Australian Government
Department of Health
Therapeutic Goods Administration

Australian Public Assessment Report for Eliglustat (as tartrate)

Proprietary Product Name: Cerdelga/Eliglustat Genzyme

Sponsor: Sanofi-Aventis Australia Pty Ltd

August 2015

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health and is responsible for regulating medicines and medical devices.
- The TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance), when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website < https://www.tga.gov.au>.

About AusPARs

- An Australian Public Assessment Record (AusPAR) provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve a prescription medicine submission.
- AusPARs are prepared and published by the TGA.
- An AusPAR is prepared for submissions that relate to new chemical entities, generic medicines, major variations, and extensions of indications.
- An AusPAR is a static document, in that it will provide information that relates to a submission at a particular point in time.
- A new AusPAR will be developed to reflect changes to indications and/or major variations to a prescription medicine subject to evaluation by the TGA.

Contents

List of commonly used abbreviations

Abbreviation	Meaning
AE	Adverse event
Ae	Amount excreted
ALB	Albumin
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANCOVA	Analysis of covariance
ANOVA	Analysis of variance
AST	Aspartate aminotransferase
$AUC_{(0\text{-}4h)}$	Area under the plasma concentration versus time curve from time zero to 4 hours post-dose
$AUC_{(0\text{-}12h)}$	Area under the plasma concentration versus time curve from time zero to 12 hours post-dose
$AUC_{(0\text{-}24h)}$	Area under the plasma concentration versus time curve from time zero to 24 hours post-dose
$AUC_{(0\text{-}inf[\infty])}$	Area under the plasma concentration versus time curve from time zero extrapolated to infinity
$AUC_{(0\text{-}last)}$	Area under the plasma concentration time curve from time zero to the time of the last concentration
ALLOQ	above the lower limit of quantification
$AUC_{(0\text{-}tau)}$	Area under the plasma concentration over the dosing interval
BCRP	Breast cancer resistance protein
bd	Twice daily
BMB	Bone marrow burden
BMD	Bone mineral density
BMI	Body mass index
BPI	Brief Pain Inventory
BQL	Below quantifiable levels
BSEP	Bile salt export pump

Abbreviation	Meaning
CCL18	Chemokine CC motif ligand 18
CHMP	Committee for Human Medicinal Products
CI	Confidence interval
CL	Total body clearance
CL/F	Apparent total body clearance
CLr	Renal clearance
C_{max}	Maximum observed plasma concentration
CNS	Central nervous system
CRCL	Creatinine clearance
CRF	Case report form
CSR	Clinical study report
Ctrough	Trough plasma concentration
CV	Confidence interval
CYP	Cytochrome P450
CYP3A	Cytochrome P450 3A subfamily (including 3A4, 3A5, and 3A7)
DDI	Drug-drug interaction
DLT	Dose-limiting toxicity
DMC	Data Monitoring Committee
DS3	Gaucher Disease Severity Scoring System during repeat dosing
DXA	Dual energy X-ray absorptiometry
ECG	Electrocardiogram
ECHO	Echocardiogram
eGFR	Estimated glomerular filtration rate
EM	Extensive Metaboliser
ERT	Enzyme replacement therapy
EU	European Union
F	Absolute oral bioavailability

Abbreviation	Meaning
FAS	Full Analysis Set
FDA	Food and Drug Administration
FSS	Fatigue Severity Score
GCP	Good Clinical Practice
GD1	Gaucher disease type 1
GFR	Glomerular filtration rate
GGT	Gamma glutamyl transferase
GL-1	Glucosylceramide
GM3	Monosialodihexosyl ganglioside
GMR	Ratio of geometric means
HDL	High density lipoprotein
HLGT	High level group term
HLT	High level term
HPLC	High performance liquid chromatography
HR	Heart rate
IAB	Independent Adjudication Board
IAR	Infusion-associated reaction
IC50	Half-maximal inhibitory concentration
ICGG	International Collaborative Gaucher Group
ICH	International Conference of Harmonisation
IM	Intermediate Metaboliser
ISS	Integrated Summary of Safety
ITT	Intent to Treat
IV	Intravenous
LC-MS/MS	Liquid chromatography with tandem mass spectrometry
LDL	Low density lipoprotein
LLOQ	Lower limit of quantification

Abbreviation	Meaning
LOCF	Last observation carried forward
LS	Least squares
LV	Left ventricular
MCV	Mean corpuscular volume
MDR1	Multi-drug resistance protein 1
MedDRA	Medical Dictionary for Regulatory Activities
MIP-1□	Macrophage inflammatory protein 1β
MMA	Methylmalonic acid
MMSE	Mini Mental State Examination
MN	Multiples of normal
MRI	Magnetic resonance imaging
ms	Millisecond
N/Av	Not available
NA	Not applicable
NADPH	Nicotinamide adenine dinucleotide phosphate (reduced form);
NSAID	Non-steroidal anti-inflammatory drug
OAT	Organic anion transporter
OATP	Organic anion transporting polypeptide
OCT	Organic cation transporter
P-gp	P-glycoprotein
PAP	Primary analysis period
PBPK	Physiologically-based pharmacokinetics
PCSA	Potentially clinically significant abnormality
PD	Pharmacodynamics
PK	Pharmacokinetics
PopPK	Population pharmacokinetics
PPS	Per Protocol Set

Abbreviation	Meaning
PT	Preferred term
q2w	Every two weeks
qd	Once daily
QOL	Quality of life
QT	The time between the start of the Q wave and the end of the T wave in the heart's electrical cycle.
QTc	Heart-rate corrected QT interval
QTcF	Heart-rate corrected QT interval using Fridericia's correction
RBC	Red blood cell
ROW	Rest of the world
SAP	Statistical analysis plan
SD	Standard deviation
SE	Standard error
SEM	Standard error of the mean
SF-36	Medical Outcomes Study 36-item Short Form
SOC	System organ class
SRT	Substrate reduction therapy
t1/2	Terminal elimination half-life
TEAE	treatment-emergent adverse event
tmax	Time of maximum observed plasma concentration
TQT	Thorough QT study
ULN	Upper limit of normal
URM	Ultra-Rapid Metaboliser
UTI	Urinary tract infection
VPC	Visual predictive check
Vz	Volume of distribution during the terminal phase
Vz/F	Apparent volume of distribution during the terminal phase

I. Introduction to product submission

Submission details

Type of submission:	New chemical entity
Decision:	Approved
Date of decision:	10 February 2015
Active ingredient(s):	Eliglustat (as tartrate)
Product name(s):	Cerdelga/Eliglustat Genzyme
Sponsor's name and address:	Sanofi-Aventis Australia Pty Ltd 12-24 Talavera Road Macquarie Park, NSW 2113
Dose form(s):	Capsule
Strength(s):	84 mg
Container(s):	Blister pack
Pack size(s):	56 capsules
Approved therapeutic use:	*Cerdelga is indicated for the long-term treatment of adult patients with Gaucher disease type 1 (GD1).*
Route(s) of administration:	Oral (PO)
Dosage:	The recommended dose of Cerdelga in CYP2D6 IMs and EMs is 84 mg twice daily taken orally. The recommended dose in CYP2D6 PMs is 84 mg once daily taken orally.[1]
ARTG number (s):	218171, 218172

Product background

This AusPAR describes the application by the sponsor to register eliglustat (Cerdelga®) hard capsule for oral administration in dosage strength of 84 mg of eliglustat (equivalent to 100 mg eliglustat tartrate) for the treatment of Gaucher disease.

Eliglustat is a member of a novel class of glucosylceramide (GL-1) synthase inhibitors that acts as substrate reduction therapy for Gaucher disease Type 1 (GD1).

Gaucher disease is caused by a deficiency of glucocerebrosidase resulting in the accumulation of its major natural substrate, glucosylceramide, particularly in the liver, spleen, and bone marrow. Inhibition of glucosylceramide synthase by eliglustat results in a

[1] IM=Intermediate metaboliser; EM=Extensive metaboliser; PM=Poor metaboliser. CYP2D6=Cytochrome P450 isozyme 2D6.

reduction in the accumulation of glucosylceramide, allowing residual endogenous glucocerebrosidase levels to clear the substrate.

The chemical structure of eliglustat is distinct from miglustat[2] although both share the same target enzyme; glucosylceramide synthase (substrate reduction therapy). Miglustat resembles the glucose moiety, whereas eliglustat is similar to the ceramide moiety of glucosylceramide.

Three drugs are currently registered in Australia for the treatment of GD. These include 2 enzyme replacement therapies (ERT) imiglucerase and velaglucerase, both for administration by parenteral route and one substrate reduction therapy (SRT) miglustat for administration by oral route. All are for the treatment of GD Type 1 which is the most common form of disease, usually without neurological involvement and with survival into adult age.

Regulatory status

This is an application to register a new chemical entity in Australia.

Eliglustat was designated an 'orphan drug' on 2 August 2013 for the proposed use in adult GD1 patients.

Eliglustat is currently under review in Europe under Centralised Procedure. The CHMP has raised additional questions on dosing in Poor Metabolisers (PM). Eliglustat was approved by FDA on August 19, 2014 including use in PM patients (reduced dose of 84 mg once daily).

An application for Cerdelga 84 mg capsule has been submitted to Japan.

A summary of the current regulatory status is provided in Table 1 below.

Table 1: International regulatory status

Country	Status	Approved indications
EU	**Pending**	**Not applicable**
USA	**Approved** **19 August 2014**	Cerdelga is indicated for the long-term treatment of adult patients with Gaucher disease type 1 (GD1) who are CYP2D6 extensive metabolisers (EMs), intermediate metabolisers (IMs), or poor metabolisers (PMs) as detected by an FDA-cleared test.
Japan	**Pending**	**Not applicable**

Product Information

The approved Product Information (PI) current at the time this AusPAR was prepared can be found as Attachment 1. For the most recent Product Information please refer to the TGA website at < https://www.tga.gov.au/product-information-pi>.

[2]Registered as Zavesca in Australia for:
the oral treatment of patients with mild to moderate Type 1 Gaucher disease, for whom enzyme replacement therapy is not a therapeutic option. Zavesca® is indicated for the treatment of progressive neurological manifestations in adult and paediatric patients with Niemann-Pick type C disease.

II. Quality findings

Introduction (if applicable)

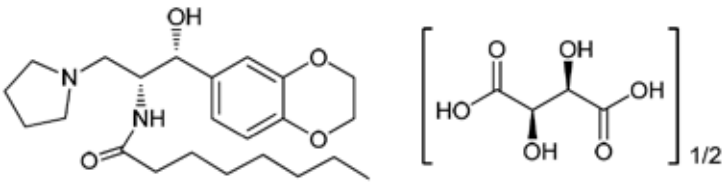
The recommended dose is one capsule twice daily, with or without food.

Eliglustat tartrate is not subject to British Pharmacopeia (BP)/European Pharmacopiea (Ph.Eur.) or US Pharmacopeia (USP) monographs.

Drug substance (active ingredient)

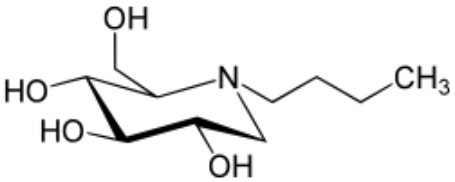
Eliglustat tartrate has the following structure (Figure 1):

Figure 1: Chemical structure of Eliglustat tartrate



Eliglustat is related to miglustat which is also used to treat Gaucher disease (structure below in Figure 2)). Miglustat is formulated as a 100 mg capsule.

Figure 2: Structure of miglustat



Eliglustat tartrate is manufactured by chemical synthesis. The active base contains two chiral centres and is chirally pure (1*R*, 2*R*).

Eliglustat has a pKa of 8.79. It is very soluble in water and across the physiological pH range. It is manufactured as white to off-white crystalline powder, as a single polymorphic form. No other stable polymorphs have been observed.

The drug substance specifications include limits for eight specified impurities and limits for the three other stereoisomers of eliglustat (1*S*, 2*R*), (1*R*, 2*S*) and (1*S*, 2*S*). Due to the high aqueous solubility of eliglustat tartrate, particle size is not controlled.

The drug substance exhibits good stability and the data provided supports a retest period of 60 months.

Drug product

The drug product is an immediate release oral capsule containing 84 mg of eliglustat (as tartrate).

The capsules are size 2 hard gelatin capsules and consist of a pearl blue-green opaque cap and a pearl white opaque body capsule with 'GZ02' printed in black on the capsule. The formulation includes glycerol dibehenate as a lubricant which is somewhat unusual but its presence at similar levels in other registered oral products is precedented. The other excipients are conventional for the dosage form.

The capsule fill is manufactured by conventional processes by wet granulation process. The capsules are packaged into Aluminium/Aclar blisters.

Stability data generated under long-term, intermediate and accelerated conditions support a shelf-life of 24 months when stored below 25°C.

The finished product aspects are acceptable.

Biopharmaceutics

During development, the 84 mg eliglustat capsule was referred to as a 100 mg capsule (as it contains 100 mg of eliglustat tartrate). This nomenclature for the 84 mg capsule strength and the other corresponding strengths is used below.

The following bioavailability and bioequivalence data were submitted:

Study GZGD02107 showed that absolute oral bioavailability (F) was about 4.49% ± 4.13% based on the mean dose-normalised area under the concentration versus time curve from time 0 to infinity ($AUC_{0-\infty}$) ($AUC_{0-\infty}/D$) for eliglustat. Eliglustat bioavailability is limited by extensive first-pass metabolism.

Study GZGD00404 assessed the food effect on single oral doses of 300 mg eliglustat (Phase Ib formulation) administered under fasting conditions or following a high-fat meal. Administration of eliglustat with a high-fat meal resulted in an approximately 15% reduction in mean peak plasma concentration (C_{max}) and 1 hour delay in the median time to C_{max} (T_{max}) relative to fasted administration. There was no change in the extent of absorption, with geometric mean ratios of 105% for AUC_{0-t} and 104% for $AUC_{0-\infty}$, and 90% confidence intervals (CIs) for both parameters contained within the (80%, 125%) equivalence range. The company considers these results support the recommendation that the capsules may be administered without regard to meals. Eliglustat was administered without regard to meals in the Phase II and Phase III studies.

The Phase Ib, II and III formulations had the same qualitative composition as the proposed commercial product. The quantitative composition was different between the 50 mg and 100 mg capsules used during early clinical development to accommodate the same capsule shell size (size 2) across the formulations. The applicant reformulated the 50 mg capsules in late Phase III to use the same common blend as the 100 mg capsules. The Phase III 100 mg formulation is the same as the proposed commercial formulation.

Study GZGD03811 assessed the relative bioavailability between the earlier 50 mg Phase III formulation (3 x 50 mg tablets) and the proposed commercial common blend formulation (1 x 150 mg dose) under fasting conditions. The study showed that the two formulations were bioequivalent for $AUC_{0-\infty}$, AUC_{0-last}, and C_{max}.

During Phase III, the capsule shell was also changed to include a pearlescent colorant (proposed for the commercial capsules). There are no concerns regarding this change affecting the performance of the capsules.

Quality summary and conclusions

A number of deficiencies and other issues requiring resolution before the product can be recommended for approval were identified during the evaluation and have been referred to the applicant for comment or resolution. These issues are minor and are expected to be easily resolved before registration of the product.

Apart from these issues, registration is recommended in respect of chemistry, manufacturing and controls and biopharmaceutics to registration of this product.

III. Nonclinical findings

Introduction

Eliglustat is an L-tartaric acid salt that exists in plasma as a free base, Genz-99067, which is the active moiety. Throughout this section, Genz-99067 is used when referring to drug exposure (such as plasma concentrations) and eliglustat is used in all other instances.

The general quality of the submitted nonclinical studies was reasonable, although pharmacokinetic data was limited in some studies.

The range of studies was consistent with EU guidelines. Pivotal studies examining repeat-dose toxicity and reproduction/development were conducted under Good Laboratory Practice (GLP) conditions. The exposure ratios are adequate to address the clinical relevance of the observed toxicities.

Two studies on juvenile animals were evaluated noting that the currently proposed indication does not include the paediatric population.

Pharmacology

Mechanism of action

Eliglustat is an inhibitor of glucosylceramide synthase, which is the enzyme responsible for the synthesis of glucosylceramide. Glucosylceramide (GL-1) is a major substrate for β-glucosidase which is deficient in Gaucher disease patients. Reducing the available substrate for β-glucosidase in these patients prevents glucosylceramide accumulation and is reported to reduce related pathology in the spleen, liver and bone marrow.

Primary pharmacology

In vitro studies demonstrated similar inhibition of glucosylceramide synthetase by eliglustat free base in human K562 erythroleukaemic cells (50% inhibitory concentration (IC_{50}) 28 nM) and canine DH-82 macrophage cells (IC_{50} 77 nM), and by eliglustat in mouse B16 melanoma cells (IC_{50} 57 nM). Eliglustat also inhibited glucosylceramide synthetase in microsomes derived from A375 melanoma cells (IC_{50} 20 nM). In vitro inhibition by eliglustat occurred at dose levels well below the clinical exposure (based on C_{max}). Metabolites of eliglustat also inhibited glucosylceramide synthetase in mouse B16 cells (IC_{50} 1.54 to >10 μM) and in microsomes from A375 melanoma cells (IC_{50} 1.09 to >30 μM), but at concentrations exceeding the clinical exposure (based on C_{max}). In vitro enzyme inhibition was similar in intact human cells and in microsomes derived from human cells.

In vivo studies were conducted in a mouse model of Gaucher disease, namely, D409V/null Gaucher type 1 mice. Eliglustat prevented the accumulation of GL-1 in the liver, lung and spleen in this mouse strain following administration either by gavage (150 mg/kg/day) or in the feed (150 to 450 mg/kg/day) over several weeks. A dose of 150 mg/kg/day in mice is approximately equivalent to the clinical exposure, based on AUC; however, only limited pharmacokinetic data are available from a 14 day study, with no data available from the 13 week study. At higher dose levels (450 mg/kg/day), the count of enlarged macrophages (Gaucher cells) in the liver was significantly lower. Eliglustat was also able to enhance treatment with Cerezyme, a recombinant human β-glucosidase by preventing re-accumulation of GL-1 after cessation of Cerezyme treatment. In normal Sprague-Dawley (SD) rats, eliglustat (50 mg/kg/day for 4 days) reduced GL-1 levels by 30%. In normal dogs, eliglustat (up to 25 mg/kg/day for 4 weeks, or 10 mg/kg/day for 13 weeks) reduced

GL-1 levels by approximately 50%. These dose levels in both rats and dogs were above the clinical exposure, based on AUC. No rat or dog models of Gaucher disease were available.

Secondary pharmacodynamics

In vitro receptor binding assays examined the potential for secondary activity of eliglustat in screening assays examining a broad range of receptors, transporters and ion channels. Significant activity (>46 to 50% inhibition) was demonstrated for 10 assays (dopamine receptor subtypes D_{2S}, D_3, $D_{4.4}$, μ-opioid, serotonin receptor subtypes 5-HT_{1A}, 5-HT_{2A}, 5-HT_{2B}, 5-HT_6, non-specific sigma and the L-type calcium (Ca^{2+}) channel) at 10 μM (4.2 μg/mL) which is 100 times the clinical exposure, based on C_{max}. In Chinese hamster ovary cells overexpressing 5-HT_{2B}, there was no significant stimulant activity of 5-HT_{2B} (associated with valvular heart disease[3]) by eliglustat at 100 μM (42 μg/mL), which is 1000 times the clinical exposure, based on C_{max}. These effects are not considered to be clinically relevant.

Safety pharmacology

Safety pharmacology studies examined the potential acute effects of eliglustat on cardiovascular, gastrointestinal, renal, respiratory and central nervous system (CNS) functions.

Effects on cardiac conduction were observed in vitro and in vivo. There was significant inhibition by eliglustat in vitro of potassium (K+) tail current (hERG) (IC_{50} 0.35 μg/mL), the sodium (Na+) channel (hNav1.5 channel) (IC_{50} 5.2 μg/mL), and Ca2+ (hCav1.2) channel (IC_{50} 10.4 μg/mL). These values are approximately 8, 117 and 240 times the clinical exposure, based on C_{max}. Ten eliglustat metabolites were also tested, with only Genz-256222 showing any appreciable inhibition of K^+ (hERG), Na^+ and Ca^{2+} channels (IC_{50} of 1.8, 13 and 18 μg/mL, respectively).

In Purkinje fibres isolated from dogs, eliglustat produced modest (approximately 10%), rate-dependent reductions in both action potential duration at 0.3 μg/mL and the maximum rate of depolarisation at 1 μg/mL (about 7 and 23 times the clinical exposure, based on C_{max}), suggestive of Na^+ channel effects. The most consistent findings in dogs in vivo (PO dosing for conscious dogs and IV dosing for anesthetized dogs) were dose-dependent increases in PR interval (≥ 50 mg/kg PO and ≥ 1 mg/kg IV) and QRS duration (≥ 10 mg/kg PO and ≥ 2.5 mg/kg IV).[4] The PR prolongation was once again consistent with effects on Na^+ channel depolarisation while the QRS effect coincided with T_{max}. The No observable adverse effect level (NOAEL) of 3 mg/kg PO for these effects was equivalent to 7 times the clinical exposure, based on $C_{max.}$ Dose-dependent reductions in heart rate, blood pressure and left ventricular depolarisation rates were seen in the IV study but C_{max} measured at the lowest dose was 45 times that expected clinically. Importantly, no effects

[3] Rothman, R.B. and M. Baumann (2009). "Serotonergic Drugs and Valvular Heart Disease." Expert Opinion on Drug Safety **8**(3): 317–329.

[4]Typically an ECG has five deflections, arbitrarily named "P" to "T" waves. The PR interval is the period, measured in milliseconds, that extends from the beginning of the P wave (the onset of atrial depolarization) until the beginning of the QRS complex (the onset of ventricular depolarization); it is normally between 120 and 200ms in duration. The Q, R, and S waves occur in rapid succession, do not all appear in all leads, and reflect a single event, and thus are usually considered together. The QRS complex is a name for the combination of three of the graphical deflections seen on a typical electrocardiogram (EKG or ECG). It is usually the central and most visually obvious part of the tracing. It corresponds to the depolarization of the right and left ventricles of the human heart. In adults, it normally lasts 0.06–0.10 s; in children and during physical activity, it may be shorter.

of eliglustat on QT_c[5] were seen at up to 80 mg/kg PO (equivalent to >20 times the clinical exposure, based on C_{max}) or 1 mg/kg IV (45 times the clinical C_{max}).

In 13 week and 52 week repeat dose studies in dogs, there was no observed effect on electrocardiogram (ECG) parameters at up to 12 times the clinical exposure. Collectively, the animal cardiovascular data suggest no ECG effects of eliglustat in man at plasma levels up to 7 times the clinical C_{max} though higher levels may lead to clinically relevant changes in cardiac conduction.

Eliglustat caused a profound inhibition of gastric transit and emptying in rats as well as a significant increase in pH of urine following 100 mg/kg oral administration (10 times the clinical dose based on C_{max}). While respiratory rate was reduced at 400 mg/kg PO, there were no significant changes to behavioural and physiological parameters in rats at this dose (corresponding to >50 times the clinical exposure based on C_{max}). The lack of CNS effect is consistent with the distribution studies which indicated negligible penetration of brain tissue.

Pharmacodynamic drug interaction

In an in vitro study, eliglustat showed no inhibition of β-glucosidase activity up to 37 μM (equivalent to >300 times the clinical exposure, based on C_{max}), and is not likely to interfere with co-administration of recombinant β-glucosidase (imiglucerase), which can be used clinically to reduce the levels of GL-1.

Pharmacokinetics

Nonclinical pharmacology studies with eliglustat were conducted in mice, rats, rabbits, dogs and monkeys.

Absorption

Eliglustat was absorbed rapidly in the gastrointestinal tract as demonstrated both in an in situ rat perfusion model against low and high permeability standards, as well as in in vivo single dose studies in mice, rats, dogs and monkeys. In all species, T_{max} was reached within 1 h; however, bioavailability was low in all species (0.8 to 12%). In rats, exposure was greater than dose proportional. Tissue distribution was extensive and similar in mice, dogs and monkeys but lower in rats. Clearance after IV administration was approximately equivalent to the hepatic blood flow in mice, dogs and monkey but lower in rats. In all species, the half-life was short (< 1.5 h). In a single dose study in rabbits, eliglustat was rapidly absorbed and metabolised, with Genz-399240 identified as the major metabolite. In repeat dose studies with eliglustat in mice, rats and dogs, exposure was greater than dose proportional and increased with the period of exposure. A gender difference was noted in rats, with a higher exposure observed in females. In a repeat dose study in rats, exposure to the major human metabolite, Genz-399240, was dose proportional with no evidence of accumulation or gender differences.

Distribution

Plasma protein binding by eliglustat was high in laboratory animals and humans. No significant red blood cell partitioning of eliglustat was observed in rats, dogs or human. Tissue distribution of radioactively labelled carbon (^{14}C) eliglustat was extensive in mice and rats but the majority of the radioactivity was found in gastrointestinal (GI) tract, liver,

[5]In cardiology, the QT interval is a measure of the time between the start of the Q wave and the end of the T wave in the heart's electrical cycle (See figure in Footnote 3 above). The QT interval represents electrical depolarization and repolarization of the ventricles. A lengthened QT interval is a marker for the potential of ventricular tachyarrhythmias like torsades de pointes and a risk factor for sudden death.

adrenal gland and kidney. Low levels of radioactivity were found in testes but these decreased with time. Low but rapidly decreasing levels of radioactivity were also detected in brain tissues in mice and in SD rats (mainly pituitary gland) but not in Long-Evans rats in blood-brain barrier protected tissues. Low levels of radioactivity were associated with melanin-containing tissues (skin and uveal tract of the eye) but decreased with time, indicating no irreversible binding. In P-gp deficient mice, there was a 10 fold increase in radioactivity in brain tissue, indicating that eliglustat is a P-gp substrate and that the mouse P-gp efflux transporter actively limits brain penetration of eliglustat.

Metabolism

Eliglustat was extensively metabolised by sequential oxidative metabolism though the octanoyl, 2,3-dihydro-1,4-benzodioxane and pyrrolidine moieties, catalysed by CYP450 enzymes. The in vitro metabolic profile of eliglustat was similar in rat, dog, monkey and human microsomes and hepatocytes. The 7-hydroxy metabolite was the major metabolite found in rat, dog, monkey and human microsomes and hepatocytes. The major CYP450 isozymes contributing to the metabolism of eliglustat in human liver microsomes were CYP2D6 and CYP3A4.

In CYP450 enzyme inhibition studies, eliglustat directly inhibited both isozymes CYP2D6 and CYP3A4 in human liver microsomes in a competitive manner with K_i values of 5.82 and 27 μM, respectively. Eliglustat was also shown to exhibit time-dependent and reduced form of nicotinamide adenine dinucleotide phosphate (NADPH) dependent inhibition of CYP2D6 in human liver microsomes in the concentration range between 0.500 and 5.56 μM. Time-dependent inhibition of CYP2D6 was also demonstrated in human hepatocytes in the concentration range 0.250 to 5.00 μM. The inhibition of both CYP2D6 and CYP3A4 are considered clinically relevant. No significant induction of CYP450 enzymes by eliglustat was identified.

The in vivo metabolite profiles of eliglustat in plasma from rat, rabbit, dog and monkey are comparable with the metabolic profile in human plasma. The metabolic pathways are also similar across species, although some rat-specific pathways were identified. The most abundant human metabolite, Genz-399240 was present in all other species but in humans was higher in proportion to the total exposure than in other species.

Excretion

The major excretion route for eliglustat and/or its metabolites was via the faeces in rats and dogs, and in rats a significant proportion of this was via the bile. In humans, the proportion excreted via the urine was higher than in rats or dogs. In all species, excretion was rapid, with the majority of the dose excreted within 24 h. No gender differences were observed in rats or dogs.

Conclusion

The pharmacokinetic profiles in rats and dogs are sufficiently similar to humans for these species to be used as models for the assessment of the toxicity of eliglustat in humans. The proportionally higher level of the metabolite Genz-399240 warranted the separate examination of the toxicity of this metabolite.

Pharmacokinetic drug interactions

Eliglustat showed minimal potential for in vitro inhibition of transporters apart from inhibition of N-methyl-quinine transport via the P-glycoprotein transporter (P-gp) (IC_{50} 22 μM). Clinical studies also reported that eliglustat produced an increased exposure to digoxin, a P-gp substrate, at clinically relevant dose levels (Clinical Pharmacology

Summary, section 2.7.2). In the MDCKII-MDR-1 cell model, eliglustat had efflux ratios of 5.7 (1μM) and 4.6 (10μM), indicating it is itself also a substrate for P-gp. The potential for eliglustat to increase the plasma concentration of other P-gp substrate drugs is considered clinically relevant.

The competitive inhibition of both CYP2D6 and CYP3A4 and the time-related inhibition of CYP2D6 at clinically relevant dose levels were described in the pharmacokinetics section above. As both of these enzymes contribute to the metabolism of eliglustat, there is potential for eliglustat to exhibit auto-inhibition, leading to accumulation with repeated dosing as well as to increase the plasma concentration of drugs which are substrates for CYP2D6 and CYP3A4. Both of these effects are considered clinically relevant.

Toxicology

Single-dose toxicity

In single dose studies in rat (oral and IV) and in dog (oral), eliglustat demonstrated low toxicity, with only general symptoms of toxicity (GI effects in rats and emesis in dogs), and no evidence of organ related toxicity. The maximum non-lethal oral dose in rats was 400 mg/kg and in dogs was 100 mg/kg. The maximum non-lethal IV dose in rats was 20 mg/kg (maximum dose tested).

Repeat-dose toxicity

Appropriately designed repeat dose studies were conducted in mice, rats and dogs with eliglustat administered in water once daily by oral gavage in the pivotal studies in rats (up to 26 weeks) and dogs (up to 52 weeks), consistent with The International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) guidelines. The recommended clinical dose is one capsule (84.4 mg eliglustat) once daily.

Relative exposure

The exposure ratios have been calculated based on animal: human AUC at steady state. Human reference values are derived from the Simulation Pharmacokinetic Analysis Report using the final model from Study POH0373 (SIM0124). The NOEL/NOAEL is shown in bold type.

Table 2: Relative exposure in repeat-dose toxicity and carcinogenicity studies

Species	Study duration	Dose (mg/kg/day) (m/f)	AUC_{0-t}[1] (ng·h/mL) (m/f)	Exposure ratio[#]
Mouse (CD-1)	14 days	61/60	nc/nc	nc
		178/215	150/301	0.7
		760/649	nc/1480	4.8
Rat (SD)	28 days	10	32.5/320	0.1/1.0
		30**	173/89.8	0.4
		100	1394/1972	5.5

Species	Study duration	Dose (mg/kg/day) (m/f)	AUC_{0-t}[1] (ng·h/mL) (m/f)	Exposure ratio#
	26 weeks	5	39.4/54.7	0.15
		15	431/1023	2.4
		50**	2424/3815	10.2
	2 years [carcinogenicity]	10	129/75.9	0.33
		25	486/415	1.5
		75	1135/825	3.4
Dog (Beagle)	28 days	5	241/56.3	0.8/0.18
		10	148/169	0.52
		25	1166/1433	4.2
	13 weeks	2	848/120	2.8/0.4
		5*	1637/1179	5.3/3.8
		10	3932/3309	11.8
	52 weeks	2	531/248	1.7/0.8
		5	2297/203	7.5/0.7
		10**	4460/3115	12.3
Human (Gaucher patients)	steady state	50-150 mg bd	307[2]	–

1AUC period from 0 to the last time point; 2AUC period from 0 to 12h is reported to be steady state; nc = not calculated; # = animal:human plasma AUC; m/f=male/female; *=NOEL; **=NOAEL.

Major toxicities

The treatment-related toxicity observed in the mouse, rat or dog studies was generally mild and reversible. In the mouse studies, the maximum tolerated dose was exceeded in two of the studies, resulting in high mortality, clinical signs of toxicity, GI tract changes and body weight loss. In the 2 week palatability study and in the 13 week study, body weight loss was observed only in the high dose, and gross pathology did not identify any target organs for systemic toxicity. The only treatment-related effect was increased relative liver weight at 150 and 350 mg/kg/day and increased absolute and relative adrenal weight at 350 mg/kg/day (equivalent to 2 to 3 times the anticipated clinical exposure, based on AUC from the 2 week palatability study).

In the rat studies, the only treatment-related changes observed were small decreases in body weight and body weight gain in females, together with minor changes in haematological and clinical chemistry parameters in males and females. All of these changes were reversed after the recovery period at all dose levels, the highest dose being 50 mg/kg/day (equivalent to 10 times the anticipated clinical exposure, based on AUC). The observed effects are not considered clinically relevant.

In the dog studies, minor decreases in body weight gain, increases in haematological parameters and clinical chemistry parameters were observed in the 4 week and 3 month studies but all changes were reversed after the recovery period. Decreased thymus weight and lymphoid atrophy in the thymus, lymph nodes and gut-associated lymphoid tissue was observed at 25 mg/kg/day after 4 weeks but after 13 weeks, minimal to moderate lymphoid depletion was observed only in the thymus, together with reduced thymus size at 10 mg/kg/day (equivalent to 12 times the anticipated clinical exposure, based on AUC). After 12 months exposure at 10 mg/kg/day, there were no treatment-related changes in clinical pathology parameters, organ weights or histopathology (equivalent to 12 times the anticipated clinical exposure, based on AUC.) The observed effects are not considered clinically relevant.

Genotoxicity

The genotoxic potential of eliglustat was examined in vitro in a bacterial reverse mutation assay and in a test for chromosomal aberrations in human blood lymphocytes, and in vivo in a mouse micronucleus assay. All assays were negative and no further testing was considered necessary. Eliglustat is not considered to have genotoxic potential.

Carcinogenicity

The carcinogenic potential of eliglustat was examined in a 2 year study in mice and in a 2 year study in rats. Dose selection in mice and rats were based on 13 week and 26 week studies, respectively, and considered appropriate. Studies were conducted in compliance with ICH S1B guidelines[6].

In mice, there was no evidence of an increase in tumour incidence in males or females. Trend analysis using Peto's test did not reveal any significant trends in tumour incidence in any organ, however, trend analysis using the Poly-3 test revealed trends for high incidences of cortical adenoma in the adrenal cortex in males, phaeochromocytoma in the adrenal medulla in females and skin fibrosarcoma in females. The incidence data for these tumours was within the range of historical controls and there was no pathological evidence of pre-neoplastic lesions. Exposure could not be determined from the available toxicokinetic data, however, there was evidence of toxicity in males at the highest dose level and plasma levels of GL-1 in treated animals were below control animal levels, indicating exposure to eliglustat. Based on exposure in a 2 week study in mice, the highest dose is approximately 3 times the clinical exposure, based on AUC. There was no evidence of an increase in treatment-related tumour incidence in mice.

In rats, there was no evidence of an increase in tumour incidence in males or females. Trend analysis using Peto's test did not reveal any significant trends in tumour incidence in any organ, however, trend analysis using the Poly-3 test revealed trends for high incidence in granulocytic leukaemia in males at 10 mg/kg/day, odontoma in males at 25 mg/kg/day and mammary gland adenoma in females at 15 and 50 mg/kg/day. There was no dose-relationship for these tumours and the incidence was within the range of historical controls. The NOAEL for tumour incidence was 75 mg/kg/day in males and 50

[6]S1b:Testing for carcinogenicity of pharmaceuticals

mg/kg/day in females (equivalent to 3.7 and 2.7 times the clinical exposure, based on AUC).

Reproductive toxicity

The reproductive and developmental toxicity of eliglustat was examined in rats, rabbits and monkeys. Appropriately designed studies were conducted for fertility and male reproductive toxicity (rats), embryofetal development (rats and rabbits) and pre/post-natal development (rats). A fertility and toxicity study in juvenile animals was also conducted; however, it was not relevant to this submission.

Table 3: Relative exposure in reproductive studies

Species	Study	Dose (mg/kg/day)	AUC_{0-4h} (ng·h/mL) (m/f)	Exposure ratio#
Rat (SD)	Male reproductive toxicity	30 (2x15)	518	1.7
		100 (2x50)	2949	10
		200 (2x100)	-	-
	Pre- and Post-natal development	10	277[1]	0.9
		30	1228	4
		100	4817	16
Species	Study	Dose (mg/kg/day)	$AUC_{0-\tau}$ (ng·h/mL) (m/f)	Exposure ratio#
Juvenile rat (SD)	Fertility	30	110/170	0.36/0.55
		60	384/786	1.3/2.6
		100	1115/1816	3.6/5.9
Rabbit (NZW)	Embryofetal development	10	9.4	0.03
		30	137	0.4
		100	1163	3.8
Human (Gaucher patients)	steady state	50-150 mg bd	307[2]	–

[1]Day 17 post coitum;[2]AUC period from 0 to 12h is reported to be steady state; # = animal: human plasma AUC

At the time of submission the sponsor had developed specific study plans for both placental transfer (PLT0266/TEP1650/1) and milk excretion (MIL0071/TEP1650/2). These reports should be submitted as soon as they are available. Nevertheless, the results of the embryofetal development studies suggested that there is placental transfer of

eliglustat and the results of the post-natal development studies in rats suggested that there was some evidence for milk transfer of eliglustat from dams to pups.

The fertility study with eliglustat in rats did not demonstrate any effect on fertility parameters at 100 mg/kg/day (equivalent to 10 times the clinical exposure, based on AUC). In a separate 4 week study on male reproductive toxicity, there was no effect on epididymal or testicular sperm count but effects on sperm motility and morphology were observed at 200 mg/kg/day (equivalent to approximately 20 times the clinical exposure, based on AUC), and increased germ cell necrosis and seminal vesicle inflammation at 100 mg/kg/day (equivalent to 10 times the clinical exposure, based on AUC). All changes were reversible after the 14 week recovery period.

A 4 week non-GLP reproductive study was conducted in four mature Cynomolgus monkeys to further evaluate the potential adverse effects of PO eliglustat on sperm production (motility, morphology, live sperm, sperm concentration and total live sperm) and reproductive organs. The study authors concluded that there were no treatment-related effects on sperm motility, morphology or viability at 72 mg/kg/day eliglustat. However, the results were so variable as to be inconclusive with such a small sample size. The most consistent parameter was sperm morphology, which appeared to show little or no change with dosing. Plasma exposure to eliglustat was also highly variable (range 22 to 1150 ng·h/mL or approximately 0.1 to 3.7 times clinical AUC) but a reduction in GL-1 levels (range 35 to 85%) was observed in all animals. This study cannot be given much evidential weight given the high level of variability in this study and the low level of reporting detail (bodyweight changes and clinical signs).

Overall, the effects on sperm observed in rats were reversible, occurred only at high exposure levels and may potentially be species-specific and are considered unlikely to be clinically relevant.

In the embryofetal toxicity study in rats, there was evidence of both maternal and fetal toxicity at 120 mg/kg/day with significant delayed ossification and a slight increase in skeletal and visceral malformations. While toxicokinetics were not available for this study, the exposure data from the pre and postnatal development study indicate that a dose of 100 mg/kg/day is approximately equivalent to 16 times the clinical exposure, based on AUC. In the embryofetal toxicity study in rabbits, there was evidence of maternal toxicity, but no evidence of embryofetal toxicity or an increase in skeletal or visceral malformations or variations at 100 mg/kg/day (equivalent to 4 times the clinical exposure, based on AUC).

The pre/postnatal development study in rats day produced maternal toxicity at the high dose level (100 mg/kg/day) resulting in an increase in postimplantation loss, reduced pup numbers and lower pup body weight during gestation and lactation. There was no treatment-related effect on viability index, lactation index or effects on pup development, including learning and memory. The FI[7] body weights and body weight gain was lower at the high dose level but there were no treatment-related effects on F1 fertility or gestation indices (equivalent to 16 times the clinical exposure).

In the 10 week fertility and toxicity study in juvenile rats at dose levels up to 25 mg/kg twice a day (bd), there was evidence of reversible toxicity at the high dose level, but no treatment-related effects on mating, fertility of fecundity. There was no evidence of a treatment-related effect on sperm count, motility or morphology at 25 mg/kg bd.

7 The F1 (first filial) generation is the generation resulting immediately from a cross of the first set of parents (parental generation (F_0)).

Pregnancy classification

The sponsor has proposed Pregnancy Category B1[8]. This should be changed to Category B3[9] due to findings in both the rat embryofetal development study and the rat pre/postnatal studies at the highest (albeit maternotoxic) doses.

Metabolites

The genotoxic potential of the most abundant human metabolite Genz-399240 was examined in vitro in a bacterial reverse mutation assay and in a test for chromosomal aberrations in human blood lymphocytes. Both assays were negative and no further testing was considered necessary. Metabolite Genz-399240 is not considered to have genotoxic potential.

In a 13 week toxicity study in rats with metabolite Genz-399240 at subcutaneous (SC) dose levels up to 6 mg/kg/day (corresponding to a Week 13 AUC of 4400 to 5200 ng·h/mL), there was no evidence of toxicity apart from a reversible increase in absolute and relative liver weights. This equates to a relative exposure of about 7 to 8 times that expected clinically (mean AUC of 631 ng·h/mL; Protocol GZGD02047).

Impurities

The proposed specifications for impurities in the drug substance have been adequately qualified.

Other studies

A pilot study in rats to examine the potential for eliglustat to induce peripheral neuropathy (as reported for miglustat) provided no evidence for neuropathy but was not definitive.

Paediatric use

Eliglustat is not proposed for paediatric use, however, a10-week fertility and toxicity study was conducted in rats (see above).

Nonclinical summary

- The nonclinical data provided were adequate to analyse and assess the nonclinical pharmacological, pharmacokinetic and toxicological properties of eliglustat in relation to its proposed clinical use, although in some cases additional pharmacokinetic data would have assisted. The data were in general accordance with the ICH guidelines. The pivotal studies were GLP compliant and conducted with the proposed clinical formulation. The exposure ratios are adequate to address the clinical relevance of the observed toxicities.

[8]Category B1: Drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human fetus having been observed.
Studies in animals have not shown evidence of an increased occurrence of fetal damage.

[9] Category B3: Drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human fetus having been observed.
Studies in animals have shown evidence of an increased occurrence of fetal damage, the significance of which is considered uncertain in humans.

- The primary pharmacology in vitro studies confirmed the ability of eliglustat to inhibit glucosylceramide synthesis (GCS) in animal and human cell lines as well as in human cell-derived microsomes at concentrations well below the clinical exposure. Metabolites of eliglustat also inhibited GCS but only at concentrations exceeding the clinical exposure. In vivo studies in a mouse model of Gaucher disease demonstrated the ability of eliglustat to prevent accumulation of glucosylceramide (GL-1) in the liver, lung and spleen over several weeks at a clinically relevant exposure. At higher exposure levels, the count of enlarged macrophages (Gaucher cells) was also lower in the mouse liver.
- In in vitro secondary pharmacodynamic studies, weak receptor binding activity (approximately 50% inhibition) for eliglustat was shown in 10 assays from a broad range of receptors, transporters and ion channels. These effects were not considered clinically relevant.
- In a standard safety pharmacology battery of studies eliglustat demonstrated in vitro inhibition of the hERG K^+ tail current, the Na+ channel hNav1.5 and the Ca2+ channel hCav1.2 at 8, 117 and 240 times the clinical exposure (based on Cmax), respectively. Cardiovascular effects such as increases in PR and QRS interval were observed in short-term dog studies but no changes in ECG parameters were observed in long-term dog studies at similar exposure levels. Eliglustat caused significant inhibition of gastric transit and emptying in rats but only at exposure levels which are not clinically relevant. Renal and respiratory effects in rats were only observed at exposure levels that are not clinically relevant. No CNS related behavioural or physiological changes were observed in rats.
- Eliglustat showed no potential pharmacodynamic drug interaction with β-glucosidase (imiglucerase) in an in vitro study at concentrations greatly in excess of the clinical exposure.
- Pharmacokinetic studies showed that eliglustat was absorbed rapidly from the gastrointestinal tract in mice, rats, dogs and monkeys but bioavailability in all species was low. Clearance was equivalent to the hepatic blood flow in mice, dogs and monkeys but lower in rats. Half-life was short in all species. In repeat-dose studies, exposure was greater than dose-proportional. There was high plasma protein binding and no significant red blood cell partitioning. Distribution of ^{14}C-eliglustat was extensive but radioactivity was mainly in the GI tract, liver, adrenal gland and kidney, with no significant levels or accumulation in melanin-containing tissues or in brain tissues. Eliglustat was extensively metabolised by sequential oxidative metabolism; the major CYP450 isozymes involved were CYP2D6 and CYP3A4. Metabolic profiles of eliglustat in plasma of rat, rabbit, dog and monkey were comparable with the human metabolic profile. The most abundant human metabolite was Genz-399240, which was also present in other species, but proportionally higher in humans than other species. Eliglustat was excreted rapidly and mainly via the faeces in rats and dogs. In humans, there was a higher proportion excreted in the urine. The pharmacokinetics results support the rat and dog as appropriate models for assessment of eliglustat-related toxicity in humans.
- Potential for pharmacokinetic drug interactions was demonstrated. Eliglustat was both a substrate and inhibitor of P-glycoprotein (P-gp). Eliglustat was also a competitive inhibitor of CYP2D6 and, to a lesser extent, CYP3A4, as well as a time-related inhibitor of CYP2D6. All of these effects are considered clinically relevant.
- Single dose studies demonstrated that eliglustat has low acute toxicity via both the oral and IV routes. There was no evidence of organ related toxicity.
- The treatment related toxicity observed in the repeat-dose mouse, rat or dog studies was generally mild and reversible. In mice (at less than the maximum tolerated dose

level), only mild organ weight changes were observed with no accompanying pathological changes. In rats, only reversible body weight and clinical chemistry changes were observed. In dogs, reversible body weight and clinical chemistry changes were observed, as well as decreased thymus weight and lymphoid atrophy in the thymus, lymph nodes and gut-associated lymphoid tissue after 4 weeks at exposures significantly higher than the clinical exposure. This effect decreased with time and was not present after 12 months. None of the effects observed in the repeat-dose studies are considered clinically relevant.

- Eliglustat did not produce any evidence of genotoxic potential in adequately conducted genotoxicity studies.
- Eliglustat did not elicit an increase in treatment-related tumours in lifetime carcinogenicity studies in mice and rats at exposure levels 3 to 4 times NADPH that anticipated clinically.
- In reproductive and developmental toxicity studies, eliglustat did not demonstrate any evidence for an effect on fertility in rats at up to approximately 10 times the clinical exposure. In a separate rat study, there was some evidence of treatment related but reversible effects on sperm motility and morphology (but not on spermatogenesis) together with increased germ cell atrophy and seminal vesicle inflammation at exposure levels approximately 10 to 20 times that anticipated clinically. While a small follow-up 4 week study in monkeys did not show any apparent adverse male reproductive effects, the results were too variable and limited to be conclusive. Embryofetal toxicity studies in rats and rabbits showed evidence of maternal toxicity in both, and delayed ossification and a slight increase in skeletal malformations only in rats at exposure levels more than 16 times clinical exposure. Increased postimplantation loss, reduced pup numbers and lower pup body weight were observed in a rat pre/postnatal study but only at overtly maternotoxic exposure levels (>16 times the clinical AUC). An Australian pregnancy classification of B3 is consistent with the animal data.
- The most abundant human metabolite Genz-399240 was negative for genotoxic potential and did not produce any evidence of significant toxicity in a 13 week SC toxicity study in rats at about 7 to 8 times the mean clinical exposure (AUC).

Nonclinical conclusions and recommendation

- There were no major deficiencies in the nonclinical dossier.
- Results from pharmacological studies on eliglustat support its use for the proposed indication and did not identify any clinically relevant off-target binding sites.
- Safety pharmacology studies identified the potential inhibition of Na^+, K^+ and Ca^{2+} channels by eliglustat. However, in vivo data from safety and repeat-dose toxicity studies suggested that there will be no ECG effects of eliglustat in man at plasma levels up to 7 times the clinical Cmax, though higher levels may potentially lead to clinically relevant increases in PR, QRS and possibly QTc intervals.
- The pharmacokinetic data on eliglustat indicate that the inhibition of P-glycoprotein and the inhibition of CYP2D6 and CYP3A4 are clinically relevant.
- The repeat dose toxicity studies did not reveal any treatment-related adverse effects of concern.
- Eliglustat is not considered to have any genotoxic or carcinogenic potential.
- The only reproductive toxicity findings of note were limited to rats and were only seen at the highest, maternotoxic doses (15 to 20 times the clinical exposure). These

included reversible effects on sperm, germ cells and seminal vesicles in a male fertility study and increased post-implantation loss, reduced pup numbers and lower pup body weight in a pre/postnatal study. Whilst these effects do not appear to be clinically relevant, an Australian pregnancy classification of B3 is consistent with such findings.

- At the time of submission the sponsor had ongoing studies of both placental transfer (PLT0266/TEP1650/1) and milk excretion (MIL0071/TEP1650/2). These reports should be submitted to the TGA as soon as they are available.

There are no nonclinical objections to the registration of eliglustat as proposed. Changes to the draft PI were recommended but the details of these are beyond the scope of this AusPAR.

IV. Clinical findings

A summary of the clinical findings is presented in this section. Further details of these clinical findings can be found in Attachment 2.

Introduction

Clinical Rationale

The following clinical rationale has been taken from the sponsor's letter of application:

> *Gaucher disease is a rare lysosomal storage disorder caused by a deficiency of the enzyme acid β-glucosidase (also known as glucocerebrosidase). Deficiency in acid β-glucosidase leads to the progressive accumulation of GL-1 (a major component of the plasma membranes of circulating blood cells), mainly in the lysosomes of macrophages. Gaucher disease causes an abundance of lipid-engorged macrophages with a characteristic 'crinkled-paper' cytoplasmic appearance (Gaucher cells) in organs of the reticuloendothelial system (primarily spleen, liver, and bone marrow, and to a lesser extent, lung). The classic manifestations of Gaucher disease are organomegaly, haematological abnormalities, and bone disease. Gaucher disease is a multi-systemic and heterogeneous disorder that is a serious and chronically debilitating condition with persistent and irreversible morbidity developing over time in the majority of patients*
>
> *Eliglustat is a specific glucosylceramide (GL-1) synthase inhibitor and resembles the ceramide substrate for the enzyme. It acts as a substrate reduction therapy for Gaucher disease type 1 (GD1) by reducing the rate of synthesis of glucosylceramide to match its impaired rate of catabolism in patients with GD1, thereby preventing glucosylceramide accumulation and alleviating clinical manifestations.*
>
> *Eliglustat's substrate reduction mechanism of action differs from that of current standard-of-care, enzyme replacement therapies (ERTs), imiglucerase (Cerezyme) and velaglucerase alfa (VPRIV). Eliglustat's chemical structure and pharmacological effects are also distinct from the approved substrate reduction therapy, miglustat, with which eliglustat shares the same target enzyme (glucosylceramide synthase). Miglustat resembles the glucose moiety of GL-1, whereas eliglustat is similar in structure to the ceramide moiety. Eliglustat shows little or no inhibition of glycosidases, with no measurable inhibition of glycosidases and digestive disaccharidases. Eliglustat is extensively metabolised by the cytochrome P450 (CYP450) enzymes into inactive metabolites, and since it is a substrate of the efflux transporter P-glycoprotein (P-gp), it is not expected to cross the blood-brain barrier or the foeto-placental unit. Due to the small molecule size, the biodistribution of*

eliglustat is likely to be more extensive than that of an enzyme and it is expected to provide benefits in tissues that are less accessible to ERT and in cells that lack mannose receptors.

Comment: The sponsor's rationale is acceptable. The application is to register eliglustat for the treatment of Gaucher disease Type 1 (GD1), the most common form of the disease. There are three types of GD, which are characterised by the absence (Type 1) or presence (Types 2 and 3) of CNS involvement. These three forms have been labelled Type 1 (adult), infantile (Type 2) and juvenile (Type 3), based on the usual age of presentation of the disease. However, it is now recognised that there is considerable variability in terms of age and presentation, natural course and neurological complications in individuals with GD1.[10]

Orphan drug designation

Eliglustat was granted orphan drug status on 2 August 2013 *'for the long-term treatment of adult patients with Gaucher disease type 1 (GD1)'*.

Related submissions

Three medicines are currently included in the Australian Register of Therapeutic Goods (ARTG) for the treatment of GD: two enzyme replacement therapies (ERT), imiglucerase (Cerezyme®) and velaglucerase (Vipriv®); and one substrate reduction therapy (SRT), miglustat (Zavesca®).

Cerezyme®, the 200 powder strength was first included in the ARTG on 25 May 1999 and the 400 powder strength on 4 July 2009. The medicine is indicated '*for long-term enzyme replacement therapy for patients with a confirmed diagnosis of Type 1 Gaucher disease that results in one or more of the following conditions: anaemia; thrombocytopenia; bone disease; hepatomegaly or splenomegaly*'. Imiglucerase is an rch powder for intravenous (IV) infusion following reconstitution.

Vipriv® was first included in the ARTG on 29 February 2012, and is indicated '*for long-term enzyme replacement therapy (ERT) for paediatric and adult patients with type 1 Gaucher disease associated with at least one of the following clinical manifestations: anaemia, thrombocytopaenia, hepato-splenomegaly*'. Velaglucerase alfa ghu is a 400 Units powder for reconstitution as a solution for IV infusion.

Zavesca® was first included in the ARTG on 23 October 2007 '*for the oral treatment of patients with mild to moderate Type 1 Gaucher disease, for whom enzyme replacement therapy is not a therapeutic option. ZAVESCA is indicated for the treatment of the progressive neurological manifestations in adult and paediatric patients with Niemann-Pick type C disease*'. Miglustat is an oral capsule (100 mg).

Comment: It is noted that Zavesca®, the SRT, is approved for patients with GD1 for whom ERT is not a therapeutic option. In contrast, eliglustat is being proposed for the treatment or GD1 irrespective of whether ERT is a therapeutic option.

Guidance

The submission includes the outcomes of a pre-submission meeting held on 20 September 2013 between officers of the TGA and representatives of the sponsor. The notes provide comments on three matters raised by the TGA Delegate at that meeting: (1) the proposed

[10] Guidelines for the treatment of Gaucher disease through the life saving drugs program. Australian Government. Department of Health and Ageing. July 2013. www.health.gove.au/lsdp.

fixed-dose regimen of 100 mg twice daily (bd) based on CYP2D6 phenotype for the target population of intermediate metabolisers and extensive metabolisers; (2) the trial design of the pivotal Phase III study (ENCORE) and the supportive Phase II study (ENGAGE); and (3) the risk mitigation strategy relating to QT prolongation. The submission included a statement from the sponsor detailing the actions it had taken relating to the issues raised in the pre-submission meeting. These matters will be discussed in the relevant sections of this Clinical Evaluation Report (CER) (see also Attachment 2).

The sponsor also provided a statement indicating that the application is consistent with the pre-submission planning form lodged on 20 September 2012, with the exception of the tabulated summary of changes provided in the submission dossier. The sponsor also provided a summary of the actions it had taken to address the issues raised in the TGA pre-submission planning letter. The sponsor stated that none of the changes to the submission '*have any impact on the scope or scale of the submission that would invalidate the information lodged with the Pre-submission Planning Form'*. The sponsor's listed comments have been examined and there appears to be no major outstanding issues, apart from the formatting of the *Adverse Effects* section of the PI. The TGA requested that format be adjusted to comply with the PI form presented on the TGA website. However, the sponsor has decided not to adjust the format of the *Adverse Effects* section of the PI as requested by the TGA and has provided a justification for not doing so in the application letter under the heading *Presentation of Adverse Effects*. The justification is considered to be unacceptable. The presentation of the proposed *Adverse Effects* section of the PI is considered to be inadequate. Consequently, the sponsor had been requested to amend this section of the PI.

Contents of the clinical dossier

Scope of the clinical dossier

The relevant clinical data provided in the submission are outlined below:

- 13 clinical pharmacology studies in healthy subjects including pharmacokinetic (PK) and/or pharmacodynamic (PD) data;
- 5 population PK and PD modelling and simulation studies;
- 30 human biomaterial studies;
- 2 pivotal Phase III clinical efficacy and safety studies [ENCORE, ENGAGE];
- 1 supportive Phase II clinical efficacy and safety study;
- 1 Phase III clinical efficacy and safety study providing supportive safety data from the eliglustat open-label, lead-in period [EDGE]; and
- Literature references; integrated summary of safety.

Paediatric data

The sponsor stated that a Paediatric Investigational Plan has been considered by the European Medicines Agency (EMA) and a waiver has been granted for all subsets of the paediatric population from birth to less than 24 months of age (EMEA-000461-PIP02-11). The sponsor is proposing that eliglustat be approved for the treatment of adult patients with GD1. The Risk Management Plan (Part III) indicates that the sponsor is planning to undertake and open-label study historical controlled PK, safety, and efficacy study in paediatric patients with 'GD1 and GD3 (cat. 3)'.

Good clinical practice

The sponsor states that the clinical studies were designed, conducted, recorded and reported in accordance with the principles of Good Clinical Practice (GCP) as stated in the ICH guidelines and in accordance with relevant national or international laws applying to the conduct of clinical trials in humans.

Pharmacokinetics

Studies providing clinical pharmacology data

Healthy subjects

The submission included 13 PK studies in approximately 390 healthy volunteers, and 2 of these studies also included PD data (see Table 4, below). Each of the 13 studies has been evaluated and the key results have been provided in the text of the CER (Attachment 2).

Table 4: Biopharmaceutic and PK studies in healthy volunteers.

Study	PK Topic	N	Treatment
00404	Food effect	24	ET (sd) 300 mg.
02107	Absolute bioavailability Mass-Balance Metabolite profiles	10	ET (sd) 50 mg IV; ET (sd) 100 mg capsule PO; ET 100 mg capsule (bd) PO; [^{14}C]-ET (sd) oral solution 100 mg (100 µCi) .
03811	Comparative bioavailability PK variability: inter-subject and intra-subject.	22	ET (sd) 150 mg - Phase III versus Common blend formulation.
00103	Ascending dose (sd)	99	ET (sd) solution, 13 doses (0.01 to 30.0 mg/kg).
00204	Ascending dose (md) PD (biomarkers)	36	ET (md), capsules (50 mg) - 3 dosed (50 mg, 200 mg, 350 mg).
01807	Interaction - Ketoconazole	36	ET (sd and md) 100 mg; ketoconazole(md) 400 mg
02007	Interaction - Paroxetine	36	ET (sd and md) 100 mg; paroxetine (md) 30 mg
02407	Interaction - Rifampin Metabolite profiling	36	ET (sd and md) 100 (PMs) or 150 mg (non-PMs); rifampin 600 mg IV (sd) and PO (md)
01907	Interaction -	24	ET (sd) 100 mg; Maalox Advanced Maximum Strength Liquid (sd);

Study	PK Topic	N	Treatment
	Acid Reducing Drugs		Tums 500 mg chewable tablets x 2 (sd); pantoprazole 40 mg (md)
03610	Interaction - Digoxin (PK)	26	ET (md) 100 mg (PMs), 150 mg (non-PMs); digoxin 0. 25 mg (sd)
04112	Interaction - Metoprolol (PK)	14	ET (md) 150 mg; metoprolol 150 mg (sd)
02707	Interaction - OCP (PK)	29	ET (md) 100 mg; Ortho-Novum 1/35
01707	Thorough QT/QTc PKs of eliglustat PK/PD analysis	45	ET (sd) 200 mg (therapeutic); ET (sd) 800 mg (supra-therapeutic); Moxifloxacin (sd) 400 mg; Placebo (sd).

Note: ET = eliglustat tartrate; sd = single-dose; md = multiple dose; OCP = oral contraceptive pill; PO = oral administration; IV = intravenous administration

Patients with GD1

The submission included four clinical efficacy and safety studies providing PK data from approximately 225 patients with GD1 (see Table 5, below). Three studies included PK, PD, and PK/PD data that were presented individually and pooled with other studies in population based analyses [Phase II, ENCORE, ENGAGE] and one study included PK data that was not presented individually but pooled with other studies in population based analyses [EDGE]. The PK and PD data from the studies have been reviewed and relevant information included in the text of the CER (Attachment 2).

Table 5: Clinical efficacy and safety studies including PK data in patients with GD1.

Study	PK Topic	N	Design features relevant to PKs of eliglustat
Phase II	Eliglustat PK Metabolite profiling PD (biomarkers) PK/PD (efficacy) PK/PD (ECG parameters)	26	Multi-centre, open-label 52-week (primary analysis period) study in treatment-naive patients (no miglustat or ERT for GD1 within 12 months prior to enrollment). All 26 patients (25 EMs and 1 PM) received a single 50 mg dose on Day 1 and initiated bd dosing on Day 2. Eighteen (18) patients were up-titrated to 100 mg bd at Day 20 based on eliglustat Ctrough level and 1 additional patient received a dose increase to 100 mg bd after 3 years of treatment. As of Month 48, no patient had received a dose increase to 150 mg. PK parameters assessed through to Week 104; PD (biomarkers) assessed at Week 52 and Month 48.
ENGAGE Phase III	Eliglustat PK PD (biomarkers) PK/PD (efficacy)	20	Multi-centre, double-blind, randomized, placebo-controlled, 39-week (primary analysis period) study in treatment-naïve GD1 patients (no SRT or ERT within 6 and 9 months, respectively, prior to enrollment). A total of 40 patients were randomized to eliglustat (n=20) or placebo (n=20). Patients

Study	PK Topic	N	Design features relevant to PKs of eliglustat
	PK/PD (ECG parameters)		randomized to eliglustat (18 EMs, 1 IM, 1 URM) received a single 50 mg dose on Day 1 and initiated 50 mg bd dosing on Day 2. Seventeen (17) of these patients (16 EMS, 1 URM) were subsequently up-titrated to 100 mg bd at Week 4, based on Ctrough level at Week 2. After completion of the primary analysis period, patients entered open-label, long-term treatment with eliglustat. PK parameters assessed through to Week 39; PD (biomarkers) assessed at Week 39.
ENCORE Phase III	Eliglustat PK PD (biomarkers), PK/PD (efficacy) PK/PD (ECG parameters)	106	Multi-centre, randomized, open-label, active comparator (Cerezyme), 52-week study in patients who reached therapeutic goals on ERT. All 106 patients randomized to eliglustat (84 EMs, 12 IMs, 4 URMs, 4 PMs, 2 'indeterminate') received a single 50 mg dose on Day 1 and 50 mg bd from Day 2 to Week 4. Thereafter, patients received a dose of 50 or 100 mg BD through Week 8 (depending on their Week 2 Ctrough level) and a dose of 50, 100 or 150 mg BD from post-Week 8 through Week 52 (depending on their Week 6 Ctrough level).At the end of titration, 20% (n=21) of patients were on 50 mg bd, 32% (n=34) on 100 mg bd, and 48% (n=51) on 150 mg bd. After completion of the primary analysis period, patients entered open-label, long-term treatment with eliglustat. PK parameters assessed through to Week 52; PD (biomarkers) assessed at Week 52.
EDGE Phase III	Eliglustat PK data pooled for PopPK and PK/PD-ECG analyses	80	Multi-centre, randomized, double-blind study to evaluate qd versus bd eliglustat in patients with GD1 (previously treated or treatment naive) who demonstrate stability on bd dosing. The study includes open-label bd dosing in all patients during which the dose may be titrated from 50 mg bd to 100 mg bd based on plasma trough concentration. Subjects achieving therapeutic goals in lead-in will be stratified to 52 weeks treatment with qd or bd dosing. Plasma concentration data from lead-in period were pooled and analyzed in PopPK analysis and a pooled PK/PD-ECG analysis. Primary analysis period was ongoing at time of submission; PK data were not summarized separately and no CSR was available. Lead-in period included 170 patients; PopPK analysis included data from 77 of these patients in the final model, and PK/PD-ECG analysis included data from 80.

Evaluator's conclusions on pharmacokinetics

- The PKs of eliglustat were well characterised based on data from 13 studies in approximately 390 healthy volunteers and 3 studies in approximately 152 patients with GD1. Eliglustat is categorised as a Biopharmaceutics Classification System (BCS)

Class 1 drug substance due to its high solubility and high permeability [DMPK10-R047; DMPK11-R039].[11] Following oral administration, eliglustat (100 mg, capsule) is rapidly absorbed (median T_{max} 1.7 hours) and undergoes extensive first pass metabolism resulting in a low mean (SD) absolute bioavailability of 4.49% (4.13%) in healthy male subjects (n=10) [GZGD02107]. Eliglustat is also a substrate for the P-gp efflux transporter [DMPK10-R020].

- Total systemic exposure ($AUC_{(0\text{-}inf)}$) to eliglustat (300 mg, capsule) was not significantly affected when administered as a single oral dose in the fed compared with the fasted state in healthy male subjects (n=24), although peak exposure (Cmax) was approximately 15% lower when administered in the fed compared with the fasted state (Cmax Ratio [fed/fasted] = 85.20% [90% CI: 67.93, 106.87]) [GZGD00404]. However, it is considered that the difference in peak exposure of eliglustat in the fed and fasted states is not clinically significant and that eliglustat can be taken with or without food.
- The Phase III formulation of eliglustat (capsule) was bioequivalent to the common blend formulation proposed for commercialisation (capsule) based on both peak exposure (Cmax) and total exposure ($AUC_{(0\text{-}inf)}$) when administered as a single dose (300 mg) in the fasting state in healthy subjects [GZGD03811]. Consequently, all PK data from the two Phase III studies [ENGAGE, ENCORE] can be considered to be directly relevant to the eliglustat formulation proposed for approval.
- The mean volume of distribution in the terminal elimination phase (Vz) in healthy male subjects (n=10) was 816 L (SD=117 L) following a single IV dose of eliglustat (50 mg), and the mean apparent volume of distribution in this phase (Vz/F) following a single oral dose of eliglustat (100 mg, capsule) was 24,403 L (standard deviation (SD) = 12,767)[GZGD02107]. The large volume of distribution indicates that eliglustat undergoes extensive tissue distribution. The in vitro data showed that eliglustat undergoes moderate protein binding, which was concentration independent over the range 0.01 (82.9%) to 1.0 μM (76.4%) [DMPK11-R031]. No data could be identified in the submission characterising the identity of the human plasma protein binding proteins. No significant red blood cell (RBC) partitioning was observed for eliglustat in humans, and RBC partitioning was independent of eliglustat concentration over the concentration range 0.1 to 1 μM (40.5 to 405 ng/mL). The in vitro red blood cell partition coefficient was 1.7 to 1.9, and the mean blood to plasma concentration ratio was 1.31 to 1.37 over the concentration range 0.1 to 1 μM (40.5 to 405 ng/mL) [DMPK11-R030].
- The in vitro and in vivo data indicate that the metabolite profile of eliglustat is complex and that the drug is extensively metabolised. In vitro metabolite profiles of eliglustat were characterized following incubation of [^{14}C]-eliglustat in liver microsomes or cryopreserved hepatocyte suspensions from humans [DMPK10-R025] or with recombinant human CYP2C19, CYP2D6 or CYP3A4 isozymes [DMPK11-R043]. The pathways involved in metabolism of eliglustat to its acid metabolites were elucidated via a correlation analysis using human liver microsomes with a range of CYP activities [DMPK08-R035] and by a metabolite-to-metabolite approach using recombinant human CYP isozymes [DMPK11-R081] and human hepatocytes [DMPK12-R005]. In

[11] The Biopharmaceutics Classification System (BCS) Guidance purpose: Expands the regulatory application of the BCS and recommends methods for classifying drugs.;Explains when a waiver for in vivo bioavailability and bioequivalence studies may be requested based on the approach of BCS. According to the BCS, drug substances are classified as follows:
Class I - High Permeability, High Solubility
Class II - High Permeability, Low Solubility
Class III - Low Permeability, High Solubility
Class IV - Low Permeability, Low Solubility

vivo metabolite profiling was investigated in a mass-balance study in healthy male subjects (n=10) [GZGD02107]. The major metabolic pathway for eliglustat involves sequential oxidation of the octanoyl moiety followed by oxidation of the 2,3-dihydro-1,4-benzodioxane moiety or combinations of oxidations in the two moieties, resulting in multiple oxidative moieties.

- In the in vivo study [GZGD02107], 21 metabolites of eliglustat were identified in plasma collected from male subjects following oral administration of [^{14}C]-eliglustat tartrate. The majority of total radioactivity exposure in plasma following oral administration was due to circulating metabolites rather than unchanged eliglustat. Of the 21 metabolites identified in human plasma, 10 had confirmed structures. Relative to parent drug, exposure was higher for 4 metabolites (Genz-256416, Genz-258162, Genz-399207, and Genz-399240), lower for 3 metabolites (Genz-120965, Genz-256222, and Genz-258179) and generally similar for the remaining 3 metabolites (Genz-311752, Genz-527842, and Genz-682042).
- Of the 10 metabolites with confirmed structures, the only major metabolite with a total exposure exceeding 10% of total drug-related exposure in plasma (15.9%) was Genz-399240. This metabolite showed a 1.3 fold increase in Cmax and 1.9 fold increase in $AUC_{(0\text{-last})}$ with repeated administration (all subjects pooled irrespective of CYP2D6 metaboliser status). Steady-state exposure (metabolite/parent drug ratio) for Genz-399240 was 8.78 fold higher than eliglustat exposure after repeated dosing of eliglustat 100 mg bd and tended to be higher in CYP2D6 URMs compared with CYP2D6 PMs. None of the 10 metabolites with confirmed structures showed any significant inhibition of glucosylceramide synthase activity (all IC_{50} values were >1 μM). Thirty-one metabolites were detected in human urine after 3 days of repeated eliglustat dosing at 150 mg bd (CYP2D6 non-PM) or 100 mg bd (CYP2D6 PM). Major metabolites in urine included primary hydroxyl metabolites Genz-256416 and Genz-311752, secondary eliglustat ketone metabolites Genz-258162 and Genz-527862 and acid metabolites Genz-399240 and Genz-399207 [DMPK11-R084].
- The in vitro human biomaterial data indicated that eliglustat is primarily metabolised by CYP2D6 and to a lesser extent by CYP3A4 [DMPK08-R035 and DMPK11-R015, DMPK11-R034]. Consistent with these findings, in vivo studies in healthy subjects who were not poor CYP2D6 metabolisers showed that eliglustat Cmax and $AUC_{(0\text{-}12h)}$ steady state values increased 7.3 fold and 8.9 fold, respectively, when eliglustat was co-administered with paroxetine (a strong CYP2D6 inhibitor) [GZGD02007, n=36], and by 3.8 fold and 4.3 fold, respectively, when eliglustat was co-administered with ketoconazole (a strong CYP3A4 and P-gp inhibitor) [GZGD1807, n=36]. In vitro human biomaterial data indicated that, in human liver microsomes from poor CYP2D6 metabolisers, eliglustat was exclusively metabolised by CYP3A4 at concentrations within the therapeutic range. Consistent with this finding, an in vivo study in healthy subjects (n=6) showed that, in poor CYP2D6 metabolisers, eliglustat Cmax and $AUC_{(0\text{-}12h)}$ values were reduced by approximately 95% when eliglustat was co-administered with rifampin (a strong CYP3A and P-gp inducer).
- After repeated dosing of eliglustat 100 mg bd for 5 days followed by a single oral dose of 100 mg of [^{14}C]-eliglustat (approximately 100 μCi), total recovery of the radioactive dose was 93.2%. The total recovery data indicated that eliglustat was excreted both through the liver via biliary secretion (51.4% of the radioactive dose was found in feces) and through the kidney (41.8% of the radioactive dose was found in urine) [GZGD02107]. Metabolism was the predominant route of elimination of eliglustat, as indicated by the < 1% total radioactivity of unchanged eliglustat in urine and the consequent low renal clearance of 5.27 L/h relative to total body clearance of 85.8 L/h. Based on this data, and the assumption that all non-renal clearance contributing to

total body clearance is hepatic clearance, it can be estimated that hepatic clearance is approximately 80.5 L/h.

- In healthy CYP2D6 non-PM subjects, mean eliglustat half-lives following single and repeated oral doses of eliglustat ranged from 3.69 to 6.48 hours, and were independent of administration route or dose. In healthy CYP2D6 PM subjects mean half-life values following a single oral dose of eliglustat were higher than CYP2D6 non-PM, and ranged from 8.91 to 11.5 hours.
- In healthy subjects, steady Cmax and $AUC_{(0\text{-}12h)}$ values from Day 3 through 12 were non-linear for doses of 50, 200, and 350 mg bd and increased more than dose proportionally [GZGD00103]. The observed supra-dose proportionality after repeated oral administration of eliglustat in healthy subjects might be related to saturation of pre-systemic first pass metabolism and auto-inhibition of CYP2D6 metabolism.
- The PKs of eliglustat demonstrated high inter-subject variability in both healthy subjects and patients with GD1, while intra-subject variability in healthy subjects was less than 30%. CYP2D6 phenotype was the primary intrinsic source of inter-subject PK variability, compared with other potential sources evaluated (such as age, gender, race, body weight). In a PopPK model, laboratory parameters reflecting impaired renal function and hepatic function had no effect on the PKs of eliglustat. However, no PK studies have been conducted in subjects with renal or hepatic impairment.
- There were PK data on a total of 152 patients with GD1 from one Phase II study [GZGD00304] and two Phase III studies [ENGAGE, ENCORE]. Following a single 50 mg dose, eliglustat was rapidly absorbed (median Tmax of 1.5 hours) and was eliminated with a mean half-life of 6.12 hours (Phase II study). After repeated dosing at 50 mg bd, mean accumulation ratios for Cmax and $AUC_{(0\text{-}4h)}$ at steady-state, compared with Day 1, were similar to those observed in healthy subjects, with respective accumulation ratios of 1.91 and 2.73 for poor CYP2D6 metabolisers (n=4), 2.43 and 3.03 for intermediate CYP2D6 metabolisers (n=5), and 2.41 and 3.99 for extensive CYP2D6 metabolisers (n=9) [ENCORE].
- In ENCORE, the PK parameters, including the concentration at the end of the dosage interval (Ctrough levels), in CYP2D6 EMs were similar for the 50 mg bd, 100 mg bd and 150 mg doses at both Week 13 and Week 52. The last dose titration occurred at Week 8, after which time doses remained stable through Week 52. Therefore, it appears reasonable to infer that the PK data at Week 13 and particularly at Week 52 reflect the steady state PKs of 50 mg bd, 100 mg bd and 150 mg bd dose regimens in CYP2D6 EMs. Consequently, these PK data provide no basis for choosing a fixed-dose 100 mg bd regimen over 50 mg bd or 150 mg bd regimens for the treatment of CYP2D6 EMs and IMs.
- PopPK modelling [POH0373] was used to simulate steady state eliglustat Cmax and $AUC_{(0\text{-}12h)}$ levels in healthy volunteers and GD1 patients following eliglustat 100 mg bd in IM and EM (combined) subjects. These simulations found that both parameters were approximately 1.7 times higher in GD1 patients compared with healthy subjects. In addition, PopPK modelling estimated that the volume of distribution of the central compartment (Vc) and clearance (CL) values were 1.71 times and 1.95 times greater, respectively, in healthy subjects compared with GD1 patients.
- PopPK modelling [POH0373] was also used to simulate eliglustat exposure by CYP2D6 phenotype across all eliglustat doses (50, 100, and 150 mg bd) in GD1 patients. Simulations of Cmax and $AUC_{(0\text{-}12h)}$, based on CYP2D6 phenotype data for repeated 100 mg bd doses, estimated that exposure in PMs was approximately 10 times higher than in EMs, approximately 2.8 times higher in intermediate metabolisers (IMs) than in EMs, and approximately 46% lower in ultra-rapid metabolisers (URMs) than in EMs.

- The in vitro and in vivo drug-drug interaction data predict that drugs which inhibit CYP2D6 or CYP3A4 activity will increase exposure to eliglustat. Physiologically based PK simulation of a worst-case scenario involving co-administration of strong inhibitors of both CYP2D6 (paroxetine) and CYP3A (ketoconazole) with eliglustat 100 mg bd in CYP2D6 EMs [n=33]/URMs [n=3] at steady state showed a 24.5 fold increase in eliglustat $AUC_{(0\text{-}12h)}$ and a 17.1 fold increase in eliglustat Cmax [SIM0105]. Simulation of co-administration of moderate inhibitors of both CYP2D6 (terbinafine) and CYP3A (fluconazole) with eliglustat 100 mg bd in a population of CYP2D6 EMs at steady state predicted an 11.65 fold increase in eliglustat $AUC_{(0\text{-}12h)}$ and a 8.85 fold increase in eliglustat Cmax [SIM106].
- In vivo, eliglustat was found to be an inhibitor of the P-gp efflux transporter (1.49 fold increase in digoxin $AUC_{(0\text{-}last)}$), and an inhibitor of CYP2D6 (2.08 fold increase in metoprolol $AUC_{(0\text{-}inf)}$) [GZGD04112, GZGD03610]. The in vitro data showed eliglustat to be a direct and time-dependent inhibitor of CYP2D6 and an inhibitor of P-gp [DMPK11-R033, DMPK10-R020, and DMPK11-R084]. Consequently, it can be predicted that eliglustat will increase exposure to drugs that are metabolised by CYP2D6 or are substrates of the P-gp efflux transporter.
- Eliglustat had no effect on ethinyl estradiol and norethindrone exposure (that is, Ortho-Novum 1/35). Therefore, eliglustat is expected to have no effects on the exposure of drugs metabolised by CYP3A4 [GZGD02707]. The in vivo study [GZGD0190] indicates that drugs which increase intra-gastric pH (such as antacids and proton pump inhibitors) are unlikely to have clinically significant effects on eliglustat exposure, despite the in vitro observation that pH 6 above resulted in decreased eliglustat solubility.
- Based on in vitro data, eliglustat is unlikely to inhibit CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2E1, CYP2J2, or CYP3A or to induce CYP1A2, CYP2B6, or CYP3A. Additionally, based on in vitro data eliglustat is unlikely to inhibit organic anion and cation transporters OAT1, OAT3, OCT1, and OCT2, organic anion transporting polypeptides OATP1B1, OATP1B3, and OATP2B1, and efflux transporters BSEP, MRP1, MRP2, MRP3, MRP4, and MRP5.
- Based on human in vitro data for ten structurally confirmed circulating metabolites of eliglustat, it is unlikely that these metabolites will be involved in clinically significant drug-drug interactions through inhibition or induction of major CYP450 drug metabolising enzymes or inhibition of clinically relevant efflux and uptake drug transporters.

Pharmacodynamics

Studies providing pharmacodynamic data

The biomarker studies (GZGD00204, ENGAGE and ENCORE) and the Thorough QT/QTc study (Study GZGD01707) are discussed below.

Biomarker studies

Overview of primary biomarker studies

The pharmacological activity of eliglustat in humans was assessed by its inhibitory effect on glucosylceramide (GL-1) synthesis, as measured by reductions in circulating levels of GL-1. Circulating levels of GL-1 were measured in plasma and dried blood spots of healthy subjects [GZGD00204] and GD1 patients (Phase II, ENGAGE, ENCORE).

Monosialodihexosyl ganglioside (GM3), a downstream ganglioside that is derived from GL-1, was also measured in plasma of GD1 patients. Plasma GL-1 and GM3 are both typically elevated in patients with GD, and reductions in these biomarkers with eliglustat therapy are consistent with inhibition of GL-1 synthesis. Two additional sphingolipids, ceramide and sphingomyelin, were also measured in GD1 patients to confirm that eliglustat did not over-inhibit GL-1 synthesis and cause a resultant abnormal accumulation of either a precursor substrate of GL-1 synthesis (ceramide) or a lipid synthesised from that same substrate by a GL-1-independent synthetic pathway (sphingomyelin).

QT interval (ECG) studies

Study GZGD01707 - 'Thorough QT/QTc study'

The submission included one Phase I study (including addendum) in healthy male and female subjects designed to evaluate the effects of eliglustat on cardiac repolarisation following administration of single oral therapeutic (200 mg) and supra-therapeutic (800 mg) doses [GZGD01707]. The therapeutic dose (200 mg) was based on the proposed dose of 100 mg bd and the supra-therapeutic dose (800 mg) was based on the administration of 100 mg bd in the presence of a strong CYP2D6 inhibitor. The study was randomised, double-blind, placebo-controlled, 4-sequence, 4-period and cross-over in design.

Evaluator's overall conclusions on pharmacodynamics

- The biomarker studies in patients with GD1 demonstrated that, by the end of the primary analysis period, median plasma GL-1 and GM3 concentrations were significantly ($p< 0.0001$) reduced versus baseline (Phase II), versus placebo (ENGAGE) and versus Cerezyme (ENCORE). These results indicate that eliglustat targets the relevant metabolic pathway in humans. In addition, a majority of eliglustat treated patients achieved normal plasma concentrations of GL-1 and GM3 by the end of the primary analysis period, indicating that inhibition of glucosylceramide synthase by eliglustat is unlikely to cause significant depletion of other physiologically important lipids through over inhibition of GL-1. Furthermore, results from the clinical studies showed that inhibition of GL-1 synthesis by eliglustat did not result in abnormal accumulation of either ceramide (the substrate from which GL-1 is derived) or sphingomyelin (a lipid synthesized from ceramide via a GL-1-independent synthetic pathway).
- In the 'Thorough QT/QTc study' in healthy volunteers [GZGD01707), the predicted mean placebo-corrected QTcF for the supra-therapeutic dose (800 mg) was 7.3 ms (upper 1-sided 95% CI limit of 8.8 ms) and the predicted mean placebo-corrected QTcF for the therapeutic dose (200 mg) was 0.43 ms (upper 1-sided 95% confidence interval (CI) limit of 1.77 ms). The upper 1-sided 95% CI limit did not exceed 10 ms for either the 800 mg or 200 mg dose at any of the study time-points. The results for therapeutic dose (200 mg) do not give rise to regulatory concern based on the relevant TGA annotated adopted EU guideline relating to QT/QTc prolongation and the pro-arrhythmic potential of non-antiarrhythmic drugs (CHMP/ICH/2/204). There was no gender effect observed at the therapeutic dose (200 mg) but placebo-corrected increased in QTcF following the supra-therapeutic dose (800 mg) were notably greater in females than in males.
- In the PK/PD (efficacy) analysis [POH395], a statistically significant relationship was observed between increasing % change in liver volume (Multiples of Normal (MN)) and increasing exposure to eliglustat ($logAUC_{(0\text{-}tau)}$ and $logC_{max}$) at Week 39 [ENGAGE]. There also appears to be a non-statistically significant association between % change in spleen volume (MN) and eliglustat exposure ($logAUC_{(0\text{-}tau)}$ and Cmax). There were no statistically significant PK/PD relationships between % change in platelet count or

absolute change in haemoglobin concentration and eliglustat exposure ($logAUC_{(0\text{-}tau)}$ and C_{max}) Week 39 in ENGAGE.

- In the PK/PD (efficacy) analysis [POH395], for patients switching from ERT to eliglustat, no apparent PK/PD trend was observed between the composite primary endpoint (% patients remaining stable for 52 weeks), and exposure ($logAUC_{(0\text{-}tau)}$ and logCmax) (ENCORE). Statistically significant associations between one component of the composite endpoint, % change in spleen volume [MN] from Baseline, and observed $logAUC_{0\text{-}tau}$ and logCmax at Week 52 (ENCORE study) were observed. There were no statistically significant PK/PD relationships between % change in liver volume, % change in platelet count or absolute change in haemoglobin concentration and eliglustat exposure ($logAUC_{(0\text{-}tau)}$ and Cmax) at Week 52 in ENCORE.
- In the PK/PD (efficacy) analysis [POH395], observed (all patients/actual doses) and predicted (IM and EM patients combined/100 mg bd) mean % changes in spleen volume (MN) from Baseline to Week 39 [ENGAGE] or Week 52 [ENCORE] based on the respective PK/PD models (predicted $logAUC_{(0\text{-}tau)}$) were similar. The sponsor argues that the similarity between the mean predicted % change in spleen volume at Week 39 [ENCORE] and at Week 52 [ENCORE] for IM and EM patients (combined) when dosed at 100 mg bd and the observed results for all patients supports the proposed dosing regimen for GD1 patients (that is, fixed-dose 100 mg bd in EMs or IMs). Matters relating to the dosing regimen will be discussed later in the CER.

Dosage selection for the pivotal studies

In the efficacy studies (Phase II study, Phase III studies ENGAGE and ENCORE), all patients began eliglustat dosing at 50 mg bd. For the Phase II study (initial clinical study in GD1 patients), a starting dose of 50 mg bd was selected based on PK data from healthy subjects indicating that following repeated 50 mg bd dosing the eliglustat Ctrough would be expected to be at or near the in vitro IC_{50} for GL-1 inhibition of approximately 10 ng/mL (based on human microsomes and human intact cells data). If eliglustat Ctrough was < 5 ng/mL at Day 10, the initial 50 mg bd dose was increased to 100 mg bd starting on Day 20 and then maintained at that dose through the remainder of the primary analysis period (52 weeks). If the eliglustat Ctrough value was ≥ 5 ng/mL on Day 10, the patient remained on 50 mg bd for the remainder of the primary analysis period (52 weeks).

In the two pivotal Phase III studies (ENGAGE; ENCORE), eliglustat was also initiated at 50 mg bd, and at Week 4 the dose was increased to 100 mg bd if eliglustat Ctrough was < 5 ng/mL at Week 2. In ENCORE, but not ENGAGE, if the eliglustat Ctrough remained at < 5 ng/mL at Week 6 in patients whose dose had been increased to 100 mg bd at Week 4, then a further dose increase to 150 mg bd at Week 8 was allowed.

The dose-titration method was used to ensure the target exposure level for efficacy was achieved, while the starting dose of 50 mg bd was chosen to minimize the risk of excessive exposure in patients who were CYP2D6 PMs or patients who were receiving chronic medications that could potentially alter eliglustat metabolism.

Although patients of all CYP2D6 phenotype were included in the trials and doses of 50, 100 and 150 mg bd were taken, the sponsor is proposing that eliglustat be approved at a fixed-dose of 100 mg bd in patients who are IMs or EMs (that is, approximately 90% of patients). The sponsor states that simplifying the eliglustat dosing regimen will aid in reducing the complexity of the regimen used in the pivotal trials.

Efficacy

Studies providing efficacy data

- 2 pivotal Phase III clinical efficacy and safety studies [ENCORE, ENGAGE];
- 1 supportive Phase II clinical efficacy and safety study;

Evaluator's conclusions on efficacy

Summary of key efficacy outcomes

(1) Treatment-naive GD1 patients

The efficacy of eliglustat (titration regimen) for the treatment of GD1 in ERT treatment-naive patients was demonstrated in one, double-blind, placebo-controlled pivotal Phase III study [ENGAGE (n=40; eliglustat n=20, placebo n=20), and supported in one Phase II open-label, single-arm, eliglustat study (n=26).

In ENGAGE, treatment-naive patients were considered to be patients who had not been treated with SRT (miglustat) or ERT within 6 or 9 months, respectively, prior to randomisation. Five (5, 12.5%) patients had received prior treatment with ERT, with 4 of these patient also having received prior treatment with SRT. The primary efficacy endpoint was the percentage change in spleen volume (MN) from Baseline to Week 39 in the eliglustat group (n=20) compared with the placebo group (n=20) in the Intent-to-Treat (ITT) population. There was a statistically significant and clinically meaningful greater reduction in spleen volume (MN) from Baseline to Week 39 (primary efficacy endpoint) in the eliglustat group compared with the placebo group: -27.77% versus +2.26%, respectively, difference = -30.03% (95% CI: -36.82, -23.24); p< 0.0001. The majority of patients in the eliglustat group achieved a clinically meaningful reduction of at least 20% in spleen volume compared with a minority of patients in the placebo group (75% versus 5%, respectively). In addition, the difference between the two treatment groups for all secondary efficacy endpoints favoured eliglustat over placebo and the treatment differences were statistically significant and clinically meaningful: difference in absolute change in haemoglobin level from Baseline to Week 39 of 1.22 g/dL (p=0.0006); difference in percentage change in liver volume from Baseline to Week 39 of -6.64% (p=0.0072); and difference in percentage change in platelet count from Baseline to Week 39 of 41.06% (p< 0.0001).

In the Phase II study, treatment-naive patients were considered to be patients who had not received ERT or miglustat within 12 months prior to enrollment. One (1, 5%) patient was enrolled who had taken miglustat more than 12 months prior to enrollment. Treatment with eliglustat resulted in 77% (20/26) (95% CI: 58%, 89%) of GD1 treatment-naive patients achieving the primary composite endpoint for success after 52 weeks of treatment: improvement in 2 of the 3 efficacy parameters (haemoglobin, platelets, spleen volume). In addition, in patients (n=19) with Baseline and Month 48 data, statistically significant and clinically meaningful improvements in spleen volume, liver volume, haemoglobin level, and platelet count were observed at Month 48. The results showed that improvement in these 4 efficacy parameters observed with eliglustat at Year 1 could be maintained or further improved with treatment through to Year 4.

(2) Patients stabilised on ERT and then switched to eliglustat

The efficacy of eliglustat (titration regimen) for the treatment of GD1 in patients stabilised on ERT was demonstrated in one pivotal, randomized, open-label, active-controlled, Phase III study [ENCORE]. In this study, GD1 patients were enrolled if they had been stabilised with ERT for at least 3 years before enrollment. In the Per Protocol set (PPS), eliglustat (n=99) was shown to be non-inferior to Cerezyme (n=47) in patients switching to

eliglustat from ERT following 52 weeks treatment. The pre-specified primary composite efficacy endpoint required that stable haemoglobin levels, platelet counts, spleen volumes and liver volumes achieved with prior Cerezyme treatment for at least 3 years be maintained for a further 52 weeks in patients switching to eliglustat. The primary composite endpoint was achieved in 84.8% (84/99) of patients switching to eliglustat compared with 93.6% (44/47) of patients treated with Cerezyme. The difference between the two treatment groups was -8.8% (95% CI: -17.6, 4.2) in favour of Cerezyme. The lower bound of the 95% CI for the difference between the two treatments (-17.6%) was within the pre-specified non-inferiority margin of 25%. In addition, the lower bound of the 95% CI for the difference between the two treatments (-17.6%) was within the non-inferiority margin of 20% suggested by the EMA. Furthermore, the upper bound 95% CI of the change from Baseline to Week 52 in the spleen volume (MN) 2.47% in the PP population was within the non-inferiority margin of 15% for this parameter recommended by the FDA.

In ENCORE**,** patients had already reached pre-specified therapeutic goals for haematological parameters (haemoglobin level and platelet count) and organ volumes (spleen, liver) at Baseline, and changes from baseline over 52 weeks were small in both treatment groups. At Week 52, over 92% of all patients met the stability criteria for each of the individual components of the composite endpoint: spleen volume (MN), excluding patients with splenectomy (95.8% [68/71] eliglustat versus 100% [39/39] Cerezyme); haemoglobin level (94.9% [94/99] eliglustat versus 100% [47/47] Cerezyme); platelet count (92.9% [92/99] eliglustat versus 100% [47/47] Cerezyme); and liver volume (MN) (96.0% [95/99] eliglustat versus 93.6% [44/47] Cerezyme). The study excluded patients with symptomatic bone disease within the year prior to study entry. In addition, Bone mineral density (BMD) was normal for the majority of patients in both treatment groups at study entry and remained stable throughout the 52 week treatment period.

Sponsor's proposed dosing recommendation

The sponsor's proposed dosing regimen for both treatment-naive and treatment-experienced patients with GD1 consists of fixed-dose eliglustat 100 mg bd in patients who are CYP2D6 extensive metabolisers (EMs) or intermediate metabolisers (IM) (approximately 90% of the potential treatment population). The sponsor's proposed treatment regimen does not involve dose titration determined by eliglustat Ctrough levels < 5 ng/mL early in treatment, nor does it include patients who are CYP2D6 PM or URM. The sponsor states that *'[s]implifying the eliglustat dosing regimen by targeting IMs and EMs only, with a single dose strength, aids in reducing the complexity around the management of concomitant medication via labelling, guidance, and education that would need to be provided for each CYP2D6 phenotypic subgroup'*.

The sponsor provided a justification for the proposed treatment regimen. In essence, the sponsor's justification for the proposed treatment regimen is considered to be based on the following factors:

a. Eliglustat us extensively metabolised by CYP2D6, and the PopPK analysis [POH373] showed that CYP2D6 phenotype was the most significant determinant of eliglustat exposure. Therefore, excluding CYP2D6 PMs from treatment eliminates the risks associated with excessive eliglustat exposure in these patients and removes the rationale for initiating treatment with 50 mg bd in all patients in order to mitigate the risks to patients who are PMs. CYP2D6 URMs can be excluded because it is unlikely that eliglustat will be effective in these patients due to negligible plasma concentrations. Limiting treatment to patients who are EMs or IMs will capture approximately 90% of the GD1 population. This aspect of the sponsor's justification is considered to be acceptable.

b. Efficacy in patients with eliglustat Ctrough levels < 5 ng/mL did not significantly differ from efficacy in patients with Ctrough levels ≥ 5 mg/mL. Consequently, measuring Ctrough levels in order to determine the most efficacious dose is not justified. Therefore, a 50® 100® 150 mg bd titration regimen is not required for efficacy reasons and cannot be justified for safety reasons if CYP2D6 PMs are excluded from treatment. This aspect of the sponsor's justification is considered to be acceptable.

c. Based on exploratory PK/PD modelling and simulation using predicted eliglustat exposure ($logAUC_{(0\text{-}tau)}$), the observed and predicted mean % changes in spleen volume (MN) from Baseline to Week 39 [ENGAGE] or Week 52 [ENCORE] were similar. Consequently, the proposed fixed-dose eliglustat 100 mg bd regimen in CYP2D6 EMs and IMs is justified, because it results in similar efficacy outcomes to those observed for the titration regimen used in all patients (irrespective of CYP2D6 metaboliser status). This aspect of the sponsor's justification is problematic for the reasons discussed below.

The main difficulty with the sponsor's proposed treatment regimen is that it has not been tested in pivotal efficacy and safety studies. The protocols for ENGAGE and ENCORE did not specify that confirmatory PK/PD analyses would be undertaken to determine alternative dosing regimens from those used in the studies. The protocols stated that *'[e]xploratory population PK-PD analyses may also be performed to evaluate and characterize exposure-response relationships'*. It is considered that the proposed treatment regimen should be considered to be exploratory, requiring confirmation by pivotal efficacy and safety studies. However, because the sponsor's proposed treatment regimen is central to its submission, relevant efficacy data from the two pivotal studies are evaluated below in order to determine whether the available data can support the proposed dosing regimen.

GD1 patients naive to previous ERT treatment

ENGAGE

In ENGAGE, all treatment-naive patients randomised to eliglustat (n=20) eliglustat were treated with 50 mg bd from the morning of Day 2 through the evening prior to the Week 4 visit. From the morning of Week 4 through Week 39, patients with eliglustat trough plasma concentrations ≥ 5 ng/mL at Week 2 continued to receive 50 mg bd and patients with eliglustat trough plasma concentrations < 5 ng/mL at Week 2 were up-titrated to 100 mg bd.

At the end of the primary analysis period (Week 39), 17 (85%) patients were being treated with 100 mg bd and 3 (15%) patients were being treated with 50 mg bd. The CYP2D6 metaboliser status of the 20 eliglustat treated patients was PM (0%, 0/20), IM (5%, 1/20), EM (90%, 18/20), and URM (5%, 1/20). Therefore, most of the patients in ENGAGE were taking 100 mg bd from Week 4 through to Week 39 (n=17, 85%) and nearly all were CYP2D6 EMs or PM (n=19, 95%). Based on these data, it can be reasonably inferred that efficacy in the eliglustat group was being driven primarily by the 100 mg bd dose in CYP2D6 EMs (the proposed treatment regimen).

In ENGAGE, when efficacy was compared in patients with average Ctrough levels < 5 ng/mL and ≥ 5 ng/mL in an exploratory subgroup analysis, there was a trend towards greater percentage change from baseline in selected parameters in the higher average Ctrough group compared with the lower average Ctrough group (see Table 6, below). However, the differences between the two groups are of doubtful clinical significance, suggesting that adjustment of dose based on the Ctrough cut-point of 5 ng/mL is not necessary.

Table 6: ENGAGE - Summary of values and changes of percentage changes in selected efficacy endpoints from Baseline to Week 39; FAS.

Efficacy Parameter	Average C_{trough} Stratum[a]	n	Mean (SD)		
			Baseline	Week 39	Change/ Percentage Change from Baseline to Week 39[b]
Spleen Volume (MN)	<5 ng/mL	9	14.76 (6.620)	11.15 (4.707)	-23.05 (10.862)
	≥5 ng/mL	11	13.19 (5.523)	9.38 (5.429)	-31.28 (13.166)
Hemoglobin (g/dL)	<5 ng/mL	9	11.79 (2.039)	12.34 (1.788)	0.55 (0.976)
	≥5 ng/mL	11	12.27 (1.681)	13.14 (1.326)	0.87 (1.207)
Platelet Count ($x10^9$/L)	<5 ng/mL	9	75.83 (13.386)	98.28 (33.233)	28.67 (36.353)
	≥5 ng/mL	11	74.41 (15.269)	99.50 (25.399)	34.20 (29.139)
Liver Volume (MN)	<5 ng/mL	9	1.52 (0.344)	1.42 (0.276)	-5.36 (7.488)
	≥5 ng/mL	11	1.37 (0.364)	1.28 (0.279)	-5.53 (6.725)
Chitotriosidase (nmoL/hr/mL)	<5 ng/mL	9	14954.6 (10078.09)	9474.1 (6534.13)	-36.24 (20.480)
	≥5 ng/mL	10	11836.1 (6120.59)	7882.2 (6140.74)	-41.86 (27.842)

a - Average Ctrough is calculated as the mean of individual values at Weeks 13, 26, and 39. b - Change or percentage change from Baseline is summarized only for patients with data at both Baseline and Week 39. The average of all values for each patient at each time point is used in the table. Last observation carried forward (LOCF) is used for 1 patient in the eliglustat group (#5303) who withdrew from the study prior to the Week 39 assessment.

The exploratory PK/PD [POH0395] modelling and simulation analysis showed that observed and predicted mean % changes in spleen volume (MN) from Baseline to Week 39 [ENGAGE] were similar, based on predicted $logAUC_{(0\text{-}tau)}$. The observed treatment difference (eliglustat - placebo) in all patients for the % change in spleen volume (MN) from baseline to Week 39 was -30.03% (95% CI: -36.82, -23.2) compared with the predicted treatment difference (eliglustat - placebo) in the proposed patient population of -34.20% (95% CI: -41.22, -27.18).

It is considered that the totality of the submitted data relating to ENGAGE support the sponsor's proposed dosing regimen in treatment-naive GD1 patients.

Phase II study [GZGD00304]

Support for the sponsor's proposed dosing regimen is also provided by data from the eliglustat single-arm Phase II study in treatment-naive GD1 patients. In this study, each patient was treated with eliglustat 50 mg bd from Day 2 and was up-titrated to 100 mg bd from Day 20 through to Week 52 if the Day 10 trough plasma concentration was < 5 ng/mL and remained on 50 mg bd if the Day 10 trough plasma concentration was ≥ 5 ng/mL. At the end of the primary analysis period (Week 52), 18 (75%) patients were being treated with 100 mg bd and 6 (25%) patients were being treated with 50 mg bd. Furthermore, 25 of the 26 patients (96%) being treated with eliglustat were CYP2D6 EMs, while only 1 patient was a CYP2D6 PM. Therefore, based on the dosage distribution and the CYP2D6 phenotypes it is reasonable to infer that the beneficial treatment effect observed with eliglustat at Week 52 was being driven primarily by patients receiving 100 mg bd who were CYP2D6 EMs (consistent with the proposed regimen).

Of the 6 patients being treated with 50 mg bd at Week 52, 5 continued to receive 50 mg bd through Month 48, while 1 received 50 mg bd for the first 3 years after which the dose was increased to 100 mg bd. No patients in the Phase II study were receiving 150 mg bd at the time of the data cut-off point, and all patients are now in their fifth year of study or greater.

There was a trend towards greater effect in the Ctrough ≥ 5 ng/mL subgroup compared with the Ctrough < 5 ng/mL subgroup, based on the % change from Baseline to Month 48 for the key efficacy endpoints of interest (see Table 7, below). However, the differences between the two groups are of doubtful clinical significance.

Table 7: Phase II - Summary of change from Baseline to Week Month 48 for haemoglobin, platelet count, spleen volume and liver volume in subgroups based on average steady state plasma trough concentrations < 5 ng/mL and ≥ 5 ng/mL; FAS.

Parameter	Trough	Baseline		Month 48		Change from Baseline to Month 48		
	ng/mL	n	Mean (SD)	n	Mean (SD)	n	Type	Mean (SD)
Hb	< 5	8	11.62 (1.791)	8	13.54 (1.425)	8	Absolute g/dL	1.93 (1.646)
(g/dL)	≥ 5	11	11.06 (1.378)	11	13.59 (1.134)	11		2.52 (1.318)
Platelet	< 5	9	69.875 (20.812)	8	105.563 (42.196)	8	Percentage	52.8% (46.33%)
109/L	≥ 5	11	67.818 (22.387)	11	139.818 (53.908)	11		125.7 % (106.1%)
Spleen	> 5	7	12.26 (1.042)	7	5.27 (1.189)	7	Percentage	-57.1% (8.74%)
MN	≥ 5	11	20.54 (11.153)	11	6.59 (4.251)	11		-66.0% (12.25%)
Liver	< 5	7	1.44 (0.285)	7	1.12 (0.205)	7	Percentage	-21.6% (11.54%)
MN	≥ 5	11	1.87 (0.420)	11	1.24 (0.317)	11		-32.1% (14.00%)

GD1 patients previously stabilised on ERT and switched to eliglustat - ENCORE

While the totality of the data for treatment-naive GD1 patients supports the sponsor's proposed treatment regimen in that patient population, the data supporting the proposed treatment regimen for patients stabilised on ERT and switched to eliglustat are significantly more problematic.

In ENCORE, all GD1 patients who had been stabilised on prior treatment with ERT and randomised to eliglustat received 50 mg bd through Week 4, and 50 mg bd or 100 mg bd through Week 8 depending on the trough plasma concentration at Week 2 (that is, < 5 ng/mL dose increased from 50 mg bd to 100 mg bd, ≥ 5 ng/mL dose remained at 50 mg bd). Postweek 8, patients in the eliglustat group received either 50 mg bd, 100 mg bd, or 150 mg bd through to Week 52, depending on the trough plasma concentration at Week 6 (< 5 ng/mL dose increased from 50 mg bd to 100 mg bd or from 100 mg to 150 mg bd, ≥ 5 ng/mL dose remained at 50 mg bd or 100 mg bd). At the end of the primary analysis period (Week 52), the distribution of patients receiving the three possible doses of eliglustat was 20% (21/106) 50 mg bd, 32% (34/106) 150 mg bd and 48% (51/106) 150 mg. Therefore, it is not possible to infer that maintenance of efficacy at Week 52 observed with the eliglustat titration regimen (50® 100® 150 mg bd) was primarily being driven by the 100 mg bd dose.

Furthermore, the PKs of 50 mg bd, 100 mg bd, and 150 mg in CYP2D6 EMs were similar at Week 13 and at Week 52 (see Table 8, below). In particular, systemic exposure ($AUC_{(0\text{-}12h)}$) at Week 13 and at Week 52 was similar for the three doses in CYP2D6 EMs and mean (SD) Ctrough levels for 50 mg bd, 100 mg bd and 150 mg bd were above ≥ 5 ng/mL at Week 13 and at Week 52. The last dose titration took place at Week 8, after which the doses remained constant through Week 52. Therefore, it appears reasonable to infer that the PKs at Week 13 and particularly at Week 52 reflect the steady state PKs of the three dose groups in CYP2D6 EMs. Consequently, the similarity of the steady state PK data for the three dose regimens at Weeks 13 and 52 in CYP2D6 EMs provides no basis for selecting the fixed-dose 100 mg bd dose regimen in preference to fixed-dose 50 or 100 mg bd dose regimens for the treatment of CYP2D6 EMs or IMs.

Table 8: ENCORE - Mean (SD) [CV%] PK parameters by dose in CYP2D6 EMs at Weeks 13 and 52.

Visit		N	C_{max} (ng/mL)	Tmax (hours)[a]	$AUC_{(0\text{-}4h)}$ (ng·h/mL)	$AUC_{(0\text{-}12h)}$ (ng·h/mL)[b]	Ctrough (ng/mL)
Week 13	50 m bd	11	27.4 (19.0) [69%]	1.48 (1, 4)	85.5 (67.3) [79%]	201 (17) [85%]	10.2 (10.2) [n=11]
Week 13	100 mg bd	31	37.2 (26.6) [72%]	1.83 (0, 4)	99.5 (58.4) [59%]	195 (103) [53%]	7.34 (4.93) [n=31]
Week 13	150 mg bd	42	39.9 (27.2) [68%]	1.94 (1, 8)	108 (76.0) [70%]	228 (157) [69%]	7.44 (6.18) [n=42]
Week 52	50 mg bd	9	26.8 (20.0) [74%]	2.05 (1, 4)	85.4 (66.4) [78%]	214 (196) [91%]	12.7 (16.0) [n=9]
Week 52	100 mg bd	30	35.1 (21.3) [61%]	2.02 (1, 4)	96.1 (52.0) [54%] [c]	201 (118) [59%] [c]	7.56 (5.17) [n=29]
Week 52	150 mg bd	41	38.1 (30.8) [81%]	1.98 (1, 4)	101 (72.9) [72%] [d]	195 (125) [64%] [d]	5.50 (3.58) [n=41]

Note: a - Tmax median (range); b - 12 hour duplicate for Weeks 13 and 52; c - N=29; d - N=40.

In ENCORE, the CYP2D6 metaboliser status of patients was PM (4%, 4/106), IM (11%, 12/106), EM (79%, 84/106), URM (4%, 4/106), indeterminate (0%, 0/106). Therefore, 91% (96/106) of the patients in ENCORE were EMs or IMs. Consequently, the observed data support treatment being limited to patients who are CYP2D6 EM and IMs, because it can be reasonably inferred that maintenance of stability in the eliglustat titration regimen is primarily being driven by the combined group of EMs plus IMs.

In ENCORE, when efficacy was compared in patients with mean steady state eliglustat Ctrough levels < 5 ng/mL and ≥ 5 ng/mL in an exploratory subgroup analysis, stability based on the composite efficacy endpoint was maintained after 52 weeks of treatment in 77.5% (31/40) of patients with mean steady state Ctrough levels < 5 ng/mL compared with 85% (56/66) of patients with mean steady-state Ctrough levels ≥ 5 ng/mL. The change from Baseline to Week 52 in the individual components of the composite endpoint generally favoured the subgroup of patients with higher mean steady state Ctrough levels compared with the subgroup of patients with lower mean steady state Ctrough levels (see Table 9, below). However, mean differences between the two subgroups for the individual components of the composite endpoint were relatively small and are of doubtful clinical significance.

Table 9: ENCORE - Change from Baseline to Week 52 for haemoglobin, platelet count, spleen volume and liver volume in subgroups with mean steady state plasma trough concentrations < 5 ng/mL and ≥ 5 ng/mL; FAS.

Parameter	Trough	Baseline		Week 52		Change from Baseline to Week 52		
	ng/mL	n	Mean (SD)	n	Mean (SD)	n	Type	Mean (SD)
Hb	< 5	40	13.4 (1.3)	39	13.2 (1.1)	39	Absolute g/dL	-0.132 (0.6999)
(g/dL)	≥ 5	66	13.8 (1.3)	66	13.5 (1.4)	66		-0.249 (0.7481)
Platelet	< 5	40	189.5 (64.6)	39	195.1 (67.6)	39	Percentage	0.85% (SD = 18.62%)
10^9/L	≥ 5	66	211.7 (86.4)	66	225.9 (89.8)	66		5.92% (SD = 18.83%)
Spleen	> 5	33	2.995 (1.3022)	33	2.969 (1.3641)	33	Percentage	-2.188% (SD = 16.0661%)
MN	≥ 5	44	3.297 (1.3776)	44	3.090 (1.3762)	44		-7.309 (SD = 13.0599%)
Liver	< 5	40	0.912 (0.1732)	40	0.953 (0.1559)	40	Percentage	4.900% (SD = 10.0195)
MN	≥ 5	66	0.955 (0.1962)	66	0.960 (0.1973)	66		0.591% (SD = 9.0213%)

In an exploratory PK/PD modelling and simulation analysis [POH0395], the composite primary endpoint in ENCORE (patients remaining stable for 52 weeks) for each CYP2D6 phenotype and eliglustat dose were plotted against observed $logAUC_{(0\text{-}tau)}$ in order to explore potential exposure-response relationships. Logistic regressions of the composite endpoint versus observed PK parameters ($logAUC_{(0\text{-}tau)}$ or logCmax) were also explored. No apparent trend was observed when the observed composite primary endpoint for each CYP2D6 phenotype and eliglustat dose at Week 52 was plotted against observed $logAUC_{(0\text{-}tau)}$. Consequently, no exploratory PK/PD analyses predicting the effect of the proposed eliglustat treatment regimen on the primary composite endpoint were undertaken.

However, PK/PD linear models in the PPS were constructed for each observed component of the composite endpoint using change from Baseline to Week 52 as the response variable, and the baseline value for the relevant component, the stratification randomisation indicator and the exposure ($logAUC_{(0\text{-}tau)}$ or logCmax) as independent variables. For the % change in spleen volume (MN) from baseline to Week 52, a statistically significant PK/PD relationship was shown for both observed $logAUC_{(0\text{-}tau)}$ (p=0.0002) and observed logCmax (p=0.0007). However, no statistically significant PK/PD relationships were shown for the other 3 components of the primary composite endpoint. Therefore, only the % change in spleen volume (MN) at Week 52 was used to establish the PK/PD model, and this model was used in analyses to predict eliglustat treatment effects in the PPS.

In the exploratory PK/PD modelling and simulation analysis, the observed and predicted % changes in spleen volume (MN) from Baseline to Week 52 were similar, based on predicted $logAUC_{(0\text{-}tau)}$ values. The observed % change in all eliglustat treated patients (n=70) was -5.96% (treatment difference from Cerezyme of -2.75% [95% CI: -8.12, 2.62])

and the predicted % change was -6.55% (treatment difference from Cerezyme of -3.44% [95% CI: -8.89, 2.00]) in simulated patients (n=70) (combined CYP2D6 EM/IMs treated with eliglustat 100 mg bd). These results were supported by an exploratory PK analysis comparing the observed and projected % change in spleen volume (MN) from Baseline to Week 52, based on logAUC(0-tau), in observed (n=70) and simulated patients (n=70), including projected results for IMs and EMs who had received 50 or 150 mg bd in the study but who would receive 100 mg bd in the proposed regimen. The results of the exploratory PK/PD analyses relating to % change in spleen volume have been used by the sponsor to support the proposed treatment regimen.

Overall, it is considered that the totality of the data from ENCORE do not provide a basis for selecting the 100 mg bd dose over the 50 mg bd or 150 mg bd dose but do support limiting treatment to patients who are EMs or IMs. The efficacy data based on the titration regimen (50® 100® 150 mg bd) do not allow inferences to be made about the potential contribution of individual doses to the observed outcomes. Furthermore, the similarity of the steady state PKs of the 50, 100, and 150 mg bd doses at Weeks 13 and 52 in CYP2D6 EMs provides no basis for preferring the fixed-dose 100 mg bd regimen over fixed-dose 50 or 150 mg bd regimens for the treatment of CYP2D6 EMs/IMs. The exploratory efficacy analysis in subgroups based on Ctrough levels supports a fixed-dose regimen rather than a dose-titration regimen but provides no insight into the most appropriate dose. The exploratory PK/PD analysis in one of the four components of the composite stability endpoint showed that the observed and predicted % change in spleen volume (MN) from Baseline to Week 52 were similar, based on the PK efficacy model ($logAUC_{(0\text{-}tau)}$). However, there was no observed exposure-response relationship between the composite stability endpoint at Week 52 for CYP2D6 and dose and observed exposure ($logAUC_{(0\text{-}tau)}$). Consequently, no exploratory analyses on the predicted effects of the proposed eliglustat treatment regimen on the composite endpoint could be undertaken. In addition, there were no apparent linear PK/PD relationships between change from Baseline to Week 52 for the haemoglobin level (g/dL), platelet count (%) or liver volume (MN) (%) and observed exposure ($logAUC_{(0\text{-}tau)}$, Cmax). Consequently, no exploratory analyses of the predicted effects of the proposed eliglustat treatment regimen on these components of the composite endpoint could be undertaken.

In summary, it is considered that the efficacy of the sponsor's proposed treatment regimen in GD1 patients stabilised on ERT and switched to eliglustat has not been adequately established by the submitted data. It is considered that the efficacy of the sponsor's proposed regimen should be evaluated in an appropriately designed non-inferiority efficacy study in patients with GD1 stabilised on ERT and switched to eliglustat. The study should aim to demonstrate the non-inferiority of the proposed regimen relative to Cerezyme using the same endpoints as those in ENCORE.

Safety

Studies providing safety data and Patient exposure

The submission included an Integrated Summary of Safety (ISS) containing data from 4 Genzyme sponsored clinical studies including 393 patients with GD1 who took at least one dose of eliglustat as of the data cut-off date of 31 January 2013. The sponsor stated that the eliglustat clinical development program is the largest program in patients with GD to date. The methodology for the pooled data analysis was summarised in an analysis plan (Version 1.0) dated 21 June 2012. The 4 studies in GD1 patients forming the basis of the clinical safety package supporting registration of eliglustat for the proposed indications were ENGAGE, ENCORE, EDGE and the Phase II study [GZGD00304].

The pooled safety set of 393 eliglustat treated patients is referred to in the submission as the eliglustat safety set and this terminology has been adopted in this CER. The 393 GD1 patients in the eliglustat safety set are derived from the following studies:

- 26 patients treated for up to 4 years in the ongoing Phase II study (1 year primary analysis period in addition to a 3 year follow-up period);
- 40 patients from the controlled, Phase III study (ENGAGE) in treatment-naive patients, including data from the both the completed primary analysis period (39 weeks) and the on-going long-term-treatment period
- 157 patients from the controlled, Phase III study (ENCORE) in patients switched from ERT to eliglustat, including data from both the completed primary analysis period (52 weeks) and the on-going long-term treatment period; and
- 170 patients from the open-label bd lead-in period (6 to 18 months) from the on-going double-blind Phase IIIb study (EDGE) comparing once a day (qd) with bd administration of eliglustat.

The approach to the evaluation of the safety data has been to: (a) review the data from the ISS for the pooled eliglustat safety set (n=393); (b) review the comparative data for eliglustat (n=106) versus Cerezyme (n=53) from ENCORE in patients with prior ERT exposure for the completed primary analysis period (Week 52), with a data cut-off date of 9 November 2012: and (c) review the comparative data for eliglustat (n=20) versus placebo (n=20) from ENGAGE in treatment-naive patients for the completed primary analysis period (Week 39), with a data cut-off date of 18 July 2012.

In addition to the pivotal safety data based on the eliglustat safety set in patients with GD1, the submission included supportive safety data from 371 healthy subjects included in the Phase I studies (single dose eliglustat, n=199; repeated-dose eliglustat, n=172). The safety data from healthy subjects has been examined, but no formal review of the data has been provided in this CER. The data in healthy volunteers do not provide additional safety information to that observed in the studies in patients with GD1.

Postmarketing data

Not applicable.

Evaluator's overall conclusions on clinical safety

The submission included safety data on a total of 393 patients with GD1 exposed to at least one dose of eliglustat (eliglustat safety set), as of the data lock of 31 January 2013. Based on the 'rule of threes', eliglustat exposure in 393 patients should be sufficient to identify adverse drug reactions associated with eliglustat occurring with an incidence for which the upper 95% confidence interval is approximately 1%.[12] However, the population exposure is too small to estimate adverse drug reactions associated with eliglustat occurring with an incidence of less than 1%.

The 393 patients included 26 from the Phase II study, 40 from the pivotal study ENGAGE in treatment-naive patients, 157 from the pivotal study ENCORE in patients previously treated with ERT and 170 patients from the lead-in period in EDGE in treatment-naive and treatment-experienced patients. Overall, 134 of the 393 patients were treatment naive or did not have recent prior exposure to ERT and 259 had recent prior exposure to ERT.

The interpretation of the safety data in the eliglustat safety set is limited due to the absence of data for patients treated with controls (placebo or active). Therefore, the

[12] Jovanovic BD and Levy PS. A look at the rule of three. The American Statistician. May 1997, Vol 51, No 1.

comparative safety data from ENCORE (eliglustat [n=106 versus Cerezyme [n=53]) and from ENGAGE (eliglustat [n=20] versus placebo [n=20]) are of particular importance in interpreting the safety data for eliglustat. However, interpretation of comparative safety data from ENGAGE should be interpreted cautiously due to the small number of patients in the eliglustat (n=20) and placebo (n=20) groups.

ISS - eliglustat safety set (n=393)

In the eliglustat safety set, 391 patients (99%) received eliglustat 50 mg bd, representing 125.6 patient-years of exposure; 319 patients (81%) received eliglustat 100 mg bd, representing 290.8 patient-years of exposure; and 98 patients (25%) received eliglustat 150 mg bd, representing 113.4 patient-years of exposure. Two (2) patients did not receive 50 mg bd because they withdrew from the study after receiving only one 50 mg dose.

In the eliglustat safety set, 349 (89%) patients received eliglustat for at least 6 months, 204 (52%) patients received eliglustat for at least 12 months, 62 (16%) patients received eliglustat for at least 24 months, and 19 (5%) patients received eliglustat for at least 60 months. The mean (SD) duration of treatment was 1.4 (1.19) years and the total duration of treatment was 535.0 patient-years.

In the eliglustat safety set, 334 (85%) patients experienced a total of 2,340 treatment-emergent adverse events (TEAEs) (437 events/100 person-years). TEAEs were reported most commonly in the System Organ Classes (SOCs) of 'infections and infestations' (47%), 'gastrointestinal disorders' (41%), and 'nervous system disorders' (32%). The most commonly reported TEAEs in the eliglustat safety set (≥ 10% of patients) were: headache (17%); arthralgia (14%); nasopharyngitis (13%); upper respiratory tract infection (11%); diarrhoea (10%), and dizziness (10%). No individual TEAEs occurred in ≥ 18% of patients.

Treatment-related TEAEs were reported in 159 (40%) patients and those reported with an incidence of ≥ 2% were: headache (5%); dizziness (5%); diarrhoea (4%); dyspepsia (4%); constipation (3%); nausea (3%); upper abdominal pain (3%); abdominal pain (3%); GORD (3%); abdominal distension (2%); dysphagia (2%); flatulence (2%); palpitations (2%); fatigue (2%); and arthralgia (2%). No individual treatment-related TEAEs occurred in ≥ 6% of patients.

No deaths were reported in the eliglustat safety set through to 31 January 2013. Across the clinical trial program, a total of 5 deaths have been reported. In all cases, the events leading to the deaths were considered not related to eliglustat and 3 of the deaths occurred while the patients were not on eliglustat treatment. Two (2) patients in EDGE died while on eliglustat treatment (one due to multiple severe traumas following a downhill skiing accident after completion of the lead-in period, and another from cardiac arrest due to haemorrhaging and massive blood loss from unspecified violence) after the 31 January 2013 cut-off date and after completion of the lead-in period. Both of the deaths reported in EDGE were considered unrelated to study drug treatment.

SAEs were reported in 9% (n=35) of patients in the eliglustat safety set (42 events; 8 events/100 person-years). The most frequently reported SAE was syncope (5 patients, 1.3%). Other SAEs reported in ≥ 1 patient were myocardial infarction (n=3, 0.8%), maternal exposure during pregnancy (n=2, 0.5%) and cholecystitis (n=2, 0.5%). Of the 42 total SAEs, 5 were considered by the investigator to be related to eliglustat treatment.

TEAEs leading to permanent eliglustat discontinuation and study withdrawal were reported in 3% (n=12) of patients. The most commonly occurring TEAEs leading to treatment discontinuation were 'cardiac disorders' (SOC): 2 patients discontinued due to ventricular tachycardia; 2 patients discontinued due to myocardial infarction; and 1 patient discontinued due to palpitations. Ten (10) of the TEAEs leading to permanent eliglustat discontinuation were considered possibly or probably related to eliglustat: lethargy (2 events); exfoliative rash (2 events); ventricular tachycardia (1 event); upper

abdominal pain (1 event); palpitations (1 event); nausea (1 event); headache (1 event); and anaemia (1 event). The percentage of patients discontinuing treatment due to TEAEs was notably less than the percentage of patients experiencing TEAEs, indicating that nearly all TEAEs were manageable without treatment discontinuation.

Syncope (a TEAE of special interest) was reported in 2% (n=8) of patients (1.7 events/100 patient-years). All syncopal events were reported in female patients, and all but one of the events appeared to be vasovagal in origin with the aetiology of 1 event being unknown. Syncope was an SAE for 5 (1%) patients and 3 of the SAEs were considered by the investigator to be related to the study drug. One (1) event led to study drug interruption and 2 led to study drug adjustment but none of the events led to permanent study drug continuation or study withdrawal. ECGs performed at the time of the syncopal events identified no precipitating cardiac aetiologies for the events.

In the eliglustat safety set, 4% (n=15) of patients reported cardiac arrhythmia events by High Level Group Terms (HLGT) or High Level Terms (HLT). The HLTs in which events were most frequently reported included cardiac conduction disorders (6 [2%] patients), supraventricular arrhythmias (4 [1%] patients), ventricular arrhythmias and cardiac arrest (4 [1%] patients), and one patient reported a TEAE in the HLT of rate and rhythm disorders not elsewhere classified (NEC). No events of ventricular fibrillation, ventricular arrhythmia, sustained ventricular tachycardia, 3rd degree heart block or Torsade de Pointes were reported. No sudden cardiac deaths were observed during the clinical trial program.

In the 389 patients in the eliglustat safety set with ECG evaluations, 28 (7.2%) had at least one potentially clinically significant PR, QRS and/or QTcF abnormality leading to a safety narrative. These abnormalities were: 2 patients with new QTcF > 480 ms (> 480 ms post-baseline, ≤ 480 ms baseline); 6 patients with QTcF change from baseline > 60 ms; 7 patients with PR > 200 ms and increase from baseline ≥ 25%; and 18 patients with QRS ≥ 120 msec.

There were no significant changes from baseline over the duration of treatment in haematology, clinical chemistry or urinalysis parameters. Similarly, there were no significant changes from baseline over the duration of treatment in vital signs (temperature, respiratory rate, blood pressure, body mass index (BMI)).

The limited safety profile in patients aged ≥ 65 years did not appear to differ significantly from that in patients aged 16 to < 65 years. TEAEs were reported more frequently in female patients than in male patients.

In the eliglustat safety set, the safety profile of patients in the upper tenth percentile of exposure subgroup was consistent with safety profile of patients in the total safety set, based on the incidence of TEAEs and SAEs. However, there are caveats with the exposure criteria used to select patients for this subgroup (Cmax, $AUC_{(0\text{-}tau)}$ and/or Ctrough), including the variability of eliglustat metabolism, the short half-life of eliglustat, the marked inter-patient variability in the PK parameters, the timing of the doses preceding the PK samples, and the wide range of therapeutic exposures observed in the clinical trials.

ENCORE - eliglustat (n=106) versus Cerezyme (n=53) - GD1 patients previously treated with ERT

In the pivotal study in GD1 patients previously stabilised on ERT [ENCORE], the safety profile at the end of the 52 week primary analysis period was notably inferior in patients who had been switched to eliglustat (n=106) compared with patients who had been maintained on Cerezyme (n=53).

The mean (SD) time on study treatment was 361.5 (24.28) days in the eliglustat group and 349.0 (36.44) days in the Cerezyme group. At the end of the 52 week primary analysis period, 20% (21/106) of patients were in 50 mg bd group, 32% (34/106) of patients were

in the 100 mg bd group, and 48% (51/106) of patients were in the 150 mg bd group. The mean number of Cerezyme infusions per patient during the 52 week primary analysis period was 24.7 (3.3), which was consistent with the every other week (q2w) dosing interval employed in this study.

In ENCORE, TEAEs were reported notably more commonly in the eliglustat group than in the Cerezyme group (92% versus 79%, respectively).

The most commonly reported TEAE in patients in both the eliglustat and Cerezyme groups was arthralgia (15% [16/106], 22 events versus 17% [9/53], 9 events, respectively).

Treatment related TEAEs also occurred notably more commonly in patients in the eliglustat group compared with the placebo group (38% [40/106] versus 11% [6/53], respectively.

For more details on TEAEs see *Evaluator's overall conclusions on clinical safety* in Attachment 2.

There were no deaths reported in the 52 week primary analysis period. SAEs were reported notably more commonly in the eliglustat group compared with the Cerezyme group (10% [11/106 versus 0% [0/53], respectively). TEAEs leading to study drug discontinuation were reported in 2 (2%) patient the eliglustat group and 1 (2%) patient in the Cerezyme group. The TEAEs leading to treatment discontinuation were palpitations (eliglustat patient after 198 days on study), myocardial infarction (eliglustat patient after 237 days on study) and psychotic disorder (Cerezyme patient after 172 days on study). Of these three TEAEs, only 'palpitations' was assessed as being related to eliglustat.

In ENCORE, medical events of interest (MEOIs) were defined as clinically significant cardiac arrhythmias or syncope from any cause. In the eliglustat group, 6 (6%) patients experienced MEOIs (8 events) compared with no patients in the Cerezyme group. The 8 MEOI reported in 6 patients eliglustat group included 4 events of syncope (including 2 SAEs) in 3 patients, and 4 events of cardiac arrhythmia in 3 patients. The 4 syncopal events in the 3 patients in the eliglustat group were vasovagal in origin and did not appear to be precipitated by cardiac events. All 4 cardiac arrhythmias were detected during extensive, routine ECG and Holter monitoring as required by the protocol. All 4 cardiac arrhythmias were A-V nodal in origin (AV block second degree [n=3]; atrioventricular (AV) block first degree [n=1]), and none were associated with clinical symptoms. When reviewed by a cardiac adjudicator as well as a cardiologist serving on the Data Monitoring Committee (DMC), none of the 4 arrhythmias were considered to be clinically significant.

Cardiac safety (including protocol specified ECG and Holter monitoring) was extensively investigated in ENCORE. Overall, is considered that there are no clinically significant cardiac concerns associated with the eliglustat doses used in the study. Time-averaged ECG results for mean change from Baseline to Week 52 for eliglustat pooled doses (n=101) versus Cerezyme (n=49) for key parameters were: Hazard ratio (HR) = -1.0 versus 1.0 beats per minute (bpm); PR = 3.8 versus -1.1 ms; QRS = 2.8 versus 1.5 ms; and QTcF -0.6 versus 2.8 msec. The PK/PD analysis modelling the relationship between the predicted change from Baseline at Week 52 for change in QTc (ΔQTc) (ΔQTcF and ΔQTcB[13]), ΔQRS, ΔHR and ΔPR at the mean geometric Cmax for the three eliglustat dose groups (50, 100, and 150 mg bd) did not identify any notable differences across the three dose groups and

[13]The QT interval is dependent on the heart rate in an obvious way (the faster the heart rate the shorter the QT interval) and may be adjusted to improve the detection of patients at increased risk of ventricular arrhythmia. There are a number of different correction formulas. The standard clinical correction is to use *Bazett's formula* named after physiologist Bazett, calculating the heart rate-corrected QT interval (QTcB). Bazett's formula is: $QTcB=QT/\sqrt{RR}$ where QTcB is the QT interval corrected for heart rate, and RR is the interval from the onset of one QRS complex to the onset of the next QRS complex, *measured in seconds*, often derived from the heart rate (HR) as 60/HR (here QT is measured in milliseconds). Fridericia has published an alternative correction formula using the cube-root of RR.QTcF=QT/$\sqrt[3]{RR}$.

nor did it raise cardiac safety concerns. Protocol specified Holter monitoring identified 4 (3.8%) patients in the eliglustat group with new post-dose Holter findings compared with 2 (3.8%) patients in the Cerezyme group. No patients in the eliglustat group had any episodes of new ventricular tachycardia (sustained or non-sustained), while 1 patient in the Cerezyme group had a single episode of non-sustained ventricular tachycardia and frequent, short episodes of non-sustained supraventricular tachycardia.

Overall, the clinical laboratory data analysed from Baseline through to Week 52 were unremarkable in both the eliglustat and Cerezyme treatment groups. No clinically meaningful changes were identified in either treatment group in haematology parameters, clinical chemistry parameters (including liver function and renal function tests) or urinalysis parameters. In addition, there were no significant changes in vital sign parameters over the treatment period from Baseline to Week 52 in vital sign parameters in either the eliglustat or the Cerezyme group.

ENGAGE - eliglustat (n=20) versus placebo (n=20) - treatment-naive GD1 patients

In the pivotal study in treatment-naive patients [ENGAGE], 20 patients were randomised to each of the two treatment groups (eliglustat and placebo). Overall, the data in this study showed that eliglustat was well tolerated and there were no marked difference in the safety profiles of eliglustat and placebo. However, the data should be interpreted cautiously as there were only 20 patients in each of the two treatment groups.

The mean (SD) treatment duration was 274.2 (26.75) days in the eliglustat group and 274.8 (10.05) days in the placebo group. Of the 20 patients randomized to eliglustat, 17 (85%) had the initial dose of 50 mg bd increased to 100 mg bd from approximately Week 4 through Week 39, and 3 (15%) remained on 50 mg bd for the duration of the study. The safety results for the primary analysis period (39 weeks) are summarised below.

A total of 18 (90%) patients in the eliglustat group (137 events) and 14 (70%) patients in the placebo group (95 events) experienced TEAEs. The most commonly reported TEAEs occurring in ≥ 15% of patients (n ≥ 3) in the eliglustat group (versus the placebo group) in descending order of frequency were: headache (30% versus 40%); upper respiratory infection (URTI) (20% versus 5%); diarrhoea (20% versus 15%); toothache (15% versus 5%); and contusion (15% versus 10%). No other TEAEs occurred in ≥ 2 patients in the eliglustat group. The most commonly reported TEAEs occurring in ≥ 15% of patients in the placebo group (versus the eliglustat group) in descending order of frequency were: arthralgia (45% versus 10%); headache (40% versus 30%); nasopharyngitis (15% versus 0%); and diarrhoea (15% versus 20%). No other TEAEs occurred in ≥ 2 patients in the placebo group.

TEAEs considered by the investigator to be related to the study drug occurred in 40% (8/20) of patients in the eliglustat group (31 events) and 45% (9/20) of patients in the placebo group (25 events). The most frequently reported treatment-related TEAEs occurring in ≥ 2 patients (≥ 10%) in either treatment group (eliglustat versus placebo), in descending order of frequency in the eliglustat group, were: diarrhoea (10% versus 20%); flatulence (10% versus 5%); abdominal pain (5% versus 10%); headache (5% versus 15%); dizziness (0% versus 10%); and pruritus (0% versus 10%).

There were no deaths, other SAEs, treatment discontinuations due to TEAEs or study withdrawals due to TEAEs reported in ENGAGE during the primary analysis period (39 weeks).

Medical events of interest (MEOI) were defined as clinically significant cardiac arrhythmias or syncope from any cause. One (1) MEOI occurred in the placebo group (non-serious ventricular tachycardia), and none occurred in the eliglustat group. Cardiac safety (including protocol specified ECG and Holter monitoring) was extensively investigated in ENGAGE. Overall, is considered that there are no clinically significant

cardiac concerns associated with the eliglustat doses used in the study. The ECG data showed that time-averaged mean changes from Baseline to Week 39 in the pooled eliglustat group (n=19) versus the placebo group (n=20) for key parameters were: PR = 3.7 versus 2.9 ms; QRS = 4.7 ms versus 1.1 ms; and QTcF = -4.3 versus -2.5 ms. The only new Holter monitoring findings (that is, post-baseline) were 1 (5.3%) patient with new non-sustained ventricular tachycardia in the placebo group and 1 (5.0%) patient with new Mobitz 1, 2nd degree AV block in the eliglustat group.

Evaluator's conclusions on safety

Integrated Safety Summary (ISS) - eliglustat safety set

The eliglustat safety set from the 4 clinical studies included 393 patients who received at least one dose of eliglustat. Of the 393 patients, 134 were treatment naive or did not have recent prior exposure to ERT and 259 had recent prior exposure to ERT. In the eliglustat safety set, 391 patients (99%) received eliglustat 50 mg bd, representing 125.6 patient-years of exposure; 319 patients (81%) received eliglustat 100 mg bd, representing 290.8 patient-years of exposure; and 98 patients (25%) received eliglustat 150 mg bd, representing 113.4 patient-years of exposure (see Table 10 below). Two patients did not receive 50 mg bd because they withdrew from the study after receiving only one 50 mg dose.

In the eliglustat safety set (n=393), 349 (89%) patients received eliglustat for at least 6 months, 204 (52%) patients received eliglustat for at least 12 months, 62 (16%) patients received eliglustat for at least 24 months, and 19 (5%) patients received eliglustat for at least 60 months. The mean (SD) duration of treatment was 1.4 (1.19) years and the total duration of treatment were 535.0 patient-years. The mean (SD) cumulative dose of eliglustat was 91,289.4 (88,608.85) mg (median 62,700.0 mg; range 50.0 to 479,950.0 mg).

Table 10: Cumulative eliglustat exposure; eliglustat safety set.

	Eliglustat Dose			
Duration (months)	50 mg BID n (%)	100 mg BID n (%)	150 mg BID n (%)	Any Dose n (%)[a]
>0 to <2	292 (74)	76 (19)	9 (2)	7 (2)
≥2 to <6	32 (8)	45 (11)	8 (2)	37 (9)
≥6 to <12	31 (8)	117 (30)	24 (6)	145 (37)
≥12 to <18	19 (5)	40 (10)	25 (6)	89 (23)
≥18 to <24	7 (2)	10 (3)	16 (4)	53 (13)
≥24 to <36	7 (2)	16 (4)	16 (4)	42 (11)
≥36 to <48	0	0	0	1 (0)
≥48 to <60	0	1 (0)	0	0
≥60 to <72	3 (1)	10 (3)	0	13 (3)
≥72 to <84	0	4 (1)	0	6 (2)
Total Patients (any duration)	391[a]	319	98	393
Patient-Years of Exposure	125.6	290.8	113.4	535.0

Note: Patient exposure at each eliglustat dose level was summarized separately. The total (any dose) column represents the summary of each patient's total duration (months) exposed to eliglustat. If a patient appears in more than 1 dose category (mg bd) for a given duration, he/she is counted only once in the total (any dose) column. Duration of eliglustat treatment (months) = ([Date of last eliglustat dose up to cut-off – date of first eliglustat dose] + 1 day)/(365.25) *12. [a] = Two patients from the Phase II study received only 1 dose of eliglustat 50 mg; these patients are included in the row for '>0 to < 2 months' (in the total [any dose] cell) but are not included in the columns by specific dose (50 mg bd).

ENCORE - primary analysis period (Week 52) eliglustat versus Cerezyme

The mean (SD) number of days on study treatment was 361.5 (24.28) in the eliglustat group and 349.0 (36.44) days in the Cerezyme group. At the end of the Week 52 treatment period, the percentage of patients receiving the 3 possible eliglustat doses was: 50 mg bd (20%; 21/106); 100 mg bd (32%; 34/106); and 150 mg bd (48%; 51/106). The mean number of Cerezyme infusions per patient during the primary analysis period (52 weeks) was 24.7 (3.3), which was consistent with the q2w dosing interval employed in this study.

ENGAGE - primary analysis period (Week 39) eliglustat versus placebo

The mean (SD) number of days on study treatment was 274.2 (26.75) days in the eliglustat group and 274.8 (10.05) days in the placebo group. Of the 20 patients randomised to eliglustat, 17 (85%) had the initial dose of 50 mg bd increased to 100 mg bd from approximately Week 4 through Week 39, and 3 (15%) remained on 50 mg bd for the duration of the study.

First round benefit-risk assessment

First round assessment of benefits

GD1 patients who are treatment-naive

The submission satisfactorily demonstrates that treatment with eliglustat (dose titration regimen) benefits treatment-naive patients with GD1, irrespective of CYP2D6 metaboliser status. While there were no pivotal studies investigating the proposed treatment regimen in treatment-naive patients, the benefits observed with the titration regimen in both ENGAGE and the supportive Phase II study appear to have been driven primarily by the 100 mg bd dose in patients who were CYP2D6 EMs or IMs. Therefore, it is considered that it can be reasonably inferred that the submitted data have satisfactorily shown that treatment with eliglustat at a dose of 100 mg bd will benefit treatment-naive patients with GD1 who are CYP2D6 EMs and PMs.

In the pivotal Phase III study [ENGAGE], there was a statistically significant and clinically meaningful greater reduction in spleen volume (MN) from Baseline to Week 39 (primary efficacy endpoint) in the eliglustat group than in the placebo group: -27.77% versus +2.26%, respectively, difference = -30.03% (95% CI: -36.82, -23.24); p< 0.0001. In the eliglustat group, 75% of patients achieved a clinically meaningful reduction of at least 20% in spleen volume compared with only 5% of patients in the placebo group. In addition, all secondary endpoints in the eliglustat group compared with the placebo group showed greater statistically significant and clinically meaningful changes from Baseline to Week 39: absolute change in haemoglobin level 1.22 g/dL (p=0.0006); percentage change in liver volume -6.64% (p=0.0072); and percentage change in platelet count 41.06% (p< 0.0001).

ENGAGE excluded patients with documented acute pathological bone involvement (such as osteonecrosis and/or pathological fractures, as assessed by X-ray and/or magnetic resonance imaging (MRI)) or patients who had experienced a bone crisis in the 12 months prior to randomisation. Eliglustat showed a positive trend on BMD in the lumbar spine, including a mean increase in total Z-score that approached statistical significance for eliglustat compared with placebo (least squares (LS) mean treatment difference = 0.2, p=0.0604). However, eliglustat did not have an effect on femur total BMD, T or Z-scores during the initial 39 weeks of treatment.

In the supportive Phase II study, 77% (95% CI: 58%, 89%) of patients (20/26) treated with eliglustat (open-label) achieved the primary composite endpoint for success after 52 weeks of treatment: improvement in 2 of the 3 efficacy parameters (haemoglobin,

platelets, spleen volume) that were abnormal at Baseline. In addition, in patients with both Baseline and Month 48 data (n=19), statistically significant and clinically meaningful improvements in spleen volume, liver volume, haemoglobin level, and platelet count were observed at Month 48. The results showed that improvement in these 4 efficacy parameters observed with eliglustat treatment at Year 1 can be maintained or improved with continued treatment through to Year 4.

In both ENGAGE and the supportive Phase II study, in all patients (irrespective of CYP2D6 phenotype) an eliglustat titration regimen (50® 100 mg bd) was employed in the primary analysis period (39 weeks and 52 weeks, respectively), with upward dose titration early in treatment for patients with eliglustat trough concentrations < 5 ng/mL. However, the sponsor is proposing that the approved treatment regimen should be 100 mg bd in patients who are CYP2D6 EMs and IMs. The sponsor's post hoc proposal is based primarily on exploratory exposure-response analyses. In both ENGAGE and the pivotal 2 study, efficacy did not significantly differ between patients with average eliglustat Ctrough levels < 5 ng/mL or ≥ 5 ng/mL. In ENGAGE, PK/PD modelling showed no clinically meaningful difference between observed (all patients) and predicted (proposed patients) mean % change in spleen volume (MN) from Baseline to Week 39, based on predicted eliglustat exposure (logAUC(0-tau).

In both ENGAGE and the Phase II study, efficacy for the eliglustat titration regimen (50® 100 mg bd) is considered to have been driven primarily by the 100 mg bd dose. Therefore, the efficacy results from the two studies support the sponsor's 100 mg dosing regimen. In ENGAGE, 17 (85%) patients had their initial 50 mg bd dose increased to 100 mg bd from Week 4 (+2 weeks) due to eliglustat trough plasma concentration being < 5 ng/mL at Week 2, and this dose was maintained through Week 39. Three (3) patients (15%) remained on 50 mg bd from Baseline through Week 39, and no patients were treated with 150 mg over this period. In the Phase II study, 18 (75%) patients had their initial 50 mg bd dose increased to 100 mg bd from approximately Day 20 due their eliglustat trough plasma concentration being < 5 ng/mL on Day 10, and this dose was maintained through Week 52. Six (6) patients (25%) remained on 50 mg bd from Baseline through Week 52, and 5 of these patients continued on 50 mg bd through Month 48 while 1 patient had a dose increase to 100 mg bd after 36 months of treatment. No patients in the Phase II study were receiving 150 mg bd at the time of the data cut-off point, and all patients are now in their fifth year of study or greater.

Nearly all patients in both ENGAGE and the supportive Phase II study were CYP2D6 EMs or IMs. Therefore, based it is considered reasonable to restrict treatment to patients with these two CYP2D6 phenotypes. In ENGAGE, the CYP2D6 metaboliser status of the 20 patients treated with eliglustat was PM (0%, 0/20), IM (5%, 1/20), EM (90%, 18/20), and URM (5%, 1/20). In the Phase II study, 25 of the 26 patients (96%) treated with eliglustat were CYP2D6 EMs while only 1 patient was a CYP2D6 PM.

GD1 patients stabilised on ERT prior to switching to eliglustat

The submission satisfactorily demonstrates that treatment with eliglustat (titration-regimen) can maintain disease stability in patients with GD1 who have been switched from prior treatment with ERT. In the pivotal study [ENCORE], eliglustat (n=99) was shown to be non-inferior to Cerezyme (n=47) in patients switching to eliglustat from ERT (PP population).

In ENCORE, an eliglustat titration regimen (50® 100® 150 mg bd) was compared with Cerezyme in GD1 patients (irrespective of CYP2D6 status) who had been stabilised with Cerezyme. The sponsor is proposing that the approved treatment regimen should be fixed-dose 100 mg bd in patients who are CYP2D6 EMs and IMs. However, it is considered that the benefits of the 100 mg bd have not been adequately demonstrated for the reasons discussed in *Evaluator's conclusion on clinical efficacy for GD1* of this CER. The benefits of

the titration-regimen in all patients irrespective of CYP2D6 metaboliser status are outlined below.

The pre-specified primary composite efficacy endpoint required that stable haemoglobin levels, platelet counts, spleen volumes and liver volumes achieved with prior Cerezyme treatment for at least 3 years be maintained for a further 52 weeks in patients switching to eliglustat. The primary composite endpoint was achieved in 84.8% (84/99) of patients in the eliglustat group compared with 93.6% (44/47) of patients in the Cerezyme group, with the percentage difference between the two treatment groups being -8.8% (95% CI: -17.6, 4.2) in favour of Cerezyme. The lower bound of the 95% CI of --17.6% for the difference between the two treatments was within the pre-specified non-inferiority margin of 25%, and within the non-inferiority margin of 20% suggested by the EMA. Furthermore, the lower bound 95% CI of -8.14% for the percentage change from Baseline to Week 52 in the spleen volume (MN) was within the non-inferiority margin of 15% for this parameter recommended by the FDA. The key analyses on non-inferiority were within the PPS.

In ENCORE**,** patients treated with ERT had already reached pre-specified therapeutic goals for haematological parameters (haemoglobin level, platelet count) and organ volumes (spleen, liver) at Baseline, and changes from Baseline to Week 52 were small in both the eliglustat and Cerezyme treatment groups. At Week 52, the percentage of patients meeting the stability criteria for the individual components of the composite endpoint in the eliglustat and Cerezyme groups, respectively, were: spleen volume (MN), excluding patients with splenectomy, 95.8% [68/71] versus 100% [39/39]; haemoglobin level (94.9% [94/99] versus 100% [47/47]); platelet count (92.9% [92/99] versus 100% [47/47]; and liver volume (96.0% [95/99] versus 93.6% [44/47]). The percentage of patients achieving stability for 3 of the 4 components (spleen volume, haemoglobin level, platelet count) was higher in the Cerezyme group compared with the eliglustat group, while the percentage of patients achieving stability for liver volume was higher in the eliglustat group compared with the Cerezyme group. The observed percentage differences between the two treatment groups for each of the individual components of the composite endpoint are considered to be clinically insignificant.

The study excluded patients with symptomatic bone disease (such as bone pain attributable to osteonecrosis and/or pathological fractures) within the year prior to study entry. However, BMD was normal for the majority of patients in both treatment groups at study entry and remained stable throughout the 52 week primary analysis period. Most patients in ENCORE had moderate to severe marrow infiltration at Baseline and showed minimal changes after 12 months of treatment, possibly reflecting local pathology in the bone marrow such as infarction and fibrosis. In addition, ENCORE patients seemed to have had a long duration of disease, which may have led to irreversible changes in the marrow, and may also have resulted in bone complications secondary to splenectomy.

First round assessment of risks

Overall, the eliglustat titration regimen (50® 100® 150 mg bd) was generally well tolerated in GD1 patients who had been previously exposed to ERT or who were treatment-naive. However, the safety profile of eliglustat (n=106) was inferior to that of Cerezyme (n=53) in the pivotal study in GD1 patients who had been stabilised on Cerezyme and then switched to eliglustat compared with patients who had remained on Cerezyme [ENCORE]. In the small pivotal study in treatment GD1 patients, the safety profiles of eliglustat (n=20) and placebo (n=20) were similar [ENGAGE], although TEAEs were reported more frequently in patients in the eliglustat group compared with the placebo group. The safety profile in the eliglustat safety set (n=393) was consistent with the safety profiles for the two eliglustat groups in the ENCORE and ENGAGE.

The sponsor is proposing that eliglustat be approved at a dose of 100 mg bd, rather than a titration regimen based on eliglustat trough concentrations early in treatment. In ENCORE, at the end of the primary analysis period (52 weeks) the patient distribution in the three eliglustat groups was 50 mg bd (n=21, 20%), 100 mg bd (n=34, 32%), and 150 mg bd (n=51, 48%). Consequently, as the safety of the eliglustat titration regimen (50® 100® 150 mg bd) is considered to have been satisfactorily demonstrated in GD1 patients previously treated with ERT [ENCORE], it can be reasonably inferred that the 100 mg bd dosing regimen is also safe for this indication. In ENGAGE, at the end of the primary analysis period (Week 39), 17 (85%) patients were taking eliglustat 100 mg bd and 3 (15%) were taking eliglustat 50 mg bd. Therefore, as the safety of the eliglustat titration regimen (50® 100 mg bd) used in ENGAGE is considered to have been satisfactorily demonstrated for treatment-naive patients, it can be reasonably inferred that the 100 mg bd dosing regimen is also is safe for this indication.

Cardiac risks associated with eliglustat

The most important potential risk associated with eliglustat relates to cardiac conduction disorders. However, the clinical safety data showed that significant conduction disorders occurred infrequently with eliglustat and adequately demonstrated the cardiac safety of the drug in the treatment regimens studied.

In ENCORE, the risk of experiencing medical events of interest (clinically significant cardiac arrhythmias or syncope from any cause) was 6% (6 patients, 8 events) in the eliglustat group compared with 0% in the Cerezyme group. The 8 medical events of special interest reported in the 6 patients in the eliglustat group included 4 events of syncope of non-cardiac origin in 3 patients and 4 events of cardiac arrhythmia in 3 patients. All 4 cardiac arrhythmias were A-V nodal in origin (AV block 2n degree [n=3]; AV block 1st degree [n=1]), and none were associated with clinical symptoms. When reviewed by a cardiac adjudicator as well as a cardiologist serving on the DMC, none of the 4 arrhythmias were considered to be clinically significant. In ENGAGE, the risk of experiencing medical events of interest (clinically significant cardiac arrhythmias or syncope from any cause) was 5% (1/20) in the placebo group (1 event of non-serious ventricular tachycardia) and 0% in the eliglustat group.

In the Integrated Safety Summary (ISS), cardiac disorders (HLGT) were reported in 15/393 (4%) patients in the eliglustat safety set (18 events; 3 events/100 person-years). Cardiac conduction disorders (HLT) were reported in 6 (2%) patients (8 events; 1 event/100-patient years) and were predominantly second degree AV block with no reports of 3rd degree AV block. Supraventricular arrhythmias (HLT) were reported in 4 (1%) patients (4 events; 1 event/100 person-years). Ventricular arrhythmias and cardiac arrest (HLT) were reported in 4 (1%) patients (5 events; 1 event/100 person years) and included 3 patients with ventricular tachycardia (4 events) and 1 patient with ventricular extrasystoles (1 event). Rate and rhythm disorders (NEC) were reported in 1 patient (tachycardia). No events of ventricular fibrillation, ventricular arrhythmia, sustained ventricular tachycardia, third degree AV block or Torsades de Pointes were reported in the eliglustat safety set. No sudden cardiac deaths were observed during the clinical trial program.

It should be noted that both pivotal studies excluded patients with clinically significant coronary artery disease, including history of myocardial infarction (MI) or ongoing signs or symptoms consistent with cardiac ischaemia or heart failure, or clinically significant arrhythmias or conduction defect such as second or third degree AV block, complete bundle branch block, prolonged QTc interval or sustained ventricular tachycardia (VT). Consequently, it is possible that patients with these conditions treated with eliglustat might be at an increased risk of adverse cardiac events.

Co-administration of medications known to prolong the QTc interval were prohibited in the 30 days prior to randomisation in the two pivotal studies [ENGAGE, ENCORE], with the exception of pre-medication for ERT infusions which were allowed up to 7 days prior to randomisation. The sponsor proposes that eliglustat not be used in combination with Class IA and Class III antiarrhythmic medications.

Both pivotal studies included restrictions on treatment with strong CYP2D6 and/or strong CYP3A4 inhibitors prior to randomisation. The sponsor proposes that eliglustat be contraindicated in patients taking a strong or moderate CYP2D6 inhibitor in combination with a strong or moderate CYP3A4 inhibitors, recommends against the use strong CYP2D6 inhibitors, advises caution with the use of strong and moderate CYP3A4 inhibitors and recommends against the use of strong CYP3A4 inhibitors. However, it is recommended that the use of strong CYP2D6 inhibitors should be contraindicated on safety grounds. The sponsor's proposal to exclude CYP2D6 PMs and URMs from treatment with eliglustat means that it will be mandatory for all patients to be CYP2D6 genotyped prior to treatment in order to determine their metaboliser status.

Overall risks - ENCORE (patients previously treated with ERT)

In the pivotal study [ENCORE], TEAEs were reported more commonly in the eliglustat group than in the Cerezyme group (92% versus 79%, respectively). However, no TEAEs were reported in > 15% of patients in the eliglustat group. The most frequently reported TEAE in both treatment groups was arthralgia and this event occurred in a similar proportion of patients in the eliglustat and Cerezyme groups (15% versus 17%, respectively). The most frequently reported TEAEs occurring in ≥ 10% of patients (in descending order of frequency were) arthralgia (15%), fatigue (14%), headache (13%), back pain (12%), nausea (12%), diarrhoea (12%), pain in extremity (11%), upper abdominal pain (10%), URT1 (10%) and sinusitis (10%).

TEAEs reported in ≥ 10% of patients in either of the two treatment groups and in ≥ 2% more patients in the eliglustat group (descending order of frequency) versus the Cerezyme group were: fatigue (14% versus 2%); headache (13% versus 2%); back pain (12% versus 6%); diarrhoea (12% versus 4%); nausea (12% versus 0%); pain in extremity (11% versus 2%); upper abdominal pain (10% versus 0%); URTI (10% versus 6%); and sinusitis (10% versus 2%). No TEAE were reported in ≥ 10% of patients in either of the two treatment groups and in ≥ 2% more patients in the Cerezyme group compared with the eliglustat group.

There were no deaths reported in the 52 week primary analysis period. However, SAEs were reported notably more commonly in the eliglustat group compared with the Cerezyme group (10% [11/106 versus 0% [0/53], respectively). The only SAE reported in more than 1 patient in the eliglustat group was syncope (n=2 [1%]). Only 1 SAE (myocardial infarction) resulted in study drug discontinuation. The time to onset of the reported SAEs was beyond 3 months in the majority of cases.

TEAEs leading to study drug discontinuation were reported in 2 (2%) patients the eliglustat group and 1 (2%) patient in the Cerezyme group. These figures indicate that nearly all TEAEs in both treatment groups were managed without resorting to treatment discontinuation. TEAEs leading to treatment discontinuation were palpitations (eliglustat patient after 198 days on study), myocardial infarction (eliglustat patient after 237 days on study) and psychotic disorder (Cerezyme patient after 172 days on study). Of these three TEAEs, only 'palpitations' was assessed as being related to eliglustat.

Medical events of interest (cardiac arrhythmias and syncope) were reported in 6 (6%) patients in the eliglustat group (3 with AV-block; 3 with non-cardiac syncope) and no patients in the Cerezyme group. Cardiac safety (including protocol specified ECG and Holter monitoring) was extensively investigated in ENCORE. Overall, is considered that

there are no clinically significant cardiac concerns associated with the eliglustat doses used in the study.

No clinically meaningful changes in haematology parameters, clinical chemistry parameters (including liver function and renal function tests) or urinalysis parameters were observed in patients treated with eliglustat or Cerezyme in the primary analysis period (52 weeks). In addition, there were no significant changes from Baseline through to Week 52 in vital sign parameters in either the eliglustat group or the Cerezyme group.

Overall risks - ENGAGE (treatment naive patients)

In the pivotal study [ENGAGE], TEAEs were reported more commonly in the eliglustat group than in the placebo group (90% versus 70%, respectively). The most commonly reported TEAEs occurring in ≥ 15% of patients (n ≥ 3) in the eliglustat group (versus the placebo group) in descending order of frequency were: headache (30% versus 40%); URT1 (20% versus 5%); diarrhoea (20% versus 15%); toothache (15% versus 5%); and contusion (15% versus 10%). No other TEAEs occurred in ≥ 2 patients in the eliglustat group. The most commonly reported TEAEs occurring in ≥ 15% of patients in the placebo group (versus the eliglustat group) in descending order of frequency were: arthralgia (45% versus 10%); headache (40% versus 30%); nasopharyngitis (15% versus 0%); and diarrhoea (15% versus 20%). No other TEAEs occurred in ≥ 2 patients in the placebo group.

There were no deaths, other SAEs, treatment discontinuations due to TEAEs or study withdrawals due to TEAEs reported during the primary analysis period (39 weeks). Medical events of special interest (clinically significant cardiac arrhythmias or syncope from any cause) were reported in 1 (5%) patient in the placebo group (non-serious ventricular tachycardia) and no patients in the eliglustat group.

No clinically meaningful changes in haematology parameters, clinical chemistry parameters (including liver function and renal function tests) or urinalysis parameters were observed in patients treated with eliglustat or placebo in the primary analysis period (39 weeks). In addition, there were no significant changes from Baseline through to Week 39 in vital sign parameters in either the eliglustat or the placebo group.

Overall risks - ISS (eliglustat safety set) - all GD1 patients irrespective of previous treatment)

The risk profile of eliglustat based on the eliglustat safety set (n=393) was consistent with the safety profiles of eliglustat observed in the two pivotal studies [ENCORE, ENGAGE]. In the eliglustat safety set, 334 (85%) patients experienced a total of 2,340 TEAEs (437 events/100 person-years). TEAEs were reported most commonly in the SOCs of 'infections and infestations' (47%), 'gastrointestinal disorders' (41%), and 'nervous system disorders' (32%). The most commonly reported TEAEs in the eliglustat safety set (≥ 10% of patients) were: headache (17%); arthralgia (14%); nasopharyngitis (13%); URTI (11%); diarrhoea (10%); and dizziness (10%).

There were no deaths reported in the eliglustat safety set through to 31 January 2013. However, across the clinical trial program, a total of 5 deaths have been reported. In all cases, the events leading to the deaths were considered not related to eliglustat and 3 of the deaths occurred while the patient was not receiving treatment with eliglustat. Two (2) patients in EDGE died while on eliglustat treatment after the 31 January 2013 cut-off date and after completion of the lead-in period and neither of the deaths was considered to be related to study drug treatment.

SAEs were reported in 9% (n=35) patients in the eliglustat safety set (42 events; 8 events/100 person-years). The most frequently reported SAE was syncope (5 patients, 1.3%). Other SAEs reported in ≥ 1 patients were myocardial infarction (n=3, 0.8%), maternal exposure during pregnancy (n=2, 0.5%), and cholecystitis (n=2, 0.5%). Of the 42

total SAEs, 5 were considered by the investigator to be related to eliglustat treatment. TEAEs leading to permanent eliglustat discontinuation and study withdrawal were reported in 3% (n=12) of patients. The most commonly occurring TEAEs leading to treatment discontinuation were 'cardiac disorders': 2 patients discontinued due to ventricular tachycardia; 2 patients discontinued due to myocardial infarction; and 1 patient discontinued due to palpitations.

Syncope (all causes) was reported in 2% (n=8) of patients (1.7 events/100 patient-years) and all patients were female. Non-cardiac causes for syncope were identified in 7 of the 8 patients, with the aetiology of 1 event being unknown. In the eliglustat safety set, 4% (n=15) of patients reported cardiac arrhythmia events (HLGT). The HLTs in which events were most frequently reported were cardiac conduction disorders (6 [2%] patients), supraventricular arrhythmias (4 [1%] patients), ventricular arrhythmias and cardiac arrest (4 [1%] patients) and rate and rhythm disorders not elsewhere classified (NEC) (1 [0.3%] patient). No events of ventricular fibrillation, ventricular arrhythmia, sustained ventricular tachycardia, third degree heart block or Torsade de Pointes were reported. No sudden cardiac deaths were observed during the clinical trial program.

There were no significant changes from baseline over the duration of treatment in haematology, clinical chemistry or urinalysis parameters. Similarly, there were no significant changes in from baseline over the duration of treatment in vital signs (temperature, respiratory rate, blood pressure and BMI).

The limited safety profile in patients aged ≥ 65 years did not appear to differ significantly from that of patients aged 16 to < 65 years. TEAEs were reported more frequently in female patients than in male patients.

Clinical Questions

Pharmacokinetics

1. Eliglustat was primarily cleared by hepatic metabolism. However, no studies were submitted investigating the potential effects of hepatic impairment on the PKs of eliglustat. Does the sponsor intend undertaking such a study? If not, please justify the decision not to undertake such a study.
2. While renal elimination of unchanged eliglustat was < 1%, the mass-balance study [GZGD02107] indicated that urinary excretion of the total administered radioactive dose was 41.8%. The results of the mass-balance study indicate that renal excretion has an important role in the elimination of eliglustat metabolites. No studies were submitted investigating the potential effects of renal impairment on the excretion of eliglustat metabolites. Does the sponsor intend undertaking such a study? If not, please justify the decision not to undertake such a study.
3. Does the sponsor have any data characterising the identity of the human plasma protein binding proteins?
4. In ENCORE, the PK parameters, including Ctrough levels, in CYP2D6 EMs were similar for the 50 mg bd, 100 mg bd and 150 mg doses at both Week 13 and Week 52. The last dose titration occurred at Week 8, after which time doses remained stable through Week 52. Therefore, it appears reasonable to infer that the PK data at Week 13, and particularly at Week 52, reflect the steady state PKs of 50 mg bd, 100 mg bd and 150 mg bd dose regimens in CYP2D6 EMs. Consequently, these PK data appear to provide no basis for preferring a fixed-dose 100 mg bd regimen over a 50 mg bd or a 150 mg bd regimen for the treatment of CYP2D6 EMs and IMs. Please comment on this observation.

5. In the exploratory PK/PD analysis [POH0395], observed and predicted % change in spleen volume (MN) from Baseline to Week 52 based on the PK/PD model (predicted $logAUC_{(0\text{-}tau)}$ in the ENCORE (PPS) were provided comparing all patients in the study with simulated patients (100 mg bd, EM/IM combined)(POH395). Please undertake similar exploratory PK/PD analyses for ENCORE using predicted % change in spleen volume (MN) from Baseline to Week 52 for the 50 mg bd and 150 mg bd doses.
6. In the exploratory PK/PD analysis [POH0395], no apparent trend was observed when the composite primary endpoint (patients remaining stable for 52 weeks), for each CYP2D6 and eliglustat dose by Week 52, was plotted against observed $logAUC_{(0\text{-}tau)}$. Please account for this observation.
7. In the exploratory PK/PD analysis [POH03095], for the % change in spleen volume (MN) from baseline at Week 52 [ENCORE], a statistically significant PK/efficacy association was shown for both observed $logAUC_{(0\text{-}tau)}$ and logCmax. However, no statistically significant PK/efficacy relationships were shown for the other 3 components of the primary composite endpoint, as there was no apparent treatment effect in the concentration range studied. Please account for this observation.
8. In the exploratory PK/PD analysis [POH03095], for the % change in spleen volume (MN) from baseline at Week 52 [ENCORE], a statistically significant PK/efficacy association was shown for both observed $logAUC_{(0\text{-}tau)}$ and logCmax. Therefore, the proposed dosing regimen for patients stabilised on ERT and switched to eliglustat is supported only by PK/PD modelling and simulation (M & S) analyses of the % change in spleen volume (MN) at Week 52. Please provide a clinical justification for using the results of these M & S analyses to support the proposed dose, given that the three other components of the composite stability end point failed to demonstrate a treatment effect in the concentration range studied in ENCORE.

Efficacy

9. What method was used to randomise patients in ENCORE (for example IVRS)?
10. In ENCORE, no statistical adjustment was made for multiple testing of the secondary and tertiary endpoints. Please justify why an adjustment for multiplicity was not used.
11. In ENCORE, the median age for patients switching from ERT to eliglustat (FAS) is given as 37.4 years in the study report while in the Summary of Clinical Efficacy it is given as 36.9 years. Please account for this apparent discrepancy.
12. In ENCORE, the percentages of patients (FAS) receiving the three possible doses of eliglustat during the 52 week treatment period were 20% (21/106) 50 mg bd, 32% (34/106) 150 mg bd, and 48% (51/106) 150 mg bd. For each treatment group, please provide the proportion of patients whose condition remained stable at Week 52 based on the composite primary efficacy composite and the corresponding results for each of the 4 components of the composite primary endpoint. Were there any statistically or clinically significant differences observed between doses? If no statistically significant differences were observed, were the analyses adequately powered to detect such differences?
13. For ENCORE, please indicate the proportion of patients in each of the three dosage groups with trough plasma concentrations < 5 ng/mL and ≥ 5 ng/mL.
14. In ENCORE, stability in the composite endpoint was maintained after 52 weeks of treatment in 31/40 (77.5%) eliglustat patients who had average steady-state Ctrough values < 5 ng/mL, compared with 56/66 (85%) patients with average

steady-state Ctrough values ≥ 5 ng/mL. Please provide the difference between the proportions with 95% confidence intervals.

15. In ENGAGE, the reduction in spleen volume (MN) was 23.05% in the patient group with average Ctrough concentrations < 5 ng/mL (n=9) and 31.28% in patients with average Ctrough levels ≥ 5 ng/mL. Please provide the results for the difference, including 95% confidence interval, between the two groups for reduction in spleen volume (MN) from Baseline to Week 39.
16. Does the sponsor intend to undertake a pivotal efficacy study in GD1 patients previously treated with ERT to assess whether a single dose regimen of eliglustat 100 mg bd can satisfactorily maintain stability in patients switched from ERT? If not, please justify.

Safety

17. In the eliglustat safety set (urinalysis), for urine protein (g/L) there appeared to be a trend over time for an increasing percentage of patients to shift from normal to abnormal.

Second round evaluation of clinical data submitted in response to questions

For details of the sponsor's responses and the evaluator's comments, see Attachment 2.

Second round benefit-risk assessment

GD1 patients who are treatment-naive

The benefit-risk balance of the proposed treatment regimen (100 mg bd limited to CYP2D6 EMs or IMs) for GD1 patients who are treatment-naive is considered to be favourable for the reasons outlined above in *First round assessment of benefits*.

GD1 patients stabilised on ERT prior to switching to eliglustat

The benefit-risk balance for the titration regimen (50® 100® 150 mg bd) used in all patients (irrespective of CYP2D6) in the pivotal study [ENGAGE] is considered to be favourable, although the exploratory subgroup analysis suggest that dose titration based on Ctrough levels < 5 ng/mL is not clinically justified if treatment is limited to CYP2D6 EMs and IMs.

It is considered that the benefit-risk balance for the proposed treatment regimen (that is, fixed-dose 100 mg bd, limited to CYP2D6 EMs or IMs) for GD1 patients who have been stabilised on ERT prior to switching to eliglustat cannot be assessed, because the benefits of the proposed 100 mg bd regimen have not been adequately demonstrated in the submitted data. The efficacy data based on the titration regimen (50® 100® 150 mg bd), do not allow inferences to be made about the potential contribution of the individual doses to the observed outcomes. Furthermore, the steady state PK data at Week 13 and Week 52 in CYP2D6 EMs appears to be similar for the 50, 100 and 150 mg bd dose regimens. Consequently, neither the efficacy data relating to the titration regimen nor the PK data relating to the individual doses contributing to the titration regimen provide a basis for selecting a fixed-dose 100 mg bd regimen in preference to a fixed-dose 50 mg bd or 150 mg bd regimen for the treatment of CYP2D6 EMs and IMs.

The exploratory subgroup efficacy analysis based on Ctrough levels (< 5 ng/mL and ≥ 5 ng/mL) supports a fixed-dose regimen rather than a dose-titration regimen (50® 100 mg

bd, or 50® 100® 150 mg bd) but provides no insight into the most appropriate fixed-dose. The exploratory PK/PD analysis for one of the four components of the composite stability endpoint showed that the observed (all patients) and predicted (simulated proposed patients) % change in spleen volume (MN) from Baseline to Week 52 were similar, based on the PK efficacy model (logAUC(0-tau). However, no exploratory PK/PD data based on the composite stability endpoint (which was the primary efficacy) or the three other components contributing to the composite stability endpoint (% change in spleen volume, % change in platelet count, absolute change in haemoglobin concentration) could be undertaken as no relationships were seen between observed logAUC(0-tau) and these outcomes over the dose range studied. There are no pivotal efficacy or safety data in the submission assessing the benefits of the proposed treatment regimen.

First round recommendation regarding authorisation

GD1 patients who are treatment-naive

It is recommended that the proposed treatment regimen (100 mg bd limited to CYP2D6 EMs or IMs) be *approved* for the reasons outlined above in *First round assessment of benefits.*

GD1 patients stabilised on ERT prior to switching to eliglustat

It is recommended that the proposed treatment regimen (100 mg bd limited to CYP2D6 EMs or IMs) be *rejected***.**

It is considered that the submission has not satisfactorily established that the proposed dose of 100 mg bd is the most appropriate dose for the proposed indication in patients who are EMs or PMs. In particular, the submission has not established that the 100 mg bd dose is more efficacious for the proposed indication in EMs or IMs than the 50 mg bd or the 150 mg bd doses used in the pivotal study in patients stabilised on ERT and switched to eliglustat [ENCORE]. Furthermore,

The specific reasons for the recommendation are:

1. There is no pivotal efficacy and safety study in patients with GD1 (EMS/IMs) stabilised on ERT and switched to eliglustat 100 mg bd demonstrating that disease stability in patients switched to eliglustat is non-inferior to disease stability in patients maintained on ERT.
2. There is no evidence indicating that the efficacy of the titration regimen used in ENCORE (50® 100® 150 mg bd) is being driven by the 100 mg bd dose rather than the 50 mg bd dose or 150 mg bd dose. At the end of the primary analysis period (Week 52), the distribution of the doses in eliglustat treated patients was 20% (21/106) 50 mg bd, 32% (34/106) 150 mg bd, and 48% (51/106) 150 mg.
3. In ENCORE, the steady state PK data at Week 13 and Week 52 in CYP2D6 EMs appears to be similar for the 50, 100 and 150 mg bd dose regimens. Consequently, the data do not provide a basis for selecting a fixed-dose 100 mg regimen in preference to a fixed-dose 50 mg bd or 150 mg bd regimen for the treatment of CYP2D6 EMs or IMs.
4. The exploratory PK/PD analysis [ENCORE] for one of the four components of the composite stability endpoint showed that the observed (all patients) and predicted (simulated proposed patients) % change in spleen volume (MN) from Baseline to Week 52 were similar, based on the PK efficacy model ($logAUC_{(0\text{-}tau)}$. Therefore, this exploratory PK/PD analysis supports the proposed treatment regimen. However, there was no apparent PK/PD relationship between the primary composite efficacy

(stability) endpoint and exposure (observed $logAUC_{(0\text{-}tau)}$) over the dose range studied. In addition, there was no PK/PD relationship between each of the three other components of the composite efficacy endpoint and exposure (observed $logAUC_{(0\text{-}tau)}$) over the dose range studied. Consequently, there are no exploratory PK/PD analyses supporting the proposed dosing regimen based on the primary composite (stability) efficacy endpoint and three of the four components of the composite endpoint (% change in liver volume, % change in platelet count and absolute change in haemoglobin level). Overall, it is considered that the post hoc, exploratory PK/PD analysis has generated a new hypothesis relating to the most appropriate dosing regimen for the treatment of GD1 patients stabilised on ERT and switched to eliglustat but has not provided a definitive assessment of the proposed regimen. It is considered that the exploratory PK/PD analysis 'should not subvert the requirement for dose response data from prospective, randomized, multi-dose-level clinical trials'.[14]

5. The exploratory efficacy analysis [ENCORE] in subgroups based on Ctrough levels supports a fixed-dose regimen rather than a dose-titration regimen but provides no insight into the most appropriate dose.

It should be noted that the pivotal study [ENCORE] supports the benefit-risk balance of the titration regimen (50® 100® 150 mg bd), based on plasma eliglustat concentrations, for all GD patients (irrespective of CYP2D6 status) switched from Cerezyme to eliglustat. However, the sponsor specifically argues against adoption of this dose-titration regimen in '*the post-approval setting'*. The sponsor considers that simplifying the eliglustat prescribing information by targeting CYP2D6 EMs and IMs with a single-dose strength (eliglustat 100 mg) reduces the risk of administration of the incorrect dose or contraindicated concomitant medication. The sponsor also considers that the dose-titration regimen is much more feasible in a clinical trial setting rather than in clinical practice, as the large fluctuations in eliglustat plasma concentrations over each 12 hour dosing interval 'results in an exquisite dependence on the timing of dosing in order to accurately determine whether dose escalation is necessary'. Furthermore, the sponsor argues that the trough target level of 5 ng/mL used in the clinical studies is not an absolute threshold for efficacy. The sponsor considers that use of this target in clinical practice '*could prove confusing to patients and clinicians who may feel that patients who are unable to achieve the 5 ng/mL concentration cannot benefit from therapy'*.

It is the opinion of this evaluator that, while the benefit-risk balance of the dose-titration regimen used in ENCORE is satisfactory, the totality of the data suggests that a single-dose eliglustat treatment regimen restricted to patients who are CYP2D6 EMs or IMs is clinically more appropriate. In addition, if such a treatment regimen is employed, determination of plasma eliglustat concentrations would not be required on either efficacy or safety grounds. However, the current submission has failed to adequately identify the most appropriate single-dose strength of eliglustat in GD patients switched from Cerezyme to eliglustat.

V. Pharmacovigilance findings

Risk management plan

The sponsor submitted a Risk Management Plan EU Risk Management Plan Version 1.0 (dated 03 September 2013, Data Lock Point (DLP) 31 January 2013) and Australian

[14] Dose Response Information to Support Drug Registration. ICH Topic E4, Step 5 (CPMP/ICH/378/950, paragraph 4.6, page 10; TGA adopted guideline.

Specific Annex Version (Version 1.0, dated November 2013) which was reviewed by the TGA's Office of Product Review (OPR).

Safety specification

The sponsor provided a summary of ongoing safety concerns which are shown at Table 11.

Table 11: Ongoing safety concerns provided by the sponsor in their RMP submission.

Important identified risks	None
Important potential risks	Drug-drug interactions – Use with cytochrome P450 (CYP)2D6 and/or CYP3A inhibitors
	Use of eliglustat in patients who are CYP2D6 poor metabolisers (PM) and/or non-genotyped patients
	Cardiac conduction disorders and arrhythmias
	Vasovagal syncope
Important missing information	Use in patients with a history of or current cardiac ischaemia or heart failure, clinically significant arrhythmias or conduction findings
	Use in patients with hepatic impairment
	Use in children
	Use during pregnancy and lactation
	Use in patients with renal impairment

Pharmacovigilance plan

The sponsor proposes routine and additional pharmacovigilance activities.

The sponsor has not provided study protocols or protocol synopses for all studies referenced in the pharmacovigilance plan. The sponsor should provide the missing study protocols or protocol synopses as soon as they become available.

With regard to references made to additional pharmacovigilance activities in the submitted EU-RMP, the sponsor has not provided consistent study name labelling or protocol number labelling throughout the document; for example the nonclinical placental and lactation study/studies is/are referred to by different names and it remains unclear whether the same study is meant. The sponsor should update the RMP document and refer to the same studies by the same name throughout.

Risk minimisation activities

The sponsor proposes routine and additional risk minimisation activities.

Reconciliation of issues outlined in the RMP report

Table 12 summarises the OPR's first round evaluation of the RMP, the sponsor's responses to issues raised by the OPR and the OPR's evaluation of the sponsor's responses.

Table 12: Reconciliation of issues outlined in the First Round RMP Evaluation Report

Recommendation in RMP evaluation report	Sponsor's response/summary of the response	OPR evaluator's comment
1. Safety considerations may be raised by the nonclinical and clinical evaluators through the consolidated section 31 request and/or the Nonclinical and Clinical Evaluation Reports respectively. It is important to ensure that the information provided in response to these includes a consideration of the relevance for the Risk Management Plan, and any specific information needed to address this issue in the RMP. For any safety considerations so raised, please provide information that is relevant and necessary to address the issue in the RMP.	*'The Sponsor confirms that the Nonclinical and Clinical Evaluation Reports have been reviewed to ensure that any responses provided to issues raised have been considered for relevance to the Risk Management Plan.'*	The sponsor's response has been noted.
2. The sponsor should clarify the above and in particular should provide a compelling justification for the following: The non-matching doses across various documents (RMP, PI, etc.) without any reference to conversion. The evidence base of the 84 mg/100 mg dosing recommendation, in particular with regard to safety and adverse events, as most studies conducted seems to involve some form of upward titration (for example 50 mg bd for 4 weeks and then 100 mg bd).	*'Cerdelga is formulated as a hard capsule for oral administration containing 84 mg eliglustat which is equivalent to 100 mg eliglustat tartrate. Information on the dose conversion for the salt was included as part of the cover letter for the application and is described in the relevant supporting documents included with the submission. For ease of reference a statement indicating the conversion from active to salt has been incorporated into the 'Product Profile' section of the ASA.* *The evidence and justifications supporting the clinical safety and effectiveness of Cerdelga for the proposed dosing schedule are fully described in the supporting documents subject of clinical evaluation. The RMP evaluator is referred to these documents which provide a full description of the clinical development program as reflected in the Clinical Evaluation Report.'*	The sponsor's response has been noted. The sponsor has not specified which documents support an immediate dose of 100 mg, in contrast to upward titration on which most clinical data is based. The issue is referred to the Delegate for decision.

Recommendation in RMP evaluation report	Sponsor's response/summary of the response	OPR evaluator's comment
3. The sponsor should provide the missing study protocols or protocol synopses, as soon as they become available.	*'A synopsis for the proposed PASS study 'A prospective multicenter observational post-authorisation safety study to characterise the long-term safety profile of eliglustat' is now available and is provided in Annex 4 of the updated Australian Specific Annex v1.1.* *As previously indicated the sponsor will provide copies of all other protocols once finalised.'*	The sponsor's response has been noted.
4. The sponsor should update the RMP document and refer to the same studies by the same name throughout.	*'An updated EU RMP v1.1 and ASA is provided as part of the responses.'*	The sponsor's response has been noted.
5. The following should be added as Ongoing Safety Concerns and become part of the pharmacovigilance plan, or a compelling justification provided: *Important Identified Risk* Gastrointestinal effects (including, but not limited to diarrhoea);	*'A discussion of GI effects including comparison with miglustat are presented in the Clinical Safety Summary. GI effects as seen with miglustat could be caused by inhibition of intestinal glycosidases. Overall, eliglustat shows little or no inhibition of glycosidases, with no measurable inhibition of several glycosidases and digestive disaccharidases. [15] Eliglustat did not inhibit acid β-glucosidase activity up to 37 µM (15 µg/mL Genz 99067) (GT-157-EF-57).* *Mild to moderate interactions were seen with peripheral BZD receptor (24% inhibition), and Cav1.2 L-type receptor (46% inhibition), both of which may be linked to GI effects such as vomiting at doses of 25 mg/kg in dogs (GT-157-TX-4).* *The decreased Ileum weights in the male groups of the 13 week dog study (GT-157-TX-15) were not correlated with any histopathology changes and therefore determined to be without toxicological significance.* *In rats, dose-related salivation was evident in the toxicology studies and GI transit was completely inhibited at a single dose of 100 mg/kg, and dogs vomited at doses ≥ 25 mg/kg. The prediction of clinical correlates to these*	This is considered acceptable.

[15] McEachern, 2007, Mol Genet Metab

Recommendation in RMP evaluation report	Sponsor's response/summary of the response	OPR evaluator's comment
	effects in laboratory animals is not straightforward, as dietary composition and feeding regimens are strictly controlled in the laboratory settings for animal studies. *In the pooled Eliglustat Safety Set, Gastrointestinal disorders was the second most frequently affected System Organ Class, with treatment-emergent AEs (TEAEs) reported in 41% of eliglustat-treated patients. However, no single Preferred Term (PT) occurred in more than 10% of eliglustat-treated patients overall and there was no consistent association with eliglustat treatment across studies (the ISS ENGAGE CSR; ENCORE CSR). In the pooled Eliglustat Safety Set, diarrhoea, abdominal pain upper, and nausea each occurred in 8 - 10% of patients.*	
	Analysis of gastrointestinal TEAEs that have been reported in ≥ 5% of eliglustat treated patients (Diarrhoea, Dyspepsia, Constipation, Nausea, Abdominal pain upper, Abdominal pain, and Gastrooesophageal reflux disease) shows that all were non serious, the majority were mild to moderate (3:1), started at a mean of 113 days after eliglustat treatment initiation, and were transient in duration (median duration of 3 days). Overall for TEAEs reported in ≥ 5% of eliglustat-treated patients in the Gastrointestinal disorders SOC, PTs of Diarrhoea, Dyspepsia, Constipation, Nausea, Abdominal pain upper, Abdominal pain, and Gastrooesophageal reflux disease were more frequently considered not related than related to eliglustat by the Investigators. The 2 most frequent TEAEs in the Gastrointestinal disorders SOC considered related to eliglustat by the investigators were Diarrhoea (17/393 patients [4%]) and Dyspepsia (16/393 [4%]). In the placebo-controlled study (ENGAGE) with treatment-naïve patients, more placebo-treated patients reported diarrhoea than eliglustat-treated patients suggesting that investigator bias (as diarrhoea is a prominent feature in miglustat) may be	

Recommendation in RMP evaluation report	Sponsor's response/summary of the response	OPR evaluator's comment
	contributing to blinded reports of diarrhoea. No single GI event reported in ENGAGE occurred at a 5% higher frequency in eliglustat-treated patients. Nausea, abdominal pain, vomiting, and diarrhoea are also commonly observed in patients treated with Cerezyme. *Across the clinical program, diarrhoea was reported in 39 (10%) eliglustat-treated patients. In the majority of patients, diarrhoea was mild, transient (median duration of 3 days), and considered more frequently not related than related to eliglustat. Most events of diarrhoea occurred in the first 6 months of eliglustat treatment. Gaucher disease itself could be contributing to the varied GI findings reported in the clinical trials. Enlargement of the liver is the rule in patients with Gaucher disease and can fill the entire abdominal cavity, particularly in splenectomized patients. The increased volume of the liver may cause distress to the patient, including episodes of pain due to liver infarction or mechanical stress on ligaments. Some of the reported GI events in this clinical program could have been related due to hepatosplenomegaly secondary to underlying Gaucher disease.* *Because of the nonspecific and transient nature of the reported GI events in eliglustat clinical trials, the inhibition of GI transit observed in animals at 100 times the human clinical exposure is not considered relevant to human usage and the clinical trial GI findings are more likely not related to eliglustat and potentially disease related. The sponsor therefore does not consider Gastrointestinal effects (including, but not limited to diarrhoea) warrants inclusion as an additional important identified risk. The ASA remains aligned with the information included in the EU RMP.'*	
Infections (including, but not limited to URTIs);	*'A drug utilisation study that covered the period between January 2003 and June 2012 has been conducted in the MarketScan database in the US. There were 168 adult patients who were treated for Gaucher disease and*	The sponsor's response is not considered acceptable. Reasons include, but are not limited to the following:

Recommendation in RMP evaluation report	Sponsor's response/summary of the response	OPR evaluator's comment
	retrospectively assessed for up to 6 months before treatment initiation to assess the frequency of comorbidities of interest (cardiac disease, arrhythmia, syncope, renal impairment, hepatic impairment, depression and/or anxiety disorders and upper respiratory infection). 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 hepatic impairment and/or cardiac disease. In animal studies, there was no indication of infections to suggest that lymphoid depletion resulted in a subsequent change in immune function. *The sponsor therefore does not consider Infections (including, but not limited to URTIs) warrants inclusion as an additional important identified risk. The ASA remains aligned with the information included in the EU RMP.'*	No reference for the drug utilisation study (DUS) has been provided, and it is unclear whether the DUS is concerned with eliglustat or includes other treatments for Gaucher disease. Whether 7.1% patients had URTIs within 6 months prior to starting is not relevant to the occurrence of infections (URTIs or more importantly other infections) while on eliglustat. The sponsor does not report on infections other than URTIs. The potential absence of one mechanism for infections in animal studies does not infer that infections do not occur. The request is made based on clinical data (for example data outlined in Table 100 of the Clinical Evaluation Report). Infection is an important risk associated with eliglustat. The recommendation remains.
Dizziness.	*'In the Integrated Safety Summary ISS, reports of dizziness that were assessed as related or not related to treatment were similar in frequency (approximately 5% of patients each). All events of dizziness (38 patients) were mild or moderate (31 patients and 7 patients, respectively) and mostly transient. The onset of dizziness was within the first week of eliglustat treatment for 14 of the 38 patients, and within the first month for one-half of the patients. An extensive analysis of dizziness as it relates to measured blood pressure or ECG intervals did not*	The sponsor does not need to include this as an Ongoing Safety Concern but not for the reasons provided by the sponsor.

Recommendation in RMP evaluation report	Sponsor's response/summary of the response	OPR evaluator's comment
	reveal any relationship between dizziness and blood pressure lowering or increase in any ECG interval. The sponsor therefore does not consider dizziness warrants inclusion as an additional important identified risk. The ASA remains aligned with the information included in the EU RMP.'	
Important Potential Risk Reduction in GI motility;	*'A potential mechanism for the GI effects observed in the eliglustat clinical trials is suggested from the in vitro receptor screening panel data (ligand binding assays) (GT 157-EF-61). A number of receptors that interacted with eliglustat at 10 µM (4.2 µg/mL), the highest concentration tested in these assays, may contribute to effects on GI function)*[16]*. Specifically, binding to the mu opioid receptor (MOP) was inhibited by 53% and binding to the kappa opioid receptor (KOP) was inhibited by 27% at 10 µM. The assays did not define whether eliglustat acted as an agonist or antagonist of these receptors, only that it inhibited binding of the assay ligand. Agonists of these opioid receptors, such as morphine, are associated with decreased intestinal motility and constipation in clinical use.*[17] *In addition to opioid receptors, eliglustat (10 µM) also interacted with the dopamine receptors D3 (69% inhibition) and D4.4 (60% inhibition), and the 5HT receptors 1A (65% inhibition), 2A (62% inhibition), 2B (55% inhibition), and 6 (73% inhibition) (GT-157-EF-61). The binding of eliglustat to these dopamine and 5HT receptors also has the potential to impact GI motility (GT-157-EF-61).* *However new data from an in vitro receptor binding assay was subsequently conducted to assess the interaction of eliglustat with dopamine receptors, serotonin receptors, µ-opioid*	The sponsor does not need to include this as an Ongoing Safety Concern but not for the reasons provided by the sponsor.

[16] Schulz R, Wtister M, and Herz A. Centrally and Peripherally Mediated Inhibition of Intestinal Motility by Opioids Naunyn-Schmiedeberg's Arch. Pharmacol. 308, 255-260 (1979)
Talley N.J. *Review article* : *5-hydroxytryptamine agonists and antagonists in the modulation of gastrointestinal motility and sensation*; *clinical implications. Aliment. Pharmacol. Ther. (1992)* ***6,*** *273-289*
[17] Holzer P. Treatment of opioid-induced gut Dysfunction. *Expert Opin. Investig. Drugs (2007) 16(2):181-194*

Recommendation in RMP evaluation report	Sponsor's response/summary of the response	OPR evaluator's comment
	receptors and sigma-receptors and demonstrated that there were no apparent inhibitory interactions with the tested receptors, as no IC50 was identified up to the highest concentration tested of 100µM (GT-157-EF-62). *Although the majority of the reduction in GI motility seen with eliglustat was possibly related to interactions with opioid and other receptors (particularly the 5HT and dopamine receptors), the clinical correlates or consequences of these receptor binding data are uncertain, as they were evident only at very high concentrations relative to the mean predicted clinical exposures. The concentration of 10 µM (or 4.2 µg/ml) that tested in the initial receptor binding assay is approximately 100 times greater than the mean predicted clinical Cmax of 44.3 ng/ml (SIM0124). Moreover, in a second study receptor binding assay to identify an IC_{50}, for binding to the dopamine, serotonin, µ-opioid and sigma-receptors, the IC_{50} was determined to be greater than the highest concentration tested of 100 µM.* *The sponsor therefore does not consider Reduction in GI motility warrants inclusion as an additional important potential risk. The ASA remains aligned with the information included in the EU RMP.'*	
Off-label use (including, but not limited to other lysosomal storage diseases).	*'Eliglustat is not intended for use in adult patients with GD1 who are CYP2D6 poor metabolisers (PM), ultra-rapid metabolisers (URM), or indeterminate metabolisers. Eliglustat has the potential to be used in such patients, however, the benefit-risk relationship has not been established in the PM and URM populations with the only commercial dose strength available of 100 mg. No PMs have been treated with dosing regimens other than 50 mg bd; their exposure is predicted to be high with a dose of 100 mg bd (predicted Cmax of 294 ng/mL), and there is no clinical experience in PMs with an off-label dosing regimen of 100 mg once daily (qd). It is possible that there might be lack of efficacy for*	This is considered acceptable.

Recommendation in RMP evaluation report	Sponsor's response/summary of the response	OPR evaluator's comment
	the URM treated with 100 mg bd, however, no conclusions can be made based on the limited clinical trial data. *Eliglustat is not expected to cross the blood-brain-barrier, and eliglustat is not expected to have any direct beneficial effect on the neurological manifestations in these diseases. Eliglustat is not intended for use in Gaucher patients with other subtypes (type 2 and type 3) and therapy with eliglustat will be initiated and supervised by a physician knowledgeable in the management of Gaucher disease. As noted in the proposed indication, the target population is adult GD1 patients who are CYP2D6 intermediate (IM) or extensive (EM) metabolisers. Information provided in the Product Information (PI) and Consumer Medicines Information (CMI) and provider education (Guide for prescriber targeting the prescribing physician, including specific details about genotyping) will reduce concerns with off-label use.* *In view very small patient population in Australia the current means of access to treatments for rare disease and the specialist oversight it is not considered relevant to reflect use non Gaucher patients as a potential risk.* *Nevertheless, the sponsor agrees that the off-label use of eliglustat in Gaucher disease type 2 and 3 is considered as important potential risks. This is reflected in the updated EU-RMP v1.1 and the ASA has been revised accordingly.'*	
Missing Information Long-term safety beyond 36 months.	*'There are no indications that the safety profile of eliglustat is different with long-term exposure based on the data available to date. Nevertheless, the sponsor agrees that the safety in long-term use is considered as missing information. This is reflected in the updated EU-RMP v1.1 and the ASA has been revised accordingly.* *In addition to Routine Pharmacovigilance to monitor AEs and SAEs in long-term treatment use of*	This is considered acceptable.

Recommendation in RMP evaluation report	Sponsor's response/summary of the response	OPR evaluator's comment
	eliglustat, the sponsor also committed to two additional risk minimisation activities including continuous monitoring of AEs in ongoing clinical trials to further describe AEs with accrued duration of exposure and to conduct a prospective multicentre observational post-authorisation study with the primary aim to characterise the long-term safety profile in eliglustat-treated patients in real world clinical practice. These activities are also reflected in the revised ASA.'	
6. The sponsor should confirm that the same or equivalent additional risk minimisation activities as in the EU will be conducted in Australia, and provide the actual materials to be used as additional risk minimisation items.	*'The sponsor confirms that the same additional risk minimisation activities as in the EU will be conducted in Australia. The local Australian risk minimisation tools are aligned with the EU risk minimisation tools.* *Revised versions of the tools have been included with the updated ASA provided with the responses to reflect updates made to the EU tools. Copies are provided in Annex 3 of the updated Australia Specific Annex, V1.1.'*	The sponsor's response has been noted.
7. The sponsor should clarify what constitutes a 'specialist' (RMP terminology) or a 'physician knowledgeable in the management of Gaucher disease' (PI document terminology), and how the sponsor plans to ensure that all prescribers of eliglustat will utilise the materials (such as the prescriber checklist) adequately.	*'The terminologies of 'specialist' and a 'physician is knowledgeable in the management of Gaucher disease' are used interchangeably in the EU RMP V1.0.In Australia patients with Gaucher disease are usually managed by a singular physician rather than a multi-disciplinary team. There are approximately 23 physicians across Australia who manage approximately 80 Gaucher patients in total. Nearly 80% of treaters are haematologists or paediatric haematologists, with the remaining 20% comprised of metabolic geneticists, a general paediatrician and an endocrinologist. Educational material will be made available to all physicians treating Gaucher patients. Due to the small number of doctors and patients involved direct feedback will be readily available on the usefulness of the tools and routine pharmacoviligance will provide confirmation that appropriate drug utilisation is occurring in Australia considering the recognised risks from drug interactions with CYP2D6 and*	The sponsor's response has been noted. ACSOM provided the following advice: *'The committee also discussed the OPR reviewer's comments regarding what constitutes a 'specialist' as described in the RMP. One member suggested use of the term, 'metabolic physician' but the committee acknowledged that a multidisciplinary team would more than likely be involved in treating a GD patient, which would also be determined based on where the patient lived for example, gastroenterologists, hepatologists, orthopaedic surgeons and general practitioners. As*

Recommendation in RMP evaluation report	Sponsor's response/summary of the response	OPR evaluator's comment
	CYP3A inhibitors. *In view of the global alignment of risk minimization measures and tools proposed to mitigate risks studies planned for the EU or USA to assess the effectiveness of tools such as the Guide for Prescriber (including the prescriber checklist) are also expected to be valid for Australia based on the similarities in population, standards of care and indication. Data generated in such studies will be informative for the ongoing review and assessment of the risk management approach in Australia.'*	*such, the committee advised that using broader terminology such as a 'physician with a detailed knowledge and experience in the treatment of Gaucher Disease' would be the most appropriate. '* Care is unlikely to be provided by a 'singular physician', but more likely by a multidisciplinary team, in accordance with best practice.
8. The sponsor should make available the prescriber education materials to all health care professionals involved in the treatment of a patient taking eliglustat.	*'The Sponsor confirms educational materials will be made available to all health care professionals involved in the treatment of a patient taking eliglustat. They will be distributed using a variety of methods which may include electronic or hard copy formats to ensure accessibility to all key stakeholders involved in the management of Gaucher patients.* *The prescriber education materials (Guide for Prescriber) are intended for the physicians/specialists who initiate/supervise treatment with eliglustat only. The physicians have the responsibility to discuss/remind the patient the importance of using the Patient Alert Card. The Patient Alert Card is a liaison tool to provide educational materials to all the other healthcare professionals who are involved in the treatment of Gaucher disease. It focuses particularly on the potential drug-drug interactions prior prescription or delivery of any additional medicinal products (including herbal products).* *All healthcare professionals are encouraged to refer to the Product Information or contact Sanofi Medical Information for additional information required.*	The sponsor's response has been noted. However, given that a multidisciplinary team is likely to provide care for patients with Gaucher disease, the recommendation remains. The sponsor should make available the prescriber education materials not only to prescribers, but to all health care professionals involved in the treatment of a patient taking eliglustat.
9. Given that the sponsor has not proposed a titration schedule for	*'The rationale for the fixed single dose regimen is explained in detail in the clinical documentation included with*	The sponsor's response has been noted. ACSOM made the

Recommendation in RMP evaluation report	Sponsor's response/summary of the response	OPR evaluator's comment
eliglustat but proposes that patients take the 84 mg/100 mg dose from the start, the sponsor should outline what additional monitoring should occur, in this initial period of administration.	*the application and subject of clinical evaluation. As demonstrated during clinical development the safety profile of eliglustat in GD1 patients does not warrant any additional monitoring as part of the initial period of administration.'*	following comments: *'In noting the relatively small population group affected by GD (and that most patients live in or around Sydney), the committee made the additional suggestion that it would also be useful to consider implementing ongoing therapeutic monitoring protocols (given the variability of results shown in the clinical trial data) and to also have a set of guidelines to ensure consistent clinical practice and knowledge sharing between the treating health professionals.'* The issue is referred to the Delegate for decision.
10. The sponsor should provide a plan on how the effectiveness of the education programme will be measured, considering that the planned drug utilisation studies only covers the EU and the US.	*'The core safety messages submitted to Health Authorities for eliglustat are consistent across the world. It is expected that due to similarities in population, standards of care and indication, data generated in relation important potential risks and missing information in other global markets such as EU or USA will be informative for the ongoing review and assessment of the risk management approach in Australia.* *Any significant feedback from effectiveness studies of risk minimisation tools from Europe will be incorporated into future RMP versions. Global activities to validate the effectiveness of risk minimisation activities are detailed in the EU RMP.'*	The sponsor's response has been noted. Additionally, the effectiveness (or lack thereof) of the proposed additional risk minimisation activities should be reported in the Periodic Safety Update Reports (PSURs).
11. SI units commonly used in Australia should be used throughout the document, (for example, [g/L] instead of [g/dL] for haemoglobin values, or [g/mol] for molecular weight rather than the	*'Recommendation accepted.'*	The sponsor's response has been noted.

Recommendation in RMP evaluation report	Sponsor's response/summary of the response	OPR evaluator's comment
non-SI designation [g/mole].		
12. A number of recommendations of changes to the draft PI were made. The details of these are beyond the scope of this AusPAR. Outstanding issues are summarised under *Summary of recommendations* below.		
13. In regard to the proposed routine risk minimisation activities, it is recommended to the Delegate that the draft consumer medicine information document be revised to accommodate the changes made to the product information document.	*No response received.*	The recommendation remains.

Summary of recommendations

Outstanding issues

It is considered that the sponsor's response has adequately addressed some of the issues identified in the RMP evaluation report. There are outstanding issues. Additional recommendations have been made.

Additional recommendations

Recommendations in regard to risk minimisation activities

In the '*Contraindications*' section, the PI should contain a statement that contraindicates treatment with eliglustat in GD1 patients who are CYP2D6 poor metabolisers (PMs) or ultra-rapid metabolisers (URMs), or in whom CYP2D6 status is indeterminate (or a statement to that effect) and the ASA updated accordingly (new recommendation).

Ongoing therapeutic monitoring protocols should be provided by the sponsor to the TGA.

Summary of outstanding issues (including additional recommendations)

Recommendations in regard to Ongoing Safety Concerns

1. 'Infections' should be added as an Important Identified Risk and become part of the pharmacovigilance plan (Recommendation 1.5 in the Round 1 RMP Evaluation Report)

Recommendations in regard to risk minimisation activities

2. The effectiveness of the proposed additional risk minimisation activities should be reported in the PSURs.
3. It is recommended to the Delegate to consider the clinical evidence of using the 100 mg bd dose without uptitration and whether monitoring should occur in this initial period of administration. Furthermore, ongoing therapeutic monitoring protocols should be provided by the sponsor (new recommendation).
4. In the 'Contraindications' section, the PI should contain a statement that contraindicates treatment with eliglustat in GD1 patients who are CYP2D6 poor metabolisers (PMs) or ultra-rapid metabolisers (URMs), or in whom CYP2D6 status is indeterminate (or a statement to that effect) and the ASA updated accordingly (new recommendation).

5. In the 'Precautions' section, the PI should include precautionary statements, under separate headings, for the following (despite some of these statements also being available in other parts of the PI document):
    a. Patients with renal impairment;
    b. Patients with hepatic impairment;
    c. Anaemia and thrombocytopaenia;
    d. Different populations of CYP2D6 metabolisers (including poor and ultra-rapid CYP2D6 metabolisers, and the need for appropriate genotyping); and
    e. Monitoring of patients on eliglustat (including but not limited to cardiac monitoring)
6. In the 'Precautions' section, under the existing 'Patients with pre-existing cardiac conditions' heading, the PI should contain a statement on patients with structural heart disease.
7. In the 'Precautions' section, the PI should contain a statement with regard to available long-term use data (or a statement to that effect).
8. In the 'Precautions' section, the PI should include a statement with regard to the ability to operate a motor vehicle or machinery, with regard to syncopal episodes, dizziness, fatigue or otherwise.
9. In the 'Adverse Reactions' section, the PI should list the known adverse reactions with special consideration, under separate headings, of cardiac disorders, and GI disorders.
10. In the 'Adverse Events' section, the PI should additionally include URTIs, nasopharyngitis, sinusitis, GI disorders (including, in separate listings, vomiting, abdominal pain, constipation, dyspepsia, GORD), paraesthesia, dizziness, weight loss, tremor, peripheral oedema, and increased creatine phosphokinase.
11. In regard to the proposed routine risk minimisation activities, it is recommended to the Delegate that the draft consumer medicine information document be revised to accommodate the changes made to the product information document.

Advice from the Advisory Committee on the Safety of Medicines (ACSOM)

Background

The committee considered a request for advice relating to an RMP for eliglustat (Cerdelga). Cerdelga's proposed indication is for the long-term treatment of adult patients with Gaucher disease type 1 (GD1).The committee noted that the additional risk minimisation activities proposed by the sponsor consist of prescriber education (only through a prescriber checklist), and a patient card. The proposed prescriber checklist and patient card for the European Union (EU) are outlined in Annex 11 of the EU RMP which was included among the agenda papers.

The committee's advice on a number of specific questions asked by the TGA is detailed below.

Advice

Can the committee comment on whether the proposed additional risk minimisation activities are sufficient?

The committee considered the small and defined population of people with Gaucher Disease (GD), the different types of GD and how the phenotype for the disease is expressed: type 1 is the most common type (approximately 90% of patients) and is characterised by multi-system disorder, hepato-splenomegaly, bone weakness/fractures

and cytopenias. Type 2 and 3 are more aggressive neurological types with most patients not reaching adulthood.

The committee also noted the proposed indication for eliglustat and discussed its pharmacokinetics. The committee advised that the wide therapeutic index of eliglustat and the complexity of its pharmacology lend itself to have a potentially wide range of interactions with other drugs. However, it is difficult to identify the strength of potential interactions with other medicines and keeping the PI up to date as new medicines come into market will also be an issue requiring further consideration.

In considering the proposed additional risk minimisation activities, the committee agreed that the patient card is a good resource, particularly as it makes it clear that eliglustat is a substrate and an inhibitor which will prompt the treating health professional to seek further assistance if they are not familiar with the treatment of GD. The committee advised that consideration could also be given to the use of a medical alert bracelet as an optional extra, which may be discussed with the patient at the time of dispensing.

The committee discussed the prescriber checklist and whether it is a useful tool for health professionals. The committee advised that the checklist needs to be useful for both prescribers and other health professionals who encounter patients with GD. In this context, the committee advised that the intent of the checklist needs to be carefully considered and defined. For example, is it intended to be an 'awareness raising' tool or will it serve a broader purpose?

The committee also discussed the RMP evaluator's comments regarding what constitutes a 'specialist' as described in the RMP. One member suggested use of the term, 'metabolic physician' but the committee acknowledged that a multidisciplinary team would more than likely be involved in treating a GD patient, which would also be determined based on where the patient lived for example gastroenterologists, hepatologists, orthopaedic surgeons and general practitioners. As such, the committee advised that using broader terminology such as a 'physician with a detailed knowledge and experience in the treatment of Gaucher Disease' would be the most appropriate.

In noting the relatively small population group affected by GD (and that most patients live in or around Sydney), the committee made the additional suggestion that it would also be useful to consider implementing ongoing therapeutic monitoring protocols (given the variability of results shown in the clinical trial data) and to also have a set of guidelines to ensure consistent clinical practice and knowledge sharing between the treating health professionals.

Key changes to the updated RMP

EU Risk Management Plan Version 1.0 (dated 3 September 2013, DLP 31 January 2013) and Australian Specific Annex Version (Version 1.0, dated November 2013) has been superseded by EU Risk Management Plan Version 1.1 (dated 2 May 2014, DLP 31 January 2013) and Australian Specific Annex Version (Version 1.1, dated July 2014).

Table 12: Summary of key changes to the updated EU-RMP

Summary of key changes between EU Risk Management Plan Version 1.0 and EU Risk Management Plan Version 1.1	
Safety specification	Important Potential Risks added: Use with strong CYP3A inducers Use with P-gp or CYP2D6 substrates Off-label use in Gaucher disease type 2 and 3

Summary of key changes between EU Risk Management Plan Version 1.0 and EU Risk Management Plan Version 1.1	
	Important Missing Information added: Safety in long-term treatment use
Pharmacovigilance activities	Updates to include new Ongoing Safety Concerns
Risk minimisation activities	Updates to include new Ongoing Safety Concerns

Suggested wording for conditions of registration

RMP

Any changes to which the sponsor agreed become part of the risk management system, whether they are included in the currently available version of the RMP document, or not included, inadvertently or otherwise.

The suggested wording is:

Implement EU Risk Management Plan Version 1.1 (dated 2 May 2014, DLP 31 January 2013) and Australian Specific Annex Version (Version 1.1, dated July 2014) as a condition of registration.

I. Overall conclusion and risk/benefit assessment

The submission was summarised in the following Delegate's overview and recommendations:

Quality

Eliglustat tartrate is manufactured by chemical synthesis. The drug product is an immediate release oral capsule containing 84 mg eliglustat (100 mg eliglustat tartrate). A shelf-life of 24 months below 25°C is proposed. Apart from minor issues which are expected to be resolved there are no outstanding issues. There are no objections to registration. Pharmaceutical Subcommittee (PSC) advice was not needed.

Bioequivalence between the developmental product and the proposed commercial product was demonstrated in a clinical study and is considered acceptable.

Note 84 mg eliglustat is equivalent to 100 mg eliglustat tartrate. During clinical development, products were referred to according to eliglustat tartrate content (50, 100, 150 mg). The same terminology is used in this report. However, the product label and prescribing information will refer to eliglustat, that is, 84 mg dosing.

Nonclinical

In vitro studies confirmed the ability of eliglustat to inhibit glucosylceramide synthesis (GCS). Metabolites of eliglustat also inhibited GCS but only at concentrations exceeding clinical exposure.

Eliglustat demonstrated in vitro inhibition of K^+, Na^+ and Ca^{2+} channels at 8, 117 and 240 times clinical exposure respectively based on C_{max}.

Eliglustat showed no pharmacodynamic drug interaction with β-glucosidase (imiglucerase) in an in vitro study at concentrations greatly in excess of clinical exposure. Results from pharmacological studies on eliglustat did not identify any clinically relevant off-target binding sites.

Eliglustat is extensively metabolised by oxidative metabolism. The major CYP450 isozymes involved were CYP2D6 and CYP3A4. Potential for pharmacokinetic drug interactions was demonstrated and considered relevant to clinical use in humans. Eliglustat was both a substrate and inhibitor of P-glycoprotein (P-gp). Eliglustat was also a competitive inhibitor of CYP2D6 and to a lesser extent, CYP3A4.

Eliglustat did not produce evidence of genotoxic potential. The most abundant human metabolite Genz-399240 was also negative for genotoxic potential. Eliglustat did not elicit increase in treatment-related tumours in lifetime carcinogenicity studies in mice and rats at exposure levels 3 to 4 times that anticipated clinically.

Eliglustat did not demonstrate evidence of effect on fertility in rats at up to 10 times clinical exposure. In a rat study, there was some evidence of treatment-related, reversible, effect on sperm motility and morphology together with increased germ cell atrophy and seminal vesicle inflammation at exposure levels 10 to 20 times that anticipated clinically. A small follow-up 4 week study in monkeys did not show any apparent adverse male reproductive effects but the results were too variable and limited to be conclusive.

Embryofetal toxicity studies in rats and rabbits showed evidence of maternal toxicity, delayed ossification and a slight increase in skeletal malformations in rats at exposure levels more than 16 times clinical exposure. Increased postimplantation loss, reduced pup numbers and lower pup body weight were observed in a rat pre/postnatal study, but only at maternotoxic levels (>16 times the clinical AUC). The sponsor has proposed Pregnancy Category B1. However, B3 is considered consistent with the animal data and has been accepted.

At the time of submission the sponsor had ongoing studies of placental transfer and milk excretion. These reports are to be provided to TGA as soon as available.

Overall, the nonclinical evaluators have no objections to registration. Recommendations for PI have been provided.

Clinical

The clinical dossier comprised 13 pharmacology studies, one Phase II study and 2 pivotal Phase III efficacy studies [ENCORE, ENGAGE]. A number of population PK analysis and computer simulations were provided. Safety data from an ongoing Phase III study [EDGE] was also included.

Pharmacokinetics

CYP2D6 phenotyping for metaboliser status was performed in all eliglustat clinical studies except the single ascending dose study [GZGD00103] and the food effect study [GZGD00404].

Absolute bioavailability [GZGD02107] involved a single dose of eliglustat 50 mg IV, 100 mg oral, followed by 100 mg bd oral for 5 days and a single radiolabeled dose of oral solution on last day in 10 healthy males [9 were CYP2D6 extensive metabolisers (EM)]. Absolute bioavailability (F) was 4.5%. Mean (dose-normalised) eliglustat AUC after IV dose was > 20 times compared to that after oral dose indicating extensive first pass effect. The volume of distribution was large indicating extensive tissue distribution. Absorption was rapid (Tmax < 2 hours). Half-life was 5 to 6 hours. Total body clearance (CL/F) after 5 days of 100 mg bd dosing was about 40% (1290 L/h) of the CL/F after a single dose (3490 L/h).

Table 13: Summary of Genz-99067 Plasma Pharmacokinetics parameters after single oral and IV doses and repeat (bd) oral doses of eliglustat in healthy adult males in Study GZGD02107

Parameter[a]	Single Dose – 50 mg IV	Single Dose - 100 mg PO (capsule)		Repeat Dose - 100 mg BID PO (capsule) x 5 days + 100 mg PO (^{14}C-eliglustat solution)[b]
N	10	10	8[c]	8
C_{max}, ng/mL	107 (25.0)	5.48 (5.01)	4.47 ± 3.03	12.1 ± 5.11
t_{max}, h	1.00 (0.50, 1.50)	1.76 (1.00, 4.00)	1.76 (1.50, 4.00)	2.00 (1.50, 2.07)
$AUC_{0-\infty}$, ng·h/mL	499 (65.7)	47.2 (52.5)	34.5 (22.5)	NA
AUC_{0-12}, ng·h/mL	NA	35.8 (35.9)	27.6 ± 18.0	76.3 ± 28.1
$t_{1/2}$, h	6.59 (0.446)	5.47 (1.39)	5.49 ± 1.33	6.48 ± 0.692
F, %	NA	4.49 (4.13)	NA	NA
CL/F, L/h	NA	3490 (2360)	3430 ± 2020	1290 ± 545
Vz/F, L	NA	24400 (12800)	25100 ± 11100	11900 ± 4650
CL, L/h	85.8 (10.4)	NA	NA	NA
Vz, L[d]	816 (117)	NA	NA	NA
LR	NA	NA	NA	2.56 ± 0.742
$AR(C_{max})$[e]	NA	NA	NA	3.13 (0.905)
$AR(AUC_{0-12})$[e]	NA	NA	NA	3.19 (0.964)

The mass balance data (AUC and Cmax) indicated that radioactivity plasma was predominantly due to circulating metabolites. Mean total recovery of total radioactive dose over entire collection period of 0-240 hours was 93% with similar distribution between urine (42%) and faeces (51%). Mean recovery fraction at steady state of unchanged (parent) eliglustat was 0.5% in urine over the dosing interval of 12 hours and 0.13% in faeces over a 24 hour collection period. Urinary excretion was rapid, with most of the radioactivity being recovered in the first 24 hours, while faecal recovery was complete by 120 hours. Thus, the data showed that predominant route of excretion of eliglustat was by metabolism with negligible excretion of unchanged drug in the urine. The low recovery of unchanged eliglustat in the faeces suggested that the drug is extensively absorbed.

Food effect [GZGD00404] was assessed in 24 healthy males with a single dose of eliglustat 300 mg (6x50 mg capsules) on Day 1 and Day 7 with or without food cross-over design. CYP2D6 phenotyping was not done in this study. The 90%CI (fed/fasted) was 89.04% to 122.51% for AUC and 67.93% to 106.87% for Cmax compared to the regulatory limits of 80 to 125%. Eliglustat was given without regard for food in clinical efficacy studies and same recommendation is proposed for inclusion in the PI.

Single dose (escalation) study [GZGD00103] investigated 13 ascending, single, doses of eliglustat tartrate (placebo, or 0.01, 0.03, 0.1, 0.3, 1, 2, 3, 5, 7, 10, 15, 20 and 30 mg/kg administered as oral solution to sequential cohorts of healthy males (N = 99) under fasting conditions. CYP2D6 metaboliser status was not determined in this study. Only 2 subjects received the highest dose of 30 mg/kg as dosing in this cohort was suspended due to dose-limiting toxicity (dizziness) in 1 subject. The results were as follows (Table 14):

Table 14: GZGD00103. PK parameters of eliglustat (free base) after administration of eliglustat as tartrate from 0.01 to 30 mg/kg to healthy subjects under fasting conditions.

Eliglustat Dose, mg/kg[b]	Parameter[a]							
	C_{max}, ng/mL	t_{max}, h	$AUC_{0-\infty}$, ng.h/mL	AUC_{0-last}[c], ng.h/mL	$t_{1/2}$, h	CL/F, L/min	Vz/F, L	CLr, mL/min
0.01	ND	ND	ND	ND	ND	ND	ND	ND
0.03	ND	ND	ND	ND	ND	ND	ND	34.5
0.1	ND	ND	ND	ND	ND	ND	ND	360 ± 254
0.3	2.68 ± 1.65	1.50	28.1 ± 16.8	15.7 ± 15.6	4.83 ± 0.37	15.7 ± 10.8	6,350 ± 3,880	222 ± 260
1	10.4 ± 7.63	2.25	151 ± 156	119 ± 119	6.54 ± 1.93	15.9 ± 16.5	8,050 ± 7,900	101 ± 46.5
2	13.3 ± 11.5	1.75	112 ± 101	101 ± 95.7	6.35 ± 1.56	34.6 ± 25.0	17,600 ± 10,200	85.0 ± 21.4
3	82.4 ± 68.7	1.75	633 ± 582	611 ± 577	7.52 ± 1.92	9.4 ± 6.75	6,140 ± 5,140	84.3 ± 31.6
5	91.1 ± 86.2	1.50	692 ± 913	672 ± 899	6.15 ± 1.30	21.0 ± 16.6	10,400 ± 8,150	133 ± 51.6
7	58.8 ± 38.5	1.75	324 ± 207	360 ± 212	5.05 ± 0.27	30.6 ± 13.7	13,500 ± 6,390	137 ± 48.8
10	267 ± 210	1.00	1,560 ± 1,070	1,550 ± 1,070	6.09 ± 1.08	15.9 ± 19.5	7,460 ± 7,900	81.0 ± 24.8
15	503 ± 332	1.00	3,040 ± 1,250	3,030 ± 1,250	6.42 ± 0.75	6.50 ± 2.82	3,580 ± 1,390	127 ± 44.5
20	557 ± 212	1.50	4,400 ± 1,480	4,380 ± 1,470	6.05 ± 0.56	6.16 ± 3.44	3,150 ± 1,580	108 ± 31.8
30	1,850 ± 1,080	1.88	10,500 ± 5,470	10,400 ± 5,340	6.75 ± 1.24	3.73 ± 2.20	2,060 ± 885	79.4 ± 14.9

Mean eliglustat Cmax and AUC increased in a dose-related manner but the slopes of log-log plots of mean versus dose were > 1 for both parameters suggesting non-linearity over the whole studied dose range. Both CL/F and volume of distribution (Vz/F) trended downward with higher doses.

Multiple dose (steady state) study [GZGD00204] was assessed using 3 ascending doses of eliglustat (50 mg bd, 200 mg bd and 350 mg bd for 12 days) administered orally to 3 cohorts of healthy subjects (n = 24; one had PM status but received placebo) of both sexes.

Single dose results on Day 1 indicated that eliglustat Cmax and AUC_{α} were non-linear following eliglustat 50 mg, 200 mg, and 350 mg dose. Results at steady state (that is, multiple dosing) also indicated that eliglustat Cmax and $AUC_{(0\text{-}12h)}$ were non-linear following 50 mg bd, 200 mg bd, and 350 mg bd on Days 3 to 12.

Mean C_{max} was 3.1 times higher on Day 12 compared to Day 1 with 50 mg bd, 4.3 times with 200 mg bd and 2.6 times with 350 mg bd dosing. Mean $AUC_{(0\text{-}12h)}$ was 2.0 to 2.4 fold greater than mean $AUC_{(0\text{-}inf)}$ after 1st dose for each of the 3 dose cohorts. The slope of the log-log plots of Cmax and AUC_{α} versus dose (50 mg, 200 mg, 350 mg) on Day 1 was approximately 2, as was the slop of the log-log plots of Cmax and $AUC_{(0\text{-}12h)}$ following 50 mg bd, 200 mg bd, and 350 mg bd dosing indicating non-linearity.

Mean values for CL/F following single-dose and after repeated dosing decreased with increasing dose and duration of dosing (Table 15):

Table 15: Summary of pharmacokinetic parameters on Days 1, 11 and 12

Parameter[1]	50 mg BID	200 mg BID	350 mg BID
Day 1			
N	8	8	8
Cmax (ng/mL)	2.48 ± 0.83	32.9 ± 30.0	107 ± 59.1
Tmax (h)	1.5	1.8	2.5
AUC(0-t) (h•ng/mL)	13.5 ± 7.12	258 ± 302	667 ± 421
AUC(inf) (h•ng/mL)	19.1 ± 7.84	294 ± 323	678 ± 425
t½ (h)	3.69 ± 1.23	5.36 ± 1.34	5.65 ± 0.40
CL/F (L/min)	44.8 ± 26.6	38.5 ± 45.6	11.7 ± 9.14
Vz/F (L)	12,641 ± 3,681	13,854 ± 13,753	5,930 ± 4,907
Day 11			
N	8	7	5
Cmax (ng/mL)	7.27 ± 4.30	119 ± 93.1	221 ± 77.0
Tmax (h)	1.5	1.5	2.0
Cmin (ng/mL)	1.40 ± 0.98	26.2 ± 25.9	47.0 ± 30.9
AUC(0-12) (h•ng/mL)	41.7 ± 25.1	715 ± 602	1,262 ± 469
t½ (h)	4.72 ± 0.88	4.51 ± 0.65	4.27 ± 1.01
CL/F (L/min)	26.7 ± 22.4	11.4 ± 11.7	4.33 ± 1.46
Vz/F (L)	8,177 ± 5,367	4,139 ± 4,152	1,585 ± 616
Day 12			
N	8	7	3
Cmax (ng/mL)	7.64 ± 4.48	142 ± 99.2	278 ± 62.0
Tmax (h)	2.0	1.5	1.0
Cmin (ng/mL)	1.60 ± 1.29	24.8 ± 24.1	33.8 ± 17.2
AUC(0-12) (h•ng/mL)	41.9 ± 28.4	747 ± 608	1,287 ± 428
t½ (h)	5.80 ± 2.73	6.01 ± 1.00	5.58 ± 0.12
CL/F (L/min)	27.4 ± 21.6	12.1 ± 16.3	4.08 ± 1.17
Vz/F (L)	12,369 ± 9,216	5,322 ± 5,864	1,979 ± 600

Source: CSR, Panel 11-2.
[1] = Mean ± SD for all parameters except for Tmax (median).

Plasma eliglustat concentrations following eliglustat at single-dose and with repeated dosing were higher in females than in males and were non-linear among dose groups and with continued dosing in both sexes.

There appeared to be rank-order relationship between eliglustat AUC_{α} on Day 1 and metaboliser status with higher values in intermediate metabolisers (IM) than in ultra-rapid metabolisers (URM). However, there was no apparent relationship between metaboliser status and the ratio of $AUC_{(0\text{-}12h)}$ on Day 10 to AUC_{α} on Day 1.

Metabolites of eliglustat: In vitro and in vivo data indicate that the metabolite profile of eliglustat is complex and that the drug is extensively metabolised. The major metabolic pathway for eliglustat involves sequential oxidation. A total of 21 metabolites of eliglustat were identified in plasma collected from male subjects following oral administration of [^{14}C]-eliglustat tartrate. Ten metabolites had confirmed structures. Relative to parent drug, exposure was higher for 4 metabolites, lower for 3 metabolites and generally similar for the remaining 3 metabolites. The only major metabolite with a total exposure exceeding 10% of total drug-related exposure in plasma (15.9%) was Genz-399240.

Pharmacokinetics in GD1 patients: Full PK data from eliglustat treated patients in 3 efficacy studies (Phase II [GZGD00304], ENGAGE, ENCORE) provided estimates of PK parameters as below (Tables 16-18):

Table 16: GZGD00304. Mean (SD) [CV%] eliglustat plasma PK parameters at selected time points over 78 weeks.

Visit [a]	N	Cmax (ng/mL)	tmax [b] (hours)	Ctrough (ng/mL)	t1/2 (hours)	AUC(0-12h) (ng·h/mL)	CL/F [c] (L/h)
Day 1	26	8.91 (6.45) [72%]	1.50 (1, 4)	NA	6.12 (2.94) [48%]	43.7 (34.6) [79%]	1240 (1040) [84%]
Day 10	24	13.2 (10.6) [80%]	2.00 (1, 3)	4.90 (5.04) [103%]	NC	98.3 (87.2) [89%]	734 (479) [65%]
Day 20	23	21.6 (9.90) [46%]	2.00 (1, 3)	4.98 (5.54) [111%]	NC	140 (81.3) [58%]	709 (425) [60%]
Week 26	23	19.7 (9.02) [46%]	2.00 (1, 6)	6.56 (5.35) [82%]	NC	139 (81.7) [59%]	734 (490) [67%]
Week 52	22	20.6 (11.4) [55%]	2.05 (0, 2)	6.61 (4.99) [76%]	NC	147 (93.3) [64%]	678 (433) [64%]
Week 78	20	19.6 (9.76) [50%]	2.00 (1, 6)	5.86 (5.33) [91%]	NC	133 (79.1) [59%]	847 (665) [79%]
Week 104	20	17.7 (7.02) [40%]	2.00, 1, 3)	4.09 (2.66) [65%]	NC	113 (48.2) [43%]	824 (709) (86%)

Source: CSR, Table 12-2. Note: NC = not calculated.
[a] Day 1 was dose 50 mg; 50 mg BD was continued through to Day 20 at which time some patients were dose adjusted to 100 mg BD. During treatment interruption (end of Week 52 through approximately Week 24), no drug was given.
[b] Median (range) reported for tmax.
[c] N=23 for CL/F on Day 1.

Table 17: ENGAGE. Mean (SD) [CV%] eliglustat plasma PK parameters at selected time points over 39 weeks; 50 mg on DAY 1 followed by 50 mg bd through Week 4 and then 100 mg bd from Week 4 to Week 39

Visit [a]	N	Cmax (ng/mL)	tmax [b] (hours)	Ctrough (ng/mL)	t1/2z (hours)	AUC(0-4h) (ng·h/mL)	AUC(0-12h) (L/h)
Day 1	20	6.45 (6.03) [94%]	1.7 (1, 4)	ND	ND	16.8 (14.1) [84%]	ND
Week 2	20	ND	ND	2.65 (2.5) [94%]	ND	ND	ND
Week 4	15	20.8 (15.4) [74%]	1.6 (1, 4)	2.57 (2.37) [92%]	ND	ND	96.7 (77.3) [80%]
Week 13	17	ND	ND	6.00 (5.29) [88%]	ND	ND	ND
Week 39	14	22.4 (18.1) [81%]	1.8 (1, 4)	4.88 (4.66) [96%]	4.4 (0.7) [15%]	60.0 (53.7) [90%]	120 (109) [91%]

Source: CSR, Table. Note: ND = not determined; N=19 AUC(0=4h) Day 1; N=14 Ctrough Week 4; N=13 AUC(0-12h) Week 4; N=16 Ctrough Week 39; N=11 t1/2z Week 39.
[a] Day 1 was dose 50 mg; followed by 50 mg BD through to Week 4 and then 100 mg BD from Week 4 through Week 39.
[b] Median (range) reported for tmax.

Table 18: ENCORE. Mean (SD) [CV%] PK parameters by dose and CYP2D6 phenotype at Week 52.

Visit			N	Cmax (ng/mL)	tmax (hours)	AUC(0-4h) (ng·h/mL)	AUC(0-12h) (ng·h/mL)
PM	Week 52	50 mg BD	4	78.5 (38.4) [49%]	3.0 (2, 4)	252 (121) [48%]	648 (231) [36%]
IM	Week 52	50 mg BD	5	34.9 (8.1) [23%]	2.0 (1, 4)	91.5 (24.0) [26%]	200 (54.3) [27%]
EM	Week 52	50 mg BD	9	26.8 (20.0) [74%]	2.5 (1, 4)	85.4 (66.4) [78%]	214 (196) [91%]
URM	Week 52	50 mg BD	4	16.6 (9.9) [60%]	2.0 (1, 2)	44.9 (25.3) [56%]	88.5 (52.0) [59%]
IM	Week 52	100 mg BD	4	58.7 (32.7) [56%]	1.5 (1, 2)	185 (115) [62%]	400 (286) [72%]
EM	Week 52	100 mg BD	30	35.1 (21.3) (61%)	2.0 (1, 4)	96.1 (52.0) [54%)	201 (118) [59%]
IM	Week 52	150 mg BD	1	2.94	3	8.79	3
EM	Week 52	150 mg BD	41	38.1 (30.8) [81%]	2.0 (1, 4)	101 (72.9) [72%]	195 (125) [64%]
URM	Week 52	150 mg BD	4	16.6 (9.90) [60%]	2.0 (1, 2)	44.9 (25.3) [56%]	88.5 (52.0) [59%]

Source: CSR, Tables 12.1 - 12.4. Note: Median (range) for Tmax.

The results confirmed the finding of non-linearity in earlier PK studies in healthy volunteers but seem to indicate a degree of stabilisation (steady state) with chronic dosing (CL/F and AUC in Phase II study Table 16 above; Cmax and AUC in ENGAGE Table 17 above) and significant differences in systemic exposures to drug (AUC) in PM and URM compared to EM and IM patients (ENCORE Table 18 above). For dosing regimens followed in these studies please see below.

Population PK and simulations: Please see CER (Attachment 2). Simulations of Cmax and $AUC_{(0\text{-}12h)}$, based on CYP2D6 phenotype data for repeated 100 mg bd doses, estimated that exposure in PMs was approximately 10 times higher than in EMs, approximately 2.8 times higher in IMs than in EMs, and approximately 46% lower in URMs than in EMs.

In vitro interaction studies: Please see CER (Attachment 2).

Clinical drug-drug interaction studies

CYP2D6, CYP3A4 and P-gp inhibition: Co-administration of a strong CYP2D6 inhibitor like paroxetine (30 mg qd for 10 days) with eliglustat (100 mg bd for 10 days) resulted in eliglustat co-administered/alone ratio of 7.3 (90%CI 5.9 to 9.1) for Cmax and 8.9 (90%CI 7.2 to 11.1) for AUC_{0-12}. Co-administration of a strong CYP3A4 and P-gp inhibitor such as ketoconazole (400 mg qd for 7 days) with eliglustat (100 mg bd for 7 days) resulted in eliglustat co-administered/alone ratio of 3.8 (90%CI 3.4 to 4.3) for Cmax and 4.3 (90%CI 3.9 to 4.7) for AUC_{0-12}.

CYP3A4 and P-gp induction: Co-administration of a potent inducer of CYP3A4 and P-gp such as Rifampin (600 mg qd for 6 days) with eliglustat (100 mg bd for 6 days) resulted in eliglustat co-administered/alone ratio of 0.049 (90%CI 0.039 to 0.061) for Cmax and 0.041 (90%CI 0.035 to 0.049) for AUC_{0-tau} in PM subjects. Co-administration of a potent inducer of CYP3A4 and P-gp such as Rifampin (600 mg qd for 6 days) with eliglustat (150 mg bd for 6 days) resulted in eliglustat co-administered/alone ratio of 0.156 (90%CI 0.110 to 0.219) for Cmax and 0.149 (90%CI 0.107 to 0.207) for AUC_{0-tau} in non-PM subjects.

Effect of gastric acid reducing agents on eliglustat exposure: Overall, the results showed that acid reducing agents (2 antacid and pantoprazole) had a small effect on exposure to eliglustat, which was unlikely to be clinically significant.

Effect of eliglustat on exposure of CYP2D6 substrate metoprolol: Consistent with the in vitro data showing that eliglustat is an inhibitor of CYP2D6, eliglustat (150 mg bd) at steady state administered with a single dose of metoprolol (50 mg), resulted in increased metoprolol exposure based on both Cmax (co-administered/alone ratio 1.53; 90% CI 1.31 to 1.79) and AUC (co-administered/alone ratio 2.08; 95%CI 1.82 to 2.38) in healthy CYP2D6 non-PMs subjects.

Effect of eliglustat on exposure of CYP3A4 substrate oral contraceptive pill (EE/NE): results of this study in healthy women of child bearing age did not show a clinically significant effect on exposures of Ethinyl Estradiol (EE) or Norethindrone (NE), regardless of phenotype. The result suggest that, in vivo, eliglustat is not a clinically significant inhibitor of CYP3A4

*Effect of eliglustat on exposure of a P-gp substrate digoxin: e*xposure to digoxin increased (Cmax ratio 1.7; 90%CI 1.56 to 1.84; AUC ratio 1.49; 90%CI 1.33 to 1.66; results pooled for phenotypes) following co-administration of a single 0.25mg dose of digoxin with eliglustat 150 mg bd (CYP2D6 non-PMs) or 100 mg bd (CYP2D6 PMs) for 7 days. The results study support the in vitro data indicating that eliglustat is a potential inhibitor of P-gp.

Pharmacodynamics

Biomarker studies: A number of biomarker studies were also conducted (see CER). Of note plasma GL-1 was measured in healthy subjects in Study GZGD00204. As expected, the pre-treatment GL-1 plasma levels were in the normal range. However, the plasma GL-1 levels decreased in a dose-dependent manner following eliglustat at 50 mg, 200 mg and 350 mg twice daily administration. Mean plasma GL-1 concentration decreased within 3 days after initiation of eliglustat in all dose cohorts and appeared to decline more rapidly at higher doses. Maximal mean percentage reductions from baseline were observed on Day 12 and were approximately 50%, 80%, and 90% for the three dose levels respectively.

Thorough QT/QTc study [GZGD01707] was conducted in healthy male and female subjects to assess the effect of single oral therapeutic (200 mg) and supra-therapeutic (800 mg) doses of eliglustat with moxifloxacin (400 mg) as positive control. The 200 mg was based on the proposed dose of 100 mg bd and the 800 mg dose was based 100 mg bd dose given with a strong CYP2D6 inhibitor. The study was randomised, double-blind, placebo-controlled, 4 treatment periods, cross-over in design in accordance with the accepted regulatory guidance. A total of 47 healthy volunteers (male 22; female 25) participated.

The mean age was 27.4 years (range: 18, 44). Two were CYP2D6 PM with remaining classified as CYP2D6 non-PM.

- After administration of a single therapeutic dose of 200 mg eliglustat, placebo-corrected change from baseline in QTcF interval was 0.42 ms (95%CI UL 1.8 ms).
- After administration of a single supra-therapeutic dose of 800 mg eliglustat, placebo-corrected change from baseline in QTcF interval was 7.3 ms (95%CI UL 8.8 ms).
- The UL of 1-sided 95%CI limit for the mean placebo-corrected change from baseline in QTcF following the single therapeutic dose (200 mg) or the supra-therapeutic dose (800 mg) did not exceed 10 ms at any time point. The UL of 1-sided 95%CI did not exceed 10 ms at any time-point following the therapeutic dose (200 mg) in either males or females. The mean placebo-corrected change from baseline in QTcF following the single supra-therapeutic dose (800 mg) was 6.4 ms (95%CI UL 8.9msec) in females and 1.9 ms (95%CI UL 4.6msec) in males.

In females, the 95%CI UL exceeded 10 ms at most time points (0.5-22.5 h) following the supra-therapeutic dose (800 mg). In males, the 95%CI UL did not exceed 10 ms any time points following the supra-therapeutic dose. In mixed-model Analysis of Variance (ANOVA), the gender effect was not statistically significant, but gender-by-treatment interaction was statistically significant.

For PK/PD modeling please see CER.

Clinical efficacy

Phase II study (GZGD00304):

The submission included one Phase II study in GD1 patients. This was the first clinical study with eliglustat in the target population. The eligible subjects were patients who had not received ERT or miglustat within 12 months prior to enrollment ('treatment-naïve').

The main inclusion criteria were (1) adult age 18 to 65 years (2) diagnosis of GD1 and documented deficiency of acid β-glucosidase activity by enzyme assay and (3) symptoms of GD1 identified within 28 days of enrollment including at least one of the following: haemoglobin (8.0 to 10.0 g/dL if female; 8.0 to 11.0 g/dL if male), platelet count 45,000 to 100,000/mm^3 or splenomegaly (MRI or spiral computed tomography (CT)) defined as spleen volume ≥ 10 times normal). The main exclusion criteria were included partial or total splenectomy, haemoglobin < 8.0 g/dL, platelets < 45,000/mm^3, evidence of neurologic or pulmonary involvement or new pathological bone involvement.

A total of 26 patients (10 males, 16 females) with GD1, with a mean age of 34 years (range 18 to 60 years) participated in the study. A total of 25/26 patients were extensive CYP2D6 metabolisers (EM). One was a poor CYP2D6 metaboliser (PM). The mean age at diagnosis was 24 years.

The study evaluated efficacy/safety/PK of 50 mg bd and 100 mg bd doses of eliglustat over a 52 weeks treatment period. The secondary objective was to assess long-term efficacy/safety/PK of eliglustat at doses of 50 mg bd, 100 mg bd or 150 mg bd. Results up to 4 years are available in this submission.

All patients (N = 26) stared with eliglustat 50 mg bd. Eliglustat trough concentrations were determined on Day 10. If the eliglustat trough concentration on Day 10 was < 5 ng/mL then the eliglustat dose was increased to 100 mg bd from Day 20 for treatment until 52 weeks. If the eliglustat trough concentration on Day 10 was ≥ 5 g/mL then the 50 mg bd dose was continued. Patients were eligible for a further dose escalation to 150 mg bd if they had been on treatment for at least 24 months and met certain pre-specified criteria (not reached therapeutic goals and other causes of inefficacy ruled out). However, no patients required dose increase to 150 mg bd.

Of the 26 patients, 6 were treated with eliglustat 50 mg bd and 18 with eliglustat 100 mg bd until 52 weeks. Two patients withdrew after receiving their first of eliglustat 50 mg on Day 1. A total of 2 22 patients competed the 52 weeks study treatment.

The main efficacy outcome was the proportion of patients demonstrating a meaningful clinical response after 52 weeks treatment with eliglustat. A meaningful clinical response was defined as an improvement in at least 2 of the 3 main efficacy parameters that were abnormal at study entry i.e. haemoglobin, platelets, and/or spleen volume. Response was defined as (1) increase in haemoglobin ≥ 0.5g/dL (2) increase in platelet count ≥ 15% and (3) reduction of ≥ 15% in spleen volume.

At Week 52 primary composite endpoint (that is, 2 of 3 parameters haemoglobin, platelets, and spleen as defined above) was achieved by 20/26 patients (77%; 95%CI 58 to 89%). The success rate was 9/10 for haemoglobin, 17/25 for platelets and 22/26 for spleen volume. At 4 years, the results including liver volume, were as follows (Table 19):

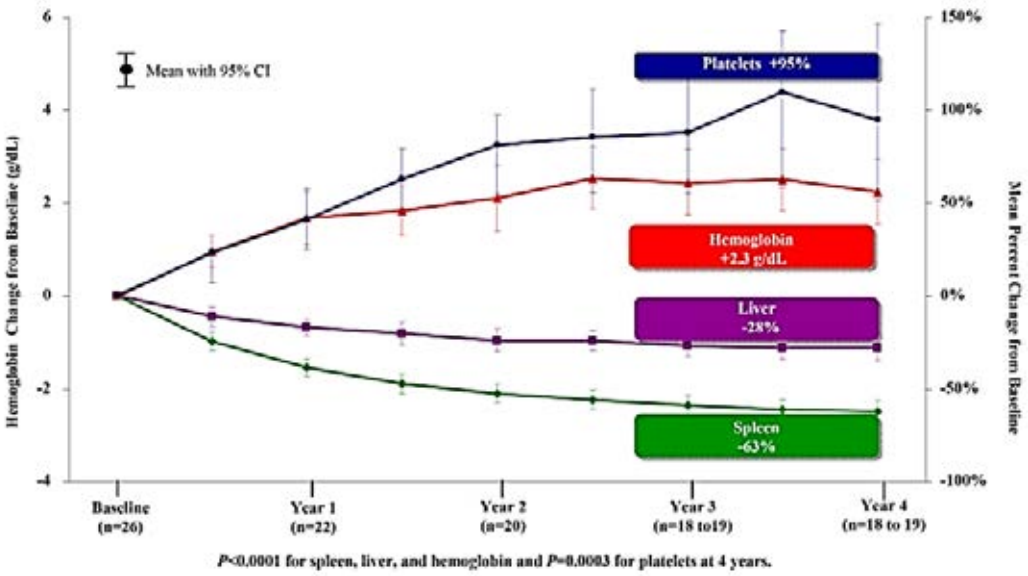
Table 19: Results at 4 years

	N	Baseline Value (Mean)	Change from Baseline (Mean)	95% Confidence Interval
Spleen Volume	18	17.32 MN	-62.5%	(-68.3, -56.7)
Haemoglobin Level	19	11.30 g/dL	2.27 g/dL	(1.57, 2.97)
Liver Volume	18	1.70 MN	-28.0%	(-34.9, -21.2)
Platelet Count	19	68.68x10^9/L	95.0%	(50.7, 139.4)

MN = multiples of normal

The 'baseline to 4 years' data are also depicted in the graph below (Figure 3):

Figure 3: Baseline to Year 4 data



P<0.0001 for spleen, liver, and hemoglobin and *P*=0.0003 for platelets at 4 years.

Of the 6 patients being treated with 50 mg bd at Week 52, five continued to receive 50 mg bd, while 1 received 50 mg bd for the first 3 years after which the dose was increased to 100 mg bd. No patients were receiving 150 mg bd at the time of data cut-off with all patients now in their fifth year of study or greater.

Pivotal study ENGAGE (GZGD02507):

This was a Phase III pivotal study supporting this submission. The design was randomised, double-blind, placebo-controlled to assess the efficacy of eliglustat in GD1 patients who had not received substrate replacement therapy (SRT) within 6 months or enzyme replacement therapy (ERT) within 9 months of randomisation. The duration of study was 39 weeks.

The main inclusion criteria were adult patient (16 to 65 years), confirmed diagnosis of GD1 with documented deficiency of acid β-glucosidase activity by enzyme assay, one of the following: Haemoglobin (8.0-11.0 g/dL if female; 8.0-12.0g/dL if male), (2) platelet count 50,000 to 100,000/mm^3, (3) splenomegaly 8-30 MN or (4) if hepatomegaly < 2.5 MN. The exclusion criteria included neurological or pulmonary involvement related to GD and clinically significant cardiac disease among others. Patients who had undergone partial or total splenectomy were excluded.

A total of 40 GD1 patients (20 male; 20 female) were randomised to eliglustat and placebo groups with 20 in each. Randomisation was stratified based on baseline spleen volume (≤ 20 MN or > 20 MN). The mean age was 32 years (range 16 to 63 years; median 30 years), 39/40 White, and one Asian. The CYP2D6 metaboliser status was PM n=0 (0%), IM n=3 (8%), EM n=36/40 (90%) and URM n=1 (3%). The two groups were similar at baseline. Five patients had received prior ERT (2 in eliglustat and 3 in placebo group) and 4 of these patients had also received prior treatment with miglustat. All patients had discontinued treatment with ERT and miglustat (SRT) at least 9 months and 6 months respectively prior to initiation of study treatment.

All patients randomised to eliglustat received a single 50 mg dose on Day 1 and 50 mg twice daily (bd) from Day 2 to Week 4. Eliglustat trough concentrations were measured at Week 2. From Week 4 to Week 39, patients with eliglustat trough concentrations ≥ 5 ng/mL at Week 2 continued to receive 50 mg bd whereas patients with eliglustat trough concentrations < 5 ng/mL at Week 2 were started on 100 mg bd eliglustat dosing.

Patients entered the single long-term treatment period following completion of placebo-controlled Week 39 treatment. During this extension phase, all patients received 50 mg bd initially Week 39 to Week 43) and eliglustat trough concentrations were measured at Week 41. From Week 43 to Week 47, patients with eliglustat trough concentrations ≥ 5 ng/mL at Week 41 continued to receive 50 mg bd and patients with eliglustat trough concentrations < 5 ng/mL at Week 41 started on 100 mg bd.

From Week 47 onwards, patients who had an eliglustat trough concentration ≥ 5 ng/mL at Week 45 continued to receive same dose of eliglustat, whereas patients who with eliglustat trough concentration < 5 ng/mL at Week 45 started receiving 100 mg bd (for patients who were on 50 mg bd) or 150 mg bd (patients who were on 100 mg bd). Patients with peak eliglustat plasma concentrations ≥ 150 ng/mL could be temporarily discontinued from treatment in either treatment period.

The primary efficacy endpoint was the percentage change in spleen volume (MN) from baseline to 39 weeks. The secondary efficacy endpoints were changes in liver volume (MN), haemoglobin level (in g/dL) and platelet counts. There were a number of tertiary and exploratory outcomes.

The report includes efficacy results at Week 39. Overall, the mean time (placebo controlled phase) on study treatment was 274.5 days (SD 19.94) days overall, and was similar in the 2 treatment groups. The Week 39 results were as follows:

Spleen volume: The mean spleen volume changed from 13.89 MN (SD 5.929) at baseline to 10.17 MN (SD 5.065) at Week 39 in eliglustat group. The mean spleen volume changed from 12.50 MN (SD 5.959) at baseline to 12.84 MN (SD 6.395) at Week 39 in placebo group.

The least squares (LS) mean percentage (%) change in spleen volume (MN) from baseline to Week 39 was -27.77% in the eliglustat group versus +2.26% in placebo group, representing a treatment difference of -30.03% (95%CI -36.82% to -23.24%) in favour of eliglustat treatment.

A total of 15/20 eliglustat treated patients showed a clinically meaningful treatment response in spleen volume (MN), defined as >20% reduction from baseline, compared with 1/20 placebo treated patient.

Using the criteria for short-term (12 to 24 months) therapeutic goals based on a publication for the ERT imiglucerase, the short term goal for reduction in spleen volume (≥ 30% reduction),9/20 eliglustat patients met this criteria at Week 39 compared with none in placebo group.

Liver volume: The mean liver volume changed from 1.44 MN (SD 0.354) at baseline to 1.35 MN (SD 0.280) at Week 39 in eliglustat group. The mean liver volume changed from 1.36 MN (SD 0.280) at baseline to 1.394 MN (SD 0.309) at Week 39 in placebo group.

The LS mean percentage change (%) in liver volume (MN) from baseline to Week 39 was -5.45% in the eliglustat group versus +1.70% in placebo group, representing a treatment difference of -6.64% (95%CI -11.37% to -1.91%) in favour of eliglustat treatment.

Most patients had mild hepatomegaly (< 1.5MN) at baseline in this study. The short-term therapeutic goal for decrease in liver volume (≥ 20% reduction) was not achieved by any patient in either group.

Haemoglobin level (Hb): The mean Hb changed from 12.05 g/dL (SD 1.816) at baseline to 12.78 g/dL (SD 1.561) at Week 39 in eliglustat group. The mean Hb changed from 12.75 g/dL (SD 1.629) at baseline to 12.17 g/dL (SD 2.010) at Week 39 in placebo group.

The LS mean change in Hb (g/dL) from baseline to Week 39 was 0.73 (SD 1.093) in the eliglustat group versus -0.58 (SD 0.890) in placebo group, representing a treatment difference of 1.22 g/dL (95%CI 0.57 to 1.88) in favour of eliglustat treatment.

The short-term therapeutic goal for Hb (≥ 11g/dL in females and ≥ 12g/dL in males) was achieved by 18/20 patients at Week 39 compared to 14/20 patients at baseline in eliglustat group. In placebo group, the goal was achieved by 14/20 patients at Week 39 compared to 17/20 at baseline in the placebo group.

Platelet count: The mean platelet count ($x10^9$/L) changed from 75.05 (SD 14.095) at baseline to 98.95 (SD 28.372) at Week 39 in eliglustat group. The mean platelet count changed from 78.48 (SD 22.611) at baseline to 71.50 (SD 25.157) at Week 39 in placebo group.

The LS mean change in platelet count ($x10^9$/L) from baseline to Week 39 was 31.71 (SD 31.801) in the eliglustat group versus -8.77 (SD 19.187) in placebo group, representing a treatment difference of 41.06 (95%CI 23.95 to 58.17) in favour of eliglustat treatment.

The short-term therapeutic goal for percentage increase from in platelet count defined (≥ 50% increase) was met by 5/20 eliglustat patients and no placebo treated patients.

For tertiary endpoints (including skeletal effect and effect on mobility) and exploratory analyses (including analysis by eliglustat C_{trough} level), please see CER. Following a request in the second round clinical evaluation, the sponsor provided some 78 weeks data (dated 7 May 2014) comprising the first 39 weeks of open-label treatment in the extension phase. The results with respect to change (%) in spleen volume (MN) were as follows (Table 20):

Table 20: % change in spleen volume

Time Point / Change	Statistic	Eliglustat (N=20)	Placebo to Eliglustat (N=20)
Baseline	n	20	20
	Mean (SD)	13.89 (5.929)	12.50 (5.959)
	Median	12.09	11.05
	Min, Max	5.94, 28.39	6.32, 25.27
Week 39 / Placebo new baseline	n	19	20
	Mean (SD)	9.55 (4.363)	12.84 (6.395)
	Median	8.26	10.97
	Min, Max	4.12, 19.25	6.63, 26.17
% Change from Baseline	Mean (SD)	-29.03 (11.085)	2.08 (8.772)
	95% CI	-34.37, -23.69	-2.03, 6.18
Week 78/ Placebo to eliglustat 39 weeks	n	18	20
	Mean (SD)	7.62 (3.482)	8.81 (4.428)
	Median	6.61	7.59
	Min, Max	3.94, 15.39	3.11, 19.36
% Change from Baseline	Mean (SD)	-44.61 (10.120)	-31.31 (10.125)
	95% CI	-49.64, -39.58	-36.04, -26.57

Please see CER (Attachment 2) for details.

Pivotal study ENCORE (GZGD02607)

This was a Phase III, open-label, active controlled study to assess therapeutic non-inferiority of eliglustat (SRT) against imiglucerase (ERT) after 52 weeks of treatment. The patients included in this trial were GD1 patients who had been treated with an enzyme replacement therapy (ERT) for at least 3 years (dosed at 30 to 130 U/kg/month in at least 6 out last 9 months) and had attained reached therapeutic goals[18].

Therefore the study essentially involved long-term ERT stable patients switching to eliglustat with assessment after 52 weeks. A long-term objective was also to assess continuing stability on eliglustat after 52 weeks. The study could not be blinded due to different routes of administration of the 2 drugs (oral versus intravenous) and double dummying was not considered appropriate.

The study included patients aged 18 years and above with a diagnosis of confirmed GD1 by documented deficiency of β glucosidase activity by enzyme assay. The exclusion criteria included patients with significant cardiac disease, among others. A total of 160 eligible patients were randomised in 2:1 ratio to eliglustat (n=106; 84 CYP2D6 EM, 12 IM, 4 URM, 4 PM, and 2 'Indeterminate' status) or imiglucerase (n=54). The randomisation was stratified based on prior ERT dosing (< or ≥ 35U/kg/q2w)

Patients in imiglucerase (Cerezyme) group received the drug by IV infusion (IVI) once every 2 weeks (dosage change due to temporary unavailability of Cerezyme during the study, that is, < or ≥ 35U/kg/q2w).

On Day 1, patients randomised to eliglustat received 50 mg bd. Eliglustat plasma trough concentration was examined at Week 2. For patients with eliglustat plasma trough concentrations < 5 ng/mL at Week 2, the dose was increased to 100 mg bd at Week 4. Patients with eliglustat plasma trough concentrations ≥ 5 ng/mL continued on 50 mg bd.

Eliglustat plasma trough levels were examined at Week 6. For patients with plasma eliglustat level < 5 ng/mL, the dose was increased at to 100 mg bd for those on 50 mg bd and to 150 mg bd for those on 100 mg bd at Week 8. The increased dose was maintained to Week 52. For patients with eliglustat plasma trough concentrations ≥ 5 ng/mL at Week 6, the dose was maintained at 50 mg bd or 100 mg bd to Week 52.

In the long-term extension phase after 52 weeks, all patients were treated with eliglustat. Patients originally randomised to eliglustat continued to receive the eliglustat dose based

[18] Defined as no bone crisis and free of symptomatic bone disease, mean Hb ≥11g/dL if female and ≥12g/dL if male and mean platelet count ≥100,000mm3. Furthermore, the inclusion criteria required spleen volume <10MN or splenectomy provided if it had occurred >3 years prior to this study and liver volume <1.5MN.

on their Week 8 dose. Post Week 52, the Cerezyme patients received eliglustat 50 mg bd. Dose adjustments could occur at Week 56 based on eliglustat plasma trough and 2-hour (peak) eliglustat concentration at Week 54. For patients with eliglustat plasma trough concentrations < 5 ng/mL at Week 54, the dose was increased at Week 56 to 100 mg bd. Patients with eliglustat plasma trough concentrations ≥ 5 ng/mL continued to receive 50 mg bd. In this group, further eliglustat plasma trough and peak concentrations were examined at Week 58. For patients with an eliglustat plasma trough concentration of < 5 ng/mL at Week 58, eliglustat dose was increased at Week 60. For patients on eliglustat 50 mg bd or 100 mg bd whose plasma trough concentration was < 5 ng/mL, the dose was increased to 100 mg bd or 150 mg bd respectively. Patients receiving eliglustat 50 mg bd or 100 mg bd with an eliglustat plasma trough concentration of ≥ 5 ng/mL at Week 58 continued on the same dose of eliglustat.

Any patient with a peak eliglustat plasma concentration ≥ 150 ng/mL in either period could be temporarily discontinued from treatment. The primary efficacy endpoint was the percentage of patients who remained stable for 52 weeks in eliglustat and Cerezyme groups. The primary analysis of non-inferiority was based on per protocol (PP) analysis set

The primary efficacy criteria for stability was a composite comprising both haematologic (Hb and platelets) and organ volumes (spleen and liver) parameters. Stable haematological parameters were defined as Hb level not decreasing >1.5g/dL *and* platelet count not decreasing >25% from baseline. Stable organ volume was defined as spleen volume (MN) not increasing >25% *and* liver volume (MN) not increasing >20% from baseline. There were a number of secondary and tertiary outcomes.

A total of 146 patients (99 eliglustat, 47 Cerezyme) were included in the PP analysis. Of these 64 (44%) were male and 82 (56%) were female. The mean age was 37.6 years (range 18.1, 69.3 years), 136 (93%) were White, 8 (5%) were Black or African American, 1 (1%) each was Asian or White/American Indian. Overall, 56 patients (38%) were in prior ERT < 35U/kg/q2w stratification group and 90 (62%) were in the prior ERT ≥ 35U/kg/q2w stratification group. Most patients in both groups were CYP2D6 EMs (77%), 12% were IMs, 4% were PMs and 3% were URMs. Overall, 25% patients had undergone a total splenectomy, and 5% were homozygous for a null mutation in the chitotriosidase gene. Patients entered the study with haematology and organ volumes that met prespecified therapeutic goals. The mean current ERT dose was 77.6 U/kg/month in eliglustat group and 78.9 U/kg/month in the placebo group. The results were as follows:

At 52 weeks, in PP population, stability as assessed by the composite efficacy endpoint (defined above) was maintained in 84/99 (84.8%; 95%CI 76.2-91.3%) eliglustat patients compared to 44/47 (93.6%; 95%CI 82.5-98.7%) patients in the Cerezyme group (Table 21):

Table 21: Stability results

Variable	Eliglustat (N=99)	Cerezyme (N=47)
Patients Stable for 52 Weeks, n (%)	84 (84.8)	44 (93.6)
Difference in Percentage Stable (Eliglustat-Cerezyme), %	-8.8	
95% Agresti and Caffo Adjusted CI on Difference in Percentage Stable	(-17.6, 4.2)	
Exact 95% CI on PercentageStable	(76.2, 91.3)	(82.5, 98.7)

The treatment difference for the 4-component composite endpoint was -8.8% (95%CI -17.6% to 4.2%). The lower margin (-17.6%) was within the sponsor's prespecified non-inferiority margin of treatment effect no worse than 25%. It was also within the 20% margin recommended by EMA. The results based on Full Analysis Set were consistent with the PP analysis.

The patients were stable on therapeutic goals with long-term ERT at baseline. ERT was allowed until a day before the start of study treatment. The (absolute) changes from baseline over 52 weeks were therefore small. The proportions of patients meeting the criteria for stability (%) for individual components of the composite were as follows (PP set) (Table 22):

Table 22: Proportion of patients meeting the criteria for stability (%) for individual components of the composite

Variable	Eliglustat (N=99)	Cerezyme (N=47)
Patients Meeting Hemoglobin Criteria, n (%)	94 (94.9)	47 (100.0)
Exact 95% CI	(0.886, 0.983)	-
Patients Meeting Platelets Criteria, n (%)	92 (92.9)	47 (100.0)
Exact 95% CI	(0.860, 0.971)	-
Patients Meeting Spleen Volume Criteria, n (%)*	68 (95.8)	39 (100.0)
Exact 95% CI	(0.881, 0.991)	-
Patients Meeting Liver Volume Criteria, n (%)	95 (96.0)	44 (93.6)
Exact 95% CI	(0.900, 0.989)	(0.825, 0.987)

*Percentages are based on non-splenectomised patients in each treatment group.

FDA recommended the use of percentage change in spleen volume (MN) for assessment of non-inferiority. The mean spleen volume changed from 3.23 MN (SD 1.37) at baseline to 3.07 MN (SD 1.38) at Week 52 in eliglustat group. The mean spleen volume changed from 2.62 MN (SD 1.08) at baseline to 2.53 MN (SD 0.99) at Week 52 in Cerezyme group (Table 23):

Table 23: Changes in spleen volume

Time Point / Change	Statistic	Eliglustat (N=99)	Cerezyme (N=47)	Treatment Difference (Eliglustat-Cerezyme)
Baseline	n	70	39	--
	Mean (SD)	3.23 (1.37)	2.62 (1.08)	--
	Median	2.87	2.23	--
	Min, Max	1.06, 7.43	1.14, 5.34	--
Week 52	n	70	39	--
	Mean (SD)	3.07 (1.38)	2.53 (0.99)	--
	Median	2.95	2.31	--
	Min, Max	0.85, 7.59	1.13, 4.88	--
% Change from Baseline to Week 52	Mean (SD)	-6.17 (14.14)	-3.01 (10.50)	--
	Median	-6.65	-5.20	--
	Min, Max	-48.7, 31.8	-22.1, 20.1	--
	LS Mean (SEM)	-6.05 (1.57)	-3.22(2.13)	-2.83 (2.68)
	95% CI	(-9.17, -2.93)	(-7.43, 1.00)	(-8.14, 2.47)
	p-value	NA	NA	0.2922

The LS mean percentage change in spleen volume (MN) from baseline to Week 52 was -6.05% in eliglustat group versus -3.22% in Cerezyme group, representing a treatment difference of -2.83% (95%CI -8.14% to 2.47%). The lower-bound of 95%CI (-8.14%) was within the non-inferiority margin of 15% proposed by the regulator for this outcome.

The study excluded patients with symptomatic bone disease within the year prior to study entry. BMD was normal for the majority of patients in both treatment groups at baseline and remained stable to 52 weeks.

At Week 52, the distribution of patients receiving the three possible doses in eliglustat group was 20% (21/106) 50 mg bd, 32% (34/106) 100 mg bd, and 48% (51/106) 150 mg. The mean number of Cerezyme infusions per patient was 24.7 consistent with the every other week dosing. The systemic exposure to eliglustat (AUC) at Weeks 13 and 52 was similar for the 3 eliglustat dose levels in CYP2D6 EM and mean C_{trough} levels were above

≥ 5 ng/mL at Weeks 13 and 52 for the 3 eliglustat dose levels. Note the last dose titration took place at Week 8 after which the doses remained constant through 52 weeks treatment period.

In an exploratory analysis, the efficacy (stability based on the composite efficacy endpoint) was achieved by 77.5% (31/40) patients in subgroup with mean steady state C_{trough} levels < 5 ng/mL versus 85% (56/66) in patients with mean steady-state C_{trough} levels ≥ 5 ng/mL at 52 week. Thus although some value in therapeutic monitoring is indicated, a fixed-dose regimen rather than a dose-titration regimen is considered reasonable clinical compromise.

In an exploratory using PK/PD modelling and simulation, the composite endpoint at 52 weeks for each CYP2D6 phenotype and eliglustat dose were plotted against observed $logAUC_{(0\text{-}tau)}$ and no trend was observed.

Clinical Safety

Four studies form the safety dataset in GD1 population comprising pooled safety set of 393 eliglustat treated patients derived from the following studies:

- 26 patients treated for up to 4 years in the ongoing Phase II study.
- 40 patients from Phase III study (ENGAGE) from the initial 39 weeks controlled period and the single arm extension.
- 157 patients from Phase III study (ENCORE) in initial 52 weeks controlled period and on-going single arm extension.
- 170 patients from ongoing Phase III EDGE comparing qd with bd administration of eliglustat which is not part of this dossier.

Of the 393 patients, 134 were treatment naive or did not have recent prior exposure to ERT and 259 had recent prior exposure to ERT. A total of 349 (89%) patients received eliglustat for at least 6 months, 204 (52%) patients received eliglustat for at least 12 months, 62 (16%) patients received eliglustat for at least 24 months and 19 (5%) patients received eliglustat for at least 60 months. The mean age (SD) of the patients in the eliglustat safety set was 37.1 (14.40) years, and most patients (98%) were in > 30 to 65 year age group (58%) and the 16 to 30 year age group (40%). Two patients were >16 and < 18 years old, and 10 patients were >65 years old.

Overall, 91% of patients in GD1 safety set were CYP2D6 extensive (EM) or intermediate (IM) metabolisers. The distribution of metaboliser status was: EM (79%), IM (12%), PMs (4%), URMs (2%), indeterminate (1%) and missing (2%).

In the eliglustat safety set, 334 (85%) patients experienced at least one AE. The most commonly reported AEs (≥ 10 of patients) were headache (17%); arthralgia (14%); nasopharyngitis (13%); URTI (11%), diarrhoea (10%) and dizziness (10%). The incidence of TEAEs was greatest in the first 6 months of treatment with eliglustat.

TEAEs reported as being related to treatment with eliglustat were reported in 159 (40%) patients. The most commonly reported treatment-related TEAEs (≥ 2% of patients) were: headache (5%), dizziness (5%), diarrhoea (4%), dyspepsia (4%), constipation (3%), nausea (3%), upper abdominal pain (3%), abdominal pain (3%), gastro-esophageal reflux (3%), abdominal distension (2%), dysphagia (2%), flatulence (2%), palpitations (2%), fatigue (2%) and arthralgia (2%).

SAEs were reported in 9% (35/393) patients in the eliglustat safety set (42 events; 8 events/100 PY). SAEs reported in ≥ 1 patient were syncope (n=5, 1.3%), myocardial infarction (n=3, 0.8%), maternal exposure during pregnancy (n=2, 0.5%) and cholecystitis (n=2, 0.5%). No deaths were reported in the eliglustat safety set as of 31 January 2013.

Some adverse outcomes of special interest were as follows:

Syncope: In the eliglustat safety set (n=193), 8 (2%) patients had a TEAE of syncope (1.7 events/100 patient-years). One (1) patient had 2 events of syncope, and the remaining 7 patients had 1 event each. All of the patients with syncope were female, with ages ranging from 21 to 63 years. Syncope was an SAE in 5 patients. One syncope event led to study drug interruption and 2 led to dose adjustment but none to permanent study discontinuation.

Cardiac arrhythmias: In the eliglustat safety set (n=393), 15 (4%) patients reported cardiac arrhythmia events by HLGT or HLT. The HLT in which events were most frequently reported included cardiac conduction disorders (6 patients), supraventricular arrhythmias (4 patients), ventricular arrhythmias and cardiac arrest (4 patients) and rate and rhythm disorders not elsewhere classified (on patient).

HLT of Cardiac conduction disorders: reported in 6 patients including 4 with AV block second degree block, 1 patient with first AV block and 1 patient with sino-atrial block. Two events (in 1 patient) were SAEs. The events occurred at all doses of eliglustat, and all patients were CYP2D6 EMs. Time from the start of dosing with eliglustat to the onset of event was 90 to 632 days. The Cmax values prior to the event and closest in chronology to the event onset ranged from 19.4 to 60.6 ng/mL. All patients were asymptomatic at the time of the events, and the events mostly occurred in the early morning hours while on Holter monitoring. No patients discontinued treatment due to cardiac conduction disorders.

HLT of Ventricular arrhythmia and cardiac arrest: was reported in 4 patients including 3 patients with ventricular tachycardia (non-sustained) and 1 patient with ventricular extra-systole. The events occurred in 3 females and 1 male, ranging in age from 23 to 60 years. Patients in whom the events occurred were taking either 50 mg or 100 mg eliglustat and occurred in CYP2D6 EM and IM patients. Days from the start of eliglustat dosing to the onset of the event ranged from the first Day 1 to 466. All patients were asymptomatic at the time of the event. Two patients, both of whom experienced ventricular tachycardia while on protocol specified Holter monitoring, withdrew from the study after the first dose of 50 mg eliglustat.

HLT of Supraventricular arrhythmia: reported in 4 patients including 2 patients with supraventricular tachycardia, 1 patient with arrhythmia and 1 patient with atrial tachycardia.

ECG: Among the 389 patients in eliglustat safety set, 28 (7.2%) had at least one potentially clinically significant PR, QRS and/or QTcF abnormality leading to a safety narrative. Of these 28 patients, the majority (n=21; 75%) of patients were from EDGE study (investigating qd versus bd dosing; safety data provided in this submission), even though this study included only 44% of the total enrolled population.

Overall, in the eliglustat safety set (n=393) was consistent with the safety profiles for the two eliglustat groups in ENGAGE and ENCORE studies. No post-marketing data are available at present. Please see CER (Attachment 2), Second round evaluation for initial data provided for 78 weeks results in ENGAGE study.

Second round evaluation – use in Poor Metabolisers (PM)

Following approval of use in PM by FDA at a reduced once daily (qd) dose of 84 mg eliglustat, the sponsor has provided details of modelling (physiologically based PK simulations) supporting this conclusion. A document with sponsor's response to questions from the European agency which discusses this modelling was also provided.

The sponsor's initial proposal was to contraindicate the use of eliglustat in PM phenotype. A full review of PK/efficacy/safety data in PM (and URM) patients in Q4 2016 was planned. However, both FDA (where approval has been granted) and the EMA (still under review) appear to have expressed a preference for the use of a single

formulation/strength (100 mg) to be made available in PM patients within the confines of the currently available data.

The number CYP2D6 PM patients who were treated with eliglustat in clinical efficacy studies was very small (5 patients in the 3 GD1 studies in this dossier, all at a dose of 50 mg bd). The proposed 100 mg qd dose has not been used in any circumstance in the clinical studies. Modelling the 100 mg qd dosing in PM patients provided the following predicted outcomes (Table 24):

Table 24: Predicted steady-state mean (5 th, 95th percentiles) Genz-99067 Pharmacokinetic parameters in CYP2D6 PM Population at 100 mg qd eliglustat (N=360)

Genz-99067 Parameters	PM 100 mg QD
C_{max} (ng/mL)	75.2 [22.0, 180]
AUC_{0-24} (ng.h/mL)	956 [179, 2660]

AUC_{0-24} = area under the plasma concentration versus time curve from time zero to the end of the dosing interval (24 hours); C_{max} = maximum observed plasma concentration; N = number of subjects; PM = poor metabolizer; QD = once daily.

These suggest that with 100 mg qd dosing in PM patients, the predicted Cmax is within the range 2.13 to 169 ng/mL derived in the clinical studies and thought to correlate with efficacy and safety. The predicted total exposure (AUC) from 0 to 24 hours is also within the exposures observed in the clinical studies (16.3 to 992 ng.h/mL). The sponsor notes that the predicted mean (956 ng.h/L) is closer to the higher side of the range (992 ng.h/L) seen in the clinical studies, so that a there is a considerable uncertainty or risk in regard to levels that may be achieved in clinical practice in PM patients using this dose regimen.

Note that the FDA approval includes a statement that *'Dosing of Cerdelga 84 mg once daily has not been studied in PMs, however the predicted systemic exposures in these patients are within the range of those observed in clinical studies.'*

Clinical evaluator's recommendation (if applicable)

GD1 patients who are treatment-naive

The clinical evaluator recommended that the proposed treatment regimen (100 mg bd limited to CYP2D6 EMs or IMs) be approved for the reasons outlined above in *First round assessment of benefits.*

GD1 patients stabilised on ERT prior to switching to eliglustat

The clinical evaluator recommended that the proposed treatment regimen (100 mg bd limited to CYP2D6 EMs or IMs) be rejected**.**

Risk management plan

EU Risk Management Plan Version 1.1 (dated 02 May 2014, DLP 31 January 2013) and Australian Specific Annex Version (Version 1.1, dated July 2014) apply to this submission. Eliglustat was referred to ACSOM and considered at its 23rd meeting held on 11 July 2014. Finalisation of RMP and agreement with the TGA is pending and will be pursued before prior to finalisation of this submission.

Risk-benefit analysis

Delegate's conclusion and recommendation

1. Eliglustat is a New Chemical Entity proposed as a substrate reduction therapy in an orphan designated indication i.e. *'long term treatment of adult patients with Gaucher Disease Type 1'*. Currently two drugs as enzyme replacement therapy and one (miglustat) as substrate reduction therapy are approved in Australia.
2. The Quality and Nonclinical data supporting this submission are satisfactory. The relevant areas support registration. Eliglustat is manufactured by chemical synthesis. Pregnancy Category B3 is proposed.
3. Eliglustat is mainly metabolised by mainly by CYP2D6 and CYP3A4. Up to 21 metabolites in plasma and 31 metabolites in urine have been identified. Ten metabolites in plasma have been structurally confirmed. Three were not metabolised by any CYP isozymes tested. The other 7 were metabolised by CYP2D6. None of the 10 metabolites with confirmed structures showed any significant inhibition of glucosylceramide synthase activity. Of the 10 metabolites, only one (Genz-399240) had a total exposure exceeding 10% of total drug-related exposure in plasma in the mass balance study.
4. Eliglustat is rapidly absorbed after oral administration and has very high First pass effect with systemic bioavailability (F) < 5%.
    a. The PK behavior was non-linear across a wide range (0.01 mg/kg to 30 mg/kg) in a single dose study. This was also confirmed in multiple dose study. PK data was also collected in the 3 efficacy studies in GD1 patient population and suggested relative stabilisation of plasma levels with chronic dosing after 3-13 weeks.
    b. However, the drug is also subject to significant risk of intra-subject variability due to potential drug interactions based on metabolism by CYP2D6 and CYP3A4. A number of interaction studies were provided. Food effect was also studied and although the Cmax did not meet the 80 to 125% criteria on the lower side, this is considered clinically acceptable. In clinical studies the eliglustat was given without regard for food and same is proposed for inclusion in the PI.
5. In exploratory pharmacodynamic studies for assessment of biomarkers, a dose dependent relationship for decrease in plasma GL-1 levels. Such linear dose relationship was not seen in PK studies as noted above or in later clinical studies. A formal dose response study was not done.
6. The proposed indication is supported by 3 clinical studies in GD1 patients with moderately severe disease. The studies comprised predominantly CYP2D6 Extensive (EM) and Intermediate (IM) metaboliser population. There was one PM metaboliser patient in Phase II study, none in ENGAGE study and 4 in ENCORE study.
7. These studies include a single arm Phase II study (n = 26) and a pivotal Phase III placebo-controlled study (ENGAGE; N = 40) in patients who had not recently received ERT or SRT therapy ('treatment naïve patients'). The placebo controlled comparison in ENGAGE was at 39 weeks of treatment and demonstrated superior efficacy in relation to effect on organ volumes (spleen and liver) and haematological outcomes (Hb level and platelet count). The primary efficacy endpoint was change (%) in spleen volume (multiples of normal MN) from baseline to 39 weeks. The mean change in spleen volume (MN) from baseline to Week 39 was -27.77% in eliglustat group versus +2.26% in placebo group. The treatment difference was -30.03% (95%CI -36.82% to -23.24%) in favour of eliglustat treatment. Similar effect

was earlier seen in the Phase II study. Long-term uncontrolled data (4 years in Phase II study; initial results at 78 weeks in ENGAGE) indicate maintenance of effect.

8. The other Phase III study (ENCORE; N = 160; 146 included in the per protocol analysis) was open-label, active-controlled and was conducted in patients who had been on long-term treatment on ERT (at least 3 years) and had achieved therapeutic goals. The patients were allowed to continue on ERT until the day before the commencement of treatment in this study. The comparator treatment groups were eliglustat and imiglucerase (Cerezyme) with non-inferiority comparison after 52 weeks of treatment.

    a. The study, therefore, examined switching the patients stabilised on ERT to eliglustat and compared maintenance of therapeutic goals in comparison with Cerezyme. Non-inferiority was established based on treatment difference using a composite endpoint (4 components; spleen and liver volumes, and Hb level and platelet count). At 52 weeks, the treatment difference (patients remaining stable as defined) was -8.8% (95%CI -17.6% to 4.2%). The lower margin (-17.6%) was within the sponsor's pre-specified non-inferiority margin for the treatment effect to be no worse than 25%. It was also within the 20% margin recommended by EMA. The FDA recommended the change in spleen volume (MN) for assessment of non-inferiority. The mean change in spleen volume (MN) from baseline to Week 52 was -6.05% in eliglustat versus -3.22% in CEREZYME group, indicating a treatment difference of -2.83% (95%CI -8.14% to 2.47%). The lower-bound of 95%CI (-8.14%) was within the non-inferiority margin of 15% proposed by the regulator.

9. In the 3 clinical studies, dosing was based on titration using plasma eliglustat trough levels (< or ≥ 5 ng/L). The proposed dosing is, however, fixed dose 100 mg bd in CYP2D6 EM and IM population (> 90% of participating population). Although a number of subgroup analyses and pharmacokinetic modelling have been done to justify the fixed 100 mg bd dose, the clinical rationale that majority of patients treated in the clinical trials were on 100 mg bd dosing and that titration using plasma drug levels did not indicate meaningful difference in outcomes is considered acceptable. For a drug with highly variable PK, any reliance on predictions from modelling carries significant uncertainty. The non-linear behavior of the drug also limits its utility to essentially choosing a single drug level because a meaningful dose response could not be shown. Therefore, for pragmatic reasons and for simplifying the management of patients on eliglustat the proposed 100 mg bd fixed dosing is considered appropriate and supported by observed data.

10. Total Safety dataset is small consisting of 393 eliglustat treated patients but is understandable in view of a rare genetic disorder. Long-term data was also available in dossier. Overall the drug was well tolerated in the adverse effects profile is acceptable in the context of a serious medical condition. The risks include cardiotoxicity in particular. The effects on cardiac repolarisation were examined in an appropriately designed dedicated QT study and the results were acceptable. The risks also include drug interactions. Contraindications to use will include use with strong or moderate CYP2D6 or CYP3A inhibitors.

11. The proposed indication is broad ('*Cerdelga is indicated for the long-term treatment of adult patients with Gaucher disease type 1'*). Switching from ERT to eliglustat is not explicitly mentioned except in the *Dosage and Administration* section [of the PI] where it is noted that '*In clinical trials enzyme replacement treatment was allowed up to the day before the first dose of eliglustat*.' Note that in the ENCORE trial, it was not clear whether optimum dosing of Cerezyme was used. In addition, although non-inferiority was established at 52 weeks based on pre-defined criterion (composite outcome for stability) which was appropriate, the numerical results were in favour

of Cerezyme for all outcomes (spleen volume, platelet count and haemoglobin) except liver volume. It is not clear whether this may be clinically significant over the long-term for any patients switching to eliglustat from ERT. The sponsor is requested to comment in its pre Advisory Committee on Prescription Medicines (ACPM) response.

a. Note miglustat (an SRT) is approved for 'oral treatment of patients with mild to moderate Type 1 Gaucher disease, for whom enzyme replacement therapy is not a therapeutic option'.

12. Overall, the Delegate considers the data sufficient to support the proposed use in GD1 patient population with CYP2D6 extensive (EM) and intermediate (IM) metaboliser phenotype. The fixed 100 mg bd dosing is appropriate based on the most clinical experience obtained in the 3 supporting clinical trials. The qualifier 'long-term' in the indication is unnecessary and does not help define the target population or provide any specific additional guidance to the physicians treating GD. The recommended wording is *'treatment of adult patients with Gaucher disease type 1'*.

13. Pending advice from ACPM, the Delegate is of the view that the pharmacokinetic modelling assessing use in PM is not sufficient to support its use at a reduced 100 mg once daily dosing. This is principally due to the observed non-linear pharmacokinetics of the drug. The predicted total exposure (AUC) was also towards the higher limit of exposures seen in the clinical studies.

a. It is also noted that alternative options are available for GD1 patients with CYP2D6 PM phenotype such as miglustat which has simple pharmacokinetics and is exclusively removed by kidney unchanged.

b. Note that approval is USA has been worded 'Cerdelga is a glucosylceramide synthase inhibitor indicated for the long term treatment of adult patients with Gaucher disease type 1 who are CYP2D6 EMs, IMs or PMs as detected by an FDA-cleared test' with separate dosing regimen for EM/IM and PM patients.

c. The drug is also not expected to be efficacious in ultra-rapid (URM) metabolisers and specific dose instructions cannot be made for patients with indeterminate metabolisers. The proposed statement in regard to these 3 groups in the Dosage and Administration section of the PI is considered appropriate.

14. The lack of study in patients with hepatic impairment is considered a deficiency. However, a study is planned but the final clinical study report is not expected until the third quarter of 2017. Meanwhile, hepatic impairment is recommended as a contraindication for inclusion in the PI.

15. No study has been done in patients with renal impairment. A study is planned with report expected in third quarter of 2017. The sponsor has indicated that only PK parent eliglustat will be examined. This may not be optimum, given that nearly 50% metabolites of eliglustat are excreted via kidneys. The current proposal for a statement in the PI, modified as recommended by the clinical evaluator, is considered acceptable at present.

16. The sponsor is requested to provide information about the availability of results of the ongoing EDGE study (qd versus bd dosing) in its pre-ACPM response. Provision of full clinical study report, when available, is proposed as a condition of registration.

Summary of issues

- Highly metabolised drug with non-linear PK.
- Fixed dose regimen (100 mg bd) for use in CYP2D6 EM and IM metabolisers not consistent with the dose titration method used in the clinical studies.
- Appropriateness of use in PM at reduce dose (100 mg once daily) based on computer modelling.
- Validity of results demonstrating maintenance of effect on switching from enzyme replacement therapy to eliglustat.

Delegate's proposed action

The Delegate had no reason to say, at this time, that the application for eliglustat should not be approved for long-term treatment of adult GD1 patients with CYP2D6 metaboliser status EM and IM at a fixed dose of 100 mg twice daily.

The Delegate was not in a position to say, at this time, that the application for eliglustat should be approved for use in adult GD1 patients with CYP2D6 PM status patients at reduced dose of 100 mg once daily.

Note 100 mg eliglustat (tartrate) is equivalent to 84 mg eliglustat. The latter is proposed for labelling and for dosing instructions in the PI.)

Delegate's request for ACPM advice

The Committee is requested to provide advice on the following specific issues:

1. Does the committee agree that the data sufficiently support use is in adult GD1 patients with CYP2D6 EM and IM metaboliser status and is the fixed 100 mg bd dosing clinically appropriate?
2. Does the committee consider the accompanying PK modelling a sufficient ground for supporting the use of eliglustat in CYP2D6 PM at reduced dose of 100 mg once daily dose?
3. Does the committee consider the demonstration of non-inferiority for switching patients who have attained therapeutic goals on enzyme replacement therapy to eliglustat as sufficiently robust? Does the Committee propose any qualifying statements in the PI?

The committee is also requested to provide advice on any other issues that it thinks may be relevant to a decision on whether or not to approve this application.

Response from sponsor

The Sponsor's comments on the issues for which the advice of the ACPM is sought and additional information requested, as outlined in the Delegate's Overview of 4 November 2014, are presented below.

Eliglustat is an oral substrate reduction therapy (SRT), designated as an orphan drug. The indication proposed by the sponsor is:

Long-term treatment of adult patients with Gaucher disease type 1 (GD1)

For CYP2D6 IMs and EMs the recommended dose is 100 mg eliglustat tartrate twice daily and for CYP2D6 PMs the recommended dose is 100 mg once daily.

Patients with GD require life-long therapy to treat a chronically debilitating disease that affects multiple vital organ systems, causing persistent and irreversible morbidity and

significantly impacting on quality of life. Existing intravenous-administered enzyme replacement therapy (ERT) are a major burden for patients and the healthcare professionals that support their administration, due to the regular infusion cycles and the need to manage potential infusion reactions.

Oral SRTs such as eliglustat provide a therapeutic option that simplifies disease management as patients can self-administer treatment and thus gain significant improvements in quality of life. Currently, the only approved SRT available to GD1 patients is miglustat (Zavesca) indicated for second-line therapy in adult patients with mild to moderate GD1 for whom ERT is not a therapeutic option. The restricted indication is due to modest efficacy and a significant adverse event (AE) profile of miglustat, with a 45% discontinuation rate and more than 65% of these patients discontinuing treatment due to diarrhoea or tremor[19], caused by the off-target effects of miglustat. Therefore there remains an unmet medical need for a safe and effective oral treatment that can be used by the broader GD1 population.

The eliglustat clinical program including a Phase II and two pivotal Phase III studies (ENGAGE and ENCORE) in both naïve patients and those stable on ERT, has been the largest clinical development program conducted to date in GD. In total almost 400 GD1 patients have been enrolled from 29 countries, including Australia, where the estimated prevalence of all three sub-types of GD is 460 patients. Overall the safety and efficacy data demonstrate the positive benefit-risk profile of eliglustat to support its approval as an additional treatment option for patients with a rare debilitating disease.

1. *Does the Committee agree that the data sufficiently support use in adult GD1 patients with CYP2D6 extensive (EM) and intermediate (IM) metaboliser status and is the fixed 100 mg twice daily (bd) dosing clinically appropriate?*

The sponsor concurs with the Delegate's assessment of the overall positive benefit/risk assessment for eliglustat in EM and IM GD1 patients at the proposed 100 mg bd dosing schedule. As noted by the Delegate the majority of patients treated in the clinical trials were on the 100 mg bd dosing and titration using plasma drug levels did not indicate meaningful differences in outcomes. In addition the safety profile shows the drug is well tolerated and the important potential risks including drug interactions and contra-indications for use with strong or moderate CYP2D6 or CYP3A inhibitors are addressed through routine risk mitigation with appropriate statements included in the PI and specific risk management tools for healthcare professionals and patients.

In the clinical studies, patients received eliglustat 50 mg bd, with subsequent dose increases based on trough plasma concentration (Ctrough), measured at frequent bi-weekly intervals, to 100 mg bd (in ENGAGE) and up to 150 mg bd (in ENCORE). This dosing algorithm, while measuring eliglustat concentration, was in effect separating patients by their ability to metabolise eliglustat. In postmarketing clinical practice, such a dose titration regimen would be complicated due to the need for repeat plasma level testing that requires precise timing.

Population pharmacokinetic (PopPK) analysis using data from healthy subjects and GD1 patients showed that CYP2D6 phenotype was the most significant determinant of exposure to eliglustat. Efficacy projections with the optimised dosing regimen proposed, based on CYP2D6 phenotype, at a dose of 100 mg bd for the IM and EM patients (the majority of GD1 patients), show that similar efficacy results can be achieved with this simplified regimen as compared with the plasma-level based dosing used in the clinical studies in both treatment-naïve and stabilised patients, as summarised below:

[19] Kuter DJ et al, Miglustat therapy in type 1 Gaucher disease: Clinical and safety outcomes ina multicentre retrospective cohort study. Blood Cells Mol Dis 2013;51:116-124

- In Phase II and ENGAGE (treatment-naïve patients), the majority of the IM or EM patients were successfully treated at the 100 mg bd dose. This is important from a clinical perspective because untreated GD1 patients have a higher disease burden than patients stable on ERT, with anaemia, thrombocytopenia, hepatosplenomegaly and skeletal disease requiring initial debulking of glucosylceramide from tissues in order to improve their clinical status. In contrast, having achieved therapeutic goals for the disease, ERT-stabilised patients have a low substrate load and low disease burden and the target for them is in essence to demonstrate maintenance of clinical stability.
- In ENCORE (ERT-stabilised patients), the projected exposure based on the physiologically-based PK modelling has shown that the IM and EM patients who were treated at 50 mg bd and would receive 100 mg bd with the proposed dosing regimen, would stay within the ranges observed in the clinical trials. For the IM and EM patients who were treated at 150 mg bd and would be assigned the 100 mg bd with the proposed dosing regimen, PK/pharmacodynamic (PD) efficacy modelling projected only an additional 4% maximum increase for individual patient spleen volume values compared to the observed changes in the study. This small change in patients with little or no splenomegaly would not be clinically significant and is comparable to the test-test variability of organ volume measurement by MRI. Thus, 100 mg bd is a dose that achieves the exposure levels proven to be safe and effective in the pivotal clinical trials in the vast majority of GD1 IM and EM patients.

2. *Does the committee consider the accompanying PK modelling a sufficient ground for supporting the use of eliglustat in CYP2D6 poor (PM) metabolisers at a reduced dose of 100 mg once daily?*

During discussions with FDA and EMA, the agencies expressed interest in including PM patients in the label. Based on FDA requested physiologically based PK simulations, the FDA and the sponsor concluded that this dose was within the range of safe and efficacious exposures achieved in the clinical trials. In light of the strong desire of the Committee for Medicinal Products for Human Use (CHMP) to also include PM patients in the EU label, with initial indications from the agency that this will be acceptable, and considering that include a 100 mg qd dosing regimen for PM patients in the EU SmPC and the Australian PI. The alignment in labelling will:

- extend treatment choice from 90% (IMs and EMs) up to 95% adult patients (including PMs) with GD1
- minimise the existing potential for off-label use in PM patients at the incorrect dose
- offer identical treatment options to Australian patients as available overseas.

Whilst the number of CYP2D6 PM patients treated with eliglustat in clinical studies is very small (N=5 PM patients in the primary analysis period of Phase II and ENCORE; N=14 PM patients in the studies including EDGE and extension periods, N=0 in ENGAGE) the same holds true for the number of PMs anticipated to be treated in the postmarketing situation (estimated up to 5% of this rare disease population). These numbers reflect the background prevalence of PMs in the general population considering the rarity of GD.

The pharmacokinetics of eliglustat in CYP2D6 PMs is expected to be linear and time-independent. The sponsor acknowledges that in non-poor metabolisers, Genz-99067 (eliglustat free base) exposure increased in a greater than dose proportional manner, likely due to CYP2D6 auto-inhibition since eliglustat is both a competitive and time-dependent inhibitor of CYP2D6 as well as a substrate of CYP2D6. In contrast, in CYP2D6 PMs with no functional CYP2D6, Genz-99067 exposure increased in a close to dose proportional manner (approximately 3 times) over the 2 fold single-dose range of 100 mg to 200 mg (based on limited data from Studies GZGD01707 and GZGD02407).

The sponsor also agrees that the predicted exposure (AUC_{0-12}) for PMs on 100 mg once daily dosing is towards the higher limit of exposure seen in the clinical studies. However, in agreement with the FDA the PM dose is provided in the interest of extending treatment to a greater proportion of GD1 patients and in the absence of a known safety risk with chronic dosing at the higher limit of exposure.

3. *Does the committee consider the demonstration of non-inferiority for switching patients who have attained therapeutic goals on enzyme replacement therapy to eliglustat as sufficiently robust? Does the committee propose any qualifying statements in the PI?*

The objective of the ENCORE study was to evaluate the ability of eliglustat to maintain disease stability in patients who had achieved therapeutic goals for GD1 while on long-term ERT. As described in the *Clinical Trials* section of the proposed Cerdelga PI, patients included in the trial were those who received treatment with Cerezyme for at least 3 years and who had received a total monthly dose of 30 to 130 U/kg of Cerezyme for at least 6 of the 9 months prior to randomisation.

The recommended dose of Cerezyme in the Australian PI is up to 60 U/kg once every two weeks, with dose increase or decrease adjustments based on achievement of therapeutic goals as assessed by routine comprehensive evaluations of the patients' clinical manifestations. The Delegate has noted it was not clear whether optimum dosing of Cerezyme was used in the study. The range of doses used reflects those approved in the participating countries including Australia and were successful in achieving the goal of maintaining disease stability and therefore representative of the optimum dose of Cerezyme.

The sponsor fully endorses the Delegate's opinion that the predefined criterion of composite endpoint for stability was appropriate. In ENCORE, eliglustat was shown to be non-inferior to Cerezyme based on the 20% non-inferiority margin recommended by the CHMP, representing a robust assessment of clinical effectiveness. In response to the Delegate's concerns on the longer term clinical significance of the numerical results for all outcomes being in favour of Cerezyme, the available data from the long term extension study of ENCORE through Week 104 confirm that patients treated with eliglustat during both treatment periods (that is, treated with eliglustat for 104 weeks), continued to maintain stability of disease during the extension period. Results were consistent across all four efficacy parameters. In addition, preference for an oral treatment was confirmed by all of the patients who completed a questionnaire after 52 weeks of treatment with eliglustat in ENCORE.

As shown in Table 25, among patients randomised to eliglustat treatment and treated for 104 weeks with eliglustat, the proportion of patients meeting the composite stability criteria was maintained with 84.8% at Week 52 and 87.4% at Week 104 (PPS) The percentage of patients meeting the criteria for stability in the individual components of the composite endpoint remained stable and is displayed in Table 26. It should also be noted that during the extension period, from Weeks 52 to 104, the patients who crossed over to eliglustat treatment from Cerezyme maintained stability of disease with 93.6% (44/47; 95% CI 82.5, 98.7) at Week 52 and 85.7% (36/42; 95% CI 71.5, 94.6) at Week 104 (PPS).

Table 25: Summary of proportion of patients who were stable: Per Protocol Set (PPS)

Variable	Eliglustat (N=99)	Cerezyme to Eliglustat (N=47)
	99	42
Patients Stable for 52 Weeks, n (%)	84 (84.8)	36 (85.7)
Exact 95% CI	(0.762, 0.913)	(0.715, 0.946)
	95	-
Patients Stable for 104 Weeks, n (%)	83 (87.4)	
Exact 95% CI	(0.790, 0.933)	-

Source: 104-Week Results Memo Report, Table 14.2.1.1.1 CI = Confidence Interval

Note: The primary efficacy criteria for success include stable hematologic parameters and organ volumes as defined in the protocol. Patient percentages are based on the total number of patients in the per protocol set in the particular treatment group.; Eliglustat patients who returned to Cerezyme were counted as failures.; The lower bound of the 95% exact CI for the overall column of the Eliglustat group will be used to claim that the majority of the Eliglustat patients were successful in maintaining stability after 52 weeks of treatment, irrespective of whether or not the non-inferiority of Eliglustat relative to Cerezyme is demonstrated.

Table 26: Summary of proportion of patients who meet stable haematologic and organ volume criteria: Per Protocol Set

Variable	Eliglustat (N=99)	Cerezyme to Eliglustat (N=47)
Patients Meeting Hemoglobin Criteria	99	41
At 52 weeks, n (%)	94 (94.9)	41 (100.0)
Exact 95% CI	(0.886, 0.983)	NA
At 104 weeks, n (%)	92 (96.8)	-
Exact 95% CI	(0.910, 0.993)	-
Patients Meeting Platelets Criteria	99	41
At 52 weeks, n (%)	92 (92.9)	37 (90.2)
Exact 95% CI	(0.860, 0.971)	(0.769, 0.973)
At 104 weeks, n (%)	89 (93.7)	-
Exact 95% CI	(0.868, 0.976)	-
Patients Meeting Spleen Volume Criteria a	71	39
At 52 weeks, n (%)	68 (95.8)	33 (97.1)
Exact 95% CI	(0.881, 0.991)	(0.847, 0.999)
At 104 weeks, n (%)	68 (95.8)	-
Exact 95% CI	(0.881, 0.991)	-
Patients Meeting Liver Volume Criteria	99	42
At 52 weeks, n (%)	95 (96.0)	40 (95.2)
Exact 95% CI	(0.900, 0.989)	(0.838, 0.994)
At 104 weeks, n (%)	91 (95.8)	-
Exact 95% CI	(0.896, 0.988)	-

Source: 104-Week Results Memo Report, Tables 14.2.1.5.1, 14.2.1.6.1, 14.2.1.7.1 and 14.2.1.8.1

CI = confidence interval; NA = not applicable

[a] Patient percentages are based on the total number of non-splenectomized patients in the particular treatment group. Note: Patient percentages are based on the total number of patients in the per protocol set in the particular treatment group; Eliglustat patients who returned to Cerezyme were counted as failures.

Overall, the data at 52 weeks show that in patients switching from ERT, eliglustat is non-inferior to Cerezyme in maintaining stability of GD1 clinical outcome parameters and that the treatment effect is maintained after 104 weeks (2 years) of treatment. On this basis the sponsor does not propose any additional qualifying statements in the PI. In addition, in a postmarketing setting, eliglustat will offer a safe and effective alternative to the current treatment options for patients who will continue to be monitored under specialist care. Based on the sponsor's in depth knowledge of the management of GD, the prescribing and initiation of treatment is overseen by a single primary physician. There are approximately 23 physicians across Australia who manage the treatment of GD patients (approximately 80 patients in total). Nearly 80% of these physicians are haematologists or paediatric haematologists, with the remaining 20% being metabolic geneticists, a general paediatrician and an endocrinologist. Additional to this specialist care provided, the

patients will also be co-monitored by the Life Saving Drugs Programme who routinely re-assess their progress.

Product information

Clean and annotated copies of the PI reflecting proposed changes to address recommendations from non-clinical, clinical and RMP evaluations requested by the Delegate were provided. The Delegate has proposed rewording of the proposed indication to remove reference to the qualifier **'long-term'** as well as include hepatic impairment as a contra-indication.

The proposed indication wording for Cerdelga is consistent with the approved PI for Cerezyme (ERT), the active comparator in the pivotal Phase III ENCORE trial, against which eliglustat was demonstrated to be non-inferior. It is also consistent with the approved US indication and that proposed for inclusion in the final approved EU SmPC. The qualifier 'long-term' highlights the need for the life-long commitment to treatment considering the progressive build-up of glucosylsphingosine (GL-1) in the absence of any treatment, due to the inherent deficiency in acid β-glucosidase that causes GD. On this basis the sponsor does not consider that any change to the proposed indication wording is warranted.

As noted by the Delegate a study in patients with hepatic impairment is planned and in the absence of definitive data the sponsor has appropriately reflected information in the "Pharmacokinetics" and "Dosage and Administration" sections of the PI. The exclusion criteria noted for ENGAGE and ENCORE aimed to exclude patients with significant (non-GD1 associated) illnesses that may have confounded trial results. No specific safety risk has been identified that would warrant a "Contra-indication" and hepatic impairment has been identified as missing information in the RMP. The PI approach is consistent with other medicines approved in Australia, and aligned with the approved US label and the proposed EU SmPC. Given the close specialist supervision that GD patients are managed under, the sponsor does not consider that a unique approach is warranted for Prescribers in Australia.

Sponsor's post approval commitments

As requested in the Delegates Overview final study reports for the placental transfer and milk excretion studies ongoing at the time of submission are being finalised and the sponsor commits to providing the reports to the TGA as soon as available.

The Delegate has proposed to include the EDGE study results comparing daily versus twice daily dosing as a condition of registration. The sponsor commits to provide the full clinical report following study completion expected by fourth quarter of 2015.

Sponsor's summary

Eliglustat offers an important alternative oral treatment option for GD, a serious debilitating condition requiring life-long therapy. The favourable benefit risk profile supports approval for EMs, IMs and PMs based on the clinical dataset from the Phase II and Phase III (ENGAGE and ENCORE) studies and additional modelling data in both treatment naïve patients and those switched from ERT, that demonstrates:

- Clinically and statistically significant improvements in the primary disease manifestations of hepatosplenomegaly, anaemia, thrombocytopenia and bone disease in patients with GD1.
- Improvements or maintenance of efficacy with continued long term eliglustat treatment.
- A safety profile that confirms the drug is well tolerated based on a comprehensive safety database of 393 patients:

- no significant safety issues identified in the pivotal clinical program or long term extension studies including up to 6.5 years for patients in the Phase II study
- no Important Identified Risks defined in the current Risk Management Plan
- comprehensive risk mitigation approach for important potential risks of drug interactions and contra-indications for use with strong or moderate CYP2D6 or CYP3A inhibitors based on statements included in the PI together with specific risk management tools for healthcare professionals and patients.

Advisory Committee Considerations

The Advisory Committee on Prescription Medicines (ACPM), having considered the evaluations and the Delegate's overview, as well as the sponsor's response to these documents, advised the following:

The ACPM, taking into account the submitted evidence of efficacy, safety and quality, considered Cerdelga hard capsule containing 84 mg of eliglustat (as tartrate) to have an overall positive benefit–risk profile for the indication:

> *Cerdelga is indicated for the treatment of adult patients with Gaucher Disease Type 1 (GD1).*

In making this recommendation the ACPM considered that it is appropriate to limit the indication to adult patients with GD Type 1 based on the clinical trial data. In addition, eliglustat inhibits ceramide synthesis in the brain and that use in children is not recommended.

The ACPM agreed that the addition of *'long term'* be omitted to be consistent with the indication for the currently approved substrate reduction therapy.

Proposed conditions of registration

The ACPM agreed with the Delegate on the proposed conditions of registration.

Proposed Product Information (PI)/Consumer Medicine Information (CMI) amendments

The ACPM agreed with the Delegate to the proposed amendments to the Product Information (PI) and Consumer Medicine Information (CMI) and specifically advised on the inclusion of the following:

· The Committee recommended inclusion of a clear statement in the PI that the 84 mg once daily dose has not been studied in the poor metaboliser subgroup of patients. This should be included under both *Special Populations and Dosage and Administration sections*.

Specific Advice

The ACPM advised the following in response to the Delegate's specific questions on this submission:

1. *Does the committee agree that the data sufficiently support use is in adult GD1 patients with CYP2D6 extensive (EM) and intermediate (IM) metaboliser status and is the fixed 100 mg bd dosing clinically appropriate?*

The ACPM considered that there were sufficient data to support the use of eliglustat in adult GD1 patients with CYP2D6 extensive (EM) and intermediate (IM) metaboliser status and that the fixed 100 mg twice daily dosing is appropriate.

2. *Does the committee consider the accompanying PK modelling a sufficient ground for supporting the use of eliglustat in CYP2D6 poor (PM) metabolisers at reduced dose of 100 mg once daily dose?*

The ACPM noted there were 5 PMs and all received a dose of 42 mg twice a day and four patients had an adequate clinical response. The ACPM noted that in CYP2D6 PMs with no functional CYP2D6, exposure increased in a relatively closer to dose proportional manner, whereas in non-poor metabolisers, eliglustat exposure increased in a greater than dose proportional manner. The reduction in rate is likely due to CYP2D6 auto-inhibition. The ACPM also noted that based on PK modelling the mean predicted exposure for PMs was toward the upper end of the clinical experience. The ACPM considered that given the limited numbers of PM patients and the very limited number of medical practitioners who treat these patients that use of eliglustat in PMs should be allowed and supported the recommendation of a reduced dose of 100 mg daily for PMs.

The ACPM agreed that a condition of registration should be the provision of the EDGE study results comparing once daily versus twice daily dosing which the sponsor expects will be available following study completion expected by the fourth quarter of 2015.

3. *Does the committee consider the demonstration of non-inferiority for switching patients who have attained therapeutic goals on enzyme replacement therapy to eliglustat as sufficiently robust? Does the committee propose any qualifying statements in the PI?*

The ACPM considered that the demonstration of non-inferiority for switching patients, who have attained therapeutic goals on enzyme replacement therapy to eliglustat in the ENCORE trial, was acceptable.

The ACPM recommended that the sponsor be requested to clarify and provide rationale for the proposed dosing (84 mg once daily), for administration with a concomitant strong CYP2D6 inhibitor and whether a contraindication would be more appropriate. Concomitant use with CYP3A4 inhibitors should also be clarified.

The ACPM advised that implementation by the sponsor of the recommendations outlined above to the satisfaction of the TGA, in addition to the evidence of efficacy and safety provided would support the safe and effective use of this product.

Outcome

Based on a review of quality, safety and efficacy, TGA approved the registration of Eliglustat Genzyme eliglustat (as tartrate) 84 mg capsule blister pack and Cerdelga eliglustat (as tartrate) 84 mg capsule blister pack indicated for:

> *Cerdelga is indicated for the long-term treatment of adult patients with Gaucher disease type 1 (GD1).*

Specific conditions of registration applying to these goods

1. The Eliglustat EU Risk Management Plan (RMP), version 1.7 (dated 23 January 2015, DLP 31 January 2013) and Australian Specific Annex Version (Version 1.4, dated 5 February 2015), included with submission PM-2013-03651-1-3, and any subsequent revisions, as agreed with the TGA will be implemented in Australia.
2. You [the sponsor] are required to submit to the TGA, for evaluation as a Category 1 submission, the full clinical study report (CSR) of 'EDGE study' as soon as the report becomes available

Attachment 1. Product Information

The Product Information approved for Cerdelga at the time this AusPAR was published is at Attachment 1. For the most recent Product Information please refer to the TGA website at < https://www.tga.gov.au/product-information-pi>.

Attachment 2. Extract from the Clinical Evaluation Report

Therapeutic Goods Administration

PO Box 100 Woden ACT 2606 Australia
Email: info@tga.gov.au Phone: 1800 020 653 Fax: 02 6232 8605
https://www.tga.gov.au