number; SD: Standard Deviation; QD: Once Daily; QOD: Every Other Day.

Table 21 - Duration of Eliglustat Exposure by CYP2D6 Metabolizer Status and Dose - Eliglustat Safety Set

Dose	Exposure	Poor Metaboliser (N = 14)	Intermediate Metaboliser (N = 50)	Extensive Metaboliser (N = 316)	Ultra-Rapid Metaboliser (N = 11)	Indeterminate (N = 2)
50 mg BID	**Duration of Eliglustat Treatment (Years)**					
	n	14	50	314	11	2
	Mean (SD)	2.3 (2.20)	1.4 (1.46)	0.4 (1.03)	0.2 (0.27)	0.1 (0.07)
	Median	1.5	0.9	0.1	0.1	0.1
	Min, Max	0.1, 7.2	0.0, 4.0	0.0, 8.5	0.1, 1.0	0.1, 0.2
	Total Duration	32.8	71.1	135.9	2.0	0.3

Dose	Exposure	Poor Metaboliser (N = 14)	Intermediate Metaboliser (N = 50)	Extensive Metaboliser (N = 316)	Ultra-Rapid Metaboliser (N = 11)	Indeterminate (N = 2)
100 mg BID	**Duration of Eliglustat Treatment (Years)**					
	n	0	19	290	11	2
	Mean (SD)		2.3 (1.40)	1.9 (2.09)	0.6 (0.89)	2.3 (2.86)
	Median		2.2	1.3	0.1	2.3
	Min, Max		0.1, 4.7	0.0, 9.2	0.1, 3.0	0.3, 4.3
	Total Duration		43.6	557.1	6.5	4.6
150 mg BID	**Duration of Eliglustat Treatment (Years)**					
	n	0	1	84	8	0
	Mean (SD)		3.1 (NA)	3.0 (1.27)	3.6 (0.85)	
	Median		3.1	3.2	3.5	
	Min, Max		3.1, 3.1	0.0, 5.1	2.4, 4.9	
	Total Duration		3.1	250.8	29.1	
50 mg QD	**Duration of Eliglustat Treatment (Years)**					
	n	6	8	52	1	1
	Mean (SD)	1.9 (1.38)	0.8 (1.28)	0.1 (0.31)	0.0 (NA)	0.0 (NA)
	Median	2.1	0.0	0.0	0.0	0.0
	Min, Max	0.1, 3.4	0.0, 3.0	0.0, 1.8	0.0, 0.0	0.0, 0.0
	Total Duration	11.2	6.3	3.8	0.0	0.0
100 mg QD	**Duration of Eliglustat Treatment (Years)**					
	n	1	6	9	0	0
	Mean (SD)	0.5 (NA)	1.0 (0.45)	0.9 (0.32)		
	Median	0.5	1.1	1.1		
	Min, Max	0.5, 0.5	0.1, 1.5	0.2, 1.1		
	Total Duration	0.5	5.8	8.4		
200 mg QD	**Duration of Eliglustat Treatment (Years)**					
	n	0	14	99	2	0
	Mean (SD)		1.7 (0.75)	2.0 (0.86)	2.4 (0.12)	
	Median		1.8	2.0	2.4	

Dose	Exposure	Poor Metaboliser (N = 14)	Intermediate Metaboliser (N = 50)	Extensive Metaboliser (N = 316)	Ultra-Rapid Metaboliser (N = 11)	Indeterminate (N = 2)
	Min, Max		0.1, 3.0	0.0, 4.4	2.3, 2.5	
	Total Duration		23.5	193.9	4.8	
Overall	**Duration of Eliglustat Treatment (Years)**					
	n	14	50	316	11	2
	Mean (SD)	3.2 (2.20)	3.1 (1.21)	3.6 (1.67)	3.9 (0.64)	2.5 (2.93)
	Median	3.5	3.4	3.5	3.6	2.5
	Min, Max	0.2, 8.7	0.1, 4.9	0.0, 9.3	3.1, 5.1	0.4, 4.5
	Total Duration	45.3	155.4	1152.2	42.5	4.9

Note: Patients' exposure at each eliglustat dose level is summarized separately.

Note: Dose regimens 50 mg QOD and 100 mg QOD are also included in "Overall".

Note: Duration of eliglustat treatment (years) = ([date of last eliglustat dose up to cut-off (date of 1st eliglustat dose)] + 1 day)/365.25.

Note: Due to rounding, the minimum values of ranges of duration show 0.0 in cases where there were patients who received <0.1 year of eliglustat treatment.

Names of input datasets: ADAM.ADEX and ADAM.ADSL

Output: texp_cyp2d6_s.rtf

Program name: DEVOPS/GZ385660/OVERALL/POOL_2017/REPORT/PGM/texp_sub.sas

Creation date of output 5.8: 23FEB2017 14:30

BID: Twice Daily; N: Number; NA: Not Applicable; SD: Standard Deviation; QD: Once Daily; QOD: Every Other Day.

RISK MANAGEMENT PLAN - PART II MODULE SIV: POPULATIONS NOT STUDIED IN CLINICAL TRIALS

SIV.1 EXCLUSION CRITERIA IN PIVOTAL CLINICAL STUDIES WITHIN THE DEVELOPMENT PROGRAMME

A summary of the exclusion criteria used for the completed clinical studies is provided in Table 22.

Table 22 - Summary of Exclusion Criteria for the Clinical Studies in Gaucher Disease

Exclusion Criterion	GZGD00304[a]	GZGD02507[b]	GZGD02607[c]	GZGD03109[d]	EFC13738[e]
Any of the following diagnoses, conditions, or prior treatments:					
Received substrate reduction therapies for Gaucher disease within 6 months prior to randomization.		X	X		X
Received miglustat	X (within12 months prior to enrollment)			X (within 6 months prior to first dose of eliglustat)	
Received ERT or corticosteroids for Gaucher disease within 12 months prior to enrollment.	X	X (ERT only, within 9 months prior to randomization)			
Received bisphosphonates within 3 months prior to enrollment.	X				
Had a partial or total splenectomy.	X	X	X (within 3 years prior to randomization)	X (within 3 years prior to first dose of eliglustat)	X (within 2 years prior to enrollment)
Ever had any radiation treatment.	X	X (in the abdominal region)			
Any evidence of neurologic (eg, peripheral neuropathy, tremor, seizures, Parkinsonism or cognitive impairment) or pulmonary involvement	X	X	X	X	X (neurological symptoms other than oculomotor apraxia)

Exclusion Criterion	GZGD00304[a]	GZGD02507[b]	GZGD02607[c]	GZGD03109[d]	EFC13738[e]
Any of the following diagnoses, conditions, or prior treatments:					
(eg, pulmonary hypertension).					
Patient is transfusion-dependent	X	X	X	X	X
Current symptomatic bone disease such as bone pain attributable to osteonecrosis and/or pathologic fracture, or has had a bone crisis in the 12 months prior to randomization.		X			
Documentation of new pathological bone involvement (osteonecrosis, pathological fractures, aseptic necrosis, lytic lesions, as assessed by X-ray or MRI) or bone crisis in the 12 months prior to enrollment.	X				
Prior bleeding varices or liver infarction	X				
Documented prior esophageal varices or liver infarction or current liver enzymes (ALT/ AST) or total bilirubin >2 times the ULN, unless the patient had a diagnosis of Gilbert Syndrome.		X	X	X	X
Any clinically significant disease, other than Gaucher disease, including cardiovascular, renal, hepatic, GI, pulmonary, neurologic, endocrine, metabolic (including hypokalemia or hypomagnesemia), or psychiatric disease, other medical conditions, or serious intercurrent illnesses.	X	X	X	X	X

Exclusion Criterion	GZGD00304[a]	GZGD02507[b]	GZGD02607[c]	GZGD03109[d]	EFC13738[e]
Any of the following diagnoses, conditions, or prior treatments:					
Clinically significant CAD including history of MI or ongoing signs or symptoms consistent with cardiac ischemia or heart failure; or clinically significant arrhythmias or conduction defect such as 2nd or 3rd degree AV block, complete bundle branch block, prolonged QTc interval, or sustained VT.		X	X	X	X (Clinically significant congenital cardiac defect)
Tested positive for the HIV antibody, Hepatitis C antibody, or Hepatitis B surface antigen.	X	X	X	X	
Received an investigational product within 30 days prior to randomization.	X (within 30 days prior to enrollment)	X	X	X (other than eliglustat within 30 days of first dose)	X
Scheduled for in-patient hospitalization, including elective surgery, during the study.	X	X	X	X	
History of cancer	X	X (within 5 years of randomization; exception: basal cell carcinoma)	X (within 5 years of randomization; exception: basal cell carcinoma)	X (within 5 years prior to the first dose; exception: basal cell carcinoma)	
Pregnancy or lactation	X	X	X	X	
Cardiac functional and/or anatomical abnormalities (eg, mitral valve prolapse, septal defects, ventricular hypertrophy) or clinically significant ECG or echocardiographic findings at the time of Screening.	X				X (Received a Class IA or Class III antiarrhythmic medicinal products within 30 days prior to enrollment)

Exclusion Criterion	GZGD00304[a]	GZGD02507[b]	GZGD02607[c]	GZGD03109[d]	EFC13738[e]
Any of the following diagnoses, conditions, or prior treatments:					
Received any medication within 30 days prior to randomization that may cause QTc interval prolongation.	X (within 30 days prior to enrollment)	X	X (Exception: premedication for ERT infusions, allowed up to 7 days prior to randomization)	X (Exception: premedication for ERT infusions, allowed up to 7 days prior to the first dose of eliglustat)	
Received (acute or chronic) treatment with a CYP3A inducer within 30 days prior to randomization.		X			X (Within two weeks prior to eliglustat administration)
Received any medication within 30 days prior to enrollment that may induce or inhibit CYP2D6.	X			X	
Received any medication that may induce CYP3A within 30 days prior to randomization, with the exception of pre-medications for ERT infusion, which are allowed up to 7 days prior to randomization.			X		
Patient is **not** a CYP2D6 PM, or is an IM with 1 allele identified as active, and has received any medication that is a strong inhibitor of CYP3A or CYP2D6 within 30 days prior to randomization, exception where a patient has been receiving a strong inhibitor of CYP3A or a strong inhibitor of CYP2D6 (but not both medications) that has been administered	X	X	X (Exception: premedication for ERT infusions, allowed up to 7 days prior to randomization)	X (Exception: premedication for ERT infusions, allowed up to 7 days prior to randomization)	

Exclusion Criterion	GZGD00304[a]	GZGD02507[b]	GZGD02607[c]	GZGD03109[d]	EFC13738[e]
Any of the following diagnoses, conditions, or prior treatments:					
chronically for at least 30 days prior to randomization and will be continued on the same dosing regimen during the Primary Analysis Period.					
Patients who received for the first time (ie, the patient is not already chronically using) any of the following medications within 30 days prior to the first dose of eliglustat: • Strong inhibitors of CYP2D6 or CYP3A • Inducers of CYP3A				X (Exception: Pre-medications for ERT infusions are allowed up to 7 days prior to the first dose of eliglustat).	
Patients who are a CYP2D6 PM or an IM with neither allele known to be active and has received treatment that is a strong inhibitor of CYP3A within 30 days prior to randomization.	X	X	X (Exception: pre-medications for ERT infusion, allowed up to 7 days prior to randomization).	X (Exception: pre-medications for ERT infusions allowed up to 7 days prior to the first dose of eliglustat.)	
Patient is a CYP2D6 non-PM or an IM with 1 allele identified as active who is chronically receiving both a strong competitive inhibitor of CYP2D6 and a strong competitive inhibitor of CYP3A and for whom no reasonable alternative medication exists. **OR** Patient is a CYP2D6 PM or an IM with neither allele known to be active who is chronically receiving a strong competitive inhibitor of CYP3A and				X	X

Exclusion Criterion	GZGD00304[a]	GZGD02507[b]	GZGD02607[c]	GZGD03109[d]	EFC13738[e]
Any of the following diagnoses, conditions, or prior treatments:					
for whom no reasonable alternative medication exists.					
Administration of strong or moderate CYP2D6 inhibitors concomitantly with strong or moderate CYP3A inhibitors in CYP2D6 IM and EM within two weeks prior to eliglustat administration					X
Unable to receive treatment with CEREZYME due to a known hypersensitivity or unwilling to receive CEREZYME treatment Q2W.			X		X
Hemoglobin level <8.0 g/dL or platelet level <45 000/mm^3 (each calculated as the mean of 2 separate blood measurements taken at least 24 hours apart during Screening).	X	X (Platelet level <50 000/mm^3)			
Documented etiology of anemia due to causes other than Gaucher disease (eg, iron, vitamin B12, folate deficiency, or hemoglobinopathies).	X				
Documented anemia due to causes other than Gaucher disease (eg, iron, vitamin B-12, and/or folate deficiency) that requires treatment not yet initiated or not yet stable under treatment for at least 3 months prior to randomization.		X		X	

Exclusion Criterion	GZGD00304[a]	GZGD02507[b]	GZGD02607[c]	GZGD03109[d]	EFC13738[e]
Any of the following diagnoses, conditions, or prior treatments:					
Documented deficiency of iron, vitamin B-12, or folate that requires treatment not yet initiated, or if not initiated the patient has not been stable under treatment for at least 3 months prior to administration of the first dose of eliglustat.				X	
Documented thalassemia minor or sickle cell trait with a platelet count of <50 000 or >130 000/mm^3.		X			
The patient is lactating					X
Participation in GZGD02507 or GZGD02607, or patient is eligible for inclusion in GZGD02507or GZGD02607 while enrollment is ongoing and has access to a physician participating in either of these studies.				X	

a Source: Phase 2 Protocol Amendment 10
b Source: ENGAGE Original Protocol and Protocol Amendment 7
c Source : ENCORE Clinical Study Report Section 8.3.2
d Source: EDGE Protocol Amendment 5
e Source: ELIKIDS Protocol Amendment 4

ALT: Alanine Aminotransferase; AST: Aspartate Aminotransferase; AV: Atrioventricular; CAD: Coronary Artery Disease; CYP: Cytochrome P450; ECG: Electrocardiogram; ERT: Enzyme Replacement Therapy; HIV: Human Immunodeficiency Virus; IM: Intermediate Metabolizer; MI: Myocardial Infarction; MRI: Magnetic Resonance Imaging; PM: Poor Metabolizer; Q2W: Every Other Week; ULN: Upper Limit of Normal; VT: Ventricular Tachycardia.

Table 23 - Important exclusion criteria in pivotal studies in the development programme

Exclusion criteria	Reason for exclusion	Is it considered to be included as missing information?	Rationale
Important chronic disease such as advanced liver and kidney disease	Clinically significant diseases As eliglustat is primarily metabolized by the liver, a potential for influence of impaired hepatic function on Genz-99067 PK exists due to its high metabolic clearance.	No	Use of eliglustat has been studied in patients with important chronic renal or hepatic disease. These are not common manifestations of GD1, however, CERDELGA is now contraindicated or not recommended in certain patients with HI based on POP13777 study results and PBPK modeling results, or not recommended in certain patients with renal impairment based on POP13778 study results (addressed in SmPC Sections 4.2, 4.3, 4.4).
Structural heart disease, recent MI, CHF, arrhythmias	Positive hERG study and other in vitro channel studies preclude the inclusion of these patients who are at increased risk of arrhythmia and conduction disorders.	Yes	Because CERDELGA is predicted to cause mild increases in ECG intervals at substantially elevated eliglustat plasma concentrations, use of CERDELGA should be avoided in patients with cardiac disease (CHF, recent acute MI, bradycardia, heart block, ventricular arrhythmia), (SmPC Section 4.4 Special warnings and precautions). The safety and efficacy of eliglustat in patients with a history of or recurrent cardiac ischemia or heart failure, clinically significant arrhythmias or conduction findings has not yet been established.
Chronic use of any QT prolonging drug prior to initiating eliglustat study	Positive hERG study	No	The thorough QT study (GZGD01707) was negative, and dose concentration-related ECG effects only became relevant at supratherapeutic doses of eliglustat. Labelling proposal that concomitant use with type IA and III antiarrhythmic medications should be avoided (SmPC Section 4.4 Special warnings and precautions for use).
Exclusion criteria with regards to use of strong or moderate inhibitors of CYP2D6 and CYP3A or inducers of CYP3A prior to initiating eliglustat	Eliglustat is predominantly metabolized by CYP2D6 and, to a lesser extent, by CYP3A4. In vitro, eliglustat is a time-dependent inhibitor of CYP2D6. Concomitant use of	No	Drug-drug interactions - Use with CYP2D6 and/or CYP3A inhibitors - Use with strong CYP3A inducers - Use with P-gp or CYP2D6 substrates is considered

Exclusion criteria	Reason for exclusion	Is it considered to be included as missing information?	Rationale
study (which evolved with knowledge based on the Phase 1 drug interaction studies and the course of clinical trial programme).	CYP2D6 and/or CYP3A4 inhibitors with CERDELGA may results in substantially elevated eliglustat plasma concentrations, and concomitant use of strong CYP 3A inducers with CERDELGA decrease concentration of eliglustat.		as an important potential risk (see Part II SVII).
Hemoglobin <8 mg/dl, platelets <45 000, Transfusion dependence	Patients with very severe hematological disease were excluded because of their potential need for transfusions that would confound the interpretation of the efficacy results and the availability of other efficacious well-established therapies.	No	Patients with severe hematological disease approaching the exclusion cutoffs showed a good clinical response.

CHF: Congestive Heart Failure; CYP: Cytochrome P450; ECG: Electrocardiogram; hERG : Human Ether-a-Go-Go Related Gene; GD1: Gaucher type 1 disease; MI: Myocardial Infarction; PBPK: Physiologically Based Pharmacokinetic; P-gp: P-glycoprotein; PK: Pharmacokinetic; SmPC: Summary of Product Characteristics.

SIV.2 LIMITATIONS TO DETECT ADVERSE REACTIONS IN CLINICAL TRIAL DEVELOPMENT PROGRAMMES

Gaucher disease is a rare disease, and a limited study patient population exists. The safety database contains data from 393 adult and 51 paediatric patients with GD1 and 6 paediatric patients with GD3 who received eliglustat in Company-sponsored clinical studies (n = 5) as of 21 June 2023. This total represents 1400 patient-years of eliglustat exposure and includes 16 patients treated for at least 8 years or longer in the Phase 2 study (GZGD00304). Based on the total number of patients exposed and the duration of exposure, this represents the largest clinical development programme in GD to date and a substantive safety database for a rare disease.

The table below addresses possible limitations of the clinical trial development programme to detect specific types of adverse drug reactions (ADR):

Table 24 - Possible limitations of the clinical trial development programme

Ability to detect adverse reactions	Limitation of trial programme	Discussions of implications for target population
Which are "uncommon"	393 adult GD1 patients, 51 pediatric GD1 patients and 6 pediatric GD3 patients were exposed to eliglustat over the	Adverse drug reactions with a frequency greater than 1 in 393 could be detected. The clinical development program can detect ADRs that are uncommon (≥1/1000 to <1/100) or more frequent. ADRs that are

Ability to detect adverse reactions	Limitation of trial programme	Discussions of implications for target population
	clinical trial programme as of the DLP.	less frequent can occur in the target population and may remain non-observed during development.
Occurring particularly with prolonged exposure	The mean (± standard deviation) duration of treatment was 3.6 (±1.63) years.	Eliglustat is a chronic therapy. The duration of eliglustat treatment at therapeutic doses in the total clinical trial population is provided in [Part II SIII]. The safety profile is not different with long-term exposure based on the cumulative clinical data available to date. Nevertheless, safety in long-term treatment use is considered as missing information.
Due to cumulative effects	Not applicable	Cumulative effects are not anticipated due to the short half-life of eliglustat, extensive metabolism and lack of tissue accumulation.
Which have a long latency	Not applicable	Adverse drug reactions with a long latency (ie, malignancies) are not anticipated from the available nonclinical and clinical study data.

ADR: Adverse Drug Reaction; DLP: Data Lock Point.

SIV.3 LIMITATIONS IN RESPECT TO POPULATIONS TYPICALLY UNDER-REPRESENTED IN CLINICAL TRIAL DEVELOPMENT PROGRAMMES

Table 25 - Exposure of special populations included or not in clinical trial development programmes

Type of special population	Exposure
Pregnant women and breastfeeding women	There have been 20 pregnancies in 19 eliglustat-treated female patients and 18 pregnancies in female partners of 16 male eliglustat-treated patients during the clinical development program. The female patient pregnancies have resulted in 14 live births from 13 pregnancies (1 set of twins), 3 elective terminations, 2 spontaneous abortions, 1 tubal pregnancy, and 1 in utero death. The 18 partner pregnancies have resulted in 18 live births. Use during pregnancy or lactation is considered as missing information.
Patients with relevant comorbidities: • **Patients with hepatic impairment**	Patients were excluded from participation in the Phase 3 trials if they had AST or ALT >2x ULN (excluding Gilbert disease), and there were no patients enrolled in the clinical trials with hepatic insufficiency. A DUS that covered the period between Jan-2003 and Jun-2012 has been conducted in the MarketScan database in the US. There were 168 adult patients who were subsequently treated for Gaucher disease and who were retrospectively assessed for up to 6 months after treatment initiation. None was found to have chronic HI. Use of eliglustat in this sub-population has been studied in a single dose Phase 1 study to assess the PK of eliglustat in subjects with mild and moderate HI (see POP13777 tabulated summary in [Annex 2] and study protocol in [Annex 3]). A total of 24 subjects were enrolled: 8 subjects with mild HI, 8 subjects with moderate HI and 8 matched healthy subjects with normal hepatic function. Eliglustat was safe and well tolerated in subjects with mild or moderate HI and in healthy subjects following a single 100 mg dose of eliglustat tartrate.

Type of special population	Exposure
• **Patients with renal impairment**	Patients with significant renal impairment were excluded from clinical trials, and very few patients were studied with mild renal insufficiency. A DUS that covered the period between Jan-2003 and Jun-2012 has been conducted in the MarketScan database in the US. There were 168 adult patients who were subsequently treated for Gaucher disease and who were retrospectively assessed for up to 6 months after treatment initiation. Less than 1% (0.6%) of the 168 patients treated for Gaucher disease from MarketScan had renal impairment. Use of eliglustat in this sub-population has been studied in a single dose Phase 1 study to assess the PK of eliglustat in subjects with severe renal impairment (see POP13778 tabulated summary in [Annex 2] and study protocol in [Annex 3]). A total of 16 subjects were enrolled; 8 subjects with severe renal impairment and 8 matched healthy subjects with normal renal function. Eliglustat was safe and well tolerated in subjects with severe renal impairment following a single 100 mg dose of eliglustat tartrate.
Populations with relevant different ethnic origin	Out of 393 GD1 patients exposed to eliglustat in the eliglustat safety set, most patients were white (82%), not of Jewish descent (78%), and not Hispanic or Latino (72%). Treatment emergent adverse events occurred in 86% of white patients. No difference was seen between black and Asian patients for the overall incidence of TEAEs (76% and 74%, respectively). There was no relationship between the occurrence of TEAEs and acid β-glucosidase genotype (ie, mutations associated with a mild [N370S] versus severe [L444P] pathology).
Subpopulations carrying known and relevant genetic polymorphisms: **Use in patients who are CYP2D6 ultra-rapid metabolizers**	All eliglustat-treated GD1 patients were characterized for CYP2D6 phenotype per protocol. Only 11 of the 393 patients (2%) were CYP2D6 URMs, most of which were treated with 150 mg BID.
Other • **Children**	Out of 393 GD1 patients exposed to eliglustat in the eliglustat safety set, 2 patients aged 16.6 and 16.9 years were enrolled and received eliglustat in a clinical trial (ENGAGE). In EFC13738, there were 57 pediatric patients (51 GD1 and 6 GD3) exposed to eliglustat. Use in children was considered as missing information initially. *"Use in children" missing information is removed from EU-RMP version 6.1 as per the request of supplementary information following the assessment report on EU-RMP version 6.0).*
• **Elderly**	Out of 393 patients exposed to eliglustat in the eliglustat safety set, 10 patients were 65 years of age and older (2.5% of the safety population). No significant differences were found in the efficacy and safety profiles of older patients and younger patients. A DUS that covered the period between Jan-2003 and Jun-2012 has been conducted in the MarketScan database in the US. There were 168 adult patients who were subsequently treated for Gaucher disease and who were retrospectively assessed for up to 6 months after treatment initiation. The elderly population represents approximately 4.8% of the known adult Gaucher population who went on to receive treatment. Thus, the number of elderly patients in the eliglustat safety set is representative of the elderly population in Gaucher disease patients. Of note, patients with GD1 were found to have a reduced life expectancy of 68 years, compared to 77 years in the US population, with the most common causes of death being malignancy, cardiovascular, and cerebrovascular. (26)

Type of special population	Exposure

ALT: Alanine Aminotransferase; AST: Aspartate Aminotransferase; BID: Twice Daily; CYP: Cytochrome P450; DLP: Data Lock Point; DUS: Drug Utilization Study; EU: European Union; GD1: Gaucher Disease Type 1; HI: Hepatic Impairment; PK: Pharmacokinetic; RMP: Risk Management Plan; TEAE: Treatment Emergent Adverse Event; URM: Ultra-Rapid metabolizer; ULN: Upper Limit of Normal; US: United States.

RISK MANAGEMENT PLAN - PART II MODULE SV: POST-AUTHORIZATION EXPERIENCE

SV.1 POST-AUTHORIZATION EXPOSURE

SV.1.1 Method used to calculate exposure

Internal data have been used as the source for the post approval exposure estimate. Post approval patient exposure data are available by month; therefore, the data presented does not correspond precisely up to the DLP of this RMP. Exposure from the cumulative experience is available from 19 August 2014 (corresponding to the date of first launch of eliglustat worldwide) through 31 August 2023.

The number of patients on treatment in any given month is an estimate based on our country office's local knowledge of the country's health care environment. The office provides its estimate to our global team on an aggregate basis, in accordance with local laws, and never includes in its report data that could allow identification of individual patients; therefore, presentation of patient exposure by age, sex, and indication is not possible. Consequently, it is only presented by region.

Approximately 1669 are the maximum number of patients cumulatively worldwide who have been exposed to commercial eliglustat in post marketing experience since 19 August 2014 up to 31 August 2023

SV.1.2 Exposure

Table 26 - Exposure by region

Region	Maximum number of treated patients
Europe	795
North America	661
Latin America	104
Japan and Pacific	48
Eurasia and Middle East	38
Africa	15
Asia (with China)	8
Total	**1669**

RISK MANAGEMENT PLAN - PART II MODULE SVI: ADDITIONAL EU REQUIREMENTS FOR THE SAFETY SPECIFICATION

SVI.1 Potential for misuse for illegal purposes

A DALA study was not performed with eliglustat as the compound has no or only a limited ability to cross the blood-brain barrier with negligible exposure in the brain and has shown no propensity for eliciting any neurological effects in toxicology studies. Potential for misuse of eliglustat for illegal purposes is considered low as this product is not known to have attributes that make it a candidate for intentional overdose, abuse, or illegal use, such as known pharmacological addictive effects.

RISK MANAGEMENT PLAN - PART II MODULE SVII: IDENTIFIED AND POTENTIAL RISKS

SVII.1 IDENTIFICATION OF SAFETY CONCERNS IN THE INITIAL RMP SUBMISSION

Not applicable because it is not an initial RMP. The first RMP approved by CHMP was version 1.7.

SVII.1.1 Risks not considered important for inclusion in the list of safety concerns in the RMP

Not applicable

SVII.1.2 Risks considered important for inclusion in the list of safety concerns in the RMP

Not applicable

SVII.2 NEW SAFETY CONCERNS AND RECLASSIFICATION WITH A SUBMISSION OF AN UPDATED RMP

No new safety concerns or reclassification have been considered since RMP version 6.1.

SVII.3 DETAILS OF IMPORTANT IDENTIFIED RISKS, IMPORTANT POTENTIAL RISKS, AND MISSING INFORMATION

The following risks have been identified for eliglustat:

- Important identified risk:
  - None
- Important potential risk(s):
  - Drug-drug interactions (DDIs) - Use with CYP2D6 and/or CYP3A inhibitors - Use with strong CYP3A inducers - Use with P-glycoprotein (P-gp) or CYP2D6 substrates;
  - Use of eliglustat in patients who are CYP2D6 indeterminate metabolizers or non-genotyped patients;
  - Cardiac conduction disorders and arrhythmias;
- Missing information
  - Use in patients with a history of or current cardiac ischemia or heart failure, clinically significant arrhythmias or conduction findings;
  - Use during pregnancy and lactation;
  - Safety in long-term treatment use;
  - Use in patients who are CYP2D6 ultra-rapid metabolizers (URMs).

SVII.3.1 Presentation of important identified risks and important potential risks

The drug substance, eliglustat tartrate, exists in plasma as a free base, Genz-99067, which is the active moiety. Throughout this module, eliglustat is used when referring to the drug product administered in each clinical study, and Genz-99067 is used when referring to clinical drug exposure (ie, concentrations in plasma or other tissues).

Table 27 - Important potential risk: Drug-drug interactions - Use with CYP2D6 and/or CYP3A inhibitors - Use with strong CYP3A inducers - Use with P-gp or CYP2D6 substrates

Potential risk	**Drug-drug interactions - Use with CYP2D6 and/or CYP3A inhibitors - Use with strong CYP3A inducers - Use with P-gp or CYP2D6 substrates**
Potential mechanism	In vitro, Genz-99067 is predominantly metabolized by CYP2D6 and, to a lesser extent, by CYP3A4. In vitro, eliglustat is a substrate and an inhibitor of the efflux transporter P-gp and a time dependent inhibitor of CYP2D6. Effect of interactions: **For strong/moderate/weak CYP2D6 inhibitors**: Increased plasma exposure of Genz-99067. **For strong/moderate/weak CYP3A inhibitors**: Increased plasma exposure of Genz-99067. **Use of strong/moderate CYP2D6 inhibitor and strong/moderate CYP3A inhibitor**: Increased plasma exposure of Genz-99067. **For strong CYP3A inducer**: Decreased plasma exposure of Genz-99067. **For P-gp inhibition by eliglustat**: Increased plasma exposure of the P-gp substrate. **For CYP2D6 inhibition by eliglustat**: Increased exposure of the CYP2D6 substrate.
Evidence source(s) and strength of evidence	Drug-drug interaction studies were conducted in healthy volunteers to investigate potential interactions between eliglustat and other drugs that are CYP2D6 or CYP3A inhibitors, CYP3A inducers, or P-gp or CYP2D6 substrates. Additionally, PBPK simulations were performed to evaluate Genz-99067 exposure under various scenarios of co administration with interacting drugs. **For strong/moderate/weak CYP2D6 inhibitors**: GZGD02007; SIM0106; SIM0319 **For strong/moderate/weak CYP3A inhibitors:** GZGD01807; SIM0106; SIM0170 (available upon request) and SIM0183, SIM0319 **Use of strong/moderate CYP2D6 inhibitor and strong/moderate CYP3A inhibitor:** SIM0105; SIM0106 **For strong CYP3A inducer:** GZGD02407 **For P-gp inhibition:** GZGD03610 **For CYP2D6 inhibition:** GZGD04112; SIM0105
Characterization of the risk	A DUS was conducted which covered the period between Jan-2003 to Jun-2012 in the MarketScan database in the US; 168 adult patients who were subsequently treated for Gaucher disease were retrospectively assessed for up to 6 months to assess the frequency of use of CYP2D6 and CYP3A inhibitors. Total and chronic uses of concomitant prescriptions were tabulated, with chronic use defined as a prescription of more than 15 days. **For strong/moderate/weak CYP2D6 inhibitors:** CYP2D6 inhibition: • Paroxetine (strong inhibitor) increased Genz 99067 exposure by 7-fold for C_{max} (mean [min,max]: 19.3 [2.67, 62.2] ng/mL versus 109.8 [55.7, 343] ng/mL) and 9-fold for AUC_{0-12} (mean [min,max]: 120 [21.2, 346] ng h/mL versus 847.9 [440, 2620] ng.h/mL) in non-PMs in vivo after repeated doses of 100 mg BID. • Terbinafine (moderate inhibitor) is predicted to increase Genz-99067 exposure by 3-fold for Cmax (mean [min, max]: 28.4 [16.7, 39.9] ng/mL versus 93.7 [61.6, 130] ng/mL) and 4-fold

Potential risk	Drug-drug interactions - Use with CYP2D6 and/or CYP3A inhibitors - Use with strong CYP3A inducers - Use with P-gp or CYP2D6 substrates
	for AUC0-12 (mean [min, max]: 217 [120, 314] ng.h/mL versus 833 [523, 1210] ng.h/mL) in EMs based on PBPK simulations after repeated doses of 100 mg BID. Similar effects would be expected with other strong (eg, fluoxetine, quinidine) or moderate (eg, duloxetine, terfinabine) inhibitors of CYP2D6. CYP2D6 inhibition in CYP2D6 EMs with mild HI (based on PBPK simulations): • The predicted mean (min, max) Genz-99067 C_{max} and AUC_{0-24} after coadministration of paroxetine (strong inhibitor) with eliglustat 84 mg QD were 155 (119, 192) ng/mL and 2630 [1840, 3450] ng.h/mL respectively. • The predicted mean (min, max) Genz-99067 C_{max} and AUC_{0-24} after coadministration of terbinafine (moderate inhibitor) with eliglustat 84 mg QD were 96.9 (82.1, 110) ng/mL and 1350 [1080, 1580] ng.h/mL respectively. • The predicted mean (min, max) Genz-99067 C_{max} and AUC_{0-24} after coadministration of ritonavir (weak inhibitor) with eliglustat 84 mg QD were 45.5 (31.0, 64.9) ng/mL and 529 (361, 797) ng.h/mL respectively. CYP2D6 inhibitory effect in CYP2D6 EMs with moderate HI is expected to be greater than that in EMs with mild HI. Cumulatively there have been 61 postmarketing case reports up to 19-Aug-2022 where a strong/moderate CYP2D6 inhibitor was used concomitantly with eliglustat. None of the associated reported AEs seem to have been caused by a drug-drug interaction with eliglustat. Ongoing monitoring of the postmarketing data up to DLP (21-Jun-2023) did not reveal any significant safety information impacting the characterization of this important potential risk. Cases of strong/moderate CYP2D6 inhibitor use concomitantly with eliglustat will continue to be monitored. **For strong/moderate/weak CYP3A inhibitors**: CYP3A inhibition: • Ketoconazole (strong inhibitor) increased Genz-99067 exposure by 4-fold for C_{max} (mean [min, max]: 18.6 [2.59, 68.4] ng/mL versus 67.2 [5.32, 220] ng/mL) and AUC_{0-12} (mean [min, max]: 113 [13.0, 503] ng/h/mL versus 474 [32.2, 2160] ng.h/mL) in non-PMs in vivo after repeated doses of 100 mg BID. • Fluconazole (moderate inhibitor) is predicted to increase Genz-99067 exposure by 2-fold for C_{max} (mean [min, max]: 28.4 [16.7, 39.6] ng/mL versus 68.4 [44.7, 95.8] ng/mL) and 3-fold AUC_{0-12} (mean [min, max]: 217 [120, 315] ng.h/mL) versus 597 [362, 880] ng/mL) in EMs based on PBPK simulations after repeated doses of 100 mg BID. The effect of CYP3A inhibitors on the systemic exposure of eliglustat in PMs has not been evaluated in clinical studies. Based on PBPK simulations: • Ketoconazole (strong inhibitor) is predicted to increase Genz-99067 exposure by 4-fold for C_{max} (mean [min, max]: 321 [303, 340] ng/mL versus 75.2 [65.5, 82.2] ng/mL) and 6-fold for AUC0-24 (mean [min, max]: 5950 [5450, 6360] ng/h/mL versus 956 [792, 1060] ng.h/mL) in PMs after repeated doses of 100 mg QD. • Fluconazole (moderate inhibitor) is predicted to increase Genz-99067 exposure by 2-fold for C_{max} (mean [min, max]: 179 [129, 233] ng/mL versus 75.2 [65.5, 82.2] ng/mL) and 3-fold AUC_{0-24} (mean [min, max]: 2820 [1880, 3900] ng.h/mL) versus 956 [792, 1060] ng.h/mL) in PMs based on PBPK simulations after repeated doses of 100 mg QD. Similar effects would be expected with other strong (eg, clarithromycin, itraconazole, cobicistat, indinavir, lopinavir, ritonavir, saquinavir, telaprevir, tipranavir, posaconazole, voriconazole, telithromycin, conivaptan, boceprevir) and moderate (eg, erythromycin, ciprofloxacin, fluconazole, diltiazem, verapamil, aprepitant, atazanavir, darunavir, fosamprenavir, imatinib, cimetidine) inhibitors of CYP3A.

	CYP3A inhibition in CYP2D6 EMs with mild HI (based on PBPK simulations): • The predicted mean [min, max] Genz-99067 C_{max} and AUC_{0-24} after coadministration of ketoconazole (strong inhibitor) with eliglustat 84 mg QD were 71.7 [32.8, 138] ng/mL and 1060 [377, 2380] ng.h/mL respectively. • The predicted mean [min, max] Genz-99067 C_{max} and AUC_{0-24} after coadministration of fluconazole (moderate inhibitor) with eliglustat 84 mg QD were 53.5 [31.6, 83.7] ng/mL and 700 [342, 1240] ng.h/mL respectively. • The predicted mean [min, max] Genz-99067 C_{max} and AUC_{0-24} after coadministration of fluvoxamine (weak inhibitor) with eliglustat 84 mg QD were 42.4 [26.4, 65.9] ng/mL and 482 [281, 850] ng.h/mL respectively. Cumulatively there have been six postmarketing case reports up to 19-Aug-2022 where a strong/moderate CYP3A inhibitor was used concomitantly with eliglustat. None of the associated reported AEs seem to have been caused by a drug-drug interaction with eliglustat. Ongoing monitoring of the postmarketing data up to DLP (21-Jun-2023) did not reveal any significant safety information impacting the characterization of this important potential risk. Cases of strong/moderate CYP3A inhibitor use concomitantly with eliglustat will continue to be monitored. **Use of strong/moderate CYP2D6 inhibitor and strong/moderate CYP3A inhibitor**: CYP2D6 and CYP3A inhibition (100 mg BID): • The combination of paroxetine (strong CYP2D6 inhibitor) and ketoconazole (strong CYP3A inhibitor) increased Genz-99067 exposure by 17-fold for Cmax (Mean (min, max): 23.8 [18.0, 30.5] ng/mL versus 406 [362, 459] ng/mL) and by 25-fold or AUC0-12 (Mean [min, max]: 185 [134, 241] ng.h/mL versus 4550 [4020, 5210] ng.h/mL) in EM/URMs based on PBPK simulations. • The combination of terbinafine (moderate CYP2D6 inhibitor) and fluconazole (moderate CYP3A inhibitor) increased Genz-99067 exposure by 9-fold for Cmax [mean [min, max]: 28.3 [16.7, 39.6] ng/mL versus 251 [184, 321] ng/mL] and by 12-fold for AUC_{0-12} (mean [min, max]: 217 [120, 315] ng.h/mL versus 2530 [1840, 3320] ng.h/mL) in EMs based on PBPK simulations. Cumulatively there have not been any postmarketing case reports up to 19-Aug-2022 where both a strong/moderate CYP2D6 inhibitor and a strong/moderate CYP3A inhibitor were used concomitantly with eliglustat. Ongoing monitoring of the postmarketing data up to DLP (21-Jun-2023) did not reveal any significant safety information impacting the characterization of this important potential risk. Cases of strong/moderate CYP2D6 inhibitor and strong/moderate CYP3A inhibitor use concomitantly with eliglustat will continue to be monitored. **For strong CYP3A inducer:** CYP3A and P-gp induction • Rifampicin (decreased Genz-99067 exposure by 84.4% for C_{max} and 85.1% for AUC_{0-12} in non-PMs in vivo after repeated doses of 127 mg BID eliglustat. Systemic exposures of eliglustat decreased by approximately 95% following co-administration of CERDELGA 84 mg BID with rifampin 600 mg PO QD in PMs. Cumulatively there have not been any postmarketing case reports up to 19-Aug-2022 where a strong CYP3A inducer was used concomitantly with eliglustat. Ongoing monitoring of the postmarketing data up to DLP (21-Jun-2023) did not reveal any significant safety information impacting the characterization of this important potential risk. Cases of strong CYP3A inducer use concomitantly with eliglustat will continue to be monitored. **For P-gp inhibition:** P-gp inhibition by eliglustat: 1.70- and 1.49-fold increases in the C_{max} and AUC_{last} of digoxin were observed following repeated doses of eliglustat 150 mg BID (CYP2D6 non-PMs) or 100 mg BID (CYP2D6 PMs). The mean renal clearance of digoxin appeared similar in the absence and presence of eliglustat. This interaction is consistent with an increase in digoxin absorption due to inhibition of P-gp mediated digoxin secretion at the intestinal level, with no decrease in its renal secretion. Cumulatively there have been 106 postmarketing case reports up to 19-Aug-2018 where a P-gp substrate was used concomitantly with eliglustat. This is particularly relevant for medications

Potential risk	Drug-drug interactions - Use with CYP2D6 and/or CYP3A inhibitors - Use with strong CYP3A inducers - Use with P-gp or CYP2D6 substrates
	with a narrow therapeutic index. None of the associated reported AEs seem to have been caused by a drug-drug interaction with eliglustat. Ongoing monitoring of the postmarketing data up to DLP (21-Jun-2023) did not reveal any significant safety information impacting the characterization of this important potential risk. Cases of P-gp substrate use concomitantly with eliglustat will continue to be monitored. **For CYP2D6 inhibition:** CYP2D6 inhibition: • Metoprolol: eliglustat (150 mg BID) increased metoprolol exposure by 1.53-fold for C_{max} and 2.08-fold for AUC in non-PMs in vivo. Dextromethorphan: eliglustat (100 mg BID) increased dextromethorphan exposure by 1.7-fold for C_{max} and 3.0-fold for AUC in EMs based on PBPK simulations. Cumulatively there have been 43 postmarketing case reports up to 19-Aug-2018 where a CYP2D6 substrate was used concomitantly with eliglustat. None of the associated reported AEs seem to have been caused by a drug-drug interaction with eliglustat. Ongoing monitoring of the postmarketing data up to DLP (21-Jun-2023) did not reveal any significant safety information impacting the characterization of this important potential risk. Cases of CYP2D6 substrate use concomitantly with eliglustat will continue to be monitored.
Risk factors and risk groups	Patients with HI. Consumption of grapefruit products (CYP3A inhibitors).
Preventability	Careful consideration on the patient's CYP2D6 phenotype, concomitant medication use, as well as hepatic and renal status.
Impact on the benefit-risk balance of the product	**For strong/moderate CYP2D6 inhibitors**: As of 19-Aug-2022, the 61 reported post marketing cases where a strong/moderate CYP2D6 inhibitor was used concomitantly with CERDELGA do not alter the current benefit-risk profile of CERDELGA. The benefit-risk balance of CERDELGA remains positive. **For strong/moderateCYP3A inhibitors:** As of 19-Aug-2022, the six post marketing case reports where a strong/moderate CYP3A inhibitor was used concomitantly with CERDELGA do not alter the current benefit-risk profile of CERDELGA .The benefit-risk balance of CERDELGA remains positive. **Use of strong/moderate CYP2D6 inhibitor and strong/moderate CYP3A inhibitor:** There have been no post marketing case reports up to 19-Aug-2022 where both a strong/moderate CYP2D6 inhibitor and a strong/moderate CYP3A inhibitor were used concomitantly with CERDELGA ; therefore, impact on benefit-risk balance could not be assessed. **For strong CYP3A inducer:** There have been no post marketing case reports up to 19-Aug-2022 where a strong CYP2D6 inducer was used concomitantly with CERDELGA; therefore impact on benefit-risk balance could not be assessed. **For P-gp inhibition:** The risk of increased plasma exposure of P-gp substrates depends on if the substrate has a narrow therapeutic index and risk profile of the particular victim drug. There is no impact on the benefit-risk balance of CERDELGA. **For CYP2D6 inhibition:** The risk of increased plasma exposure of CYP2D6 substrates depends on if the substrate has a narrow therapeutic index and risk profile of the particular victim drug. There is no impact on the benefit-risk balance of CERDELGA.
Public health impact	Given the worldwide prevalence of Gaucher disease (expected to be 1/40 000 to 1/125 000 in the general population); the potential public health impact is low.

AE: Adverse Event; AUC_{0-12}: Area under the plasma concentration curve at steady state over the dosing interval (ie, 12 hours); BID: Twice Daily; C_{max}: Maximum Concentration; CYP: Cytochrome P450; DLP: Data Lock Point; DUS: Drug Utilization Study; EM: Extensive Metabolizer; HI: Hepatic Impairment; PBPK: Physiologically Based Pharmacokinetic; P-gp: P-Glycoprotein; PM: Poor Metabolizer; QD: Once Daily; URM: Ultra-Rapid Metabolizer; US: United States.

Table 28 - Important potential risk: Use of eliglustat in patients who are CYP2D6 indeterminate metabolizers or non-genotyped patients

Potential risk	**Use of eliglustat in patients who are CYP2D6 indeterminate metabolizers or non-genotyped patients**
Potential mechanism	Not applicable
Evidence source(s) and strength of evidence	POH0373, SIM0105, SIM0183, and clinical studies.
Characterization of the risk	Frequency with 95 % CI All eliglustat treated Gaucher disease type 1 patients were characterized for CYP2D6 phenotype per protocol but this information was not used for dosing. In Phase 2/3 studies, dosing of eliglustat was determined by monitoring Genz-99067 C_{trough}. All patients were started at 50 mg BID and then maintained or titrated up to 100 mg BID and 150 mg BID doses based on monitoring Genz-99067 minimum plasma concentration observed in the dosing interval during repeated dosing (C_{trough}), as well as any further dose titration (up and down) over the course of the trial. Subsequent modeling has revealed that at the 100 mg BID dose, IM and EM patients were treated safely and effectively. No PMs received a higher dose than 50 mg BID in the clinical trials. Based on PBPK modeling, a 100 mg QD is proposed for PMs. The PBPK-predicted mean C_{max} in PMs at a 100 mg QD dose (75.2 ng/mL) will likely not result in QT-related safety concerns based on the concentration-QT relationship established in the thorough QT study. Furthermore, this predicted mean C_{max} is within the safe and effective range of C_{max} observed for eliglustat in the clinical development program (2.13 to 261 ng/mL [see 2.7.2 Table 47]). The PBPK-predicted mean area under the plasma concentration curve from time 0 to 24 hours (AUC_{0-24}) at 100 mg QD in PMs (956 ng.h/mL) is comparable to the observed mean AUC_{0-24} for IMs at the 100 mg BID dose (mean AUC_{0-12} value of 400 ng.h/mL (N = 4) which corresponds to an approximately mean AUC_{0-24} value of 800 ng.h/mL [see 2.7.2 Table 47]), and it is also within the exposures that were observed in the clinical development program (16.3 to 992 ng.h/mL [see 2.7.2 Table 47]). Cumulatively there have been two postmarketing case reports up to 19-Aug-2022 of patients reportedly CYP2D6 indeterminate metabolizers or in non-genotyped patients. Cases of such patients will continue to be monitored. Ongoing monitoring of the postmarketing data up to DLP (21-Jun-2023) did not reveal any significant safety information impacting the characterization of this important potential risk. Severity and nature of risk Non-genotyped or indeterminate patients are either CYP2D6 PM, EMs, IMs or URMs and can be initiated on either once or twice a day dosing. For PMs: Patients may receive a higher dose (ie, 100 mg BID) than labeled. Simulation of exposure at 100 mg BID using PBPK-modeling in CYP2D6 PMs predicted a mean steady-state C_{max} of 96.9 ng/mL and AUC_{0-12} of 877 ng.h/mL (Table 33; 272); thus, chronically achieving exposure observed in the higher range of the Phase 2/3 clinical trials. In simulations of PMs receiving 100 mg BID using PBPK-modeling, in the presence of one strong CYP3A inhibitor (worst case scenario for PMs), exposure was predicted to increase to a C_{max} of 448 ng/mL (min-max: 335-548) and mean area under the plasma concentration curve from time 0 to 24 hours (AUC_{0-12}) of 5100 ng.h/mL (min-max: 3740-6360). No experience has been obtained with other dosing regimens that use the 100 mg commercial strength, such as the 100 mg QD regimen. For IMs and EMs: Patients may receive a lower dose than labeled (ie, 100 mg QD). This may result in lack of effect. For URMs: Patients may not achieve adequate concentrations to achieve a therapeutic effect at 100 mg BID. No dosing recommendation for URMs can be given. This may result in lack of effect.

<table>
<tr><th>Potential risk</th><th>Use of eliglustat in patients who are CYP2D6 indeterminate metabolizers or non-genotyped patients</th></tr>
<tr><td></td><td>Seriousness/outcomes
Not applicable.
Background incidence/prevalence
CYP2D6 phenotype predicted based on genotype Gaucher disease type 1 patients in the final pooled Eliglustat Safety Set
<table>
<tr><th>CYP2D6 phenotype</th><th>Patients (%) in the final pooled Eliglustat Safety Set</th></tr>
<tr><td>Poor</td><td>14 (4)</td></tr>
<tr><td>Intermediate</td><td>50 (13)</td></tr>
<tr><td>Extensive</td><td>316 (80)</td></tr>
<tr><td>Ultra-rapid</td><td>11 (3)</td></tr>
<tr><td>Indeterminate</td><td>2 (1)</td></tr>
<tr><td>Total</td><td>393</td></tr>
</table>
CYP: Cytochrome P450.
The background prevalence of Indeterminate metabolizers in the general population is unknown. The percentage of patients with Indeterminate CYP2D6 phenotype in the clinical trials was less than 1% (2 patients out of 393).
Impact on individual patient
Lack of testing or indeterminate metabolizer may result in a non-eligible patient receiving eliglustat (URM, indeterminate) or in the incorrect dose being administered to the non-genotyped patient (PMs, IMs and EMs).</td></tr>
<tr><td>Risk factors and risk groups</td><td>Not applicable</td></tr>
<tr><td>Preventability</td><td>Limitation of use in indeterminate metabolizer patients in addition to labeling around the use of CYP2D6 genotyping of patients prior to treatment with eliglustat.</td></tr>
<tr><td>Impact on the benefit-risk balance of the product</td><td>Given the expected low prevalence of CYP2D6 indeterminate metabolizers or non-genotyped patients, the impact on the benefit-risk balance is low. The two reported cases of administration of CERDELGA in an indeterminate metabolizer does not alter the current benefit-risk profile of CERDELGA. The benefit-risk balance of CERDELGA remains positive.</td></tr>
<tr><td>Public health impact</td><td>Given the worldwide prevalence of Gaucher disease (expected to be 1/40 000 to 1/125 000 in the general population); the potential public health impact is low. In addition, is available for patients who are not eligible for eliglustat treatment.</td></tr>
</table>

AUC_{0-12}: Area under the plasma concentration curve at steady state over the dosing interval (ie, 12 hours); AUC_{0-24}: Area under the plasma concentration curve at steady state over the dosing interval (ie, 24 hours); BID: Twice Daily; CI: Confidence Interval; C_{max}: Maximum Concentration; C_{trough}: Minimum Plasma Concentration (trough concentration); CYP: Cytochrome P450; DLP: Data Lock Point; EM: Extensive Metabolizer; ERT: Enzyme Replacement Therapy; IM: Intermediate Metabolizer; PBPK: Physiologically Based Pharmacokinetic; PM: Poor Metabolizer; QD: Once Daily; URM: Ultra-Rapid Metabolizer.

Table 29 - Cardiac conduction disorders and arrhythmias

Potential risk	Cardiac conduction disorders and arrhythmias
Potential mechanism	Cardiac conduction disorders and Ventricular arrhythmia Eliglustat is a multi-ion channel inhibitor; it is less likely that eliglustat could be torsadogenic. Although no significant QTc increases were seen in a thorough (TQT) study in healthy volunteers, based on PK/PD modeling, eliglustat plasma concentrations 11-fold above those

Potential risk	Cardiac conduction disorders and arrhythmias
	expected at the indicated dose are predicted to cause mild increases in the PR, QRS, and QTc intervals of 20.4, 7.1, and 14.2 msec, respectively. It does not appear that exposure correlated with the incidence of AV conduction findings or ventricular arrhythmia in the clinical trial. Most of these events were incidental findings on prescheduled Holter monitoring.
Evidence source(s) and strength of evidence	ISS; ISS ECG Report; GZGD00304, GZGD02507; GZGD02607; GZGD03109; EFC13738; Aggregate AE Report.
Characterization of the risk	Frequency with 95 % CI Cardiac conduction disorders There were a total of 6/393 patients (2%) in the final pooled Eliglustat Safety Set who experienced an AE in the MedDRA HLT of Cardiac conduction disorders: type 1 AV block second degree in 4 patients (1%), AV block in 1 patient (verbatim is 2:1 AV block), AV block first degree in 1 patient with a prior history of AV block, and Sinoatrial block in 1 patient. In all patients except 1 with type 1 AV block second degree, the events were deemed related by the Investigator. Of note, centrally read Holter and telemetry findings available from the ISS dataset as of 31-Jan-2013 reveal a more complete assessment of findings, regardless of investigator assessment of clinical significance. Of the 8 patients in whom second degree AV block (Mobitz 1) was detected by per protocol Holter monitoring, 6 patients were on eliglustat and 2 patients were in screening. Two of these patients on eliglustat also experienced 2:1 AV block. There was 1 patient on eliglustat with first degree AV block who had a history of AV block and prolonged PR on screening. Finally, all 3 patients who had a sinus pause >2.5 msec on Holter were on eliglustat. The comparative exposures were 535 patient-years for eliglustat, 50.7 patient-years for CEREZYME and 15.06 patient-years for placebo. There was no new onset of first-degree AV block, new onset of atrial fibrillation, pacemaker placement or sudden death in any clinical trial patient. No clinically significant safety findings were reported in the pediatric patient population with regards to the important potential risk of cardiac conduction disorders and arrhythmias. Ventricular arrhythmia There were a total of 7/393 patients (1.8%) in the final pooled Eliglustat Safety Set who experienced an AE in the MedDRA HLT of Ventricular arrhythmia and cardiac arrest: (non-sustained) VT in 4 patients (3 NSVT and 1 short run of VT), Ventricular extrasystole in 2 patients, and cardiac arrest in 1 patient. In 3 patients, the events (2 of which were VT and 1 was ventricular extrasystole) were deemed related by the Investigator. Centrally read Holter data from ENGAGE and ENCORE as well as telemetry data from Phase 2 were reviewed in their totality and did not discriminate as to whether an investigator reported a finding as an AE. There were a total of 14 patients with NSVT on Holter findings across the Phase 2 and Phase 3 studies as of the database lock; 5 patients on eliglustat (in 2 patients after the first 50 mg dose in the Phase 2 trial), 7 patients in screening and 1 each in a placebo and CEREZYME patient. Furthermore, all episodes of NSVT were monomorphic and slow. No events of ventricular fibrillation, ventricular arrhythmia or sustained VT were noted, and no events of Torsade de Pointes were reported in the clinical trial population. One patient died of cardiac arrest due to massive blood loss following blunt abdominal trauma and spleen rupture. This death was considered not related to eliglustat. No clinically significant safety findings were reported in the pediatric patient population with regards to the important potential risk of cardiac conduction disorders and arrhythmias. Cumulatively there have been 11 case reports of cardiac conduction disorders and arrhythmias received postmarketing up to 19-Aug-2022. These cases were reviewed and were found to be similar in nature, severity and frequency to those reported in the clinical trial setting and consistent with the known safety profile of CERDELGA. Ongoing monitoring of the postmarketing data up to DLP (21-Jun-2023) did not reveal any significant safety information impacting the

Potential risk	Cardiac conduction disorders and arrhythmias
	characterization of this important potential risk. Cases of cardiac conduction disorders and arrhythmias will continue to be monitored. Severity and nature of risk Cardiac conduction disorders In all patients, AEs were mild in severity. No patient experienced a higher block than Mobitz 1 second-degree AV block. Events occurred in males and females equally, ages 24 to 69 years, at all doses of eliglustat in EMs. Event onset from first eliglustat dose was 91-632 days. Maximum Concentration values closest in chronology to the event onset ranged from 19.4 to 60.6 ng/mL. All events were asymptomatic and mostly occurred in the early morning hours. These data suggest that there is no relationship between these findings and eliglustat treatment. No patient discontinued treatment due to cardiac conduction disorders. Ventricular arrhythmia In all patients, AEs were asymptomatic and mild or moderate in severity, except for 1 patient who experienced a severe AE of cardiac arrest. Events occurred in 5 females and 2 males, ages ranged from 23 to 60 years, at both the 50 and 100 mg dose, and all patients except 1 IM and 1 PM were EMs. Event onset from first eliglustat dose was 1 to 1632 days. Available C_{max} values on the day of the event were 44.2 and 70.7 ng/mL for 2 patients, and 3.0 and 5.0 ng/mL for the 2 patients that discontinued after their first dose. Seriousness/outcomes Cardiac conduction disorders One patient had 2 SAEs (2:1 AV block and Mobitz 1 second degree AV block) and recovered after treatment interruption and dose reduction. Ventricular arrhythmia One patient had an SAE of VT on continuous telemetry after the first 50 mg dose; the patient recovered and was discontinued from the study. One additional patient had an SAE of (non-sustained) VT noted during the end of study Holter monitoring. One patient died of cardiac arrest due to massive blood loss following blunt abdominal trauma and spleen rupture. Background incidence/prevalence Cardiac conduction disorders The presence of AV block in the Gaucher population is unknown. Background incidence and prevalence in the general population is provided: Data from 24-hour ambulatory ECG recordings in healthy volunteers showed second degree AV block in 6.5% of participants. (64) In a population-based study conducted in Iceland, third degree AV block was found in 0.04% of participants. (65) In the community-based Framingham heart study, 1.6% of patients had a first-degree AV block at baseline. (66) A pause that is 3 seconds and perhaps somewhat longer does not necessarily indicate disease, since it can occur in the normal heart. (67) A DUS that covered the period between Jan-2003 and Jun-2012 has been conducted in the MarketScan database in the US; 168 adult patients who were subsequently treated for Gaucher disease were retrospectively assessed for up to 6 months before treatment initiation. No case of cardiac disease (CHF, CAD, IHD/MI) in patients receiving Gaucher treatment within 180 days was recorded. Ventricular arrhythmia The presence of ventricular arrhythmia in the Gaucher population is unknown. A DUS which covered the period between Jan-2003 and Jun-2012 has been conducted in the MarketScan database in the US. One hundred sixty eight (168) adult patients who were subsequently treated for Gaucher disease were retrospectively assessed for up to 6 months before treatment initiation. The results showed 1 case of arrhythmia out of the 168 Gaucher disease patients (0.6%) receiving Gaucher treatment within 180 days. Background incidence and prevalence in the general population is provided:

Potential risk	Cardiac conduction disorders and arrhythmias
	Data from 24-hour ambulatory ECG recordings in healthy volunteers showed VT in 2% of participants. (64) The incidence of NSVT in the general population varies between 0% and 4%. (68) It is more common with increasing age and occurs equally among men and women. These incidence figures are drawn from studies using prolonged recordings in relatively small numbers of normal subjects. It is likely, however, that a single 24-hour recording significantly underestimates the true frequency of this often asymptomatic and intermittent arrhythmia. The prevalence of Torsade de Pointes is unknown. Torsade de Pointes is a life-threatening arrhythmia and may present as sudden cardiac death. From US vital statistics in 1998, sudden cardiac deaths accounted for 63% of all cardiac deaths. (69) In the US, 450 000 sudden cardiac deaths occur per year. (70) Torsade de Pointes probably accounts for fewer than 5% and is 2 to 3 times more common in women than in men. Women have longer QT intervals and have more QT prolongation secondary to drug therapy. <u>Impact on individual patient</u> The magnitude of an increased PR interval defines a patient's risk of first-degree AV block and, if symptomatic, is routinely treated with medications and/or pacemaker placement. In most references an increase in PR interval is considered to be benign. In one study, PR prolongation was associated with increased risks of atrial fibrillation (1.12), pacemaker implantation (1.22), and increase in death (1.08) compared to those without PR prolongation in an ambulatory setting. This study challenges the longstanding perception that PR interval prolongation or first-degree AV block has a benign prognosis. (66) Mobitz type 1 AV block can occur in individuals who have high vagal tone, such as younger persons or highly conditioned athletes at rest. The prognosis is excellent in these settings, as progressive block does not appear to occur. Asymptomatic patients with sinoatrial nodal pauses often do not require treatment. Clinical presentations of ventricular arrhythmia range from asymptomatic individuals to cardiac arrest. The risk of sudden cardiac death is linked to the severity and type of underlying cardiac disease. (70) The finding of NSVT of short duration and monomorphic quality can be considered low risk in patients with no underlying structural cardiac disease. By definition, NSVT is self-limiting, lasting less than 30 seconds. As such, patients with NSVT are less likely to develop symptoms than those with sustained VT, and most patients with NSVT are asymptomatic. For patients with NSVT who are asymptomatic and have no evidence of structural heart disease, no specific medical therapy is indicated. The finding of a long QTc interval does not necessarily predict a patient will develop ventricular arrhythmia or Torsade de Pointes but has been associated as a marker for Torsades de Pointes with some drug products. Of note, multi-ion channel blockers such as eliglustat have been shown to be associated with a lower incidence of Torsade de Pointes. (71)
Risk factors and risk groups	<u>Cardiac conduction disorders</u> Patients with a prior history of conduction disease are more likely to experience blocks. There is an increased risk of first degree block with increased age as well as some medical conditions (eg, IHD, congenital heart disease, drugs, alcohol use, thyroid disease). Mobitz 1 second degree AV block can occur in normal subjects, athletes, older adults, and in patients with certain heart diseases or who are taking drugs that block the AV node (eg, digoxin, beta blockers, calcium channel blockers). <u>Ventricular arrhythmia</u> Patients with compromised heart function such as cardiomyopathy, heart failure and ischemia are at increased risk for ventricular arrhythmia. Coronary heart disease was identified as the underlying cause of 62% of sudden cardiac deaths. Higher rates of sudden cardiac death were associated with increased age and male gender. (69) Patients with congenital long QT syndrome are at greater risk for a long QTc interval. The use of medications that are known torsadogens or potential torsadogens are also known to increase the QTc interval, which may put a patient at increased risk of Torsade de Pointes. The effect of taking multiple drugs may be additive.

Potential risk	Cardiac conduction disorders and arrhythmias
	Use of concomitant CYP2D6 and CYP3A inhibitors Extensive metabolizers and IMs using concomitant strong or moderate CYP2D6 inhibitors together with strong or moderate CYP3A inhibitors, and PMs using a strong CYP3A inhibitor are at increased risk to achieve substantially elevated eliglustat exposure which could potentially lead to increases in ECG intervals. Hepatic impairment Since metabolism is the predominant route of elimination, CYP2D6 EM patients with severe HI, as well as CYP2D6 EM patients with mild or moderate HI using a strong or moderate CYP2D6 inhibitor, are at increased risk to achieve substantially elevated eliglustat exposure which could potentially lead to increases in ECG intervals.
Preventability	Controlling eliglustat exposure by limiting interacting concomitant medications, such as CYP2D6 and CYP3A inhibitors, as well as taking into account patient's hepatic status, will limit the increase in QRS, QTc and PR duration. Warning against the use of eliglustat in patients with pre-existing cardiac conditions and the concomitant use of eliglustat with class IA and class III antiarrhythmic. Limitation of use to patients with dual metabolic pathway clearance of eliglustat.
Impact on the benefit-risk balance of the product	As per current DLP, the reported cases of cardiac conduction disorders and arrhythmias following the administration of CERDELGA do not alter the current benefit-risk profile of CERDELGA. The benefit-risk balance of CERDELGA remains positive.
Public health impact	Given the worldwide prevalence of Gaucher disease (expected to be 1/40 000 to 1/125 000 in the general population), the potential public health impact is low.

AE: Adverse Event; AV: Atrioventricular; CAD: Coronary Artery Disease; CHF: Coronary Heart Failure; CI: Confidence Interval; C_{max}: Maximum Concentration; CYP: Cytochrome P450; DLP: Data Lock Point; DUS: Drug Utilization Study; ECG: Electrocardiogram; EM: Extensive Metabolizer; HLT: High Level Term; IHD: Ischemic Heart Disease; IM: Intermediate Metabolizer; ISS: Integrated Safety Summary; HI: Hepatic Impairment; MedDRA: Medical Dictionary for Regulatory Activities; MI: Myocardial Infarction; NSVT: Non-Sustained Ventricular Tachycardia; PD: Pharmacodynamic; PK: Pharmacokinetic; PM: Poor Metabolizer; SAE: Serious Adverse Event; US: United States VT: Ventricular Tachycardia.

SVII.3.2 Presentation of the missing information

Table 30 - Missing information: Use in patients with a history of or current cardiac ischemia or heart failure, clinically significant arrhythmias or conduction findings

Missing Information	Use in patients with a history of or current cardiac ischemia or heart failure, clinically significant arrhythmias or conduction findings
Evidence source(s) and strength of evidence	The safety and efficacy of eliglustat in patients with a history of or recurrent cardiac ischemia or heart failure, clinically significant arrhythmias or conduction findings has not yet been established.
Anticipated risk/consequence of the missing information	Because CERDELGA is predicted to cause mild increases in ECG intervals at substantially elevated eliglustat plasma concentrations, use of CERDELGA should be avoided in patients with cardiac disease (CHF, recent acute MI, bradycardia, heart block, ventricular arrhythmia), (SmPC Section 4.4 Special warnings and precautions).

CHF: Chronic Heart Failure; ECG: Electrocardiogram; MI: Myocardial Infarction; SmPC: Summary of Product Characteristics.

Table 31 - Missing information: Use during pregnancy and lactation

Missing Information	Use during pregnancy and lactation
Evidence source(s) and strength of evidence	Eliglustat is intended for use in patients of childbearing age. Preclinical reproductive toxicity studies showed there is measurable, albeit low, milk excretion and placental transfer of eliglustat and/or its related materials. It is not known whether eliglustat can affect reproductive capacity or cause fetal harm when administered to pregnant or breast-feeding women. Excretion of eliglustat in human breast milk has not been studied.
Population in need for further characterization	During the clinical development program, the frequency of pregnancy was low. No conclusion can be drawn regarding the safety of eliglustat during pregnancy, embryonic, or fetal development, parturition, postnatal development and breast feeding. However, preclinical reproductive toxicity studies were negative and eliglustat is not expected to cross the placenta. Cumulatively from postmarketing sources no new safety information identified that would have an impact on the understanding and characterization of missing information.

Table 32 - Missing information: Safety in long-term treatment use

Missing Information	Safety in long-term treatment use
Evidence source(s) and strength of evidence	In the aggregate report of AEs from the studies GZGD00304, GZGD02507, GZGD02607, GZGD03109 (submitted in RMP v4.0), the median duration of treatment was 3.5 years in 393 patients, with a maximum duration of eliglustat treatment of 9.3 years. Among those patients, 122 patients (31%) were treated over 4 years. No clinically significant safety findings were reported in the pediatric patient population related to long-term exposure from EFC13738 study. No new safety concern has been considered related to long-term exposure.
Anticipated risk/consequence of the missing information	Therefore, long-term safety data from clinical trials have been gathered, which will be complemented by long-term safety data from the prospective ICGG safety sub-registry that will describe the long-term risks in eliglustat treated patients in real-world clinical practice.

ICGG: International Collaborative Gaucher Group; RMP: Risk Management Plan.

Table 33 - Missing Information: Use in patients who are CYP2D6 URMs

Missing Information	Use in patients who are CYP2D6 URMs
Evidence source(s) and strength of evidence:	During clinical development, a limited number of URM patients (N = 11) with GD1 disease were treated with eliglustat. As a result, the amount of observed PK data available from URM patients in clinical studies that can be used to project exposures is currently limited. This is precluding a confident prediction of the full range of exposures that may occur in these subpopulations in the wider postmarketing setting, which in turn limits the ability to ensure that plasma levels will remain in the safe and efficacious range under conditions of commercial use. CYP2D6 URM patients were excluded from paediatric clinical study.
Population in need for further characterization	Additional PK, safety and efficacy data from URMs patients treated with eliglustat are necessary to provide adequate dosing guidance for a chronic treatment in these small subpopulations. Therefore, a dosing regimen based on CYP2D6 phenotype is proposed for postmarketing use.

CYP: Cytochrome P450; GD1: Gaucher Disease Type 1; N: Number; PK: Pharmacokinetics; URM: Ultra-Rapid Metabolizer.

RISK MANAGEMENT PLAN - PART II MODULE SVIII: SUMMARY OF THE SAFETY CONCERNS

Summary of the safety concerns

Important identified risk	None
Important potential risks	Drug-drug interactions - Use with CYP2D6 and/or CYP3A inhibitors - Use with strong CYP3A inducers - Use with P-gp or CYP2D6 substrates Use of eliglustat in patients who are CYP2D6 indeterminate metabolizers or non-genotyped patients Cardiac conduction disorders and arrhythmias
Missing information	Use in patients with a history of or current cardiac ischemia or heart failure, clinically significant arrhythmias or conduction findings Use during pregnancy and lactation Safety in long-term treatment use Use in patients who are CYP2D6 ultra-rapid metabolizers

CYP: Cytochrome P450; P-gp: P-Glycoprotein.

RISK MANAGEMENT PLAN - PART III: PHARMACOVIGILANCE PLAN (INCLUDING POST-AUTHORIZATION SAFETY STUDIES)

Planned pharmacovigilance actions include routine pharmacovigilance activities, additional pharmacovigilance activities to further characterize and assess the important potential risks, and the collection of additional data on the safety profile in long term treatment use.

III.1 ROUTINE PHARMACOVIGILANCE ACTIVITIES

No routine pharmacovigilance activities beyond adverse reactions reporting and signal detection are deemed necessary to monitor the risks of eliglustat.

The safety profile of eliglustat will continue to be further characterized in real life setting through postmarketing safety surveillance, encompassing analysis of spontaneous reporting of ADRs in periodic safety reports, product technical complaints (PTCs) relating to AEs, signal detection and data mining activities.

III.2 ADDITIONAL PHARMACOVIGILANCE ACTIVITIES

An educational program has been implemented to ensure that Healthcare Professionals (HCPs) have adequate knowledge on key steps to be performed before treatment initiation (especially assessment of patient eligibility for treatment - ie, adult patient with GD1 and appropriate CYP2D6 genotype, assessment of concomitant drugs, assessment of appropriate dose of CERDELGA, patient education and during therapy. This educational program consists in a Guide for Prescriber targeting physicians who initiate and supervise eliglustat treatment and through delivery to the patient of a Patient Card to provide information to other HCPs regarding important DDIs with eliglustat, and to ensure that the eliglustat patient's risks for DDI reach the relevant HCPs.

Effectiveness evaluation is performed, as follows:

- Clinical actions through a DUS performed in Europe that will evaluate co-prescriptions (the protocol for DUS performed in Europe is available in [Annex 3]). Use of data from different regions is deemed necessary and appropriate as Gaucher disease is a rare disease: use of multiple data sources may allow to collect more robust information.
- In addition, a DUS has evaluated co-prescriptions of concomitant medications of interest and genotyping assessment in the US (US DUS is tabulated in [Annex 2, Table 2 - Completed studies]). Initially, in this DUS, genotyping information was expected to be available in the US MarketScan claims database. However, the claims database was unable to capture the genotyping status of these patients as complimentary genotyping services are offered, so there was no need for health insurance reimbursement. Thus, to be able to estimate the proportion of patients who were genotyped for CYP2D6, an alternative data source was added to the study. United States patients from the ICGG Gaucher Registry database who initiated eliglustat between 18 September 2014 and 30 September 2017 were included. The claims database was used to evaluate the dose and duration of eliglustat

therapy and prescribed concomitant medications of interest. This study is now completed and not anymore included in the RMP pharmacovigilance plan.

- Clinical actions through prospective ICGG safety sub-registry to characterize the long-term safety profile of eliglustat, that will evaluate the patient characteristics and utilization patterns (protocol synopsis is available in [Annex 3]).

Table 34 - Additional pharmacovigilance activities (category 1 to 3) summary

Prospective ICGG safety sub-registry (ELISAFE) (OBS14099) (category 1)
Study short name and title A prospective ICGG safety sub-registry to characterize the long-term safety profile of eliglustat.
Rationale and study objectives To characterize the long-term safety profile of eliglustat in real-world clinical practice. To describe the patients' characteristics and utilization patterns. Safety concerns addressed are: • Safety in long-term treatment use; • Use of eliglustat in patients who are CYP2D6 indeterminate metabolizers or non-genotyped patients; • Use of eliglustat in patients who are ultra-rapid metabolizers.
Study design Safety sub-registry of the ICGG Gaucher Registry conducted Non-interventional, international, multicenter, prospective post-authorization safety study
Study populations The target study population will include patients enrolled in the ICGG main registry in 20-40 registry sites who are initiating treatment with eliglustat or imiglucerase as part of routine management of their disease. At least 100 eliglustat-treated patients will be enrolled.
Milestones • Concept protocol: Submitted within 3 months after approval • Final Protocol approval: Protocol dated 23-Aug-2016 approved by EMA on 01-Dec-2016 • Start date of data collection: 18-Apr-2018 • Report: Progress reports will be reported in PSURs. Latest progress report submitted in the PBRER covering the period 20-Aug-2020 to 19-Aug-2022. • Interim report: Interim analyses report was submitted to EMA on 07-July 2023. • End of data collections: Four years after the last CERDELGA patient has been enrolled in the study. Based on the actual start of data collection date and recruitment of 32 months, the expected date of the end of data collection is Q1 2025. • Final report of study results: Q3 2025

Drug utilization study of eliglustat in Europe using electronic healthcare records (ELIGLC06913) (category 3)
Study short name and title Drug utilization study of eliglustat in Europe using electronic healthcare records.
Rationale and study objectives To assess compliance/adherence to the labeling with regard to DDI. Safety concern addressed is: • Drug-drug interaction.
Study design Retrospective cohort study using electronic health records
Study populations All patients treated with eliglustat in the selected databases from the date of eliglustat launch and will last for 3 years.
Milestones • Pilot study report: Q4 2014 • Submission of final protocol[a]: May-2015 • Submission of final report: Q4 2024

a The revised EU drug utilization study protocol was submitted to PRAC in Nov-2015 and approved in Feb-2016. It is appended in [Annex 3].

CYP: Cytochrome P450; DDI: Drug-Drug Interaction; EU: European Union; EMA: European Medicines Agency; ICGG: International Collaborative Gaucher Group; PBRER: Periodic Benefit Risk Evaluation Report; PRAC: Pharmacovigilance Risk Assessment Committee; PSUR: Periodic Safety Update Report; Q: Quarter.

III.3 SUMMARY TABLE OF ADDITIONAL PHARMACOVIGILANCE ACTIVITIES

Table 35 - Ongoing and planned additional pharmacovigilance activities

Study status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorization (key to benefit risk)				
Prospective ICGG safety sub-registry (OBS14099) Ongoing	To characterize the long-term safety profile of eliglustat in real-world clinical practice.	• Safety in long-term treatment use • Use of eliglustat in patients who are CYP2D6 indeterminate metabolizers or non-genotyped patients • Use of eliglustat in patients who	Concept protocol	Submitted within 3 months after approval.
			Final Protocol approval	Protocol dated 23-Aug-2016 approved by EMA on 01-Dec-2016. Start date of data collection: 18-Apr-2018.
	To describe the patient's characteristics and utilization patterns		Report	Progress reports will be reported in PSURs. Latest progress report submitted in the PBRER covering the period 20-Aug-2020 to 19-Aug-2022.

Study status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
		are ultra-rapid metabolizers	Interim report	An interim analysis of study results will be performed two years after the last CERDELGA patient has been enrolled in the study, and an interim analyses report was submitted to EMA on 07-July 2023.
			End of data collections	Four years after the last CERDELGA patient has been enrolled in the study.
			Final report of study results	Q3 2025
Category 3 - Required additional pharmacovigilance activities (by the competent Authority)				
Study Status	**Summary of objectives**	**Safety concerns addressed**	**Milestones**	**Due dates**
Drug utilization study of eliglustat in Europe using electronic healthcare records. (ELIGLC06913) Ongoing	To assess compliance/adherence to the labeling with regard to DDI.	Drug-Drug Interaction	Pilot study report	Q4 2014
			Submission of final protocol[a]	May-2015
			Submission of final report	Q4 2024

a The revised EU drug utilization study protocol was submitted to PRAC in Nov-2015 and approved in Feb-2016. It is appended in [Annex 3].

CYP: Cytochrome P450; DDI: Drug-Drug Interaction; EU: European Union; EMA: European Medicines Agency; ICGG: International Collaborative Gaucher Group; PBRER: Periodic Benefit Risk Evaluation Report; PRAC: Pharmacovigilance Risk Assessment Committee; PSUR: Periodic Safety Update Report; Q: Quarter.

RISK MANAGEMENT PLAN - PART IV: PLANS FOR POST-AUTHORIZATION EFFICACY STUDIES

Studies on eliglustat efficacy/effectiveness that are ongoing or planned are described in Table 36. No planned efficacy studies are specific obligations and/or conditions of the market authorization.

Table 36 - Planned and on-going post-authorization efficacy studies

Study Status	Summary of objectives	Efficacy uncertainties addressed	Milestones	Due date
Collect and report long-term efficacy data from the ICGG Gaucher Registry. Ongoing	To determine the long-term longitudinal efficacy data on eliglustat-treated patients.	Long-term efficacy	Registry report will be submitted biennial (once every two years) starting in Q4 2016	Latest biennial report was submitted in Dec-2022 Last report in Q4 2035

FPI: First Patient In; GD1: Gaucher Disease Type 1; GD3: Gaucher Disease Type 3; ICGG: International Collaborative Gaucher Group; PK: Pharmacokinetic; Q: Quarter.

RISK MANAGEMENT PLAN - PART V: RISK MINIMIZATION MEASURES (INCLUDING EVALUATION OF THE EFFECTIVENESS OF RISK MINIMIZATION ACTIVITIES)

The safety concerns relevant for eliglustat are primarily managed through routine risk minimization (proposed SmPC and Patient Information Leaflet [PIL], as well as prescription status of the product [Section 4.2 of the SmPC - Posology and method of administration, specifies that therapy with CERDELGA should be initiated and supervised by a physician knowledgeable in the management of Gaucher disease]).

However, two important potential risks have been considered as requiring additional risk minimization measures to guide appropriate patient selection and improve the safety use of eliglustat:

- Drug-drug interactions (DDIs)
  - Use with cytochrome P450 (CYP) 2D6 and/or CYP3A inhibitors.
  - Use with strong CYP3A inducers.
  - Use with P-glycoprotein (P-gp) substrates or CYP2D6 substrates.
- Use of eliglustat in patients who are CYP2D6 indeterminate metabolizers or non-genotyped patients.

Drug-drug interactions (DDIs) with CYP2D6 and/or CYP3A inhibitors, and prescription of CERDELGA which does not follow the posology of the label with respect to CYP2D6 metabolizer status are situations that may lead to increased eliglustat exposure. At 11-fold increases above levels expected at the indicated dose, predicted mild increases in the ECG intervals may occur.

Use of eliglustat with strong CYP3A inducers substantially decreases the exposure of Genz-99067, which may reduce its therapeutic effectiveness.

Use of eliglustat with P-gp or CYP2D6 substrates increases plasma exposure of these drugs, which may require lower doses of these drugs.

To reinforce knowledge and adherence of the initial eliglustat prescribers to these risks that need to be evaluated prior to the initiation of eliglustat, and to provide a means of communication to other HCPs prescribing drugs to eliglustat patients regarding important DDI with eliglustat, the applicant has implemented the following educational materials:

- A Guide for Prescriber: Targeted to specialists initiating and supervising CERDELGA treatment including a checklist of steps to be performed prior to initiation of CERDELGA.
- A Patient Card: Targeted to non- CERDELGA prescribing HCPs regarding important DDIs with CERDELGA and to ensure that the patient’s risk for DDI reach the relevant HCPs. It is also targeted to patients who will be educated regarding self-medication, and to present the card to all other HCPs at each visit.

In RMP update version 5.1, the content of eliglustat educational materials [Annex 6] was revised to reflect new recommendations in patients with hepatic or renal impairment, based on the POP13777 and POP13778 study results and based on feedback from CHMP and PRAC on the type variation II including EU-RMP version 5.0 (EMA/CHMP/772520/2017).

The routine and additional risks minimization measures are presented in this Module.

Details of additional risk minimization activities are provided in [Annex 6].

V.1 ROUTINE RISK MINIMIZATION MEASURES

Table 37 - Description of routine risk minimization measures by safety concern

Safety concern	Routine risk minimization activities
Drug-drug interactions - Use with CYP2D6 and/or CYP3A inhibitors - Use with strong CYP3A inducers - Use with P-gp or CYP2D6 substrates	**Routine risk communication:** • Labeled in sections 4.2, 4.3, 4.4, 4.5 and 5.2 of SmPC. • Labeled in sections 2 and 3 of PIL. **Routine risk minimization activities recommending specific clinical measures to address the risk:** None **Other routine risk minimization measures beyond the Product Information:** None
Use of eliglustat in patients who are CYP2D6 indeterminate metabolizers or non-genotyped patients	**Routine risk communication:** • Labeled in sections 4.1, 4.2 and 5.2 of SmPC. • Labeled in sections 2 and 3 of PIL. **Routine risk minimization activities recommending specific clinical measures to address the risk:** Before initiation of treatment with CERDELGA, patients should be genotyped for CYP2D6 to determine the CYP2D6 metabolizer status. **Other routine risk minimization measures beyond the Product Information:** None
Cardiac conduction disorders and arrhythmias	**Routine risk communication:** • Labeled in sections 4.3, 4.4 and 4.5 of SmPC. • Labeled in section 2 of PIL. **Routine risk minimization activities recommending specific clinical measures to address the risk:** None **Other routine risk minimization measures beyond the Product Information:** None
Use in patients with a history of or current cardiac ischemia or heart failure, clinically significant arrhythmias or conduction findings	**Routine risk communication:** • Labeled in section 4.4 of SmPC. • Labeled in section 2 of PIL.

Safety concern	Routine risk minimization activities
	Routine risk minimization activities recommending specific clinical measures to address the risk: None **Other routine risk minimization measures beyond the Product Information:** None
Use during pregnancy and lactation	**Routine risk communication:** • Labeled in section 4.6 of SmPC. • Labeled in section 2 of PIL. **Routine risk minimization activities recommending specific clinical measures to address the risk:** None **Other routine risk minimization measures beyond the Product Information:** None
Safety in long-term treatment use	**Routine risk communication:** None **Routine risk minimization activities recommending specific clinical measures to address the risk:** None **Other routine risk minimization measures beyond the Product Information:** None
Use in patients who are CYP2D6 ultra-rapid metabolizers	**Routine risk communication:** • Labeled in sections 4.2 and 4.4 of SmPC. • Labeled in section 2 of PIL. **Routine risk minimization activities recommending specific clinical measures to address the risk:** None **Other routine risk minimization measures beyond the Product Information:** None

CYP: Cytochrome P450; P-gp: P-Glycoprotein; PIL: Patient Information Leaflet; SmPC: Summary of Product Characteristics.

V.2 ADDITIONAL RISK MINIMIZATION MEASURES

Table 38 - Additional risk minimization measures

Guide for Prescriber	
Objectives	The Guide for Prescriber aims to minimize the risks of • Drug-drug interactions • Use of eliglustat in patients who are CYP2D6 indeterminate metabolizers or non-genotyped patients with the following measures: - Remind physicians of required steps to perform before CERDELGA initiation and during follow-up in order to minimize the potential for

	substantially elevated eliglustat plasma concentration or situations that may require lowering of a concomitant treatment - Remind physicians of recommendations in patients with hepatic or renal impairment - Remind physicians of recommended dosing regimen for IM and EM adult patients is 84 mg twice a day and for IM and EM paediatric patients the dosing regimen should be selected based on age and body weight - Remind physicians of recommended dosing regimen for PM adult patients is 84 mg once a day and for PM paediatric patients the dosing regimen should be selected based on age and body weight - Remind physicians of key information to be delivered to patients at treatment initiation regarding drug-drug interactions, and including provision of the Patient Card - Provide supportive information to physicians regarding genotyping assessment
Rationale for the additional risk minimization activity	**Justification for the risk of DDIs**: Eliglustat is metabolized primarily by CYP2D6 and to a lesser extent by CYP3A4 and concomitant administration of substances affecting CYP2D6 or CYP3A4 activity may alter eliglustat plasma concentrations: • Concomitant administration with CYP2D6 and/or CYP3A strong/moderate/weak inhibitors may result in increase in eliglustat exposure. • Concomitant administration of CYP3A inducers may decrease eliglustat exposure leading to potential lack of efficacy. • Eliglustat is a substrate of the efflux transporter P-gp. Concomitant administration of eliglustat with P-gp or CYP2D6 substrate substances may increase the plasma concentration of those substances. • Concomitant administration of CERDELGA with P-gp substrates may increase exposure of Pgp substrates via P-gp inhibition. • Concomitant administration of CERDELGA with CYP2D6 substrates may increase exposure of CYP2D6 substrates via CYP2D6 inhibition. • Patient's renal and hepatic status may influence eliglustat exposure in some cases addressed in the tool. **Justification for the risk of use of eliglustat in patients who are CYP2D6 indeterminate metabolizers or non-genotyped patients:** The CYP2D6 phenotype significantly influences eliglustat exposure. Eliglustat bioavailability was predicted to be approximately 20 times greater for CYP2D6 PMs as compared to EM. Conversely, eliglustat bioavailability was estimated to be approximately half for ultra-rapid metabolizers when compared to EM, exposing patients to decreased therapeutic effectiveness of eliglustat (POH0373).
Target audience and planned distribution path	Target audience: Physicians initiating and supervising treatment with CERDELGA. Distribution path: To be adapted country by country to local situations: mailing, medical representatives, and others
Plans to evaluate the effectiveness of the interventions and criteria for success	• Drug utilization studies in patients treated with CERDELGA using electronic health care records will be performed to evaluate physician understanding of important risks involving DDIs clinical actions. • Performance of genotyping assessment prior to the initiation of treatment will be assessed through a DUS in patients treated with eliglustat using US electronic health care records and a prospective ICGG safety sub-registry.

	Criteria for success: • Estimation of the proportion, type and duration of concomitant medication use (CYP2D6 and CYP3A strong/moderate or weak inhibitors, strong CYP3A inducers, P-gp and CYP2D6 substrates) in patients treated with CERDELGA. • Estimation of the proportion of CYP2D6 genotyping in patients treated with eliglustat. • United States DUS final report (sign-off date: 05-Nov-2018, see [Annex 2]) concludes that based on data from US patients in the ICGG Gaucher Registry, suggested compliance with CYP2D6 genotype testing in the US is high. While data from the MarketScan database indicate that up to 25% of patients are prescribed some CMIs after they have initiated eliglustat therapy, there was no evidence that patients on eliglustat were prescribed CMIs in contraindicated situations that could have led to significant drug-drug interactions.
Patient card	
Objectives	The patient card aims to minimize the risks of DDIs with the following measures: • Remind the patient / caregiver not to start medication without professional supervision • Remind the patient / caregiver not to consume grapefruit products • Liaison tool to inform HCPs about patient's current Gaucher treatment and the importance being aware of potential drug-drug interactions with eliglustat
Rationale for the additional risk minimization activity	Patients may be subject to self-medication and may have interactions with HCPs not familiar with eliglustat safety specifications. The Patient Card is a simple and efficient tool to alert HCPs prescribing medications to patients regarding important DDI interactions, and to ensure that the information reaches the relevant HCP at all points of care.
Target audience and planned distribution path	Target audience: Both the patient / caregiver and any HCP who may prescribe or deliver drugs to the patient that may interact with CERDELGA. Distribution path: This card will be delivered to the patient / caregiver by the physician initiating and supervising the treatment. It will be kept by the patient and presented to any HCP. It will combine: • Reminders for the patient / caregiver about the risk of self-medication and excessive consumption of grapefruit products, and importance of showing the card to any HCP. • Information for any HCP regarding DDIs and provide contact points for additional information**.**
Plans to evaluate the effectiveness of the interventions and criteria for success	Drug utilization studies in patients treated with CERDELGA using electronic health care records will be performed to evaluate physician understanding of important risks involving DDIs clinical actions. Criteria for success: • Estimation of the proportion, type and duration of concomitant medication use (CYP2D6 and CYP3A strong/moderate or weak inhibitors, strong CYP3A inducers, P-gp and CYP2D6 substrates) in patients treated with CERDELGA. • United States DUS final report (sign-off date: 05-Nov-2018, see [Annex 2]) concludes that based on data from US patients in the ICGG Gaucher Registry, suggested compliance with CYP2D6 genotype testing in the US is high. While data from the MarketScan database indicate that up to 25% of patients are prescribed some CMIs after they have initiated eliglustat therapy, there was no

	evidence that patients on eliglustat were prescribed CMIs in contraindicated situations that could have led to significant drug-drug interactions.

CMI: Concomitant Medication of Interest; CYP: Cytochrome P450; DDI: Drug-Drug Interaction; DUS: Drug Utilization Study; EM: Extensive Metabolizer; ICGG: International Collaborative Gaucher Group; HCP: Healthcare Professional; P-gp: P-Glycoprotein; PM: Poor Metabolizer; US: United States.

V.3 SUMMARY OF RISK MINIMIZATION MEASURES

Table 39 - Summary table of pharmacovigilance activities and risk minimization activities by safety concern

Safety concern	Risk minimization measures	Pharmacovigilance activities
Drug-drug interaction: Use with CYP2D6 and/or CYP3A inhibitors - Use with strong CYP3A inducers - Use with P-gp or CYP2D6 substrates	**Routine risk minimization measures:** • Labeled in sections 4.2, 4.3, 4.4, 4.5 and 5.2 of SmPC. • Labeled in sections 2 and 3 of PIL. **Additional risk minimization measures:** • Guide for Prescriber • Patient Card	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** Drug utilization study in Europe.
Use of eliglustat in patients who are indeterminate metabolizers or non-genotyped patients	**Routine risk minimization measures:** • Labeled in sections 4.1, 4.2 and 5.2 of SmPC. • Labeled in sections 2 and 3 of PIL. • Before initiation of treatment with CERDELGA, patients should be genotyped for CYP2D6 to determine the CYP2D6 metabolizer status. **Additional risk minimization measures:** Guide for Prescriber	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** Prospective ICGG safety sub-registry.
Cardiac conduction disorders and arrhythmias	**Routine risk minimization measures:** • Labeled in sections 4.3, 4.4 and 4.5 of SmPC • Labeled in section 2 of PIL. **Additional risk minimization measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** None
Use in patients with a history of or current cardiac ischemia or heart failure, clinically significant arrhythmias or conduction findings	**Routine risk minimization measures:** • Labeled in section 4.4 of SmPC. • Labeled in section 2 of PIL. **Additional risk minimization measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** None
Use during pregnancy and lactation	**Routine risk minimization measures:** • Labeled in section 4.6 of SmPC. • Labeled in section 2 of PIL.	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:**

Safety concern	Risk minimization measures	Pharmacovigilance activities
	Additional risk minimization measures: None	None **Additional pharmacovigilance activities:** None
Safety in long-term treatment use	**Routine risk minimization measures:** None **Additional risk minimization measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** Prospective ICGG safety sub-registry.
Use in patients who are CYP2D6 ultra-rapid metabolizers	**Routine risk minimization measures:** • Labeled in sections 4.2 and 4.4 of SmPC. • Labeled in section 2 of PIL. **Additional risk minimization measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** Prospective ICGG safety sub-registry.

CYP: Cytochrome P450; ICGG: International Collaborative Gaucher Group; P-gp: P-Glycoprotein; PIL: Patient Information Leaflet; SmPC: Summary of Product Characteristics.

RISK MANAGEMENT PLAN - PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN

Summary of risk management plan for CERDELGA (Eliglustat)

This is a summary of the risk management plan (RMP) for CERDELGA. The RMP details important risks of CERDELGA how these risks can be minimized, and how more information will be obtained about CERDELGA's risks and uncertainties (missing information).

CERDELGA's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals (HCPs) and patients on how CERDELGA should be used.

This summary of the RMP for CERDELGA should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of CERDELGA's RMP.

I. THE MEDICINE AND WHAT IT IS USED FOR

CERDELGA is authorized for the long-term treatment of adult patients with Gaucher disease type 1 (GD1). The target population is patients who are Cytochrome P4502D6 poor metabolizers (PMs), intermediate metabolizers (IMs) or extensive metabolizers (EMs) (see SmPC for the full indication). CERDELGA is proposed for paediatric patients with GD1 who are 6 years and older with a minimum body weight of 15 kg, who are stable on enzyme replacement therapy (ERT), and who are CYP2D6 PMs, IMs or EMs. (see SmPC for the full indication). It contains eliglustat as the active substance and it is given by oral route of administration.

Further information about the evaluation of CERDELGA's benefits can be found in CERDELGA's EPAR, including in its plain-language summary, available on the European Medicines Agency (EMA) website, under the medicine's webpage:

https://www.ema.europa.eu/en/documents/overview/CERDELGA-epar-medicine-overview_en.pdf

II. RISKS ASSOCIATED WITH THE MEDICINE AND ACTIVITIES TO MINIMIZE OR FURTHER CHARACTERIZE THE RISKS

Important risks of CERDELGA, together with measures to minimize such risks and the proposed studies for learning more about CERDELGA's risks, are outlined in the next sections.

Measures to minimize the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and HCPs;

- Important advice on the medicine's packaging;
- The authorized pack size - the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status - the way a medicine is supplied to the patient (eg, with or without prescription) can help to minimize its risks.

Together, these measures constitute routine risk minimization measures.

In the case of CERDELGA, these measures are supplemented with additional risk minimization measures mentioned under relevant important risks, outlined in the next sections.

In addition to these measures, information about adverse reactions is collected continuously and regularly analyzed, including periodic safety update report (PSUR) assessment so that immediate action can be taken as necessary. These measures constitute routine pharmacovigilance activities.

If important information that may affect the safe use of CERDELGA is not yet available, it is listed under "missing information" outlined in the next section.

II.A List of important risks and missing information

Important risks of CERDELGA are risks that need special risk management activities to further investigate or minimize the risk, so that the medicinal product can be safely taken. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of CERDELGA. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (eg, on the long-term use of the medicine);

Table 40 - List of important risks and missing information

Important identified risk	None
Important potential risks	Drug-drug interactions - Use with CYP2D6 and/or CYP3A inhibitors - Use with strong CYP3A inducers - Use with P-gp or CYP2D6 substrates Use of eliglustat in patients who are CYP2D6 indeterminate metabolizers or non-genotyped patients Cardiac conduction disorders and arrhythmias
Missing information	Use in patients with a history of or current cardiac ischemia or heart failure, clinically significant arrhythmias or conduction findings Use during pregnancy and lactation Safety in long-term treatment use Use in patients who are CYP2D6 ultra-rapid metabolizers

CYP: Cytochrome P450; P-gp: P-Glycoprotein.

II.B Summary of important risks

Table 41 - Important risks with corresponding risk minimization activities and additional pharmacovigilance activities: Drug-drug interactions - Use with CYP2D6 and/or CYP3A inhibitors - Use with strong CYP3A inducers - Use with P-gp or CYP2D6 substrates

Important potential risk: Drug-drug interactions - Use with CYP2D6 and/or CYP3A inhibitors - Use with strong CYP3A inducers - Use with P-gp or CYP2D6 substrates	
Evidence for linking the risk to the medicine	Drug-drug interaction studies were conducted in healthy volunteers to investigate potential interactions between eliglustat and other drugs that are CYP2D6 or CYP3A inhibitors, CYP3A inducers, or P-gp or CYP2D6 substrates. Additionally, PBPK simulations were performed to evaluate Genz-99067 exposure under various scenarios of co-administration with interacting drug. **For strong/moderate/weak CYP2D6 inhibitors**: GZGD02007; SIM0106; SIM0319 **For strong/moderate/weak CYP3A inhibitors:** GZGD01807; SIM0106; SIM0170 and SIM0183, SIM0319 **Use of strong/moderate CYP2D6 inhibitor and strong/moderate CYP3A inhibitor:** SIM0105; SIM0106 **For Strong CYP3A inducer:** GZGD02407 **For P-gp inhibition:** GZGD03610 **For CYP2D6 inhibition:** GZGD04112; SIM0105
Risk factors and risk groups.	• Patients with hepatic impairment. • Consumption of grapefruit products (CYP3A inhibitors).
Risk minimization measures	**Routine risk minimization measures:** • Labeled in sections 4.2, 4.3, 4.4, 4.5 and 5.2 of SmPC. • Labeled in sections 2 and 3 of PIL. **Additional risk minimization measures:** • Guide for Prescriber. • Patient Card.
Additional pharmacovigilance activities	Drug utilization study in Europe (ELIGLC06913).

CYP: Cytochrome P450; PBPK: Physiologically Based Pharmacokinetic; P-gp: P-Glycoprotein; SmPC: Summary of Product Characteristics

Table 42 - Important risks with corresponding risk minimization activities and additional pharmacovigilance activities: Use of eliglustat in patients who are CYP2D6 indeterminate metabolizers or non-genotyped patients

Important potential risk: Use of eliglustat in patients who are CYP2D6 indeterminate metabolizers or non-genotyped patients	
Evidence for linking the risk to the medicine	POH0373, SIM0105, SIM0183, and clinical studies.
Risk factors and risk groups.	Not applicable

Important potential risk: Use of eliglustat in patients who are CYP2D6 indeterminate metabolizers or non-genotyped patients	
Risk minimization measures	**Routine risk minimization measures:** • Labeled in sections 4.1, 4.2 and 5.2 of SmPC. • Labeled in sections 2 and 3 of PIL. • Before initiation of treatment with CERDELGA, patients should be genotyped for CYP2D6 to determine the CYP2D6 metabolizer status. **Additional risk minimization measures:** Guide for Prescriber
Additional pharmacovigilance activities	Prospective ICGG safety sub-registry (OBS14099).

CYP: Cytochrome P450; ICGG: International Collaborative Gaucher Group; SmPC: Summary of Product Characteristics.

Table 43 - Important risks with corresponding risk minimization activities: Cardiac conduction disorders and arrhythmias

Important potential risk: Cardiac conduction disorders and arrhythmias	
Evidence for linking the risk to the medicine	ISS; ISS ECG Report; GZGD00304, GZGD02507; GZGD02607; GZGD03109; EFC13738; Aggregate AE Report.
Risk factors and risk groups.	Cardiac conduction disorders Patients with a prior history of conduction disease are more likely to experience blocks. There is an increased risk of first-degree block with increased age as well as some medical conditions (eg, IHD, congenital heart disease, drugs, alcohol use, thyroid disease). Mobitz 1 second degree AV block can occur in normal subjects, athletes, older adults, and in patients with certain heart diseases or who are taking drugs that block the AV node (eg, digoxin, beta blockers, calcium channel blockers). Ventricular arrhythmia Patients with compromised heart function such as cardiomyopathy, heart failure and ischemia are at increased risk for ventricular arrhythmia. Coronary heart disease was identified as the underlying cause of 62% of sudden cardiac deaths. Higher rates of sudden cardiac death were associated with increased age and male gender. (69) Patients with congenital long QT syndrome are at greater risk for a long QTc interval. The use of medications that are known torsadogens or potential torsadogens are also known to increase the QTc interval, which may put a patient at increased risk of Torsade de Pointes. The effect of taking multiple drugs may be additive. Use of concomitant CYP2D6 and CYP3A inhibitors Extensive metabolizers and IMs using concomitant strong or moderate CYP2D6 inhibitors together with strong or moderate CYP3A inhibitors, and PMs using a strong CYP3A inhibitor are at increased risk to achieve substantially elevated eliglustat exposure which could potentially lead to increases in ECG intervals. Hepatic impairment Since metabolism is the predominant route of elimination, CYP2D6 IM and PM patients with any degree of HI and CYP2D6 EM patients with moderate and severe HI, as well as CYP2D6 EM patients with mild HI using a strong or moderate CYP2D6 inhibitor, are at increased risk to achieve substantially elevated eliglustat exposure which could potentially lead to increases in ECG intervals.

Important potential risk: Cardiac conduction disorders and arrhythmias	
Risk minimization measures	**Routine risk minimization measures:** • Labeled in sections 4.3, 4.4 and 4.5 of SmPC. • Labeled in section 2 of PIL. **Additional risk minimization measures:** None

AE: Adverse Event; AV: Atrioventricular; CYP: Cytochrome P450; ECG: Electrocardiogram; EM: Extensive Metabolizer; HI: Hepatic Impairment; IHD: Ischemic Heart Disease; IM: Intermediate Metabolizer; ISS: Integrated Safety Summary; PM: Poor Metabolizer; PIL: Patient Information Leaflet; SmPC: Summary of Product Characteristics.

Table 44 - Missing information with corresponding risk minimization activities: Use in patients with a history of or current cardiac ischemia or heart failure, clinically significant arrhythmias or conduction findings

Missing Information: Use in patients with a history of or current cardiac ischemia or heart failure, clinically significant arrhythmias or conduction findings	
Risk minimization measures	**Routine risk minimization measures:** • Labeled in section 4.4 of SmPC. • Labeled in section 2 of PIL. **Additional risk minimization measures:** None

PIL: Patient Information Leaflet; SmPC: Summary of Product Characteristics.

Table 45 - Missing information with corresponding risk minimization activities: Use during pregnancy and lactation

Missing information: Use during pregnancy and lactation	
Risk minimization measures	**Routine risk minimization measures:** • Labeled in section 4.6 of SmPC. • Labeled in section 2 of PIL. **Additional risk minimization measures:** None

PIL: Patient Information Leaflet; SmPC: Summary of Product Characteristics.

Table 46 - Missing information with corresponding additional pharmacovigilance activities: Safety in long-term treatment use

Missing information: Safety in long-term treatment use	
Risk minimization measures	**Routine risk minimization measures:** None **Additional risk minimization measures:** None
Additional pharmacovigilance activities	Prospective ICGG safety sub-registry (OBS14099).

ICGG: International Collaborative Gaucher Group.

Table 47 - Missing information with corresponding risk minimization activities additional pharmacovigilance activities: Use in patients who are CYP2D6 ultra-rapid metabolizers

Missing information: Use in patients who are CYP2D6 ultra-rapid metabolizers	
Risk minimization measures	**Routine risk minimization measures:** • Labeled in sections 4.2 and 4.4 of SmPC. • Labeled in section 2 of PIL. **Additional risk minimization measures:** None
Additional pharmacovigilance activities	Prospective ICGG safety sub registry (OBS14099).

ICGG: International Collaborative Gaucher Group; PIL: Patient Information Leaflet; SmPC: Summary of Product Characteristics.

II.C Post-authorization development plan

II.C.1 Studies which are conditions of the marketing authorization

The following studies are conditions of the marketing authorization:

Table 48 - Studies which are conditions of the marketing authorization

Prospective ICGG safety sub-registry (OBS14099)
Purpose of the study: A prospective ICGG safety sub registry to characterize the long-term safety profile of eliglustat. To describe the patient's characteristics and utilization patterns.

ICGG: International Collaborative Gaucher Group.

II.C.2 Other studies in post-authorization development plan

Table 49 - Other studies in post-authorization development plan

Drug utilization study of eliglustat in Europe using electronic healthcare records (ELIGLC06913)
Purpose of the study: To assess compliance/adherence to the labeling with regard to drug-drug interactions.

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RISK MANAGEMENT PLAN - PART VII: ANNEXES

ANNEX 4 SPECIFIC ADVERSE DRUG REACTION FOLLOW-UP FORMS

NOT APPLICABLE

ANNEX 6 DETAILS OF PROPOSED ADDITIONAL RISK MINIMIZATION ACTIVITIES

Draft key messages of the additional risk minimization measures

1. **Physician educational material:**
    - The Summary of Product Characteristics
    - Guide for prescriber
    - Patient card

1.1 Guide for prescriber:

The prescriber guide shall contain the following key elements:

- CERDELGA is indicated for the long-term treatment of adult patients with Gaucher disease type 1 (GD1). CERDELGA is also indicated for paediatric patients with GD1 who are 6 years and older with a minimum body weight of 15 kg, who are stable on enzyme replacement therapy (ERT), and who are CYP2D6 poor metabolizers (PMs), intermediate metabolisers (IMs) or extensive metabolisers (EMs).
- Before initiation of treatment with CERDELGA, patients must be genotyped for CYP2D6 to determine the CYP2D6 metaboliser status. CERDELGA is indicated in patients who are CYP2D6 PMs, IMs or EMs.
- For adult patients: The recommended dose is 84 mg eliglustat twice daily in CYP2D6 IMs and EMs. The recommended dose is 84 mg eliglustat once daily in CYP2D6 PMs.
- For paediatric patients: The recommended dose regimen in CYP2D6 IMs, EMs and PMs is as below:

Weight	CYP2D6 EMs and IMs	CYP2D6 PMs
≥ 50 kg	84 mg twice daily	84 mg once daily
25 to < 50 kg	84 mg twice daily	42 mg once daily
15 to < 25 kg	42 mg twice daily	21 mg once daily

- Patients should be informed that consumption of grapefruit or its juice should be avoided.
- Eliglustat is contraindicated in patients who are CYP2D6 IMs or EMs who are taking a strong or moderate CYP2D6 inhibitor concomitantly with a strong or moderate CYP3A inhibitor. Eliglustat is also contraindicated in patients who are CYP2D6 PMs taking a strong CYP3A inhibitor. Use of eliglustat under these conditions results in substantially elevated plasma concentrations of eliglustat. This may cause mild increases in the PR, QRS, and QTc intervals.
- Use of eliglustat with strong CYP3A inducers substantially decreases the exposure to eliglustat, which may reduce the therapeutic effectiveness; therefore concomitant administration is not recommended. Use of a moderate CYP3A inhibitor with eliglustat is not recommended in PMs.
- A once daily dose of eliglustat is recommended when a strong CYP2D6 inhibitor is used concomitantly in IMs and EMs.

- Caution should be used with moderate CYP2D6 inhibitors in IMs and EMs. Caution should be used with strong or moderate CYP3A inhibitors in IMs and EMs. Caution should be used with weak CYP3A inhibitors in PMs.
- In CYP2D6 EMs with severe hepatic impairment, CERDELGA is contraindicated. In CYP2D6 EMs with mild or moderate hepatic impairment taking a strong or moderate CYP2D6 inhibitor, CERDELGA is contraindicated.
- In CYP2D6 EMs with mild hepatic impairment taking a weak CYP2D6 inhibitor or a strong, moderate or weak CYP3A inhibitor, a once daily dose of eliglustat is recommended.
- In CYP2D6 IMs or PMs with any degree of hepatic impairment, CERDELGA is not recommended.

1.2 <u>Patient card</u>:

The patient card shall contain the following key elements:

- Information for healthcare professionals:
  - This patient is using eliglustat (CERDELGA) for the treatment of Gaucher disease type 1.
  - Eliglustat should not be used concomitantly with medicines that may have an impact on liver enzymes that play a role in the metabolism of eliglustat. In addition, patient's hepatic or renal status may have an impact on the metabolism of eliglustat.
  - Using eliglustat together with such products or in patients with hepatic or renal impairment may either make eliglustat less effective, or it may increase the eliglustat levels in the patient's blood.
- Information for the patient / caregiver:
  - Always consult the doctor who prescribed eliglustat before you start using other medicines.
  - Do not consume grapefruit products.

2. <u>The patient information pack</u>:

- Patient information leaflet
- Patient card