



Australian Government  
Department of Health  
Therapeutic Goods Administration

## AusPAR Attachment 2

# Extract from the Clinical Evaluation Report for Eliglustat (as tartrate)

Proprietary Product Name: Cerdelga

Sponsor: Sanofi-Aventis Australia Pty Ltd

**First round evaluation: 28 April 2014**

**Second round evaluation: 28 August 2014**

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## About the Extract from the Clinical Evaluation Report

- This document provides a more detailed evaluation of the clinical findings, extracted from the Clinical Evaluation Report (CER) prepared by the TGA. This extract does not include sections from the CER regarding product documentation or post market activities.
- The words [Information redacted], where they appear in this document, indicate that confidential information has been deleted.
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## 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
$AUC_{(0-4h)}$	Area under the plasma concentration versus time curve from time zero to 4 hours post-dose
$AUC_{(0-12h)}$	Area under the plasma concentration versus time curve from time zero to 12 hours post-dose
$AUC_{(0-24h)}$	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 above the lower limit of quantification
$AUC_{(0-\tau)}$	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
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
CL <sub>r</sub>	Renal clearance
C <sub>max</sub>	Maximum observed plasma concentration
CNS	Central nervous system
CRCL	Creatinine clearance
CRF	Case report form
CSR	Clinical study report
C <sub>trough</sub>	Trough plasma concentration
CV	Coefficient of variation
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
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
IC <sub>50</sub>	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
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 $\beta$	Macrophage inflammatory protein 1 $\beta$
MMA	Methylmalonic acid
MMSE	Mini Mental State Examination
MN	Multiples of normal
MRI	Magnetic resonance imaging
msec	Millisecond
N/Av	Not available
NA	Not applicable
NADPH	Nicotinamide adenine dinucleotide phosphate (reduced form)
NC	Not calculated
ND	Not determined
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
PM	Poor Metaboliser
PopPK	Population pharmacokinetics
PPS	Per Protocol Set
PR	Interval between P and R waves of electrocardiogram
PT	Preferred term
q2w	Every two weeks
QD	Once daily
QOL	Quality of life
QT	Interval between Q and T waves on ECG
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
t <sub>1/2</sub>	Terminal elimination half-life
TEAE	treatment-emergent adverse event

$T_{max}$	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
$V_z$	Volume of distribution during the terminal (z) phase
$V_z/F$	Apparent volume of distribution during the terminal (z) phase

## 1. Introduction

### 1.1. 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  $\beta$ -glucosidase (also known as glucocerebrosidase). Deficiency in acid  $\beta$ -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 metabolized 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 characterized by the absence (Type 1) or presence (Types 2 and 3) of central nervous system (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 GD1.1.

## 1.2. 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)'.

## 1.3. Guidance

The submission includes a TGA 'Note for File' reporting 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 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).

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.

## 2. Contents of the clinical dossier

### 2.1. Scope of the clinical dossier

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

- 13 clinical pharmacology studies in healthy subjects including PK and/or 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.

## 2.2. 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 an open-label study historical controlled PK, safety, and efficacy study in paediatric patients with 'GD1 and GD3 (cat. 3)'.

## 2.3. 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 International Conference on Harmonisation (ICH) guidelines, and in accordance with relevant national or international laws applying to the conduct of clinical trials in humans.

# 3. Pharmacokinetics

## 3.1. Studies providing clinical pharmacology data

### 3.1.1. Clinical studies

#### 3.1.1.1. Healthy subjects

The submission included 13 PK studies in approximately 390 healthy volunteers, and 2 of these studies also included PD data (see Table 1, below). Each of the 13 studies have been evaluated and the key results have been provided in the text of this CER.

**Table 1: 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; [ <sup>14</sup> 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.

Study	PK Topic	N	Treatment
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 - Acid Reducing Drugs	24	ET (sd) 100 mg; Maalox Advanced Maximum Strength Liquid (sd); 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

### 3.1.1.2. Patients with GD1

The submission included four clinical efficacy and safety studies providing PK data from approximately 225 patients with GD1 (see Table 2, 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 this CER.

**Table2: 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-naïve 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 C <sub>trough</sub> 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) PK/PD (ECG parameters)	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 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 C <sub>trough</sub> 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 C <sub>trough</sub> level) and a dose of 50, 100 or 150 mg BD from post-Week 8 through Week 52 (depending on their Week 6 C <sub>trough</sub> 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.

Study	PK Topic	N	Design features relevant to PKs of eliglustat
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 analysed in PopPK analysis and a pooled PK/PD-ECG analysis. Primary analysis period was ongoing at time of submission; PK data were not summarised 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.

### 3.1.1.3. Pharmacokinetic parameters

The PK parameters in the individual clinical studies were determined using non-compartmental PK methods employing well known and appropriate statistical software packages. All PK parameters were standard and appropriate for the characterization of the PKs of eliglustat (free base) and its metabolites. In the following description of the PKs of eliglustat tartrate, the analyte eliglustat (free base) will be termed eliglustat.

### 3.1.1.4. Bioanalytical methods

Eliglustat was the primary drug-related moiety quantified in all clinical PK studies. In addition, 10 metabolites of eliglustat with confirmed structures were quantified in plasma from healthy subjects [GZGD02107, GZGD02407], and in GD1 patients [Phase II study]. Plasma was chosen as the matrix for quantification of eliglustat and its metabolites, due to radioactivity being mainly distributed in the plasma compartment of whole blood [GZGD02107], and low red blood cell eliglustat partitioning [DMPK11-R030].

Validated bioanalytical assays were developed for the determination of eliglustat in human plasma and human urine using liquid chromatography with tandem mass spectrometry (LC-MS/MS) over the concentration range 0.5 ng/mL to 1000 ng/mL. The method validation included the evaluation of specificity, accuracy, precision, stability, linearity, and limits of quantitation.

Given the primary role of CYP2D6 in the metabolism of eliglustat and the existence of multiple polymorphisms known to effect CYP2D6 activity, CYP2D6 phenotyping for prediction of metaboliser status was performed in all eliglustat clinical studies except the initial single ascending dose study [GZGD00103] and the food effect study [GZGD00404]. The polymorphism was identified using the Luminex xTAG® CYP2D6 Kit v3 or the Roche AmpliChip® Cytochrome P450 Genotyping test and Affymetrix GeneChip Microarray Instrumentation.

### 3.1.2. Pharmacokinetic and pharmacodynamic modelling

The submission included 5 PK/PD studies/reports using modelling and simulation methods (see Table 3, below). Two (2) population PK (PopPK) studies used pooled data from healthy subject and/or GD1 patient studies, and 3 three PK/PD modelling and simulation studies used in vitro data from the human biomaterial studies and/or in vivo data from healthy subjects

and/or GD1 patients to predict the effect of CYD2D6 phenotype on exposure. The studies have been reviewed and relevant data included in the text of this CER.

**Table 3: Pharmacokinetic and pharmacodynamic modelling studies.**

Study	PK Topic	Objectives
POH0373	PopPK PK/PD (ECG)	(1) To develop a PopPK model for eliglustat to describe concentration-time data arising from Phase I and available Phase II data; identify and quantify covariate effects; evaluate the final model using simulation techniques; (2) To fit the PopPk model developed in Objective 1 to the full dataset comprising all Phase I, 2, and 3 data; re-evaluate and quantify covariates; re-evaluate the refined model using simulation techniques; and (3) To develop QT, QTcB, QTcF, PR, QRS and heart rate models.
POH0395	PK/PD (efficacy)	To explore the PK/PD relationship between treatment efficacy and PK parameters for eliglustat in patients with GD 1 from the Phase III studies.
SIM0105	PBPK modelling	To use prior in vitro and in vivo information on the metabolism and kinetics of eliglustat in the Simcyp Population-based Simulator (Version 10.1) to predict plasma concentration-time profiles of eliglustat and to evaluate the likely impact of co-administration of paroxetine and ketoconazole on the pharmacokinetics ( $C_{max}$ and AUC) of eliglustat using various dosage regimens.
SIM0106	PBPK modelling	To use the model developed previously for eliglustat in the Simcyp Population Based Simulator (V11.1) to predict plasma concentration-time profiles of eliglustat and to evaluate the likely impact of co-administration of fluconazole and terbinafine, moderate inhibitors of CYP3A4 and CYP2D6, respectively, on the pharmacokinetics ( $C_{max}$ and AUC) of eliglustat using various dosage regimens.
SIM0124	Simulations: exposure versus CYP2D6 phenotype	(1) To simulate steady state plasma exposure to eliglustat for a patient population with GD1, containing CYP2D6 phenotype PM, IM, EM and URM categories, based on frequencies from published data, following eliglustat tartrate at doses of 50, 100, and 150 mg BD; (2) To simulate steady state plasma exposure to eliglustat for a healthy subject population, containing CYP2D6 IM and EM categories, based on frequencies from published data, following eliglustat tartrate at doses of 100 mg BD; and (3) To simulate steady state plasma exposure for each CYP2D6 phenotype PM, IM, EM, URM categories following eliglustat tartrate at doses of 50, 100, and 150 mg bd according to a cross-over design to obtain dose-related exposure increases for GD1 patients.

### 3.1.3. In vitro human biomaterial studies

The submission included 30 in vitro human biomaterial studies designed to characterize the PK profile of eliglustat, including absorption, distribution, metabolism, excretion and the potential for drug-drug interactions through CYP isozymes and drug transporters. The studies were sponsored by the Genzyme Corporation, and were undertaken between approximately 2009



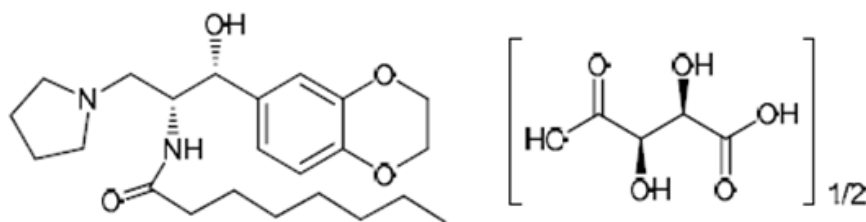
and 2013. The studies were stated to be non-GLP compliant. The studies have been reviewed and relevant results provided in the text of this CER. It is suggested that the in vitro human biomaterial studies should also be evaluated by the nonclinical evaluator.

### 3.2. Summary of pharmacokinetics

#### 3.2.1. Physicochemical characteristics of the active substances

The chemical structure of eliglustat tartrate is presented below in Figure 1.

**Figure 1: Chemical structure of eliglustat tartrate.**



Eliglustat tartrate Drug Substance (DS) is a white to off-white crystalline powder, which is highly soluble in water and meets the minimum dose-based solubility requirements for a BCS Class 1 compound ( $\geq 2$  mg/mL) at physiologic pH (pH = 1.0, 4.5, 6.8 and 7.5) and 37°C. The DS is soluble in methanol, methylene chloride and ethanol at concentrations greater than 40 mg/mL and slightly soluble (<5 mg/mL) in acetone, acetonitrile, 1,4-dioxane, ethyl acetate, isopropyl alcohol, tert-butyl methyl ether, tetrahydrofuran and toluene.

#### 3.2.2. Pharmacokinetic in healthy subjects

##### 3.2.2.1. Absorption

The absorption of eliglustat was assessed in vitro in the human colon adenocarcinoma Caco-2 cell permeability model at concentrations of 12.5, 125, and 1250  $\mu$ M [DMPK10-R047]. In this study, eliglustat exhibited higher permeability at all tested concentrations than the internal high permeability standard of labetalol. The ratios of permeability of eliglustat to that of labetalol were 2.0, 1.9 and 1.6 at concentrations of 12.5, 125 and 1250  $\mu$ M, respectively. The oral human absorption of eliglustat following a single oral dose of eliglustat (100 mg and 150 mg) was predicted to be greater than 99% in a computer simulation study using GastroPlus™ software [DMPK10-R048]. Eliglustat was demonstrated to be a substrate of the P-gp efflux transporter [DMPK10-R020], but not of the BCRP efflux transporter [DMPK11-R039].

**Comment:** The data from studies DMPK10-R047 and DMK10-R048 support the BCS Class 1 designation of eliglustat as being both highly soluble and highly permeable.

##### 3.2.2.2. Bioavailability

###### 3.2.2.2.1. Absolute bioavailability (GZGD02107)

The objectives of Study GZGD02107 were to evaluate the absolute bioavailability of eliglustat and the absorption, metabolism and excretion of [ $^{14}$ C]-eliglustat in healthy male subjects. The study was an open-label, fixed-sequence design with 4 treatment periods: (1) single-dose eliglustat 50 mg IV over 1 hour on Day 1 (morning); (2) single-dose eliglustat 100 mg oral capsule on Day 8 (morning); (3) multiple-dose eliglustat 100 mg bd oral capsules Day 9 (evening) through to Day 14 (evening); and (4) single-dose [ $^{14}$ C]-eliglustat 100 mg oral solution (approximately 100  $\mu$  Ci) on Day 15 (morning). In this section of the CER, the results of the absolute bioavailability assessment will be reviewed, while the results relating to multiple administration of eliglustat and absorption, metabolism, and excretion of [ $^{14}$ C]-eliglustat will be reviewed in the relevant sections of the CER.

The study enrolled 10 healthy males, 9 of whom were extensive CYP2D6 metabolisers. All 10 subjects participated in treatment periods 1 and 2 and remained in the study centre for 3 nights during each treatment period. Eight (8) of the 10 subjects participated in treatment periods 3 and 4. These subjects remained in the study centre following completion of treatment period 2 and were discharged on or after Day 19 of treatment period 4 (but no later than Day 26) when  $\geq 90\%$  of the administered radioactive dose had been recovered and radioactivity in both urine and feces from 2 consecutive samples was  $\leq 1\%$  of the administered radioactive dose. The two subjects not participating in treatment periods 3 or 4 were discharged following completion of treatment Period 2. The key PK results from treatment periods 1 and 2 are summarised below in Table 4.

**Table 4: GZGD02107 - PK parameters for eliglustat in plasma following single dose eliglustat tartrate 50 mg IV or 100 mg eliglustat tartrate oral capsule in healthy male volunteers (n=10).**

Parameter [1]		IV 50 mg (n=10) Day 1	PO 100 mg (n=10) Day 8
F (%)		NA	4.49 $\pm$ 4.13
C <sub>max</sub>	ng/mL	107 $\pm$ 25	5.48 $\pm$ 5.01
T <sub>max</sub>	hour (range)	1 (0.5, 1.5)	1.76 (1, 4)
AUC <sub>(0-inf)/D</sub>	(ng·h/mL)/ (mg)	11.8 $\pm$ 1.56	0.560 $\pm$ 0.623
t <sub>1/2</sub>	hour	6.59 $\pm$ 0.436	5.47 $\pm$ 1.39
CL (IV); CL/F (PO)	L/h	85.8 $\pm$ 10.4	3493 $\pm$ 2364
V <sub>z</sub> (IV); V <sub>z</sub> /F (PO)	L	816 $\pm$ 117	24403 $\pm$ 12767

[1] Mean  $\pm$  standard deviation, except median (range) for T<sub>max</sub>.

**Comment:** The mean  $\pm$  SD absolute bioavailability (F%) was 4.49%  $\pm$  4.13%. The mean dose-normalized eliglustat AUC<sub>(0-inf)</sub> value after eliglustat tartrate IV administration was approximately 21-fold greater than after oral administration. These results indicate that eliglustat has limited bioavailability after oral administration, due to extensive first-pass metabolism.

#### 3.2.2.2.2. *Relative bioavailability phase III versus commercial formulation (Study GZGD03811)*

The primary objective of pilot Study GZGD03811 was to determine the within-subject PK variability and relative bioavailability of single oral doses of eliglustat 150 mg administered as the Phase III formulation (3 x 50 mg capsules) and the common blend proposed commercial formulation (1 x 150 mg capsule) in healthy adult subjects. The secondary objectives were to estimate the between-subject and total variability, and the safety and tolerability of the two formulations.

The study was single-site, single-dose, randomized, open-label, 2-treatment, 2-sequence, 4-period and replicated in design. It included a screening period (Days -45 to -4), Period 1 (Days -3 to 4), Period 2 (Days 8 to 11), Period 3 (Days 15 to 18), Period 4 (Days 22 to 25), and a safety follow-up visit (Day 29  $\pm$  1 day). There was a 7-day washout between dosing in each period. Subjects received a total of 4 single oral doses of eliglustat under fasting conditions, with the

Phase III formulation (3 x 50 mg capsules) being the reference (R) treatments and the common blend formulation (1 x 150 mg) being the test (T) treatment. Subjects were randomized to one of two treatment sequences (TRTR [Sequence 1] or RTRT [Sequence 2]).

Overall, 22 subjects were randomized and 22 completed the study and were included in the PK analysis (TRTR [n=11] and RTRT [n=11]). The mean age of the 22 subjects was 31.8 years (range: 23, 45), the mean BMI was 25.6 kg/m<sup>2</sup> (range: 20.4, 30.9), 11 were male and 11 were female, and there were 20 CYP2D6 extensive metabolisers and 2 CYP2D6 intermediate metabolisers.

The GMR and 90% CI for the PK parameters were calculated using standard methodology for assessment of bioequivalence. The statistical analysis of the relative bioavailability of eliglustat is summarised below in Table 5.

**Table 5: GZGD03811 - Statistical analysis of relative bioavailability of eliglustat; PK population.**

Parameter (Unit)	Treatment	n	Geometric Means	95% CI of the Geometric Means	Ratio (%) of Geometric Means (T/R)	90% CI of the Ratio	Intra-Subject CV (%)
AUC <sub>last</sub> (ng•h/mL)	R	22	97.91	66.90, 143.29	100.58	94.13, 107.47	21.3
	T	22	98.48	65.72, 147.57			
AUC <sub>0-inf</sub> (ng•h/mL)	R	22	102.35	70.51, 148.56	100.33	94.02, 107.07	20.5
	T	22	102.69	69.01, 152.81			
C <sub>max</sub> (ng/mL)	R	22	14.93	10.64, 20.96	102.10	94.58, 110.21	21.8
	T	22	15.24	10.51, 22.10			

Note: T = Test treatment (1 x 150 mg common blend capsule); R = Reference treatment (3 x 50 mg Phase III capsules).

The mean plasma concentrations of eliglustat versus time on linear and logarithmic scales and by treatment and occasion (T1, T2, R1, and R2) were presented. The PK parameters were similar for the two treatments, and marked inter-subject variability (CV%) was observed for the parameters for both treatments. For the between-subject comparison, the SD estimates for treatments T and R were similar for AUC<sub>(0-inf)</sub> (0.89 versus 0.82, respectively), AUC<sub>(0-last)</sub> (0.90 versus 0.83, respectively), and C<sub>max</sub> (0.82 versus 0.74, respectively). The likelihood ratio test indicated that there was no significant difference at  $\alpha = 0.05$  for the between-subject SD comparisons.

**Comment:** The 90% CIs for the ratio of the GMR for each of the three parameters (AUC<sub>(0-last)</sub>, AUC<sub>(0-inf)</sub> and C<sub>max</sub>) for the comparison between the common blend formulation proposed for commercial release and the Phase III formulation were completely enclosed within the standard bioequivalence interval of 80% to 125%. The intra-subject variability for each of the three parameters for both formulations was less than 30%, indicating that eliglustat is not a highly variable drug within-subjects.

#### 3.2.2.2.3. Influence of food (Study GZGD00404)

Study GZGD00404 (Phase Ib) was a single centre, non-randomized, cross-over study designed to assess the effect of food on the safety, PKs, and bioavailability of eliglustat in healthy male subjects. Twenty-four (24) male subjects were sequentially assigned to 1 of 2 treatment cohorts (fasted:fed or fed:fasted) to receive single-dose eliglustat 300 mg (6 x 50 mg capsules) on Day 1 and Day 7 with or without food (high-fat breakfast) in a cross-over design (6 day washout period). All 24 subjects completed both periods of the study.

The PK parameters and statistical analysis for eliglustat derived from plasma concentrations of eliglustat are summarised below in Table 6.

**Table6: GZGD00404 - PKs and statistical analysis for eliglustat after 300 mg dose of eliglustat tartrate under fed and fasted conditions; n=24 healthy male volunteers.**

Pharmacokinetic parameters in fed and fasted states [1]				Statistical analysis fed versus fasted [2]		
Parameter		Fed	Fasted	Parameter	GMR (Fed:Fasted)	90% CI
$C_{max}$	ng/mL	79.1 ± 65.9	88.3 ± 76.2	$C_{max}$	85.20	67.93, 106.87
AUC(0-t)	h·ng/mL	678 ± 638	606 ± 585	AUC(0-t)	104.69	88.83, 123.37
AUC <sub>(0-inf)</sub>	h·ng/mL	696 ± 656	623 ± 601	AUC <sub>(0-inf)</sub>	104.44	89.04, 122.51
$T_{max}$	hour	3.00	2.00			
t <sub>1/2</sub>	hour	6.11 ± 1.37	6.68 ± 1.09			

[1] = Mean ± standard deviation, except median for  $T_{max}$  [2] = Geometric mean ratio (GMR), based on natural log-transformed data.

**Comment:** In this study, the two primary pre-specified PK parameters were  $C_{max}$  and AUC<sub>(0-inf)</sub>. The study showed that there was no food effect on AUC<sub>(0-inf)</sub> as the 90% CI for this parameter was within the pre-specified bioequivalence limits of 80% to 125%. However, there was a food effect on  $C_{max}$  as the 90% CI for this parameter was not enclosed entirely within the pre-specified bioequivalence limits of 80% to 125%. In the fed state, the geometric mean  $C_{max}$  was 15% lower than in the fasted state and the median  $T_{max}$  was 1 hour longer (3 versus 2 hours, respectively). The sponsor states that the decrease in  $C_{max}$  in the fed state is 'not likely to be of clinical significance, and that [eliglustat] can be administered without regard to meals'. It is considered that the sponsor's conclusions are reasonable. In this study, the eliglustat tartrate 50 mg capsule used for dosing was not identical to the capsule proposed for registration.

#### 3.2.2.2.4. Single dose escalation study (GZGD00103)

The objectives of Phase Ia Study GZGD00103 included determination of the safety, tolerability, and pharmacokinetic profiles of up to 13 ascending, single, fasting doses of eliglustat tartrate administered as a solution to sequential cohorts of healthy male subjects under fasting conditions (0.01 mg/kg, 0.03 mg/kg, 0.1 mg/kg, 0.3 mg/kg, 1.0 mg/kg, 2.0 mg/kg, 3.0 mg/kg, 5.0 mg/kg, 7.0 mg/kg, 10.0 mg/kg, 15.0 mg/kg, 20.0 mg/kg, and 30.0 mg/kg). The objectives also included determination of preliminary data on the pharmacodynamic effects of eliglustat tartrate at the doses tested as measured by expression of gangliosides (for example, GM-1) on polymorphonuclear (PMN) cells.

A maximum of 104 subjects were planned to participate in this single-site study. Subjects were screened and assigned sequentially to 1 of 13 cohorts, and each cohort included 8 subjects (6 active treatments and 2 placebo). Within each dosing cohort, subjects were randomly assigned to receive active treatment or placebo. A total of 99 subjects were enrolled in the study and

received study medication (74 active treatments and 25 placebo). The CYP2D6 metaboliser status of subjects in this study was not determined.

Only 2 subjects received the highest dose (30 mg/kg), as dosing in this cohort was suspended at the direction of the sponsor due to dose-limiting toxicity (DLT) of dizziness in 1 subject. There were no other reports of DLT in the study. Plasma concentrations increased in a dose-related manner and decayed at essentially the same rate over the 100-fold dose range from 0.3 to 30 mg/kg, with the concentrations at the two lowest doses being below the limit of quantification of the assay or too sparse for analysis. Mean eliglustat values for  $C_{max}$ ,  $AUC_{(0-t)}$ , and  $AUC_{(0-inf)}$  increased in a dose-related manner, but the slopes of the log-log plots of mean  $C_{max}$  and  $AUC_{(0-inf)}$  versus dose were  $> 1$  for both parameter suggesting non-linearity over the dose range studied. Dose normalized  $C_{max}$  and  $AUC_{(0-inf)}$  were inconsistent over the dose range 0.3 to 30 mg/kg, and tended to increase with dose, suggesting non-linearity. Mean apparent total body clearance (CL/F) and apparent volume of distribution during the terminal ( $\lambda_z$ ) phase ( $V_z/F$ ), whether raw or normalized to body weight and/or body surface area, trended downward at higher doses of eliglustat, whereas mean  $t_{1/2}$  and renal clearance (CLr) were essentially independent of dose. Eliglustat was excreted in the urine after all doses, indicating that eliglustat tartrate was absorbed at the lower doses (0.01 to 0.1 mg/kg) even though a majority of plasma concentrations were below the LLOQ. Mean urinary excretion of unchanged eliglustat over the first 8 hours accounted for only 0.16% to 1.34% of the administered dose.

**Comment:** Overall, the results of this study suggest non-linearity of eliglustat over the dose range 0.3 to 30 mg/kg. However, the results are inconclusive due to the relatively high intersubject variability in the studied parameters. Furthermore, there were only 2 subjects with eliglustat data in the 30 mg/kg cohort. In addition, the CYP2D6 metaboliser status of the subjects was not determined.

#### 3.2.2.2.5. Multiple dose escalation study (GZGD00204)

The objectives of Phase Ib Study GZGD00204 included the determination of the safety, tolerability, and PK profiles of 3 ascending doses of eliglustat (50 mg bd, 200 mg bd, 350 mg bd) when administered orally to unique cohorts of healthy subjects of both sexes. The objectives also included collection of preliminary data exploring the use of GM-1 levels as a potential marker of the PD effects, of eliglustat tartrate at the 3 doses tested, as measured by expression of gangliosides (for example, GM-1) on polymorphonuclear cells in healthy subjects.

The study was single-centre (USA), multi-dose, double-blind, and placebo-controlled. It included 3 phases: screening (up to 21 days); treatment (13 days); and safety follow-up ( $7 \pm 1$  days). Eligible subjects were sequentially assigned to 1 of the 3 ascending dose cohorts in groups of 12 per cohort; 8 to active treatment and 4 to placebo. Within each cohort, subjects were randomly assigned, stratified by sex, and blinded to active treatment or placebo.

Within each dose cohort, the mean plasma concentrations on Days 10, 11, and 12 were comparable, but substantially higher than those after the first dose. Based on the half-life after the first dose, the predicted accumulation with bd dosing was 12% to 30%. However, for the 50 mg cohort, the mean  $C_{max}$  increased 3.1-fold from 2.48 ng/mL (Day 1) to 7.64 ng/mL (Day 12), and increases of approximately 4.3-fold were observed for the 200 mg bd cohort (32.9 @ 142 ng/mL) and 2.6-fold for the 300 mg bd cohort (107 @ 278 ng/mL). Furthermore, the mean values for  $AUC_{(0-12h)}$  at steady state were 2.0-fold to 2.4-fold greater than the mean values for  $AUC_{(0-inf)}$  following the first dose for each of the three doses. The slope of the log-log plots of  $C_{max}$  and  $AUC_{(0-inf)}$  versus dose (50 mg, 200 mg, 350 mg) on Day 1 was approximately 2, as was the slope of the log-log plots of  $C_{max}$  and  $AUC_{(0-12h)}$  on Day 10 following 50 mg bd, 200 mg bd, and 350 mg bd on Day 3 through Day 12.

Steady state was reached after approximately 60 hours of bd dosing. Mean values for CL/F following both single-dose administration and at steady state decreased with increasing dose and duration of dosing. With the exception of Day 12 for the 50 mg bd dose and Day 1 for the

200 mg bd dose, there was also a decrease in  $V_z/F$  with increased dose and duration of dosing. Mean values for the half-life ranged from 3.69 to 6.01 hours, and did not appear to be dependent on dose or duration of dosing.

In this study, mean plasma concentrations in female subjects were consistently higher than in male subjects. At the 50 mg bd dose, female subjects had an approximately 2-fold higher  $C_{max}$  and  $AUC_{(0-inf)}$  after the first dose and a 2-fold to 3-fold higher  $C_{max}$  and  $AUC_{(0-12)}$  on Days 10, 11, and 12. Although mean values for  $C_{max}$  were more comparable between males and females at the higher doses, mean values for  $AUC_{(0-inf)}$  and/or  $AUC_{(0-12h)}$  were 1.5-fold to 2-fold higher in females. In addition, pre-dose (trough) concentrations on Days 11 and 12 were approximately 2.7-fold higher in females than in males. The higher exposure in female subjects did not appear to be a consequence of differences in body weight, because the mean body weights were comparable for both genders within each dosing cohort.

As a consequence of the higher values for  $AUC_{(0-inf)}$  and  $AUC_{(0-12h)}$ , the mean values for  $CL/F$  and  $V_z/F$  were lower in females than in males for the 50 mg bd and 350 mg bd cohorts, although more comparable for the 200 mg bd cohort. However, mean values for half-life were not dependent on gender. The  $C_{max}$  and  $AUC_{(0-inf)}$  parameters were non-linear for both sexes following single-dosing and at steady state on Day 10 for the  $C_{max}$  and  $AUC_{(0-12h)}$ .

In this study, all subjects were genotyped for CYP2D6 metaboliser status, but only 1 subject was classified as a poor metaboliser and this subject was randomized to placebo rather than eliglustat tartrate. There appeared to be rank-order relationship between eliglustat  $AUC_{(0-inf)}$  on Day 1 and metaboliser status with values being greater in intermediate metabolisers than in ultra-rapid metabolisers. However, there was no apparent relationship between metaboliser status and the ratio of  $AUC_{(0-12h)}$  on Day 10 to  $AUC_{(0-inf)}$  on Day 1, indicating that metaboliser status did not contribute to non-linearity at steady state.

**Comment:** The single-dose results indicate that the  $C_{max}$  and  $AUC_{(0-inf)}$  of eliglustat on Day 1 were non-linear following eliglustat 50 mg, 200 mg, and 350 mg. The steady state results also indicate that the  $C_{max}$  and  $AUC_{(0-12h)}$  of eliglustat on Day 10 were non-linear following eliglustat 50 mg bd, 200 mg bd, and 350 mg bd on Days 3 through 12. The results indicate that both  $C_{max}$  and  $AUC$  increase disproportionately with dose following both single-dose administration and at steady state. The mechanism for non-linearity in eliglustat for both dose and continued dosing is unknown, but might be due to eliglustat inhibiting its own metabolism through CYP2D6. Plasma eliglustat concentrations following eliglustat at single-dose and at steady were higher in female subjects than in male subjects, and were non-linear among doses and with continued dosing in both sexes.

### 3.2.2.3. Distribution

#### 3.2.2.3.1. Volume of distribution

The mean (SD) volume of distribution in the terminal elimination phase ( $V_z$ ) following a single IV dose of eliglustat 50 mg to 10 healthy male volunteers was 816 (117) L, and the mean (SD) apparent volume of distribution in the terminal elimination phase ( $V_z/F$ ) following a single PO dose of eliglustat 100 mg (capsule) was 24,403 (12,767) L [GZGD02107].

#### 3.2.2.3.2. Plasma protein binding

The plasma protein binding of eliglustat in human plasma was determined at concentrations of 0.01, 0.1, and 1.0  $\mu\text{M}$  [DMPK11-R031]. After 4 hours of incubation, the mean (SD) percent bound of eliglustat to human plasma proteins was 82.9% (1.59%), 79.5% (1.10%) and 76.4% (2.49%) at 0.01, 0.1 and 1.0  $\mu\text{M}$ , respectively.

**Comment:** Human plasma protein binding of eliglustat was moderate (76.4% to 82.9%), and concentration-independent over the range 0.01 to 1  $\mu\text{M}$  (4.05 to 405 ng/mL)

[DMPK11-R031]. No information was provided on the identity of the human plasma binding proteins.

#### 3.2.2.3.3. *Erythrocyte distribution*

Partitioning between red blood cells and plasma for eliglustat and human whole blood was determined using [<sup>14</sup>C]-eliglustat [DMPK11-R030]. In male human whole blood, the mean partition coefficient (K[RBC/plasma]) was  $1.68 \pm 0.254$  and  $1.83 \pm 0.200$  at 0.1 and 1.0  $\mu\text{M}$  of [<sup>14</sup>C]-eliglustat, respectively. The mean (SD) blood-to-plasma concentration ratio was 1.31 (0.114) and 1.37 (0.0898) at 0.1 and 1.0  $\mu\text{M}$  of [<sup>14</sup>C]-eliglustat, respectively. In female human whole blood, the mean (SD) partition coefficient (K[RBC/plasma]) was 1.83 (0.0767) and 1.86 (0.178) at 0.1 and 1.0  $\mu\text{M}$  of [<sup>14</sup>C]-eliglustat respectively. The mean (SD) blood-to-plasma concentration ratio was 1.32 (0.0299) and 1.34 (0.0695) at 0.1 and 1.0  $\mu\text{M}$  of [<sup>14</sup>C]-eliglustat, respectively.

**Comment:** No significant red blood cell partitioning was observed for eliglustat, and red blood cell partitioning was independent of eliglustat concentration over the range 0.1 to 1  $\mu\text{M}$  (40.5 to 405 ng/mL). The in vitro red blood cell partition coefficient (K[RBC/plasma]), 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  $\mu\text{M}$  (40.5 to 450 ng/mL). No significant gender difference in the red blood cell partition coefficient was observed in humans [DMPK11-R030].

#### 3.2.2.3.4. *Tissue distribution*

There were no tissue distribution studies in humans.

### 3.2.2.4. *Metabolism*

#### 3.2.2.4.1. *Study GZGD02107 - human in vivo study in healthy male subjects*

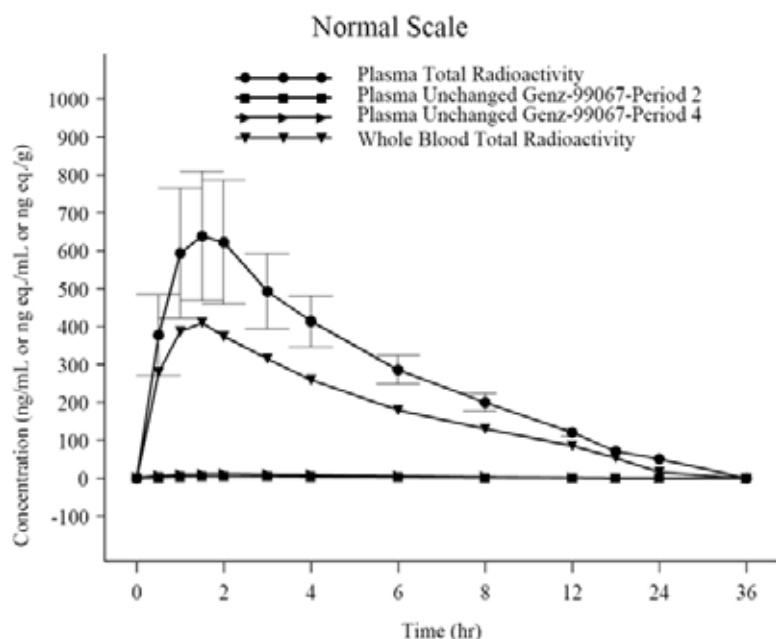
Study GZGD02107 evaluated the PKs, mass balance, and metabolic profile of eliglustat in an open-label, fixed-sequence, cross-over design in which healthy adult male CYP2D6 non-PM subjects received a single IV dose of 50 mg (n=10), a single oral (capsule) dose of 100 mg (n=10), and multiple oral (capsule) doses of eliglustat 100 mg bd for 5 days followed by a single oral (solution) dose of <sup>14</sup>C-eliglustat 100 mg (approximately 100  $\mu\text{Ci}$ ) (n=8).

Consistent with the low absolute bioavailability for eliglustat, the unchanged eliglustat to total radioactivity ratios for  $C_{\text{max}}$  and  $\text{AUC}_{(0-\text{inf})}$  in plasma indicate that the majority of the exposure to total radioactivity is due to circulating metabolites. The mean  $C_{\text{max}}$  for total radioactivity in plasma was approximately 53-fold higher than the mean  $C_{\text{max}}$  for unchanged eliglustat in plasma, and the mean  $\text{AUC}_{(0-\text{inf})}$  value for total radioactivity in plasma was approximately 71-fold higher than the mean  $\text{AUC}_{(0-\text{tau})}$  value for unchanged eliglustat in plasma.

The mean concentration-time profiles for total radioactivity in plasma and whole blood and unchanged eliglustat at specified time-points after a single-dose 100 mg (approximately 100  $\mu\text{Ci}$ ) oral dose of [<sup>14</sup>C]-eliglustat tartrate and a single-dose 100 mg eliglustat capsule are presented below in Figure 2.



**Figure 2: GZGD02107 - Mean (SD) concentration time-profiles on Day 15 (Period 4 [n=8]) for total radioactivity (ng eq/mL) in plasma and whole blood (ng eq/g) following single PO dose of 100 mg [<sup>14</sup>C]-eliglustat, and for unchanged eliglustat (ng/mL) following a single PO dose of 100 mg of eliglustat as a capsule on Day 8 (Period 2 [n=8]) and after repeat bd PO with the final dose of 100 mg [<sup>14</sup>C]-eliglustat on Day 15 (Period 4 [n=8]).**



Following single oral administration of [<sup>14</sup>C]-eliglustat (100 mg, approximately 100  $\mu$ Ci) to 8 healthy male subjects, radio-HPLC analysis of plasma extracts showed 17 different radiolabelled peaks (including one peak for unchanged eliglustat). The metabolite concentrations were significantly higher than the concentration for unchanged eliglustat, and the concentration of unchanged eliglustat declined to low levels by 8 hours post-dose.

#### 3.2.2.4.2. Human biomaterial studies

##### (a) Predicted hepatic clearance

Eliglustat was predicted to have moderate hepatic in vivo metabolic clearance in humans based on extrapolation from in vitro clearance in human liver microsomes [DMPK11-R035] and human hepatocytes [DMPK11-R036] over the concentration eliglustat concentration range 0.05 to 1  $\mu$ M (20.2 to 40 ng/mL). In DMPK11-R035, the mean (SD) extrapolated in vivo hepatic metabolic blood clearance values were 9.57 (0.0274), 11.0 (0.151), and 10.6 (0.0244) mL/min/kg at eliglustat concentrations of 0.05, 0.2, and 1.0  $\mu$ M, respectively, corresponding to 46%, 53%, and 51% of hepatic blood flow (HBF), respectively. In DMPK11-R036, were mean extrapolated in vivo hepatic metabolic blood clearance values were 10.1 (0.486), 10.0 (0.670), and 7.59 (0.364) mL/min/kg at eliglustat concentrations of 0.05, 0.2, and 1.0  $\mu$ M, corresponding to 49%, 48%, and 37% of HBF, respectively.

##### (b) Metabolite profile

In vitro metabolite profiles of eliglustat were characterized following incubation of [<sup>14</sup>C]-eliglustat in liver microsomes or cryopreserved hepatocyte suspensions from humans and several nonclinical species [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].



A total of 22 putative human metabolites were identified in vitro, and structures for 9 metabolites were confirmed. Metabolism occurred in three structural regions of eliglustat namely on the octanoyl, 2,3-dihydro-1,4-benzodioxane and pyrrolidine moieties. Major metabolites were derived from oxidation of the octanoyl moiety, including 7-hydroxyl metabolite Genz-256416, 6-hydroxyl metabolite Genz-311752, and 7-ketone metabolite Genz-258162.

(c) CYP450 isozymes involved in the metabolism of eliglustat

In incubations of eliglustat with recombinant human CYP isozymes over the eliglustat concentration range of 0.01 to 1  $\mu\text{M}$  (4.05 to 405 ng/mL), eliglustat was metabolized by CYP2D6, CYP3A4, and CYP2C19, but was relatively stable in incubations with CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2E1 and CYP3A5 [DMPK08-R035; DMPK11-R015].

In incubations of eliglustat in human liver microsomes from pooled donors of undetermined CYP2D6 phenotype, in the presence and absence of CYP isozyme selective inhibitors, eliglustat was metabolized primarily by CYP2D6 and CYP3A4, and to a lesser extent by CYP2C19, at concentrations of 0.01 to 10  $\mu\text{M}$  (4.05 to 4050 ng/mL). The estimated relative contribution of CYP isozymes to the metabolism of eliglustat in human liver microsomes was concentration-dependent. The relative contribution of CYP2D6 remained approximately within 50% to 60% at concentrations from 0.01 to 1.0  $\mu\text{M}$  (4.05 to 405 ng/mL), and was reduced to 35% at a concentration of 10  $\mu\text{M}$  (4050 ng/mL). In contrast, the relative contribution of CYP3A4 ranged from 15% to 52% with a greater contribution at higher incubation concentrations of eliglustat. In addition, CYP2C9 contributed to approximately 15% at a concentration of 10  $\mu\text{M}$  (4050 ng/mL), CYP1A2 contributed approximately 12% at a concentration of 0.01  $\mu\text{M}$  (4.05 ng/mL), and CYP2C19 contributed to approximately 16% to 19% at concentrations of 0.01 and 0.05  $\mu\text{M}$  (4.05 and 20.2 ng/mL).

In incubations of eliglustat in pooled human liver microsomes from a CYP2D6 poor metaboliser donor, in the presence and absence of CYP isozyme-selective inhibitors, eliglustat was exclusively metabolized by CYP3A4 at concentrations of 0.01 and 0.05  $\mu\text{M}$  (4.05 and 20.2 ng/mL). At both concentrations, metabolism of eliglustat was completely inhibited in the presence of a CYP3A inhibition, but no inhibition of eliglustat metabolism was observed with isozyme-selective inhibitors of CYP1A2, CYP2C9, CYP2C19, or CYP2D6 [DMPK11-R034].

(d) CYP450 isozymes involved in the metabolism of eliglustat metabolites

Ten (10) structurally-confirmed metabolites of eliglustat, namely Genz-256416, Genz-311752, Genz-258179, Genz-258162, Genz-527862, Genz-256222, Genz-120965, Genz-399207, Genz-399240, and Genz-682042, were also each separately incubated with human CYP isozymes (CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, CYP2J2, CYP3A4, CYP3A5) at a metabolite concentration of 1  $\mu\text{M}$ . Three (3) metabolites (Genz-399207, Genz-399240, and Genz-682042) were not metabolized by any of the recombinant human CYP isozymes tested. The other 7 metabolites (Genz-256416, Genz-311752, Genz-258179, Genz-258162, Genz-527862, Genz-256222, and Genz-120965) were metabolized by CYP2D6, but were not significantly metabolized by the other CYP isozymes tested [DMPK11-R081].

### 3.2.2.5. Excretion

#### 3.2.2.5.1. Mass balance study (GZGD02107)

The mass balance study [GZGD02107] showed that, after repeated dosing of eliglustat 100 mg bd for 5 days followed by a single oral dose of 100 mg dose  $^{14}\text{C}$ -eliglustat 100 mg (approximately 100  $\mu\text{Ci}$ ) in 8 healthy male volunteers, mean total recovery of the radioactive dose over the entire collection period of 0 to 240 hours was 93.2%, with approximately equal distribution between urine (41.8%) and feces (51.4%). The mean recovery fraction at steady state of unchanged eliglustat was 0.466% in urine over the dosing interval of 12 hours and 0.128% in feces over a 24 hour collection period. Urinary excretion was rapid, with most of the

radioactivity being recovered in the first 24 hours, while fecal recovery was essentially complete by 120 hours. The results of the mass balance study are summarised below in Table 7.

**Table 7: GZGD02107 - Summary of mean (SD) PK parameters for eliglustat (GENZ-99067) and total radioactivity in urine and feces following administration of 14C-eliglustat 100 mg oral solution.**

Matrix	Analyte	Total Ae (mg) (N=8)	Total % Excreted (%) (N=8)	CL <sub>R</sub> (L/hr) (N=8)
Urine	Genz-99067	0.400 (0.150)	0.466 (0.177)	5.27 (0.727)
	Total Radioactivity	42.5 (5.24)	41.8 (5.12)	7.91 (0.570)
Feces	Genz-99067	0.110 (0.0950)	0.128 (0.111)	NA
	Total Radioactivity	NC	51.4 (3.96)	NA
Urine and Feces	Total Radioactivity	NA	93.2 (2.08)	NA

Note: Units for total radioactivity total Ae are mg equivalents. Recovery for eliglustat (GENZ-99067) was calculated over the 12-hour dosing interval for urine and the 24-hour collection period for feces. NA = not applicable; NC = not calculated.

**Comment:** The mass balance data indicate that the predominant route of excretion of eliglustat is through metabolism, with minimal excretion of the unchanged drug in the urine. The low recovery of unchanged eliglustat in the feces suggests that the drug is extensively absorbed.

#### 3.2.2.5.2. Renal clearance

The mass balance study [GZGS02107] in 8 healthy male volunteers showed that the mean renal clearance of unchanged eliglustat was 5.27 L/h. The mean recovery fraction at steady state of unchanged eliglustat was 0.466% in urine over the dosing interval of 12 hours.

#### 3.2.2.6. Intra- and inter-individual variability of pharmacokinetic parameters

Intersubject variability in the PKs of eliglustat was high in both healthy subjects and patients with GD1. In ENGAGE (Phase III study), the coefficients of variation (CVs [%]) for C<sub>max</sub> and AUC<sub>(0-4h)</sub> were 94% and 84%, respectively, following a single oral dose of eliglustat 50 mg on Day 1 in 20 patients with GD1, and the mean CVs (%) at Week 39 following eliglustat 100 mg bd for C<sub>max</sub>, C<sub>trough</sub>, AUC<sub>(0-4h)</sub> and AUC<sub>(0-12h)</sub> were 81%, 96%, 90%, and 91%, respectively, in 14 patients. In ENGAGE, nearly all patients were extensive CYP2D6 metabolisers (18/20). The results for intersubject variability in the eliglustat exposure parameters observed in ENGAGE were typical for these parameters observed in other studies in patients with GD1 and in healthy subjects.

Intra-subject variability in the PKs of eliglustat were investigated in Study GZGD03811, and showed that the CVs (%) for the AUC<sub>(0-last)</sub>, AUC<sub>(0-inf)</sub> and C<sub>max</sub> were < 30% following a single-dose of 150 mg (both commercial and Phase III formulation) to healthy volunteers.

### 3.2.3. Pharmacokinetics in the target population

#### 3.2.3.1. Clinical studies in patients with GD1

The PKs of eliglustat in GD1 patients was determined from full PK profiles obtained for all eliglustat treated patients in three clinical efficacy and safety studies (Phase II [GZGD00304], ENGAGE [GZGD02507], ENCORE [GZGD02607]). In each study, based on eliglustat C<sub>trough</sub> measurements at protocol-specified time-points measured early in treatment doses were

increased or maintained at the same level (that is, up-titrated if  $C_{\text{trough}} < 5$  ng/mL; maintained at same level if  $C_{\text{trough}} \geq 5$  ng/mL).

### 3.2.3.1.1. Phase II study [GZGD00304]

This study was an open-label study in which all patients (n=26) received 1 dose of eliglustat 50 mg on Day 1, and 50 mg bd from Day 2 through Day 19. If the eliglustat trough plasma level was  $\geq 5$  ng/mL on Day 10, then the patient remained on 50 mg bd through at least 24 months. If the eliglustat trough plasma level was  $< 5$  ng/mL on Day 10, then the dose was increased to 100 mg bd at Day 20, and the patient generally continued to receive this dose through at least 24 months. Patients receiving 100 mg bd could be considered for a further dose increase to 150 mg bd during the extension period if they met certain criteria (for example, had been on treatment for at least 24 months, had not reached therapeutic goals established for patients receiving Cerezyme, and if all other causes for lack of treatment effect had been evaluated and ruled out).

The PK parameters for eliglustat at Days 1, 10, and Weeks 26, 52, 78 and 104 are summarised below in Table 8. The PKs of eliglustat were characterized by rapid absorption, non-linearity, and large inter-subject variability. On Day 1, eliglustat was rapidly absorbed following a single 50 mg dose with a median  $T_{\text{max}}$  of 1.5 hours, and was eliminated with a mean half-life of 6.12 hours. Large inter-subject variability was observed for  $C_{\text{max}}$  (72% CV) and  $AUC_{(0-12h)}$  (79% CV) on Day 1. Moderate to large inter-subject variability was observed with repeated doses throughout and following the dose adjustment period. Relative to Day 1, mean accumulation ratios at Day 10 (following 9 days of dosing at 50 mg bd) were 1.47 for  $C_{\text{max}}$  and 2.03 for  $AUC_{(0-12h)}$ , and at Week 104 were 2.43 and 3.05 for the corresponding parameters, respectively.  $CL/F$  decreased at Day 10 relative to Day 1, but then remained constant throughout repeated bd dosing. There were no apparent changes in median  $T_{\text{max}}$  values over time.

The one CYP2D6 PM treated in the study had a 3.62-fold higher  $C_{\text{max}}$  (22.4 ng/mL) and a 5.58-fold higher  $AUC_{(0-last)}$  (207 ng·h/mL) than the median exposure values of the 25 CYP2D6 EMs patients.

Of the 6 metabolites detectable in plasma, Genz-399240 and Genz-399207 had 8-fold and 3-fold higher exposure, respectively, relative to parent eliglustat, while Genz-527862, Genz-311752, Genz-258162, and Genz-256416 had similar or lower exposures relative to parent eliglustat.

**Table 8: GZGD00304 - Mean (SD) [CV%] eliglustat plasma PK parameters at selected time points over 78 weeks.**

Visit [a]	N	$C_{\text{max}}$ (ng/mL)	$T_{\text{max}}$ [b] (hours)	$C_{\text{trough}}$ (ng/mL)	$t_{1/2}$ (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	13.3(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 (1,3)	6.61 (4.99) [76%]	NC	147 (93.3) [64%]	678 (433) [64%]

Visit [a]	N	C <sub>max</sub> (ng/mL)	T <sub>max</sub> [b] (hours)	C <sub>trough</sub> (ng/mL)	t <sub>1/2</sub> (hours)	AUC <sub>(0-12h)</sub> (ng·h/mL)	CL/F [c] (L/h)
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%)

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 54), no drug was given. [b] Median (range) reported for T<sub>max</sub>. [c] N=23 for CL/F on Day 1.

### 3.2.3.1.2. ENGAGE (Phase III study)

ENGAGE was a multi-centre, double-blind, randomized, placebo-controlled, 39-week (primary analysis period) study to confirm the safety and efficacy of eliglustat in treatment-naïve GD1 patients. The study included 40 randomized patients, 20 to eliglustat and 20 to placebo. All 20 patients randomized to eliglustat (18 CYP2D6 EMs, 1 IM, and 1 URM) received a single 50 mg dose on Day 1 and then continued 50 mg bd from Day 2 to Week 4. Thereafter, 17 patients (16 EMs, 1 URM) with C<sub>trough</sub> < 5 ng/mL levels at Week 2 were up-titrated to 100 mg bd from Week 4 through Week 39, while the remaining 3 patients with C<sub>trough</sub> ≥ 5 ng/mL levels at Week 2 continued on 50 mg bd through Week 39. The PK results for the patient group treated with 50 mg on Day 1, 50 mg bd from Day 2 through to Week 4, and 100 mg bd from Week 4 through 39 are summarised below in Table 9.

**Table 9: 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 to Week 4 and then 100 mg bd from Week 4 through Week 39.**

Visit [a]	N	C <sub>max</sub> ng/mL	T <sub>max</sub> [b] h	C <sub>trough</sub> ng/mL	t <sub>1/2z</sub> h	AUC <sub>(0-4h)</sub> ng·h/mL	AUC <sub>(0-12h)</sub> (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%]

ND = not determined; N=19 AUC<sub>(0-4h)</sub> Day 1; N=14 C<sub>trough</sub> Week 4; N=13 AUC<sub>(0-12h)</sub> Week 4; N=16 C<sub>trough</sub> Week 39; N=11 t<sub>1/2z</sub> 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 T<sub>max</sub>.

Eliglustat was rapidly absorbed after a single 50 mg dose (median  $T_{max}$  = 1.74 hours). At Week 39, mean steady state  $C_{trough}$  and  $C_{max}$  were 5.45 ng/mL and 18.1 ng/mL for the 50 mg bd dosing regimen (n=3), 4.88 ng/mL and 22.4 ng/mL for the 100 mg bd dosing regimen (n=14). For the 3 patients who remained on 50 mg bd through Week 39, accumulation ratios were 1.81 and 1.88 for  $C_{max}$  and  $AUC_{(0-4h)}$ , respectively. No patient had a peak eliglustat concentration above 150 ng/mL in the primary analysis period (the pre-defined threshold of clinical concern). Inter-subject variability in PK parameters at Week 39 (apart from  $t_{1/2z}$ ) was high in the 100 mg bd group.

### 3.2.3.1.3. ENCORE (Phase III study)

ENCORE was a multicentre, randomized, open-label, 52-week study in patients who had reached therapeutic goals on ERT and had then been randomized to eliglustat (n=106) or Cerezyme (n=54). All 106 patients randomized to eliglustat (84 CYP2D6 EMs, 12 IMs, 4 URM, 4 PMs, and 2 'Indeterminate' status) received a single 50 mg dose of eliglustat 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  $C_{trough}$  level) and a dose of 50, 100 or 150 mg bd from post-Week 8 through Week 52 (depending on their Week 6  $C_{trough}$  level). At the end of the primary analysis period (Week 52), the percentage of patients receiving the 3 possible eliglustat doses was: 20% (21/106) on 50 mg BD; 32% (34/106) on 100 mg BD; and 48% (51/106) on 150 mg bd. An additional 54 patients were randomized to Cerezyme (q2w equivalent ERT dose) in the primary analysis period. After completion of the primary analysis period, patients entered an open-label long-term treatment period in which all were treated with eliglustat.

Following the first 50 mg dose on Day 1, eliglustat was absorbed rapidly, with a median  $T_{max}$  ranging from 1.12 to 3.51 hours and a mean  $C_{max}$  ranging from 3.31 to 40.1 ng/mL.

Mean steady-state  $C_{max}$  in CYP2D6 EMs at Week 52 was 26.8, 35.1 and 38.1 ng/mL for the 50, 100 and 150 mg bd dosing regimens, respectively. CYP2D6 EMs comprised 79% of the study population (84 of 106 patients).

Two (2) CYP2D6 EMs receiving a dose of 150 mg bd had  $C_{max}$  values of 169 ng/mL and 261 ng/mL, respectively, at Week 52 (the latter patient had an inadvertent overdose of 450 mg at Week 52).

No other  $C_{max}$  values greater than 150 ng/mL were reported for any patient during the primary analysis period (that is, the pre-define threshold of clinical concern).

The Week 52 data for  $C_{max}$ ,  $T_{max}$ ,  $AUC_{(0-4h)}$  and  $AUC_{(0-12h)}$  by CYP2D6 phenotype and dose for patients with relevant data are summarised below in Table 10.

**Table 10: ENCORE - Mean (SD) [CV%] PK parameters by dose and CYP2D6 phenotype at Week 52.**

Visit			N	$C_{max}$ (ng/mL)	$T_{max}$ (hours)	$AUC_{(0-4h)}$ (ng·h/mL)	$AUC_{(0-12h)}$ (ng·h/mL)
PM	Week 52	50mg BD	4	78.5 (38.4) [49%]	3.0 (2, 4)	252 (121) [48%]	648 (231) [36%]
IM	Week 52	50mg BD	5	34.9 (8.1) [23%]	2.0 (1, 4)	91.5 (24.0) [26%]	200 (54.3) [27%]
EM	Week 52	50mg BD	9	26.8 (20.0) [74%]	2.5 (1, 4)	85.4 (66.4) [78%]	214 (196) [91%]

Visit			N	C <sub>max</sub> (ng/mL)	T <sub>max</sub> (hours)	AUC <sub>(0-4h)</sub> (ng·h/mL)	AUC <sub>(0-12h)</sub> (ng·h/mL)
URM	Week 52	50mg 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%]

Note: Median (range) for T<sub>max</sub>. \*N = 29, \*\*N = 40.

Based on graphical evaluation of C<sub>trough</sub> levels, patients appeared to be at steady state at Week 52 for all dosing regimens. Descriptive statistics of C<sub>trough</sub> by visit, dosing regimen, and CYP2D6 phenotype for Weeks 2, 6, 13, 26, and 52 are shown below in Table 11.

**Table 11: ENCORE - Mean (SD) [CV%] trough levels by CYP2D6 phenotype, dose and time.**

Dose	CYP2D6	N	Week 2	Week 6	Week 13	Week 26	Week 52
50 mg BD	PM	4	46.5 (11.5) [25%]	41.2 (13.7) [33%]	43.7 (18.1) [42%]	39.2 (13.2) [34%]	40.0 (14.8) [37%]
	IM	12	9.29 (7.35) [79%]	9.97 (4.43) [44%] a	7.84 (4.50) [58%] b	9.46 (3.23) [34%] b	10.0 (5.53) [55%] c
	EM	84	2.65 (4.12) [156%]	10.8 (9.46) [88%] d	10.2 (10.2) [99%] e	16.0 (17.6) [110%] f	12.7 (16.0) [125%] g
	URM	4	0.508 (0.337) [66%]	-	-	-	-
100 mg BD	IM	5	-	8.19 (5.27) [64%] h	12.7 (6.26) [49%] h	17.1 (5.35) [31%] h	18.2 (18.0) [99%] h



Dose	CYP2D6	N	Week 2	Week 6	Week 13	Week 26	Week 52
	EM	70	-	5.38 (4.91) [91%]	7.34 (4.93) [67%] i	7.26 (3.76) [52%] j	7.56 (5.17) [68%] j
	URM	4	-	1.54 (0.698) [45%]	-	-	-
150 mg bd	IM	1	-	-	1.36	1.10	1.62
	EM	42	-	-	7.44 (6.18) [83%]	6.50 (4.80) [74%] l	5.50 (3.58) [65%] m
	URM	4	-	-	5.67 (6.53) [115%]	2.77 (1.96) [71%]	3.72 (2.35) [63%]

Note: a N=8; b N=7; c N=5; d N=13; e N=11; f N=10; g N=9; h N=4; i N=31; j N=29; k N=30; l N=31; m N=41.

**Comment:** The mean  $C_{max}$  and  $AUC_{(0-12h)}$  values in CYP2D6 EMs in the 50 mg bd, 100 mg bd and 150 mg bd groups are similar at Week 52. The  $C_{max}$  values were 26.8, 35.1, 38.1 ng/mL for the 50 mg bd, 100 mg bd and 150 mg bd dose groups, respectively, and the corresponding  $AUC_{(0-12h)}$  values for the three dose groups were 214, 201 and 195 ng·h/mL, respectively. In addition, the mean  $C_{trough}$  levels are similar in CYP2D6 EMs in the 50 mg bd, 100 mg bd and 150 mg bd groups at Week 52 (12.7, 7.56 and 5.50, respectively). 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, might reflect the steady state PKs of the three dose groups in CYP2D6 EMs. If this is the case, then the PK data for the three dose regimens does not provide a basis for selecting one of the regimens over another for the fixed-dose treatment of CYP296 EMs. The sponsor is requested to comment on this observation.

### 3.2.4. Population PK analyses

#### 3.2.4.1. Population PK analysis (POH0373)

The submission included a population PK (popPK) analysis (POH0373) using data from healthy volunteers and patients with GD1. The primary aims of the analysis were to describe and quantify the PKs of eliglustat PK, to identify covariate effects that describe variability in the PKs of eliglustat, and to characterize and quantify the concentration-effect relationship of eliglustat with ECG and heart rate parameters. The analysis was conducted in accordance with the relevant FDA2 and EMA3 guidelines using NONMEM version VII Level 2.0, the Intel Fortran Compiler XE for Mac OSX, and R 2.12.0. The results of the PK analysis were comprehensively reported in accordance with the relevant TGA adopted EMA guideline.3.

The total number of patients considered for inclusion in the final covariate model included 516 eliglustat treated healthy volunteers and GD1 patients with measurable eliglustat concentrations from 10 Phase I studies (GZGD00103, GZGD00204, GZGD00404, GZGD01707, GZGD01807, GZGD01907, GZGD02007, GZGD02107, GZGD02407 and GZGD02707), one Phase II study (GZGD00304), and two Phase III studies (ENCORE; EDGE). The final covariate model included data for all 26 patients in the Phase II study, 98 of 106 patients receiving eliglustat in

the primary analysis period of ENCORE, and 80 of 170 patients (77 in the final model) in the Lead-in Period of EDGE. After excluding patients without a known CYP2D6 phenotype, a total of 405 subjects with 12,234 concentrations were used to develop the final model.

#### 3.2.4.1.1. Final Model

The best model to fit the dataset was a 2-compartment disposition model with an oral bioavailability fraction (F) followed by a sequential zero and first-order absorption process. A total of 13 covariate relationships were included in the final covariate model, with 6 of these covariates being included on F. The key findings derived from the final covariate model are summarised below:

- In CYP2D6 EMs, the bioavailability (F) of eliglustat was estimated to be 4.17%, and in CYP2D6 PMs the bioavailability of eliglustat was estimated to be approximately 20 times greater relative to CYP2D6 EMs. The bioavailability of eliglustat was estimated to be approximately half for CYP2D6 URM relative to CYP2D6 EMs. The clearance of eliglustat was estimated to be fractionally less (0.703) in CYP2D6 PMs compared with CYP2D6 not-PMs.
- The increase in eliglustat bioavailability after repeat (chronic dosing) was also dependent on CYP2D6 phenotype, and was estimated to increase 1.16 times for CYP2D6 PMs and 1.99 times for CYP2D6 not-PMs.
- Ketoconazole, paroxetine, and rifampin were all found to have a significant effect on eliglustat bioavailability, demonstrating the involvement of both CYP3A and CYP2D6 in first-pass metabolism. The ketoconazole and paroxetine covariate effects on eliglustat bioavailability were described with E<sub>max</sub> models, where the maximum effect represented a proportional increase in bioavailability. The maximal effect (E<sub>max</sub>) of ketoconazole on exposure was estimated to be 3.49, with the time taken to reach 50% of the maximal effect being < 1 day. For paroxetine, the maximal effect was dependent on CYP2D6 phenotype, with the value for IMs being estimated independently. The effect of paroxetine on exposure was greater for subjects who were not CYP2D6 PMs or IMs (E<sub>max</sub> of 7.17), with the time taken to reach 50% of the maximal effect being <1 day. The rifampin effect was modelled as a direct reduction in bioavailability after rifampin administration (estimated to be 0.709).
- Healthy subjects had central compartment volume of distribution (V<sub>c</sub>) and clearance (CL) estimates that were 1.71 times and 1.95 times greater, respectively, than the corresponding values for GD1 patients. There was also a differential effect between healthy subjects and GD1 patients on V<sub>c</sub>, with the linear increase in V<sub>c</sub> with weight being higher in healthy subjects compared with GD1 patients.

#### 3.2.4.2. Simulation PK analysis (SIM0124)

The data from the final model derived from the PopPK analysis [POH0373] was used in the PK analysis [SIM0124] for additional simulations of eliglustat exposure in patients with GD1, taking into account estimates of the frequency of each CYP 2D6 genotype in the general population.<sup>4</sup> The key results of the simulations are summarised below:

- Mean (SD) simulated eliglustat exposure at steady state for the overall GD1 patient population (750 PM at 50 mg bd, 650 IM at 100 mg bd, 8450 EM at 100 mg bd, 150 URM at 150 mg bd) was 44.3 (46.3) ng/mL for the C<sub>max</sub> and 307 (353) ng·h/mL for the AUC<sub>(0-12h)</sub>.
- The mean (SD) simulated exposure at steady state for combined IM and EM in the GD1 patient population (650 IM at 100 mg bd, 8450 EM at 100 mg bd) was 36.0 (35.1) ng/mL for the C<sub>max</sub> and 237 (237) ng·h/mL for the AUC<sub>(0-12h)</sub>.
- Mean (SD) simulated eliglustat exposure at steady state for healthy subjects for the combined IM and EM phenotypes (650 IM at 100 mg bd, 8450 EM at 100 mg bd) was 21.7 (21.2) ng/mL for the C<sub>max</sub> and 138 (139) ng·h/mL for the AUC<sub>(0-12h)</sub>.



### 3.2.5. Pharmacokinetic interactions

#### 3.2.5.1. *In vitro - Human biomaterial studies*

##### 3.2.5.1.1. *Induction of CYP450 isozymes*

- Eliglustat showed low potential to induce CYP1A2, CYP2B6 or CYP3A4 activity in primary cultures of human hepatocytes at the 0.01, 0.1, and 1  $\mu\text{M}$  (4.05, 40.5, 405 ng/mL) concentrations tested [DMPK08-R040], and CYP1A2, CYP2B6, and CYP3A4 in plated cultures of human hepatocytes at the 10  $\mu\text{M}$  (4050 ng/mL) concentration tested [DMPK08-R048].
- Treatment of cultured human hepatocytes with a pool of ten eliglustat metabolites at concentrations > 10-fold of their predicted steady state  $C_{\text{max}}$  at a 150 mg dose caused, on average, little or no change (less than 2-fold increase) in CYP1A2, CYP2B6 and CYP3A4/5 activity and corresponding mRNA levels for CYP1A2, CYP2B6 and CYP3A4 [DMPK11-R079]. The metabolites were Genz-256416, Genz-311752, Genz-399207, Genz-258179, Genz-120965, Genz-527862, Genz-399240, Genz-682042, Genz-258162, and Genz-256222.

##### 3.2.5.1.2. *Inhibition of CYP450 isozymes*

- Eliglustat exhibited inhibitory potential at predicted therapeutic exposures on CYP2D6 in human liver microsomes [DMPK08-R034, DMPK08-R036], cryopreserved human hepatocytes (DMPK11-R022), and recombinant human CYP2D6 [DMPK11-R033]. Eliglustat also inhibited CYP2D6 in a time-dependent manner over the concentration range 0.500 to 5.56  $\mu\text{M}$ , but not at concentrations greater than 5.56  $\mu\text{M}$  through 50  $\mu\text{M}$  [DMPK08-R036].
- No direct or time-dependent inhibition of other tested CYP450 isozymes (CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2E1 CYP2J2, or CYP3A [testosterone probe substrate]) by eliglustat was observed at concentrations up to 50  $\mu\text{M}$  [DMPK08-R036], indicating a low likelihood for clinical drug-drug interactions mediated by eliglustat inhibition of these CYP450 isozymes.
- Three (3) metabolites inhibited CYP2D6 in either a competitive (Genz-256416 and Genz-256222) or time-dependent (Genz-120965) manner, and 2 metabolites showed direct (Genz-256222) or time-dependent (Genz-120965) inhibition of CYP3A in human liver microsomes [DMPK11-R040]. However, at therapeutic exposures in GD1 patients none of the 10 metabolites tested are predicted to exhibit drug-drug interaction potential on the major CYP isozymes tested (CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A).

##### 3.2.5.1.3. *Effects of eliglustat and selected metabolites on P-gp efflux transporter*

- Eliglustat was shown to be a substrate of the P-gp efflux transporter in the MDCKII and MDCKII-MDR1 cell models, and an inhibitor of the P-gp efflux transporter in the MDCKII-MDR1 cell model using 3H-digoxin as probe substrate [DMPK10-R020]. The inhibitory  $\text{IC}_{50}$  of eliglustat toward the human P-gp transporter was approximately 22  $\mu\text{M}$  (8900 ng/mL).
- In the MDR1-expressing LLC-PK1 cell model using 3H-digoxin as probe substrate in the presence of a mixture of 10 confirmed eliglustat metabolites, pooled at concentrations > 10-fold of their predicted  $C_{\text{max}}$  at 150 mg bd, the net efflux of digoxin was 80% that observed in the absence of the metabolites [DMPK11-R080]. The result indicates that the pooled metabolites tested did not significantly inhibit the P-gp efflux transporter.

##### 3.2.5.1.4. *Effects of eliglustat and selected metabolites on BCRP transporter*

- In the breast cancer resistance protein (BCRP) expressing cell model, eliglustat was shown not to be a BCRP substrate. However, in the BCRP expressing LLC-PK1 cell model using 3H prazosin as probe substrate eliglustat was shown to be an inhibitor of BCRP mediated

transport of prazosin [ DPMK11-039]. The inhibitory  $IC_{50}$  of eliglustat toward the human BCRP transporter was 126  $\mu\text{M}$  (51000 ng/mL).

- In BCRP expressing LLC-PK1 cell model using 3H-prazosin as probe substrate in the presence of a mixture of 10 confirmed eliglustat metabolites [DMPK11-R080], pooled at concentrations > 10-fold of their predicted  $C_{\text{max}}$  at 150 mg bd dose of eliglustat, the net efflux ratio of prazosin was 107% of that in the absence of metabolites, indicating that the pooled metabolites did not inhibit BCRP-mediated efflux.

#### 3.2.5.1.5. *Effects of eliglustat and selected metabolites on the BSEP*

- DMPK13-R027 was designed to evaluate eliglustat as an inhibitor of the human bile salt export pump (BSEP, ABCB11/sP-gp) in individual BSEP expressing and control membranes vesicles using the probe substrate 3H-taurocholate at a concentration of 0.4  $\mu\text{M}$ . BSEP is mainly expressed in the canalicular membrane of hepatocytes where it facilitates excretion into the bile. The ability of eliglustat to inhibit human BSEP expressed in vesicles was evaluated at 0.1, 0.3, 1, 3, 10, 30, 100 and 300  $\mu\text{M}$  eliglustat concentrations by measuring the accumulation of probe substrate (taurocholic acid). To achieve complete inhibition of BSEP, the experiment was repeated at concentrations of 3, 10, 30, 100, 300, 500, 750 and 1,000  $\mu\text{M}$  eliglustat. In the repeat experiment at 1,000  $\mu\text{M}$ , eliglustat inhibited the accumulation of taurocholic acid in BSEP expressing vesicles with an  $IC_{50}$  of 325  $\mu\text{M}$  (131,000 ng/mL), and with maximal inhibition of 94%.
- A mixture of ten eliglustat metabolites, pooled at concentrations >10-fold of their predicted steady-state  $C_{\text{max}}$  at a 150 mg bd dose of eliglustat was assessed for potential inhibition of the BSEP transporter [DMPK11-R080]. The percentage net cleared volume of transporter specific substrate (taurocholic acid) in the presence of the pooled metabolites relative to the absence of pooled metabolites was 101.2%, indicating that eliglustat does not inhibit BSEP transporter.

#### 3.2.5.1.6. *Effects of eliglustat and selected metabolites on MRP efflux and OATP, OAT, and OCT uptake transporters*

- DMPK10-R019 was designed to investigate the interaction of eliglustat tartrate with the human multidrug resistant protein (MRP) efflux transporters (MRP1, MRP2, MRP3, MRP4 and MRP5) and the human hepatic organic anion transporting polypeptides (OATP) and organic cation transporters (OCT) (OATP1B1, OATP1B3, OATP2B1, OAT1, OAT3, OCT1 and OCT2). The interactions were studied in the vesicular transport system model and in the stably transfected cell model. The results showed that eliglustat: (1) had no significant effects on the MRP efflux transporters; (2) had no significant effect on the OAT1 uptake transporter; (3) inhibited OAT3 mediated E3S transport with an  $IC_{50}$  of 198  $\mu\text{M}$  (maximal inhibition of 67%); (4) inhibited OATP1B1 mediated E3S transporter with an  $IC_{50}$  of 150  $\mu\text{M}$  (maximal inhibition of 70%); (5) inhibited OATP1B3 mediated Fluo-3 transport with an  $IC_{50}$  of 100  $\mu\text{M}$  (maximal inhibition of 85%); (6) stimulated OATP2B1 mediated E3S transport (maximal effect 225% compared with control); (7) inhibited OCT1 mediated TEA transport with an  $IC_{50}$  of 40  $\mu\text{M}$  (maximal inhibition of 92%); (8) inhibited OCT2 mediated metformin transport with an  $IC_{50}$  of 21  $\mu\text{M}$  (maximal inhibition 98%).
- In DMPK10-R019, eliglustat did not show transporter specific accumulation at time-points tested or concentrations tested in the OATP1B1 substrate feasibility experiment. The presence of OATP1B1 inhibitor, cerivastatin (100  $\mu\text{M}$ ) had little influence on the transporter specific accumulation of eliglustat. In the presence of OATP1B3 inhibitor fluvastatin (30 $\mu\text{M}$ ), the OATP1B3 specific accumulation of the metabolite Genz-112638 decreased from 1.7-fold to 1.5-fold.
- The effects of a pool of ten eliglustat metabolites on OATP1B1, OATP1B3, OAT1, OAT3, OCT1 and OCT2, MRP2 transporters was investigated [DMPK11-R080]. The metabolites were

pooled at concentrations > 10-fold of their  $C_{max}$  at a predicted 150 mg bd dose of eliglustat. The results showed that the pool of ten eliglustat metabolites: (1) did not inhibit OAT1, OAT3, OATP1B1, OCT2 and MRP2, mediated transport of typical substrates; and (2) inhibited OATP1B3 and OCT1 mediated transport of typical substrates by 17% and 39%, respectively.

### 3.2.5.2. Clinical implication of in vitro interaction data

#### 3.2.5.2.1. Effect of CYP2D6, CYP3A4 and P-gp inhibition on eliglustat exposure

In the in vivo study in healthy subjects [GZDGD02007], both peak ( $C_{max}$ ) and systemic ( $AUC_{(0-12h)}$ ) eliglustat exposure markedly increased when eliglustat (100 mg bd x 10 days) was co-administered with the strong CYP2D6 inhibitor paroxetine (30 mg qd x 10 days). In the in vivo study in healthy subjects [GZDGD01807], both peak ( $C_{max}$ ) and systemic ( $AUC_{(0-12h)}$ ) eliglustat exposure increased when eliglustat (100 mg bd x 7 days) was co-administered with the strong CYP3A4 and P-gp inhibitor ketoconazole (400 mg qd x 7 days). The results of these in vivo studies were consistent with the data from the in vitro human biomaterial studies indicating that eliglustat is primarily metabolized by CYP2D6 and to a lesser extent by CYP3A4. The bioequivalence results for both studies are summarised below in Table 12.

**Table 12: Eliglustat exposure in the presence of strong inhibitors of CYP2D6, CYP3A4 and P-gp.**

Study	Mechanism	CYPD6	n	Interacting drug	Substrate	Eliglustat co-administration/alone	
						$C_{max}$ Ratio	$AUC_{(0-12h)}$ Ratio
GZGD 02007	CYP2D6 strong inhibition	Non-PM [a]	36	Paroxetine 30 mg qd x 10 days	Eliglustat tartrate 100 mg bd x 10 days	7.3 (90%CI: 5.9, 9.1)	8.9 (90%CI: 7.2, 11.1)
GZGD 01807	CYP3A4 and P-gp strong inhibition	Non-PM [b]	36	Ketoconazole 400 mg qd x 7 days	Eliglustat tartrate 100 mg bd x 7 days	3.8 (90%CI: 3.4, 4.3)	4.3 (90%CI: 3.9, 4.7)

[a]: EM = 27; IM = 8; URM = 1 [b]: EM = 26; IM = 9; URM = 1

#### 3.2.5.2.2. Effect of CYP3A and P-gp induction on eliglustat exposure

The in vivo study in healthy subjects [GZD02407] investigated the PK interaction between co-administered eliglustat and rifampin (a potent inducer of CYP3A4 and P-gp, and an inhibitor of OATPs). In poor CYP2D6 metabolisers (PMs), eliglustat tartrate (150 mg bd x 6 days) in combination with rifampin (600 mg qd x 6 days) reduced the steady state  $C_{max}$  of eliglustat by approximately 95% and the steady state  $AUC_{(0-12h)}$  by approximately 96% compared with eliglustat alone. This results suggests that in poor CYP2D6 metabolisers, eliglustat is primarily metabolized by CYP3A4. In non-poor CYP2D6 metabolisers, eliglustat in combination with rifampin reduced the steady state  $C_{max}$  of eliglustat by approximately 84% and the steady state  $AUC_{(0-12h)}$  by approximately 85% compared with eliglustat alone. The bioequivalence results are summarised below in Table 13.

**Table 13: GZGD02407 - Eliglustat exposure (steady state) in the presence of rifampin; CYP2D6 PMs and non-PMs.**

Mechanism	CYPD6	n	Interacting drug	Substrate	Eliglustat (co-administration/alone)	
	phenotype				C <sub>max</sub> Ratio	AUC <sub>(0-12h)</sub> Ratio
CYP3A4 and P-gp strong induction	PM	6	Rifampin [b] 600 mg qd x 6 days	Eliglustat tartrate 100 mg bd x 6 days	0.049 (90%CI: 0.039, 0.061)	0.041 (90%CI: 0.035, 0.049)
	Non-PM [a]	19	Rifampin [b] 600 mg qd x 6 days	Eliglustat tartrate 150 mg bd x 6 days	0.156 (90%CI: 0.110, 0.219)	0.149 (90%CI: 0.107, 0.207)

[a]: EM = 12; IM = 2; URM = 5 [b]: The first dose of rifampin was administered IV.

### 3.2.5.2.3. Effect of acid-reducing agents on eliglustat exposure

In vitro dissolution tests indicated that eliglustat is highly soluble at a pH of less than 6 and is less soluble at a higher pH. Therefore, acid reducing agents have the potential to reduce the bioavailability of eliglustat by increasing gastro-intestinal pH, resulting in decreased solubility and potentially reduced absorption of the medicine. The in vivo study [GZGD1907] assessed the potential interaction between eliglustat and two antacids (Maalox and Tums) and a proton-pump inhibitor (Protonix = pantoprazole) in healthy subjects. The four treatments were: Treatment A = single oral dose (1 capsule) of eliglustat 100 mg; Treatment B = single oral dose of Maalox Advanced Maximum Strength Liquid (equivalent to approximately 1600 mg aluminium hydroxide, 1600 mg magnesium hydroxide, and 160 mg of simethicone) within 3 minutes before a single oral dose of eliglustat 100 mg; Treatment C = single oral dose (2 tablets) of Tums 500 mg (calcium carbonate 500 mg) chewable tablets within 3 minutes before a single oral dose of eliglustat 100 mg; and Treatment D = 40 mg (1 tablet) of Protonix qd on Days 18 through 24, with Protonix 40 mg being given on Day 25 within 3 minutes before a single dose of eliglustat 100 mg. Overall, the results of the study showed that acid reducing agents had a small effect on exposure to eliglustat, which is unlikely to be clinically significant. The bioequivalence results are summarised below in Table 14.

**Table 14: GZGD01907 - Eliglustat exposure following co-administration with acid reducing agents.**

	Ratio	Estimate	90% CI	
C <sub>max</sub>	B/A	1.15	0.99, 1.32	B = Maalox + eliglustat tartrate (n=23); A = eliglustat tartrate (n=24)
	C/A	1.12	0.96, 1.30	C = Tums + eliglustat tartrate (n=21); A = eliglustat tartrate (n=24)
	D/A	1.08	0.91, 1.27	D = Protonix + eliglustat tartrate (n=21); A = eliglustat tartrate (n=24)

	Ratio	Estimate	90% CI	
AUC <sub>(0-inf)</sub>	B/A	1.14	0.99, 1.30	B = Maalox + eliglustat tartrate (n=23); A = eliglustat tartrate (n=24)
	C/A	1.09	0.94, 1.26	C = Tums + eliglustat tartrate (n=21); A = eliglustat tartrate(n=24)
	D/A	1.09	0.92, 1.28	D = Protonix + eliglustat tartrate (n=20); A = eliglustat tartrate (n=24)

#### 3.2.5.2.4. Effect of eliglustat on exposure of the CYP2D6 substrate metoprolol

Consistent with the in vitro data showing that eliglustat is an inhibitor of CYP2D6 [DMPK08-R034, DMPK08-R036, DMPK11-R022, DMPK11-R033], eliglustat (150 mg bd) at steady state administered with a single dose of metoprolol (50 mg), a sensitive CYP2D6 probe substrate, resulted in increased metoprolol exposure based on both C<sub>max</sub> and AUC<sub>(0-inf)</sub> values in healthy CYP2D6 non-PMs [GZGD04112]. The bioequivalence results are summarised below in Table 15.

**Table 15: GZGD04112 - Metoprolol exposure alone and when co-administered with eliglustat.**

Mechanism	CYPD6	n	Metoprolol	Eliglustat	Metoprolol (co-administration/alone)	
phenotype			Tartrate		C <sub>max</sub> Ratio	AUC <sub>(0-inf)</sub> Ratio
CYP2D6 inhibition	Non-PM [a]	14	Midazolam 50 mg single-dose	Eliglustat tartrate  150 mg bd x 6 days	1.53  (90%C I: 1.31, 1.79)	2.08  (95%CI: 1.82, 2.38)

[a]: EM = 8; IM = 5; URM = 1

#### 3.2.5.2.5. Effect of eliglustat on exposure of the CYP3A4 substrate OCP (EE/NE)

The in vitro data showed inconsistent inhibitory effects of eliglustat on CYP3A4. In DMPK08-R034, eliglustat inhibited CYP3A4 in human liver microsomes when midazolam was used as the probe substrate, but not when testosterone was used as the probe substrate. In DMPK08-R036, eliglustat did not inhibit CYP3A4/5 (both midazolam and testosterone as probe substrates) in human liver microsomes. In an in vitro study [GZGD0207], the effects of multiple dose eliglustat (100 mg bd) on the PKs of Ortho-Novum 1/35 (norethindrone 1.0 mg [NE] plus ethinyl estradiol 0.35 mg [EE]) were investigated in healthy women of childbearing potential. In this study, all subjects underwent a 1-cycle run-in with Ortho-Novum 1/35, preceded by at least 3 cycles with an OCP other than Ortho-Novum 1/35. The PK analysis was performed independently of CYP2D6 phenotype status (PM = 3, IM = 3, IM to EM = 6, EM = 7, EM to URM = 10, URM = 1).

During Treatment Period 1, subjects received single daily doses of Ortho-Novum 1/35 for a standard 28-day cycle (active drug for 21 days followed by non-active drug for 7 days), and blood was sampled for PK analysis of NE and EE on Day 21 (that is, Ortho-Novum alone; reference treatment). During Treatment Period 2, Ortho-Novum 1/35 was taken alone from Days 29 through 38 and in combination with eliglustat 100 mg bd from Days 39 through 49 (no evening dose on Day 49), and blood was sampled for PK analysis of NE and EE on Day 49 (that is, Ortho-Novum 1/35 plus eliglustat; test treatment). Exposure to NE and EE was not effected

by eliglustat, with the 90% CIs for the geometric LS mean ratios of NE and EE (co-administration/Ortho-Novum 1/35 alone) being within the pre-defined no effect limits of 80% to 125%. The results suggest that, in vivo, eliglustat is not a clinically significant inhibitor of CYP3A4. The bioequivalence results are summarised below in Table 16.

**Table 16: Norethindrone and ethinyl oestradiol exposure following treatment Periods 1 (Ortho-Novum alone) and 2 (Ortho-Novum co-administered with eliglustat); n=29 paired subjects.**

Parameters	Norethindrone		Ethinyl Oestradiol	
	Ratio %	90% CI	Ratio %	90% CI
AUC <sub>(0-24h)</sub> ,SS Ratio (Period 2/1) [a]	99.4	95.8, 103	102.2	98.6, 106
C <sub>max</sub> , ss Ratio (Period 2/1) [a]	103.1	95.9, 111	103.5	99.6, 108

[a]: Period 1 = Ortho-Novum alone on Day 21 (reference); Period 2 = Ortho-Novum co-administered with eliglustat tartrate on Day 49 (test).

#### 3.2.5.2.6. Effect of eliglustat on the P-gp substrate digoxin

In vitro data showed that eliglustat was a substrate of the efflux transporter P-gp and a potential inhibitor of P-gp [DMPK10-R020]. In an in vivo study in healthy subjects [GZGD03610], exposure to digoxin 0.25 mg (a P-gp substrate) increased following co-administration of a single-dose of digoxin with eliglustat 150 mg bd (CYP2D6 non-PMs) or 100 mg bd (CYP2D6 PMs) for 7 days. The results of the in vivo study support the in vitro data indicating that eliglustat is a potential inhibitor of P-gp. The bioequivalence results are summarised below in Table 17.

**Table 17: GZGD03610 - Digoxin exposure (P-gp substrate) in the presence of eliglustat.**

Mechanism	CYPD6	Substrate	Eliglustat tartrate	Digoxin (co-administration/alone)	
	phenotype	(n=28)	(n=27)	C <sub>max</sub> Ratio (%)	AUC(last) Ratio
P-gp inhibition	Pooled [a]	Digoxin 0.25 mg single-dose	Eliglustat tartrate [b] x 7 days	1.70 (90% CI: 1.56, 1.84)	1.49 (90% CI: 1.33, 1.66)

[a]: PM = 4, IM = 1 EM = 19; URM = 4. [b]: In PM, 100 mg bd x 7 days; in non-PM eliglustat tartrate 150 mg bd x 7 days.

#### 3.2.5.3. Physiologically based PK (PBPK) modelling using SimCYP

In addition to the in vitro and in vivo CYP450 studies reviewed above, the submission also included two studies undertaken using the Simcyp Population-based Simulator to evaluate eliglustat exposure under various simulations with interacting drugs (SIM0105; SIM0106). The results of the two simulation studies are summarised below in Table 18.



**Table 18: PBPK simulations of eliglustat exposure in the presence of moderate and strong inhibitors of CYP2D6, CYP3A4, and P-gp.**

Mechanism	CYP2D6 Phenotype	Interacting Drug (dose)	Substrate Drug (dose)	Substrate Ratio (90% CI) <sup>a</sup>		Study
				C <sub>max</sub>	AUC <sub>0-12</sub>	
Moderate CYP2D6 inhibition	EM	Terbinafine (250 mg QD for 10 days)	Eliglustat (100 mg BID for 18 days) <sup>b</sup>	3.30	3.85	SIM0106
Strong CYP3A and P-gp inhibition	PM	Ketoconazole (400 mg QD for 7 days)	Eliglustat (100 mg BID for 15 days) <sup>b</sup>	4.62	5.81	SIM0105
Moderate CYP3A inhibition	EM	Fluconazole (400 mg QD then 200 mg QD for 10 days)	Eliglustat (100 mg BID for 18 days) <sup>b</sup>	2.40	2.75	SIM0106
Moderate CYP3A inhibition	PM	Fluconazole (400 mg QD then 200 mg QD for 10 days)	Eliglustat (100 mg BID for 18 days) <sup>b</sup>	2.74	3.10	SIM0106
Strong CYP3A, CYP2D6, and P-gp inhibition	EM/URM <sup>c</sup>	Ketoconazole (400 mg QD for 9 days) + Paroxetine (30 mg QD for 9 days)	Eliglustat (100 mg BID for 18 days) <sup>b</sup>	17.1	24.5	SIM0105
Moderate CYP3A, and CYP2D6 inhibition	EM	Fluconazole (400 mg QD then 200 mg QD for 10 days) + Terbinafine (250 mg QD for 10 days)	Eliglustat (100 mg BID for 18 days) <sup>b</sup>	8.85	11.7	SIM0106

a. Ratio of co-administered treatment)/(reference treatment alone) b. Simulations performed at eliglustat doses of 50 mg bd and/or 150 mg bd were presented separately, but have not been included in this CER as the proposed dose for approval is 100 mg bd.c.Virtual trials comprised 33 (93.6%) EM subjects and 3 (7.4%) URM subjects.

The observed effects of moderate inhibitors of CYP2D6 and CYP3A were qualitatively similar to strong inhibitors, but the magnitude of the effect was smaller. Additionally, simulations involving moderate or strong CYP2D6 inhibitors showed a decrease in predicted C<sub>max</sub> and AUC ratios with increasing dose of eliglustat, consistent with increasing eliglustat doses leading to a reduction in active CYP2D6 in the liver and gut through auto-inhibition, thereby reducing the contribution of CYP2D6 to the metabolism of eliglustat.

### 3.2.6. Pharmacokinetics in special groups

#### 3.2.6.1. Hepatic impairment

There were no studies investigating the PKs of eliglustat in patients with hepatic impairment. In the PopPK analysis (POH0373), mean AST 23.8 U/L (ranging up to a maximum of AST of 77 U/L), mean ALT 21.9 U/L (ranging up to a maximum of 104 IU/L) and mean total bilirubin of 12.5 µmol/L (ranging up to a maximum of 51 µmol/L) had no effects on the PKs of eliglustat. However, as eliglustat is primarily cleared by hepatic metabolism hepatic impairment has the potential to increase systemic exposure to eliglustat.

#### 3.2.6.2. Renal impairment

There were no studies investigating the PKs of eliglustat in patients with renal impairment. In the PopPK analysis (POH0373), mean creatinine clearance of 121 mL/min (ranging down to a minimum value of down to 47 mL/min) did not effect the PKs of eliglustat. As renal clearance of unchanged eliglustat is minimal it can be predicted that renal impairment is unlikely to increase systemic exposure to eliglustat. However, approximately 50% of the metabolites of eliglustat are renally excreted suggesting that renal impairment has the potential to increase systemic exposure to eliglustat metabolites.

#### 3.2.6.3. Age

The PopPK analysis (POH0373) did not identify age as a significant covariate influencing the PKs of eliglustat in pooled data from healthy subjects and patients with GD1. The mean age of the 516 subjects from all studies contributing to the final covariate model was 30.6 years, the

median age was 26 years and the age range was from 18 to 71 years. There were no PK studies exclusively in patients aged  $\geq 65$  years of age or  $< 18$  years of age.

#### **3.2.6.4. Genetic factors**

The main source of intrinsic variability identified in the PopPK analysis (POH0373) was CYP2D6 phenotype. The absolute bioavailability of eliglustat based was predicted to be approximately 20 times higher in poor CYP2D6 metabolisers compared with extensive CYP2D6 metabolisers, and approximately 50% lower in ultra rapid CYP2D6 metabolisers compared with extensive CYP2D6 metabolisers.

#### **3.2.6.5. Other factors**

##### **3.2.6.5.1. Sex**

In the multiple dose study in healthy subjects (GZGD00204), mean plasma eliglustat concentrations in female subjects (n=12) were consistently higher than in male subjects (n=12). At the 50 mg bd dose, female subjects had an approximately 2-fold higher  $C_{max}$  and  $AUC_{(0-inf)}$  after the first dose and a 2-fold to 3-fold higher  $C_{max}$  and  $AUC_{(0-12)}$  on Days 10, 11, and 12 after repeated doses. Although mean values for  $C_{max}$  were more comparable between males and females at the higher doses, mean AUC values were 1.5-fold to 2-fold higher in females. Pre-dose (trough) concentrations on Days 11 and 12 were approximately 2.7-fold higher in female subjects than in male subjects. The higher exposure in female subjects did not appear to be a consequence of differences in body weight as the mean body weights were comparable for both genders within each dosing cohort. As a consequence of the higher values for  $AUC_{(0-inf)}$  and  $AUC_{(0-12h)}$  in females compared with males, the mean values for CL/F and  $V_z/F$  were lower in females compared with males for the 50 mg bd and 350 mg bd cohorts, although more comparable for the 200 mg bd cohort. Mean half-life values were not dependent on gender. In the PopPK analysis (POH0373), sex was not identified as a significant covariate in the 516 patients contributing to the final covariate model (59.1% [n=305] males; 40.9% [n=211] females).

##### **3.2.6.5.2. Weight**

In the PopPK analysis (POH373), total body weight had a significant effect on eliglustat exposure. In patients with GD1 (mean body weight 72.4 kg, range 41 to 136 kg), the volume of distribution of the central compartment increased with body weight.

##### **3.2.6.5.3. Race**

In the PopPK analysis (POH373), which included 65% Caucasians, 9% African-Americans, 9% Jewish, 7% Hispanics, 7% Asians, and 3% others, race/ethnicity was not identified as a significant covariate influencing the PKs of eliglustat.

### **3.2.7. Summary of 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 BCS Class 1 drug substance due to its high solubility and high permeability [DMPK10-R047; DMPK11-R039]. 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 ( $AUC_{(0-inf)}$ ) 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 ( $C_{max}$ ) was approximately 15% lower when administered in the fed compared with the fasted state ( $C_{max}$  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 ( $C_{max}$ ) and total exposure ( $AUC_{(0-inf)}$ ) 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 ( $V_z$ ) 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 ( $V_z/F$ ) following a single oral dose of eliglustat (100 mg, capsule) was 24,403 L (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  $\mu$ M (76.4%) [DMPK11-R031]. No data could be identified in the submission characterising the identity of the human plasma protein binding proteins. No significant RBC partitioning was observed for eliglustat in humans, and RBC partitioning was independent of eliglustat concentration over the concentration range 0.1 to 1  $\mu$ M (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  $\mu$ M (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 metabolized. 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 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  $C_{max}$  and 1.9-fold increase in  $AUC_{(0-last)}$  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  $>1 \mu$ M). 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 metabolized 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  $C_{max}$  and  $AUC_{(0-12h)}$  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 metabolized 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  $C_{max}$  and  $AUC_{(0-12h)}$  values were reduced by approximately 95% when eliglustat was co-administered with rifampin (a strong CYP3A4 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  $\mu$ Ci), 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  $C_{max}$  and  $AUC_{(0-12h)}$  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 (for example, 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  $T_{max}$  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  $C_{max}$  and  $AUC_{(0-4h)}$  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  $C_{\text{trough}}$  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  $C_{\text{max}}$  and  $AUC_{(0-12h)}$  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-fold higher in GD1 patients compared with healthy subjects. In addition, PopPK modelling estimated that the volume of distribution of the central compartment ( $V_c$ ) 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  $C_{\text{max}}$  and  $AUC_{(0-12h)}$ , based on CYP2D6 phenotype data for repeated 100 mg bd doses, estimated that exposure in PMs was approximately 10-fold higher than in EMs, approximately 2.8-fold higher in IMs than in EMs, and approximately 46% lower in URM 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  $AUC_{(0-12h)}$  and a 17.1-fold increase in eliglustat  $C_{\text{max}}$  [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 11.7-fold increase in eliglustat  $AUC_{(0-12h)}$  and a 8.85-fold increase in eliglustat  $C_{\text{max}}$  [SIM106].
- In vivo, eliglustat was found to be an inhibitor of the P-gp efflux transporter (1.49-fold increase in digoxin  $AUC_{(0-last)}$ ), and an inhibitor of CYP2D6 (2.08-fold increase in metoprolol  $AUC_{(0-inf)}$ ) [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, DMPK11-R084]. Consequently, it can be predicted that eliglustat will increase exposure to drugs that are metabolized 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 metabolized by CYP3A4 [GZGD02707]. The in vivo study [GZGD0190] indicates that drugs which increase intra-gastric pH (for example, antacids, 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 metabolizing enzymes or inhibition of clinically relevant efflux and uptake drug transporters.

## 4. Pharmacodynamics

### 4.1. Biomarker studies

#### 4.1.1. 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 synthesized from that same substrate by a GL-1-independent synthetic pathway (sphingomyelin).

#### 4.1.2. Results of primary biomarker studies

Plasma GL-1 was measured in healthy subjects in Study GZGD00204 as an exploratory biomarker of the pharmacological activity of eliglustat. Although pre-treatment GL-1 plasma concentrations were in the normal range, as expected in healthy subjects, plasma GL-1 concentration decreased in a dose-dependent manner following repeat administration of eliglustat at 50 mg bd, 200 mg bd and 350 mg bd in healthy males and females. 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 50 mg bd, 200 mg bd, and 350 mg bd regimens, respectively.

Plasma GL-1 and GM3 concentrations, which were elevated in the majority of treatment-naive GD1 patients (Phase II, ENGAGE) and were normal in most GD1 patients who had already achieved therapeutic goals on ERT prior to initiating eliglustat therapy (ENCORE), decreased with repeated dosing of eliglustat 50 mg to 150 mg bd in both populations. By the end of the primary analysis period of each study, median plasma GL-1 and GM3 concentrations were significantly reduced relative to baseline (Phase II) or placebo (ENGAGE) or Cerezyme (ENCORE). In addition, a majority of eliglustat treated patients had achieved normal plasma concentrations of GL-1 and GM3 by the end of the primary analysis periods, 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 dependent synthetic pathways.

Plasma sphingomyelin concentrations were normal (or slightly below normal) in all GD1 patients at Baseline and, although increasing slightly following repeated dosing of eliglustat 50 mg to 150 mg bd, remained within normal range (or slightly below normal) at the end of the primary analysis period. Plasma ceramide concentrations fluctuated modestly over time, with

occasional low or high values reported, but the majority of patients had plasma ceramide values within the normal range at the end of the primary analysis period. These results confirm that inhibition of GL-1 synthesis by eliglustat did not result in abnormal accumulation of ceramide.

#### 4.1.3. Exploratory biomarker study

In addition to the biomarkers described above relating directly to the mechanism of action of eliglustat, a sub-study [GZGD03310] of exploratory bone and inflammatory biomarker response to eliglustat tartrate was undertaken in patients with GD1 (n=26) participating in the Phase II study. The bone-biomarkers included bone alkaline phosphatase, CTX and calcitonin. Considerable variability was seen with all the bone biomarkers. For the bone resorption biomarker (CTX), the mean value was increased from baseline at Week 52 (p=0.021), then returned to near baseline values at subsequent visits. For the bone formation biomarker (bone alkaline phosphatase), mean values at all visits were similar to baseline and percentage changes from baseline were small and not statistically significant. Mean calcitonin values decreased from baseline at Week 52, and showed continued decline at Week 104. Mean values at Weeks 104 and 156 were similar, and changes from baseline at these visits were statistically significantly lower than baseline (p=0.0014 at Week 104; p=0.0079 at Week 156). The mean (SD) calcitonin value at Baseline was 13.5 (6.4) pg/mL and at Week 156 was 7.5 (6.9) pg/mL (c.f., reference < 9.4 pg/mL). Inflammatory biomarkers of special interest (IL-8, IL-10, IL-18, MIP-1 $\alpha$ , and MIP-1 $\beta$ ) showed consistent, statistically significant decreases from baseline at all time points. In addition, correlations were seen between plasma eliglustat concentrations and changes from baseline in IL-8, MIP-1 $\beta$ , and TNF receptor-2. It was concluded that 'additional study is warranted in a larger population of patients to further elucidate the correlations between these biomarkers and eliglustat therapy'.

## 4.2. QT interval (ECG) studies

### 4.2.1. 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 repolarization 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 randomized, double-blind, placebo-controlled, 4-sequence, 4-period and cross-over in design.

The study enrolled 47 healthy male (n=22) and female (n=25) subjects, and these subjects were randomized to one of 4 treatment sequences. All 47 subjects were included in the ECG safety analysis and the general safety analysis, while 42 subjects (18 males, 24 females) completed the study and were included in the PK analysis. The mean age of the 47 randomized subjects was 27.4 years (range: 18, 44), mean height 166.7 cm (range: 149.5, 190.0), mean weight 72.4 kg (range: 51.7, 96.1), and mean BMI 26.0 kg/m<sup>2</sup> (range: 19.0, 33.5). Of the 47 subjects, 2 were classified as CYP2D6 PMs with all others being classified as CYP2D6 non-PMs.

The mean C<sub>max</sub> at the therapeutic dose of 200 mg (26.536 ng/mL) was comparable to those reported in the Phase II study, but the maximum total and peak exposures at the 200 mg dose were higher than those observed in the Phase II study. The mean C<sub>max</sub> (299 ng/mL) at the supra-therapeutic dose of eliglustat (800 mg) exceeded the maximum steady-state concentration observed in the Phase II and Phase III studies in GD1 patients who were CYP2D6 IMs and EMs (combined) receiving 100 mg bd (108 ng/mL) and for GD1 patients of all phenotypes receiving 50, 100, or 150 mg bd (169 ng/mL), excluding 1 patient reaching 261 ng/mL as a result of an inadvertent overdose.

The ECG analysis set consisted of all randomly assigned subjects with available matched Baseline and treatment data at the same time point. The following cardiac variables were assessed from continuous ECG Holter monitoring: QTcF, QTcB, QTcG, QTcI, QRS, PR, and RR intervals, and T wave and U wave morphologies. Subjects were treated with placebo, 400 mg of moxifloxacin, 200 mg of eliglustat (therapeutic dose), and 800 mg of eliglustat (supra-therapeutic dose) in a 4-way cross-over (4 treatment periods). Each subject participated in the study for approximately 71 days, inclusive of the time required for the screening phase (up to 31 days), 4 separate admission phase days (1 day in each treatment period), 4 separate treatment phase days (1 day in each treatment period), 4 separate follow-up phase days (1 day in each treatment period), 3 separate washout periods (at least 5 to 7 days after Treatment Periods 1, 2, and 3 up to 21 days or more), and a final follow-up visit (at least 5 to 7 days after Treatment Period 4).

The primary endpoint to assess cardiac repolarization was based on the QTcF interval. Linear mixed-effects models were used to characterize the relationship between treatment and ECG parameter. Each dependent variable was doubly corrected for Baseline on Day 1 before dosing and for time-matched placebo treatment (that is, the so-called double-delta ( $\Delta\Delta$ ) correction). The secondary endpoints (QT, QTcB, QTcG, QTcI, QRS, PR, RR) were analysed in a similar fashion to the primary endpoint (QTcF). The T wave and U wave morphologies were not analysed statistically, but were presented using tables and listings. Linear mixed-effects models were used to characterize the concentration-effect relationship between various ECG parameters and eliglustat concentrations.

The key conclusions relating to cardiac electrophysiology are summarised below:

- The PK-PD results summarizing the slopes of the relationships between eliglustat plasma concentration predicted QTc change at  $C_{max}$  are provided below in Table 19, below. A positive relationship was observed between eliglustat plasma concentrations and placebo-corrected QTcF intervals. After administration of a single therapeutic dose (200 mg) of eliglustat (mean  $C_{max}$  26.536 ng/mL), the expected increase in the placebo-corrected change from baseline in the QTcF interval was 0.42 ms with an upper 1-sided 95% CI of 1.8 ms. After administration of a single supra-therapeutic dose (800 mg) of eliglustat (mean  $C_{max}$  299.213 ng/mL), the expected increase in the placebo-corrected change from baseline in the QTcF interval was 7.3 ms with an upper 1-sided 95% CI of 8.8 ms.

**Table 19: GZGD01707 (addendum) - Placebo-corrected change from baseline versus plasma concentration, estimates from linear mixed-model for QTc interval; ECG safety analysis set.**

QT Parameter	Slope of Plasma Conc.	Standard Error of Plasma Conc.	P value <sup>a</sup>	Treatment Group			
				Genz-112638 200 mg		Genz-112638 800 mg	
				Predicted QTc at Mean Therapeutic $C_{max}$ of 26.536	Upper 1-sided 95% CI Limit of Predicted QTc	Predicted QTc at Mean Therapeutic $C_{max}$ of 299.213	Upper 1-sided 95% CI Limit of Predicted QTc
QTcF	0.0252	0.0019	0.0000	0.421	1.766	7.290	8.778
QTcI	0.0240	0.0018	0.0000	0.122	1.512	6.660	8.179
QTcG	0.0230	0.0018	0.0000	0.230	1.655	6.509	8.058
QTcB	0.0296	0.0026	0.0000	0.795	2.280	8.865	10.583

CI = confidence interval; Conc = concentration; QTc - corrected QT interval; QTcB = corrected Bazzett's QT interval; QTcF=corrected Fridericia's QT interval; QTcG=QTc interval using group correction; QTcI=individual QTc interval. <sup>a</sup> P value was <0.00001; however, was displayed to only 4 decimal places. Note: Linear mixed model was fit for change from placebo-corrected Baseline versus the plasma concentration as a fixed effect

with subject included in the model as a random effect. Double-delta was calculated individually, not model based. Upper 95% CI limit is the upper 1-sided 95% linear mixed-model-based confidence limit.

- The largest time-matched mean differences versus placebo in QTcF were 0.7 ms (upper 1-sided 95% CI of 3.5 msec) observed at 10 hours after the single therapeutic (200 mg) dose, and 6.5 ms (upper 1-sided 95% CI of 9.3 msec) observed at 7 hours after the single supra-therapeutic dose (800 mg). These values were lower than that observed with moxifloxacin (positive control) observed at 4 hours after dosing (that is, 12.1 ms [2-sided 90% CI = 8.1, 16.1 msec]).
- The upper 1-sided 95% CI limit for the mean placebo-corrected change from baseline in the QTcF following both the single therapeutic dose (200 mg) and the supra-therapeutic dose (800 mg) did not exceed 10 ms at any time point. The placebo-corrected QTcF mean change from Baseline and upper 1-sided 95% CI limit for the moxifloxacin treatment group were greater than the corresponding values for the supra-therapeutic dose of eliglustat (800 mg) at all time points.
- The mean placebo-corrected change from baseline in QTcF following the single therapeutic dose (200 mg) was -0.4 ms (upper 1-sided 95% CI limit = 1.9 msec) in females and -0.8 ms (upper 1-sided 95% CI limit = 1.7 msec) in males. The upper 1-sided 95% CI limit 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 (upper 1-sided 95% CI limit = 8.9 msec) in females and 1.9 ms (upper 1-sided 95% CI limit = 4.6 msec) in males. In females, the upper 95% CI limit exceeded 10 ms at all time points (0.5 to 22.5 hours) following the supra-therapeutic dose (800 mg), apart from 0.5, 1, 10, and 22.5 hours. In males, the upper 1-sided 95% CI limit did not exceed 10 ms any time points (0.5 to 22.5 hours) following the supra-therapeutic dose (800 mg). In the mixed-model ANOVA used to estimate the placebo-corrected change from Baseline in QTcF (msec), the gender main effect was not-statistically significant ( $p=0.1911$ ), but the gender-by-treatment interaction was statistically significant ( $p<0.0001$ ).
- Based on linear mixed effects modelling, for every 100 ng/mL increase in eliglustat plasma concentration,  $\Delta\Delta\text{QTcF}$  increased by 2.44 ms (95% CI: 0.36, 4.52 msec). The eliglustat concentration that produced an upper 95% CI increase in  $\Delta\Delta\text{QTcF}$  of 10 ms was approximately 250 ng/mL, which was higher than the pooled maximum  $C_{\text{max}}$  level in GD1 patients treated with eliglustat 50, 100 or 150 mg bd in the primary analyses periods of the Phase II study, ENGAGE and ENCORE of 169 ng/mL (excluding 1 patient with a level of 261 ng/mL due to inadvertent overdose). At the mean  $C_{\text{max}}$  values of 24 ng/mL in the 200 mg dose group and 255 ng/mL in the 800 mg dose group, the expected increases in  $\Delta\Delta\text{QTcF}$  were 0.54 ms (95% CI: -1.23, 2.31) and 6.31 ms (95% CI: 2.68, 9.93 msec), respectively.
- Based on linear mixed effects modelling, for every 100 ng/mL increase in eliglustat plasma concentration,  $\Delta\Delta\text{PR}$  increased by 4.60 ms (95% CI: 3.06, 6.14). At the mean  $C_{\text{max}}$  values of 24 ng/mL in the 200 mg dose group and 255 ng/mL in the 800 mg dose group, the expected increases in  $\Delta\Delta\text{PR}$  were 1.42 ms (95% CI: 0.0914, 2.74 msec) and 11.1 ms (95% CI: 8.44, 13.76), respectively.
- Based on linear effects modelling, for every 100 ng/mL increase in eliglustat plasma concentration,  $\Delta\Delta\text{QRS}$  increased by 1.33 ms (95% CI: 0.39 to 2.29 msec). At the mean  $C_{\text{max}}$  values of 24 ng/mL in the 200 mg dose group and 255 ng/mL in the 800 mg dose group, the expected increases in  $\Delta\Delta\text{QRS}$  were 0.36 ms (95% CI: -0.39 to 1.11 msec) and 3.33 ms (95% CI: 1.54 to 5.12 msec), respectively.

#### 4.2.2. Population PK analysis (POH0373)

The objectives of the PopPK analysis (POH0373) included development of PD models that described the concentration-effect of eliglustat on ECG data from the Phase I 'Thorough QT/QTc' study in healthy volunteers, and the three studies in GD1 patients (Phase II [GZGD00304], ENGAGE [GZGD02507], ENCORE [GZGD02607]). Additionally, covariates that described variability in PD model parameters were identified and incorporated into the models. Data were modelled using the delta ( $\Delta$ ) method, whereby the change in ECG parameters from baseline values was modelled as a function of time-matched eliglustat concentrations.

The analysis included raw ECG data from a total of 249 subjects, including 4302 nominal time-matched QT observations from 248 subjects, 4246 nominal time-matched corrected QT observations (QTcB and QTcF) from 233 subjects, 4289 nominal time-matched PR observations from 248 subjects, 4296 nominal time-matched QRS observations from 248 subjects, and 4305 nominal time-matched HR observations from 248 subjects. The primary endpoint for the QT analysis was the QTcF, as there was no relationship between QTcF and HR.

The key findings of the analysis are summarised below:

- The best model to describe QTcF was a two-part linear model, where no relationship was observed between  $\Delta$ QTcF and eliglustat concentrations  $\leq 100$  ng/mL, but a linear increase in  $\Delta$ QTcF was observed for concentrations  $> 100$  ng/mL of 0.0223 ms per ng/mL. The only covariate found to significantly effect the  $\Delta$ QTcF was baseline QTcF on the intercept. The typical response predicted that the highest eliglustat concentration observed in the nominal time-matched ECG data of 761 ng/mL resulted in an increase from baseline in QTcF of 15.7 ms.
- Simulations indicated that eliglustat concentrations predicted to result in the QTcF interval for the typical subject (with a baseline QTcF interval of 401 msec) reaching the thresholds of 450, 480, and 500 ms are 2250, 3600, and 4495 ng/mL, respectively.
- In this model,  $\Delta$ QTcF at a concentration of 200 ng/mL was predicted to be 3.23 ms (upper 95% CI of 3.41 msec), which was less than the estimate based on the results of the 'Thorough QT/QTc' study [GZGD1707].
- The relationship between the eliglustat concentration and the PR interval was weakly positive, with the best model predicting an increase in PR of 0.0404 ms per ng/mL increase in concentration. The typical predicted  $\Delta$ PR for the maximum concentration observed in the nominal time-matched ECG data of 761 ng/mL was 31 ms. The concentration predicted to result in a PR interval of 200 ms for the typical subject (with a baseline PR interval of 158 msec) was 1040 ng/mL.
- The relationship between the eliglustat concentration and the QRS was also found to be weakly positive, with the best model to describe the data predicting an increase in QRS of 0.0111 ms per ng/mL increase in concentration. This model predicts a typical  $\Delta$ QRS of 8 ms for the maximum concentration of 761 ng/mL observed in the data used in the analysis.
- An Emax model was developed to describe the relationship between eliglustat concentration and  $\Delta$ HR. However, the typical value of Emax was estimated to be very small (1.16 BPM). Therefore, the analysis suggests that eliglustat concentration has a negligible effect on HR.
- Simulations to assess the predicted ECG parameters at an eliglustat concentration of 150 ng/mL (the level of clinical concern in the clinical studies in GD1 patients) estimated the median value (10-90% range) to be 403 ms (379-428 msec) for QTcF, 163 ms (138, 194 msec) for the PR interval, and 91 ms (80-104 msec) for the QRS interval.



### 4.3. PK/PD relationship between efficacy and PK parameters

#### 4.3.1. Study POH0395

The objective of the analyses in POH395 was to explore the PK/PD relationship between treatment efficacy and PK parameters of eliglustat in the Phase III studies [ENGAGE; ENCORE]. The PK/PD analysis was used to predict the efficacy of the proposed CYP2D6 phenotype guided dosing regimen in treatment experienced and treatment-naïve patients with GD1 (that is, fixed-dose 100 mg bd in CYP2D6 EMs or IMs). The methodology used in the analyses was comprehensively reported.

The PK/PD relationships for each CYP2D6 phenotype and recommended dose were analysed by modelling the efficacy outcomes and predicted PK parameters. Model predicted PK parameters for each CYP2D6 phenotype at the recommended dose were used instead of observed PK parameters. The observed PK parameters for each CYP2D6 phenotype were confounded by the dose being titrated based on  $C_{trough}$  levels rather than CYP2D6 phenotype. Two sets of model predicted PK data were available for the analyses; the PBPK model and the PopPK model (POH0373).

The PBPK model was constructed primarily from in vitro data using SimCYP® software [SIM0105] and exhibited the largest degree of nonlinearity in eliglustat PKs. However, the conversion ratios estimated from the PBPK simulations for EMs from the SimCYP modelling were used to project both IM and EM patient pharmacokinetic parameters when treated with 100 mg bd. The conversion ratios estimated at steady state for EMs for 100/150 mg were 0.53 for  $C_{max}$  and 0.52 for  $AUC_{(0-tau)}$ , and for 100/50 mg were 2.85 for  $C_{max}$  and 3.03 for  $AUC_{(0-tau)}$ .

The PopPK model [POH0373] provided two simulations. The first simulation predicted mean (SD) PK parameters for  $AUC_{(0-tau)}$ ,  $\log AUC_{(0-tau)}$ ,  $C_{max}$ , and  $\log C_{max}$  based on CYP2D6 phenotype for each recommended dose (see Table 20, below). A total of 10000 simulations were conducted, with 750 simulations for one PM patient at a dose of 50 mg bd, 650 simulations for one IM patient at a dose of 100 mg bd, 8450 simulations for one EM patient at a dose of 100 mg bd and 150 simulations for one URM patient at a dose of 150 mg bd. The number of simulations for the patient in each phenotype category was chosen based on the frequency of this phenotype in the general population per published data.

**Table 20: Population PK model predicted mean eliglustat steady-state PK parameters by recommended dose and CYP 2D6 phenotype.**

Eliglustat dose	CYP2D6 phenotype	Mean $AUC_{0-tau}$	SD $AUC_{0-tau}$	Mean $C_{max}$	SD $C_{max}$
50 mg BID	PM	1185.5	369.16	148.85	41.33
100 mg BID	IM	597.79	411.42	88.19	58.32
100 mg BID	EM	208.75	191.95	32.02	28.93
100 mg BID	IM/EM	236.54	237.33	36.03	35.06
150 mg BID	URM	160.25	186.41	24.62	28.22
		Mean $\log AUC_{0-tau}$	SD $\log AUC_{0-tau}$	Mean $\log C_{max}$	SD $\log C_{max}$
50 mg BID	PM	7.0296	0.3146	4.9644	0.2808
100 mg BID	IM	6.1480	0.7433	4.2480	0.7240
100 mg BID	EM	4.9697	0.8972	3.1054	0.8854
100 mg BID	IM/EM	5.0538	0.9375	3.1870	0.9230
150 mg BID	URM	4.5907	1.0166	2.7252	1.0022

The second simulation was performed to estimate within-subject exposure ratios ( $AUC_{(0-tau)}$  and  $C_{max}$ ). As seen mainly in ENCORE, some patients who were CYP2D6 EMs or IMs were dosed at 50 mg bd or 150 mg bd during the main efficacy period following the initial dose titration period rather than the sponsor's proposed regimen of 100 mg bd for CYP2D6 EMs or IMs. The second simulation was used to explore the efficacy response in these CYP2D6 EMs and IMs if they had been treated with the proposed 100 mg bd dose, rather than with the actual 50 mg bd or 150 mg bd dose. A total of 1000 simulations were conducted for one PM, IM, EM and URM patient

each receiving 50 mg bd, 100 mg bd and 150 mg bd eliglustat doses for each period using a 3-period crossover design, based on the PopPK model taking account both inter- and intra-subject variability (SIM0124). PK parameters ( $AUC_{(0-\tau)}$  and  $C_{max}$ ) were predicted for each dose and each CYP2D6 phenotype. Only the 5th to 95th percentiles of each PK parameter for each dose and each CYP2D6 phenotype were used in order to exclude simulation outliers. Within-subject ratios were calculated for each patient and between eliglustat doses (see Table 21, below).

**Table 21: Estimated within-subject exposure ratios for eliglustat doses based on population PK model predicted parameters.**

CYP2D6 Status	Parameter	Statistics	$AUC_{(0-\tau)}$ : 100mg BID /50mg BID	$AUC_{(0-\tau)}$ : 100mg BID /150mg BID	$C_{max}$ : 100mg BID /50mg BID	$C_{max}$ : 100mg BID /150mg BID
PM	Ratio	Mean(SD)	2.01(0.23)	0.67(0.07)	2.07(0.51)	0.69(0.17)
IM	Ratio	Mean(SD)	2.01(0.21)	0.67(0.07)	2.07(0.53)	0.69(0.19)
EM	Ratio	Mean(SD)	2.02(0.31)	0.67(0.09)	2.10(0.61)	0.70(0.20)
URM	Ratio	Mean(SD)	2.01(0.26)	0.67(0.09)	2.07(0.74)	0.70(0.23)
PM	log(Ratio)	Mean(SD)	0.69(0.11)	-0.41(0.10)	0.70(0.24)	-0.41(0.25)
IM	log(Ratio)	Mean(SD)	0.69(0.11)	-0.41(0.11)	0.69(0.25)	-0.41(0.26)
EM	log(Ratio)	Mean(SD)	0.69(0.14)	-0.41(0.13)	0.71(0.26)	-0.40(0.29)
URM	log(Ratio)	Mean(SD)	0.69(0.12)	-0.41(0.13)	0.68(0.31)	-0.41(0.29)

#### 4.3.2. ENGAGE - treatment-naive patients

The efficacy and safety data from this pivotal Phase III study are discussed in detail later in this CER. The primary objective of the study was to confirm the efficacy and safety of eliglustat after 39 weeks of treatment in GD1 patients compared with placebo. Forty (40) patients naive to treatment with ERT were randomized to eliglustat (n=20) or placebo (n=20) during the 39-week primary analysis period. All patients randomized to eliglustat received a single 50 mg dose on Day 1 and repeat doses of 50 mg bd from Day 2 to Week 4. From the morning of Week 4 through Week 39, patients (n=3) whose eliglustat trough concentrations were  $\geq 5$  ng/mL at Week 2 continued to receive 50 mg bd and patients (n=17) whose eliglustat trough concentrations were  $< 5$  ng/mL at Week 2 received an increased dose of 100 mg bd. The CYP2D6 metaboliser status of the 20 patients randomized to eliglustat were EM (n=18), IM (n=1) and URM (n=1).

The primary efficacy endpoint was the % change in spleen volume (MN) from Baseline to Week 39. Secondary efficacy endpoints included absolute change from Baseline to Week 39 in haemoglobin level (g/dL), % change from Baseline to Week 39 in liver volume (MN), and % change from Baseline to Week 39 in platelet count ( $10^9/L$ ). The relationship between these endpoints and the PK exposure parameters ( $\log AUC_{(0-\tau)}$  and  $\log C_{max}$ ) were explored in the PK/PD analysis. Efficacy versus  $\log AUC_{(0-\tau)}$  was considered to be the primary PK/PD analysis and efficacy versus  $\log C_{max}$  was considered to be the secondary PK/PD analysis. Log parameters were used as visual inspection of distribution indicated better normality of the log transformed data than the non-log transformed data.

##### 4.3.2.1. Key results

In essence, the exploratory PK/PD analyses were undertaken to support the proposed fixed-dose dose regimen of 100 mg bd in CYP 2D6 EM/IM metabolisers in treatment-naive GD1 patients, which notably differs from the actual treatment regimen used in the pivotal study [ENGAGE].

A linear model was fitted using the FAS for each endpoint using change from Baseline to Week 39 as the response variable, and the baseline value for each relevant endpoint and observed

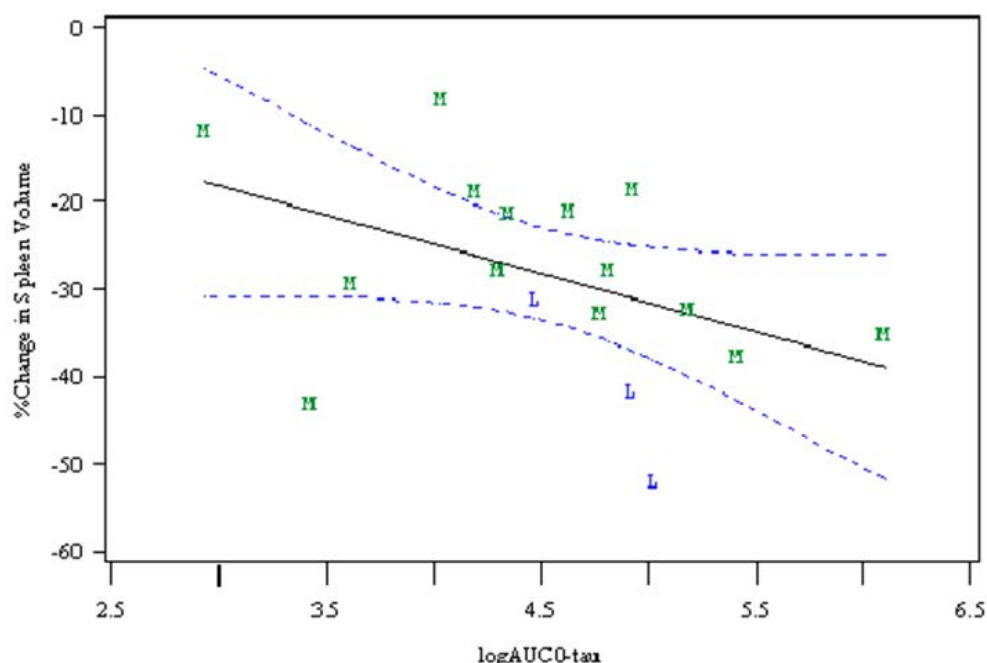
exposure ( $\log AUC_{(0-\tau)}$ ;  $\log C_{\max}$ ) as independent variables. P-value for testing the exposure effect was provided. The model is given below using  $\log AUC_{(0-\tau)}$  as an example:

PD response =  $\beta_0 + \beta_1 \cdot \text{baseline} + \beta_2 \cdot \log AUC_{(0-\tau)} + \text{error}$ ; where  $\beta_0$  is the intercept and error is the random error.

The FAS included 17 patients (14 receiving 100 mg bd and 3 receiving 50 mg bd), and the analysis was undertaken irrespective of CYP2D6 metaboliser status. Only the results for the primary efficacy endpoint (% change in spleen volume from baseline to week 39) and the primary PK parameter ( $\log AUC_{(0-\tau)}$ ) are described in detail in this CER. The results for the secondary analyses based on the  $\log C_{\max}$  were consistent with the primary analyses based on  $\log AUC_{(0-\tau)}$ .

The observed % change in spleen volume (MN) from Baseline to Week 39 versus observed  $\log AUC_{(0-\tau)}$  is summarised below in Figure 3. There was a linear PK/PD relationship between % change in spleen volume from baseline at Week 39 and  $\log AUC_{(0-\tau)}$ , but the relationship was not statistically significant ( $p=0.1019$ ).

**Figure 3: ENGAGE - Observed percent (%) change in spleen volume (MN) from baseline to Week 39 versus observed  $\log AUC_{(0-\tau)}$ ; FAS (n=17).**



Symbols (actual dose at week 39) - M = 100 mg BD; L=50 mg bd. AUC0-tau = area under the time concentration curve from time 0 to 12 hours. Patients with any CYP2D6 phenotype were included in the analysis. Mean baseline spleen volume was included in the analysis. PD response (% change in spleen volume) =  $4.75 - 0.22 \cdot \text{Baseline spleen volume} - 6.70 \cdot \log AUC_{0-\tau}$ ;  $p=0.102$ .

Based on the PK/PD model described, the effects of eliglustat on % change in spleen volume (MN) from Baseline to Week 39 were predicted for PM patients if given 50 mg bd, IM or EM patients if given 100 mg bd or URM patients if given 150 mg bd. The mean effect on % change in spleen volume (MN) from Baseline to Week 39 at the PopPK (POH0373) predicted eliglustat mean  $\log AUC_{(0-\tau)}$  for each CYP2D6 phenotype/dose population was calculated. The predicted effect of eliglustat on % change in spleen volume (MN) from Baseline to Week 39 for each CYP2D6 phenotype/dose was similar or better than the observed effect for all patients (see Table 22 below).

**Table 22: ENGAGE - Observed and predicted % change in spleen volume (MN) from Baseline to Week 39 based on the PK efficacy model (logAUC(tau); FAS.**

Response	Patients	n	% change in spleen volume (MN); Baseline to Week 39
Observed	All patients	20	-27.77% (95% CI: -32.57, -22.97)
Predicted	PM patients dosed at 50 mg bd	17	-45.14% (95% CI: -66.45, -23.84)
Predicted	IM/EM patients dosed at 100 mg BD	17	-31.91% (95% CI: -39.09, -24.72)
Predicted	URM patients dosed at 150 mg BD	17	-28.81% (95% CI: -34.59, -23.03)

The simulation results for IM/EM patients at their PopPK predicted logAUC<sub>(0-tau)</sub> when dosed at 100 mg bd and the corresponding % change in spleen volume based on the PK efficacy model (logAUC<sub>(tau)</sub>) are summarised below in Table 23. The estimated mean eliglustat effect based on the simulated data was similar to the observed effect. However, this is not surprising as 19 of the 20 eliglustat treated patients with observed data were EMs (n=18) or IMs (n=1), and 17 (85%) of patients were treated with 100 mg bd from Week 4 through Week 39. The estimated placebo least square means and 95% CIs were slightly different for the observed and the simulation analyses due to different eliglustat data being used in the ANCOVA model for the two analyses.

**Table 23: ENGAGE - Observed and predicted % change in spleen volume (MN) from Baseline to Week 39 based on the PK efficacy model (logAUC(tau); FAS.**

Response	Patients	n	% change in spleen volume (MN); Baseline to Week 39	Treatment difference (eliglustat - placebo)
Observed	All patients	20	-27.77% (95% CI: -32.57, -22.97)	-30.03% (95% CI: -36.82, -23.24)
Simulated	IM/EM at 100 mg BD	20	-32.14% (95% CI: -37.09, -27.18)	-34.20% (95% CI: -41.22, -27.18)

As regards other results in this study, statistically significant PK/PD relationships were observed for % change in liver volume from Baseline to Week 39 for logAUC<sub>(0-tau)</sub> and logC<sub>max</sub> (p=0.0111 and p=0.0161 respectively). However, no PK/PD relationships were observed for either % change in platelets from Baseline to Week 39 or change in haemoglobin concentration from Baseline to Week 39 for either logAUC<sub>(0-tau)</sub> or C<sub>max</sub>.

#### 4.3.3. ENCORE - ERT experienced patients

The efficacy and safety data from this pivotal Phase III study are discussed in detail later in this CER. The primary objective of this study was to assess the efficacy and safety of eliglustat compared with Cerezyme after 52 weeks of treatment of GD1 patients who reached therapeutic goals with ERT. Patients were randomized to eliglustat (n=106) or Cerezyme (n=54) for 52 weeks (the primary analysis period). Randomisation was stratified by ERT dose (<35 U/kg/q2w or ≥35 U/kg/q2w) prior to any unanticipated treatment interruption, dose reduction, or

regimen change resulting from the temporary unavailability of Cerezyme that occurred at the time of the study. All patients randomized to eliglustat received a starting dose of 50 mg bd and the dose was increased through 100 mg bd to a maximum of 150 mg bd to achieve a  $C_{\text{trough}}$  level of  $\geq 5$  ng/mL at pre-specified time-points. The PPS was defined as the primary analysis set (eliglustat  $n=99$ , Cerezyme  $n=47$ ). The distribution of eliglustat doses in the PPS at Week 52 was 19 (19%) patients on 50 mg bd (4=PM, 5=IM, 10=EM), 33 (33%) patients on 100 mg bd (4=IM, 29=EM), and 46 (46%) on 150 mg bd (1=IM, 39=EM, 4=URM, 2=indeterminate).

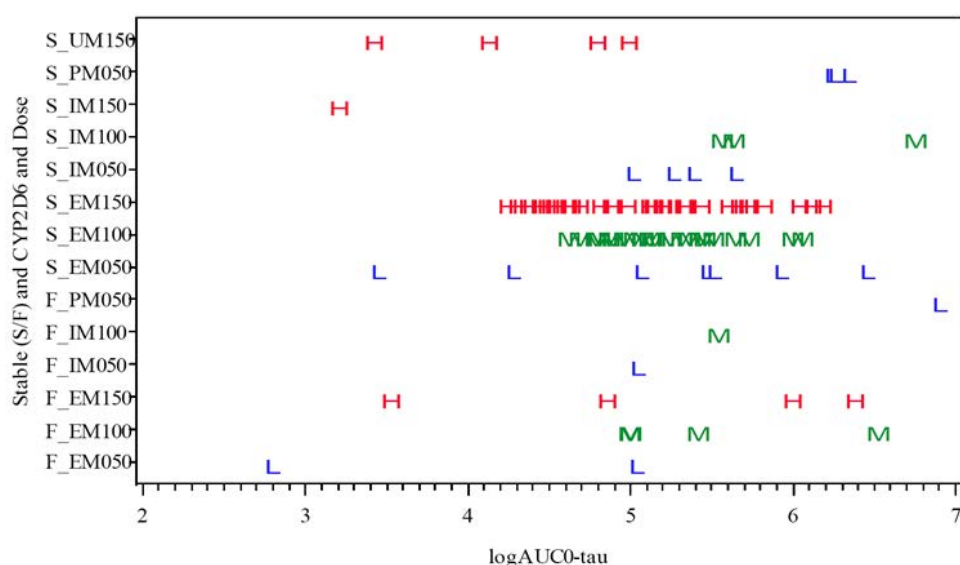
In essence, the PK/PD analyses were undertaken to support the sponsors proposed dosing regimen of eliglustat 100 mg bd for IM and EM patients switching from ERT to eliglustat. The PK/PD analyses were carried out for the observed primary composite endpoint (percentage of patients who remained stable at Week 52) and its 4 components, including the endpoint of % change in spleen volume (MN) at Week 52. Similar to the analyses for the ENGAGE study, the analyses used predicted  $\log AUC_{(0-\tau)}$  (primary analysis) and  $\log C_{\text{max}}$  (secondary analysis) values, and were carried out using the study-defined primary analysis population (that is, the PP Set).

#### 4.3.3.1. Key results

In essence, the exploratory PK/PD analyses were undertaken to support the sponsor's proposed dosing regimen of eliglustat 100 mg bd for IM/EM patients switching from ERT to eliglustat, which notably differed from the actual dosing regimen used in the pivotal study [ENCORE]. The PK/PD analyses were carried out for the observed primary composite endpoint (percentage of patients who remained stable at Week 52) and its 4 components, including the endpoint of % change in spleen volume (MN) at Week 52. The analyses used predicted  $\log AUC_{(0-\tau)}$  (primary analysis) and predicted  $\log C_{\text{max}}$  (secondary analysis) exposures, and were carried out using the study-defined primary analysis population (that is, the PPS).

The composite observed primary endpoint (patients remaining stable for 52 weeks) for each CYP2D6 phenotype and eliglustat dose at Week 52 were plotted against observed  $\log AUC_{(0-\tau)}$  in order to explore potential PK/PD relationships. Logistic regressions of the observed composite endpoint versus observed PK parameters ( $\log AUC_{(0-\tau)}$  or  $\log C_{\text{max}}$ ) were also explored. No apparent PK/PD trend was observed (see Figure 4, below). Consequently, no further exploratory PK/PD analysis were undertaken to predict the effect of the simulated proposed dosing regimen on the composite primary endpoint.

**Figure 4: ENCORE - Observed primary composite endpoint (stable/failure), CYP2D6 phenotype and eliglustat dose versus observed  $\log AUC_{(0-\tau)}$ ; PPS.**



Symbols (actual dose at week 52) - H = 150 mg BD; M = 100 mg BD; L=50 mg bd.



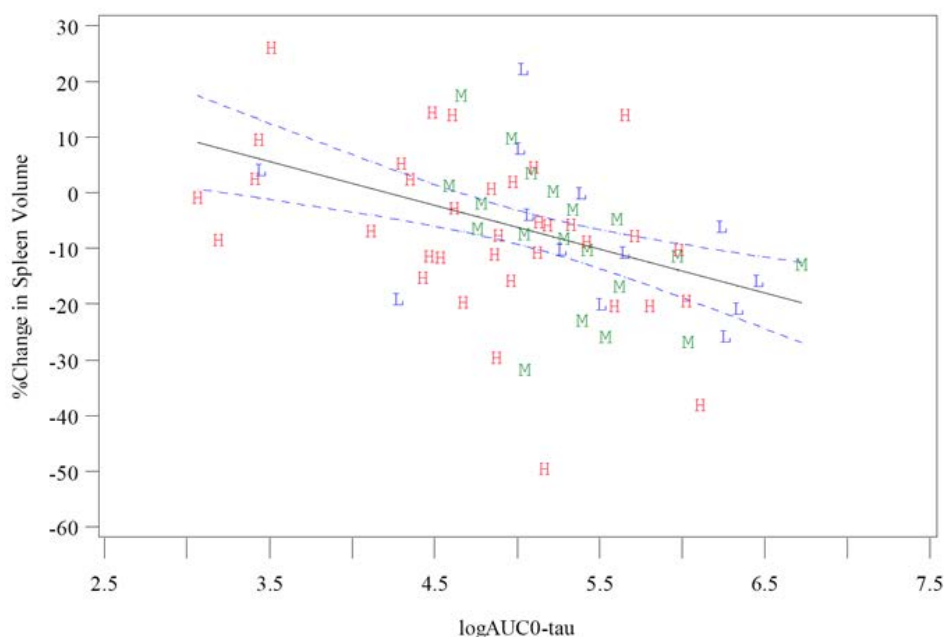
Exploratory PK/PD linear models for each observed component of the composite endpoint using change from Baseline to Week 52 as the response variable, and baseline value for the component, stratification randomisation indicator and exposure ( $\log AUC_{(0-\tau)}$  or  $\log C_{\max}$ ) as independent variables. The model is given below using  $AUC(0-\tau)$  as an example:

$$\text{PD response} = \beta_0 + \beta_1 * \text{baseline} + \beta_2 * (\text{baseline equivalent ERT high dose group} = \text{yes}) + \beta_3 * \log AUC_{0-\tau} + \text{error}, \text{ where } \beta_0 \text{ is the intercept and error is the random error.}$$

For the % change in spleen volume (MN) from baseline to Week 52, a statistically significant PK/PD relationship was shown for both observed  $\log AUC_{(0-\tau)}$  ( $p=0.0002$ ) and observed  $\log C_{\max}$  ( $p=0.0007$ ). 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 then used to predict eliglustat treatment effects in the PPS.

The observed  $\log AUC_{(0-\tau)}$ /efficacy prediction line, with 95% confidence band, for % change in spleen volume (MN) in the PPS is presented below in Figure 5. Patients in the three dosing groups appeared to have similar exposures. The sponsor states that this can be explained by the dose titration steps during the initial weeks of the study based on  $C_{\text{trough}}$  levels ( $< 5 \text{ ng/mL}$  up-titrated to next dose;  $\geq 5 \text{ ng/mL}$  maintained on same dose).

**Figure 5: ENCORE - Observed % change in spleen volume (MN) from baseline by week 52 versus observed  $\log AUC_{(0-\tau)}$ ; PPS (n=67).**



Symbols (actual dose at week 52) - H = 150 mg BD; M = 100 mg BD; L=50 mg bd.  $AUC_{0-\tau}$  = area under the time concentration curve from time 0 to 12 hours. Patients with any CYP2D6 phenotype were included in the analysis. Mean baseline spleen volume and % of patients in ERT high baseline dose group were included in the analysis. PD response (% change in spleen volume) =  $32.09 - 1.27 * (\text{ERT high baseline dose group}) + 0.57 * \log AUC_{0-\tau}$ ;  $p < 0.001$ .

Based on the above PK/efficacy model, effects for PM patients if given 50 mg bd, IM or EM patients if given 100 mg bd or URM patients if given 150 mg bd were predicted for the same number of patients as in the PK/PD analysis set (N=67). The predictions were carried using the eliglustat predicted mean  $\log AUC_{(0-\tau)}$ , derived from the PopPK analysis [POH0373], for each CYP2D6 phenotype at the recommended dose. Predicted rather than observed PK parameters were used in the analyses for due to confounding of the observed PK parameters due to dosing being determined by  $C_{\text{trough}}$  levels.

The predicted eliglustat effects for PM patients if given 50 mg bd or IM/EM patients if given 100 mg bd were similar or better than the observed effect in all patients, and worse for URM patients if given 150 mg bd. However, the predicted effects for URM patients if given 150 mg bd were comparable to the observed Cerezyme effect in ENCORE of -2.75% (95% CI: -8.12, 2.62). The results are summarised below in Table 24. The PK/PD results using the predicted  $\log C_{\max}$  efficacy model were consistent with PK/PD results using the predicted  $\log AUC_{(0-\tau)}$  efficacy model.

**Table 24: ENCORE - Observed and predicted % change in spleen volume (MN) from Baseline to Week 52 based on the PK/PD model ( $\log AUC_{(0-\tau)}$ ) in eliglustat treated patients; PPS.**

Response	Eliglustat treated patients	n	% change in spleen volume (MN); Baseline to Week 39
Observed	All patients	70	-5.96% (95% CI: -9.12, -2.80)
Predicted	PM patients dosed at 50 mg bd	67	-22.19% (95% CI: -30.66, -13.17)
Predicted	IM/EM patients dosed at 100 mg BD	67	-6.63% (95% CI: -9.74, -3.53)
Predicted	URM patients dosed at 150 mg BD	67	-2.99% (95% CI: -6.61, 0.63)

The simulation results for IM/EM patients their predicted  $\log AUC_{(0-\tau)}$  when dosed at 100 mg bd and the corresponding % change in spleen volume based on the PK efficacy model ( $\log AUC_{(0-\tau)}$ ) are summarised below in Table 25. The observed and predicted % change in spleen volume from Baseline to Week 52 were similar, based on predicted  $\log AUC_{(0-\tau)}$ . The estimated Cerezyme least square means and 95% CIs were slightly different for the observed and simulation analyses due to different eliglustat data being used in the ANCOVA model for the two analyses.

**Table 25: ENCORE - Observed and predicted % change in spleen volume (MN) from Baseline to Week 52 based on the PK/PD model ( $\log AUC_{(0-\tau)}$ ) in eliglustat treated patients; PPS.**

Response	Eliglustat Treated Patients	n	% change in spleen volume (MN); Baseline to Week 52	Treatment difference (eliglustat [n=70] - Cerezyme [n=39])
Observed	All patients	70	-5.96% (95% CI: -9.12, -2.80)	-2.75% (95% CI: -8.12, 2.62)
Simulated	IM/EM at 100 mg BD	70	-6.55% (95% CI: -9.75, -3.35, 1.22)	-3.44% (95% CI: -8.89, 2.00)

Among the 70 eliglustat treated patients included in the PPS analysis of % change in spleen volume (MN) at Week 52 versus Cerezyme, there were 3 PMs, 8 IMs, 54 EMs, 3 URMs and 2 patients with CYP2D6 indeterminate phenotype. By Week 52, all PM patients were dosed at 50 mg bd, all URM patients were dosed at 150 mg bd, and 3 out of 8 IM patients and 17 out of 54 EM patients were dosed at 100 mg bd. These patients received eliglustat doses corresponding to

the phenotype recommended dosing regimen. The rest of the IM/EM patients and 2 patients with indeterminate CYP2D6 phenotype were dosed at either 50 mg bd or 150 mg bd.

To confirm that the proposed phenotype based dosing regimen would not adversely effect the efficacy results of those IM and EM patients in the PPS who were actually dosed at 50 mg bd or 150 mg bd, and who would be treated with the higher or lower dose of 100 mg bd under the proposed regimen, respectively, an additional analysis was performed for those patients. Individual patient exposure projections for EMs and IMs to 100 mg bd were made for  $AUC_{(0-\tau)}$  and  $C_{max}$  corresponding to dose change from 50 mg to 100 mg bd or 150 mg to 100 mg bd, based on the PopPK simulations mean within-subject exposure ratios. These patient exposure projections were then applied to the established PK/PD model ( $\log AUC_{(0-\tau)}$ ) to obtain projected % change in spleen volume (MN) for IM and EM patients when dosed at 100 mg bd. Eliglustat data (n=70) and Cerezyme data (n=39) were then analysed using the same ANCOVA model as used in the ENCORE study.

The eliglustat data included the projection values for the IM and EM patients who received 50 mg bd or 150 mg bd and who would be administered 100 mg bd in the proposed dosing regimen, and the observed values for the others patients. Two (2) patients who had indeterminate CYP2D6 status and received 150 mg bd were projected to 100 mg bd. For Cerezyme patients, the observed % changes in spleen volume values were used. The projected eliglustat effect and its difference from Cerezyme were similar to the observed results (see Table 26, below).

**Table 26: ENCORE - Observed and projected % change in spleen volume (MN) from Baseline to Week 52 based on the PK/PD model ( $\log AUC_{(\tau)}$ ); PPS.**

Response	Patients	n	% change in spleen volume (MN); Baseline to Week 52	Treatment difference (eliglustat [n=70] - Cerezyme [n=39])
Observed	All patients	70	-5.96% (95% CI: -9.12, -2.80)	-2.75% (95% CI: -8.12, 2.62)
Simulated	All patients	70	-5.21% (95% CI: -8.41, -2.02)	-2.00% (95% CI: -7.43, 3.43)

#### 4.4. 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% 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 (MN) and increasing exposure to eliglustat ( $\log AUC_{(0-\tau)}$  and  $\log C_{\max}$ ) at Week 39 [ENGAGE]. There also appears to be a non-statistically significant association between % change in spleen volume (MN) and eliglustat exposure ( $\log AUC_{(0-\tau)}$  and  $C_{\max}$ ). There were no statistically significant PK/PD relationships between % change in platelet count or absolute change in haemoglobin concentration and eliglustat exposure ( $\log AUC_{(0-\tau)}$  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 ( $\log AUC_{(0-\tau)}$  and  $\log C_{\max}$ ) (ENCORE). Statistically significant associations between one component of the composite endpoint, % change in spleen volume [MN] from Baseline, and observed  $\log AUC_{(0-\tau)}$  and  $\log C_{\max}$  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 ( $\log AUC_{(0-\tau)}$  and  $C_{\max}$ ) 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  $\log AUC_{(0-\tau)}$ ) were similar. The sponsor argues that the similarity between the mean predicted % change in spleen volume at Week 39 [ENGAGE] 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.

## 5. 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  $C_{\text{trough}}$  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  $C_{\text{trough}}$  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  $C_{\text{trough}}$  value was  $\geq 5$  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  $C_{\text{trough}}$  was <5 ng/mL at Week 2. In ENCORE, but not ENGAGE, if the eliglustat  $C_{\text{trough}}$  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.

## 6. Clinical efficacy

### 6.1. Pivotal efficacy studies

#### 6.1.1. ENGAGE (GZGD02507)

##### 6.1.1.1. Study design, objectives, locations and dates

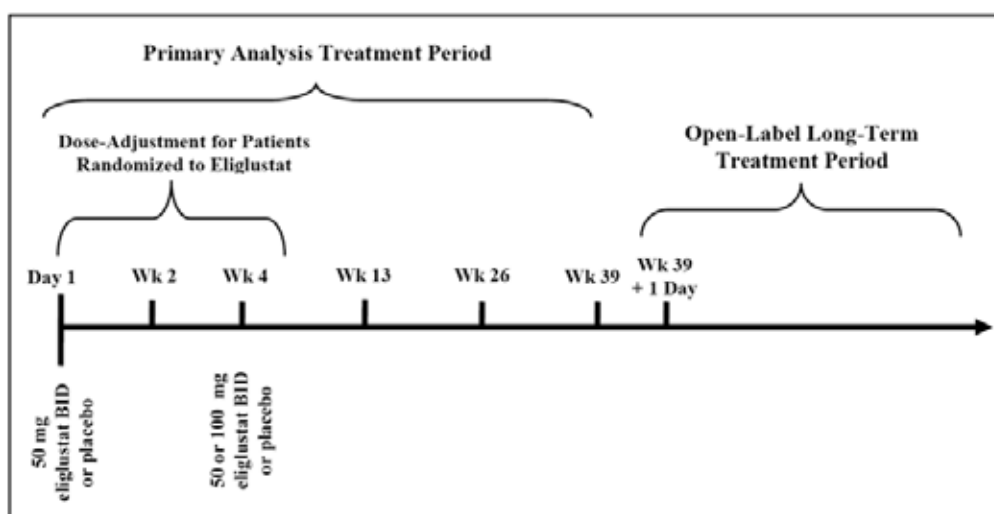
ENGAGE was a Phase III, multi-national, multi-centre, double-blind, randomized, placebo-controlled study to confirm the safety and efficacy of eliglustat in patients who had not received substrate replacement therapy (SRT) within 6 months prior to randomisation or had not received enzyme replacement therapy (ERT) within 9 months prior to randomisation.

The primary objective of the study was to confirm the efficacy and safety of eliglustat after 39 weeks of treatment in patients with GD1 (the primary analysis period).

The secondary objective of the study was to determine the long-term efficacy, safety, and PKs of eliglustat in patients with GD1.

The study comprised a screening period (Days -45 to -1), a randomized, placebo-controlled, double-blind primary analysis period (Day 1 to Week 39), an open-label long-term treatment period (post-Week 39 through study completion), and a follow-up phone call approximately 30 to 37 days after the last dose of study medication. The study is outlined schematically in Figure 6, below.

**Figure 6: ENGAGE - Study time-line.**



The study was conducted at a total of 26 sites in Latin America, the United States, Canada, the Middle East and Northern Africa, India, and Europe, and 17 of the study centres randomized at least 1 eligible patient. The coordinating investigator is located at the Hematology Research Center of Ministry of Health and Social Development, Moscow, Russia. The first patient consented to treatment on 5 November 2009, and the last patient visit for the primary analysis period occurred on 12 July 2012. The data cut-off date for the clinical study report was 18 July 2012, and the report was dated 28 March 2013.

The study was conducted in accordance with Good Clinical Practice (GCP) as defined by the International Conference on Harmonisation (ICH), the principles defined in the Declaration of Helsinki and its amendments, and all applicable national and international laws. The protocol was reviewed and approved by each site specific institutional review board (IRB) or independent ethics committee (IEC) prior to initiating treatment at the site. The study was sponsored by Genzyme, a Sanofi Company, USA.

#### **6.1.1.2. Inclusion and exclusion criteria**

The inclusion criteria are listed below:

1. The patient (and/or their parent/legal guardian) is willing and able to provide signed informed consent prior to any study-related procedures.
2. The patient is 16 to 65 years old at the time of randomisation.
3. The patient's Tanner Stage should be  $\geq 4$  prior to randomisation.
4. The patient has a diagnosis of Gaucher disease type 1 confirmed by a documented deficiency of acid  $\beta$ -glucosidase activity by enzyme assay.
5. The patient has the following symptoms of Gaucher disease during the Screening period:
  - a. At least one of the following laboratory abnormalities:
    - i. Haemoglobin level of 8.0 to 11.0 g/dL if female or 8.0 to 12.0 g/dL if male (the mean of 2 measurements from separate blood samples collected at least 24 hours apart during Screening).
    - ii. Platelet count of 50,000 to 100,000/mm<sup>3</sup> (the mean of 2 measurements from separate blood samples collected at least 24 hours apart during Screening).
  - b. Splenomegaly (spleen volume of 8 to 30 multiples of normal [MN]).
  - c. If hepatomegaly is present, the liver volume must be  $< 2.5$  MN.
6. The patient consents to provide a blood sample to Genzyme for genotyping for Gaucher disease (unless the patient's Gaucher genotype is already available), chitotriosidase, and for genotyping of CYP2D6 to categorize the patient's predicted rate of metabolism.
7. Male patients agree to use a medically accepted method of contraception throughout the study.
8. Female patients of childbearing potential must have a documented negative pregnancy test prior to dosing. In addition, all female patients of childbearing potential must use a medically accepted form of contraception throughout the study (either a barrier method or contraceptive with norethindrone and ethinyl estradiol).
9. The patient is willing to abstain from consumption of grapefruit or grapefruit juice for 72 hours prior to administration of the first dose of placebo or eliglustat and throughout the duration of the study.

The study also included comprehensive pre-specified discontinuation /withdrawal criteria. These have been examined and are considered to be appropriate. Procedures were specified for follow-up of patients who discontinued or withdrew from treatment in order to ascertain the

reasons and collect AE data (if relevant). Patients who discontinued or withdrew from treatment were not replaced.

#### **6.1.1.3. Study treatments**

The study treatments were undertaken using eliglustat tartrate capsules (50 mg and 100 mg) and matching placebo (50% Avicel PH101 and 50% Lactose Monohydrate USP/Ph-Eur) identical in appearance to the active treatment capsules.

The eliglustat dosing regimen was modelled on a regimen previously shown to be efficacious in a Phase II study in treatment-naïve GD1 patients, and considered to be generally well tolerated in both GD1 patients and healthy subjects. Given the highly variable PKs of eliglustat, each patient's dose could be escalated (up to a maximum dose of 100 mg bd) to target a trough concentration of at least 5 ng/mL. Concomitant medications known to alter the metabolism of eliglustat were restricted during the primary analysis period.

Patients who met all eligibility criteria based on screening assessments were randomized to eliglustat or placebo during the 39-week primary analysis period. Randomisation was stratified based on the patient's baseline spleen volume ( $\leq 20$  multiples of normal [MN] or  $> 20$  MN), and within each stratum patients were randomized in a 1:1 ratio to each treatment group.

All patients randomized to eliglustat received a single 50 mg dose on Day 1 and repeat doses of 50 mg twice daily (bd) from Day 2 to Week 4, and eliglustat trough concentrations were measured at Week 2. From the morning of Week 4 through Week 39, patients with eliglustat trough concentrations  $\geq 5$  ng/mL at Week 2 continued to receive 50 mg bd and patients with eliglustat trough concentrations  $< 5$  ng/mL at Week 2 received an increased dose of 100 mg bd. Patients randomized to placebo received placebo capsules on the morning of Day 1 and bd from the morning of Day 2 through Week 39.

Patients entered the long-term treatment period following completion of the Week 39 assessment. All patients received eliglustat at an initial dose of 50 mg bd from post-Week 39 (Day 1 of the long-term treatment period) through Week 43, and eliglustat trough concentrations were measured at Week 41. From Week 43 through Week 47, patients with eliglustat trough concentrations  $\geq 5$  ng/mL at Week 41 continued to receive 50 mg bd and patients with eliglustat trough concentrations  $< 5$  ng/mL at Week 41 received an increased dose of 100 mg bd. From Week 47 through study completion, patients who had an eliglustat trough concentration  $\geq 5$  ng/mL at Week 45 continued to receive their same dose of eliglustat and patients who had an eliglustat trough concentration  $< 5$  ng/mL at Week 45 received an increased dose of either 100 mg bd (for patients who had been receiving 50 mg bd) or 150 mg bd (for patients who had been receiving 100 mg bd).

Following approval of Protocol Amendment 5 (dated 12 July 2011), patients who experienced peak eliglustat plasma concentrations  $\geq 150$  ng/mL were temporarily discontinued from treatment irrespective of the treatment period. If the patient was in the primary analysis then he/she was removed from treatment, but was permitted to initiate open-label treatment, and if the patient was in the long-term treatment period then treatment could be resumed. Open-label treatment could be initiated or resumed either at a reduced dose or at the bd dose being taken prior to treatment, depending on the peak plasma concentration and the treatment period in which it was reported, concurrent safety findings, and adjustments of concomitant medications. Subsequent dose decreases or increases were permitted based on continued evaluation of the patient's data.

During the long-term treatment period, dose decreases were permitted in the event of poor tolerability. The lowest dose allowed in the study is 50 mg once daily (qd), and the highest dose allowed is 100 mg bd in the primary analysis period and 150 mg bd in the long-term treatment period. All patients remaining in the study are currently receiving open-label eliglustat therapy in the long-term treatment period. Patients may continue to receive study treatment for a total of up to 6 years, or until the study is terminated by the sponsor.

Treatment with any of the following medications within 30 days prior to randomisation was prohibited: investigational products; medications that may cause QTc interval prolongation; inducers of CYP3A4; strong inhibitors of CYP3A4, if the patient was a CYP2D6 poor metaboliser or an indeterminate metaboliser with neither allele known to be active; strong inhibitors of CYP3A4 or CYP2D6, if the patient was not a CYP2D6 poor or indeterminate metaboliser, except where a patient had chronically received either medication (but not both) for at least 30 days prior to randomisation and was continuing the same dosing regimen during the primary analysis period.

#### **6.1.1.4. Efficacy variables**

The main efficacy variables were:

- Spleen and liver volumes: Spleen and liver volumes were assessed by MRI at Screening, Weeks 26, 39, 65, 78, 104, and 130, every 6 months thereafter, and at study completion. The MRI was performed 2 times at Week 26 for a subset of patients (up to 20 patients) who completed 6 months of treatment (Week 26) to test/re-test variability of volumetric MRIs. The MRI was to be performed at the same time of day, and patients were required to fast for at least 6 hours prior to the MRI in order to reduce the meal effect. If the spleen or liver volume increased > 30% above the Baseline value at any study visit the assessment was to be repeated in approximately 4 weeks and the average of both measurements was to be used in the study analyses. MRIs were assessed centrally by blinded reviewer for determination of spleen and liver volume.
- Platelet count: Platelet count was assessed at Screening, Weeks 4 and 13, every 3 months thereafter, and at study completion. Two blood samples were to be collected at least 24 hours apart only at Screening, Weeks 39, 78, and 130, every 12 months thereafter, and at study completion. The average of the 2 platelet count values for each of these visits was to be used in the efficacy analyses. In the event that a patient was missing 1 of the 2 assessments at a particular time-point, then the single assessment was used. Local laboratories conducted the analyses.
- Haemoglobin level: Haemoglobin level was assessed at Screening, Weeks 4 and 13, every 3 months thereafter, and at study completion. Two blood samples were to be collected at least 24 hours apart only at Screening, Weeks 39, 78, and 130, every 12 months thereafter, and at study completion. The average of the 2 haemoglobin values for each of these visits was to be used in the efficacy analyses. In the event that a patient is missing 1 of the 2 assessments at a particular time-point, then the single assessment was used. Local laboratories conducted the analyses.

#### **6.1.1.5. Efficacy endpoints**

##### **6.1.1.5.1. Primary efficacy endpoint**

The primary efficacy endpoint was the percentage change in spleen volume in MN from Baseline to 39 weeks of treatment with eliglustat as compared to placebo.

##### **6.1.1.5.2. Secondary efficacy endpoints**

For the double-blind, primary analysis period there were three secondary efficacy endpoints:

- the change in haemoglobin levels (in g/dL) from Baseline to Week 39;
- the percentage change in liver volumes (in MN) from Baseline to Week 39; and
- the percentage change in platelet counts from Baseline to Week 39.

#### 6.1.1.5.3. *Other efficacy endpoints*

- Tertiary efficacy endpoints included: Biomarkers (CCL18 and chitotriosidase); bone disease assessments (X-ray, DXA, MRI, and bone marrow burden score); GD assessments (mobility, bone crisis, and bone pain); and QOL questionnaires (BPI, FSS, and SF-36).
- Exploratory efficacy endpoints included: GD severity score system (DS3) and investigational biomarkers including GL-1 assayed from DBS on filter paper and from plasma, as well as ceramide, sphingomyelin, and MIP1- $\beta$  (assayed from plasma).

#### 6.1.1.6. *Randomisation and blinding methods*

During the double-blind primary analysis period, the identity of the study drug was blinded to the patient, Investigator, and to the Genzyme Investigational Team. In addition, the PK data were also blinded to the Investigator and the Genzyme Investigational Team. Genzyme Clinical Pharmacy Research Services remained unblinded throughout the study in order to provide the appropriate investigational product to patients. The appropriate drug kits were assigned to each patient by the Interactive Voice Response System/ Interactive Web Response System (IVRS/IWRS) according to treatment randomisation and dose-adjustment PK results entered by the central laboratory.

#### 6.1.1.7. *Analysis populations*

The Full Analysis Set [FAS] (n=40) included all patients who had signed informed consent and received at least one dose of study drug. The FAS was also described in the CSR as the Intent-to-Treat (ITT) population. The Per Protocol [PP] (n=38) set was defined as all patients without major protocol deviations expected to interfere with the assessment of efficacy and meeting at least 80% drug compliance during the double-blind primary analysis period (39 weeks). The PP set excluded patients with haematological impairments as a result of medically determined aetiologies other than GD. Major protocol deviations were prospectively defined in the Statistical Analysis Plan (SAP). The PP set was determined prior to the database lock and study unblinding. Safety analyses were performed in the safety population defined as all patients who received at least 1 dose of eliglustat or placebo (n=40). PK analysis was performed on all patients who received at least 1 dose of eliglustat and had evaluable PK data.

#### 6.1.1.8. *Sample size*

Allowing for a drop-out rate of 20%, approximately 36 male and female patients were to be randomized in a 1:1 ratio to receive eliglustat tartrate or placebo in order to provide at least 28 evaluable patients at the end of the double-blind PAP (39 weeks). This sample size assumes a 25% decrease in spleen volume in MN for eliglustat tartrate and a 5% decrease in spleen volume in MN for placebo at 39 weeks. This sample size also assumes a standard deviation of 15%, a two-sided, two-sample t-test with a 5% level of significance and power of 92%.

The secondary efficacy endpoint analyses of haemoglobin levels, liver volumes (MN), and platelet counts were powered at 91%, 89%, and 56.5%, respectively, based on the sample size calculation for the primary efficacy endpoint (spleen volume). These power estimates assume a two-sided, two-sample t-test with a 5% level of significance for each efficacy endpoint and a 20% drop-out rate. Furthermore, these power estimates also assume increases from Baseline of 1.3 for eliglustat versus 0 for placebo in haemoglobin levels (in g/dL) at 39 weeks, decreases from Baseline of 12.5% for eliglustat versus 0% for placebo in liver volumes (in MN) at 39 weeks, and increases from Baseline of 25% for eliglustat versus 0% for placebo in platelet counts at 39 weeks. Standard deviations of 1 g/dL, 10%, and 30% were assumed for haemoglobin levels, liver volumes, and platelet counts, respectively.



### **6.1.1.9. Statistical methods**

#### **6.1.1.9.1. General**

The primary analysis of efficacy was undertaken in the FAS (ITT population). Repeat analyses of all primary and secondary endpoints and selected tertiary and exploratory endpoints were performed in the PPS. Sensitivity analyses for the primary and secondary endpoints were performed for the Week 39 Completer Analysis Set. All efficacy analyses were conducted at the 5% level of significance. For all efficacy endpoints, last observation carried forward (LOCF) was used if a result was unavailable for Week 39.

#### **6.1.1.9.2. Primary efficacy analysis**

The primary efficacy endpoint was the percentage change in spleen volume in MN from Baseline to Week 39 for eliglustat compared with placebo. The primary efficacy endpoint was tested using an analysis of covariance (ANCOVA) model fitted with treatment and Baseline spleen severity. Normal distribution of the residuals was confirmed using the Shapiro-Wilk test at a 5% level of significance. Mean percentage change, standard error, and 95% confidence intervals (CIs) were summarised for both treatments and for the treatment difference; p-value was also provided for the treatment difference (5% significance level). Spleen volumes were listed and values, changes, and percentage changes were descriptively summarised for each visit by treatment, by Baseline spleen severity, by site and, for by average steady-state trough plasma concentration of eliglustat for the eliglustat group.

#### **6.1.1.9.3. Secondary efficacy analyses**

The three secondary efficacy endpoints were analysed in a similar manner to the primary efficacy endpoint. However, a closed-testing procedure was used in order to account for multiplicity of secondary efficacy endpoint testing. In the closed-testing procedure, the three secondary efficacy endpoints were analysed sequentially dependent on a statistically significant treatment effect for the preceding endpoint (5% significance level). The sequential order was: (i) absolute change in haemoglobin levels (in g/dL) from Baseline to Week 39; (ii) percentage change in liver volumes (in MN) from Baseline to Week 39; and (iii) percentage change in platelet counts (/mm<sup>3</sup>) from Baseline to Week 39.

An additional analysis evaluated within-patient change from Baseline to Week 39 (patients randomized to eliglustat) and from Week 39 to Week 78 (patients randomized to placebo) for percentage changes in spleen volume, liver volume, and platelet count, and absolute change in haemoglobin level. These analyses include all 26 patients with available data at both time points as of the data cut-off date of 18 July 2012, when all patients had completed the primary analysis period. A paired T-test was used for analysis of endpoints with normally distributed data, and a Wilcoxon signed-ranks test was used for analysis of endpoints with non-normally distributed data.

#### **6.1.1.9.4. Tertiary efficacy analyses**

Selected tertiary efficacy endpoints were analysed similarly to the primary efficacy endpoint unless the data were non-normally distributed, in which case the ANCOVA was performed on ranked data. With the exception of the exploratory biomarkers, Baseline values for the endpoint were included in the ANCOVA model.

### **6.1.1.10. Participant flow**

The study randomized a total of 40 patients; 20 patients to eliglustat and 20 to placebo. Of the 40 patients, 39 completed the study and 1 patient in the eliglustat group elected to withdraw on Day 166. An additional 32 patients were screened, but were not randomized because they failed to complete screening procedures, did not meet all eligibility criteria, or elected to withdraw prior to randomisation. Eligibility criteria most commonly not met were spleen size (6 to 30

MN) and platelet count (50,000 to 130,000/mm<sup>3</sup>). The disposition of all 40 randomized patients is summarised below in Table 27.

**Table 27: ENGAGE - Patient disposition; all randomized patients.**

	<b>Eliglustat (N=20)</b>	<b>Placebo (N=20)</b>
Randomized, n (%)	20 (100)	20 (100)
Treated, n (%)	20 (100)	20 (100)
Completed Week 39, n (%)	19 (95)	20 (100)
Withdrew Prior to Week 39, n (%)	1 (5) <sup>a</sup>	0
Wishes to Withdraw	1 (5) <sup>a</sup>	0

a = Patient treated withdrew consent on Day 166

#### **6.1.1.11. Major protocol deviations**

Major protocol deviations were reported for 23 patients and were pre-defined as deviations 'expected to impact the scientific soundness of the study or the rights, safety, or welfare of human subjects'. No patient was excluded from the FAS due to a protocol deviation. One patient was excluded from the PPS due to a dosing deviation that could potentially have affected the efficacy analysis. The major protocol deviations have been examined and it is considered unlikely that the deviations have invalidated the efficacy analyses.

Two patients had a deviation from study eligibility: 1 patient with a residual enzyme activity of 8.70 nmol/hr/mg, which was at the lower end of the normal range (7.5 to 14.5 nmol/hr/mg). The sponsor became aware of this deviation after the patient had initiated study treatment, and permitted the patient to continue in the trial as the patient had a confirmed homozygous mutation of the acid  $\beta$ -glucosidase gene and Baseline clinical manifestations that were consistent with the diagnosis of GD including moderate splenomegaly (10.92 MN) and moderate thrombocytopenia (95 x10<sup>9</sup>/L); 1 patient with a residual enzyme activity of 15.7 nmol/hr/mg, which was above the normal range (7.5 to 14.5 nmol/hr/mg). The Investigator enrolled the patient based on homozygous mutations of the acid  $\beta$ -glucosidase gene, clinical findings including splenomegaly and bone fracture, and a family history of Gaucher disease in all of the patient's male siblings as well as one uncle who also screened for this study. At Baseline, the patient had severe splenomegaly (20.16 MN), moderate hepatomegaly (1.84 MN), and moderate thrombocytopenia (82.5 x10<sup>9</sup>/L).

#### **6.1.1.12. Baseline data**

##### **6.1.1.12.1. Baseline demographic characteristics**

Of the 40 randomized patients, 20 were male and 20 were female, the mean age was 31.8 years (range: 16.1, 62.9 years), the mean baseline BMI was 23.4 kg/m<sup>2</sup> (range: 18.0, 39.0 kg/m<sup>2</sup>), 39 (98%) were White, and 1 (3%) was Asian. The CYP2D6 metaboliser status was PM n=0 (0%), IM n=3 (8%), EM n=36 (90%), and URM n=1 (3%). The basic demographic characteristics were similar for the eliglustat and placebo treatment groups.

##### **6.1.1.12.2. Baseline disease characteristics**

The mean age of GD at diagnosis was 21.1 years, and the mean age at onset of first GD symptoms was 16.0 years. Of the 40 patients, 37 had one or both of the common allelic mutations of the acid  $\beta$ -glucosidase gene (N370S, L444P). The mean residual acid  $\beta$ -glucosidase activity was 2.14 nmol/hr/mg (range: 0.0, 15.7 nmol/hr/mg); splenomegaly  $\leq$  20 MN (low severity) was reported in 33 patients and  $>$  20 MN (high severity) was reported in 7 patients; hepatomegaly none/mild was reported in 15 patients and moderate in 25 patients; anaemia was not present in 32 (80%) patients, mild in 4 (10%) patients, moderate in 3 (8%) patients, and severe in 1 (3%) patient; and mild thrombocytopenia was reported in 3 (8%) patients, moderate in 30 (75%) patients



and severe in 7 (18%) patients. In general, the baseline disease characteristics of the two treatment groups were similar and the observed differences are unlikely to have biased the efficacy analysis.

#### *6.1.1.12.3. Medical history*

The medical history of patients included in this study was consistent with those expected for patients with GD1. Review of the tabulated summary of significant medical/surgical history findings in the FAS indicates that the most common findings were gastrointestinal/hepatic conditions (70% of patients in each group) followed by haemopoietic conditions (65% of patients in each group) and musculoskeletal disorders (65% of patients in each group). Medical history findings consistent with GD in the FAS included organomegaly, thrombocytopenia, and musculoskeletal pain (including 10% in each treatment group with arthralgia), disc disease, and low bone mineral density/osteopenia. Medical conditions unrelated to GD reported in the study population included hypertension (5 patients) and diabetes (3 patients). At screening, all 40 patients tested negative for sickle cell and thalassemia, HIV, hepatitis B, and hepatitis C.

#### *6.1.1.12.4. Pre-treatment medications*

Pre-treatment medications were reported to have been taken by 22 (55%) patients in the total patient population (safety set) (10 [50%] in the placebo group and 12 [60%] in the eliglustat group). Medications taken by  $\geq 10\%$  of the total number of in the safety set were analgesics (18%), calcium products (15%), 'other ophthalmologicals' (13%), anti-inflammatories/non-steroids for topical use (10%), oral iron (bivalent) preparations (10%), other antihistamines for systemic use (10%).

Five (5) patients had received prior ERT with alglucerase or imiglucerase, including 2 patients randomized to eliglustat and 3 patients randomized to placebo, and 4 of these patients had also received prior treatment with miglustat. As required by protocol, all patients had discontinued treatment with ERT and miglustat at least 9 months and 6 months, respectively, prior to initiation of study treatment.

#### *6.1.1.12.5. Concomitant medications*

Concomitant medications (1 or more) were taken by 31 (78%) patients during the primary analysis period (39 weeks); 15 (75%) in the placebo group and 16 (80%) in the eliglustat group. Concomitant medications taken by  $\geq 10\%$  of patients in the total safety set (placebo versus eliglustat) included: paracetamol (8 [40%] versus 7 [35%]); ibuprofen (4 [20%] versus 4 [20%]); loratidine (4 [20%] versus 1 [5%]); and amoxicillin (2 [10%] versus 3 [15%]). The range of concomitant medications taken by patients in the study was extensive, but no marked differences were observed between the two treatment groups.

Two (2) patients in the eliglustat group had a prohibited change in nutritional supplements during the primary analysis period (1 patient increased the dose of vitamin B-12 and ferrous sulfate; 1 patient discontinued folic acid approximately 2 weeks prior to the week 39 haemoglobin assessment). Seven (7) patients in the eliglustat group took 1 or more concomitant medications with the potential to cause drug-drug interactions with eliglustat (4 patients received medications known to prolong the QTc interval on a temporary basis, 2 patients received treatment with moderate CYP3A4 inhibitors, 1 patient received a CYP3A4 inducer). Eight (8) patients in the placebo group took 1 or more concomitant medications with the potential to cause drug-drug interactions with eliglustat (all 8 received medications known to increase the QTc interval [1 experienced sustained ventricular tachycardia and separate episodes of palpitation and chest pain], 2 of the 8 patients also received medications known to be CYP3A4 inducers).

#### *6.1.1.13. Treatment compliance and extent of exposure*

Treatment compliance was determined at each study site visit through counting and recording the number of remaining capsules. Compliance was at least 90% for all patients, with the

exception of 2 patients in the placebo group (1 x compliance 80.3% and 1 x compliance 86.3%) and 1 patient in the eliglustat group (61.6% compliance).

The mean (SD) time on study treatment was 274.5 (19.94) days overall, and was similar in the 2 treatment groups (274.8 [10.05] days in the placebo group and 274.2 [26.75] days in the eliglustat group).

#### 6.1.1.14. Results for the primary efficacy endpoint - spleen volume (MN)

Eliglustat demonstrated superior efficacy compared with placebo for the primary efficacy endpoint of % reduction in spleen volume from Baseline to Week 39. The least squares (LS) mean percentage change in spleen volume (MN) from Baseline to Week 39 was -27.77% in the eliglustat group compared with +2.26% in the placebo group, resulting in a statistically significant treatment difference of -30.03% (95% CI: -36.82, -23.24),  $p < 0.0001$  (see Table 28, below).

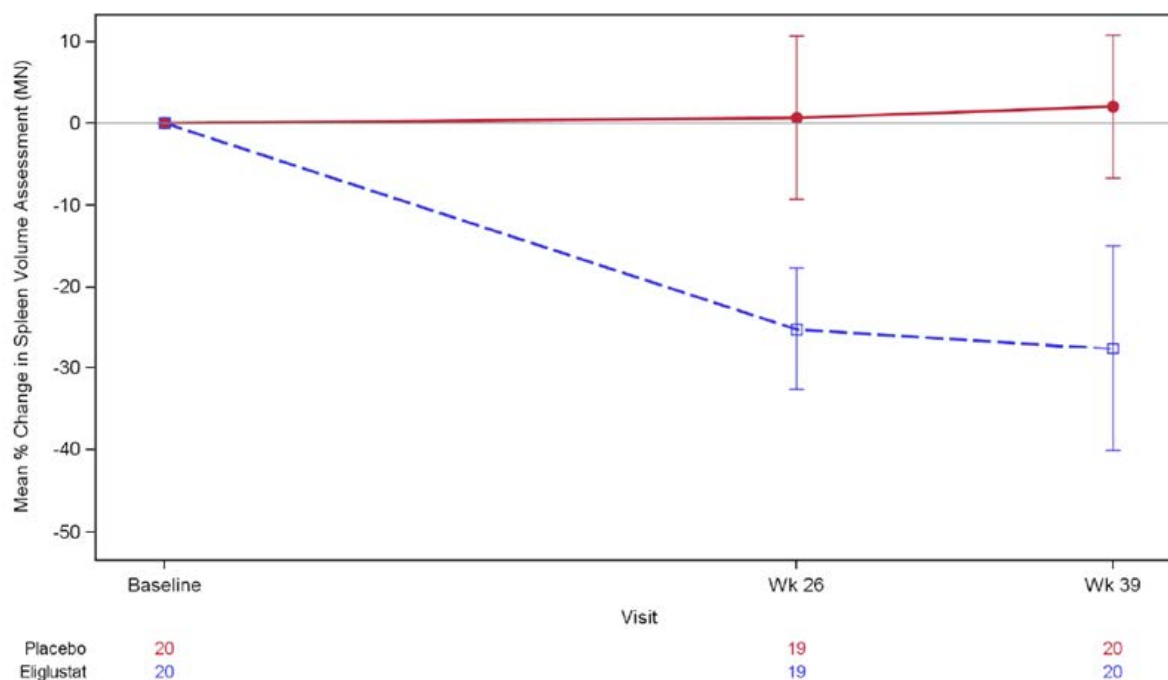
**Table 28: ENGAGE - Percentage change in spleen volume (MN) from baseline to Week 39; FAS.**

Time Point / Change	Statistic	Eliglustat (N=20)	Placebo (N=20)	Treatment Difference (Eliglustat-Placebo)
Baseline	n	20	20	NA
	Mean (SD)	13.89 (5.929)	12.50 (5.959)	NA
	Median	12.09	11.05	NA
	Min, Max	5.94, 28.39	6.32, 25.27	NA
Week 39	n	20	20	NA
	Mean (SD)	10.17 (5.065)	12.84 (6.395)	NA
	Median	8.34	10.97	NA
	Min, Max	4.12, 21.90	6.63, 26.17	NA
% Change from Baseline to Week 39	Mean (SD)	-27.58 (12.591)	2.07 (8.777)	NA
	Median	-29.03	4.20	NA
	Min, Max	-51.52, 0.00	-20.91, 13.68	NA
	LS Mean (SEM)	-27.77 (2.37)	2.26 (2.37)	-30.03 (3.35)
	95% CI	-32.57, -22.97	-2.54, 7.06	-36.82, -23.24
	p-value	NA	NA	<0.0001

NA = not applicable; SD = standard deviation; SEM = standard error of the mean; LS = least squares; CI = confidence interval; MN = multiples of normal Note: Baseline refers to the last assessment prior to the first dose of study drug on Day 1. The average of all Week 39 values is used for each patient. Last observation carried forward (LOCF) is used for 1 patient in the eliglustat group who withdrew from the study prior to the Week 39 assessment. Percentage change from Baseline is summarised only for patients with data at both Baseline and Week 39. Statistical estimates are based on an ANCOVA model that included treatment group, Baseline spleen severity, and a continuous variable for the Baseline observation.

All patients in the study had splenomegaly at Baseline, with mean spleen volumes of 13.89 MN for the eliglustat treatment group and 12.50 MN for the placebo group. The eliglustat treatment group showed a marked percentage reduction in mean spleen volume (MN) by the first post-Baseline assessment at Week 26 (-25.16%), and a continued reduction in mean spleen volume (MN) through Week 39 (-27.58%). In contrast, the placebo group showed small mean percentage increases in spleen volume (MN) at Week 26 (+0.73%) and at Week 39 (+ 2.07%). The mean percentage change from baseline in spleen (MN) volume over time is shown below in Figure 7.

**Figure 7: ENGAGE - Mean (SD) percentage change from baseline in spleen volume (MN) over time; FAS.**



All 19 patients in the eliglustat treatment group with post-Baseline data achieved a reduction in spleen volume (MN) at both Week 26 and Week 39, with percentage reductions from Baseline to Week 39 ranging from -7.68% to -51.52%. The 1 other patient in this treatment group discontinued after approximately 23 weeks of eliglustat therapy and did not have post-Baseline imaging assessments. This patient had a Baseline spleen volume of 21.9 MN, which was carried forward to Week 39. In the placebo group, 13 patients had increases in spleen volume (MN) of from 0.14% to 13.68% during the 39 weeks of double-blind treatment, and 6 patients had modest reductions in spleen volume ranging from -2.78% to -8.96%. One patient in the placebo group had a large reduction in spleen volume (MN) of -20.91% during primary analysis period (39 weeks), and no reason for this change was identified.

Secondary analyses of the primary efficacy endpoint were performed in the PPS (n=38) and the Week 39 Completer Set (n=39). Statistically significant treatment differences ( $p < 0.0001$ ) between eliglustat and placebo for the percentage reduction in spleen volume (MN) from Baseline to Week 39 were observed in both of these analyses. In the PPS analysis, the least squares (LS) mean percentage reduction in spleen volume (MN) was -28.48% in the eliglustat group compared with an increase of +2.10% in the placebo group, resulting in a statistically significant treatment difference of -30.58% (95% CI: -37.16, -23.99),  $p < 0.0001$ . In the Week 39 Completer Set, the least squares (LS) mean percentage reduction in spleen volume (MN) was -29.05% in the eliglustat group compared with an increase of +2.08% in the placebo group, resulting in a statistically significant treatment difference of -31.13% (95% CI: -37.62, -24.64),  $p < 0.0001$ .

Overall, 15 of the 20 eliglustat treated patients showed a clinically meaningful treatment response in spleen volume (MN), defined as >20% reduction from Baseline to Week 39, compared with 1 of the 20 placebo treated patients. Evaluation of eliglustat treated patients did not suggest a clear relationship between treatment response and acid  $\beta$ -glucosidase genotype (that is, mutations associated with a mild [N370S] versus severe [L444P] pathology).

**Comment:** The percentage change from baseline in spleen volume (MN) at Week 39 was statistically significantly greater in the eliglustat group than in the placebo group (eliglustat minus placebo: -30.03% [95% CI: -36.82, -23.24],  $p < 0.0001$ ). The study was

powered assuming a 25% decrease in spleen volume for eliglustat and a 5% decrease for placebo at Week 39 (that is, a 20% placebo-corrected reduction in spleen volume [MN] in the eliglustat group from Baseline to Week 39). Therefore, as the mean reduction in spleen volume (MN) at Week 39 in the eliglustat group relative to the placebo group was approximately 30%, it can be reasonably inferred that this effect is clinically significant based on study criteria. Furthermore, 15 (75%) patients in the eliglustat group achieved clinically meaningful reductions in spleen volume (MN) of more than 20% from Baseline to Week 39 compared with 1 (5%) patient in the placebo group.

The study included an exploratory efficacy analysis based on published data for Cerezyme relating to the percentage of patients achieving Gaucher Disease Short Term (12 to 24 months) Therapeutic Goals.<sup>5,6</sup> The criteria for the therapeutic goals based on the publication by Pastores et al (2004)<sup>5</sup> were pre-specified in the SAP. The short term goal for reduction in spleen volume (MN) specified in the SAP was  $\geq 30\%$ . In the eliglustat group 9 (45%) patients had a reduction in spleen volume (MN) of  $\geq 30\%$  at Week 39 compared with no patients in the placebo group.

### 6.1.1.15. Results for the secondary efficacy endpoints

#### 6.1.1.15.1. Haemoglobin level

A statistically significant increase in haemoglobin level was observed following 39 weeks of treatment with eliglustat, relative to placebo. The least squares mean increase in haemoglobin from Baseline to Week 39 was 0.69 g/dL in the eliglustat group compared with a decrease of -0.54 g/dL in the placebo group, resulting in a significant treatment difference of 1.22 g/dL (95%CI: 0.57, 1.88) ( $p=0.0006$ ). The results in the PPS and 39 Week Completer Set were consistent with the results in the FAS. The results for the analysis in the FAS are summarised below in Table 29.

**Table 29: ENGAGE - Absolute change in haemoglobin (g/dL) from baseline to Week 39; FAS.**

Time Point / Change	Statistic	Eliglustat (N=20)	Placebo (N=20)	Treatment Difference (Eliglustat-Placebo)
Baseline	n	20	20	NA
	Mean (SD)	12.05 (1.816)	12.75 (1.629)	NA
	Median	12.05	12.90	NA
	Min, Max	8.15, 15.25	9.65, 16.30	NA
Week 39	n	20	20	NA
	Mean (SD)	12.78 (1.561)	12.17 (2.010)	NA
	Median	12.95	12.25	NA
	Min, Max	8.85, 15.30	7.85, 15.00	NA
Change from Baseline to Week 39	Mean (SD)	0.73 (1.093)	-0.58 (0.890)	NA
	Median	0.70	-0.65	NA
	Min, Max	-1.45, 3.15	-2.50, 0.70	NA
	LS Mean (SEM)	0.69 (0.23)	-0.54 (0.23)	1.22 (0.32)
	95% CI	0.23, 1.14	-1.00, -0.08	0.57, 1.88
	p-value	NA	NA	0.0006

Notes as for Table 28, above.

The majority of patients in this study were not anaemic at Baseline, with mean haemoglobin levels of 12.05 g/dL (range: 8.15, 15.25) in the eliglustat group and 12.75 g/dL (range: 9.65, 16.30) in the placebo group. The eliglustat group showed increases in haemoglobin level from Week 4 through Week 39, while haemoglobin levels in the placebo group trended downward during the same time period.

Of the 19 patients in the eliglustat treatment group with data at Week 39, 15 (79%) patients had an absolute increase in haemoglobin level from Baseline to Week 39 (range: 0.25, 3.15 g/dL), including 7 (37%) patients who had an increase in haemoglobin of at least 1 g/dL. In the placebo group, 14 (70%) patients had absolute decreases in haemoglobin level (range: -0.15 to -2.5 g/dL), and 6 (30%) patients had absolute increases in haemoglobin level (range: 0.05 to 0.7 g/dL) from Baseline to Week 39.

**Comment:** The majority of patients in this study were not anaemic at baseline. The short term (12 to 24 months) therapeutic goals for haemoglobin levels defined in the SAP were  $\geq 11.0$  g/dL for females and  $\geq 12.0$  g/dL for males. In the eliglustat group (n=20), the percentage of patients already at these levels at baseline was 70% (n=14) and the percentage of patients at the goal at Week 39 was 90% (n=18). In the placebo group (n=20), the percentage of patients already at these levels at baseline was 85% (n=17) and the percentage of patients at the goal at Week 39 was 70% (n=14). Overall, the results indicate that there is clinically meaningful benefit as regards improvement in haemoglobin level in patients treated with eliglustat compared with placebo.

#### 6.1.1.15.2. Liver volume

A statistically significant reduction in liver volume (MN) was observed following 39 weeks treatment with eliglustat, relative to placebo. The LS mean percentage decrease in liver volume (MN) from Baseline to Week 39 was -5.20% in the eliglustat group compared with an increase of +1.44% in the placebo group, resulting in a significant treatment difference of -6.64% (95%CI: -11.37, -1.91),  $p=0.0072$ . The results in the PPS and the 39 Week Completer Set were consistent with the results in the FAS. The results in the FAS are summarised below in Table 30.

**Table 30: ENGAGE - Percentage change in liver volume (MN) from baseline to Week 39; FAS.**

Time Point / Change	Statistic	Eliglustat (N=20)	Placebo (N=20)	Treatment Difference (Eliglustat-Placebo)
Baseline	n	20	20	NA
	Mean (SD)	1.44 (0.354)	1.36 (0.280)	NA
	Median	1.36	1.29	NA
	Min, Max	0.93, 2.18	0.93, 1.98	NA
Week 39	n	20	20	NA
	Mean (SD)	1.35 (0.280)	1.39 (0.309)	NA
	Median	1.25	1.32	NA
	Min, Max	0.91, 1.90	0.90, 1.98	NA
% Change from Baseline to Week 39	Mean (SD)	-5.45 (6.886)	1.70 (8.004)	NA
	Median	-5.23	0.54	NA
	Min, Max	-18.95, 9.09	-14.29, 18.25	NA
	LS Mean (SEM)	-5.20 (1.64)	1.44 (1.64)	-6.64 (2.33)
	95% CI	-8.53, -1.87	-1.89, 4.78	-11.37, -1.91
	p-value	NA	NA	0.0072

Notes as for Table 28, above.

Most patients had mild or moderate hepatomegaly at Baseline, with mean liver volumes of 1.44 MN in the eliglustat group and 1.36 MN in the placebo group. In the eliglustat group, a mean percentage reduction in liver volume (MN) was apparent by the first post-Baseline assessment at Week 26 (-2.97%) and mean liver volume continued to decrease through Week 39 (-5.45%). In contrast, the placebo group had mean percentage increases in liver volume at both Week 26 (+1.25%) and Week 36 (+1.70%).

Of the 19 patients in the eliglustat group with post-Baseline data, 16 (84%) achieved a reduction in liver volume by Week 39, ranging from -2.15% to -18.95%. Of the 20 patients in the

placebo-group with post-baseline data, 7 (35%) achieved a reduction in liver volume by Week 39, ranging from -1.49% to -14.29%.

**Comment:** The majority of patients in this study had moderate hepatomegaly at Baseline, and 70% of patients in both treatment groups had baseline liver volumes < 1.5 MN. The short term (12 to 24 months) therapeutic goal for decrease from baseline in liver volume (MN) defined in the SAP was  $\geq 20\%$ . At Week 39, no patients in either the eliglustat group or the placebo group had achieved reductions in liver volume (MN) of  $\geq 20\%$ . Overall, the results indicate that eliglustat reduces liver volume to a statistically significantly greater extent than placebo, but the difference between the two treatments is of doubtful clinical significance.

#### 6.1.1.15.3. Platelet count

The LS mean percentage increase in platelet count from Baseline to Week 39 was 32% in the eliglustat group compared with a decrease of 9% in the placebo group, resulting in a significant treatment difference of 41% (95% CI: 24, 58),  $p < 0.0001$ . The results in the PPS and the 39 Week Completer Set were consistent with the results in the FAS. The results in the FAS are summarised below in Table 31.

**Table 31: ENGAGE - Percentage change in platelet count (109/L) from baseline to Week 39; FAS.**

Time Point / Change	Statistic	Eliglustat (N=20)	Placebo (N=20)	Treatment Difference (Eliglustat-Placebo)
Baseline	n	20	20	NA
	Mean (SD)	75.05 (14.095)	78.48 (22.611)	NA
	Median	78.75	76.25	NA
	Min, Max	50.5, 98.5	50.5, 128.5	NA
Week 39	n	20	20	NA
	Mean (SD)	98.95 (28.372)	71.50 (25.157)	NA
	Median	101.50	66.25	NA
	Min, Max	40.0, 161.0	36.0, 125.5	NA
% Change from Baseline to Week 39	Mean (SD)	31.71 (31.801)	-8.77 (19.187)	NA
	Median	29.17	-7.88	NA
	Min, Max	-21.57, 87.16	-51.74, 29.80	NA
	LS Mean (SEM)	32.00 (5.95)	-9.06 (5.95)	41.06 (8.44)
	95% CI	19.94, 44.06	-21.12, 3.00	23.95, 58.17
	p-value	NA	NA	<0.0001

Notes as for Table 28, above.

All 40 patients had low platelet counts at Baseline, and the majority (93%) were classified with moderate-to-severe thrombocytopenia. Mean platelet counts at Baseline were similar for the eliglustat (75.05 x10<sup>9</sup>L) and placebo (78.48 x10<sup>9</sup>L) groups. The eliglustat group achieved increases in platelet counts from Week 4 through Week 39, while platelet counts in the placebo group decreased during this same time period.

Of the 19 patients in the eliglustat group with data at Week 39, 16 (84%) had an increase in platelet count from Baseline to Week 39, ranging from 2.47% to 87.16%. Of the 20 patients in the placebo group with data at Week 39, 15 (75%) had a decreases in platelet count at Week 39, ranging from -4.66% to -51.74%.

**Comment:** The short term (12 to 24 months) therapeutic goal for percentage increase from Baseline in the platelet count defined in the SAP was  $\geq 50\%$ . At Week 39, 25% (n=5) of patients in the eliglustat group had increases in the platelet count  $\geq 50\%$  compared with no patients in the placebo group. Overall, the results of this study



suggest that the statistically significant increase in platelet count following 39 weeks of treatment with eliglustat, relative to placebo, is clinically meaningful.

#### **6.1.1.16. Tertiary efficacy endpoints**

- Chitotriosidase and CCL18 were measured as biomarkers of GD1 disease activity. The percentage reduction from Baseline to Week 39 in mean normalised chitotriosidase levels was greater in the eliglustat group (-39%) compared with the placebo group (-5%), and the difference between the two groups was statistically significant (-44.4% [SEM = 9.68],  $p < 0.0001$ ). The summary results for CCL18 were not included in the CSR due to unexpected and inconsistent results for plasma levels.
- Bone marrow burden (BMB) scores, which indicate the degree of bone marrow infiltration with Gaucher cells, decreased significantly from Baseline to Week 39 in the eliglustat group compared with placebo. The BMB score was calculated by summing 6 MRI-based scores for the lumbar spine (T1-weighted, T2-weighted, and infiltration pattern) and femur (T1-weighted, T2-weighted, and sites of involvement). From Baseline to Week 39, the LS mean total BMB score decreased by -1.1 in the eliglustat group and was unchanged in the placebo group, resulting in a statistically significant treatment difference of -1.1 ( $p = 0.0021$ ). Baseline total BMB scores indicated that bone marrow infiltration was marked to severe (score = 9 to 16) in 16 (80%) patients in the eliglustat group and 15 (75%) placebo patients, with the remaining patients having moderate bone marrow infiltration (score = 5 to 8). In the eliglustat group ( $n = 20$ ), the mean (SD) total BMB score decreased from 10.9 (2.62) at Baseline to 9.8 (2.55) at Week 39, and reflected improvements in bone marrow infiltration in both the femur and spine. In contrast, in the placebo group ( $n = 20$ ) the mean (SD) total BMB score was 9.8 (2.75) at Baseline and 9.8 (2.84) at Week 39, indicating no change in bone marrow infiltration over 39 weeks of treatment.
- Bone mineral density (BMD) was assessed by dual energy X-Ray absorptiometry (DXA). Evaluation of percentage changes in total BMD and absolute changes in T-scores and Z-scores in the lumbar spine suggested a positive trend of eliglustat over placebo during the 39 week primary analysis period. However, the absolute change in total spine Z-score from Baseline to Week 39 for eliglustat, relative to placebo, was not statistically significant (LS mean treatment difference = 0.2,  $p = 0.0604$ ). No positive trends were apparent for the worst effected femur at Baseline, and no changes in the femur were statistically significant. Study eligibility criteria excluded patients with symptomatic bone disease. Consequently, patients in this study had comparatively little bone involvement at Baseline relative to the prevalence and severity of skeletal manifestations in the broader Gaucher disease population.
- Gaucher assessments, which included an assessment of the patient's current mobility status, the severity of bone pain within the preceding 4 weeks, and the occurrence of any bone crises since the previous visit, were unremarkable for the vast majority of patients at all time points. Of the 40 patients, 37 (93%) had unrestricted mobility at each time point (Baseline, Week 26, and Week 39). One (1) patient in the eliglustat group reported an improvement in mobility from Baseline to Week 39. No patient required a wheelchair or was bedridden at any time point. The majority of patients had no bone pain or very mild-to-moderate bone pain at each time point. No patient reported severe or extreme bone pain at any time point. Bone crises were not reported for any patient at Baseline (as per the study eligibility criteria). One patient in the placebo group reported a bone crisis at the Week 39 visit.
- With the exception of a trend toward improvement in physical functioning, eliglustat did not have a marked effect on health-related quality of life during the 39 week primary analysis period.

#### 6.1.1.16.1. *Exploratory efficacy endpoints*

The study included a number of exploratory efficacy endpoints including Gaucher Disease Severity (DS3) Total Score, which measures disease burden in GD1 patients across 3 domains (bone, hematologic, visceral), the percentage of patients meeting therapeutic goals, GD related exploratory biomarkers, and PK/efficacy relationships. The results relating to the main biomarkers and the PK/efficacy data have been reviewed in the PD section of this CER. The exploratory data relating to the percentage of patients meeting therapeutic goals based on the pre-specified definitions provided in the SAP have been discussed above for each of the primary and secondary efficacy endpoints. The percentage of patients reaching short term (12 to 24 months) are summarised using criteria relating to Cerezyme from the published literature.<sup>5, 6</sup> No patients in either treatment group met all 4 therapeutic goals at Week 39, but more patients in the eliglustat group achieved, 2 or 3 goals compared with placebo.

The exploratory efficacy endpoint of mean DS3 score was statistically significantly reduced from Baseline to Week 39 to a greater extent in the eliglustat group (-0.46) compared with the placebo group (-0.06), with the LS mean treatment difference being statistically significant ( $p=0.0452$ ). The mean Total DS3 scores at Week 39 were 4.24 for eliglustat and 4.37 for placebo, and it is unlikely that the difference between these scores are clinically meaningful given that the maximum possible total DS3 score is 19. In addition, while the reduction in score from Baseline to Week 39 for two of three domains contributing to the total DS3 score (bone and visceral) were greater in the eliglustat group compared with the placebo group the numerical differences were small and unlikely to be clinically significant. There was no difference between the two treatment groups as regards the score for change from Baseline to Week 39 for the haematologic domain of the DS3.

### 6.1.2. **ENCORE (GZGD02607)**

#### 6.1.2.1. *Study design, objectives, locations and dates*

ENCORE was a Phase III, multi-national, multi-centre, open-label, active comparator study designed to evaluate the efficacy and safety of eliglustat in patients with GD1 who had been treated with enzyme replacement therapy (ERT) for at least 3 years and had reached therapeutic goals.

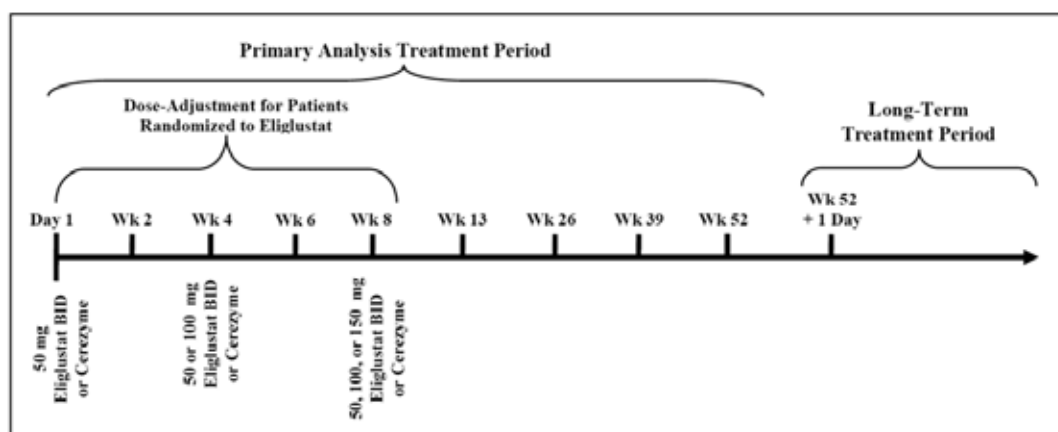
The primary objective of the study was to assess the efficacy and safety of eliglustat compared with Cerezyme (imiglucerase) after 52 weeks of treatment in patients with GD1 who had reached therapeutic goals with ERT.

The secondary objective was to demonstrate that, in patients with GD1 who had reached therapeutic goals with ERT, the majority of patients switched to eliglustat remained stable after 52 weeks treatment.

The tertiary objective of the study was to evaluate the long-term efficacy, safety, and PKs of eliglustat in patients with GD1 who had reached therapeutic goals.

The study included a screening period (Days -45 to -1), a primary analysis treatment period (Day 1 to Week 52), a long-term treatment period (post-Week 52 through study completion), and a safety follow-up period (30 to 37 days after the last dose of study medication). Patients who met all eligibility criteria were randomized to receive treatment with eliglustat or Cerezyme during the 52-week primary analysis period. After Week 52, all patients who remained in the study were eligible to receive open-label eliglustat in the long-term treatment period. The total duration of participation for each patient was planned to last for at least 104 weeks, and participation could continue for up to 5.5 years. The study is outlined schematically in Figure 8, below.



**Figure 8: ENCORE - Study time-line.**

The study was conducted at a total of 39 sites in Latin America, the United States (US), Canada, Australia, the Middle East and Europe, with 34 of these sites randomizing at least 1 eligible patient. The coordinating investigator is located at Addenbrooke's Hospital, Cambridge, UK. The first patient consented on 15 September 2009, and the last patient's visit for the primary analysis period (52 weeks) occurred on 9 November 2012 (corresponding to the data cut-off point for the primary analysis period). The CSR was dated 8 July 2013.

The study was conducted in accordance with Good Clinical Practice (GCP) as defined by the International Conference on Harmonisation (ICH), the principles defined in the Declaration of Helsinki and amendments, and all applicable national and international laws. The protocol was reviewed and approved by each site specific institutional review board (IRB) or independent ethics committee (IEC) prior to initiating treatment at the site. The study was sponsored by Genzyme, a Sanofi Company, USA.

**Comment:** The study was open-label in design. Consequently, the study is subject to the well known biases associated with such designs. The sponsor stated that '[s]ince Cerezyme and eliglustat have different routes of administration (intravenous and oral, respectively), a double-dummy design with placebo capsules and infusions would have required patients to take 2 treatments for 52 weeks (oral capsules bd and intravenous (IV) infusions q2w). This design would have placed an undue burden on study patients and dissuaded participation in the setting of other marketed treatment options. All four components of the composite endpoint, spleen and liver volumes and haemoglobin and platelet levels, are objective measurements. Finally, a double-dummy design would not have permitted an important patient-reported assessment of treatment preference that is, oral versus intravenous treatment. While an open-label design has limitations from potential patient and/or physician bias, the Sponsor concluded that successful completion of the study would require minimizing study burden to patients'. The sponsor's rationale for the open-label design of this study is considered to be acceptable.

#### 6.1.2.2. Inclusion and exclusion criteria

The study included patients aged  $\geq 18$  years of age with a diagnosis of GD1 confirmed by a documented deficiency of  $\beta$  glucosidase activity by enzyme assay. In addition, patients were required to have received treatment with ERT for at least 3 years, and for at least 6 of the 9 months prior to randomisation were required to have received a total monthly dose of 30 to 130 U/kg of ERT. Patients were also required to have reached GD therapeutic goals prior to randomisation defined as: (a) no bone crisis and free of symptomatic bone disease; (b) mean haemoglobin level  $\geq 11$  g/dL if female and  $\geq 12$  g/dL if male at the time of screening; and (c) mean platelet count  $\geq 100,000$  mm<sup>3</sup> at the time of screening. Furthermore, spleen volume was required to be  $< 10$  x normal or total splenectomy was required (provided that it had occurred  $> 3$  years prior to randomisation). The liver volume was required to be  $< 1.5$  x normal.

The inclusion and exclusion criteria are considered to be appropriate. The study also included criteria relating to removal of patients from treatment of the study. Patients who had prematurely withdrawn from the study and had received at least one dose of study treatment were asked to return to the study site for follow-up assessment.

### **6.1.2.3. Study treatments**

The study treatments were undertaken using eliglustat tartrate capsules (50, 100, 150 mg) and Cerezyme IV preparations labelled according to each participating country's specific regulatory requirements.

#### **6.1.2.3.1. Primary analysis period (through Week 52)**

On Day 1 of the study (within 7 days after randomisation), patients randomized to eliglustat received 50 mg bd. Dose adjustment could occur at Week 4 based on eliglustat plasma trough concentration at Week 2. For patients with eliglustat plasma trough concentrations < 5 ng/mL at Week 2, the dose was increased at Week 4 to 100 mg bd. Patients with eliglustat plasma trough concentrations  $\geq$  5 ng/mL continued to receive 50 mg bd. For patients with eliglustat plasma trough concentrations < 5 ng/mL at Week 6, the dose was increased at Week 8 to 100 mg bd for those on 50 mg bd and 150 mg bd for those on 100 mg bd, and the increased dose was maintained through Week 52. For patients with eliglustat plasma trough concentrations  $\geq$  5 ng/mL at Week 6, the dose was maintained at 50 mg bd or 100 mg bd through Week 52.

#### **6.1.2.3.2. Long-term treatment period**

In the long-term treatment period all patients were treated with open-label eliglustat. Patients originally randomized to eliglustat in the primary analysis period continued to receive the eliglustat dose based on their eliglustat plasma trough concentration at Week 6. At the Week 52 + 1 Day visit, patients originally randomized to Cerezyme received 50 mg of eliglustat bd. Dose adjustments could occur at Week 56 based on plasma trough and 2-hour (peak) concentrations of eliglustat 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  $\geq$  5 ng/mL continued to receive 50 mg bd.

Plasma trough and peak concentrations of eliglustat were also collected at Week 58. For patients with an eliglustat plasma trough concentration of < 5 ng/mL at Week 58, the 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  $\geq$  5 ng/mL at Week 58 continued on the same dose of eliglustat.

#### **6.1.2.3.3. Dose modifications bases on peak eliglustat plasma concentrations $\geq$ 150 ng/mL**

Following a similar amendment to the ENCORE protocol (dated 6 July 2011) to that for ENGAGE. In either period of the study any patient with a peak eliglustat plasma concentration  $\geq$  150 ng/mL would have been temporarily discontinued from treatment and, if applicable, removed from the primary analysis period. Following completion of additional protocol specified evaluations, the patient may have been permitted to initiate/resume open-label eliglustat, either at a reduced dose or at the dose prior to treatment discontinuation, depending on the peak plasma concentration and the treatment period in which it was reported, any concurrent safety findings, and any adjustments of concomitant medications. Subsequent dose decreases or increases would have been permitted based on continued evaluation of the patient's data, in consultation with the sponsor.

During the long-term treatment period, dose decreases were also permitted in the event of poor tolerability, and were managed in consultation with the Sponsor and, as appropriate, the DMC. The lowest dose allowed in this study (either period) was 50 mg qd, and the highest dose allowed (either period) was 150 mg bd.

#### 6.1.2.3.4. *Change in treatment due to clinical decline on eliglustat during the study*

During the course of the study, if an eliglustat patient experienced a decline (that is, deterioration) in GD in at least 1 of the following specified criteria then switching to Cerezyme q2w as study drug was permitted: (a) haemoglobin fell to < 8 g/dL and remained < 8 g/dL when testing was repeated in approximately 2 weeks; (b) platelet count fell to < 45,000/mm<sup>3</sup> and remained < 45,000/mm<sup>3</sup> when testing was repeated in approximately 2 weeks or if clinically significant bleeding occurred that was considered by the investigator to be due to the low platelet count; and (c) any other decline in GD status which, in the opinion of the investigator, warranted a return to ERT (Cerezyme).

Patients who switched from eliglustat to Cerezyme q2w continued to be followed in the study, and their data were collected on the eCRF. These patients were followed in the study until objective measures of disease activity that had resulted in the switch to Cerezyme returned to baseline levels (for example, platelet count, spleen volume), or no additional occurrence or further worsening of disease activity occurred (for example, bone crisis, bone fracture, worsening bone pain). Once the parameters that resulted in the switch back to Cerezyme were in an acceptable range, the patient was discontinued from the study and no longer received study supplied Cerezyme.

#### 6.1.2.3.5. *Prior medications*

Information on all prior medications and therapies taken within 30 days prior to informed consent was recorded in the eCRF. Prohibited prior medications were specified in the protocol and the exclusion criteria. Grapefruit, grapefruit juice, and grapefruit products were not permitted at any time during the primary analysis period. Restrictions and prohibitions on prior medications are consistent with those discussed for ENGAGE.

#### 6.1.2.3.6. *Concomitant medications*

Information on all concomitant medications (defined as all prescription and non-prescription medications, including herbal supplements) taken by the patient from the time of informed consent through the final follow-up assessment, including all premedication administered prior to Cerezyme infusions in the primary analysis period, was recorded on the patient's eCRF.

#### 6.1.2.4. *Efficacy variables*

The main efficacy variables were:

- Platelet count and haemoglobin level: Whole blood samples were collected for local laboratory determination of platelet count and haemoglobin level. At selected time-points, 2 blood samples were collected at least 24 hours apart, and the average of the 2 platelet counts was used in the study analyses. In the event that a patient was missing 1 of the 2 assessments at a particular timepoint, then the single assessment was used in the analysis.
- Spleen MN volume and Liver MN volume: MRI scans without contrast agent were obtained from patients who had been fasting for at least 6 hours prior to the procedure. Central readers evaluated the digital images to determine spleen and liver volumes and calculate MN using the following formulae: spleen MN = volume in CC/weight in kg \* 2; liver MN = volume in CC/weight in kg \* 2. The assessment prior to randomisation (Screening) was reviewed by 1 central reader, and was used as the Baseline in the analyses. The assessments at Week 26 and Week 52 were each reviewed by 2 central readers. In the event of a > 5% discrepancy between readers, the value that was closest to that of an adjudicating third reader was used in the analyses. If the spleen or liver volume (in MN) increased > 30% above Baseline values, a repeat measurement was obtained within approximately 4 weeks, and this repeat measurement was used in the analyses.

### **6.1.2.5. Efficacy endpoints**

#### **6.1.2.5.1. Primary efficacy endpoint**

The primary efficacy endpoint was the percentage of patients who remained stable for 52 weeks (the primary analysis period) assessed for both treatment groups separately along with the difference between the 2 treatment groups. The primary efficacy criteria for success included stable haematologic parameters and organ volumes. Stable haematological parameters were defined as haemoglobin level not showing a decrease > 1.5 g/dL from Baseline, AND platelet count not decreasing > 25% from Baseline. Stable organ volume was defined as spleen volume (MN) not increasing > 25% from Baseline, if applicable, AND liver volume (MN) not increasing > 20% from Baseline. For a patient to be considered to have demonstrated a clinically meaningful response to treatment, the haematological parameters must have remained stable, and the organ volumes must have remained stable. Instances of failure to meet the primary endpoint were required to be reviewed and confirmed by a blinded Independent Adjudication Board (IAB).

**Comment:** The primary efficacy endpoint was a composite endpoint requiring all 4 components to meet pre-defined criteria. The sponsor considered that the composite efficacy endpoint was more sensitive than a single component efficacy endpoint. The sponsor stated that published data indicate that a composite endpoint is twice as sensitive in detecting instability as platelet count, which had been used in a maintenance study comparing the effects of miglustat and Cerezyme.<sup>7</sup> The FDA indicated to the sponsor that the efficacy endpoint for its evaluation will be the percentage change in spleen volume from Baseline to Week 52.

#### **6.1.2.5.2. Secondary efficacy endpoints**

The secondary efficacy endpoints included: Total T- and Z-scores for bone mineral density (DXA) of femur and lumbar spine; haemoglobin level; platelet count; spleen volume (MN); and liver volume (MN).

#### **6.1.2.5.3. Tertiary efficacy endpoints**

The tertiary efficacy endpoints included: Biomarkers (CCL18 and chitotriosidase); bone disease assessments (X-ray, MRI and bone marrow burden score); Gaucher assessments (mobility, bone crisis, and bone pain); Quality of Life (QOL) (Brief Pain Inventory [BPI], Fatigue Severity Score [FSS], Short Form-36 Health Survey [SF-36]); and treatment preference (oral versus IV therapy).

#### **6.1.2.5.4. Exploratory efficacy endpoints**

The main exploratory endpoints included Gaucher disease Severity Score System (DS3) and the percentage changes from Baseline in investigational biomarkers, including GL-1, GM3, ceramide, hsCRP, apo-B-100, sphingomyelin, and MIP-1 $\beta$ .

### **6.1.2.6. Randomisation and blinding methods**

Eligible patients underwent a stratified randomisation into 1 of 2 groups based on the q2w equivalent of the patient's ERT dose prior to any unanticipated treatment interruption, dose reduction, or regime change resulting from the temporary unavailability of Cerezyme which occurred in the study period (that is, <35 U/kg/q2w or  $\geq$ 35 U/kg/q2w). Stratified patients were randomized in a 2:1 ratio to receive eliglustat or Cerezyme, respectively, for 52 weeks (the primary analysis treatment period). The actual method used to conduct the randomisation could not be identified in the submission.

This was an open-label study. However, selected efficacy and safety evaluations were performed by external central readers who were blinded to treatment assignment. These blinded evaluations included organ volume and bone imaging data, ECG and Holter monitor data, and

nerve conduction data. The IAB, who were blinded to patient randomisation, reviewed and confirmed instances of failure to meet the primary efficacy endpoint.

#### **6.1.2.7. Analysis populations**

- Full Analysis Set (FAS): The FAS included all patients who signed informed consent and received at least 1 dose of study drug. The FAS is equivalent to the intent-to-treat (ITT) population referred to in the protocol.
- Per Protocol Set (PPS): The PPS included patients in the FAS who were at least 80% compliant with treatment during the primary analysis period, had no major protocol deviations expected to interfere with the assessment of efficacy as defined in the SAP, and did not exhibit haematological decline as a result of medically determined aetiologies other than GD. Eliglustat patients who transitioned back to ERT (Cerezyme) due to a decline in GD were included in the PPS and were considered treatment failures regardless of their Week 52 assessments.
- Week 52 Completer Analysis Set: This analysis set includes patients in the FAS who completed 52 weeks of treatment and had complete assessments at both Baseline and Week 52.
- Safety Set: This analysis set included all patients who received at least 1 dose of study drug.
- Pharmacokinetic analysis set: This set included all patients who received at least 1 dose of eliglustat and had measurable drug concentrations.

#### **6.1.2.8. Sample size**

A sample size of 132 patients (88 eliglustat: 44 Cerezyme) was needed for this study to provide at least 105 evaluable patients in the PPS for analysis. The sample size of 132 in the PPS was based on expected stability rates of 95% for the Cerezyme treatment group (active comparator) and 85% for the eliglustat treatment group (test treatment). The sample size of 132 patients provides a power of 85% to detect a non-inferiority stability margin of 25%, at a one-sided significance level of 0.025, allowing for a non-evaluable/drop-out rate of 20%.

Additionally, a sample size of 132 patients would provide > 95% power to test the non-inferiority of eliglustat relative to Cerezyme for the percentage change in spleen volume at 52 weeks with a non-inferiority margin of 15%. This sample size and power calculation additionally assumes: (a) one-sided significance level of 0.025; (b) drop-out/non-evaluable rate of 20%; (c) treatment difference of 0% at 52 weeks in percentage changes from baseline in spleen volume (MN) between eliglustat treatment arm and the Cerezyme treatment arm; and (d) standard deviation (SD) of 15% at 52 weeks in percentage from baseline in spleen volume (MN) for eliglustat treatment arm and the Cerezyme treatment arms.

#### **6.1.2.9. Statistical methods**

##### **6.1.2.9.1. General**

The primary efficacy analysis of non-inferiority was in the PPS. For the FAS, 2 summaries of the primary efficacy endpoint were presented; one counted patients not completing 52 weeks of treatment as failures; and one included patients with complete data at both Baseline and Week 52.

The efficacy analyses were performed according to the final SAP, with the following major changes from the planned analyses: (a) addition of an FDA recommended efficacy endpoint of the percentage change in spleen volume (MN) from baseline to Week 52; (b) the per protocol population definition was amended to include patients who used prohibited medications; and (c) additional sensitivity analyses of the difference in proportions for the primary efficacy analysis were conducted.

### 6.1.2.9.2. Primary efficacy analysis

The percentage of patients remaining stable, including the exact 95% CI, was calculated at Week 52 for both the eliglustat and Cerezyme groups. The 95% exact CIs for the eliglustat and Cerezyme groups were also calculated for each of the 2 randomisation stratification groups.

The 95% CI for the difference between the eliglustat and Cerezyme groups was calculated as a weighted combination of the differences between the two groups within the 2 randomisation stratification groups. If the lower-bound of the 95% CI for the difference was within the non-inferiority margin of 25%, then eliglustat treatment was declared non-inferior to Cerezyme treatment. This analysis supported the primary objective of the study, which was to compare the efficacy of eliglustat and Cerezyme after 52 weeks treatment in maintaining stability in patients who had reached therapeutic goals with ERT.

In order to support the secondary objective of the study, if the lower bound of the 95% exact CI for the eliglustat group was > 50%, then eliglustat treatment was claimed to be successful in maintaining stability in the majority of patients after 52 weeks, irrespective of whether eliglustat was determined to be non-inferior to Cerezyme.

The FDA recommended efficacy endpoint was the percentage change in spleen volume (in MN) from baseline to Week 52. This endpoint was used to evaluate the non-inferiority of eliglustat compared with Cerezyme. The primary analysis of non-inferiority was in the PPS. Percentage changes in spleen volumes (MN) from Baseline to Week 52 were tested using an ANCOVA model that included treatment effect, randomisation stratum and baseline spleen volume. Natural logarithm differences were used. The difference, with two-sided 95% CI, in the percentage change in spleen volume (MN) between the eliglustat and Cerezyme groups was calculated. Eliglustat treatment was declared non-inferior to Cerezyme treatment if the lower-bound of the 95% CI for the difference in the percentage change in spleen volume (MN) was within the non-inferiority margin of 15%.

### 6.1.2.9.3. Secondary efficacy analyses

The secondary efficacy endpoints were summarised by randomisation strata and by treatment group at Baseline and at relevant study visits during the primary analysis period (52 weeks). In addition, absolute changes in total T- and Z-scores for femur and lumbar spine (DXA) parameters and haemoglobin levels (g/dL), percentage changes in platelet counts, percentage changes in liver volumes, and percentage changes in spleen volumes (MN) from Baseline to Week 52 were analysed.

These secondary efficacy endpoints were tested in the FAS and the PPS using an ANCOVA. In a sensitivity analysis, the data were ranked and the ANCOVA was performed on the ranked data. In either case, the ANCOVA included a treatment effect (eliglustat or Cerezyme), the baseline value for the parameter being analysed, and the stratification randomisation indicator (equivalent ERT dose < 35 U/kg/q2w or equivalent ERT dose ≥ 35 U/kg/q2w). Natural logarithm differences were used for the parameters that were analysed using percentage changes. The statistical tests were conducted at the 5% level of significance. The data obtained at the Week 52 assessment or the last available assessment in the case of early withdrawal/missing data were used for the Week 52 assessment for the FAS analysis. The subset of FAS patients with data at both Baseline and Week 52 were analysed in a similar manner. In addition to the analyses of continuous secondary efficacy endpoints, a binary (yes/no) composite endpoint involving stable and normal haematologic parameters and organ volumes was analysed in a similar manner as the primary efficacy endpoint.

**Comment:** No statistical adjustment was undertaken to account for multiple tests for the secondary efficacy endpoint analyses. Therefore, all secondary efficacy analyses should be considered to be exploratory rather than confirmatory.



#### 6.1.2.9.4. Tertiary and exploratory efficacy analyses

For each endpoint, descriptive statistics (continuous variables) or frequencies and percentages of outcomes (categorical variables) were summarised for each visit by treatment. The changes from Baseline in the tertiary and exploratory efficacy endpoints were summarised by treatment group, as appropriate.

#### 6.1.2.10. Participant flow

In total, 206 patients were screened at 39 study centres. In total, 160 screened patients were randomized in a 2:1 ratio to eliglustat (n=106) or Cerezyme (n=54), and 46 screened patients were not randomized. One (1) patient in the Cerezyme group was randomized but did not receive study treatment. One (1) patient in the eliglustat group switched to Cerezyme treatment and completed the 52 week primary analysis period. Two (2) patients in the eliglustat group and 1 patient in the Cerezyme group did not complete the primary analysis period due to AEs. The patient disposition is summarised in below in Table 32.

**Table 32: ENCORE - Summary of patient disposition; all randomized patients.**

	Eliglustat (N=106)	Cerezyme (N=54)	Total (N=160)
Randomized, n (%)	106 (100)	54 (100)	160 (100)
Treated, n (%)	106 (100)	53 (98)	159 (99)
Completed Week 52, n (%)	104 (98)	52 (96)	156 (98)
On Treatment	103 (97)	52 (96)	155 (97)
On Switched Treatment(Cerezyme)	1 (1)	0	1 (1)
Did Not Complete Week 52, n (%)	2 (2)	2 (4)	4 (3)
ADVERSE EVENT	2 (2)	1 (2)	3 (2)
NON-COMPLIANCE WITH STUDY DRUG	0	1 (2)	1 (1)
WITHDRAWAL BY SUBJECT	0	0	0
LOST TO FOLLOW-UP	0	0	0
DECLINE IN GAUCHER DISEASE	0	0	0
TRANSITION FROM ELIGLUSTAT TO CERAZYME	0	0	0
STUDY TERMINATED BY SPONSOR	0	0	0
OTHER	0	0	0

#### 6.1.2.11. Major protocol deviations

No patient was excluded from the FAS (n=159; eliglustat n=106, Cerezyme n=53) due to a protocol deviation. Protocol deviations included any change, divergence, or departure from the study design or procedures defined in the protocol. The deviations recorded most frequently during the study in both treatment groups included the occurrence and timing of visits/procedures not performed per protocol, intermittent drug non-compliance, and the use of a restricted concomitant medication.

Protocol deviations that resulted in exclusion from the PPS were pre-defined in the SAP. The PPS included 146 patients (99 in the eliglustat group, 47 in the Cerezyme group). Fourteen (14) all randomized patients were excluded from the PPS (7 [7%] in eliglustat group and 7 [13%] in the Cerezyme group). The reasons for exclusion of patients from the PPS (eliglustat versus Cerezyme) were: did not reach Week 52 (2 [2%] versus 1 [2%]); dosing compliance < 80% (2 [2%] versus 3 [6%]); mismatch between randomized dose stratum and actual pre-study Cerezyme dose (2 [2%] versus 2 [4%]); missing Baseline and/or Week 52 platelet count or haemoglobin value (1 [1%] versus 0%); and randomized but not dosed (0% versus 1 [2%]).

#### 6.1.2.12. Baseline data

The baseline demographic characteristics for the 146 patients (99 eliglustat, 47 Cerezyme) included in the PPS (primary efficacy analysis population) were summarised. For the total 146 patients, 64 (44%) were male and 82 (56%) were female, the mean age was 37.6 years (range: 18.1, 69.3 years), the mean BMI was 24.9 kg/m<sup>2</sup> (range: 16.8, 49.4 kg/m<sup>2</sup>), 136 (93%) were White, 8 (5%) were black or African American, 1 (1%) each was Asian or white/American Indian, 56 (38%) were in the prior ERT < 35 U/kg/q2w stratification group and 90 (62%) were

in the prior ERT  $\geq 35$  U/kg/q2w stratification group. The baseline demographic characteristics of both treatment groups were well balanced.

The baseline disease characteristics were well balanced between the two treatment groups. On average, patients had GD symptom onset at 14 years of age and were diagnosed with GD1 at 18 years of age. One or both of the common allelic mutations of the acid  $\beta$ -glucosidase gene (N370S, L444P) were present in 89% of patients in the PPS. Residual enzyme activity varied considerably (range: 0 to 9.9 nmol/hr/mg) but was, on average, similar between treatment groups (mean values of 1.18 nmol/hr/mg for eliglustat and 1.08 nmol/hr/mg for Cerezyme). Most patients in both groups were CYP2D6 EMs (77%), 12% were IMs, 4% were PMs, and 3% were URMs. Overall, 25% of study patients had undergone a total splenectomy, and 5% were homozygous for a null mutation in the chitotriosidase gene.

Patients entered the study with haematology values and organ volumes that met pre-specified therapeutic goals. At Baseline, the eliglustat and Cerezyme groups had mean (SD) spleen volumes of 3.23 (1.37) MN and 2.62 (1.08) MN, respectively; mean (SD) liver volumes of 0.95 (0.191) MN and 0.92 (0.162) MN, respectively; mean (SD) haemoglobin levels of 13.6 (1.25) g/dL and 13.8 (1.29) g/dL, respectively; and mean (SD) platelet counts of 207 (81)  $\times 10^9/L$  and 192 (57)  $\times 10^9/L$ , respectively.

As this study was conducted while commercial supplies of Cerezyme were limited, additional data were collected to ensure that patients were clinically stable on long-term ERT treatment and not experiencing acute fluctuations in disease status. GD history, as well as Cerezyme treatment history, was obtained for the following time-points: prior to initiation (ever) of ERT; prior to any unanticipated (starting June 2009) treatment interruption, dose reduction, or regimen change of Cerezyme; and during any unanticipated (starting June 2009) treatment interruption, dose reduction, or regimen change of Cerezyme. Comparing patient disease activity across these time points demonstrated that Cerezyme patients did not change substantially with respect to clinical symptoms, organ volumes and haematology parameters.

The medical history of patients included in this study was consistent with those expected for patients with GD1. Review of the tabulated summary of significant medical/surgical history findings in the PP indicates that the most common findings were gastrointestinal/hepatic conditions (66% in the eliglustat group, 51% in the Cerezyme group) followed by haemopoietic conditions (39% in the eliglustat group, 53% in the Cerezyme group).

Pre-treatment (prior) medications were reported to have been taken by 99% (157/159) of patients in the safety set, and there were no imbalances between the two treatment groups in the percentage of patients reporting prior medications or in the type or medications. In the PPS, all patients in both treatment groups had received prior treatment with Cerezyme, and the time on Cerezyme until randomisation were 9.8 years (range: 3.1, 18.2 years) in the eliglustat group and 10.2 (range: 3.2, 17.1 years). Current ERT therapy was Cerezyme in 77% of patients in the eliglustat group and 81% of patients in the placebo group, and the respective percentages of patients taking velaglucerase were 20% and 17%. The mean (SD) current ERT dose was 77.6 (34.16) U/kg/month in the eliglustat group and 78.9 (38.51) U/kg/month in the placebo group. History of unanticipated treatment interruption, dose reduction or regimen change of Cerezyme was reported in 72% of patients in the eliglustat group and 60% of patients in the placebo group. Transition from Cerezyme to another GD treatment was reported in 18% of patients in the eliglustat group (16% to velaglucerase, 2% to miglustat) and 13% of patient in the Cerezyme group (all to velaglucerase).

Concomitant medications (1 or more) were reported in 87% (139/159) of patients in the safety set in the primary analysis period (week 52), and there were no marked imbalances between the two treatment groups in the percentage of patients reporting prior medications or in the type or medications. Five (5) patients in the eliglustat group were reported to have received either strong or moderate inhibitors of CYP2D6, 2 patients were reported to have received



inducers of CYP3A4, and no patients were reported to have received either strong or moderate inhibitors of CYP3A4. The 5 eliglustat patients receiving either strong or moderate inhibitors of CYP2D6 were all receiving treatment for chronic pre-existing conditions (that is, depression, hypertension) and continuation of the same dosing regimen was allowed per protocol. Nine (9) of the eliglustat-treated patients were reported to have received a medication for more than 15 consecutive days with the potential to increase the QTc interval.

#### 6.1.2.13. Treatment compliance and extent of exposure

Patient compliance with the eliglustat treatment regimen was determined at each study site visit through counting and recording the number of remaining capsules. Patient compliance with Cerezyme infusions was determined at each site visit. In the safety set, 94% (101/106) of eliglustat patients had  $\geq 90\%$  compliance from Day 1 through Week 52 compared with 92% (49/53) of Cerezyme treated patients.

In the safety set, the mean (SD) total time on study treatment from Day 1 to Week 52 was 361.5 (24.28) days in the eliglustat group and 349.0 (36.44) days in the Cerezyme group. In the eliglustat group at the end of the primary analysis period, 20% (21/106) of patients were on 50 mg bd, 32% (34/106) of patients were on 100 mg bd, and 48% (51/106) were on 150 mg bd. The mean (SD) number of Cerezyme infusions per patient during the primary analysis period was 24.7 (3.3), which was consistent with the q2w dosing regimen employed in this study.

#### 6.1.2.14. Results for the primary efficacy outcome

##### 6.1.2.14.1. Composite endpoint

Eliglustat successfully met the pre-specified criteria to be declared non-inferior to Cerezyme in maintaining stability in patients with GD1. Stability as assessed by the composite efficacy endpoint was maintained after 52 weeks of treatment in 84.8% of patients in the eliglustat group and 93.6% of patients in the Cerezyme group (see Table 33, below). Non-inferiority was established as the lower-bound of the 95% CI for the difference between treatments (-17.6%) was within the pre-specified non-inferiority margin of 25%. The lower bound of the 95% CI for the difference between treatments (-17.6%) was also within the 20% non-inferiority margin suggested by the European Medicines Agency (EMA). In addition, the lower bound of the 95% exact CI for the eliglustat group (76.2%) supports the claim that the majority of eliglustat-treated patients maintained stability after 52 weeks of treatment as it was greater than 50%.

**Table 33: ENCORE - Proportion of patients who remained stable for 52 weeks; composite endpoint in the PPS.**

Variable	Eliglustat (N=99)	Cerezyme (N=47)
Patients Stable for 52 Weeks, n (%)	83 (83.8)	44 (93.6)
Difference in Percentage Stable (Eliglustat-Cerezyme), %	-9.8	
95% Agresti and Caffo Adjusted CI on Difference in Percentage Stable	(-18.6, 3.3)	
Exact 95% CI on Percentage Stable	(75.1, 90.5)	(82.5, 98.7)

Eighteen (18) patients (15/99 [15.2%] eliglustat and 3/47 [6.4%] Cerezyme) did not meet the composite endpoint for stability at Week 52. One (1) eliglustat patient failed to remain stable in 2 clinical parameters (that is, spleen volume and platelet count), while the remaining 17 patients failed to remain stable in 1 of the clinical parameters. No baseline demographic or GD characteristics were consistently present in the patients that failed to meet the composite endpoint. Overall, the patient age in this group ranged from 18 to 62 years and 56% (10/19) were female. In the eliglustat group not meeting the composite stability endpoint at Week 52, there was a similar distribution of patients with average eliglustat trough plasma

concentrations <5 ng/mL (n=7) and ≥ 5 ng/mL (n=8) and in the number of splenectomized patients with and without (n=7).

The proportion of patients meeting the criteria for stability in the individual components of the composite endpoint is summarised below in Table 34. To meet the composite endpoint for stability, a patient was required to remain stable in all 4 parameters. Overall, greater than 92% of patients in both treatment groups met the stability criteria for each individual component of the composite endpoint: 92.9% to 96.0% for eliglustat versus 93.6% to 100% for Cerezyme.

**Table 34: ENCORE - Proportion of patients meeting primary endpoint stability criteria at Week 52; PPS.**

Variable	Eliglustat (N=99)	Cerezyme (N=47)
Patients Meeting Hemoglobin Criteria, n (%) Exact 95% CI	94 (94.9) (0.886, 0.983)	47 (100.0) -
Patients Meeting Platelets Criteria, n (%) Exact 95% CI	92 (92.9) (0.860, 0.971)	47 (100.0) -
Patients Meeting Spleen Volume Criteria, n (%)* Exact 95% CI	67 (94.4) (0.862, 0.984)	39 (100.0) -
Patients Meeting Liver Volume Criteria, n (%) Exact 95% CI	95 (96.0) (0.900, 0.989)	44 (93.6) (0.825, 0.987)

Note: \* Patient percentages are based on the total number of non-splenectomized patients in each treatment group. Stability criteria: haemoglobin did not decrease > 1.5 g/dL from Baseline; platelet count did not decrease > 25% from Baseline; spleen volume (MN) did not increase > 25% from baseline (not applicable for splenectomized patients); liver volume (MN) did not increase > 20% from Baseline.

**Comment:** Based on the composite endpoint analysis at Week 52 in the PPS, eliglustat was non-inferior to Cerezyme as regards maintenance of GD stability based on the primary composite efficacy endpoint of haemoglobin level, platelet count, spleen volume (MN) and liver volume (MN). The proportion of patients meeting the stability criteria for haemoglobin level, platelet count, and spleen volume was greater in the Cerezyme group than in the eliglustat group, while the reverse was seen for stability criterion of liver volume. In each treatment group, the proportion of patients meeting the composite stability efficacy endpoint at Week 52 was similar in patients stratified on the basis of pre-study ERT dose (that is, < 35 versus ≥ 35 U/kg/q2w). The results for the non-inferiority analysis in the FAS were consistent with the primary analysis in the PPS.

#### 6.1.2.14.2. Percentage change in spleen volume (FDA recommended efficacy endpoint)

The least squares (LS) mean percentage change in spleen volume (MN) from Baseline to Week 52 in the eliglustat group was -6.05% compared with -3.22% in the Cerezyme group (see Table 35, below). Eliglustat was declared non-inferior to Cerezyme as the lower-bound of the 95% CI for the difference was within the FDA recommended non-inferiority margin of 15%.

**Table 35: Values and percentage change in spleen volume (MN) from Baseline to Week 52; PPS.**

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 (1.39)	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)	-6.07 (14.35)	-3.01 (10.50)	--
	Median	-6.65	-5.20	--
	Min, Max	-48.7, 31.8	-22.1, 20.1	--
	LS Mean (SEM)	-5.96 (1.59)	-3.21(2.15)	-2.75 (2.71)
	95% CI	(-9.12, -2.80)	(-7.47, 1.06)	(-8.12, 2.62)
	p-value	NA	NA	0.3118

Note: Percentage changes are summarised only for patients who have both data at Baseline and the specified time point. Baseline refers to last assessment prior to first study dose/infusion. Estimates are based on an ANCOVA model that includes treatment group, the baseline value for the parameter being analysed, and the stratification randomisation indicator. Eliglustat Patient [information redacted] who returned to Cerezyme is excluded from the analysis.

### 6.1.3. Results for the secondary endpoint

#### 6.1.3.1. Haemoglobin level

Haemoglobin levels were normal at baseline in both treatment groups, with mean values of 13.6 g/dL (range: 11.1, 17.3) in patients in the eliglustat group and 13.8 g/dL (range: 11.2 to 16.0) in the Cerezyme group. At Week 52 the proportion of patients meeting the stability criteria for haemoglobin level (decrease not > 1.5 g/dL) was 95% and 100% for eliglustat and Cerezyme, respectively (see Table 35, above). However, there was a statistically significant increase in haemoglobin observed following 52 weeks of treatment with Cerezyme, relative to eliglustat. In the PPS, the LS mean absolute change in haemoglobin from Baseline to Week 52 was -0.22 g/dL for the eliglustat treatment group compared with 0.05 g/dL for the Cerezyme group, resulting in a significant difference of -0.28 g/dL ([95% CI: -0.52, -0.03], p=0.0253). However, the lower bound of the 95% CI of this difference (-0.52 g/dL) suggest that the difference between the two treatment in haemoglobin levels is not clinically significant.

#### 6.1.3.2. Platelet count

Platelet counts were similar at baseline in both treatment groups, with mean values of 206.8 x 10<sup>9</sup>/L (range: 100.5 to 511.0 x 10<sup>9</sup>/L) in patients in the eliglustat group and 192.3 x 10<sup>9</sup>/L (range: 102.0 to 339.5 x 10<sup>9</sup>/L) in patients in the Cerezyme group. At Week 52, the proportion of patients meeting the stability criteria for platelet counts (decrease from Baseline not > 25%) was 92.9% for the eliglustat group and 100% and Cerezyme group. There was no statistically significant difference between the two treatment groups in mean percentage change from baseline in platelet count after 52 weeks treatment.

#### 6.1.3.3. Liver volume:

Most patients had normal liver volumes at Baseline, with mean liver volumes of 0.95 MN (range: 0.5, 1.5) in the eliglustat group and 0.91 MN (range: 0.6, 1.3) in the Cerezyme group. At Week 52 mean liver volumes were essentially unchanged from baseline (0.96 and 0.94 MN for the eliglustat and Cerezyme groups, respectively). At Week 52, the proportion of patients meeting

the stability criteria for liver volume (increase from Baseline not > 20%) was 96.0% in the eliglustat group and 93.6% in the Cerezyme group.

#### **6.1.3.4. Composite secondary efficacy endpoint**

In addition to the continuous secondary efficacy endpoints, a binary (yes/no) composite endpoint involving stable and 'normal' haematological parameters and organ volumes was analysed in a similar manner to the primary efficacy endpoint. Stable and 'normal' haematological parameters were defined as: haemoglobin level remains  $\geq 11$  g/dL if female or  $\geq 12$  g/dL if male OR if haemoglobin level falls below these levels the decrease is not > 1.5 g/L from Baseline; AND the platelet count remains  $\geq 100,000/\text{mm}^3$  OR if the count falls below this number the decrease is not > 25% from Baseline. Stable organ volumes were defined as: spleen volume (MN) does not decrease > 25% from baseline, if applicable; AND liver volume (MN) does not decrease > 20% from Baseline. At 52 Weeks, 91/99 patients in the eliglustat group were stable and normal (91.9% [95% CI: 84.7, 96.4]) compared with 44/47 patients in the Cerezyme group (93.6% [95% CI: 82.5, 98.7]).

#### **6.1.3.5. Bone mineral density (DXA)**

Study eligibility criteria required a minimum of 3 years of treatment with ERT and excluded patients with symptomatic bone disease (for example, bone pain attributable to osteonecrosis and/or pathological fractures) within the year prior to study entry. BMD was normal for the vast majority of patients in both treatment groups at study entry, as measured by total BMD, T-scores (peak density) and Z-scores (age-adjusted density) for the total lumbar spine and total femur. Normal BMD was maintained for the majority of patients following 52 weeks of treatment in the primary analysis period (52 weeks), with both eliglustat and Cerezyme. There was no significant difference in mean change from baseline between the two treatments.

#### **6.1.4. Tertiary and exploratory efficacy endpoints**

Minimal differences between groups were observed after 52 weeks of treatment with respect to Bone Marrow Burden Score, Gaucher Disease Severity Score, Gaucher assessments (mobility, bone pain, bone crises), quality of life questionnaires (pain, BPI; fatigue, FSS; and general health, SF-36) and various biomarkers (plasma chitotriosidase activity and ceramide, C-reactive protein, apo-B-100, MIP-1 $\beta$  and sphingomyelin concentrations). Substantial reductions in plasma concentrations of GL-1 and GM3 with eliglustat, but not with Cerezyme, are consistent with eliglustat's mechanism of action as a substrate reduction therapy that inhibits glucosylceramide synthase. Following 52 weeks of treatment, eliglustat patients confirmed preference for an oral treatment with reasons given for the preference including: more convenient, taken at home, given by tablets, and felt better after treatment.

### **6.2. Supportive efficacy study**

#### **6.2.1. Supportive Phase II study (GZGD00304)**

##### **6.2.1.1. Design, objectives, locations and date**

The submission included one, supportive, Phase II, open-label, multi-national, multi-centre study in patients with GD1 [GZGD00304]. This study was the first clinical study with eliglustat in the target population. The study was conducted at 7 sites in 5 countries (Russia, Argentina, US, Israel, Mexico). The data of first patient consent was 16 June 2006 and the study report was dated 28 September 2012. At the date of data cut-off for the report (16 December 2011), all patients remaining in the study were in their fifth year of treatment. The study was conducted in accordance with the principles of Good Clinical Practice (GCP). The study was sponsored by Genzyme Corporation, a Sanofi Company, USA.

The primary objective of this study was to evaluate the efficacy, safety, and PK effects of eliglustat administered at doses of 50 mg bd or 100 mg bd to patients with GD1 for 52 weeks.

The secondary objective was to determine the long-term efficacy, safety, and PK effects of eliglustat, at doses of 50, 100, or 150 mg bd, administered from approximately Week 54 through study completion.

#### **6.2.1.2. Inclusion and exclusion criteria**

The main inclusion criteria are: (1) aged 18 to 65 years at enrollment, willing and able to provide written informed consent; (2) a diagnosis of GD1 and a documented deficiency of acid  $\beta$ -glucosidase (glucocerebrosidase) activity by enzyme assay; (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, or 8.0 to 11.0 g/dL if male, platelet count 45,000 to 100,000/mm<sup>3</sup>, and splenomegaly (MRI or spiral CT) defined as spleen volume  $\geq$  10 times normal; (4) consent to provide a blood sample for genotyping for GD, chitotriosidase, and genetic assessment of cytochrome P450 (for example, cytochrome P450 2D6 [CYP2D6] and other isoenzymes); (6) males consent to reliable method of birth control from screening through 30 day study follow-up; (7) females have negative pregnancy child-bearing potential must use a reliable form of contraception for the same period as male patients; (8) weight between 50 and 120 kg at enrollment.

The main exclusion criteria were: (1) partial or total splenectomy; (2) haemoglobin level  $<$  8.0 g/dL or platelet count  $<$  45,000/mm<sup>3</sup>; (3) treatment with miglustat within 12 months prior to enrollment; (4) ERT or corticosteroids for treatment of GD within 12 months prior to enrollment; (5) treatment with bisphosphonates within 3 months prior to enrollment; (6) evidence of GD with neurologic or pulmonary involvement; (7) documentation of new pathological bone involvement; (8) transfusion dependent; (9) anaemia due to causes other than GD; (10) previous radiation treatment; (11) prior bleeding varices or liver infarction; (12) clinically significant disease other than GD; (13) cardiac functional and/or anatomical abnormalities or clinically significant ECG or ECHO findings at screening; (14) positive for HIV antibody, Hepatitis C antibody, or Hepatitis B surface antigen positive; (15) received an investigational product with 30 days prior to enrollment; (16) scheduled for hospitalization, including elective surgery, during the study; (17) history of cancer; (18) pregnant or lactating; and (19) received any medication within 30 days prior to enrollment that may induce or inhibit CYP2D6, or cause QT interval prolongation.

#### **6.2.1.3. Study treatment**

The study comprised a screening period (prior to Day 0), dose adjustment/treatment (through Week 4), initial steady-state treatment (to Week 52), a treatment interruption period (Week 52 to Week 53-54), long-term steady-state treatment (results given through 48 months of treatment), and safety follow-up. Treatment was initiated in all patients with eliglustat 50 mg bd and 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 the remainder of the initial 52 Week treatment period, but if the eliglustat trough concentration on Day 10 was  $\geq$  5 ng/mL then the dose remained at 50 mg bd. Patients were eligible for a further dose adjustment to 150 mg bd if they had been on treatment for at least 24 months and met certain pre-specified criteria. However, no patients had required dose increases to 150 mg bd.

#### **6.2.1.4. Efficacy variables and outcomes**

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 (haemoglobin, platelets, and/or spleen volume). Response from Baseline to Week 52 was defined as follows: (1) an increase in haemoglobin of  $\geq$  0.5 g/dL; (2) an increase in platelets of  $\geq$  15%; and (3) a reduction of  $\geq$  15% in total spleen volume (based on MRI or spiral CT).



In addition to the main efficacy outcome, change in liver volume from Baseline to 52 weeks was identified as an efficacy endpoint. Long-term efficacy endpoints included changes from Baseline in haemoglobin, platelet count, spleen and liver volume, biomarkers, patient self-reported QoL, Gaucher disease assessments (mobility, bone crisis, and bone pain), and bone disease assessments (MRI, DXA, and x-ray).

#### **6.2.1.5. Sample size and statistical methods**

No hypothesis testing was planned for this study. Consequently, the study provided no formal sample size or power calculations. For the main efficacy outcome, the proportion of response and a 95% CI were constructed. The efficacy analyses were undertaken on the ITT population and the PP population. The ITT population was also referred to as the FAS and included all patients who signed the consent and received at least one dose of eliglustat. Any patient missing 20% or more of eliglustat doses during the primary analysis period (52 weeks) were not included in the PP population. In addition, patients in the FAS who did not complete Week 52 or who had major protocol deviations were not included in the PP population. Major protocol violations were prospectively defined in the SAP.

#### **6.2.1.6. Participant flow**

A total of 26 patients (10 males, 16 females) with GD1, with a mean age of 34 years (range: 18, 60), were enrolled into the study, the mean baseline BMI was 22.6 kg/m<sup>2</sup> (range: 18.5, 36.0 kg/m<sup>2</sup>). Of the 26 patients, 25 were extensive CYP2D6 metabolisers and 1 was a poor CYP2D6 metaboliser. The mean age at diagnosis was 24 years (range: 6, 59 years).

Of the 26 patients, 6 were treated with eliglustat 50 mg bd and 18 with eliglustat 100 mg BD; 2 patients who received treatment withdrew after receiving their first and only dose of eliglustat 50 mg on Day 1. On approximately Day 20 (ranging from Day 19 to Day 29), 18 of the 24 patients (75%) who continued in the study beyond Day 1 had their dose increased 100 mg bd (based on Day 10 C<sub>trough</sub> levels < 5 ng/mL), while 6 patients continued to receive a dose of 50 mg bd (based on Day 10 C<sub>trough</sub> levels ≥ 5 ng/mL). Of the 6 patients who continued 50 mg bd from approximately Day 20 through 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 time the dose was increased to 100 mg bd. No patients in the study had their dose increased to 150 mg bd. Mean time on treatment for patients in the safety set was 37.3 months, ranging from 0 to 48.6 months.

Twenty-two (22) patients (85%) completed the Week 52 assessment; 4 patients discontinued prior to the Week 52 (2 due to AEs, 2 for other reasons). Nineteen (19) patients (73%) completed the Month 48 assessment. The 7 patients who did not complete the Month 48 assessment included 4 who discontinued prior to Week 52 and an additional 3 who discontinued between Week 52 and Month 48. Of the 7 patients who discontinued before the Month 48 assessment, 3 discontinued due to AEs, 1 withdrew consent, and 3 discontinued for other reasons.

#### **6.2.1.7. Results for the primary efficacy endpoint at Week 52**

The primary composite endpoint for success at Week 52 was achieved by 20 of the 26 patients in the FAS: 77% (95% CI: 58%, 89%), p<0.0001. The results for the three components contributing to the composite endpoint assessment in the FAS were: (a) proportion of patients with abnormal baseline haemoglobin achieving success = 90% (9/10); (b) proportion of patients with abnormal baseline platelet count achieving success = 68% (17/25); and (c) proportion of patients with abnormal baseline spleen volume achieving success = 85% (22/26). Patients with no Week 52/last assessment data were counted as treatment failures (4 patients for composite, spleen and platelet endpoints and 1 patient for haemoglobin endpoint).

Of the 22 patients who completed 52 weeks of the study, 91% (20/22) met the primary composite endpoint for success. In the PP set, 94% (16/17) of patients met the primary composite endpoint for success.

### 6.2.1.8. Results for haematologic and organ volume parameters after 48 Months of treatment

The haemoglobin levels normalized in most patients during the first year of treatment, and further increases were observed from Year 1 through Year 4. For patients (n=19) who had haemoglobin concentration data at both Baseline and Month 48, a mean increase of 2.27 (95% CI: 1.57, 2.97) was observed;  $p < 0.0001$ .

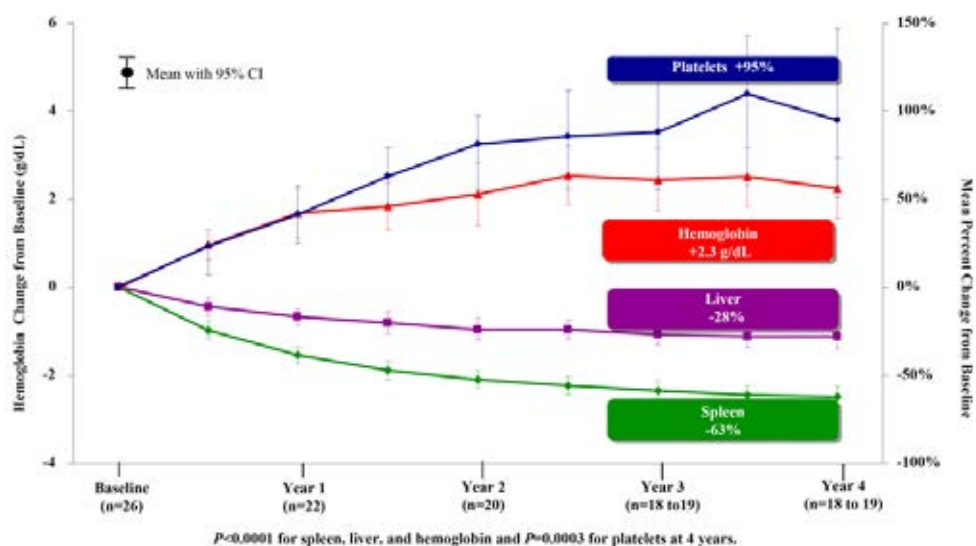
Increases in platelet counts were observed for a number of patients in the first year of treatment, and these increased further or were maintained after 4 years on eliglustat therapy. For patients (n=19) who had platelet count data at both Baseline and Month 48, a mean (SD) increase of 56.711 (50.9677)  $\times 10^9/L$  was observed. This equates to a mean increase from Baseline of Month 48 of 95.0% (95% CI: 50.7, 139.4);  $p = 0.0003$ .

Spleen volume decreased consistently within the first 24 months of the study, and these decreases continued through 48 months of treatment. For patients (n=18) who had spleen volume data at both Baseline and Month 48, the mean reduction in spleen volume (MN) from Baseline to Month 48 was -62.5% (95% CI: -68.3, -56.7);  $p < 0.0001$ .

Liver volume tended to decrease consistently across the 48 months of treatment, particularly within the initial 6 months of treatment. For patients (n=18) who had liver volume data at both Baseline and Month 48, the mean reduction in liver volume (MN) from Baseline to Month 48 was -28.0% (95% CI: -34.9, -21.2);  $p < 0.0001$ .

The results for changes in haematologic and organ volume parameters after 48 months of treatment are summarised below in Figure 9.

**Figure 9: GZGD00304 - Improvements in haematologic and organ volume parameters after 48 months of treatment.**



### 6.2.1.9. Other efficacy outcomes

This study included numerous additional efficacy endpoints. These endpoints have been examined and support the Week 52 and Month 48 outcomes described above suggesting that eliglustat might be a beneficial treatment for patients with GD1. However, given that the study is open-label and uncontrolled, the numerous additional endpoints have not been formally evaluated as they are considered to be exploratory rather than confirmatory.



### **6.3. Efficacy in sub-groups**

#### **6.3.1. Sex**

The efficacy results (FAS) for haemoglobin, platelet, liver volume (MN) and spleen volume (MN) in male and female patients for each of the 3 clinical efficacy and safety studies were summarised. In ENCORE, 47 male and 59 female GD1 patients were switched from ERT to eliglustat, in ENGAGE 8 female and 12 male GD1 treatment-naive patients were treated with eliglustat, and in the Phase II study were 10 males and 16 females were treated. Overall, small clinically insignificant differences were noted in each of the studies, but patient numbers in ENGAGE and the Phase II study were relatively small for both the male and female sub-groups. In the largest study (ENCORE), the observed differences between males and females in the efficacy outcomes are unlikely to be clinically significant.

#### **6.3.2. Age**

In the submitted data, the median age of patients in the 3 clinical efficacy and safety studies was between 30 and 40 years, and ranged from 16.1 to 69.3 years. There were only 2 patients aged less than 18 years, and 2 patients aged  $\geq 65$  years. The efficacy results (FAS) for haemoglobin, platelet, liver volume (MN) and spleen volume (MN) by age group (above and below the median) for each of the 3 clinical efficacy and safety studies were summarised. No marked differences were noted in the efficacy parameters based on the age groups examined.

#### **6.3.3. Race**

No meaningful comparison across racial groups could be made for the efficacy outcomes in the 3 clinical efficacy and safety studies as approximately 87% (126/145) of eliglustat treated patients (FAS) were White: 95% (19/20) in ENGAGE; 73% (16/26) in the Phase II study; and 92% (91/99) in ENCORE.

### **6.4. Evaluator's conclusion on clinical efficacy for GD1**

#### **6.4.1. Summary of key efficacy outcomes**

##### **6.4.1.1. 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 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 (miglustat). 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 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: that is, -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-naïve 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-naïve patients achieving the primary composite endpoint for success after 52 weeks of treatment: that is, 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.

#### **6.4.1.2. Patients stabilized on ERT and then switched to eliglustat**

The efficacy of eliglustat (titration regimen) for the treatment of GD1 treatment-naïve patients 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 stabilized with ERT for at least 3 years before enrollment. In the 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 lower bound 95% CI of the change from Baseline to Week 52 in the spleen volume (MN) of -2.62% 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, 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: that is, 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, BMD was normal for the majority of patients in both treatment groups at study entry, and remained stable throughout the 52 week treatment period.

#### **6.4.2. Sponsor's proposed dosing recommendation**

The sponsor's proposed dosing regimen for both treatment-naïve 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) (that is, approximately 90% of the potential treatment population). The sponsor's proposed treatment regimen does not involve dose titration determined by eliglustat  $C_{\text{trough}}$  levels  $< 5$  ng/mL early in treatment, nor does it include patients who are CYP2D6 poor metabolisers (PM) or ultra-rapid metabolisers (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 located in the Clinical Overview and the Summary of Clinical Efficacy. In essence, the sponsor's justification for the proposed treatment regimen is considered to be based on the following factors:

- a. Eliglustat is extensively metabolized by CYP2D6, and the PopPK analysis [POH0373] 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 URM 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  $C_{\text{trough}}$  levels < 5 ng/mL did not significantly differ from efficacy in patients with  $C_{\text{trough}}$  levels  $\geq$  5 mg/mL. Consequently, measuring  $C_{\text{trough}}$  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 ( $\log AUC_{(0-\tau)}$ ), 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.

#### **6.4.2.1. GD1 patients naive to previous ERT treatment**

##### **6.4.2.1.1. 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  $\geq$  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 (that is, the proposed treatment regimen).

In ENGAGE, when efficacy was compared in patients with average  $C_{\text{trough}}$  levels < 5 ng/mL and  $\geq$  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  $C_{\text{trough}}$  group compared with the lower average  $C_{\text{trough}}$  group (see Table 36, below). However, the differences between the two groups are of doubtful clinical significance, suggesting that adjustment of dose based on the  $C_{\text{trough}}$  cut-point of 5 ng/mL is not necessary.

**Table 36: ENGAGE - Summary of values and changes of percentage changes in selected efficacy endpoints from Baseline to Week 39; FAS.**

Efficacy Parameter	Average $C_{\text{trough}}$ Stratum <sup>a</sup>	n	Mean (SD)		Change/Percentage Change from Baseline to Week 39 <sup>b</sup>
			Baseline	Week 39	
Spleen Volume (MN)	<5 ng/mL	9	14.76 (6.620)	11.15 (4.707)	-23.05 (10.862)
	$\geq$ 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)
	$\geq$ 5 ng/mL	11	12.27 (1.681)	13.14 (1.326)	0.87 (1.207)
Platelet Count ( $\times 10^9/L$ )	<5 ng/mL	9	75.83 (13.386)	98.28 (33.233)	28.67 (36.353)
	$\geq$ 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)
	$\geq$ 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)
	$\geq$ 5 ng/mL	10	11836.1 (6120.59)	7882.2 (6140.74)	-41.86 (27.842)

a - Average  $C_{\text{trough}}$  is calculated as the mean of individual values at Weeks 13, 26, and 39.

b - Change or percentage change from Baseline is summarised 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  $\log AUC_{(0-\tau_{\text{au}})}$ . 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-naïve GD1 patients.

#### 6.4.2.1.2. 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-naïve 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  $\geq$  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 (that is, 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  $C_{\text{trough}} \geq 5$  ng/mL subgroup compared with the  $C_{\text{trough}} < 5$  ng/mL subgroup, based on the % change from Baseline to Month 48 for the key efficacy endpoints of interest (see Table 37, below). However, the difference between the two groups are of doubtful clinical significance.

**Table 37: Phase II - Summary of change from Baseline to 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  $\geq 5$  ng/mL; FAS.**

Parameter	Trough ng/mL	Baseline		Month 48		Change from Baseline to Month 48		
		n	Mean (SD)	n	Mean (SD)	n	Type	Mean (SD)
Hb (g/dL)	< 5	8	11.62 (1.791)	8	13.54 (1.425)	8	Absolute g/dL	1.93 (1.646)
	$\geq 5$	11	11.06 (1.378)	11	13.59 (1.134)	11		2.52 (1.318)
Platelet $10^9/L$	< 5	9	69.875 (20.812)	8	105.563 (42.196)	8	Percentage	52.8% (46.33%)
	$\geq 5$	11	67.818 (22.387)	11	139.818 (53.908)	11		125.7 % (106.1%)
Spleen MN	> 5	7	12.26 (1.042)	7	5.27 (1.189)	7	Percentage	-57.1% (8.74%)
	$\geq 5$	11	20.54 (11.153)	11	6.59 (4.251)	11		-66.0% (12.25%)
Liver MN	< 5	7	1.44 (0.285)	7	1.12 (0.205)	7	Percentage	-21.6% (11.54%)
	$\geq 5$	11	1.87 (0.420)	11	1.24 (0.317)	11		-32.1% (14.00%)

#### **6.4.2.2. GD1 patients previously stabilized on ERT and switched to eliglustat - ENCORE**

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

In ENCORE, all GD1 patients who had been stabilized on prior treatment with ERT and randomized 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,  $\geq 5$  ng/mL dose remained at 50 mg bd). Post-week 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 (that is, < 5 ng/mL dose increased from 50 mg bd to 100 mg bd or from 100 mg to 150 mg bd,  $\geq 5$  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 38, below). In particular, systemic exposure ( $AUC_{(0-12h)}$ ) at Week 13 and at Week 52 was similar for the three doses in CYP2D6 EMs, and mean (SD)  $C_{trough}$  levels for 50 mg bd, 100 mg bd and 150 mg bd were above  $\geq 5$  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 38: ENCORE - Mean (SD) [CV%] PK parameters by dose in CYP2D6 EMs at Weeks 13 and 52.**

Visit		N	$C_{max}$ ng/mL	$T_{max}$ hours <sup>a</sup>	$AUC_{(0-4h)}$ ng·h/mL	$AUC_{(0-12h)}$ ng·h/mL <sup>b</sup>	$C_{trough}$ ng/mL
Week 13	50 mg 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%]	2.50 (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%] <sup>c</sup>	201 (118) [59%] <sup>c</sup>	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%] <sup>d</sup>	195 (125) [64%] <sup>d</sup>	5.50 (3.58) [n=41]

Note: a -  $T_{max}$  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  $C_{trough}$  levels  $< 5$  ng/mL and  $\geq 5$  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  $C_{trough}$  levels  $< 5$  ng/mL compared with 85% (56/66) of patients with mean steady-state  $C_{trough}$  levels  $\geq 5$  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  $C_{trough}$  levels compared with the subgroup of patients with lower mean steady state  $C_{trough}$  levels (see Table 39, 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 39: 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 ng/mL	Baseline		Week 52		Change from Baseline to Week 52		
		n	Mean (SD)	n	Mean (SD)	n	Type	Mean (SD)
Hb (g/dL)	< 5	40	13.4 (1.3)	39	13.2 (1.1)	39	Absolute g/dL	-0.132 (0.6999)
	≥ 5	66	13.8 (1.3)	66	13.5 (1.4)	66		-0.249 (0.7481)
Platelet 10 <sup>9</sup> /L	< 5	40	189.5 (64.6)	39	195.1 (67.6)	39	Percentage	0.85 % (SD = 18.62%)
	≥ 5	66	211.7 (86.4)	66	225.9 (89.8)	66		5.92% (SD = 18.83%)
Spleen MN	> 5	33	2.995 (1.3022)	33	2.969 (1.3641)	33	Percentage	-2.188% (SD = 16.0661%)
	≥ 5	44	3.297 (1.3776)	44	3.090 (1.3762)	44		-7.309% (SD = 13.0599%)
Liver MN	< 5	40	0.912 (0.1732)	40	0.953 (0.1559)	40	Percentage	4.900% (SD=10.0195)
	≥ 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  $\log AUC_{(0-\tau)}$  in order to explore potential exposure-response relationships. Logistic regressions of the composite endpoint versus observed PK parameters ( $\log AUC_{(0-\tau)}$  or  $\log C_{max}$ ) 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  $\log AUC_{(0-\tau)}$ . 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 ( $\log AUC_{(0-\tau)}$  or  $\log C_{max}$ ) 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  $\log AUC_{(0-\tau)}$  ( $p=0.0002$ ) and observed  $\log C_{max}$  ( $p=0.0007$ ). 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  $\log AUC_{(0-\tau)}$  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 ( $n=70$ ) (that is, 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  $\log AUC_{(0-\tau)}$ , 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  $C_{\text{trough}}$  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 ( $\log AUC_{(0-\tau)}$ ). However, there was no observed exposure-response relationship between the composite stability endpoint at Week 52 for CYP2D6 and dose and observed exposure ( $\log AUC_{(0-\tau)}$ ). 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 ( $\log AUC_{(0-\tau)}$ ,  $C_{\text{max}}$ ). 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 stabilized 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 stabilized 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.

## 7. Clinical safety

### 7.1. Studies providing evaluable safety data

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-naïve 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 (6-18 months) from the on-going double-blind Phase IIIb study (EDGE) comparing 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-naïve patients for the completed primary analysis period (Week 39), with a data cut-off date of 18 July 2012.

In ENGAGE and ENCORE, safety was assessed through continuous monitoring of adverse events (AEs; SAEs) and concomitant medications, as well as through evaluation of standard clinical parameters including cardiac electrophysiology (12-lead ECG, 24-hour dual-lead Holter), echocardiograms (ECHO) with Doppler, physical examinations, vital sign measurements, neurological examinations, nerve conduction testing, neuropsychological testing by Mini-Mental State Examination (MMSE), standard clinical laboratory tests (haematology, serum chemistry, urinalysis), and chest X-rays. AEs (including SAEs) were recorded from the time of informed consent through completion of the safety follow-up period (30 to 37 days after the last treatment dose), and were obtained through spontaneous reporting or elicited during open-ended questioning or evaluation at each study visit or during bi-weekly phone contact. Medical events of interest (MEOI) were recorded from the first dose of study medication until completion of the safety follow-up period. All other safety assessments were performed at the time points indicated in the schedules.

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.

## **7.2. Exposure**

### **7.2.1. 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 naïve 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 40 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

was 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 40: Cumulative eliglustat exposure; eliglustat safety set.**

Duration (months)	Eliglustat Dose			
	50 mg BID n (%)	100 mg BID n (%)	150 mg BID n (%)	Any Dose n (%) <sup>a</sup>
>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)
<b>Total Patients (any duration)</b>	<b>391<sup>a</sup></b>	<b>319</b>	<b>98</b>	<b>393</b>
<b>Patient-Years of Exposure</b>	<b>125.6</b>	<b>290.8</b>	<b>113.4</b>	<b>535.0</b>

Note: Patient exposure at each eliglustat dose level was summarised 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).

### 7.2.2. 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.

### 7.2.3. 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 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.

## 7.3. Demographics

### 7.3.1. Integrated safety summary - eliglustat safety set

The mean age (SD) of the patients in the eliglustat safety set was 37.1 (14.40) years, and most patients (98%) were in the > 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. The mean (SD) weight was 68.2 (6.06) kg and the mean (SD) BMI was 24.1 (4.60) kg/m<sup>2</sup>. Of the total number of patients in the eliglustat safety population (n=393), 49% were male, 51% were female, most were White (82%), and most (89%) were not current smokers. By geographic region, 27% of patients were enrolled in the US, 11% were enrolled in the EU, 3% were enrolled in Japan, and 59% were enrolled in other countries (grouped together under rest of the word [ROW] due to the small number of patients enrolled in some countries.). In the ROW group, most patients were enrolled in Brazil (66/393 [17%]), the Russian Federation (43/393 [11%]),

Argentina (33/393 [8%]), and China (25/393 [6%]). Other countries where a small percentage of patients were enrolled ( $\leq 3\%$  per country) were Australia, Canada, Colombia, Croatia, Egypt, India, Israel, Lebanon, Mexico, Portugal, Serbia, and Tunisia. Overall, 91% of patients in GD1 safety set were CYP2D6 PMs or IMs. The distribution of metaboliser status was: EMs (79%); IMs (12%); PMs (4%); URM (2%); indeterminate (1%); and missing (2%).

In the eliglustat safety set, 86% of patients had at least 1 of the 2 common GD mutations of the acid  $\beta$ -glucosidase gene (N370S, L444P). The mean (SD) residual acid  $\beta$ -glucosidase enzyme activity was 1.32 (2.689) nmoL/hr/mg, with high inter-patient variability in residual activity. A total of 21% of patients had undergone a total splenectomy, and patients who had undergone splenectomy were excluded from the Phase II study and ENGAGE. A total of 66% of patients in the GD1 eliglustat safety set had recent ERT exposure (within 9 months prior to first dose of eliglustat). Patients who received ERT within 12 months prior to enrolment were excluded from the Phase II study and patients who received ERT within 9 months prior to enrolment were excluded from ENGAGE, while patients entering the ENCORE study were required to have received ERT for at least 3 years prior to the study. The mean time interval between GD1 diagnosis and start of eliglustat treatment was longer in the studies that required patients to have been previously treated with ERT (EDGE = 15.79 years; ENCORE = 19.25 years) compared with the studies that prohibited treatment within 9 to 12 months before enrollment (Phase II study = 10.11 years; ENGAGE = 11.21 years).

### **7.3.2. ENCORE - primary analysis period (Week 52) eliglustat versus cerezyme**

The baseline demographics characteristics of patients in ENCORE have been previously described in this CER.

### **7.3.3. ENGAGE - primary analysis period (Week 39) eliglustat versus placebo**

The baseline demographics characteristics of patients in ENGAGE have been previously described in this CER.

## **7.4. Adverse events**

### **7.4.1. Overview of adverse events**

#### **7.4.1.1. Integrated safety summary - eliglustat safety set**

In the eliglustat safety set, 334 (85%) patients experienced a total of 2,340 TEAEs (437 events/100 person-years), and the majority of these events were considered to be mild in severity. TEAEs considered to be related to the study drug were reported in 159 (40%) patients (446 events; 83 events/100 person-years), indicating that the majority of events were considered to be unrelated to the study drug. TEAEs reported as leading to study drug discontinuation were reported in 13 (3%) patients (22 events; 4 events/100 person-years), and TEAEs leading to withdrawal from the study were reported in 12 (3%) patients (22 events; 4 events/100 person-years). Serious AEs (SAEs) were reported in 35 (9%) patients (42 events; 8 events/100 person-years), and events considered to be related to the study drug were reported in 5 (1%) patients (6 events; 1 event/100 person-years). No deaths were reported in the eliglustat safety set as of 31 January 2013.

#### **7.4.1.2. ENCORE - primary analysis period (Week 52) eliglustat versus cerezyme**

In ENCORE, TEAEs were reported more commonly in the eliglustat group than in the Cerezyme group (92% versus 79%, respectively), and most TEAEs were considered by the investigator to be unrelated to the study drug. Severe TEAEs were experienced by 13 (12%) patients in the eliglustat group (29 events) and 4 (8%) patients in the Cerezyme group (6 events). SAEs were reported more commonly in the eliglustat group than in the Cerezyme group (10% [11/106] versus 0% [0/53]). No deaths were reported in either treatment group. The overview of TEAEs is provided below in Table 41.

**Table 41: ENCORE - Overview of TEAEs; safety set.**

AE Category	Eliglustat (N=106)		Cerezyme (N=53)		Total (N=159)	
	Patients n (%)	Events n	Patients n (%)	Events n	Patients n (%)	Events n
Patients with:						
Any TEAE	97 (92)	656	42 (79)	141	139 (87)	797
Related TEAEs	40 (38)	109	6 (11)	10	46 (29)	119
Not related TEAEs	96 (91)	547	41 (77)	131	137 (86)	678
Mild TEAEs	94 (89)	478	37 (70)	103	131 (82)	581
Moderate TEAEs	49 (46)	149	19 (36)	32	68 (43)	181
Severe TEAEs	13 (12)	29	4 (8)	6	17 (11)	35
MEOIs	6 <sup>a</sup> (6)	8 <sup>a</sup>	0 (0)	0	6 <sup>a</sup> (4)	8 <sup>a</sup>
IARs	0 (0)	0	2 (4)	6	2 (1)	6
Serious TEAEs	11 (10)	11	0 (0)	0	11 (7)	11
Deaths	0 (0)	0	0 (0)	0	0 (0)	0
TEAEs leading to study drug discontinuation	2 <sup>b</sup> (2)	2	1 (2)	1	3 (2)	3

MEOI = medical event of interest; TEAE = treatment-emergent adverse event. Related TEAEs are defined as possibly, probably, or definitely related; not related TEAEs are defined as not related or remote/unlikely. IARs are defined as any AE related (that is, possible, probable, or definite) to and occurring during or just after a Cerezyme infusion. a One eliglustat patient experienced syncope prior to the MEOI definition being in place and is included in this table. b One eliglustat patient identified in the Source Table discontinued study drug on completion of Week 52 and is not included in this table.

#### 7.4.1.3. *ENGAGE - primary analysis period (Week 39) eliglustat versus placebo*

In ENGAGE, TEAEs were reported more commonly in the eliglustat group than in the placebo group (90% versus 70%, respectively), and most TEAEs were considered by the investigator to be unrelated to the treatment drug. There were no severe TEAEs, SAEs or deaths reported in either treatment group. The overview of TEAEs is provided below in Table 42.

**Table 42: ENGAGE - Overview of TEAEs; safety set.**

AE Category	Placebo (N=20)		Eliglustat (N=20)		Total (N=40)	
	Patients n (%)	Events n	Patients n (%)	Events n	Patients n (%)	Events n
Patients with:						
Any TEAE	14 (70)	95	18 (90)	137	32 (80)	232
Related TEAEs	9 (45)	25	8 (40)	31	17 (43)	56
Not related TEAEs	14 (70)	70	18 (90)	106	32 (80)	176
Mild TEAEs	14 (70)	85	16 (80)	94	30 (75)	179
Moderate TEAEs	6 (30)	10	15 (75)	43	21 (53)	53
Severe TEAEs	0	0	0	0	0	0
MEOIs	1 (5)	1	0	0	1 (3)	1
Serious TEAEs	0	0	0	0	0	0
Deaths	0	0	0	0	0	0
TEAEs leading to discontinuation	0	0	0	0	0	0

MEOI = medical event of interest; TEAE = treatment-emergent adverse event Note: Related TEAEs are defined as possibly, probably, or definitely related; not related TEAEs are defined as not related or remote/unlikely.

#### 7.4.2. **Common adverse events**

##### 7.4.2.1. *Integrated safety - eliglustat safety set*

A total of 334 (85%) patients in the eliglustat safety experienced 1 or more TEAEs. The three most frequently reported 'system, organ, classes' (SOCs) with TEAEs were 'infections and infestations' (184/393 [47%]), 'gastrointestinal disorders' (163/393 [41%]), and 'nervous

system disorders' (126/393 [32%]). The most commonly reported TEAEs ( $\geq 10$  of patients) were: headache (17%); arthralgia (14%); nasopharyngitis (13%); URTI (11%), diarrhoea (10%); and dizziness (10%).

#### **7.4.2.2. ENCORE - primary analysis period (Week 52) eliglustat versus cerezyme**

TEAEs occurring in  $\geq 5\%$  more patients in the eliglustat group than in the Cerezyme group by SOC were: 'infections and infestations' (56% versus 36%); 'gastrointestinal disorders' (54% versus 17%); 'musculoskeletal and connective tissue disorders' (39% versus 30%); 'nervous system disorders' (35% versus 9%); 'general disorders and administration site conditions' (27% versus 8%); 'investigations' (23% versus 17%); 'injury, poisoning and procedural complications' (20% versus 11%); 'respiratory thoracic and mediastinal disorders' (19% versus 4%); 'skin and subcutaneous tissue disorders' (15% versus 4%); 'reproductive and breast disorders' (10% versus 4%); 'cardiac disorders' (8% versus 2%); 'ear and labyrinth disorders' (8% versus 2%); and 'neoplasms benign, malignant and unspecified (including cysts and polyps)' (6% versus 0%). The TEAEs occurring in  $\geq 5\%$  more patients in the Cerezyme group than in the eliglustat by SOC were reported only for 'hepatobiliary disorders' (13% versus 5%).

##### **7.4.2.2.1. Infections and infestations:**

In the SOC of 'infections and infestations', TEAEs occurred in 56% of patients in the eliglustat and 36% of patients in the Cerezyme group. In this SOC, TEAEs reported in  $\geq 5\%$  of patients in either of the two treatment groups and in  $\geq 2\%$  more patients in the eliglustat group than in the Cerezyme group, in decreasing order of frequency in the eliglustat group, were: URTI (10% versus 6%); sinusitis (10% versus 2%); influenza (6% versus 4%); viral gastroenteritis (5% versus 2%). In this SOC, the only TEAE reported in  $\geq 5\%$  of patients in either of the two treatment groups and in  $\geq 2\%$  more patients in the Cerezyme group than in the eliglustat group in this SOC was UTI (5% versus 9%).

##### **7.4.2.2.2. Gastrointestinal disorders:**

In the SOC of 'gastrointestinal disorders', TEAEs were reported in 54% of patients in the eliglustat group and 17% of patients in the Cerezyme group. In this SOC, TEAEs reported in  $\geq 5\%$  of patients in either of the two treatment groups and in  $\geq 2\%$  more patients in the eliglustat group than in the Cerezyme group, in decreasing order of frequency in the eliglustat group, were: diarrhoea (12% versus 4%); nausea (12% versus 0%); upper abdominal pain (10% versus 0%); dyspepsia (7% versus 2%); GORD (7% versus 0%); and constipation (5% versus 0%). In this SOC, the only TEAE reported in  $\geq 5\%$  of patients in either of the two treatment groups and in  $\geq 2\%$  more patients in the Cerezyme group than in the eliglustat group was toothache (6% versus 2%).

##### **7.4.2.2.3. Nervous system disorders:**

In the SOC of 'nervous system disorders', TEAEs were reported in 35% of patients in the eliglustat group and 9% of patients in the Cerezyme group. In this SOC, TEAEs reported in  $\geq 5\%$  of patients in either of the two treatment groups and in  $\geq 2\%$  more patients in the eliglustat group than in the Cerezyme group, in decreasing order of frequency in the eliglustat group, were headache (13% versus 2%) and dizziness (8% versus 0%). In this SOC, no TEAEs were reported in  $\geq 5\%$  of patients in either of the two treatment groups and in  $\geq 2\%$  more patients in the Cerezyme group than in the eliglustat group.

##### **7.4.2.2.4. General disorders and administration site conditions:**

In the SOC of 'general disorders and administration site conditions', TEAEs were reported in 27% of patients in the eliglustat group and 8% of patients in the Cerezyme group. In this SOC, TEAEs reported in  $\geq 5\%$  of patients in either of the two treatment groups and in  $\geq 2\%$  more patients in the eliglustat group than in the Cerezyme group, in decreasing order of frequency in the eliglustat group, were fatigue (14% versus 2%) and asthenia (8% versus 0%). In this SOC,

no TEAEs were reported in  $\geq 5\%$  of patients in either of the two treatment groups and in  $\geq 2\%$  more patients in the Cerezyme group than in the eliglustat group.

*7.4.2.2.5. Respiratory thoracic and mediastinal disorders:*

In the SOC of 'respiratory thoracic and mediastinal disorders', TEAEs were reported in 19% of patients in the eliglustat group and 4% of patients in the Cerezyme group. In this SOC, TEAEs reported in  $\geq 5\%$  of patients in either of the two treatment groups and in  $\geq 2\%$  more patients in the eliglustat group than in the Cerezyme group, in decreasing order of frequency in the eliglustat group, were cough (7% versus 4%) and epistaxis (5% versus 0%). In this SOC, no TEAEs were reported in  $\geq 5\%$  of patients in either of the two treatment groups and in  $\geq 2\%$  more patients in the Cerezyme group than in the eliglustat group. The only other TEAE in this SOC reported in  $\geq 2\%$  of patients overall was oropharyngeal pain (4%, eliglustat versus 0%, Cerezyme).

*7.4.2.2.6. Skin and subcutaneous tissue disorders:*

In the SOC of 'skin and subcutaneous tissue disorders', TEAEs were reported in 15% of patients in the eliglustat group and 4% of patients in the Cerezyme group. In this SOC, the only TEAEs reported in  $\geq 5\%$  of patients in either of the two treatment groups and in  $\geq 2\%$  more patients in one group compared with the other was rash (5%, eliglustat versus 0%, Cerezyme). The only other TEAE in this SOC reported in  $\geq 2\%$  of patients overall was contact dermatitis (1%, eliglustat versus 4%, Cerezyme).

*7.4.2.2.7. Musculoskeletal and connective tissue disorders:*

In the SOC of 'musculoskeletal and connective tissue disorders', TEAEs were reported in 39% of patients in the eliglustat group and 30% of patients in the Cerezyme group. In this SOC, TEAEs reported in  $\geq 5\%$  of patients in either of the two treatment groups and in  $\geq 2\%$  more patients in the eliglustat group than in the Cerezyme group, in decreasing order of frequency in the eliglustat group, were back pain (12% versus 6%), pain in extremity (11% versus 2%), and bone pain (6% versus 2%). In this SOC, no TEAEs were reported in  $\geq 5\%$  of patients in either of the two treatment groups and in  $\geq 2\%$  more patients in the Cerezyme group than in the eliglustat group.

*7.4.2.2.8. Investigations:*

In the SOC of 'investigations', TEAEs were reported in 23% of patients in the eliglustat group and 17% of patients in the Cerezyme group. In this SOC, the only TEAE reported in  $\geq 5\%$  of patients in either of the two treatment groups and in  $\geq 2\%$  more patients in one group compared with the other was CK increased (7%, eliglustat versus 2%, Cerezyme).

*7.4.2.2.9. Injury, poisoning and procedural complications:*

In the SOC of 'injury, poisoning and procedural complications', TEAEs were reported in 20% of patients in the eliglustat group and 11% of patients in the Cerezyme group. In this SOC, the only TEAE reported in  $\geq 5\%$  of patients in either of the two treatment groups and in  $\geq 2\%$  more patients in one group compared with the other was contusion (5%, eliglustat versus 0%, Cerezyme).

*7.4.2.2.10. Cardiac disorders:*

In the SOC of 'cardiac disorders', TEAEs were reported in 8% of patients in the eliglustat group and 2% of patients in the Cerezyme group. In this SOC, the only TEAE reported in  $\geq 5\%$  of patients in either of the two treatment groups and in  $\geq 2\%$  more patients in one group compared with the other was palpitations (5%, eliglustat versus 0%, Cerezyme). No other TEAEs in this SOC were reported in  $\geq 2\%$  of patients.



#### 7.4.2.2.11. *Hepatobiliary disorders:*

In the SOC of 'hepatobiliary disorders', TEAEs were reported in 5% of patients in the eliglustat group and 13% of patients in the Cerezyme group. In this SOC, the only TEAE reported in  $\geq 5\%$  of patients in either of the two treatment groups and in  $\geq 2\%$  more patients in one group compared with the other was hepatomegaly (1%, eliglustat versus 6%, Cerezyme).

Hepatomegaly was the only TEAE in this SOC that occurred in  $\geq 5\%$  of patients in the Cerezyme group and  $\geq 2\%$  more commonly than in the eliglustat group.

#### 7.4.2.2.12. *Neoplasms benign, malignant and unspecified (including cysts and polyps):*

Of note, in this SOC TEAEs were reported notably more commonly in the eliglustat group than in the Cerezyme group (6% versus 0%). None of the individual TEAEs in this SOC occurred in more than 1 patient. The reason(s) for the different incidence of TEAEs between the two treatment groups in this SOC are unknown.

#### 7.4.2.3. **ENGAGE - primary analysis period (Week 39) eliglustat versus placebo**

A total of 18 (90%) patients in the eliglustat group and 14 (70%) of patients in the placebo group had at least 1 TEAE. The most commonly reported TEAEs occurring in  $\geq 15\%$  of patients (that is,  $n \geq 3$ ) 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  $\geq 2$  patients in the eliglustat group. The most commonly reported TEAEs occurring in  $\geq 15\%$  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  $\geq 2$  patients in the placebo group.

#### 7.4.3. **Treatment-related adverse events**

##### 7.4.3.1. **Integrated safety summary - eliglustat safety set**

TEAEs reported as being related to treatment with eliglustat were reported in 159 (40%) patients. The two most frequently reported SOCs ( $\geq 10\%$  of patients) were 'gastrointestinal disorders' (22%), and 'nervous system disorders' (13%). The most commonly reported treatment-related TEAEs ( $\geq 2\%$  of patients) 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%).

##### 7.4.3.2. **ENCORE - primary analysis period (Week 52) eliglustat versus cerezyme**

TEAEs reported as being related to the study drug were reported in 38% (40/106) of patients in the eliglustat group and 11% (6/53) of patients in the Cerezyme group. The two most frequently reported SOCs ( $\geq 10\%$  of patients in either treatment group) were 'gastrointestinal disorders' (19%, eliglustat versus 2%, Cerezyme), and 'nervous system disorders' (13%, eliglustat versus 0%, Cerezyme).

TEAEs reported as being related to drug-treatment ( $\geq 2\%$  of patients in either treatment group) and occurring more commonly in the eliglustat group (descending order of frequency) than in the Cerezyme group were: diarrhoea (5% versus 0%); arthralgia (4% versus 0%); headache (4% versus 0%); fatigue (4% versus 0%); somnolence (3% versus 0%); dyspepsia (3% versus 2%); GORD (3% versus 0%); nausea (3% versus 0%); splenomegaly (3% versus 0%); pain in extremity (2% versus 0%); asthenia (2% versus 0%); dizziness (2% versus 0%); tremor (2% versus 0%); upper abdominal pain (2% versus 0%); constipation (2% versus 0%); dry mouth (2% versus 0%); dysphagia (2% versus 0%); flatulence (2% versus 0%); blood folate decreased (2% versus 0%); blood homocysteine increased (2% versus 0%); palpitations (2% versus 0%); throat irritation (2% versus 0%).

TEAEs reported as being related to drug-treatment ( $\geq 2\%$  in of patients in either treatment group) and occurring more commonly in the Cerezyme group (descending order of frequency) than in the eliglustat group were: blood cholesterol increased (4% versus 0%); extravasation (2% versus 0%); infusion site induration (2% versus 0%); back pain (2% versus 1%); and anxiety (2% versus 0%).

#### 7.4.3.3. *ENGAGE - primary analysis period (Week 39) eliglustat versus placebo*

TEAEs considered by the investigator to be related to the study drug occurred in 40% (8/20) of patients in the eliglustat group and 45% (9/20) of patients in the placebo group. The most frequently reported TEAEs reported to be related to the study drug and occurring in  $\geq 2$  patients 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%).

#### 7.4.4. Adverse events by time of onset

##### 7.4.4.1. *Integrated safety summary - eliglustat safety set*

The incidence of TEAEs (overall), was greatest in the first 6 months of treatment with eliglustat and then slowly decreased over the remaining 48 months of treatment (see Table 43, below).

**Table 43: ISS - TEAEs by time of onset relative to the start of treatment; eliglustat safety set.**

	All Eliglustat (N=393)	
	Overall TEAEs	Related TEAEs
Duration of Eliglustat Treatment (months)	Patients n (%)	Patients n (%)
0 to $\leq 6$	298/393 (76)	121/393 (31)
>6 to $\leq 12$	186/348 (53)	52/348 (15)
>12 to $\leq 18$	101/204 (50)	17/204 (8)
>18 to $\leq 24$	49/114 (43)	11/114 (10)
>24 to $\leq 30$	22/62 (35)	3/62 (5)
>30 to $\leq 36$	8/32 (25)	0/32 (0)
>36 to $\leq 42$	7/20 (35)	1/20 (5)
>42 to $\leq 48$	7/19 (37)	0/19 (0)

##### 7.4.4.2. *ENCORE - primary analysis period (Week 52) eliglustat versus cerezyme*

In this study it was stated that time to onset of the reported SAEs was beyond 3 months in the majority of cases with start dates. No other time to onset data could be identified for the TEAEs reported in this study.

##### 7.4.4.3. *ENGAGE - primary analysis period (Week 39) eliglustat versus placebo*

In this study, TEAEs occurred more frequently in the first 3 months of the study in both the eliglustat and placebo groups, and in both treatment groups the increased incidence of TEAEs in the first 3 months was primarily driven by gastrointestinal events. In the eliglustat group, 76 (55.5%) events in 16 (80%) patients occurred in the first 3 months of treatment (0 to  $\leq 3$  months), 36 (26.3%) events in 14 (70%) patients occurred from > 3 months to  $\leq 6$  months, and 25 (18.2%) events in 9 (47%) patients occurred from > 6 months to  $\leq 9$  months. In the placebo group, 47 (49.5%) events in 13 (65%) patients occurred in the first 3 months of treatment (0 to

≤ 3 months), 17 (17.9%) events in 8 (40%) patients occurred from > 3 months to ≤ 6 months, and 31 (32.6%) events in 10 (50%) patients occurred from > 6 months to ≤ 9 months.

#### **7.4.5. Deaths and other serious adverse events**

##### **7.4.5.1. Deaths**

In the ISS (eliglustat safety set), there were no deaths as of the data cut-off date of 31 January 2013. No deaths were reported in ENCORE or in ENGAGE. Two deaths were reported in healthy subjects in the Phase I program while the subjects were not taking eliglustat. Two additional deaths in GD1 patients were reported: 1 in the Phase II study [GZGD00304] occurred 6.5 months following withdrawal from the study due to lacerated spleen 2 days after laparoscopic cholecystectomy; 1 patient after the EDGE lead-in period due to multiple trauma following a skiing accident occurring approximately 562 days after starting eliglustat treatment (considered to be unrelated to treatment).

##### **7.4.5.2. Other SAEs**

###### *7.4.5.2.1. Integrated safety summary - eliglustat safety set*

SAEs were reported in 9% (35/393) of patients in the eliglustat safety set (42 events; 8 events/100 person-years). 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%). Of the 42 SAEs, 5 were considered by the investigator to be related to eliglustat treatment.

###### *7.4.5.2.2. ENCORE - primary analysis period (Week 52) eliglustat versus cerezyme*

SAEs were reported in 10% (11/106) of patients in the eliglustat group (11 events) and no patients in the Cerezyme group. The only SAE reported in more than 1 patient in the eliglustat group was syncope (n=2 [1%]).

###### *7.4.5.2.3. ENGAGE - primary analysis period (Week 39) eliglustat versus placebo*

There were no SAEs reported in ENGAGE in either the placebo or eliglustat groups.

#### **7.4.6. Adverse events leading to study drug discontinuation**

##### **7.4.6.1. Integrated safety summary (ISS) - eliglustat safety set**

A total of 12/393 (3%) patients had at least 1 TEAE leading to permanent eliglustat discontinuation and study withdrawal. The onset of the TEAEs ranged from 1 day (the day of first dose) to 382 days after the first dose, with onset at ≤111 days for 15 of the TEAEs and ≥198 days for the other 6 TEAEs. One (1) additional patient from the Phase II study temporarily discontinued study drug due to 'abscess', but resumed study treatment at a later date and did not withdraw from the study. All other patients who discontinued eliglustat treatment due to a TEAE also withdrew from the study.

TEAEs grouped as 'cardiac disorders' (SOC) were the most frequently reported TEAEs leading to discontinuation of eliglustat and withdrawal from the study: 2 patients discontinued due to ventricular tachycardia; 2 patients discontinued due to myocardial infarction; and 1 patient discontinued due to palpitations. One (1) additional patient discontinued due to an acute myocardial infarction occurring after the 31 January 2013 database cut-off point. One (1) TEAE (asthenia) leading to discontinuation of eliglustat was considered to be related to GD. Most TEAEs leading to discontinuation were categorised as mild or moderate. There were 5 SAEs leading to discontinuation of eliglustat: myocardial infarction (severe/SAE), myocardial infarction (moderate/SAE), ventricular tachycardia (mild/SAE), injury (severe/SAE), and malignant hepatic neoplasm (severe/SAE).

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).

#### **7.4.7. ENCORE - primary analysis period (Week 52) eliglustat versus cerezyme**

TEAEs leading to study drug discontinuation were reported in 2 (2%) patients in the eliglustat group and 1 (2%) patient in the Cerezyme group. The events 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 3 events, only 'palpitations' was assessed as related to eliglustat.

#### **7.4.8. ENGAGE - primary analysis period (Week 39) eliglustat versus placebo**

No TEAEs leading to treatment discontinuation were reported in either the eliglustat or the placebo group.

#### **7.4.9. Adverse events of special interest**

##### **7.4.9.1. Integrated summary of safety - eliglustat safety set**

Cardiac TEAEs of special interest included syncope (as a possible marker of Torsades de Pointes) and all MedDRA preferred terms under the higher level group term (HLGT) of 'Cardiac arrhythmias'. The HLGT of 'Cardiac arrhythmias' were analysed using the 4 higher level terms (HLTs) of Cardiac conduction, rate and rhythm disorders; Supraventricular arrhythmias; and Ventricular arrhythmias and Cardiac arrest.

##### **7.4.9.1.1. 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. The events were mild for 2 patients, moderate for 2 patients, and severe for 4 patients. All of the patients with syncope were female, with ages ranging from 21 to 63 years. Two (2) of the patients had a prior history of syncope, and 2 of the patients were being treated for hypertension. In 7 patients, syncope was consistent with vasovagal responses triggered by fasting, dehydration, blood draw, recent change in hypertensive medications, or pain, while no trigger factors could be identified for 1 patient. ECGs performed at the time of syncope were normal.

Syncope was an SAE in 5 (1%) patients; 3 of the SAEs were considered by the investigator to be related to study drug (2 possibly related, 1 definitely related). 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.

##### **7.4.9.1.2. 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 [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 or sustained ventricular tachycardia were reported. No sudden cardiac deaths were observed during the clinical trial program.

The HLT of Cardiac conduction disorders (6 [2%] patients) included 4 patients with AV block 2nd degree (2 of whom had a history of AV block), 1 patient with AV block 1st degree (history of AV block), and 1 patient with sino-atrial block. Two events (in 1 patient) were SAEs. All events were mild in severity, and all but 1 patient with AV block 2nd degree were deemed by the investigator to be related to the study drug. No patient experienced a higher block than Mobitz type 1. Events occurred in males and females equally, ranging in age from 24 to 69 years. The

events occurred at all doses of eliglustat, and all patients who experienced the events were CYP2D6 EMs. Time from the start of dosing with eliglustat to the onset of event was 90 to 632 days. The  $C_{max}$  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.

The HLT of Ventricular arrhythmia and cardiac arrest (4 [1%] patients) included 3 patients with ventricular tachycardia (all non-sustained) and 1 patient with ventricular extra-systole. One event of ventricular tachycardia was an SAE. All events were considered mild in severity. 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 all but 1 were CYP2D6 EMs (the remaining patient was a CYP2D6 IM). Days from the start of eliglustat dosing to the onset of the event ranged from the first day (following the first dose) to day 466. All patients were asymptomatic at the time of the event. Two (2) 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.

The HLT of Supraventricular arrhythmia (4 [1%] patients) included 2 patients with supraventricular tachycardia, 1 patient with arrhythmia, and 1 patient with atrial tachycardia.

#### *7.4.9.1.3. Potentially clinically significant abnormalities in ECG parameters*

In the 389 patients in the eliglustat safety set with ECG evaluations, 28 (7.2%) patients had at least one potentially clinically significant PR, QRS and/or QTcF abnormality leading to a safety narrative. These abnormalities are listed below:

- 2 patients with new QTcF > 480 ms (that is, > 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%;
- 18 patients with QRS ≥ 120 ms.

Of the 28 patients with outlier events, the majority (n=21; 75%) of patients were from EDGE, eventhough this study included only 44% of the total enrolled population and treatment duration at cut-off date was not longer than the other studies. While ECG monitoring in EDGE was similar to that conducted for the other studies; the sponsor postulates that no central reading of the machine-read ECGs in this study probably led to the higher identified incidence of outliers. The sponsor stated that review the observed ECG changes in the eliglustat safety set by both the ECG central reader (for the Phase II, ENGAGE, and ENCORE studies) and the cardiology expert (for EDGE) did not identify factors indicating that the changes were drug related.

#### **7.4.9.2. ENCORE - primary analysis period (Week 52) eliglustat versus cerezyme**

##### *7.4.9.2.1. Medical events of interest (MEOIs)*

In this study, MEOIs were defined as clinically significant cardiac arrhythmias detected by electrophysiological monitoring such as ECG or Holter monitoring that did not meet SAE criteria, as well as syncope from any cause. In the eliglustat group, 6 (6%) patients experienced MEOI (8 events) compared with no patients in the Cerezyme group. The 8 MEOIs reported in the 6 patients in the eliglustat group included 4 events of syncope (including 2 SAEs) in 3 patients, and 4 events of cardiac arrhythmia in 3 patients.

All 4 syncope events in the 3 (3%) patients in the eliglustat group (including serious and non-serious) were vasovagal in origin with identifiable predisposing risk factors (that is, blood draw, fasting conditions and pain). One (1) patient had a prior medical history of syncope. ECGs, obtained as part of post-event diagnostic testing, did not reveal any cardiac arrhythmias as the



potential cause for the syncopal events. One (1) patient had a PR interval >200 ms at the Week 52 visit (approximately 8 months after the syncope event).

All 4 cardiac arrhythmia events in the eliglustat group were deemed clinically significant by the investigator (1st or 2nd degree AV block) and were detected either during scheduled Holter monitoring or extensive, routine ECG monitoring as required by the protocol. All cardiac arrhythmias were A-V nodal in origin (AV block 2nd degree [n=3]; AV block 1st degree [n=1]) and none were associated with clinical symptoms. None of the arrhythmias were considered to be clinically significant.

#### 7.4.9.2.2. Cardiac safety report

The submission included a Cardiac Safety Report, dated 13 June 2013, for ENCORE (CSR, Appendix 16,2.8). The ECG and Holter monitoring data were centrally read (blinded) in the USA, and the key results are summarised below.

#### 7.4.9.2.3. ECG data

ECGs were read at a central site, and also read by the investigator at the study site at the time they were performed to determine if there were any safety concerns. In the time-averaged analysis, mean post-Baseline ECG values were calculated as the average of assessments at 1, 2, 3, and 4 hours post-dose and Baseline values were defined as the average of the 3 pre-dose ECG readings on Day 1. Data were available for Day 1, Weeks 4, 13, 26, 39 and 52.

Time-averaged ECG results of mean change from Baseline to Week 52 for eliglustat pooled doses (n=101) versus Cerezyme (n=49) for key parameters were: HR = -1.0 versus 1.0 bpm; PR = 3.8 versus -1.1 ms; QRS = 2.8 versus 1.5 ms; QTcF -0.6 versus 2.8 ms.

The key results were: (i) no patient had a QTcF > 480 ms; (ii) no patient with a QTcF change from baseline > 60 ms; (iii) QTcF new > 450 ms for males or > 470 ms females reported in 4 (3.8%) patients in the eliglustat group; (iv) QRS new > 100 ms and increase from baseline  $\geq 25\%$  reported in 1 (2.0%) patient in the Cerezyme group, and 2 (1.9%) patients in the eliglustat group; (v) PR new > 200 ms and increase from baseline of  $\geq 25\%$  reported in 4 (3.8%) patients in the eliglustat group; (vi) bradycardic outliers (minimum post-dose HR < 50 bpm and  $\geq 25\%$  decrease from baseline) reported in 5 (4.7%) patients in the eliglustat group; and (vii) tachycardic (maximum post-dose HR > 100 bpm and  $\geq 25\%$  increase from baseline) outliers reported 1 (2.0%) patient in the Cerezyme group, and 1 (0.9%) patient in the eliglustat group.

The results of the new ECG morphologies were summarised. The key results were: (i) new abnormal U waves reported in 1 (0.9%) patient in the eliglustat group; (ii) new ST segment depression change reported in 1 (2.0%) patient in the eliglustat group, and 5 (4.7%) patients in the eliglustat group; (iii) new T wave inverted reported in 5 (9.8%) patients in the Cerezyme group, and 6 (5.7%) patients in the eliglustat group; and (iv) new complete RBBB reported in 1 (0.9%) patient in the eliglustat group.

This report included a PK/PD analysis that modelled the relationship between the predicted change from Baseline at Week 52 for  $\Delta$ QTc ( $\Delta$ QTcF and  $\Delta$ QTcB),  $\Delta$ QRS,  $\Delta$ HR and  $\Delta$ PR at the mean geometric  $C_{max}$  for the three eliglustat dose groups (50, 100, and 150 mg bd). All ECG/PK matches were included in the analysis irrespective of the dose of eliglustat or when the ECG and PK samples were taken. There were no notable differences in the parameters for each of the three doses, and the results do not give rise to concern relating to cardiac safety. Of note, the  $C_{max}$  levels were similar for each of the three doses.

#### 7.4.9.2.4. Holter monitoring

Routine Holter monitoring (24-hour dual lead) was performed in the screening period prior to Day -7 (that is, baseline reading), Week 13 ( $\pm 14$  days), and Week 65 ( $\pm 14$  days). Baseline data were compared to Week 13 and study completion/early termination (if applicable). The analyses included heart rate, ventricular events, supraventricular events, and conduction

abnormalities. Data were summarised by treatment group, and by dose for the eliglustat group, as differences from Baseline for quantitative variables and frequencies of treatment-emergent abnormalities for heart rate, ventricular, and supraventricular arrhythmic disorders. Additional 24-hour Holter monitoring and ECGs were required if the patient had eliglustat peak plasma concentrations  $\geq 150$  ng/mL that were accompanied by a related AE, a cardiac concern, or an MEOI, or if the eliglustat peak plasma concentration was  $> 250$  ng/mL.

New post-dose Holter findings (on Week 13) compared with baseline were summarised. The key results were: (i) new non-sustained ventricular tachycardia reported in 1 (1.9%) patient in the Cerezyme group; (ii) VT proarrhythmia reported in 1 (1.9%) patient in the Cerezyme group; new Mobitz I 2nd degree AV block reported in 2 (1.9%) patients in the eliglustat group; new 2:1 AV block reported in 1 (1.0%) patient in the eliglustat group; and 1 (1.0%) patient in the eliglustat group with new sinus pauses  $> 2.5$  ms.

The new post-dose Holter findings from the study-mandated readings were not necessarily associated with an AE in the clinical database. Overall, 4 (3.8%) patients in the eliglustat group had 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.

#### **7.4.9.3. ENGAGE - primary analysis period (Week 39) eliglustat versus placebo**

MEOIs were defined using the same criteria as those in ENGAGE. In this study, 1 (5%) patient in the placebo (1/20) group and no patients in the eliglustat (0/20) experienced an MEOI. The one MEOI in the placebo group was mild, non-serious, ventricular tachycardia. The study appendices included a Cardiac Safety Report, dated 20 March 2013 and the key results of this report are summarised below.

No patients in the study meet the following criteria: post-baseline QTcF  $\geq 480$  ms; QTcF change from baseline  $> 60$  ms; post-baseline PR interval  $> 200$  ms with  $\geq 25\%$  increase from baseline; peak eliglustat concentration ( $C_{max}$ )  $\geq 150$  ng/mL; and seizure (other than 1 hypoglycaemic seizure in a patient with a history of diabetes mellitus). Two (2) patients in the eliglustat group reached the threshold for pre-defined QRS abnormality criteria as defined in this study (QRS  $\geq 120$  msec). At the therapeutic doses used in this study, the central tendency analysis also showed an increase in QRS with a maximal mean effect of +6.8 ms for the eliglustat all doses group (upper bound of the 2-sided 90% CI at 9.9 msec). Holter monitoring was undertaken in a similar manner to that in ENCORE. The only new Holter 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 I 2nd degree AV block in the eliglustat group.

The mean time-averaged changes from Baseline to Week 39 for the key ECG parameters (eliglustat pooled doses [n=19] versus placebo [n=20]) were: HR = -6.2 versus -0.9 bpm ( $\Delta = -5.3$  bpm); PR = 3.7 versus 2.9 ( $\Delta = 0.8$  msec); QRS = 4.7 versus -1.1 ( $\Delta = 5.8$  msec); and QTcF = -4.3 versus -2.5 ( $\Delta = -1.8$  msec).

## **7.5. Laboratory tests**

### **7.5.1. Haematology**

#### **7.5.1.1. Integrated summary of safety - eliglustat safety set**

In the eliglustat safety set, most haematology parameters were assessed in the clinical studies at Baseline and at 13 week intervals through Week 338 (Month 78). Clinical laboratory evaluations were generally performed at central laboratories, however, local laboratories could be used at the investigator's discretion for safety monitoring.



Changes in mean haemoglobin concentration and platelet count over time were efficacy outcomes and both parameters increased from baseline following eliglustat treatment. In general, there were no significant trends over time in changes in mean values for other haematology parameters. For most haematology parameters, the majority of patients remained in the same baseline category (low, normal, or high), and there did not appear to be a trend of worsening over time for any parameter. For each parameter, the majority of patients in each treatment group were in the normal category at Baseline. The following observations were noted relating to mean changes in haematology parameters (other than haemoglobin and platelet count) over time, and to shifts normal to baseline to outside the normal range at Weeks 26, 26, 52 or 78 in  $\geq 10\%$  of patients:

**7.5.1.1.1. Erythrocyte count:**

Mean erythrocyte counts remained consistent over time (baseline, weeks 52 and 78). At Week 26, 37/358 patients (10%) had a shift from normal to low and 1 patient (<1%) had a shift from normal to high. At Week 52, 23/222 patients (10%) had a shift from normal to low, and 2/222 patients (1%) had a shift from normal to high. At Week 78, 16/132 patients (12%) had a shift from normal to low, and 5/132 patients (4%) had a shift from normal to high.

**7.5.1.1.2. Haematocrit:**

Mean haematocrit remained consistently within the normal range over a 2 year period. At Weeks 26 and 52, 13% of patients had a shift from normal to low (45/358 patients and 28/223 patients, respectively). At Week 78, 16/132 patients (12%) had a shift from normal to low, and 1/132 patient (1%) had a shift from normal to high.

**7.5.1.1.3. Reticulocyte count:**

There were no clinically meaningful changes in the reticulocyte count from baseline to weeks 26, 52, and 78. At Week 26, 2/99 patients (2%) had a shift from normal to low, and 2/99 patients (2%) had a shift from normal to high. At Week 52, 3/48 patients (6%) had a shift from normal to low, and 1/48 (2%) had shift from normal to high. At Week 78, 2/20 patients (10%) had a shift from normal to low, and 1/20 patients (5%) had a shift from normal to high.

**7.5.1.1.4. White cell counts and differentials:**

There were no clinically significant changes in mean leucocyte, lymphocyte, neutrophil, eosinophil, basophil, and monocyte counts over time, and counts remained within the normal range over a 2 year period.

**7.5.1.1.5. Lymphocyte/leukocyte ratio:**

At Week 26, 8/156 patients (5%) had a shift from normal to low and 18/156 patients (12%) had a shift from normal to high. At Week 52, 8/156 (5%) had a shift from normal to low, and 6/104 (6%) patients had a shift from normal to high. At Week 78, 3/56 (5%) of patients had a shift from normal to low, and 4/65 (6%) of patients had a shift from normal to high.

**7.5.1.2. ENCORE - primary analysis period (Week 52) eliglustat versus cerezyme**

There were no marked changes in mean haematology parameters or shifts in category (normal, low, high) from Baseline to Week 52 in either the eliglustat or Cerezyme groups. Clinically significant post-baseline haematology result was reported in 9 (8.5%) patients in the eliglustat group and 3 (5.6%) patients in the Cerezyme group. The clinically significant findings in the eliglustat group were decreased haemoglobin (4 patients), increased leukocytes (3 patients), decreased platelet count (2 patients), decreased haematocrit (2 patients), increased MCV (1 patient), decreased erythrocytes (1 patient), and increased neutrophils (1 patient). The clinically significant findings in the Cerezyme group were decreased platelet count (2 patients) and decreased erythrocytes (1 patient). The majority of the clinically significant post-baseline haematology results were considered to be unrelated to the study drug.

### **7.5.1.3. *ENGAGE - primary analysis period (Week 39) eliglustat versus placebo***

There were no marked changes in mean haematology parameters or shifts in category (normal, low, high) from Baseline to Week 39 in either the eliglustat or Cerezyme groups. Clinically significant post-baseline hematology results were reported in 3 (15%) patients in the eliglustat group and 1 (5%) patient in the placebo group. In the eliglustat group, 1 patient had 3 events (low erythrocyte count [Week 13], low haemoglobin concentration [Week 13], low haematocrit [Week 39]), 2 patients had 1 event each (low platelets [Week 4], low monocytes [Week 14]). In the placebo group, 1 patient had 1 event (low platelets [Week 13]).

### **7.5.2. Clinical chemistry**

#### **7.5.2.1. *Integrated summary of safety - eliglustat safety set***

In the eliglustat safety set, the standard range of clinical chemistry parameters was assessed at Baseline and at 13 week intervals. Generally, mean changes from Baseline were small and there were no obvious clinically significant trends in the chemistry parameters. For most clinical chemistry parameters, the majority of patients remained in the same category (low, normal, or high), and there did not appear to be a tendency towards worsening values over time for any parameter. For most chemistry parameters, the majority patients were in the normal category at Baseline and remained in this category through Week 104. The following changes were considered noteworthy:

- Mean ALT, AST and total bilirubin levels did not increase over time, while mean GGT values were lower than Baseline values for the majority of time points, and slightly higher at Week 104.
- Serum albumin, alkaline phosphatase, LDH, and protein mean values did not increase over time and were consistently the same or lower than the corresponding Baseline mean for each parameter through Week 104.
- Mean values for fasting glucose tended to increase slightly over time compared with mean Baseline values. However, mean values remained within the normal range. At Week 104, 5/47 patients (11%) had a shift in fasting glucose from normal to high.
- Mean CK values tended to increase over 24 months compared with mean Baseline values, but absolute values were not increased beyond levels expected with moderate exercise.
- No significant changes were observed in serum electrolytes over time (calcium, chloride, magnesium, phosphorous, potassium and sodium).
- Mean creatinine values were slightly higher than baseline over time.
- Mean total cholesterol values varied slightly from Baseline through Week 104. However, mean values for high-density lipoprotein cholesterol were similar to Baseline at Week 104, and calculated mean low-density lipoprotein cholesterol values were lower than Baseline at Week 104.
- Mean folic acid and homocysteine values increased over time. At Week 52, 11/89 patients (12%) had a shift in folic acid RBC values from normal to low, and 3/89 patients (3%) had a shift from normal to high. At Week 13, 3/23 patients (13%) had a shift in serum folic acid from normal to low and 2/19 (11%) had a shift from normal to low at Week 78. At Week 104, 4/20 patients (20%) had a shift in serum folic acid levels from normal to low for this parameter.
- Mean Vitamin B12 levels decreased over time. At Week 13, 5/24 patients (21%) had a shift in vitamin B12 levels from normal to low, and at Week 26, 3/24 patients (13%) had a shift from normal to low. At Week 52, 8/124 patients (6%) had a shift from normal to low, and at Week 104, 2/20 patients (10%) had a shift from normal to low.

- No significant changes were observed in ferritin, iron, and iron binding capacity values over time. At Week 13, 1/5 patients (20%) had a shift in total iron binding capacity from normal to low, but this shift did not persist over time.
- At Week 13, 12/123 patients (10%) had a shift in C-reactive protein from normal to high and 1 patient (1%) had a shift from normal to low. At Week 26, 11/115 patients (10%) had a shift in C-reactive protein from normal to high, and no patients had a shift from normal to low. At Week 78, 1/15 patients (7%) had a shift in C-reactive protein from normal to high, and no patients had a shift from normal to low.

#### **7.5.2.2. ENCORE - primary analysis period (Week 52) eliglustat versus cerezyme**

There were no marked differences between the treatment groups at Baseline for any of the chemistry parameters. Generally, mean changes from Baseline were small in each treatment group, and there did not appear to be any clinically relevant trends relating to the chemistry parameters in either treatment group. For most chemistry parameters, the majority of patients remained in the same category over the study (low, normal, or high), and there did not appear to be a trend of worsening over time in the either treatment group for any parameter.

Clinically significant post-baseline chemistry results were observed in 21 (19.8%) patients in the eliglustat group and 8 (15.1%) patients in the Cerezyme group. Most of these results were recorded as TEAEs unrelated to the study drug. In the eliglustat group, the clinically significant findings were: elevated CK (7 patients); elevated ALT (4 patients); elevated cholesterol, including elevated LDL and/or decreased HDL (4 patients); decreased folic acid (4 patients); elevated GGT (3 patients); elevated homocysteine (3 patients); elevated C-reactive protein (3 patients); elevated AST (2 patients); elevated glucose (2 patients); decreased iron or ferritin (2 patients); increased MMA (1 patient); and decreased vitamin B-12 (1 patient). In the Cerezyme group, the clinically significant findings were: elevated ALT (4 patients); elevated AST (3 patients); elevated GGT (2 patients); elevated glucose (1 patient); elevated CK (1 patient); decreased folic acid (1 patient); increased cholesterol, including elevated LDL and/or decreased HDL (1 patient); and increased bilirubin (1 patient).

#### **7.5.2.3. ENGAGE - primary analysis period (Week 39) eliglustat versus placebo**

There were no marked differences between the treatment groups at Baseline for any of the chemistry parameters. Generally, mean changes from Baseline were small in each treatment group, and there did not appear to be any clinically relevant trends relating to the chemistry parameters in either treatment group. For most chemistry parameters, the majority of patients remained in the same category over the study (low, normal, or high), and there did not appear to be a trend of worsening over time in the either treatment group for any parameter. One (1) patient in each treatment group had clinically significant post-baseline chemistry results: high homocysteine, high MMA, and low vitamin B-12 at Week 39, each recorded as TEAEs in 1 patient in the eliglustat group; low vitamin B-12 at Week 39 recorded as a TEAE in 1 patient in the placebo group'

### **7.5.3. Urinalysis**

#### **7.5.3.1. Integrated summary of safety - eliglustat safety set**

In the eliglustat safety set, urinalysis was performed in all clinical studies at protocol-specified time-points and urine pH was analysed over time at 13 week intervals. In the eliglustat safety set, the mean urinary pH at Baseline was 5.92 and showed no marked change from this level through to Week 104. There appeared to be no clinically meaningful shifts from normal to abnormal for an extensive range of urinary parameters examined in patients in the eliglustat safety.

For urine protein concentration (g/L), there appeared to be trend over time in the percentage of patients shifting from normal to abnormal. However, there were very few reports of TEAEs of

proteinuria in the eliglustat safety set (3 [0.8%] patients, each with 1 event). The low incidence of TEAEs of proteinuria suggests that the observation relating to shifts in urinary protein concentration from normal to abnormal are unlikely to be clinically significant. In addition, TEAEs in the SOC of 'renal and urinary disorders' were reported in 4.8% (19/393) of patients, and the only TEAE (PT) reported in  $\geq 5$  patients was haematuria (7 [3.6%] patients, 7 events).

#### **7.5.3.2. ENCORE - primary analysis period (Week 52) eliglustat versus cerezyme**

Clinically significant post-baseline urinalysis results were reported in 4 patients in the eliglustat group and 2 patients in the Cerezyme group. Most of these results were recorded as TEAEs unrelated to the study drug. The clinically significant urinalysis findings were occult blood (4 patients in the eliglustat group), increased leukocyte esterase (1 patient in each treatment group), and elevated glucose (1 patient in the Cerezyme group).

Proteinuria was reported as a TEAE in 1/106 (1%) patient in the eliglustat group and no (0/53) patients in the Cerezyme group. TEAEs in the SOC of renal and urinary disorders were reported in 4 (4%) patients in the eliglustat group and 2 (4%) patients in the Cerezyme group, and the only event reported in more than 1 patient was haematuria (2 [2%] patients in the eliglustat group, 1 [2%] patients in the Cerezyme group).

#### **7.5.3.3. ENGAGE - primary analysis period (Week 39) eliglustat versus placebo**

There were no patients in either the eliglustat or the placebo treatment group with post-baseline clinically significant urinalysis findings. There were no reports of proteinuria as a TEAE in either the eliglustat or placebo groups. TEAEs in the SOC of renal and urinary disorders were reported in 1 (5%) patient in the eliglustat group and 1 (5%) patient in the placebo group.

## **7.6. Other safety assessments**

### **7.6.1. Vital signs**

In the eliglustat safety set (n=393), there were no clinically meaningful changes from Baseline to Week 13 and Week 52 in mean values for the vital signs of temperature, heart rate, respiration rate, systolic blood pressure and diastolic blood pressure. There were no clinically meaningful changes in mean height, weight and BMI over the course of treatment in patients in the eliglustat safety set (n=393).

### **7.6.2. Echocardiograms**

Post-Baseline echocardiogram data were collected at Week 39 in ENGAGE and at Week 52 in ENCORE, and the data were pooled for analysis. The collection of echocardiogram data was not standardized per protocol, and the echocardiograms were not centrally read, and therefore no definitive conclusions can be made based on the data. Overall, the mean (SD) change from Baseline in LV mass was 1.4 g (42.92 g), ranging from -88 g to 131 g. LV mass increases  $\geq 20$  g were reported in 26/114 (23%) patients, and LV mass decreases  $\geq 20$  g were reported in 20/114 (18%) patients. Overall, the mean (SD) change in LV ejection fraction was -0.13% (8.399%), ranging from -18.0% to 20.0%. Increases in the LV ejection fraction of  $\geq 20\%$  were reported in 4/125 (3%) patients and decreases in the LV ejection fraction of  $\geq 20\%$  were reported in 2/125 (2%) patients.

### **7.6.3. Nerve conduction studies**

In the Phase II study (single-arm eliglustat), nerve conduction tests were performed at Screening, Weeks 52 and 104, and then annually. Four (4) patients (20%) had TEAEs of abnormal nerve conduction studies, and 2 of these patients also had other neuropathy TEAEs. One (1) additional patient had a TEAE of peripheral neuropathy reported following a neurological examination. All of these TEAEs were considered mild and non-serious, and 3 were considered by the investigator to be possibly related to eliglustat treatment (2 x nerve conduction studies abnormal; 1 x neuropathy peripheral).

In ENCORE, nerve conduction testing was assessed and recorded at Screening, Week 52 and was also to be performed if clinical symptoms or signs of nerve conduction abnormality were present. Test results performed up to Week 13 were considered the Baseline values. The local neurologist or neurophysiologist recorded the test results and the data was also sent to a blinded central reviewer for analysis. Baseline values were similar in both the eliglustat and Cerezyme treatment groups. In both groups, mean and median values for Baseline and Week 52 assessments were within the normal range. Four (4) patients in the eliglustat group experienced a TEAE of mild (n=3) or moderate (n=1) peripheral neuropathy and 3 patients in the eliglustat group experienced TEAEs recorded as a result of abnormal nerve conduction studies. The results of the Week 52 nerve conduction tests were available in 6/7 patients with TEAEs and indicated either no change from Baseline or findings of no clinically significant consequence as assessed by the central reader.

#### **7.6.4. Mean mini mental state examination (MMSE)**

The MMSE is a 30-point questionnaire, with higher scores indicating better cognition. The change in MMSE score was small during eliglustat treatment. The mean (SD) baseline score was 29.2 (1.35) in pooled eliglustat treated patients from the Phase II study, ENCORE and ENGAGE (n=222), the mean (SD) post-Baseline score (worst case) was 29.1 (1.98) (n=147), and mean (SD) change from Baseline was 0.0 (2.03) (n=147).

### **7.7. Safety issues in special groups**

#### **7.7.1. Age**

In the eliglustat safety set (ISS), patients in the > 30 to 65 year age group had a slightly higher overall incidence of TEAEs (202/226 [89%]), compared with the two other age groups (16 to 30 year group, 124/157 [79%] and > 65 year group, 8/10 [80%]). The 16 to 30 year age group included 2 patients aged 16 to < 18 years. Among the TEAEs reported in patients aged >65 years in the eliglustat safety set, most were in the SOCs of 'infections and infestations' (4 patients, [40%]), 'nervous system disorders' (4 patients, [40%]), and 'gastrointestinal disorders' (3 patients, [30%]). The reported TEAEs in these SOCs were similar to those occurring most frequently for the overall eliglustat safety set (that is, nasopharyngitis, URTI, UTI, diarrhoea, nausea, headache, and dizziness). All TEAEs reported in patients aged > 65 years were mild with the exception of the following moderate events, dizziness, nausea, excoriation, and fall (1 event each) and headache (2 patients reporting 1 event each). No SAEs were reported in patients aged >65 years. The safety data for patients aged > 65 years should be interpreted cautiously as there were only 10 patients in this age group.

#### **7.7.2. Gender**

In the eliglustat safety set (ISS), TEAEs were reported in 84% (161/191) of male patients and 86% (173/202) of female patients.

TEAEs reported more frequently ( $\geq 5\%$  difference) in female patients than male patients (in decreasing order of frequency) were: headache (20% versus 13%); arthralgia (18% versus 10%); dizziness (13% versus 6%); nausea (12% versus 5%); back pain (12% versus 6%); abdominal pain upper (11% versus 6%); pain in extremity (11% versus 5%); fatigue (11% versus 4%), influenza (9% versus 3%); UTI (9% versus 2%); cough (8% versus 3%); and bone pain (7% versus %). Syncope was also reported more frequently in female patients (8 [4%]) than in male (0 [0%]) patients. An analysis of ECG findings by gender showed no apparent differences. No TEAEs occurred more frequently in male patients with a  $\geq 5\%$  difference compared with female patients.

The majority of male and female patients in the eliglustat safety set experience non-serious TEAEs. The overall incidence of SAEs was 7% (14/91) in male patients, and 10% (21/202) in

female patients. The only SAE reported more frequently ( $\geq 2\%$  difference) in female patients than in male patients was syncope (2% versus 0%, respectively).

### 7.7.3. Race

The majority of patients in the eliglustat safety set (ISS) were Caucasian (n=323, 82%), followed by Asian (n=42, 11%), black or African American (n=17, 4%), unknown (n=10, 3%), and multiple (n=1, 0.3%). The incidence of TEAEs in the eliglustat safety set (ISS) was 86% (279/323) in Caucasian patients, 74% (21/42) in Asian patients, 76% (13/17) in black or African American patients, 100% (10/10) in unknown patients, and 100% (1/1) in multiple patients. However, the imbalance in patient numbers between the different racial groups is considered to precluded meaningful interpretation of the differences in TEAEs among the groups.

### 7.7.4. Safety in patients in the upper 10th percentile for plasma exposure

The sponsor stated that, due to the dose-titration method used in the Phase II and Phase III studies, analyses of TEAEs by dose may not be particularly informative. Therefore, the sponsor undertook a sensitivity analysis to determine whether any trends in TEAEs and SAEs could be identified in patients with higher eliglustat exposures. In the eliglustat safety set, 69/393 (17.6%) patients were categorised as having plasma exposure to eliglustat in the upper 10th percentile of exposure based on exceeding the thresholds for one or more PK parameters (that is,  $C_{max}$  [67.4 ng/mL];  $AUC_{(0-\tau)}$  [459 ng.h/mL];  $C_{trough}$  [19.9 ng/mL]).

Of the 69 patients in the subgroup, 57 (83%) had at least 1 TEAE. The SOC with the most frequently reported TEAEs were 'gastrointestinal disorders' (38/69 patients [55%]), 'infections and infestations' (35/69 patients [51%]), 'musculoskeletal and connective tissue disorders' (27/69 patients [39%]), and 'nervous system disorders' (26/69 patients [38%]). The most frequently reported TEAEs occurring in  $\geq 10\%$  of patients were: arthralgia (23%); headache (20%); nausea (19%); nasopharyngitis (14%); fatigue (14%); URTI (13%); dizziness (13%); diarrhoea (13%); influenza (12%); abdominal pain upper (12%) and back pain (12%). Most of the TEAEs were mild or moderate in intensity.

The incidence of two TEAEs was higher in the subgroup than in the eliglustat safety set as a whole: arthralgia (16/69 patients [23%] versus 55/393 patients [14%]); and nausea (13/69 patients [19%] versus 33/393 patients [8%]). Cardiac disorders occurred in 4/69 patients (6%) in the subgroup, which was similar to the incidence in the eliglustat safety set as a whole (41/393 patients [10%]). TEAEs of acute myocardial infarction, AV block 2nd degree, palpitations and ventricular tachycardia were each reported in 1 patient.

SAEs were reported in 11/69 (16%) patients in the subgroup. SAEs of syncope occurred in 2/69 (3%) patients, and other SAEs occurring in 1 patient each were hepatic neoplasm malignant, uterine leiomyoma, acute myocardial infarction, medical device pain, device malfunction, cholecystitis, nasal septum deviation, mammoplasty, and aortic aneurysm.

A total of 53/393 (13%) patients in the eliglustat group exceeded the  $C_{max}$  threshold (67.44 ng/mL) at least once, and 44 (83%) of these patients had at least 1 TEAE. The most frequently reported TEAEs occurring in  $\geq 10\%$  of patients were: arthralgia (26%); headache (23%); nausea (23%); influenza (15%); URTI (15%); dizziness (15%); fatigue (13%); nasopharyngitis (13%); diarrhoea (13%); abdominal pain upper (13%); bone pain (11%); and back pain (11% each). A total of 3/393 (0.8%) patients in the eliglustat safety set exceeded the  $AUC_{(0-\tau)}$  threshold at least twice (all 3 with at least 1 TEAE), and a total of 32/593 patients exceeded the  $C_{trough}$  threshold at least twice (28 patients with at least 1 TEAE).

## 7.8. Post-marketing data

Not applicable.



## 7.9. 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%.<sup>8</sup> 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 (that is, placebo or active). Therefore, the 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.

### 7.9.1. 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 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 ( $\geq 10\%$  of patients) were: headache (17%); arthralgia (14%); nasopharyngitis (13%); upper respiratory tract infection (11%); diarrhoea (10%), and dizziness (10%). No individual TEAEs occurred in  $\geq 18\%$  of patients.

Treatment-related TEAEs were reported in 159 (40%) patients and those reported with an incidence of  $\geq 2\%$  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  $\geq 6\%$  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  $\geq 1$  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 HLT or 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 (that is, > 480 ms post-baseline,  $\leq 480$  ms baseline); 6 patients with QTcF change from baseline > 60 ms; 7 patients with PR > 200 ms and increase from baseline  $\geq 25\%$ ; and 18 patients with QRS  $\geq 120$  ms.

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, BMI).

The limited safety profile in patients aged  $\geq 65$  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 10th 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 ( $C_{max}$ ,  $AUC_{(0-tau)}$  and/or  $C_{trough}$ ), 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.

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

In the pivotal study in GD1 patients previously stabilized on Cerezyme [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) were 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 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). TEAEs occurring in  $\geq 5\%$  more patients in the eliglustat group (descending order of frequency) versus the Cerezyme group by SOC were: 'infections and infestations' (56% versus 36%); 'gastrointestinal disorders' (54% versus 17%); 'musculoskeletal and connective tissue disorders' (39% versus 30%); 'nervous system disorders' (35% versus 9%); 'general disorders and administration site conditions' (27% versus 8%); 'investigations' (23% versus 17%); 'injury, poisoning and procedural complications' (20% versus 11%); 'respiratory thoracic and mediastinal disorders' (19% versus 4%); 'skin and subcutaneous tissue disorders' (15% versus 4%); 'reproductive and breast disorders' (10% versus 4%); 'cardiac disorders' (8% versus 2%); 'ear and labyrinth disorders' (8% versus 2%); and 'neoplasms benign, malignant and unspecified (including cysts and polyps)' (6% versus 0%). The only SOC group with TEAEs reported in  $\geq 5\%$  more patients in the Cerezyme group than in the eliglustat group was 'hepatobiliary disorders' (13% versus 5%).

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). TEAEs reported in  $\geq 5\%$  of patients in either of the two treatment groups and in  $\geq 2\%$  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%); sinusitis (10% versus 2%); asthenia (8% versus 0%); dizziness (8% versus 0%); dyspepsia (7% versus 2%); GORD (7% versus 0%); cough (7% versus 4%); influenza (6% versus 4%); bone pain (6% versus 2%); viral gastroenteritis (5% versus 2%); constipation (5% versus 0%); epistaxis (5% versus 0%); rash (5% versus 0%); contusion (5% versus 0%) and palpitations (5% versus 0%). The only TEAEs reported in  $\geq 5\%$  of patients in either of the two treatment groups and in  $\geq 2\%$  more patients in the Cerezyme group versus the eliglustat group were hepatomegaly (6% versus 1%), toothache (6% versus 2%), and UTI (5% versus 9%).

Notably treatment related AEs also occurred more commonly in patients in the eliglustat group compared with the placebo group (38% [40/106] versus 11% [6/53], respectively). TEAEs reported as being related to drug-treatment ( $\geq 2\%$  of patients in either treatment group) and occurring  $\geq 2\%$  more patients in the eliglustat group (descending order of frequency) versus the Cerezyme group were: diarrhoea (5% versus 0%); arthralgia (4% versus 0%); headache (4% versus 0%); fatigue (4% versus 0%); somnolence (3% versus 0%); GORD (3% versus 0%); nausea (3% versus 0%); splenomegaly (3% versus 0%); pain in extremity (2% versus 0%);

asthenia (2% versus 0%); dizziness (2% versus 0%); tremor (2% versus 0%); upper abdominal pain (2% versus 0%); constipation (2% versus 0%); dry mouth (2% versus 0%); dysphagia (2% versus 0%); flatulence (2% versus 0%); blood folate decreased (2% versus 0%); blood homocysteine increased (2% versus 0%); palpitations (2% versus 0%); and throat irritation (2% versus 0%). TEAEs reported as being related to drug-treatment ( $\geq 2\%$  in of patients in either treatment group) and occurring in  $\geq 2\%$  more patients in the Cerezyme group (descending order of frequency) were: blood cholesterol increased (4% versus 0%); extravasation (2% versus 0%); infusion site induration (2% versus 0%); and anxiety (2% versus 0%).

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). The only SAE reported in more than 1 patient in the eliglustat group was syncope (n=2 [1%]). Only 1 SAE resulted in study discontinuation (myocardial infarction). 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%) 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 AV nodal in origin (AV block second degree [n=3]; 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 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: HR = -1.0 versus 1.0 bpm; PR = 3.8 versus -1.1 ms; QRS = 2.8 versus 1.5 ms; and QTcF -0.6 versus 2.8 ms. The PK/PD analysis modelling the relationship between the predicted change from Baseline at Week 52 for  $\Delta$ QTc ( $\Delta$ QTcF and  $\Delta$ QTcB),  $\Delta$ QRS,  $\Delta$ HR and  $\Delta$ PR at the mean geometric  $C_{max}$  for the three eliglustat dose groups (50, 100, and 150 mg bd) did not identify any notable differences across the three dose groups and 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.

### **7.9.3. ENGAGE - eliglustat (n=20) versus placebo (n=20) - treatment-naive GD1 patients**

In the pivotal study in treatment-naive patients [ENGAGE], 20 patients were randomized 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  $\geq 15\%$  of patients (that is,  $n \geq 3$ ) 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  $\geq 2$  patients in the eliglustat group. The most commonly reported TEAEs occurring in  $\geq 15\%$  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  $\geq 2$  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  $\geq 2$  patients ( $\geq 10\%$ ) 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, it 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.

## 8. First round benefit-risk assessment

### 8.1. First round assessment of benefits

#### 8.1.1. 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 (for example, osteonecrosis and/or pathological fractures, as assessed by X-ray and/or 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 (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: that is, 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  $C_{\text{trough}}$  levels  $< 5$  ng/mL or  $\geq 5$  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 ( $\log AUC_{(0-\tau)}$ ).

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.

#### **8.1.2. GD1 patients stabilized 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 stabilized 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 Section 7.4.2 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 (for example, 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.

## 8.2. 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 stabilized 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 safe for this indication.

### 8.2.1. 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 2<sup>nd</sup> degree [n=3]; AV block 1<sup>st</sup> 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 2<sup>nd</sup> degree AV block with no reports of 3<sup>rd</sup> 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%) patient (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, 3<sup>rd</sup> 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 URM from treatment with eliglustat would mean that it will be mandatory for all patients to be CYP2D6 genotyped prior to treatment in order to determine their metaboliser status.

### **8.2.2. 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  $\geq 10\%$  of patients in either of the two treatment groups and in  $\geq 2\%$  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  $\geq 10\%$  of patients in either of the two treatment groups and in  $\geq 2\%$  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, it 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.

### **8.2.3. 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  $\geq 15\%$  of patients (that is,  $n \geq 3$ ) 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  $\geq 2$  patients in the eliglustat group. The most commonly reported TEAEs occurring in  $\geq 15\%$  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  $\geq 2$  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.

#### **8.2.4. 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 ( $\geq 10\%$  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  $\geq 1$  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, 3rd 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 (that is, temperature, respiratory rate, blood pressure, BMI).

The limited safety profile in patients aged  $\geq 65$  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.

### **8.3. First round assessment of benefit-risk balance**

#### **8.3.1. GD1 patients who are treatment-naive**

The benefit-risk balance of the proposed treatment regimen (that is, 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 benefit* and *First round assessment of risk*.

### **8.3.2. GD1 patients stabilized 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  $C_{\text{trough}}$  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 stabilized 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  $C_{\text{trough}}$  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 ( $\log AUC_{(0-\tau)}$ ). 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 (that is, % change in spleen volume, % change in platelet count, absolute change in haemoglobin concentration) could be undertaken as no relationships were seen between observed  $\log AUC_{(0-\tau)}$  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.

## **9. First round recommendation regarding authorisation**

### **9.1. GD1 patients who are treatment-naive**

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

### **9.2. GD1 patients stabilized on ERT prior to switching to eliglustat**

It is recommended that the proposed treatment regimen (that is, 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 stabilized 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) stabilized 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 ( $\log AUC_{(0-\tau)}$ ). 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  $\log AUC_{(0-\tau)}$ ) 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  $\log AUC_{(0-\tau)}$ ) 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 stabilized 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'.<sup>9</sup>
5. The exploratory efficacy analysis [ENCORE] in subgroups based on  $C_{\text{trough}}$  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 (that is, 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.

## 10. Clinical questions

### 10.1. Clinical questions

#### 10.1.1. 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 characterizing the identity of the human plasma protein binding proteins?
4. In ENCORE, the PK parameters, including C<sub>trough</sub> 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 (see CSR, Tables in study synopsis). 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<sub>(0-tau)</sub> 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<sub>(0-tau)</sub>. 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  $\log AUC_{(0-\tau)}$  and  $\log C_{\max}$ . 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  $\log AUC_{(0-\tau)}$  and  $\log C_{\max}$ . Therefore, the proposed dosing regimen for patients stabilized 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 endpoint failed to demonstrate a treatment effect in the concentration range studied in ENCORE.

#### 10.1.2. Efficacy

1. What method was used to randomize patients in ENCORE (for example, IVRS)?
2. 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.
3. In ENCORE, the median age for patients switching from ERT to eliglustat (FAS) is given as 37.4 years in the CSR, while in the Summary of Clinical Efficacy it is given as 36.9 years. Please account for this apparent discrepancy.
4. 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?
5. For ENCORE, please indicate the proportion of patients in each of the three dosage groups with trough plasma concentrations  $< 5$  ng/mL and  $\geq 5$  ng/mL.
6. 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  $C_{\text{trough}}$  values  $< 5$  ng/mL, compared with 56/66 (85%) patients with average steady-state  $C_{\text{trough}}$  values  $\geq 5$  ng/mL. Please provide the difference between the proportions with 95% confidence intervals.
7. In ENGAGE, the reduction in spleen volume (MN) was 23.05% in the patient group with average  $C_{\text{trough}}$  concentrations  $< 5$  ng/mL ( $n=9$ ) and 31.28% in patients with average  $C_{\text{trough}}$  levels  $\geq 5$  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.
8. 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.

#### 10.1.3. Safety

1. 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.

## 11. Second round evaluation of clinical data submitted in response to questions

### 11.1. Pharmacokinetics

#### 11.1.1. Question 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.

##### **11.1.1.1. Sponsor's response:**

The sponsor has planned a study to investigate the pharmacokinetics of eliglustat in subjects with impaired hepatic function. The study in hepatic-impaired subjects was included with the dossier submission in Module 1.13.1, Part III of RMP v1.0 as an additional pharmacovigilance activity to address the missing information 'Use in patients with hepatic impairment'. The final study protocol is planned to be completed in Q2 2015, and the final clinical study report is planned to be submitted in Q3 2017.

##### **11.1.1.2. Clinical evaluator's comment:**

The sponsor's commitment to undertake and submit a study investigating the PKs of eliglustat in subjects with hepatic impairment is noted. In the absence of PK data in patients with hepatic impairment, it is recommended that the Precautions section of the PI include a paragraph headed Hepatic impairment. This paragraph should specifically state that eliglustat has not been studied in patients with hepatic impairment. This paragraph should also state - 'the two pivotal studies (ENGAGE and ENCORE) excluded patients with documented prior oesophageal varices or liver infarction or current liver enzymes (ALT/AST or total bilirubin) greater than 2 times the upper limit of normal, unless the patient had a diagnosis of Gilbert Syndrome.'

#### 11.1.2. Question 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.

##### **11.1.2.1. Sponsor's response:**

The sponsor's response has been edited. However, the clinical evaluator warrants that the key features of the response have been provided below.

The sponsor has planned a study to investigate the pharmacokinetics of eliglustat in subjects with impaired renal function. The eliglustat metabolite profiling in human urine was consistent with that in human plasma, mainly as sequential oxidative metabolites. Among the 10 structure elucidated metabolites, a single metabolite (Genz-399240) was identified in human plasma at levels exceeding 10 percent of total drug-related exposure. This disproportionate metabolite was qualified in genotoxicity assays (GT-157-TX-60; GT-157-TX-62) and in a separate 13-week toxicology study conducted in rats (GT-157-TX-61); and no unique toxicities were identified.

Additionally, no significant contribution of the 10 metabolites to the pharmacological activity of eliglustat is expected, as Genz-399240 does not inhibit the target, glucosylceramide synthase,

and the other 9 metabolites exhibited at least 55-fold less activity than eliglustat for glucosylceramide synthase inhibition.

The metabolites were also evaluated in vitro for inhibitory effects on hERG, sodium and calcium cardiac ion channels, and no inhibitory effects on these cardiac ion channels were observed except Genz-256222 with  $IC_{50}$ 's for the  $K^+$ ,  $Na^+$ , and  $Ca^{++}$  ion channels of 1.8, 13, and 18  $\mu\text{g}/\text{ml}$ , respectively. Data from clinical studies where this metabolite was quantified indicate that the mean plasma  $C_{\text{max}}$  of Genz-256222 ranged from 1.2 to 7.88 ng/ml at steady state; values that are at least 228-fold lower than the ion channel activities.

For all these reasons, the study in renal impaired subjects will only assess the pharmacokinetics of the parent drug. The proposed study will be added to Part III of the updated RMP (v1.1) as an additional pharmacovigilance activity to address the missing information 'Use in patients with renal impairment'. The final study protocol is planned to be completed in Q2 2015, and the final clinical study report is planned to be submitted in Q3 2017.

#### **11.1.2.2. Clinical evaluators comment:**

The sponsor's commitment to undertake and submit a study investigating the PKs of eliglustat in subjects with renal impairment is noted. The sponsor proposes PK investigation of the parent drug, but not the metabolites. The sponsor's decision not to undertake investigation of the PKs of the metabolites is based on data suggesting that accumulation of the metabolites in patients with renal impairment is unlikely to have clinically significant safety consequences. This proposal is considered to be acceptable.

In the absence of PK data in patients with renal impairment it is recommended that the Precautions section of the PI include a paragraph headed Renal impairment. This paragraph should specifically state that eliglustat has not been studied in patients with renal impairment. This paragraph should also state 'the two pivotal studies (ENGAGE and ENCORE) excluded patients with clinically significant renal disease'.

#### **11.1.3. Question 3**

Does the sponsor have any data characterizing the identity of the human plasma protein binding proteins?

##### **11.1.3.1. Sponsor's response:**

The sponsor's response has been edited. However, the clinical evaluator warrants that the key features of the response have been provided below.

The identity of the human plasma protein(s) to which eliglustat binds has not been characterised. Total protein binding of eliglustat in human plasma was determined in vitro using rapid equilibrium dialysis. Eliglustat exhibited moderate plasma protein binding in humans and was generally independent of drug concentration ranging from 82.9% at 0.01  $\mu\text{M}$  to 76.4% at 1.0  $\mu\text{M}$ . This concentration range covers the eliglustat steady state  $C_{\text{max}}$  (0.11  $\mu\text{M}$ , 44.3 ng/mL) at the therapeutic dose of 100 mg twice daily.

##### **11.1.3.2. Clinical evaluator's comment:**

The sponsor's response is acceptable.

#### **11.1.4. Question 4**

In ENCORE, the PK parameters, including  $C_{\text{trough}}$  levels, in CYP2D6 EMs were similar for the 50 mg bd, 100 mg bd and 150 mg bd doses at both Week 13 and Week 52 (see CSR, Tables in study synopsis). 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.

#### 11.1.4.1. Sponsor's response:

The sponsor's response has been edited. However, the clinical evaluator warrants that the key features of the response have been provided below.

In ENCORE study, GD 1 patients were titrated to the higher dose if their  $C_{trough}$  were less than 5 ng/mL. This method of dose titration separated patients according to their ability to metabolize eliglustat, while maintaining them in a similar range that has been shown to be safe and efficacious. It also resulted in similar observed exposure for 50 mg bd, 100 mg bd and 150 mg bd doses since patients titrated to the different dose groups were presumed to differ in their ability to metabolize eliglustat. Therefore, the study-observed exposures for these 3 doses cannot be the same as if CYP 2D6 IM/EM patients had been randomized to 50 mg bd, 100 mg bd or 150 mg bd directly without titration, and thus cannot provide a comparison for these exposures.

To provide a fair comparison using the observed data, exposure at different doses within the same patients should be compared. Table 44 (see below) describes the steady-state Genz-99067 plasma  $C_{trough}$  for CYP2D6 IM/EM patients at Weeks 2, 6, and 13 by planned dose groups after dose titration (50 mg bd, 100 mg bd and 150 mg bd). Genz-99067 plasma  $C_{trough}$  rose with each dose increase from 50 mg bd to 100 mg bd and 150 mg bd groups, demonstrating that, without dose titration, the exposures at each dose level would not be similar. The concentration units were not provided for the  $C_{trough}$  levels in Table 44, but it is reasonable to infer from the totality of the PK data that they were ng/mL.

**Table 44: ENCORE - Descriptive statistics of GENZ-99067  $C_{trough}$  at Weeks 2, 6, and 13 for CYP2D6 IM/EM eliglustat patients (PK set).**

Planned dose after titration	Week/Dose	N	Mean	SD	Min	Max
ELIGLUSTAT 50 mg BID	Week 2 /50 mg BID	17	11.7	7.58	6.20	32.3
	Week 6 /50 mg BID	17	12.4	7.39	5.06	31.6
	Week13 /50 mg BID	17	9.83	8.27	0.00	29.6
ELIGLUSTAT 100 mg BID	Week 2 /50 mg BID	31	2.42	1.01	1.06	4.60
	Week 6 /100 mg BID	31	9.87	4.82	5.09	24.8
	Week13 /100 mg BID	31	7.35	4.49	1.15	24.2
ELIGLUSTAT 150 mg BID	Week 2 /50 mg BID	41	1.07	0.849	0.21	4.50
	Week 6 /100 mg BID	41	2.48	1.26	0.53	4.77
	Week13 /150 mg BID	41	7.62	6.15	1.06	26.1

For eliglustat patients with a planned dose of 50 mg bd,  $C_{trough}$  were summarised if this patient was dose at 50 mg bd at Weeks 2, 6 and 13 with no missing data. For eliglustat patients with a planned dose of 100 mg bd,  $C_{trough}$  were summarised if this patient was dose at 50 mg bd at Week 2, 100 mg bd at Weeks 6 and 13 with no missing data. For eliglustat patients with a planned dose of 150 mg bd,  $C_{trough}$  were summarised if this patient was dose at 50 mg bd at Week 2, 100 mg bd at Week 6 and 150 mg bd at Week 13 with no missing data. Two patients with indeterminate CYP2D6 phenotype were also included.

In clinical practice, the dose titration used in the study would be complicated by the need for the repeat testing of plasma levels in the setting of potentially large fluctuations in exposure and would require the health care provider/patient to precisely time the last dose so that the plasma level could be accurately interpreted. An optimized dosing regimen based on CYP2D6 phenotype has been subsequently proposed, building upon the approach used in the clinical trials, with a recommended use of eliglustat for the IM and EM patients (which constitute the

majority of GD1 patients) using a single dosing regimen of 100 mg bd for both naïve and ERT-stabilized patients to aid 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. 100 mg bd is a dose that will achieve the exposure levels proven to be safe and effective in our pivotal clinical trials in the vast majority of GD1 patients (that is, IM and EM patients) and that has been shown to be efficacious in the sickest patients (treatment-naïve patients).

Clinical experience supports the choice of 100 mg bd as an appropriate dose for the IM and EM target patient population, whether treatment-naïve or stable on ERT. The majority of the treatment-naïve patients with an IM or EM phenotype were successfully treated at the 100 mg bd dose (Phase II and ENGAGE studies). This is important from a clinical perspective because untreated GD1 patients have a higher disease burden than patients stable on ERT and, consequently, require initial debulking of glucosylceramide from tissues in order to improve their clinical status. In contrast, ERT-stabilized patients have a low substrate load and low disease burden and the target for them is in essence to demonstrate maintenance of stability. If treatment-naïve patients with a higher disease burden can be treated successfully at 100 mg bd, it is expected that this dose would also be sufficient for ERT-stabilized patients.

It has been suggested by TGA that the lack of a dose-response in ENCORE study makes it difficult to determine the correct dose for these patients. However, a lack of dose-response in ERT-stabilized patients is not unexpected. Patients enrolled in ENCORE study had received ERT for > 3 years and were considered clinically stable by virtue of meeting pre-specified therapeutic goals. Due to their already-low substrate load and low disease burden, these patients first need to re-accumulate substrate to a critical level before clinical changes occur. In addition, the clinical impact of efficacy endpoint changes observed in ERT-stabilized patients can be misleading because the changes are occurring on normal or near-normal baseline values and result in values that remain within the therapeutic goals. Lastly, since Gaucher disease is a chronic condition with largely reversible features, gradual improvements that continue beyond the timeframe of a short-term clinical trial (where stability would be the goal for ERT-stabilized patients) are clinically acceptable and expected, as evidenced by the long-term therapeutic goals for ERT that extend out to 2 to 5 years.

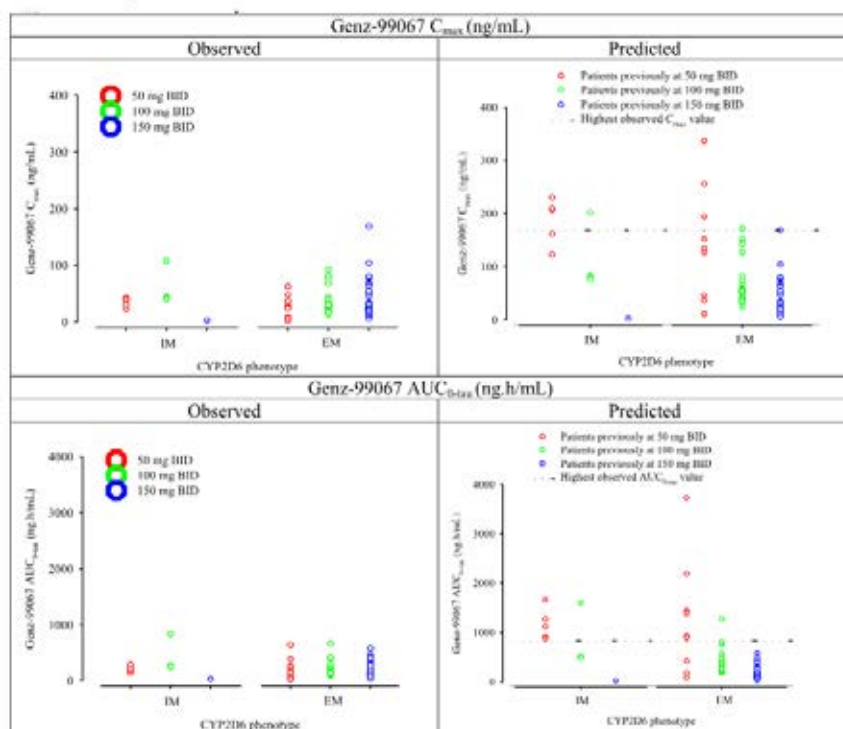
The PK/efficacy analysis also supports the choice of 100 mg bd for all IM and EM patients. For the IM and EM patients who were treated at 50 mg bd in ENCORE and would be treated at 100 mg bd with the proposed CYP2D6 phenotype dosing regimen, their efficacy would be expected to be similar or better. For the IM and EM patients who were treated at 150 mg bd and would be treated at 100 mg bd with the proposed dosing regimen, PK/PD modelling projects only an additional 4% maximum increase for individual patient spleen volume values compared to the observed changes in the study with this decrease in dose, which is a small change relative to the essentially normal spleen volumes (therapeutic goal for spleen volume is  $\leq 2$  to 8MN) and is comparable to the test-test variability of organ volume measurement by magnetic resonance imaging (MRI). Such a small change in patients with little or no splenomegaly would not be clinically or medically noticeable. Thus, 100 mg bd is an effective dose for IM and EM patients receiving a chronic therapy, and the added exposure from a 150 mg bd dose is not expected to provide any meaningful clinical benefit.

If a 150 mg bd dosing regimen were instead proposed for all IM and EM patients, the predicted higher Genz-99067 exposures in patients who were treated at 50 and 100 mg bd (especially those slower metabolisers who were treated with 50 mg bd) could lead to potential safety concerns as it will move some values outside of the range of exposure encountered in the clinical trials. Individual Genz-99067 exposure projections were performed using the physiologically-based PBPK model to determine the range of exposures that would be expected if all ENCORE patients were to receive a 150 mg bd dosing regimen. Fourteen IM and EM patients who had received eliglustat 50 mg bd by Week 52 based on the  $C_{\text{trough}}$  algorithm and 34

IM and EM patients who received 100 mg bd were used in this analysis (PK set). For those patients, observed exposure parameters ( $C_{max}$  and  $AUC_{0-\tau}$ ) were projected to the exposures that would be expected for 150 mg bd dosing using the exposure ratios estimated based on PBPK simulations from EMs.

Figure 10 illustrates the observed exposures for these patients, as well as the predicted exposures, which are higher than the ranges observed in the clinical study. 150 mg bd is therefore not an appropriate dose for all patients in our target IM and EM patient population.

**Figure 10: ENCORE - Observed and 150 mg bd PBPK-Model projected GENZ-99067  $C_{max}$  and  $AUC_{0-\tau}$  in the ENCORE study - Week 52.**



With a 50 mg bd dosing regimen, while Genz-99067 lower exposure for those patients who were treated at 100 and 150 mg bd would not bring a safety concern, decreased efficacy is predicted in some ENCORE patients. As described in the response to PK Question 5, for IM and EM patients dosed at 100 mg bd or 150 mg bd in the study, their projected % change in spleen volume (MN) at Week 52 if dosed at 50 mg bd were provided based on the PK/PD model and PopPK predicted  $\log AUC_{(0-\tau)}$  ratios between doses. Table 45 presents IM and EM patients' individual % change in spleen volume values with an increase from baseline > 15% at the projected value of 50 mg bd or at the observed value at 100 mg bd or 150 mg bd. As specified in ENCORE study, an increase in % change in spleen volume from baseline beyond a pre-specified treatment failure threshold (in this case, increase from baseline > 25%) would result in a change in the composite endpoint status from stable (success) to failure. When projecting IM and EM patients dosed at 100 mg bd or 150 mg bd to be dosed at 50 mg bd, 5 patients who had observed spleen volume value increases < 25% (and were observed composite endpoint successes) in the ENCORE primary analysis period (PAP) had projected % change in spleen volume values that were > 25% (became treatment failures). Clearly, 50 mg bd would not provide sufficient efficacy in all patients in our IM and EM target patient population.

In conclusion, the 100 mg bd regimen is predicted to maintain efficacy in the entire population without creating potential safety concerns based on higher than previously studied exposure.



**Table 45: ENCORE - Listing of EM and IM eliglustat patients with any observed or projected spleen volume (MN) increase > 15% from Baseline to Week 52 if given a different dose (per protocol set and ~ logAUC<sub>0-tau</sub>).**

Actual eliglustat dose received post titration	CYP2D6 Phenotype	Observed Composite endpoint	Spleen Volume %Change from baseline	
			Observed	Projected to 50 MG BID
150 MG BID	Extensive	SUCCESS	6.28	15.38
150 MG BID	Indeterminate	FAILURE	11.00	20.45
100 MG BID	Extensive	FAILURE	11.30	17.32
<b>150 MG BID</b>	<b>Extensive</b>	<b>SUCCESS</b>	15.87	<b>25.87</b>
<b>150 MG BID</b>	<b>Extensive</b>	<b>SUCCESS</b>	15.96	<b>25.87</b>
<b>150 MG BID</b>	<b>Extensive</b>	<b>SUCCESS</b>	16.48	<b>26.50</b>
<b>100 MG BID</b>	<b>Extensive</b>	<b>SUCCESS</b>	20.21	<b>26.71</b>
<b>150 MG BID</b>	<b>Extensive</b>	<b>SUCCESS</b>	22.58	<b>32.99</b>
50 MG BID	Extensive	FAILURE	25.93	--
150 MG BID	Extensive	FAILURE	37.55	49.20

For all IM and EM patients, their spleen volume % changes were projected to effects if given 50 mg bd. The projected spleen volume % changes were calculated based on the established PK/PD model and projecting patient's observed exposure to the exposure on the projected dose by multiplying the PopPK predicted mean AUC<sub>0-tau</sub> ratios between doses. For IM and EM patients already on the projected dose in each corresponding projection analysis, their observed values were used. There were 2 patients on eliglustat 150 mg bd with indeterminate CYP2D6 phenotype and treated as IM and EM phenotype in the projection analysis. For PM and URM patients, the observed spleen volume % changes were used. Eliglustat patient [information redacted] who returned to Cerezyme was excluded from the analysis. Note: Patient identification numbers have been removed from the table.

#### **11.1.4.2. Clinical evaluator's comment:**

Using the observed data from ENCORE in CYP2D6 IM/EM patients comparing exposure at different doses within the same patient group the sponsor argues that without dose titration exposures at each dose level would not be similar (see Table 44, above). Despite the sponsor's claim, it is considered that the steady-state Week 13 data from Table 44 do show similar mean C<sub>trough</sub> levels for the 100 mg bd and 150 mg bd doses, while the mean C<sub>trough</sub> levels for both doses were lower than the mean C<sub>trough</sub> level for the 50 mg bd dose. However, inter-subject variability in the steady-state Week 13 mean C<sub>trough</sub> levels was high for each of the three doses, with the C<sub>trough</sub> ranges for both the 100 mg bd dose and the 150 mg bd dose being enclosed within the C<sub>trough</sub> range for the 50 mg bd dose. It is considered that the Table 44 steady-state Week 13 C<sub>trough</sub> data do not support selection of one dose in preference to the other two doses for the treatment of CYP2D6 IM/EM patients. However, the only way to definitively compare C<sub>trough</sub> levels across the three dose groups would be to randomize a population of CYP2D6 IM/EM patients to fixed-dose treatment with 50 mg bd, 100 mg bd or 150 mg bd and then measure steady-state C<sub>trough</sub> levels.

The sponsor states that, in clinical practice, the dose titration regimen used in ENCORE 'would be complicated by the need for the repeat testing of plasma levels in the setting of potentially large fluctuations in exposure and would require the health care provider/patient to precisely time the last dose so that the plasma level could be accurately interpreted'. However, the use of dose titration in clinical practice is not unusual and the difficulties referred to by the sponsor could be overcome without too much inconvenience to the patient. In ENCORE, plasma trough levels for determination of subsequent dose escalation (Week 4 and Week 8) were determined at only two time-points (Week 2 and Week 6). Therefore, it is considered that determination of



exposure at Weeks 2 and 6 would not be too onerous for a drug which will be administered indefinitely.

The sponsor argues that the PK/efficacy analysis supports the choice of 100 mg bd for all IM/EM patients. The sponsor states that for CYP2D6 IM/EM patients in ENCORE who were treated with 50 mg bd, efficacy would be expected to be similar or better if treated with the proposed regimen of 100 mg bd. Based on the results of the submitted analysis this is considered to be a reasonable conclusion. In addition, the sponsor states that for CYP2D6 IM/EM patients in ENCORE treated with 150 mg bd, the PK/PD model predicts that the maximum increase in spleen volume would be only 4% greater if dosed at 100 mg bd. The sponsor considers that the greater reduction in spleen volume in CYP2D6 IM/EM patients treated with 150 mg bd compared with 100 mg bd is not expected to provide any clinically meaningful benefit. Based on the results of the submitted analysis this is considered to be a reasonable conclusion.

The sponsor also provided PK/PD modelling and Pop/PK simulation data showing that CYP2D6 EM patients (n=5) treated with 100 mg bd (n=1) or 150 mg bd (n=4) with a successful composite response would fail the composite response criteria due to decreased reduction in spleen volume if administered a projected dose of 50 mg bd (see Table 45). Therefore, the sponsor concludes that the 50 mg bd dose would not provide sufficient efficacy in all patients in the CYP2D6 IM/EM target population. Based on the results of the submitted analysis this is considered to be a reasonable conclusion.

The sponsor expressed concern about the safety of a 150 mg bd dosing regimen for the treatment of the CYP2D6 IM/EM target population. The sponsor noted that the predicted higher Genz-99067 exposures for the 150 mg bd regimen for patients treated at 50 mg bd and 100 mg bd (especially those slower metabolisers who were treated with 50 mg bd) will move some GENZ-99607  $C_{max}$  values outside of the range of exposure encountered in the clinical trials (see Figure 10, above). Consequently, the sponsor concludes that the 150 mg bd dose is not an appropriate dose for all patients in CYP2D6 IM/EM target population. Based on the results of the submitted analysis this is considered to be a reasonable conclusion.

Review of the observed steady-state (Week 52) data from ENCORE show that the mean  $\pm$  SD  $C_{max}$  values in CYP2D6 EMs were  $26.8 \pm 20.0$  ng/mL (n=9),  $35.1 \pm 21.3$  ng/mL (n=30) and  $38.1 \pm 30.8$  ng/mL (n=41) for the 50 mg bd, 100 mg bd and 150 mg bd dosing regimens, respectively. The corresponding  $C_{max}$  values in CYP2D6 IMs were  $34.9 \pm 8.11$  ng/mL (n=5),  $58.7 \pm 32.7$  ng/mL (n=4), and  $2.94$  ng/mL (n=1) for the 50 mg bd, 100 mg bd and 150 mg bd dosing regimens, respectively. The eliglustat concentration threshold of clinical concern in the primary analysis period was 150 ng/mL. Two CYP2D6 EM patients receiving a dose of 150 mg bd had  $C_{max}$  values of 169 ng/mL and 261 ng/mL, respectively; at Week 52 (the latter patient had an inadvertent overdose of 450 mg at Week 52). No other  $C_{max}$  values > 150 ng/mL were reported for any patient during the primary analysis period.

#### 11.1.5. Question 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  $\log AUC_{(0-\tau)}$ ) 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.

##### 11.1.5.1. Sponsor's response:

The sponsor's response has been edited. However, the clinical evaluator warrants that the key features of the response have been provided below.

The predicted % changes in spleen volume (MN) from baseline to Week 52 based on the PK/PD model and PopPK predicted  $\log AUC_{(0-\tau)}$  are provided for simulated IM and EM patients dosed at 50 mg and 150 mg bd (see Table 46 [50 mg bd] and Table 47 [150 mg bd], below). It should be noted that corrected data has been provided for the ENCORE study. The data presented below includes these corrected data and differs slightly from the data in Table 48 in POH0395 due to this correction (see Table 48, below).

For simulated IM and EM patients dosed at 50 mg bd, the mean estimated eliglustat treatment effect (-1.36%) was reduced (that is, a smaller decrease) compared to the observed effect (-6.05%) in the study. For simulated IM and EM patients dosed at 150 mg bd, the mean estimated eliglustat treatment effect (-9.72%) was increased (i.e. a larger decrease) compared to the observed effect (-6.05%) in the study. For simulated IM and EM patients dosed at 100 mg bd, the mean estimated eliglustat treatment effect (-6.55%) was similar to the observed effect (-5.96%) in the study.

**Table 46: ENCORE - Observed results and predicted % change in spleen volume from Baseline at Week 52 for IM and EM patients dosed at 50 mg bd based on PD~logAUC0-tau Model and Simulation (PP Set).**

Data/ CYP2D6	Statistic	Eliglustat (N=99)	Cerezyme (N=47)	Treatment difference (Eliglustat-Cerezyme)
<b>Observed</b>	<b>N</b>	<b>70</b>	<b>39</b>	--
All patients	LS mean (95% CI)	-6.05 (-9.17,-2.93)	-3.22 (-7.43,1.00)	-2.83 (-8.14,2.47)
<b>Simulated</b>	<b>N</b>	<b>70</b>	<b>39</b>	--
IM and EM 50 mg BID simulated	Mean of LS mean (Monte Carlo 95% CI)	-1.36 (-4.63,1.92)	--	--
IM and EM 50 mg BID simulated	Mean of LS mean (Mean of 95% CI)	-1.36 (-4.52,1.80)	-3.12 (-7.38,1.15)	1.76 (-3.61,7.13)

Note: For the PK/PD, each eliglustat treated patient's spleen volume % change value was simulated based on estimated PD~logAUC0-tau model and his/her observed baseline value, the stratification randomisation indicator and simulated logAUC0-tau. LogAUC0-tau values were simulated based on PopPK predicted IM and EM AUC0-tau mean and variability. For each simulation, 70 eliglustat-treated patients were simulated and compared to observed Cerezyme data (N=39). 1000 simulations were summarised by averaging results using the same ANCOVA model as used in the CSR. In addition, Monte Carlo mean and 95% CI for simulated eliglustat effect were provided. Eliglustat patient [information redacted], who returned to Cerezyme, was excluded from establishing the PK/PD model.

**Table 47: ENCORE - Observed results and predicted % change in spleen volume from Baseline at Week 52 for IM and EM patients dosed at 150 mg bd based on PD~logAUC<sub>(0-tau)</sub> Model and Simulation (PP Set).**

Data/CYP2D6	Statistic	Eliglustat (N=99)	Cerezyme (N=47)	Treatment difference (Eliglustat-Cerezyme)
<b>Observed</b>	<b>N</b>	<b>70</b>	<b>39</b>	<b>--</b>
All patients	LS mean	-6.05	-3.22	-2.83
	(95% CI)	(-9.17,-2.93)	(-7.43,1.00)	(-8.14,2.47)
<b>Simulated</b>	<b>N</b>	<b>70</b>	<b>39</b>	<b>--</b>
IM and EM 150 mg BID simulated	Mean of LS mean (Monte Carlo 95% CI)	-9.72 (-12.99,-6.44)	NA	NA
IM and EM 150 mg BID simulated	Mean of LS mean (Mean of 95% CI)	-9.72 (-12.88,-6.56)	-3.12 (-7.38,1.15)	-6.60 (-11.97,-1.23)

Note: Same as above for Table 46.

**Table 48: (POH0395): ENCORE - Observed results and predicted % change in spleen volume from Baseline at Week 52 for IM and EM patients dosed at 50 mg bd based on PD~logAUC<sub>(0-tau)</sub> Model and Simulation (PP Set).**

Data/CYP2D6	Statistic	Eliglustat(N=99)	Cerezyme(N=47)	Treatment difference (Eliglustat-Cerezyme)
Observed	N	70	39	
All patients	LS Mean(95%CI)	-5.96(-9.12,-2.80)	-3.21(-7.47,1.06)	-2.75(-8.12,2.62)
Simulated	N	70	39	
IM/EM 100 mg BID simulated	mean of LS Mean (Monte Carlo 95%CI)	-6.55(-9.91,-3.23)		
IM/EM 100mg BID simulated	mean of LS Mean (mean of 95%CI)	-6.55(-9.75,-3.35)	-3.10(-7.42,1.22)	-3.44(-8.89,2.00)

Note: Same as above for Table 46.

Similar to methods used in study POH0395, logAUC<sub>(0-tau)</sub> for each patient was simulated based on estimated logAUC<sub>(0-tau)</sub> mean and standard deviation (SD) from the PopPK predicted PK parameters for the IM and EM population. Table 49 (below) summarizes the PopPK predicted Genz-99067 PK parameters based on CYP2D6 phenotype for relevant eliglustat doses, which were simulated using the same PopPK model with IM and EM at 50 mg bd and 150 mg bd added. The patient's % change in spleen volume response was simulated based on the established PK/efficacy model using the ENCORE study data with the patients' baseline characteristics sampled from the observed data without replacement and a random error simulated based on the variability observed in the study.

**Table 49: Pop-PK model predicted mean eliglustat steady state-PK parameters by dose and CYP2D6 phenotype.**

Eliglustat dose	CYP2D6 phenotype	Mean AUC <sub>0-tau</sub>	SD AUC <sub>0-tau</sub>	Mean C <sub>max</sub>	SD C <sub>max</sub>
50 mg BID	PM	1185.5	369.16	148.85	41.33
<b>50 mg BID</b>	<b>IM</b>	<b>298.89</b>	<b>205.71</b>	<b>44.09</b>	<b>29.16</b>
<b>50 mg BID</b>	<b>EM</b>	<b>104.37</b>	<b>95.98</b>	<b>16.01</b>	<b>14.46</b>
<b>50 mg BID</b>	<b>IM and EM</b>	<b>118.27</b>	<b>118.67</b>	<b>18.02</b>	<b>17.53</b>
100 mg BID	IM	597.79	411.42	88.19	58.32
100 mg BID	EM	208.75	191.95	32.02	28.93
100 mg BID	IM and EM	236.54	237.33	36.03	35.06
<b>150 mg BID</b>	<b>IM</b>	<b>896.68</b>	<b>617.12</b>	<b>132.28</b>	<b>87.49</b>
<b>150 mg BID</b>	<b>EM</b>	<b>313.12</b>	<b>287.93</b>	<b>48.03</b>	<b>43.39</b>
<b>150 mg BID</b>	<b>IM and EM</b>	<b>354.81</b>	<b>356.00</b>	<b>54.05</b>	<b>52.58</b>
150 mg BID	URM	160.25	186.41	24.62	28.22
		<b>Mean logAUC<sub>0-tau</sub></b>	<b>SD logAUC<sub>0-tau</sub></b>	<b>Mean logC<sub>max</sub></b>	<b>SD logC<sub>max</sub></b>
50 mg BID	PM	7.0296	0.3146	4.9644	0.2808
<b>50 mg BID</b>	<b>IM</b>	<b>5.4548</b>	<b>0.7433</b>	<b>3.5548</b>	<b>0.7240</b>
<b>50 mg BID</b>	<b>EM</b>	<b>4.2765</b>	<b>0.8972</b>	<b>2.4123</b>	<b>0.8854</b>
<b>50 mg BID</b>	<b>IM and EM</b>	<b>4.3607</b>	<b>0.9375</b>	<b>2.4939</b>	<b>0.9230</b>
100 mg BID	IM	6.1480	0.7433	4.2480	0.7240
100 mg BID	EM	4.9697	0.8972	3.1054	0.8854
100 mg BID	IM and EM	5.0538	0.9375	3.1870	0.9230
<b>150 mg BID</b>	<b>IM</b>	<b>6.5534</b>	<b>0.7433</b>	<b>4.6535</b>	<b>0.7240</b>
<b>150 mg BID</b>	<b>EM</b>	<b>5.3751</b>	<b>0.8972</b>	<b>3.5109</b>	<b>0.8854</b>
<b>150 mg BID</b>	<b>IM and EM</b>	<b>5.4593</b>	<b>0.9375</b>	<b>3.5925</b>	<b>0.9230</b>
150 mg BID	URM	4.5907	1.0166	2.7252	1.0022

The IM and EM (patients with either IM or EM status) population was simulated with 92.86% EM patients and 7.14% IM patients based on the CYP2D6 PM, IM, EM, URM percentages in the literature. Source SIM0124.

To further explore the effects of 50 mg bd and 150 mg bd on the % change in spleen volume for IM and EM patients, additional analyses were performed to project each individual patient's observed spleen volume % change value to either 50 mg bd or 150 mg bd in addition to mean population prediction. In ENCORE, all PMs received 50 mg bd, all URM patients received 150 mg bd, and EMs/IMs received 50 mg bd, 100 mg bd or 150 mg bd through Week 52. In POH0395, the % change in spleen volume at Week 52 in the 50 mg bd or 150 mg bd IM and EM patients were projected to values as if they had received 100 mg bd, and the projected eliglustat effect was summarised in Table 50 in POH0395 (see Table 50 below). For PM, URM and 100 mg bd IM and EM patients, their observed values were used since projection was not needed.

**Table 50: (POH0395): ENCORE - Observed and projected % change in spleen volume from Baseline to Week 52 based on individual patient projection and PK/efficacy model (logAUC<sub>(0-tau)</sub>); PPS.**

Data/CYP2D6	Statistic	Eliglustat(N=99)	Cerezyme(N=47)	Treatment difference (Eliglustat-Cerezyme)
Observed	N	70	39	
All patients	LS Mean(95%CI)	-5.96(-9.12,-2.80)	-3.21(-7.47,1.06)	-2.75(-8.12,2.62)
Projected	N	70	39	
All patients	LS Mean(95%CI)	-5.21(-8.41,-2.02)	-3.22(-7.53,1.09)	-2.00(-7.43,3.43)

For IM/EM patients administered 50 mg bd or 150 mg bd by Week 52, % change in spleen volumes were projected to 100 mg bd by projecting their exposure to 100 mg bd based on the PopPK model - predicted mean AUC<sub>0-tau</sub> ratios between 100 mg BD/50 mg bd or 100 mg BD/150 mg bd using the established PK/efficacy model. Two patients who had indeterminate CYP2D6 status and received 150 mg bd were also projected to 100 mg bd. For other patients, the observed percent changes in spleen volumes were used. Eliglustat patient [information redacted] who returned to Cerezyme was excluded from the analysis.

Table 51 (see below) adds similar projection analyses for individual % change in spleen volume values in all IM and EM patients projected to effects at 50 mg bd and 150 mg bd, using  $\log AUC_{(0-\tau)}$ . Analysis using  $\log C_{\max}$  provided similar results. The estimated within-subject exposure ratios between 50 mg bd and 150 mg bd for projections are presented in Table 52 (see below), and exposure ratios between 50 mg bd and 100 mg bd or 150 mg bd and 100 mg bd were presented in Table 53 in POH0395. The projected eliglustat mean treatment effects decreased 5.50% if all IM and EM patients were projected to 50 mg bd, increased 2.05% if all IM and EM patients were projected to 150 mg bd compared to the observed effect in the study, and were similar to the observed effect if all IM and EM patients were projected to 100 mg bd.

**Table 51: ENCORE - Observed results and projected % change in spleen volume (MN) from Baseline to Week 52 based on individual patient projection.**

Data/CYP2D6	Statistic	Eliglustat (N=99)	Cerezyme (N=47)	Treatment difference (Eliglustat- Cerezyme)
<b>Observed</b>	<b>N</b>	<b>70</b>	<b>39</b>	<b>--</b>
All patients	LS mean	-6.05	-3.22	-2.83
	(95% CI)	(-9.17,-2.93)	(-7.43,1.00)	(-8.14,2.47)
<b>Projected</b>	<b>N</b>	<b>70</b>	<b>39</b>	<b>--</b>
<b>IM and EM: 50 mg BID, PM: 50 mg BID, URM:150 mg BID</b>	LS mean	<b>-0.55</b>	<b>-3.23</b>	<b>2.69</b>
	(95% CI)	<b>(-3.72,2.63)</b>	<b>(-7.52,1.06)</b>	<b>(-2.72,8.09)</b>
IM and EM: 100 mg BID, PM: 50 mg BID, URM: 150 mg BID	LS mean	-5.33	-3.23	-2.10
	(95% CI)	(-8.48,-2.18)	(-7.48,1.03)	(-7.46,3.26)
<b>IM and EM: 150 mg BID, PM: 50 mg BID, URM: 150 mg BID</b>	LS mean	<b>-8.10</b>	<b>-3.22</b>	<b>-4.88</b>
	(95% CI)	<b>(-11.25,-4.96)</b>	<b>(-7.47,1.03)</b>	<b>(-10.23,0.47)</b>

For all IM and EM patients, spleen volume %changes were projected to effects if given 50 mg BID, 100 mg BID or 150 mg BID, respectively, for each corresponding projection analysis. The projected spleen volume % changes were calculated based on the established PK/PD model and projecting a patient's observed exposure to the exposure on the projected dose by multiplying the PopPK predicted mean  $AUC_{0-\tau}$  ratios between doses. For IM and EM patients already on the projected dose in each corresponding projection analysis, their observed values were used. There were 2 patients on eliglustat 150 mg bd with indeterminate CYP2D6 phenotype and treated as IM and EM in the projection analysis. For PM/URM patients, the observed spleen volume % changes were used. Eliglustat patient [information redacted], who returned to Cerezyme, was excluded from the analysis. BID=bd

**Table 52: Estimated within-subject exposure ratios of 50 mg bd and 150 mg bd eliglustat doses bases on population pharmacokinetic model predicted parameters.**

CYP2D6 Status	Parameter	Statistics	$AUC_{0-\tau}$ : 50 mg BID /150 mg BID	$C_{\max}$ : 50 mg BID /150 mg BID
PM	Ratio	Mean (SD)	0.334(0.036)	0.341(0.088)
IM	Ratio	Mean (SD)	0.335(0.037)	0.343(0.088)
EM	Ratio	Mean (SD)	0.335(0.042)	0.343(0.098)
URM	Ratio	Mean (SD)	0.336(0.041)	0.355(0.149)
PM	log(Ratio)	Mean (SD)	-1.102(0.109)	-1.107(0.251)
IM	log(Ratio)	Mean (SD)	-1.100(0.108)	-1.102(0.252)
EM	log(Ratio)	Mean (SD)	-1.102(0.126)	-1.110(0.281)
URM	log(Ratio)	Mean (SD)	-1.098(0.122)	-1.085(0.292)

Exposure ( $AUC_{0-\tau}$  or  $C_{max}$ ) were simulated for each dose and each CYP2D6 phenotype using a 3-period crossover design based on PopPK model taking account both inter- and intra- subject variability. 1000 simulations for each dose and each CYP2D6 phenotype were done. For each dose and each CYP2D6 phenotype, exposures within 5th to 95th percentiles were used in within-subject ratios calculations. Subjects with an exposure outside of 5th to 95th percentiles in any period were not included in the calculation. Exposure ratios of 50 mg BD/100 mg bd and 100 mg BD/150 mg bd were provided in POH0395.

**Table 53: (POH0395) - Estimated within-subject exposure ratios among eliglustat doses based on population pharmacokinetic model predicted parameters.**

CYP2D6 Status	Parameter	Statistics	$AUC_{0-\tau}$ : 100mg BID /50mg BID	$AUC_{0-\tau}$ : 100mg BID /150mg BID	$C_{max}$ : 100mg BID /50mg BID	$C_{max}$ : 100mg BID /150mg BID
PM	Ratio	Mean(SD)	2.01(0.23)	0.67(0.07)	2.07(0.51)	0.69(0.17)
IM	Ratio	Mean(SD)	2.01(0.21)	0.67(0.07)	2.07(0.53)	0.69(0.19)
EM	Ratio	Mean(SD)	2.02(0.31)	0.67(0.09)	2.10(0.61)	0.70(0.20)
URM	Ratio	Mean(SD)	2.01(0.26)	0.67(0.09)	2.07(0.74)	0.70(0.23)
PM	log(Ratio)	Mean(SD)	0.69(0.11)	-0.41(0.10)	0.70(0.24)	-0.41(0.25)
IM	log(Ratio)	Mean(SD)	0.69(0.11)	-0.41(0.11)	0.69(0.25)	-0.41(0.26)
EM	log(Ratio)	Mean(SD)	0.69(0.14)	-0.41(0.13)	0.71(0.26)	-0.40(0.29)
URM	log(Ratio)	Mean(SD)	0.69(0.12)	-0.41(0.13)	0.68(0.31)	-0.41(0.29)

$AUC_{0-\tau}$  = area under the concentration time curve from time 0 to 12 hours; BID = twice daily;  $C_{max}$  = maximum plasma concentration of Genz-99067 Exposure ( $AUC_{0-\tau}$  or  $C_{max}$  was simulated 1000 times for each dose and each CYP2D6 phenotype using a 3 period crossover design based on the PopPK model, which took into account both inter- and intra- subject variability. Subjects with an exposure outside of 5th to 95th percentiles in any period were not included in the calculation. Source SIM0124.

In addition, Table 54 below lists the individual % change in spleen volume values in IM and EM patients if a different eliglustat dose from the observed dose was to be given in the projection. A patient's values were listed if any of the observed or projected spleen volume increases was > 15% in any projection analysis using  $\log AUC_{(0-\tau)}$ . Analysis using  $\log C_{max}$  provided similar results. As specified in the ENCORE study, the increase in % change in spleen volume from baseline to beyond a pre-specified treatment failure threshold (in this case, increase from baseline > 25%) would result in a change in the composite endpoint status from stable (success) to failure. For all IM and EM patients, spleen volume % changes were projected to effects if given 50 mg bd, 100 mg bd or 150 mg bd, respectively, for each corresponding projection analysis. The projected spleen volume % changes were calculated based on the established PK/PD model and projecting patient's observed exposure to the exposure on the projected dose by multiplying the PopPK predicted mean  $AUC_{0-\tau}$  ratios between doses. For IM and EM patients already on the projected dose in each corresponding projection analysis, their observed values were used. There were 2 patients on eliglustat 150 mg bd with indeterminate CYP2D6 phenotype and treated as IM and EM in the projection analysis. For PM/URM patients, the observed spleen volume % changes were used. Eliglustat patient [information redacted] who returned to Cerezyme was excluded from the analysis.

**Table 54: ENCORE - Listing of EM/IM eliglustat patients with and observed or projected spleen volume (MN) increase > 15% from Baseline to Week 52 if given a different dose (PP set and  $\sim\log\text{AUC}_{(0-\tau)}$ ).**

Actual eliglustat dose received post titration	CYP2D6 Phenotype	Observed Composite endpoint	Spleen Volume %Change from baseline			
			Observed	Projected to 50 MG BID	Projected to 100 MG BID	Projected to 150 MG BID
150 MG BID	Extensive	SUCCESS	6.28	15.38	9.58	--
150 MG BID	Indeterminate	FAILURE	11.00	20.45	14.39	--
100 MG BID	Extensive	FAILURE	11.30	17.32	--	7.97
<b>150 MG BID</b>	<b>Extensive</b>	<b>SUCCESS</b>	15.87	<b>25.87</b>	19.54	--
<b>150 MG BID</b>	<b>Extensive</b>	<b>SUCCESS</b>	15.96	<b>25.87</b>	19.54	--
<b>150 MG BID</b>	<b>Extensive</b>	<b>SUCCESS</b>	16.48	<b>26.50</b>	20.14	--
<b>100 MG BID</b>	<b>Extensive</b>	<b>SUCCESS</b>	20.21	<b>26.71</b>	--	16.61
<b>150 MG BID</b>	<b>Extensive</b>	<b>SUCCESS</b>	22.58	<b>32.99</b>	<b>26.30</b>	--
<b>50 MG BID</b>	<b>Extensive</b>	<b>FAILURE</b>	25.93	--	<b>19.42</b>	<b>15.94</b>
150 MG BID	Extensive	FAILURE	37.55	49.20	41.69	--

Note: Patient identification numbers have been removed from this table.

When projecting all IM and EM patients to 50 mg bd, 5 patients who had observed spleen volume value increases < 25% (and were considered composite endpoint successes) in the ENCORE PAP had projected % change in spleen volume values that became > 25% (became a treatment failure). Of note, the spleen volume in all 5 patients ranged from 2.2 to 5.5 MN at Baseline. Thus, none of the patients would have shown a projected increase in their spleen volume > 8 MN (upper limit of the therapeutic goal for spleen volume) if given 50 mg bd, allowing them to remain within the long-term therapeutic goal established for spleen in patients with GD who received treatment with imiglucerase.

When projecting all IM and EM patients to 100 mg bd, only 1 patient would change his composite endpoint status from success to failure. Note that this patient [information redacted] was considered a treatment failure with a % change in spleen volume increase of 31.02% in POH0395. With the recent data update, this patient's spleen volume change was updated to 22.58% and his composite endpoint was updated to success. When projecting his % change in spleen volume from the effects of 150 mg bd to 100 mg bd, his value would have increased from 22.58% to 26.30%. Both values are close to the treatment failure threshold of 25%. When projecting all IM and EM patients to either 100 mg or 150 mg bd, there was one patient (Patient ID=[information redacted]) whose % change in spleen volume became less than a 25% increase. However, this patient would have remained a failure, as she was not able to maintain a stable platelet count after 52 weeks of treatment.

All GD1 patients participating in the ENCORE study had spleen volumes < 8 MN (mean spleen volume 3.23 MN at Baseline, range 0.85 to 7.59 MN), which are well within the published long-term therapeutic goals for spleen (< 8 MN) in GD. In general, the projected individual changes in spleen volume using any of the eliglustat doses (50 mg, 100 mg and 150 mg bd) compared to the observed changes in the ENCORE study would not be considered to be of clinical significance, even for those patients who were considered to be successes at the dose they received during the trial and who would now become failures at the projected doses, as their spleen volumes would have remained within the established therapeutic goals. However, for all IM and EM patients, a 100 mg bd dose projects and predicts an efficacy effect on spleen volume similar to what was observed in the study.



As described in the response to PK Question 4, a single dosing regimen of 100 mg bd for both treatment-naïve and enzyme replacement therapy (ERT)-stabilized patients has been proposed. 100 mg bd is the dose that will achieve the exposure levels proven to be safe and effective in our pivotal clinical trials in the vast majority of GD1 patients (that is, IM and EM patients) without plasma monitoring, and that has been shown to be efficacious in the sickest patients (treatment-naïve patients).

#### 11.1.5.2. Clinical evaluator's comment:

For ENCORE, PK/PD modelling and PopPK logAUC<sub>(0-tau)</sub> simulation analysis showed that the mean predicted % reduction in spleen volume (MN) was similar to the mean observed % reduction in the 100 mg bd group (-6.55% versus -5.96%, respectively), lower in the 50 mg bd group (-1.36% versus -6.05%, respectively), and higher in the 150 mg bd group (-9.72% versus -6.05%). These results were consistent with the observed and projected % change in spleen volume (MN) results from Baseline to Week 52 based on individual patient projections.

For ENCORE, spleen volume (MN) % changes projected to 50 mg bd, 100 mg bd, and 150 mg bd for all CYP2D6 IM/EM patients suggested that 100 mg bd was more efficacious than 50 mg bd, based on composite primary endpoint criteria. However, the sponsor notes that all projected individual changes in spleen volume for all doses compared to observed doses would not be considered to be clinically significant (irrespective of shifts to failure from success) as spleen volumes remained within established therapeutic goals.

As mentioned in the sponsor's response, corrected data were presented for ENCORE. The corrected data arose from the addition of results from one subject that should have been included in the analysis. The Key Revisions to the efficacy data are summarised below in Table 55. The sponsor's response also listed all original CSR data affected by the revisions. The numerical revisions did not change the overall interpretation of the study results or change the study conclusions. The corrected data have been included in the first round CER and all relevant data in the second round CER are the corrected results unless otherwise specified.

**Table 55: ENCORE - Key revisions to eliglustat arm efficacy data.**

Endpoint	Revised Value	Initial Value (reported in the dossier)
Patients Stable for 52 Weeks, n (%) (Eliglustat treatment group)	84 (84.8%)	83 (83.8%)
Difference in Percentage Stable (Eliglustat-Cerezyme), %	-8.8%	-9.8%
Lower bound of the 95% CI in the difference in percentage between the eliglustat and Cerezyme treatment groups	-17.6%,	-18.6%
Patients Meeting Spleen Volume Criteria, n (%)* (Eliglustat treatment group)	68 (95.8%)	67 (94.4%)
Mean % Change from Baseline to Week 52 (Eliglustat treatment group)	-6.17% 95% CI: (-9.17, -2.93)	-6.07% 95% CI: (-9.12, -2.80)
Treatment Difference (Eliglustat-Cerezyme) in % Change in Spleen Volume from Baseline to Week 52 (FDA-Recommended Efficacy Endpoint)	-2.83% 95% CI: (-8.14, 2.47) p-value: 0.2922	-2.75% 95% CI: (-8.12, 2.62) p-value: 0.3118

\* Patient percentages are based on the total number of non-splenectomised patients in the particular treatment group.

### 11.1.6. Question 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  $\log AUC_{(0-\tau)}$ . Please account for this observation.

#### 11.1.6.1. Sponsor's response:

Overall, there were very few failures in the composite endpoint (patients remaining stable for 52 weeks) for the eliglustat arm in the ENCORE trial (15/99 GD1 patients). Furthermore, ENCORE patients were maintained in a well-defined and limited range of exposure that has been shown to be safe and efficacious through dose titration based on  $C_{\text{trough}}$  (5 ng/mL) while targeting Genz-99067  $C_{\text{max}}$  below 150 ng/mL. Given the limited range of exposure and success of the trial, it is not unexpected that no trend was observed between the composite primary endpoint (patients remaining stable for 52 weeks) and the observed Genz-99067 exposure.

#### 11.1.6.2. Clinical evaluator's comment:

The sponsor's response is acceptable.

### 11.1.7. Question 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  $\log AUC_{(0-\tau)}$  and  $\log C_{\text{max}}$ . 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.

#### 11.1.7.1. Sponsor's response:

The sponsor's response has been edited. However, the clinical evaluator warrants that the key features of the response have been provided below.

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 Gaucher disease while on long-term enzyme replacement therapy (ERT). ENCORE patients were maintained in a well-defined and limited range of exposure of Genz-99067 that has been shown to be safe and efficacious, through dose titration based on  $C_{\text{trough}}$  (5 ng/mL) while targeting  $C_{\text{max}}$  below 150 ng/mL. Given the limited range of exposure and the success of the trial in maintaining disease stability, it is not unexpected that most of the components of the primary composite endpoint did not show appreciable changes from baseline (when those values were already normal or near-normal), and therefore did not demonstrate a statistically significant PK/efficacy relationship. Importantly, the lack of a relationship does not equate to a lack of treatment effect, as the majority of eliglustat-treated patients (85%) were able to maintain stability in all four components of the composite endpoint after 52 weeks of treatment. Based on this high rate of patient stability, eliglustat met the criterion to be declared non-inferior to Cerezyme. The results for each component of the primary composite endpoint are discussed in more detail below.

##### 11.1.7.1.1. Spleen effects

In ENCORE, a significant PK/efficacy relationship was observed for the % change in spleen volume (multiples of normal [MN]) from baseline to Week 52. This relationship is most likely a reflection of the baseline characteristics of the enrolled patients. In this study, the inclusion criterion for patients with an intact spleen was a spleen volume < 10 multiples of normal (MN). All enrolled patients had a spleen volume < 8 MN and in patients randomized to eliglustat, spleen volumes ranged from 0.58 to 7.59 MN (mean 3.23 MN). Patients treated with imiglucerase are expected to achieve a decrease in spleen volume, with a long-term therapeutic goal of spleen volume < 8 MN. A mild degree of splenomegaly is allowed within the therapeutic

goals because, despite treatment, spleen volume does not completely normalize in most patients. Pastores et al (2004) defined splenomegaly as a splenic mass greater than the normal 0.2% of total body weight in kilograms. Thus, the mean pre-treatment spleen volume in ENCORE patients was above the normal spleen volume, even though it was < 8 MN and thus defined as being 'at the therapeutic goal.' Genzyme believes that the mild degree of splenomegaly, even though within the therapeutic goal, allowed for further improvement and explains the significant PK/efficacy correlation observed.

#### 11.1.7.1.2. Platelet effects

No statistically significant PK/efficacy relationship was observed for % change in platelet count. This is not unexpected given that all patients enrolled in ENCORE had to have a normal or close-to-normal platelet counts (mean of two values  $\geq 100,000/\text{mm}^3$  at the time of screening, and thus had little capacity for further improvement with treatment. In patients randomized to eliglustat treatment, the platelet count ranged from 100,500 to 511,000/ $\text{mm}^3$  (mean 206,750/ $\text{mm}^3$ ). Among these patients, approximately 10% had platelet counts  $> 100,000/\text{mm}^3$  and  $< 120,000/\text{mm}^3$ . The therapeutic goal for Gaucher patients with thrombocytopenia depends upon their pre-treatment spleen status, degree of splenic enlargement, and degree of thrombocytopenia. The goal of the ENCORE study was to maintain clinical stability and therefore patients were not necessarily expected to show an improvement in platelet count. However, an increase in platelet count was observed with eliglustat treatment in some patients, especially those with an intact spleen and mild thrombocytopenia (between 100,000 and  $< 120,000/\text{mm}^3$ ).

Of note, statistically significant PK/efficacy associations for % change in platelet count were shown for both observed  $\log\text{AUC}_{(0-\tau)}$  (P-value = 0.007) and observed  $\log\text{C}_{\max}$  (P-value = 0.016) after removing an outlier that significantly impacted the PK/PD modeling fitting. The outlier was a CYP 2D6 PM patient (Patient [information redacted]) who received doses of 50 mg bd and showed a large decrease in platelet count (-43%). Sensitivity analyses were conducted and presented in POH0395 for the % change in platelet count after excluding this patient. Also, note, there was another apparent outlier (Patient [information redacted]) with a large increase in platelet count (108%). However, inclusion or exclusion of this patient in the platelets PK/PD analysis had negligible effects on PK/PD relationships. Therefore, no other patient data exclusion was made.

Based on the established PK/efficacy models, the eliglustat effect prediction and projection analyses for % change in platelet count that excluded patient [information redacted] were also presented in POH0395. Both the predicted and projected mean effects of eliglustat in IM and EM patients if given 100 mg bd were similar to the observed eliglustat effect in the study. The projection analyses did not result in any additional patients with a  $> 25\%$  decrease in platelet count (platelet threshold for 'treatment failure'). Projections further confirmed that IM and EM patients receiving doses of 100 mg bd would not have affected their composite endpoint status.

#### 11.1.7.1.3. Liver and haemoglobin effects

No statistically significant PK/efficacy relationships were observed for % change in liver volume and the absolute change in haemoglobin. All ENCORE patients presented with normal (haemoglobin) or near-normal (liver volume) baseline values, which were maintained after 52 weeks of treatment. Therefore, it is not unexpected that no relationship was observed.

#### 11.1.7.1.4. Conclusion

In ENCORE, the expected treatment effect (that is, maintenance of all four clinical components) was seen across the Genz-99067 concentration range studied. Importantly, the lack of a PK/efficacy relationship for 3 of the 4 parameters does not equate to a lack of treatment effect, as the majority of eliglustat-treated patients (85%) were able to maintain stability in all four components of the composite endpoint after 52 weeks of treatment. Based on this high rate of patient stability, eliglustat met the criterion to be declared non-inferior to Cerezyme.

Furthermore, Genzyme believes that the lack of a PK/efficacy relationship for haemoglobin, platelet count and liver volume is due to the normal or near-normal baseline values for these parameters in patients previously stabilized on long-term ERT.

**11.1.7.2. Clinical evaluator's comment:**

The sponsor's response is considered to be satisfactory.

**11.1.8. Question 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  $\log AUC_{(0-\tau)}$  and  $\log C_{\max}$ . Therefore, the proposed dosing regimen for patients stabilized 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.

**11.1.8.1. Sponsor's response**

The sponsor provided a detailed response, which was similar in content to the data provided in response to the previous questions. Therefore, the results of the previously discussed data have not been repeated. The sponsor's conclusions relating to Question 8 are provided below.

ERT-stabilized patients have a low substrate load and low disease burden, and the treatment objective for them is to maintain stability. ENCORE patients had normal or close to normal Baseline values for all 4 components of the primary endpoint: haemoglobin, platelet count, spleen and liver volume, and had little or no capacity to improve further. Therefore, as discussed in the response to PK Question 7, the lack of a PK/efficacy relationship in some of the components of the composite primary endpoint does not equate to a lack of treatment effect, as the majority of eliglustat-treated patients were able to maintain stability in all four components of the composite endpoint after 52 weeks of treatment. Furthermore, 100 mg bd is a dose demonstrated to be effective in treatment-naïve patients, who have a higher disease burden and represent a higher bar for efficacy; this dose is expected to provide efficacy in ERT-stabilized patients as well. PK/PD analyses support the conclusion that 100 mg bd will maintain the IM and EM proposed target population, including ERT-stabilized patients, within the exposure range proven to be effective in clinical trials. Based on the efficacy arguments mentioned above as well as the considerations around the dose titration based on  $C_{\text{trough}}$  and the desire to keep exposure levels in the real world (post-market setting) within the range known to be safe and effective under clinical trial conditions, Genzyme considers 100 mg bd to be the optimal dose for IM and EM patients, both treatment-naïve as well as ERT-stabilized.

**11.1.8.2. Clinical evaluator's comment:**

The sponsor is considered to have adequately addressed the question.

**11.2. Efficacy**

**11.2.1. Question 1**

What method was used to randomize patients in ENCORE (for example, IVRS)?

**11.2.1.1. Sponsor's response:**

The sponsor's response has been edited. However, the clinical evaluator warrants that the key features of the response have been provided below.

Once the Investigator confirmed that the patient met the eligibility requirements via the Eligibility Confirmation Form, the Investigator or designee obtained a Request for Patient

Randomisation form and completed the Site Information and Patient Information sections. The form was then faxed to Genzyme Clinical Pharmacy Research Services (CPRS). The CPRS Clinical Pharmacist assigned the patient the next available treatment assignment number (corresponding to the appropriate randomisation strata). Genzyme CPRS then completed the Patient Randomisation Assignment section and faxed the form back to the clinical site within 48 hours (two business days). Finally, to verify that the investigator or designee received and acknowledged the treatment randomisation, the investigator or designee then completed the Site Confirmation of Receipt section and faxed the form back to Genzyme CPRS.

ENCORE randomisation was a stratified randomisation. Patients were stratified into 1 of 2 groups ( $< 35$  U/kg/q2w or  $\geq 35$  U/kg/q2w) based on the q2w equivalent of the patient's ERT dose (prior to any unanticipated treatment interruption, dose reduction, or regimen change that may have occurred). The stratified patients were randomized in a 2:1 ratio to receive eliglustat or Cerezyme, respectively, for 52 weeks (the primary analysis treatment period).

**11.2.1.2. Clinical evaluator's comment:**

The sponsor's response is satisfactory.

**11.2.2. Question 2**

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.

**11.2.2.1. Sponsor's response:**

In the ENCORE study, formal inferential statistical testing for non-inferiority was performed only on the primary endpoint, a composite of the 4 clinical parameters of haemoglobin, platelets, liver and spleen. The secondary endpoints, the 4 individual components of the composite and measures of bone density, were summarised, and estimates of differences between the treatment groups were generated using descriptive statistics and ANCOVA, but formal statistical testing for non-inferiority was not performed. The tertiary endpoints were similarly treated. Since this study was not designed to show non-inferiority in the each of the individual secondary and tertiary endpoints, hypothesis testing was neither planned nor performed for this trial and there was no need to adjust for multiplicity.

**11.2.2.2. Clinical evaluator's comment:**

The sponsor's response is satisfactory.

**11.2.3. Question 3**

In ENCORE, the median age for patients switching from ERT to eliglustat (FAS) is given as 37.4 years in the CSR, while in the Summary of Clinical Efficacy it is given as 36.9 years. Please account for this apparent discrepancy.

**11.2.3.1. Sponsor's response:**

The sponsor's response has been edited. However, the clinical evaluator warrants that the key features of the response have been provided below.

In the Summary of Clinical Efficacy, the median patient age displayed in the ENCORE column (36.9 years) represents the median age for the entire study (all 159 patients in both treatment arms in the FAS). The median age for all patients in the FAS (36.9 years) is the value used to determine the age threshold for the By-Age subgroup analyses.

The median age for only those patients switching from Enzyme Replacement Therapy (ERT) to eliglustat (that is, the eliglustat arm,  $n=106$  [FAS]) was not used in these analyses, and is therefore not displayed in the Summary of Clinical Efficacy. As noted by the Agency, the median age for those patients (37.4 years [FAS]).

**11.2.3.2. Clinical evaluator's comment:**

The sponsor's response is satisfactory.

**11.2.4. Question 4**

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?

**11.2.4.1. Sponsor's response:**

The sponsor's response has been edited. However, the clinical evaluator warrants that the key features of the response have been provided below.

In ENCORE, the primary efficacy endpoint was evaluated for non-inferiority in the PPS, as outlined in the protocol and statistical analysis plan. The primary efficacy endpoint was the percentage of eliglustat-treated patients in the PPS who maintained stability in the composite endpoint [95% CI]. This composite stability response, along with the stability response for each of the 4 components of the composite endpoint, stratified by eliglustat dose, is presented below in Table 56.

In the PPS, the percentages of patients maintaining composite stability (78.9%-87.5%) and stability in each of the components (89.5%-100%) at Week 52 were high and similar across the 3 doses. The observed differences between dose groups were neither statistically significant, as demonstrated by the p-values, nor clinically meaningful. The slight percentage differences in composite stability across dose groups correspond to single-patient differences in the 100 mg bd group relative to the 50 mg bd group (1 less stable patient) and the 150 mg bd group (1 more stable patient). The results in the FAS were also presented and were consistent with the results presented for the PPS.

In this study, patients were not randomized to a particular dose level. Instead, patients were required to titrate across dose levels in order to achieve a minimum plasma exposure, and so it was not possible to prospectively predict the distribution of patients across doses. Therefore, detecting differences in efficacy across specific dose levels, without regard to plasma exposure, was not part of the planned analysis and was not considered in the power calculations.



**Table 56: ENCORE - Percentage (95% CI) maintaining stability at 52 Weeks by eliglustat dose group (PPS).**

	50 mg BID n=19 mean [95%CI]	100 mg BID n=32 mean [95%CI]	150 mg BID n=48 mean [95%CI]
Primary Composite Endpoint	78.9 [54.4, 93.9]	84.4 [67.2, 94.7] p1 = 0.624 vs 50 mg BID	87.5 [74.8, 95.3] p2 = 0.381 vs 50 mg BID p3 = 0.691 vs 100 mg BID
Secondary Component Endpoints			
Hemoglobin	94.7 [74.0, 99.9]	93.8 [79.2, 99.2] p1 = 0.885 vs 50 mg BID	95.8 [85.7, 99.5] p2 = 0.845 vs 50 mg BID p3 = 0.677 vs 100 mg BID
Liver	94.7 [74.0, 99.9]	96.9 [83.8, 99.9] p1 = 0.707 vs 50 mg BID	95.8 [85.7, 99.5] p2 = 0.845 vs 50 mg BID p3 = 0.811 vs 100 mg BID
Platelets	89.5 [66.9, 98.7]	93.8 [79.2, 99.2] p1 = 0.587 vs 50 mg BID	93.8 [82.8, 98.7] p2 = 0.553 vs 50 mg BID p3 > 0.999 vs 100 mg BID
Spleen*	92.3 [64.0, 99.8]	100 [NA,NA] p1 > 0.999 vs 50 mg BID	94.7 [82.3, 99.4] p2 = 0.749 vs 50 mg BID p3 > 0.999 vs 100 mg BID
1: p-value from logistic regression comparing 100 to 50 mg BID 2: p-value from logistic regression comparing 150 to 50 mg BID 3: p-value from logistic regression comparing 150 to 100 mg BID *Note: Spleen result includes patients without total splenectomy			

**11.2.4.2. Clinical evaluator's comment:**

The sponsor's response adequately addresses the question.

**11.2.5. Question 5**

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.

**11.2.5.1. Sponsor's response:**

The distribution of category of average trough plasma concentration (< 5 ng/mL, ≥ 5 ng/mL) within each dose group is presented below in Table 57. Average trough refers to the average of all available pre-dose measurements taken at Weeks 13, 26, 39, and 52. It should be noted that this study was designed as a dose titration study, whereby all patients were started on a dose of 50 mg bd. At study Week 4, patients either continued on 50 mg bd or escalated to 100 mg bd based on the Week 2 trough plasma concentration. At Week 8, patients who had escalated to 100 mg bd were either maintained at that dose or were escalated to 150 mg bd based on the Week 6 trough plasma concentration. Once on 150 mg bd, no further escalation was possible. Therefore the apparent differences between proportions in the lower and higher plasma categories within dose group can be attributed to the study design. Despite having average trough concentrations < 5 ng/mL, some patients in the 50 mg bd (19-21%) and 100 mg bd dose groups (25-26%) did not titrate to a higher dose because the single trough concentration value at Week 2 or Week 6, which were used to determine their dose, were ≥ 5 ng/mL.



**Table 57: ENCORE - Distribution of average trough category within dose group.**

Average Trough (ng/mL) <sup>1</sup>	50 mg BID		100 mg BID		150 mg BID		Overall	
	<5	≥5	<5	≥5	<5	≥5	<5	≥5
Per Protocol Set	4/19 (21%)	15/19 (79%)	8/32 (25%)	24/32 (75%)	24/48 (50%)	24/48 (50%)	36/99 (36%)	63/99 (64%)
Full Analysis Set	4/21 (19%)	17/21 (81%)	9/34 (26%)	25/34 (74%)	27/51 (53%)	24/51 (47%)	40/106 (38%)	66/106 (62%)

1: Category of trough reflects the average of pre-dose measurements taken at Weeks 13, 26, 39, and 52.

#### 11.2.5.2. Clinical evaluator's comment:

The sponsor's response is satisfactory. There was a notable number of patients in the 50 mg bd dose group (19-21%) and the 100 mg bd dose group (25-25%) who were not titrated upwards due to their  $C_{trough}$  levels being < 5 ng/mL at Week 2 or Week 6. This observation is consistent with the high inter-subject variability in eliglustat plasma concentration seen in each of the three eliglustat dose groups.

#### 11.2.6. Question 6

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  $C_{trough}$  values < 5 ng/mL, compared with 56/66 (85%) patients with average steady-state  $C_{trough}$  values ≥ 5 ng/mL. Please provide the difference between the proportions with 95% confidence intervals.

##### 11.2.6.1. Sponsor's response:

The sponsor's response has been edited. However, the clinical evaluator warrants that the key features of the response have been provided below.

In ENCORE, the primary efficacy endpoint was evaluated for non-inferiority in the PPS. The proportion stable in the composite endpoint analysed by category of average trough concentration, the difference in proportions between the categories, and the 95% CI and p-value from a logistic regression, for both the PPS and the FAS patients completing 52 weeks of treatment, are summarised below in Table 58. Maintenance of stability was not different between the average trough concentration categories in either analysis population, as evidenced by the 95% CI and the p-values. The majority of patients (80.6%-87.5%) maintained clinical stability in each average trough concentration group. Corrected data were presented for the ENCORE trial.

**Table 58: ENCORE - Summary of primary composite endpoint by average trough category.**

Average Trough <sup>1</sup>	< 5 (ng/mL)	≥ 5 (ng/mL)	Difference
Number and percentage meeting Composite Endpoint [95% CI]: Per Protocol Set N=99	29/36 80.6 [64.0, 91.8]	55/63 87.3 [76.5, 94.4]	-6.7 [-27.0, 13.9] P <sup>2</sup> = 0.371
Number and percentage meeting Composite Endpoint [95% CI]: Full Analysis Set Completing 52 Weeks N=104	32/40 80.0 [64.4, 90.9]	56/64 87.5 [76.8, 94.4]	-7.5 [-26.9, 12.4] P <sup>2</sup> = 0.306
1: Category of trough reflects the average of pre-dose measurements taken at Weeks 13, 26, 39, and 52. 2: p-value from a logistic regression model with composite endpoint as the dependent variable and average trough category as the independent variable.			

##### 11.2.6.2. Clinical evaluator's comment:

The sponsor's response is satisfactory.

### 11.2.7. Question 7

In ENGAGE\*, the reduction in spleen volume (MN) was 23.05% in the patient group with average  $C_{\text{trough}}$  concentrations < 5 ng/mL (n=9) and 31.28% in patients with average  $C_{\text{trough}}$  levels  $\geq$  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.

\* In the questions originally submitted to the sponsor, Question 7 inadvertently referred to ENCORE rather than ENGAGE. The sponsor confirmed with the TGA that the question referred to ENGAGE and provided the relevant data. Question 7 in the first round clinical evaluation report has been amended in order to refer to ENGAGE rather than ENCORE.

#### 11.2.7.1. Sponsor's response:

The sponsor's response has been edited. However, the clinical evaluator warrants that the key features of the response have been provided below.

The reductions in spleen volume (MN) figures quoted in this question refer to raw changes from baseline. In ENGAGE, the difference in spleen volume reduction between plasma trough concentration categories at Week 39 was summarised using ANCOVA, adjusting for baseline. Hence the adjusted figures in Table 59 below differ slightly from the figures in the Evaluator's question. The category of average trough concentrations (< 5 ng/mL versus  $\geq$  5 ng/mL) reflects the average of pre-dose measurements at Weeks 13, 26 and 39. Percent reduction in spleen volume was not different between the average trough concentration groups as evidenced by the 95% CI of the difference and p-value. The study was powered to detect a clinically meaningful reduction in spleen volume (-20%), which was achieved by both average trough groups.

**Table 59: ENGAGE - Summary of percent change in spleen volume trough concentration.**

Average Trough <sup>1</sup>	< 5 (ng/mL)	$\geq$ 5 (ng/mL)	Difference
Number of patients	9	11	
Least Square Mean Percent Change in Spleen Volume MN (SEM)	-23.26 (4.18)	-31.11 (3.77)	7.85 (5.65)
95% CI			[-4.08, 19.78] P <sup>2</sup> = 0.183
1: Category of trough concentration reflects the average of pre-dose measurements taken at Weeks 13, 26, and 39.			
2: p-value from an analysis of covariance model adjusting for baseline.			
Note: MN=Multiples of Normal			
Note: SEM= Standard Error of the Mean			

#### 11.2.7.2. Clinical evaluator's comment:

The sponsor's response adequately addresses the question.

### 11.2.8. Question 8

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.

#### 11.2.8.1. Sponsor's response:

The sponsor provided a detailed and comprehensive response justifying its decision not to undertake a further study. Most of the details of the response were included in the information provided by the sponsor in response to the PK and Efficacy questions. The sponsor's conclusions are provided below.

The sponsor does not intend to undertake a further study in GD1 patients previously treated with ERT to assess whether a single dose regimen of 100 mg bd can satisfactorily maintain

stability in patients switched from ERT. The sponsor maintains that data from the clinical development program conducted to date are robust and sufficient to support 100 mg bd as the optimal dose for all CYP2D6 IM/EM patients, in both treatment-naïve patients and patients switched from ERT.

The clinical program conducted with eliglustat represents the largest population of GD1 patients studied to date. Considering the challenges of undertaking clinical trials in rare disease populations, an approach to support a simplified dosing regimen based on the totality of evidence from the clinical program is justified.

The Phase II/III program demonstrates that 100 mg bd dosing resulted in a favourable clinical response in both treatment-naïve as well as in ERT-stabilized patients. The small gain in clinical efficacy expected to be achieved with a higher daily dose is not clinically meaningful, and the 100 mg bd regimen is predicted to be an adequate dose for IMs and EMs that maintains a favourable risk/benefit profile.

The only exposure-response relationship in ERT-stabilized patients was with spleen volume, which showed a shallow slope predicting only a 4% maximum increase for individual patient spleen volume values following a reduction in dose from 150 mg bd to 100 mg bd, comparable to the test-test variability of organ volume measurement by MRI. That predicted increase would not alter the composite endpoint results of ENCORE. In treatment-naïve patients, the clinical response continues over time as seen in the 4 year Phase II study, with patients reaching Gaucher disease treatment goals regardless of their eliglustat exposure or  $C_{\text{trough}}$  levels.

In conclusion, Genzyme considers 100 mg bd to be the optimal dose for IM and EM maintenance patients based on existing clinical trial data in both treatment-naïve and maintenance patients, and does not believe it is necessary to undertake an additional pivotal efficacy study to demonstrate the efficacy of the proposed CYP2D6 phenotype-based dose of 100 mg bd. Therefore the clinical program has shown that the proposed 100 mg bd regimen provides a robust clinical response for CYP2D6 IMs and EMs and should be considered an effective and safe dose regimen for a life-long chronic treatment for this GD1 population.

#### **11.2.8.2. Clinical evaluator's comment:**

The sponsor indicated that it did not intend to undertake a further study in GD1 patients previously treated with ERT to assess whether the proposed eliglustat 100 mg bd can satisfactorily maintain stability in CYP2D6 IM/EM patients switched from ERT. In support of its position the sponsor provided an extremely comprehensive and detailed justification (27 pages in length). Significant sections of the justification had been previously covered in the sponsor's responses to the PK and efficacy clinical questions discussed above, while new efficacy data from ENGAGE relating to a 39-week extension period to the initial 39 weeks primary analysis period were also included (see below for a summary of the report relating to the 78-week data). The issues raised in the sponsor's response have been discussed in the *Second Round Assessment of Benefits*. Overall, the sponsor's justification for the proposed treatment regimen is considered to be persuasive.

### **11.3. Safety**

#### **11.3.1. Question 1**

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.

##### **11.3.1.1. Sponsor's response:**

The sponsor's response has been edited. However, the clinical evaluator warrants that the key features of the response have been provided below.

In the Integrated Summary of Safety (ISS) examination of urinalysis, urine protein was not highlighted for extensive analysis. Therefore, a more in-depth analysis of the urine protein findings has been carried out in this response. This analysis, which examined clinically significant proteinuria, proteinuria shift tables evaluated by baseline status, number of proteinuria events, and persistence of proteinuria, does not reveal a safety signal for eliglustat.

In Section 7.3.2 of the ISS, under Clinically Significant Urinalysis Assessments it is stated 'A total of 28 patients had an abnormal urinalysis finding (12 males and 16 females). Of these 28 patients, 10 had normal urinalysis at Baseline and the others (18) had some abnormality at Baseline. No findings of medical significance were identified upon further review.' All 4 patients with proteinuria deemed clinically significant by the investigator had abnormal proteinuria at baseline. All 4 patients were receiving concomitant medications that could contribute to proteinuria. Evaluation of the last available urine protein assessment reveals that the majority of these 4 patients had the same or improved proteinuria as compared to baseline.

ISS Table 7.1.2.3.3, which is a Pooled Summary of Shifts in Urinary Lab Assessments (regardless of clinical significance) over 13-week intervals, was analysed with respect to proteinuria. As can be expected, the total number of patients (N) with both a baseline and follow-up urinalysis assessment generally decreased over time. Three hundred and seventy-seven patients (377/393, 96%) had a baseline urine protein assessment. After Week 52, each successive 13-week interval had considerably fewer patients with a follow-up assessment – and this is consistent with the drop-off in assessments as only 52% (204/393) of the ISS patients had received eliglustat for at least 12 months, with 16% (62/393) of the ISS safety set having received eliglustat for 24 months. Moreover, at Week 143 and up to the last data point at Week 338, there were fewer than 30 patients with post-baseline urine protein assessments at any timepoint, which represents less than 10% of patients who had a baseline urine protein assessment.

Up until Week 143, the percentage of patients who shifted from a normal urine protein assessment (no proteinuria) at baseline to an abnormal post-baseline urine protein (proteinuria) assessment ranged from 0-12% with no increasing trend over time. In fact, the higher percentages occurred at the earlier time-points, with 12% occurring at Week 13 and the lower percentages of 0-5% occurring during Weeks 78-143. The absolute number of patients with a normal baseline assessment and an abnormal post-baseline assessment ranged from 10-25 patients between Weeks 13 and 143. Beyond Week 143, the percentages of shift from normal to abnormal assessment trend upwards (especially at Weeks 156, 169, 208, and 273, with > 10% of patients having an abnormal post-baseline assessment of urine protein); however, the absolute number of patients with abnormal post-baseline assessments is very small (2-3 patients) as is the total number of patients with any urinalysis results. Thus, while the shift tables show an increased percentage of patients with proteinuria over time, the absolute number of patients is small and needs to be taken into account in the analysis. The absolute number of patients evaluated at later time points (beyond Week 143) is so small as to make percentages less relevant, and therefore in the opinion of the Sponsor is not suggestive of a safety signal.

There were a total of 68 patients who had an abnormal urine protein finding at any post-baseline timepoint in the study. Twenty six patients (26/377, 6.9%) with an available baseline urine protein assessment had an abnormal urine protein assessment at their last available post-baseline evaluation. Interestingly, an analysis of patients with abnormal urine protein assessment at baseline revealed that 50 patients reverted back to normal urine protein assessment at their last post-baseline visit, suggesting that these findings of abnormal urine protein were events of transient proteinuria. Similarly, a majority of the 68 patients with any post-baseline urine protein (40/68, 59%) had only a single event of abnormal urine over the course of the integrated safety set, again suggesting that these were events of transient proteinuria. Transient proteinuria is a known clinical entity that is commonly seen in younger

individuals and is associated with exercise. Several patients had 2-5 events of proteinuria, and one patient experienced 8 events. This patient had a prior medical history of chronic urethritis, which can include proteinuria as part of the disease process. In the 68 patients for whom urine protein result was quantitated (trace, 1+ or higher), all had either trace or 1+ protein. Only one patient had 2+ protein as an isolated event at Week 65, and all other findings in this patient (up to Week 78) were negative for proteinuria.

There were three patients out of 68 with any abnormal urine protein assessment that had persistent proteinuria over time (more than 3 positive consecutive findings which coincided with the last available assessment). One patient had negative urine protein at baseline and 1+ proteinuria at Weeks 13, 26 and 52 (the only available data points). This patient had a Urinary Tract Infection on Day 190 (approximately Week 27) of treatment and was diagnosed as being pregnant at Week 26. One patient had no proteinuria at baseline and from Weeks 13-26, had trace urine protein from Weeks 39-52, and 1+ proteinuria at Week 65 (last available data point). At Week 65, this patient had simultaneous proteinuria and the new finding of 1+ leukocyte esterase, thus suggesting infection as a cause of the proteinuria. One patient had negative urine protein at Week 26 and trace urine protein on Weeks 39, 52 and 65 (last available data point). This patient was receiving other concomitant medications associated with proteinuria (Prilosec, Naproxen).

In conclusion, proteinuria was recorded for most patients at only one visit out of all urinalysis assessments. Proteinuria was transient in most cases and when quantitated, and it was low-grade in all but one patient. Thus, there is no meaningful evidence to suggest that persistent proteinuria can be ascribed temporally to eliglustat use. Evaluation of urine protein by urinalysis is a sensitive, but nonspecific finding that requires clinical context for interpretation. This analysis confirms that there is no safety signal with respect to developing proteinuria associated with eliglustat use when evaluated at any point post-baseline, using the last evaluated measurement, or when evaluated over a persistent time course during the study.

#### **11.3.1.2. Clinical evaluator's comment:**

The sponsor's response is satisfactory.

### **11.4. ENGAGE - Evaluation of 78-week results memo report**

#### **11.4.1. Overview of the study**

The sponsor provided the 78-Week Results Memo Report, following a specific request from the TGA subsequent to the provision of the S31 Response. The Memo Report was dated 7 May 2014 (that is, after completion of the first round CER). The objective of the report was to summarize safety and selected efficacy data collected during the first 39 weeks of the open-label Long-Term Treatment Period of ENGAGE in GD1 patients who were ERT-naive. The open-label, 39-week extension period followed the initial 39-week randomized, placebo-controlled, double-blind, Primary Analysis Period (PAP).

Patients entered the 39-week long-term treatment period following completion of the Week 39 PAP assessment. Although the maximum eliglustat dose allowable in the PAP was 100 mg bd, dose escalation to 150 mg bd was permitted in the long-term treatment period. Following the Week 39 PAP assessment, all patients entering the long-term treatment period were treated with an initial dose of 50 mg bd through to Week 43 after which time patients received 50 mg bd or 100 mg bd through to Week 47 (depending on  $C_{\text{trough}} < 5 \text{ ng/mL}$  or  $\geq 5 \text{ ng/mL}$  at Week 41), followed by 50 mg bd, 100 mg bd or 150 mg bd from Week 47 through to completion (depending on  $C_{\text{trough}} < 5 \text{ ng/mL}$  or  $\geq 5 \text{ ng/mL}$  at Week 45). The long-term treatment period is ongoing and each patient may continue to receive treatment for up to 6 years.

In total, 40 patients were randomized to the initial 39-week PAP (20 eliglustat, 20 placebo), 39 (98%) patients completed Week 39 (19 [95%] eliglustat, 20 [100%] placebo), and 38 (95%)



patients completed Week 78 (18 [95%] eliglustat, 20 [100%] placebo). All patients randomized to placebo in the 39-week PAP continued treatment with eliglustat in the 39-week open-label, extension period. The demographic and baseline disease characteristics of the 40 patients in the FAS have been summarised in the first round clinical evaluation report.

The mean (SD) total time on eliglustat was 556.3 (12.4) days for patients initially randomized to eliglustat (including 276.2 (7.38) days in the extension period), and 276.0 (7.66) days for the placebo-eliglustat group (all in the extension period).

#### 11.4.2. Efficacy

##### 11.4.2.1. Primary efficacy endpoint

The results for the primary efficacy endpoint of % change in spleen volume from Baseline to Week 39 have been presented in the first round CER. The observational analysis presented in the Memo Report summarised only the available data at each time-point up to Week 78 with no LOCF adjustments for missing data. In addition, all changes from Baseline in the Memo Report were calculated without covariate adjustment for baseline values in spleen volume. The results for spleen volume over time are summarised below in Table 60 from the Memo-Report. All patients in the study presented with splenomegaly at Baseline, with mean spleen volumes of 13.89 MN for the eliglustat treatment group and 12.50 MN for the placebo group. In the eliglustat treatment group, the mean % reduction in spleen volume (MN) from Baseline through Week 39 was -29.03% with continued reduction from Baseline through to Week 78 of -44.61%. In the placebo-eliglustat group, the mean % change in spleen volume (MN) from Baseline through to Week 39 was +2.08% (that is, after 39 weeks treatment with placebo), and -31.31% from Week 39 through to Week 78 (that is, after 39 weeks treatment with eliglustat).

**Table 60: (Memo-Report): Spleen volume (MN) over time; FAS.**

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

Note: Change and percentage change is summarised only for patients who have data at Baseline and the specified time point; Baseline refers to the last assessment prior to first study dose in the double-blind Primary Analysis Period (PAP) through 39 weeks. However, for patients randomized to Placebo in the PAP, their new baseline was the last assessment on or before Week 39 for the open-label extension.

##### 11.4.2.2. Key secondary efficacy endpoints

1. Haemoglobin (g/dL): In the eliglustat group, the mean (SD) absolute change from Baseline was 0.76 (1.114) g/dL at Week 39 and 1.02 (0.844) g/dL at Week 78. In the placebo-eliglustat group, the mean (SD) absolute change from Baseline at Week 39 was -0.58

(0.890) g/dL (that is, following 39 weeks placebo) and 0.79 (0.818) g/dL from Week 39 through to Week 78 (that is, following 39 weeks eliglustat).

2. Platelet count (109/L): In the eliglustat group, the mean (SD) % change from Baseline was 32.55 (32.443) % at Week 39 and 58.16 (41.068) % at Week 78. In the placebo-eliglustat group, the mean (SD) % change from Baseline at Week 39 was -8.77 (18.187) % (that is, following 39 weeks placebo) and 39.82 (37.367) % from Week 39 through to Week 78 (that is, following 39 weeks eliglustat).
3. Liver volume (MN): In the eliglustat group, the mean (SD) % change from Baseline was -5.66 (7.002) at Week 39 and -11.18 (9.345) % at Week 78. In the placebo-eliglustat group, the mean (SD) % change from Baseline at Week 39 was 1.70 (8.004) % (that is, following 39 weeks placebo) and -7.31 (9.974) % from Week 39 through to Week 78 (that is, following 39 weeks eliglustat).

### 11.4.2.3. Safety

The overview of the safety data from the Memo Report are summarised below in Table 61. The focus in the following review of safety is on the initially randomized eliglustat patients continuing treatment with eliglustat in the open-label, long-term, extension period.

**Table 61: (Memo Report): Overview of treatment-emergent adverse events; safety set.**

AE Category	Eliglustat PAP (N=20) 39 wks		Placebo PAP (N=20) 39 wks		Eliglustat Ext (N=19) 39 wks		Placebo to Eliglustat Ext (N=20) 39 wks		Total (N= 40) 78 wks	
	Events	Patients n (%)	Events	Patients n (%)	Events	Patients n (%)	Events	Patients n (%)	Events	Patients n (%)
Patients with:										
Any TEAEs	135	18 (90)	95	14 (70)	93	15 (79)	92	15 (75)	415	36 (90)
Related	32	9 (45)	25	9 (45)	25	8 (42)	19	9 (45)	101	24 (60)
Not related	103	18 (90)	70	14 (70)	68	13 (68)	73	12 (60)	314	35 (88)
Mild	93	16 (80)	85	14 (70)	67	14 (74)	85	13 (65)	330	34 (85)
Moderate	42	15 (75)	10	6 (30)	24	10 (53)	7	5 (25)	83	23 (58)
Severe	0	0 (0)	0	0 (0)	2	2 (11)	0	0 (0)	2	2 (5)
Serious	0	0 (0)	0	0 (0)	2	1 (5)	0	0 (0)	2	1 (3)
Deaths	0	0 (0)	0	0 (0)	0	0 (0)	0	0 (0)	0	0 (0)
TEAEs leading to discontinuation	0	0 (0)	0	0 (0)	0	0 (0)	0	0 (0)	0	0 (0)

In the extension-period, 15 (79%) patients experienced TEAEs. TEAEs (PT) reported in  $\geq 2$  patients were: headache (5, 26%); upper respiratory tract infection (3, 16%); bronchitis (2, 11%), nasopharyngitis (2, 11%); otitis media (2, 11%); nasal congestion (2, 11%); abdominal pain (2, 11%); abdominal distension (2, 11%); arthralgia (2, 11%); back pain (2, 11%); myalgia (2, 11%); acne (2, 11%); and proteinuria (2, 11%). The TEAEs (PT) reported in eliglustat patients treated for up to 78 weeks do not give rise to concern. The TEAEs (PT) for eliglustat in the 39-week long-term extension period were consistent with those reported for eliglustat in the 39-week PAP. In the PAP (Week 1 to Week 39), TEAEs reported in  $\geq 3$  patients ( $\geq 15\%$  of patients) were nasopharyngitis, diarrhoea, headache, and arthralgia.

There were no deaths in the study. There was 1 patient (1/40, 2.5%) treated with eliglustat during the PAP who reported 2 SAEs during the extension period (atrioventricular block, atrioventricular block second degree). These events were reported as mild, recovered/resolved, and were noted during protocol driven Holter and ECG monitoring. They did not lead to study discontinuation and were considered by the investigator to have a probable relationship to eliglustat. There were no TEAEs leading to withdrawal from the study.



## 12. Second round benefit-risk assessment

### 12.1. Second round assessment of benefits

#### 12.1.1. GD1 patients who are ERT-naive

The totality of the submitted evidence supports the benefits of the sponsor's proposed fixed-dose eliglustat 100 mg bd treatment regimen in GD1 ERT-naive patients who are CYP2D6 intermediate or extensive metabolisers. Of note, the benefits observed with the eliglustat titration regimen in ERT-naive patients in both the pivotal Phase III study (ENGAGE [GZGD020507]) and the supportive Phase II Study (GZGD00304) appear to have been driven primarily by the 100 mg bd dose in GD1 CYP2D6 IM/EM patients.

##### 12.1.1.1. ENGAGE (GZGD020507)

In the pivotal Phase III study [ENGAGE], the majority of ERT-naive GD1 patients treated with eliglustat in the 39-week, double-blind, placebo-controlled primary analysis period (PAP) were CYP2D6 EMs receiving 100 mg bd (80%, 16/20). Of the 20 patients in the study, the CYP2D6 metaboliser status was PM (0%, 0/20), IM (5%, 1/20), EM (90%, 18/20), and URM (5%, 1/20). In this study, 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 the 100 mg bd dose was maintained through to Week 39. Three (3) patients (15%) remained on 50 mg bd from Baseline through to Week 39, while no patients were treated with 150 mg bd in the PAP.

In the PAP, 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 to only 5% of patients in the placebo group. In addition, all secondary endpoints in the eliglustat group compared to the placebo group showed greater statistically significant and clinically meaningful changes from Baseline to Week 39; the differences between the two treatment groups for the 3 secondary efficacy endpoints were 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% ( $p < 0.0001$ ).

The sponsor's S31 Response included new efficacy data from an open-label, extension period of 39 weeks (that is, total efficacy data from this study for eliglustat treated patients now available for up to Week 78). In patients treated with eliglustat 50 mg bd or 100 mg bd in the PAP,  $C_{\text{trough}}$  levels were estimated at the start of the open-label, extension period and patients were treated with 50 mg bd, 100 mg bd or 150 mg depending on the  $C_{\text{trough}}$  results. In addition, patients who had been originally randomized to placebo in the PAP were switched to eliglustat at Week 39 and received doses of 50 mg bd, 100 mg bd, or 150 mg bd. The data showed that in eliglustat treated patients, reductions in spleen volume achieved at Week 39 ( $n = 19$ ) were maintained through to Week 78 ( $n = 18$ ). Similar effects were observed for the other 3 clinical outcomes of interest (reduction in liver volume, increase in haemoglobin level, and increase in platelet count).

Patients originally randomized to placebo in the PAP (Day 0 through to Week 39) and switched to eliglustat 50 mg bd, 100 mg bd, or 150 mg bd in the open-label extension period (Week 39 through to Week 78) showed similar outcomes at Week 78 to eliglustat treated patients at Week 39, despite the fact that 7 of the 20 CYP2D6 EM patients received 150 mg bd in the extension period. The sponsor considers that this shows that a dose above 100 mg in treatment-naive CYP2D6 EM patients (that is, 150 mg bd) does not result in further meaningful clinical outcomes. The efficacy outcomes at Week 78 in the placebo-eliglustat group were marginally

superior to the eliglustat-eliglustat group, although the differences between the two groups are considered to be clinically insignificant. The Week 39 and Week 78 results for both treatment groups are summarised below in Table 62.

**Table 62: ENGAGE - Mean (SD) changes from Baseline following treatment with eliglustat for 39 weeks in the randomized period (from Day 0 to Week 39) vs. extension period for placebo-randomized patients switched to eliglustat (from Week 39 to Week 78); FAS.**

Outcome	Eliglustat (n=19)	Placebo switch to Eliglustat (n=20)
	Week 39	Week 78
Percentage change in spleen volume (MN) (%)	-29.03 (11.085)	-31.31 (10.125)
Percentage change in liver volume (MN) (%)	-5.66 (7.002)	-7.31 (9.974)
Absolute change in haemoglobin level (g/dL)	0.76 (1.114)	0.79 (0.818)
Percentage change in platelet count (%)	32.55 (32.443)	39.82 (37.367)

The sponsor's s31 Response included comparative efficacy data for patients treated in the PAP grouped by average  $C_{trough}$  levels (< 5 ng/mL versus  $\geq$  5 ng/mL). Using an ANCOVA model, the LS mean (SEM) percent change in spleen volume (MN) was -23.26 (4.18) % in the < 5 ng/mL group (n=9) and -31.11 (3.77) % in the  $\geq$  5 ng/mL group, with a mean (SEM) percent difference of 7.85 (5.65) %, (95% CI: -4.08, 19.78), p=0.183. The study was powered to detect a clinically meaningful reduction in spleen volume (MN) of 20%. The mean reduction in spleen volume (MN) in both  $C_{trough}$  groups was > 20%, and the observed difference between the two groups was neither statistically significant nor clinically meaningful.

Of the 16 patients who were CYP2D6 EMs and received eliglustat 100 mg bd in the PAP, 8 (50%) had average  $C_{trough}$  levels of < 5 ng/mL and 8 (50%) had average  $C_{trough}$  levels  $\geq$  5 ng/mL. The  $C_{trough}$  levels were determined by averaging the pre-dose measurements taken at Weeks 13, 26, and 39. Information provided in the sponsor's S31 Response indicates that the two  $C_{trough}$  groups had similar disease characteristics at Baseline. At Week 39, both  $C_{trough}$  groups achieved clinically meaningful improvements in outcomes, although improvement in the  $\geq$  5 ng/mL for each of the outcomes was marginally greater than in the < 5 mg/mL group (see Table 63 below). One (1) EM patient in the  $\geq$  5 ng/mL group had missing data at Week 39. In this study, a clinically meaningful reduction in spleen volume (MN) was defined as  $\geq$  20%. The range of reduction in spleen volume (MN) in the  $C_{trough}$  < 5 ng/mL group indicates that not all patients in this group achieved a reduction of  $\geq$  20%. However, the totality of the data for the four efficacy outcomes are considered to be sufficiently robust to support the proposed fixed-dose treatment regimen of eliglustat 100 mg bd in CYP2D6 IM/EM patients.

**Table 63: ENGAGE - Mean (SD) change from Baseline over the first 39 Weeks of eliglustat 100 mg bd in CYP2D6 EM patients, FAS.**

Outcome	< 5 ng/mL (n=8)	$\geq$ 5 ng/mL (n=7)	Overall (n=15)
Percentage change in spleen volume (MN) (%)	-24.504 (10.6414)	-31.524 (6.3883)	-27.780 (9.3410)
Range (maximum, minimum)	(-42.66, -7.68)	(-39.56, -20.89)	(-42.66, -7.68)
Absolute change in haemoglobin level (g/dL)	0.463 (1.0049)	1.286 (0.9045)	0.847 (1.0180)
Percentage change in liver volume (MN) (%)	-6.025 (7.7120)	-7.659 (5.0182)	-6.787 (6.4220)
Percentage change in platelet count (%)	32.629 (36.7273)	33.244 (31.7866)	32.916 (33.2802)

ENGAGE excluded patients with documented acute pathological bone involvement (for example, osteonecrosis and/or pathological fractures, as assessed by X-ray and/or 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 (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.

### 12.1.1.2. Phase II Study (GZGD00304)

The supportive Phase II study in ERT-naive GD1 patients (n=26) was of 4 years duration with a PAP of 52 weeks. All 26 patients received a single 50 mg dose of eliglustat on Day 1 and 50 mg bd on Day 2, while 18 patients were up-titrated to 100 mg bd on Day 20 based on  $C_{trough}$  levels (< 5 ng/mL). One (1) additional patient received a dose increase to 100 mg bd after 3 years of treatment. No patients received a dose increase to 150 mg bd from Day 0 through to Year 4. Of the 26 eliglustat treated patients, 25 (96%) were CYP2D6 EMs and 1 was a CYP2D6 PM.

Treatment with eliglustat resulted in 77% (20/26) (95% CI: 58%, 89%) of patients achieving the primary composite endpoint for success after 52 weeks of treatment (that is, improvement in 2 of the 3 efficacy parameters of haemoglobin, platelets, and 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.

In the S31 Response, the sponsor provided data indicating that of the 16 CYP2D6 EM patients who received eliglustat over the 4 year treatment period, 9 patients had steady state  $C_{trough}$  levels  $\geq$  5 ng/mL and 7 patients had steady state  $C_{trough}$  levels < 5 ng/mL. The treatment responses in the two groups were compared at Month 12 and at Month 48 (see Table 64, below). Both groups showed clinically meaningful changes at Month 12 and Month 48, but improvement was more marked in the  $C_{trough} \geq$  5 ng/mL group. The sponsor states that the 'apparently smaller relative changes observed in the < 5 ng/mL group for all parameters are consistent with their less severe baseline disease status, as baseline values that are closer to normal range at start of treatment may limit the magnitude of improvement'.

Furthermore, after 48 months of treatment both  $C_{trough}$  groups (< 5 ng/mL versus  $\geq$  5 ng/mL) reached similar mean values for haemoglobin level (13.6 g/dL versus 13.6 g/dL, respectively), platelet count ( $100 \times 10^9/L$  versus  $125 \times 10^9/L$ , respectively), spleen volume (5.5 MN versus 6.8 MN, respectively) and liver volume (5.5 MN versus 6.8 MN, respectively). In addition, in an ANCOVA mode adjusting for Baseline differences between the two groups, no statistically significant differences were observed between the two  $C_{trough}$  groups in mean change from Baseline to Month 48 in any of the 4 efficacy parameters. The data are supportive of the sponsor's proposed fixed-dose treatment regimen in CYP2D6 IM/EM patients.

**Table 64: Phase II study - Mean (SD) change from Baseline by average steady state trough concentration for CYP2D6 EM patients treated with 100 mg bd.**

	Week 52/Month 12		Week 208/Month 48	
	< 5 ng/mL (n=7)	$\geq$ 5 ng/mL (n=9)	< 5 ng/mL (n=7)	$\geq$ 5 ng/mL (n=9)
Percentage change in spleen volume (MN) (%)	-37.457 (9.4509)	-39.533 (9.4783)	-55.100 (7.6861)	-63.411 (10.0088)
Absolute change in haemoglobin level (g/dL)	1.436 (0.6951)	2.061 (1.3858)	1.664 (1.5897)	2.372 (1.4252)
Percentage change in liver volume (MN) (%)	-11.657 (9.1668)	-20.833 (11.4156)	-19.233 (10.6714)	-30.656 (14.6901)
Percentage change in platelet count (%)	39.171 (30.3759)	53.689 (37.4197)	40.686 (33.6417)	116.833 (94.2473)

### 12.1.2. GD1 patients stabilized on ERT and switched to eliglustat

The major issue following the first round clinical evaluation was whether or not the submitted data were sufficient to support the benefits of the proposed eliglustat 100 mg bd fixed-dose regimen in GD1 patients who were CYP2D6 intermediate or extensive metabolisers stabilized on ERT and switched to eliglustat.

Following the first round clinical evaluation, it was considered that the data in the original submission did not support the benefits of the proposed eliglustat regimen in this group of patients, but did support the benefits of the eliglustat titration regimen used in the pivotal Phase III study [ENCORE] in this patient group. In particular, it was considered that the original submission provided no adequate data on which to conclude that the benefits of the proposed 100 mg bd dose were superior to the benefits of a 50 mg bd dose or inferior to a 150 mg bd dose for the proposed patient population. Therefore, due to the uncertainty surrounding the most appropriate eliglustat dose for the fixed-dose regimen it was recommended that the submission to approve the proposed regimen in this patient group be rejected. However, following review of the totality of the evidence provided by the sponsor it is now considered that the benefits of the proposed eliglustat 100 mg bd fixed-dose regimen for the treatment of GD1 patients (CYP2D6 IM/EM) previously stabilized on ERT have been adequately demonstrated.

In ENCORE, all patients randomized to eliglustat were started on 50 mg bd, with increase to 100 mg bd at Week 4 for patients with  $C_{\text{trough}}$  levels < 5 ng/mL at Week 2 and increase to 100 mg bd (for patients on 50 mg bd) or 150 mg bd (for patients on 100 mg bd) at Week 8 for patients with  $C_{\text{trough}}$  levels < 5 ng/mL at Week 6. Following a protocol amendment, patients with peak eliglustat levels > 150 ng/mL were to be temporarily discontinued from treatment and removed from the primary 52 week analysis period if the peak level occurred during this period.

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 switched to eliglustat. The primary composite endpoint was achieved in 84.8% (84/99) of patients in the eliglustat titration group compared to 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 treatment groups 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) for the difference between the two treatment groups (-2.83% [95% CI: -8.14, 2.47]) was within the non-inferiority margin of 15% for this parameter recommended by the FDA. The primary analyses were undertaken in the PPS and were supported by similar results in the FAS analyses.

The Baseline values for all 4 components of the composite primary endpoint were at normal or close to normal levels for both the eliglustat and Cerezyme treatment groups (that is, spleen volume, liver volume, haemoglobin level, platelet count). Consequently, the 4 components of the composite endpoint had little or no capacity to improve following the switch to eliglustat, but could regress if eliglustat was unable to maintain stability. The study showed that normal or close to normal Baseline values for the 4 outcome criteria could be maintained through to Week 52 in both the eliglustat titration and Cerezyme treatment groups. In addition, based on a binary (yes/no) composite endpoint involving stable and normal haematology and organ volume values at Week 52, 91/99 patients in the eliglustat titration group were stable and normal (91.9% [95% CI: 84.7, 96.4]) compared to 44/47 patients in the Cerezyme group (93.6% [95% CI: 82.5, 98.7]).

In the S31 Response, data were provided indicating that the percentage of patients in the PPS meeting the composite primary endpoint was similar in the group with  $C_{\text{trough}}$  levels < 5 ng/mL and  $\geq$  5 ng/mL: 29/36, 80.6% (95% CI: 64.0, 91.8) versus 55/63, 87.3% (95% CI: 76.5, 94.4); difference of -6.7% (95% CI: -27.0, 13.9),  $p=0.371$ . The majority of patients in both  $C_{\text{trough}}$  groups maintained stability over the 52 weeks of treatment with eliglustat. The results are considered to support the sponsor's proposal to use a fixed-dose regimen rather than a titration regimen (50@ 100@ 150 mg bd) based on  $C_{\text{trough}}$  levels early in treatment.

In the S31 Response, data were provided indicating that the results for the primary composite endpoint in the PPS at Week 52 were similar in the three dosage groups: 78.9% (95% CI: 54.4,

93.9) versus 84.4% (95% CI: 67.2, 94.7) versus 87.5% (95% CI: 74.8, 95.3) for the 50 mg bd (n=19), 100 mg bd (n=32) and 150 mg bd (n=48) groups, respectively. There were no statistically significant differences for the relevant pair-wise comparisons between the treatment groups. Similar results were observed for each of the 4 individual components of the primary composite endpoint. The results indicate that each of the three dosage regimens used in the study can maintain adequate stability over 52 weeks treatment (that is, 50 mg bd, 50 mg bd @ 100 mg bd, and 50 mg @ 100 mg @ 150 mg). Patients were titrated to the higher dose if their  $C_{trough}$  level was < 5 ng/mL.

In essence, the Week 52 comparison between the three dose groups in the PPS can be interpreted as a comparison in patients who were CYP2D6 IMs/EMs, as nearly all patients were CYP2D6 IMs or EMs (that is, 89/99 [90%]) (see Table 65 below). In the PPS, CYP2D6 IM/EM patients included in the 50 mg bd, 100 mg bd, and 150 mg bd treatment groups comprised 78% (15/19), 100% (32/32) and 88% (42/48) of the total CYP2D6 phenotype, respectively. Titrating dose based on  $C_{trough}$  levels worked for the small number of patients who were CYP2D6 PMs (n=4) or URM (n=4), as the respective final dose groups were 50 mg bd and 150 mg bd. However, the presence of CYP2D6 IM/EM patients in the three different dose groups must reflect intersubject variability in  $C_{trough}$  levels in these patients, resulting in some  $C_{trough}$  levels being < 5 ng/mL and some being  $\geq$  5 ng/mL. Information on inter-subject variability in  $C_{trough}$  levels in CYP2D6 IM/EM patients can be obtained from the PK data set for ENCORE. In the 100 mg bd dose group, the  $C_{trough}$  mean (SD) was 7.56 (5.17) ng/mL (CV= 68.4%) in CYP2D6 EM patients (n=29) and 18.2 (18.0) ng/mL (CV=98.9%) in CYP2D6 IM patients (n=4). In addition, of the 29 patients in the 100 mg bd group (PPS) who were CYP2D6 EMs, 8 (28%) had  $C_{trough}$  levels < 5 ng/mL and 21 (72%) had  $C_{trough}$  levels  $\geq$  5 ng/mL.

**Table 65: ENCORE - Summary of CYP2D6 metaboliser status by treatment group; PPS.**

CYP2D6 Phenotype	50 mg BD (n=19)	100 mg BD (n=32)	150 mg (n=48) *	Total (n=99)
Poor (PM)	4 (21)	0	0	4 (4)
Intermediate (IM)	5 (26)	4 (13)	1 (2)	10 (10)
Extensive (EM)	10 (53)	28 (88)	41 (85)	79 (80)
Ultra-rapid (URM)	0	0	4 (8)	4 (4)
Indeterminate	0	0	0	0

\* The percentages in the table are based on the total number of patients in the 150 mg group (n=48) rather than the number of patients with CYP2D6 phenotype data in the column (n=46).

The S31 Response included Week 52 data comparing outcome in the 29 patients (PPS) from ENCORE in the 100 mg bd group who were CYP2D6 EMs based on average  $C_{trough}$  levels < 5 ng/mL (n=8) and  $\geq$  5 ng/mL (n=21). The percentage of patients meeting the primary composite endpoint was higher in the  $\geq$  5 ng/mL group compared to the < 5 ng/mL group at Week 52, with substantial overlap of the exact 95% CIs (see Table 66, below).

**Table 66: ENCORE - Proportion of patients meeting stable composite endpoint at Week 52 in eliglustat patients who were CYP2D6 EM; PPS.**

Week 52	< 5 ng/mL (n=8)	$\geq$ 5 ng/mL (n=21)	Overall (n=29)
Patients meeting composite primary endpoint, n (%)	6 (75.0%)	19 (90.5%)	25 (86.2%)
	[95% CI: 0.349, 0.968]	[95% CI: 0.696, 0.988]	[95% CI: 0.683, 0.961]

The Baseline and Week 52 values for each of the 4 individual components of the primary composite endpoint were similar for both the < 5 ng/mL and the  $\geq$  5 ng/mL groups (see Table 67 below).



**Table 67: ENCORE - Mean (SD) Baseline and Week 52 results by average plasma steady state trough concentration for CYP2D6 EM patients treated with 100 mg bd.**

	< 5 ng/mL (n=8)		≥ 5 ng/mL (n=21)	
	Baseline	Week 52	Baseline	Week 52
Spleen volume (MN)	3.774 (2.3698)	3.530 (2.3572)	3.158 (1.4770)	3.048 (1.5209)
Haemoglobin level (g/dL)	12.850 (1.1430)	12.725 (1.1254)	13.802 (1.3166)	13.605 (1.1941)
Liver volume (MN) (	0.928 (0.1306)	1.019 (0.1143)	0.955 (0.2090)	0.961 (0.2192)
Platelet count ( x 10 <sup>9</sup> /L)	204.375 (69.5731)	200.438 (60.8678)	247.405 (110.3006)	259.929 (110.3701)

The results indicate that, for each of the 4 individual components of the primary composite endpoint, Baseline stability in patients treated with 100 mg bd can be maintained through to Week 52, irrespective of C<sub>trough</sub> level < 5 ng/mL or ≥ 5 ng/mL. There was a high percentage of stable patients for each of the 4 components contributing to the composite endpoint in both the < 5 ng/mL (n=8) and ≥ 5 ng/mL (n=21) groups at Week 52: that is, haemoglobin 100% (8/8) versus 95.2% (20/21); platelet count 87.5% (7/8) versus 95.2% (20/21); spleen volume 100% (5/5) versus 100% (12/12); and liver volume 87.5% (7/8) versus 100% (21/21). The observed difference in outcomes between the two C<sub>trough</sub> groups might, at least in part, be due to the imbalance in patient numbers between the two groups. Overall, the results suggest that the benefits of treatment in CYP2D6 IM/EM patients treated with eliglustat 100 mg bd will be clinically meaningful, irrespective of whether C<sub>trough</sub> levels are < 5 ng/mL or ≥ 5 ng/mL. The clinical data provide support for the sponsor's proposed treatment regimen of 100 mg bd in CYP2D6 IM/EM patients.

Further support for the proposed treatment regimen comes from the PK/PD modelling and simulation analysis. PK/PD modelling and PopPK logAUC<sub>(0-tau)</sub> simulation was used to predict mean % change in spleen volume (MN) from Baseline to Week 52 in simulated CYP2D6 IM/EM patients (n=70) dosed at 50 mg bd, 100 mg bd and 150 mg bd. The analyses showed that the observed and predicted results were most similar for the 100 mg bd dose (-5.96% and -6.55%, respectively). The predicted and observed results for the 50 mg bd dose were -6.05% and -1.36%, respectively, and for the 150 mg bd were -6.05% and -9.72%, respectively. The data suggest that 100 mg bd is the most appropriate dose. Similar results were reported using a PK/PD modelling/simulation analysis based on individual % change in spleen volume (MN) from Baseline to Week 52 in all IM and EM patients projected to 50 mg bd, 100 mg bd and 150 mg bd.

PK/PD modelling and PopPK logAUC<sub>(0-tau)</sub> simulation analysis was used to project % change in spleen volume from Baseline to Week 52 in 6 patients (CYP2D6 EMs x 5; indeterminate x 1) actually treated with 100 mg if treated with 150 mg bd (that is, model simulated dose). For these 6 patients, the analysis projected a maximum 4.5% increase in % change in spleen volume (MN) from Baseline to Week 52 for simulated 150 mg bd dosing compared to the observed increase for actual 100 mg bd dosing. The sponsor states that a 4.5% increase in spleen volume (MN) is similar to the test-retest variability of spleen volume (MN) measured by MRI determined during ENGAGE, and is less than the 12% variability reported in the literature. The sponsor states that such a small change in spleen volume would not be clinically noticeable. All 6 patients had spleen volumes (MN) that met the long-term therapeutic goal for Cerezyme of ≤ 2 to 8 MN, and all would have remained at the therapeutic goal despite the small predicted increases in spleen volumes. The modelling and simulation analysis suggests that the benefits of treatment with 100 mg bd in CYP2D6 EMs are unlikely to be clinically significantly different to treatment with 150 mg bd in this patient population.

PK/PD modelling and PopPK logAUC<sub>(0-tau)</sub> simulation analysis was used to project % change in spleen volume (MN) from Baseline to Week 52 in CYP2D6 IM/EM actually treated with 100 mg or 150 mg bd if treated with 50 mg bd (that is, model simulated dose). Five (5) CYP2D6 EM patients treated with 100 mg bd (n=1) or 150 mg bd (n=4) during the study had observed

spleen volume (MN) increases of < 25% in the PAP (that is, composite endpoint success, stability maintained). If these 5 patients had been treated with 50 mg bd then the projected % change in spleen volume (MN) for each of the patients would have been > 25%, shifting them from composite endpoint treatment successes to failures. The modelling and simulation analysis suggests that a dose of 50 mg bd would not be sufficient to maintain stability in all patients in the target population of CYP2D6 IM/EM patients.

PBPK simulations showed that observed  $C_{max}$  (ng/mL) levels at Week 52 for the 50 mg bd and 100 mg bd dose groups in CYP2D6 IM/EM patients would increase if projected to 150 mg bd. This creates potential safety concerns relating to the 150 mg bd dose as some projected  $C_{max}$  levels exceeded the safety target of 150 ng/mL. The modelling and simulation analysis suggest that the 100 mg bd dose might be safer than the 150 mg bd dose in the proposed population of CYP2D6 IM/EM patients.

## 12.2. Second round assessment of risks

The second round assessment of risks remains unchanged from the first round assessment. Additional safety data from ENGAGE provided in the S31 Response raised no new safety signals in eliglustat treated patients for 78 weeks.

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 stabilized 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 to 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 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 safe for this indication.

## 12.3. Second round assessment of benefit-risk balance

The benefit-risk balance is favourable for the proposed treatment regimen of eliglustat 100 mg bd in CYP2D6 IM/EM patients who are ERT-naive or who have been stabilized on ERT and switched to eliglustat.

Excluding patients who are CYP2D6 PMs from treatment with 100 mg bd will mitigate the risks associated with excessive exposure to eliglustat in these patients, while excluding patients who are CYP2D6 URM from treatment with 100 mg bd will mitigate the risks of lack of efficacy due to negligible exposure to eliglustat in these patients. The data from ENCORE showed that all patients who were CYP2D6 PMs (n=4) remained at the initial dose of 50 mg bd, while all patients who were URM (n=4) were titrated up to 150 mg bd. It can be anticipated that



restricting treatment to CYP2D6 IM/EM patients will capture approximately 90% of GD1 patients.

The PopPK analysis demonstrated that CYP2D6 metaboliser status was the most significant determinant of eliglustat exposure. The submitted data from ENGAGE and ENCORE supports the conclusion that efficacy in patients with eliglustat  $C_{\text{trough}}$  levels  $< 5$  ng/mL does not differ significantly from patients with eliglustat  $C_{\text{trough}}$  levels  $\geq 5$  ng/mL.

The totality of the submitted evidence in CYP2D6 IM/EM patients suggests that: (1) the benefits of the 100 mg bd dose are superior to the benefits of the 50 mg bd, while the safety risks are similar for the two doses; and (2) there is unlikely to be a clinically meaningful difference in the benefits of the 100 mg bd dose and the 150 mg dose, while the risks of the 150 mg bd dose are potentially greater than the risks of the 100 mg bd dose.

### 13. Second round recommendation regarding authorisation

1. It is recommended that eliglustat be approved for the long-term treatment of adult patients with GD1. It is recommended that eliglustat be approved for GD1 patients who are ERT-naive, and for GD1 patients who have been stabilized on ERT and for whom a switch to eliglustat is considered to be appropriate.
2. It is recommended that eliglustat be used only in patients who are CYP2D6 intermediate or extensive metabolisers, and contraindicated in poor, ultra-rapid or indeterminate CYP2D6 metabolisers.
3. It is recommended that the approved eliglustat dose be 84 mg taken twice daily (that is, equivalent to eliglustat tartrate 100 mg taken twice daily).

### 14. References

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