20 November 2014
EMA/57549/2015
Committee for Medicinal Products for Human Use (CHMP)

Cerdelga

(eliglustat)

Procedure No. EMEA/H/C/003724

Applicant: Genzyme Europe BV

Assessment report for an initial marketing authorisation application

Assessment report as adopted by the CHMP with all commercially confidential information deleted

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List of abbreviations

Abbreviation	Definition
ADME	Absorption, Distribution, Metabolism, and Excretion
AE	Adverse event
ALT	Alanine aminotransferase
ALT	Alanine aminotransferase
ANCOVA	Analysis of covariance
AP	Action Potential
APD	Action Potential Duration
AST	Aspartate aminotransferase
AUC	Area under the curve
AUC_{0-12}	Area under the plasma concentration versus time curve from time zero to 12 hours postdose
AUC_{0-4}	Area under the plasma concentration versus time curve calculated using the trapezoidal method from time zero to 4 hours
$AUC_{0-\infty}$	Area under the plasma concentration versus time curve extrapolated to infinity (Note: this is denoted in the data listings as 'AUC')
AUC_{0-t}	Area under the concentration versus time curve from time zero to the time of the last measurable concentration after dose administration
AUC_{0-tau}	Area under the plasma concentration versus time curve calculated using the trapezoidal method from time zero to dosing interval (Note: this is denoted in the data listings as 'AUCτ')
AUC_{last}	Area under the plasma concentration versus time curve from time zero to the time of the last concentration above the lower limit of quantification
AV	Acceptance Value
BID	Bis in die (twice daily)
BMB	Bone marrow burden
BMD	Bone mineral density
BMI	Body mass index
BP	Blood pressure
BPI	Brief Pain Inventory
BQL	Below the limit of quantification
BUN	Blood urea nitrogen
CCL18	Chemokine CC motif ligand 18
CEP	Certification of suitability to the monographs of the European Pharmacopoeia
CHO	Chinese Hamster Ovary
CI	Confidence interval
C_{max}	Maximum plasma concentration
COC	Cyclic Olefin Co-polymer
CPP	Critical Process Parameter
CQA	Critical Quality Attribute
CSR	Clinical study report
C_{trough}	Plasma concentration before treatment administration during repeated dosing
CV	Coefficient of variation
CV	Cardiovascular
CYP	Cytochrome P450 enzyme
DALA	Drug abuse and Liability Assessment

DBS	Dried blood spots
DMC	Data Monitoring Committee
DMF	*N*,*N*-Dimethylformamide
DMSO	Dimethyl sulfoxide
DNA	Deoxyribonucleic acid
DoE	Design of Experiments
DP	Drug Product
DS3	Gaucher Disease Severity Scoring System
DSC	Differential Scanning Calorimetry
DXA	Dual-energy X-ray absorptiometry
EC	European Commission
ECG	Electrocardiogram
ECHO	Echocardiogram
eCRF	Electronic case report form
EM	Extensive metabolizer
ERT	Enzyme replacement therapy
EtOAc	Ethyl acetate
EU	European Union
F	Oral bioavailability
FAS	Full Analysis Set
FDA	Food and Drug Administration
FMEA	Failure Mode and Effects Analysis
FSS	Fatigue Severity Scale
FTIR	Fourier Transform Infra-Red spectroscopy
GC	Gas Chromatography
GCP	Good Clinical Practice
GCS	Glucosylceramide synthase
GD1	Gaucher Disease Type 1
Genz-112638	eliglustat tartrate
Genz-399240	disproportionate metabolite (M24)
Genz-99067	the active moiety eliglustat
GGT	Gamma glutamyl transferase
GI	Gastrointestinal
GL-1	Glucosylceramide
GLP	Good Laboratory Practice
GM1	Monosialotetrahexosylganglioside
HDL	High-density lipoprotein
HDPE	High Density Polyethylene
HEENT	Head, ears, eyes, nose, and throat
hERG	Human ether-a-go-go related gene
HIV	Human immunodeficiency virus
HPLC	High Performance Liquid Chromatography
HR	Heart rate
IC_{50}	half maximal inhibitory concentration
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
ID	Identification
IEC	Independent ethics committee
IM	Intermediate metabolizer
INN	International Non-proprietary Name

INR	International normalized ratio
IP1	Inositol-1-phosphate
IPA	Isopropyl Alcohol
IPC	In-process Control
IRB	Instructional review board
IV	Intravenous
IVRS	Interactive voice-response system
IWRS	Interactive web-response system
KF	Karl Fischer
KOP	Kappa Opioid Receptor
KPP	Key Process Parameter
LC-MS/MS	liquid chromatography with tandem mass spectrometry method
LDH	Lactate dehydrogenase
LDL	Low-density lipoprotein
LLOQ	Lower limit of quantification
LOCF	Last observation carried forward
LOQ	Limit of Quantification
LS	Least squares
LSC	Liquid scintillation counting
LV	Left ventricular
MAA	Marketing Authorisation Application
MAH	Marketing Authorisation Holder
MCS	Mental Component Summary
MCV	Mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
MEOI	Medical event of interest
MHRA	Medicines and Health Products Regulatory Agency
MIP-1β	Macrophage inflammatory protein 1 beta
MMA	Methylmalonic acid
MMSE	Mini Mental State Examination
MN	Multiples of normal
MOP	Mu Opioid Receptor
MRD	Maximum Rate of Depolarization
MRI	Magnetic resonance imaging
MTD	Maximum Tolerated Dose
MVTR	Moisture/Vapour Transmission Rate
NA	Not applicable
NC	Not Calculated
NCI CTCAE	National Cancer Institute Common Toxicology Criteria for Adverse Events
ND	Not determined
NMT	Not more than
NOAEL	No observed adverse effect level
NOEL	No observed effect level
NSAIDs	Non-steroidal anti-inflammatory drugs
PAR	Proven Acceptable Range
PCE	Process Control Element
PCS	Physical Component Summary
PCTFE	Polychlorotrifluoroethylene
PE	Petroleum Ether
PETG	Glycollated Polyethylene Terapthalate

P-gp	P-glycoprotein
Ph. Eur.	European Pharmacopoeia
PK	Pharmacokinetic
PO	By mouth
PopPK	Population Pharmacokinetic
PPS	Per Protocol Set
PR	Interval between the P wave onset and R wave onset of the electrocardiogram
PT	Prothrombin time
PTT	Partial thromboplastin time
QbD	Quality by Design
QC	Quality control
QD	Once daily
QOL	Quality of life
QRS	interval between the Q wave onset and S wave onset of the electrocardiogram
QT	QT interval
QTcB	Corrected QT interval (Bazett's formula)
QTcF	Corrected QT interval (Fridericia's formula)
QTcQ	heart-rate corrected QT interval using an animal-specific correction factor
QTcV	heart-rate corrected QT interval using Van de Water's formula
QTPP	Quality Target Product Profile
QWBA	Quantitative Whole-Body Autoradiography
RBC	Red blood cell
RH	Relative Humidity
RP-HPLC	Reverse Phase High Performance Liquid Chromatography
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	Standard deviation
SE	Standard Error
SEM	Standard error of the mean
SF-36	36-Item Short Form Health Survey
SI	International System of Units
SmPC	Summary of Product Characteristics
SOC	System organ class
SRT	Substrate reduction therapy
STIR	Short T1 inversion recovery
$T_{1/2}$	Terminal half-life
TAMC	Total Aerobic Microbial Count
TEAE	Treatment-emergent adverse event
TGA	Thermogravimetric Analysis
TK	Toxicokinetics
t_{max}	Time to reach Cmax
TSE	Transmissible Spongiform Encephalopathy
TYMC	Total Yeast and Mould Count
UA	Upstroke amplitude
UK	United Kingdom
URM	Ultrarapid metabolizer
US / USA	United States / United States of America
UV	Ultra-Violet spectroscopy
XRPD	X-Ray Powder Diffraction

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Genzyme Europe BV submitted on 20 September 2013 an application for Marketing Authorisation to the European Medicines Agency (EMA) for Cerdelga, through the centralised procedure falling within the Article 3(1) and point 4 of Annex of Regulation (EC) No 726/2004.
The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 21 February 2013.

Cerdelga, was designated as an orphan medicinal product EU/3/07/514 on 4 December 2007. Cerdelga was designated as an orphan medicinal product in the following indication: Treatment of Gaucher Disease.

The applicant applied for the following indication:

Cerdelga is indicated for the long-term treatment of adult patients with Gaucher disease type 1 (GD1). The target population is patients who are CYP2D6 intermediate (IM) or extensive (EM) metabolisers.

Following the CHMP positive opinion on this marketing authorisation, the Committee for Orphan Medicinal Products (COMP) reviewed the designation of Cerdelga as an orphan medicinal product in the approved indication. The outcome of the COMP review can be found on the Agency's website: ema.europa.eu/Find medicine/Rare disease designations.

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application. The applicant indicated that eliglustat was considered to be a new active substance.

The application submitted is

composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain tests or studies.

Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0041/2012 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP was not yet completed as some measures were deferred.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did submit a critical report addressing the possible similarity with authorised orphan medicinal products.

New active Substance status

The applicant requested the active substance eliglustat (as tartrate) contained in the above medicinal

product to be considered as a new active substance in itself, as the applicant claims that it is not a constituent of a product previously authorised within the Union.

Protocol Assistance

The applicant received Protocol Assistance from the CHMP on 24 September 2009 and 17 February 2011. The Protocol Assistance pertained to clinical aspects of the dossier.

Licensing status

The product was not licensed in any country at the time of submission of the application.

1.2. Manufacturers

Manufacturer(s) responsible for batch release

Genzyme Ireland Limited
IDA Industrial Park
Old Kilmeaden Road
Waterford
Ireland

1.3. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Pieter de Graeff Co-Rapporteur: Harald Enzmann

CHMP Peer reviewer: Arantxa Sancho-Lopez

- The application was received by the EMA on 20 September 2013.
- The procedure started on 23 October 2013.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 10 January 2014
- The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 10 January 2014
- The PRAC Rapporteur's Risk Management Plan (RMP) Assessment Report as endorsed by PRAC on 6 February 2014
- During the meeting on 20 February 2014, the CHMP agreed on the consolidated List of Questions to be sent to the applicant. The final consolidated List of Questions was sent to the applicant on 20 February 2014
- The applicant submitted the responses to the CHMP consolidated List of Questions on 22 May 2014
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 1 July 2014
- The PRAC RMP Advice and assessment overview as adopted by PRAC on 10 July 2014 (Annex 6).
- During the CHMP meeting on 24 July 2014, the CHMP agreed on a list of outstanding issues to be in writing and/or in an oral explanation by the applicant
- The applicant submitted the responses to the CHMP List of Outstanding Issues on 20 August 2014.

- The PRAC RMP Advice and assessment overview as adopted by PRAC on 11 September 2014
- During the meeting on 25 September 2014, the CHMP agreed on a second list of outstanding issues to be addressed in writing and/or in an oral explanation by the applicant
- The applicant submitted the responses to the CHMP second List of Outstanding Issues on 17 October 2014
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Outstanding Issues to all CHMP members on 28 October 2014
- PRAC Rapporteur's Risk Management Plan (RMP) Assessment Report as endorsed by PRAC on 6 November 2014
- The Rapporteurs circulated the Joint updated Assessment Report on the applicant's responses to the List of Outstanding Issues to all CHMP members on 12 November 2014
- During the meeting on 20 November 2014, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a Marketing Authorisation to Cerdelga
- The CHMP adopted a report on similarity of eliglustat tartrate (Cerdelga) with velaglucerase alfa (Vpriv) on 20 November 2014

2. Scientific discussion

2.1. Introduction

Gaucher disease (GD) is a rare lysosomal storage disorder caused by a deficiency of the enzyme acid β-glucosidase (also known as glucocerebrosidase). One of a group of inherited sphingolipidoses, GD is a multi-systemic and heterogeneous disorder that is a serious (and chronically debilitating) condition given the persistent and irreversible morbidity that will develop over time in the majority of patients. The classic manifestations of GD are organomegaly, haematological abnormalities, and bone disease.

Acid β-glucosidase is the rate-limiting enzyme in the catabolism of complex glycosphingolipids, catalysing the hydrolysis of glucosylceramide (GL-1) to glucose and ceramide. Glucosylsphingosine (also known as lyso-GL1), the deacylated form of GL-1, is a minor substrate for the same enzyme. Deficiency in acid β-glucosidase leads to the progressive accumulation of GL-1 (a major component of the plasma membranes of circulating blood cells), primarily in the lysosomes of macrophages. The hallmark of GD is the abundance of lipid-engorged macrophages with a characteristic "crinkled-paper" cytoplasmic appearance (Gaucher cells) in organs comprising the reticuloendothelial system (primarily spleen, liver, and bone marrow, and to a lesser extent, lung). Macrophages are central to the pathophysiology of GD because of their active role in phagocytosing damaged and senescent cells that are constantly being produced in the blood (including white blood cells, red blood cells, and platelets), and in recycling their cellular components. The decreased ability to degrade GL-1 (and other complex glycosphingolipids) and their resulting accumulation leads to the proliferation of macrophages and their subsequent differentiation into chitotriosidase and CCL18 (Chemokine CC motif ligand 18)-secreting Gaucher cells.

Infiltration of the reticuloendothelial system by Gaucher cells gives rise to many of the cardinal clinical signs and symptoms of the disease: infiltration of the liver and spleen causes hepatosplenomegaly and hypersplenism, leading to anaemia and thrombocytopaenia; infiltration of the bone marrow

causes marrow infarction, pancytopaenia, and low bone mineral density (BMD); and less commonly, infiltration of the lungs causes interstitial lung disease and pulmonary hypertension. This progressive organ pathology in turn gives rise to massive organomegaly with abdominal distention, discomfort, pain, and early satiety; fatigue; easy bruising/bleeding; splenic rupture; chronic bone pain and acute bone crises; osteonecrosis; marrow infarction; and pathological fractures.

Three main clinical types of GD have been described, all of which are inherited in an autosomal recessive manner and caused by mutations in the GBA gene located at chromosome 1q22. The most common form, Gaucher disease type 1 (GD1), has historically been characterised as lacking central nervous system (CNS) involvement, although in recent years it has become more appreciated that a small percentage of GD1 patients may develop peripheral neuropathy (<15%), and that both GD1 patients and carriers have an increased risk of developing Parkinson's disease in adulthood. Gaucher disease type 2 (GD2) is the acute neuronopathic form that presents in early infancy and leads to death by age 3. Gaucher disease type 3 (GD3) is the chronic neuronopathic form that presents from late infancy onward and has a lifespan that may extend into early adulthood[1].

Gaucher disease is an orphan disease. The prevalence of GD (all types) is approximately 0.3 per 100,000 in the general population, with GD1 being the most common subtype. Estimates of the prevalence for GD1 range widely by geography and ethnicity (*Grabowski, 1997, Genet Test*).

Two treatment approaches aimed at lowering GL-1 levels are currently available for GD1: (1) enzyme replacement therapy (ERT) with recombinant acid β -glucosidase, which augments the deficient enzyme activity in patients and catabolises stored GL-1 in lysosomes, and (2) substrate reduction therapy (SRT), which acts by partially inhibiting the enzyme glucosylceramide synthase, thereby reducing rate of synthesis of GL-1 to better match the impaired rate of catabolism in patients. Currently, there are two approved recombinant ERTs for the treatment of GD in the EU: imiglucerase (Cerezyme®) and velaglucerase alfa (VPRIV™). The currently available ERT requires regular intravenous (IV) infusions (generally every 2 weeks) for the duration of a patient's lifetime. Oral SRT, which acts by partially inhibiting the enzyme glucosylceramide synthase, represents a more convenient alternative therapeutic strategy for GD. The only currently approved SRT option available for patients with GD1 is miglustat (Zavesca™). Miglustat is a second-line therapy (indicated in adult patients with mild to moderate GD1 for whom ERT is not a therapeutic option).

Eliglustat (Cerdelga) is a potent and specific inhibitor of glucosylceramide synthase, and acts as a SRT for GD1. The goal of this approach is to reduce 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. The drug substance, eliglustat tartrate (Genz-112638), is an L-tartaric acid salt, and exists in plasma as a free base, Genz-99067, which is the active moiety. In this AR, "eliglustat" is used when referring to the drug product administered in each clinical study, and "Genz-99067" is used when referring to clinical drug exposure (i.e., concentrations in plasma or other tissues).

The Applicant applied for the following indication: "Cerdelga is indicated for the long-term treatment of adult patients with Gaucher disease type 1 (GD1). The target population is patients who are CYP2D6 intermediate (IM) or extensive (EM) metabolisers".

The CHMP granted the following, modified indications: "Cerdelga is indicated for the long-term treatment of adult patients with Gaucher disease type 1 (GD1), who are CYP2D6 poor metabolisers (PMs), intermediate metabolisers (IMs) or extensive metabolisers (EMs)".

[1] *Grabowski, 2010, The Online Metabolic and Molecular Basis of Inherited Metabolic Disease*

Cerdelga is supplied as hard capsules in one dose-strength with 84.4 mg of eliglustat (as tartrate; 84.4 mg of eliglustat is equivalent to 100 mg of eliglustat tartrate). Eliglustat is to be taken orally, twice daily (EM and IM) or once daily (PM).

The clinical development programme for eliglustat presented in this application was supported by two Phase 3 pivotal studies (ENGAGE and ENCORE), and one Phase 3b study (EDGE).

2.2. Quality aspects

2.2.1. Introduction

The finished product is presented as hard gelatin capsules containing 84.4 mg eliglustat (as tartrate salt) as active substance.

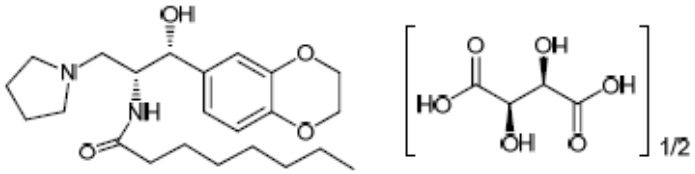
Other ingredients are microcrystalline cellulose, lactose monohydrate, hypromellose, glycerol dibehenate, gelatin, potassium aluminium silicate (E555), titanium dioxide (E171), yellow iron oxide (E172), indigotine (E132), shellac glaze, black iron oxide (E172), propylene glycol and ammonium hydroxide 28%.

The product is available in glycollated polyethylene terapthalate (PETG)/cyclic olefin copolymer (COC).PETG/polychlorotrifluoroethylene (PCTFE)/aluminium blisters.

2.2.2. Active Substance

General information

The chemical name of eliglustat tartrate is N-((1*R*,2*R*)-1-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)octanamide (2*R*,3*R*)-2,3-dihydroxysuccinate and has the following structure:



Eliglustat tartrate is a white to off-white crystalline powder, highly soluble in water and methanol and is not hygroscopic. Two molecules of eliglustat form a salt with one molecule of tartaric acid counter-ion.

Eliglustat exhibits stereoisomerism due to the presence of two chiral centres, both of which have *R* configuration. Enantiomeric purity is controlled routinely by chiral HPLC and specific optical rotation. Polymorphism has not been observed for Eliglustat tartrate.

Eliglustat tartrate is a new active substance and neither eliglustat, nor an isomer, mixture of isomers, complex or derivative or salt, have been previously authorised as medicinal products in the European Union.

Manufacture, characterisation and process controls

Eliglustat tartrate is synthesized by a single manufacturer in seven main steps using well-defined commercially available starting materials. Starting materials were re-defined during the procedure at the request of CHMP, and as a result, development and validation of new analytical methods for the

re-defined materials is required but could not be achieved during the procedure. Although no immediate impact on quality is envisaged, the development and validation of these analytical methods is considered vital to maintain quality throughout the lifecycle of the product. The applicant has committed to completing this work within 6 months of granting of the marketing authorisation.

Both stereocentres are introduced selectively under substrate control. The only potential genotoxic compound is used in an early step and is eliminated by the process and controlled in intermediate specifications.

Quality by Design (QbD) methodology was used in the development of the manufacturing process including risk assessment (fishbone and FMEA), design of experiments (DoE) and multi-variate models for some steps in the process. Critical quality attributes (CQAs) of the active substance were identified and linked to those of the finished product, and are well controlled by the process. They include levels of organic impurities, enantiomeric purity, residual solvents, residual metals and inorganic impurities. Critical process parameters (CPPs) with an impact on CQAs were identified, and suitable limits for these have been set in the process description. However, neither a design space, nor proven acceptable ranges (PARs) are claimed by the applicant and the QbD aspects were used only to ensure a robust process was developed.

The characterisation of the active substance and its impurities is in accordance with the EU guideline on chemistry of new active substances. Potential and actual impurities were well discussed with regards to their origin and characterised.

Adequate in-process controls are applied during the synthesis. The specifications and control methods for intermediate products, starting materials and reagents have been presented.

Specification

The active substance specification is based on the active substance critical quality attributes (CQAs) and includes tests for appearance (visual), colour (visual), identity (FTIR, RP-HPLC), thermal analysis (DSC), assay (RP-HPLC), impurities (RP-HPLC), chiral analysis (chiral HPLC), counter ion (ion exclusion HPLC), residual solvents (GC), elemental impurities (Ph. Eur.) and residue on ignition (Ph. Eur.).

Impurities present at higher than the qualification threshold according to ICH Q3A were qualified by toxicological and clinical studies and appropriate specifications have been set.

The analytical methods used have been adequately described and non-compendial methods appropriately validated in accordance with the ICH guidelines.

Batch analysis data on 25 pilot and commercial scale batches of the active substance used for stability, registration, and clinical trials are provided. The results are within the specifications and consistent from batch to batch.

Stability

Stability data were provided for 13 commercial scale batches of active substance from the proposed manufacturer used for clinical trials and registration and stored in a container closure representative of the intended commercial package for up to 5 years under long term conditions (25 ºC / 60% RH) and for up to 12 months under accelerated conditions (40 ºC / 75% RH). Results of 4 batches stored under intermediate conditions (30 ºC / 75% RH) were also provided. Of the batches tested, 4 were manufactured using the intended commercial process whilst 9 were produced using an earlier process. The differences between the earlier process and the final commercial process are minor and are unlikely to impact stability. The storage conditions used are in accordance to the ICH guidelines.

Photostability testing following the ICH guideline Q1B was performed on one batch.

Results from forced degradation studies were also provided on one batch exposed to a range of conditions including high temperature, high humidity, in the presence of an oxidant, and in an open container. Analysis included tests for appearance, colour identity, thermal analysis, impurities, chiral analysis, counter ion, elemental impurities and assay. The analytical methods used were the same as for release and were stability indicating.

The stability results indicate that the drug substance manufactured by the proposed supplier is sufficiently stable. The stability results justify the proposed retest period in the proposed container.

2.2.3. Finished Medicinal Product

Description of the product and Pharmaceutical development

Pharmaceutical development was aimed at developing an immediate release hard gelatin capsule for oral administration containing 84.4 mg of eliglustat.

Eliglustat tartrate is highly soluble but has poor flow properties and thus development focused on the selection of excipients to improve its flow. Studies were undertaken to determine the compatibility of filler, binder, lubricant and the capsule shells with the active substance. The result of these studies indicated that a combination of lactose monohydrate and microcrystalline cellulose as fillers, and hypromellose E15 as binder conferred the best flow properties on the granules and these were therefore selected as excipients for the final formulation. The ratio of excipients was optimized to further improve flow properties. The inclusion of excipients had no negative impact on the solubility of eliglustat in the finished product. The finished product shows dissolution rate typical of immediate release hard gelatin capsules.

Different formulations were used for different phases of the clinical trials and comparative dissolution studies demonstrated that minor changes in the formulations were unlikely to have any detectable impact on formulation quality and *in vivo* performance. In addition, a bioequivalence study was performed, showing bioequivalence between the phase III clinical formulation and the proposed commercial formulation.

Hard gelatin and hypromellose capsules were both evaluated during development. Hard gelatin capsules were selected because they exhibited a faster dissolution profile.

All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur. standards. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC.

The pharmaceutical development of the finished product contains QbD elements. The QTPP was defined as an immediate release capsule containing the requisite quality and quantity of active substance, stable over the targeted shelf-life of the finished product. Dissolution, appearance, assay, content uniformity, specified degradation products and integrity of primary packaging for moisture protection were identified as CQAs.

The manufacturing development has been evaluated through the use of risk assessment and design of experiments to identify the critical product quality attributes and critical process parameters. A risk analysis was performed using the failure mode effect analysis (FMEA) method in order to define critical process steps and process parameters that may have an influence on the finished product quality attributes. The risk identification was based on the prior knowledge of products with similar formulations and manufacturing processes as well as on the experience from formulation development, process design and scale-up studies. The critical process parameters have been adequately identified. The CPPs identified are weight of drug substance dispensed and quantity of purified water added at granulation. The discriminatory power of the dissolution method has also been demonstrated.

The primary packaging is aluminium PETG/COC.PETG/PCTFE-aluminium blisters. The material complies with Ph. Eur. and EC requirements. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

Manufacture of the product and process controls

The manufacturing process consists of the following main steps: dispensing and mixing of active substance and excipients, wet granulation, drying, milling and blending, filling and encapsulation, and finally, packaging and release. The process is considered to be a standard manufacturing process.

Dispensing of an accurate quantity of eliglustat and water for granulation are essential to finished product quality and are thus considered critical steps. In addition, moisture content, capsule fill weight, and appearance are monitored by in-process controls to ensure finished product quality.

Major steps of the manufacturing process have been validated by a number of studies. It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner. The in-process controls are adequate for this type of manufacturing process and pharmaceutical form.

Product specification

The finished product release specifications contain appropriate tests for this kind of dosage form and include appearance of the contents (visual inspection), appearance of the capsule (visual inspection), identity (HPLC and UV), assay (HPLC), degradation products (HPLC), uniformity of dosage forms (Ph. Eur.), microbial enumeration (Ph. Eur.) and dissolution (Ph. Eur.).

Batch analysis results are provided for three production and fifteen pilot scale batches confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

Stability of the product

Stability data of three production scale batches of finished product stored under long term conditions (25ºC / 60% RH) and under intermediate conditions (30 ºC / 75% RH) for up to 36 months and for up to 6 months under accelerated conditions (40 ºC /75% RH) according to the ICH guidelines were provided. The batches of medicinal product are identical to those proposed for marketing and were packed in the primary packaging proposed for marketing. Samples were tested for appearance, assay, degradation products, dissolution, moisture and microbial enumeration. Moisture was evaluated for information purposes only. The analytical procedures used are stability indicating. The only trends of note were a 4% decrease in assay for 1 batch at intermediate conditions after 36 months and a 0.5% increase in water content after 6 months at accelerated conditions. However, all test results complied with the proposed specifications and the observed changes are not of concern.

In addition, 3 batches were exposed to light as defined in the ICH Guideline on Photostability Testing of New Drug Substances and Products.

Results of storage under stressed conditions were also provided for three batches. Stressed conditions included temperature cycling for up to 24 days, high temperature and humidity, and high temperature in an open container. The finished product is not photosensitive but degradants are produced at high temperature and humidity, under which conditions, the gelatin hard capsules become brittle due to cross-linkage. However, since this has not been observed under non-stressed storage, special storage conditions are not required.

Based on the available stability data, the shelf-life as stated in the SmPC is acceptable.

Adventitious agents

It is confirmed that the lactose is produced from milk from healthy animals in the same condition as those used to collect milk for human consumption and that the lactose has been prepared without the use of ruminant material other than calf rennet according to the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents Via Human and Veterinary Medicinal Products.

Gelatin obtained from bovine sources is used in the product. A valid TSE CEP from the suppliers of the gelatin used in the manufacture is provided.

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

The applicant has applied QbD principles in the development of the active substance and finished product and the manufacturing process. However, no design spaces were claimed for the manufacturing processes of the active substance or the finished product.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way. Data has been presented to give reassurance on viral/TSE safety.

2.2.6. Recommendation(s) for future quality development

In the context of the obligation of the MAH's to take due account of technical and scientific progress, the CHMP recommends the following points for investigation:

the applicant should develop, validate and implement analytical methods to control quality of 2 re-defined starting materials.

1. For the first starting material, an HPLC method is required to control impurities and once implemented, the specification should be revised to include limits for unspecified and total impurities.

2. For the second starting material, a GC assay and impurities method is required.

3. Also for the second starting material, the control of certain solvents (DMF, EtOAc, PE) is required by adding limits to the specification or demonstrating absence in a suitable intermediate or active substance based on batch history.

The MAH has agreed to address these recommendations within 6 months of the granting of a marketing authorization.

2.3. Non-clinical aspects

2.3.1. Introduction

The drug substance used in nonclinical studies was physically and chemically comparable to that produced for clinical trials and ultimately for marketing. The nonclinical pharmacology studies conducted with eliglustat showed potent and specific inhibition of glucosylceramide (GL-1) synthesis in vitro and reduced levels of GL-1 in vivo in both normal mice and Gaucher disease type 1 (GD1) mouse models, confirming the mechanistic basis for the eliglustat pharmacological effect. In addition to these pharmacodynamic studies and a number of investigative pharmacology and toxicology studies, the nonclinical program for eliglustat included a comprehensive program of safety pharmacology, pharmacokinetics (PK), genotoxicity, reproductive toxicity, acute-dose and repeat-dose toxicology, juvenile toxicology, and carcinogenicity studies. Although the target population of the proposed indication does not include pediatrics, the juvenile toxicology studies were conducted as part of a paediatric investigational plan. Carcinogenicity studies were conducted in two species, the mouse and the rat.

All the pivotal preclinical safety studies were conducted in compliance with a GLP. Dose range finding studies do not all claim GLP compliance but were conducted in a GLP-compliant facility.

2.3.2. Pharmacology

Primary pharmacodynamic studies

In vitro studies were conducted with eliglustat to determine the potency and efficacy in cell systems. Reduction in GL-1 was measured in a human microsome assay with an IC50 of around 20 nM. Similar IC50 values were seen in whole cells (human K562 erythropoietic cells), using membrane expression of GM1 as endpoint. In murine and canine cells, potency was a little lower with IC50 values of around 60 nM and 80 nM respectively. No studies have been performed with human Gaucher cells.

None of the 10 metabolites of eliglustat had IC50 values in the nM range, indicating that these metabolites do not contribute to the pharmacological activity of eliglustat. Potency was measured as inhibition of GL-1 in microsomes, or inhibition of GM3 surface expression in intact cells.

Several studies were performed with an in vivo mouse Gaucher disease model (D409V/null GD1 mice), in which GL1 levels as biomarker in liver, spleen and lung begin to accumulate measurably starting at 3 months of age, and Gaucher cells begin to appear by 4 months of age. In-feed dosing appeared to be more efficacious than dosing by oral gavage, presumably due to a more sustained delivery of the drug. Doses from 150 mg/kg/day up to 450 mg/kg/day were tested, which showed greater efficacy for the higher doses: GL-1 levels were reduced up to 80% in liver, and 70-80% in lung and spleen. At the lower dose of 150 mg/kg/day, further accumulation of GL-1 was inhibited, but limited effect was seen on the “debulking” of cells with high GL-1 levels. Pre-treatment of mice with imiglucerase (currently used for treatment of GD), resulted in “debulking” the cells of GL-1, which was further reduced or maintained by subsequent treatment with eliglustat, most effectively at 450 mg/kg/day. The effect of imiglucerase on GL-1 levels in lung tissue is limited, due to the restricted distribution to alveolar macrophages. Treatment with eliglustat has an additional effect on lung GL-1 levels, reducing it further from 40% to 80%.

To quantify the Gaucher cells, staining of the liver with CD68, a general marker for macrophages, was performed. Treatment with eliglustat caused a reduction in CD68 positive staining. Only limited toxicokinetic parameters were measured in these studies which cannot be compared to clinical parameters, but from the repeated dose toxicity studies it can be deduced that the exposures in these studies are higher than the clinical exposure in patients at all tested doses.

In addition to the GD1 mouse disease model, efficacy of eliglustat in terms of reduction in plasma GL-1 levels was also evaluated in healthy animals. A modest effect of up to 30% reduction in GL-1 plasma levels was achieved in rats at doses of 10, 25 or 50 mg/kg when dosed for 4 days. Plasma GL-1 was not evaluated in the GD1 mouse model, and therefore these values cannot be compared to the disease model. Despite a clear increase in exposure at higher doses, no dose response relationship was observed in healthy rats. In dogs, liver GL1 was measured, which also showed a decrease after treatment with up to 25 mg/kg/day for up to 13 weeks, of around 50% compared to untreated controls. The effect was reversible, as shown by normalization of GL1 levels at 2 weeks after treatment cessation. As with rats, the effect was not dose-related. Although the doses used in healthy rats and dogs are lower than the doses used in the GD1 mouse model, exposures are likely higher, based on data from the repeated dose toxicity studies.

Secondary pharmacodynamic studies

In a receptor screen, eliglustat showed significant inhibition of ligand binding at 9 targets, when tested in a panel of 80 different receptors, transporters, and ion channels at 10 µM. These included the dopamine receptors D3 and D4.4, the serotonin receptors 5-HT1A, 5-HT2A, 5-HT2B, and 5-HT6, the mu opioid receptor, the nonspecific sigma receptor, and the Ca2+ ion channel (L, verapamil site). Although the concentration of 10 µM was much higher than the predicted systemic C_{max} in patients, high local concentrations in the gut could be reached. Indeed, in pre-clinical species, effects on gastrointestinal transit were seen.

Safety pharmacology programme

No effects on CNS parameters were observed after treatment of rats with up to 400 mg/kg of eliglustat. A reversible decrease in respiratory rate was seen in rats treated with 400 mg/kg.
Severe effects on gastrointestinal transit were observed in rats treated with 100 mg/kg or higher. Transit was (almost) completely inhibited. This effect could be due to high local concentration of eliglustat, leading to interactions with secondary targets as seen in the receptor screen. Other effects on the GI tract have been observed in the repeated dose toxicity studies.

The hERG channel assay showed that eliglustat has a potential for prolongation of the action potential and the QT interval from a concentration of 0.1 µg/ml. Subsequent studies on sodium and calcium channels also showed a potential for blockade of these ion channels, with IC_{50} values of 5.2 and 10.4 µg/ml, respectively. Effects on cardiac action potential in dog Purkinje fibres are in line with effects seen for the sodium and calcium channels. From a concentration of 0.3 µg/ml or higher, action potential parameters were decreased in a dose-dependent manner. This is in contrast to the hERG channel assay, which indicates a possible prolongation of the action potential. Overall, from in vitro and ex vivo studies it can be concluded that at concentrations of 0.1 µg/ml or above, eliglustat is expected to have direct effects on QRS complex duration and QT interval. This concentration is around 2-fold above the mean predicted clinical C_{max} of 44.3 ng/ml. Several cardiovascular effects were seen in two in vivo dog studies. In telemetered conscious dogs, no effects were seen at a dose of 3 mg/kg resulting in a C_{max} around 6.5-fold of the clinical C_{max}, while higher doses showed increases in QRS duration, PR interval and heart rate, and a decrease in RR interval. In the cardiac conduction study in anesthetized dogs no NOEL could be determined, as all doses showed increases in atrio-ventricular

and intra-ventricular conduction times and intra-ventricular velocity. Prolongation of the QT interval (adjusted for the decrease in heart rate) was also observed at the mid dose. No relevant activity against the hERG channel, cardiac sodium or calcium channels was observed for the 10 metabolites of eliglustat.

Pharmacodynamic drug interactions

No meaningful pharmacodynamic interaction was observed between eliglustat and imiglucerase, which indicates that both drugs can be used simultaneously in patients.

2.3.3. Pharmacokinetics

Absorption

Eliglustat is a highly permeable drug and is rapidly absorbed. Bioavailability is low in all non-clinical species suggesting the involvement of transporters and/or extensive first-pass metabolism. Systemic exposure increases in a more than dose-proportional manner in rats over the dose range 5 to 50 mg/kg/day and over the dose range 15 to 50 mg/kg/BID, while dose-proportional increases are observed between 50 and 100 mg/kg/BID. In dogs, systemic exposure increases dose-proportional in males and more than dose-proportional in females over the dose range 2 to 10 mg/kg. Multiple dosing generally leads to slight accumulation in rats and dogs. In juvenile rats, maximum plasma concentrations are reached later than in adults. Compared to adults, AUCs were slightly higher while the C_{max} was lower at the same dose. Exposure reduced over the study period indicating an increase in enzyme activity and/or transporter activity that is consistent to what is known about the ontology of the enzymes involved in the biotransformation of eliglustat.

Distribution

The generally high volumes of distribution across the non-clinical species indicate extensive tissue distribution of eliglustat. However, the extent of distribution is concentration-dependent as the plasma-protein binding diminishes at increasing plasma concentrations leading to higher free fractions available for distribution to tissues. At clinically relevant concentrations, the free fraction is significant lower in the non-clinical species than in humans. Drug-derived radioactivity is widely distributed to body tissues and still present after 12 to 24 hours in several tissues, mainly associated with absorption, metabolism and excretion. Drug-related material may cross the blood-brain and the blood-testes barrier, and may bind, although not irreversibly, to melanin. No significant red blood cell partitioning is observed for eliglustat. Placental transfer of trace amounts of eliglustat and metabolites was observed in rats .

Metabolism

Eliglustat is extensively metabolised in all non-clinical species, but major species differences exist. CYP2D6, CYP3A4 and CYP2C9 are involved in the metabolism, with CYPs 2D6 and 3A4 involved at clinically relevant concentrations. Metabolic pathways involve sequential oxidation of the octanoyl moiety being the major pathway, followed by oxidation of the 2,3-dihydro-1,4-benzodioxane moiety or a combination of oxidation in the two moieties. In addition, rat specific pathways are identified.

Excretion

Elimination of eliglustat is rapid with generally high systemic clearances and very short plasma half-lives of within 1.5 hour for all non-clinical species. Drug clearance is preliminary determined by hepatic clearance while renal clearance is negligible. Eliglustat is hence predominantly excreted via

faeces in the non-clinical species. In urine, eliglustat is mainly excreted as metabolites. Excretion of trace amounts of eliglustat and/or its related materials into milk was observed in rats .

Transporters

Eliglustat is a substrate for the efflux transporter P-gp at clinically relevant concentrations. No BCRP-mediated transport of eliglustat is expected in the intestine or uptake via OATP1B1 and OATP1B3 in the portal vein.

Drug interactions

Eliglustat is not expected to inhibit P-gp, BCRP, BSEP, OAT1B1, OATP1B3, OCT1, OAT3 and OCT2 at clinically relevant systemic concentrations, although it is an inhibitor of these transporters. At portal vein concentrations however, eliglustat may inhibit OCT1. In the intestine, inhibition of P-gp-mediated transport cannot be excluded.

2.3.4. Toxicology

Single dose toxicity

Acute dose toxicity studies were performed in rat and dog, which served to determine dose levels for following repeated dose toxicity studies. Single IV dosing of 3 up to 20 mg/kg in rat was well tolerated and the acute NOAEL for one-hour IV infusion was considered to be 20 mg/kg. Single dosing of rat with 200 up to 1000 mg/kg eliglustat or repeated dose of 200 and 400 mg/kg for 10 and 3 days respectively administered via oral gavage was not well tolerated. The maximum tolerated dose was below 200 mg/kg. For dogs treated with a single dose 25, 35, 50 and 100 mg/kg eliglustat in fasted and fed state and repeatedly dosed with 25 mg/kg for 10 days the MTD was determined as 25 mg/kg in fed animals.

Repeat dose toxicity

In mice, single and repeated dose studies not conducted under GLP resulted in the design of a 13 week repeated dose GLP study in mice. In this study, CD-1 mice were administered 0, 50, 150 and 350 mg/kg eliglustat per day. Animals treated with higher dose-levels of eliglustat (≥ 350 mg/kg/day) showed a decrease in body weight. Observed increase in weight of liver and adrenal glands cannot be explained due to missing secondary symptoms, but are regarded as target organs.

The remainder of repeated dose toxicity studies with eliglustat was executed in rat and dog. Treatment with eliglustat showed adverse effects on GI tract, hematology parameters related to hemoglobin and coagulation process, kidney (rat), liver (rat), reproductive organs and thymus and other lymphoid organs.

Gastrointestinal System (GI) effects were observed in all nonclinical species in toxicology studies. These effects limited the maximum dose administered in several repeat-dose studies. Vomiting and salivation were observed in both rats and dogs. Lymphoid atrophy in GI tract was observed in one female dog administered 10 mg/kg eliglustat for 28 days and in a male in the recovery group. Haemorrhage of cecum and colon was already observed in lowest dose treatment group in 13 weeks study in Beagle Dog. Animals treated with the highest dose in that same study had a decreased Ileum weight.

Several coagulation and hemoglobin related hematology parameters were affected in rat administered mid and high doses for 3 and 26 weeks, which was not noted in dog studies. Clinically no changes in hematology parameters were observed, therefore the observed changes in hemoglobin and coagulation related parameters in treated rats are unlikely to be clinical relevant.

In kidneys of rats dosed with 50 mg/kg eliglustat for 26 weeks renal pelvis dilation (1/14 female and 1/14 male) was observed along with an increase in K levels in serum and a decrease in urinary pH. Rats dosed with 100 mg/kg eliglustat for 28 days had elevated Na (males), K, P and Cl levels in serum and a relatively higher weight of the kidneys was observed in recovery animals.

In dogs, no clear difference regarding effect on kidneys were observed between treated animals and control animals. Clinically, elevation of serum electrolytes was not noted. A slight increase in urinary pH was observed in treated subjects. Since pre-clinical and clinical effects on kidney and secondary parameters are not in line, it is unlikely that above described effects are clinical relevant.

An increase in liver weight (relative to body weight) and increased ALT levels were observed in rats treated with the highest dose eliglustat for 28 days. In recovery animals an increase in ALP level was observed. The effects were not seen in the 26 weeks study in rat and not in Beagle dogs treated with eliglustat. The liver effects are of a lesser severity as compared to a compound of the same pharmacological class, miglustat. In clinical studies slight changes in enzyme levels are noted, pointing towards a slight increase in liver activity, which is not unexpected.

In female rats dosed with 50 mg/kg for 26 weeks the lumen of uterus was dilated and hyperkeratosis of the vagina was observed. Since this was only observed in one rat study this effect is likely not clinically relevant. In male beagle dogs dosed 10 mg/kg Eliglustat for 52 weeks a greater incidence of seminiferous epithelial degeneration and segmental hypoplasia of the testes was observed. The exposure after dosing dogs with10 mg/kg for 52 weeks is 4460 ng.h/mL, which is 3.7 times higher the clinical AUC level.

Lymphoid atrophy of the thymus and lymph nodes was observed in female dogs dosed ≥ 10 mg/kg Eliglustat for 28 days, which seems reversible. This effect was also observed in male recovery animals.

Genotoxicity and Carcinogenicity

In carcinogenicity studies in rat treatment with eliglustat did not prove to be carcinogenic at doses up to 75 mg/kg/day. The AUC values for the high dose after 13 weeks treatment are for male rats dosed 75 mg/kg/day 1135 ng.h/mL and for female rats dosed 50 mg/kg/mL, 825 ng.h/mL. These exposure values are below clinically relevant exposures in an intermediate metaboliser population. In mice, increases in benign cortical adenoma in the adrenal cortex in high dose males coincided with cortical hyperplasia. The tumour incidence was within historical control range.

Reproduction Toxicity

After 15 days at 100 mg/kg/day eliglustat there was a moderate to marked, subacute inflammation in coagulating glands of male rats. At higher, non-tolerable doses, a lower percentage of motile sperm occurred and the percentage of morphologically normal sperm was lower. The morphological abnormality was mainly separation of the head from the flagellum. After 14 weeks, the values were similar to controls. Lower prostate weights, bilaterally atrophied coagulating glands, sloughed cells in the epididymis and acute inflammation of the coagulating glands were noted at ≥50 mg/kg BID. Germ cell necrosis in the testis, epithelial hyperplasia in the forestomach and severe complete atrophy of thymus and spleen showed at 100 mg/kg BID. All effects showed reversibility. The NOEL for effects on spermatogenesis and male reproductive organs also was 15 mg/kg BID, which is below the intended human exposure. A non-GLP study in 4 cynomolgus monkeys showed no significant effects on spermatogenesis, however this study is deemed not suitable for risk assessment due to shortcomings in study design (no control group and only one dose group) and documentation.

In rats, 120 mg/kg/day eliglustat caused an increased number of late resorptions, dead foetuses, post implantation losses and lower foetal body weights. Also foetuses showed a higher incidence of dilated cerebral ventricles, abnormal number of ribs or lumbar vertebrae, and many bones showed poor ossification. The NOEL for maternal toxicity in rats was 30 mg/kg/day and the NOEL for embryofetal development in rats was 30 mg/kg/day, without a safety margin. In rabbits, eliglustat showed minimal effects in females at 30 mg/kg/day (slight decrease in body weight gain). No effects on foetuses were seen at 100 mg/kg/day, also without a safety margin. In rats, the NOAEL for the F1 generation was 100 mg/kg/day eliglustat, as the observed lower mean body weight and minimally lower mean body weight gains did not affect learning and memory, locomotor activity, sexual development, mating or fertility.
In juvenile toxicity studies, no major toxicity was observed. Two groups of animals (rats) were used to determine effects of eliglustat on toxicity parameters and on fertility parameters. Females used for the toxicity part of the study showed minimal delay in vaginal opening, but this was not significant in the females used for fertility evaluation. In prostate en epididymis an increase in inflammatory cell foci was found, which persisted during recovery phase for epididymis only. Other observed effects are in line with observed effects in adult animals in repeated dose toxicity studies. Currently this application concerns an adult population. For this patient group, these effects are not relevant.

Metabolites and impurities
The disproportionate human metabolite Genz-399240 was found not genotoxic and not toxic in a repeat-dose study up to 6 mg/kg/day, which corresponds to ca. 8 times the intended human exposure.
Impurities Genz-256146 and Genz-684453 have been detected as potential mutagenic substances. However, both impurities have been tested with a bacterial reverse mutation assay and found negative.

2.3.5. Ecotoxicity / environmental risk assessment

Table of endpoints

Substance (INN / Invented Name): eliglustat			
CAS-number (if available): 928659-70-5			
PBT screening		Result	**Conclusion**
Bioaccumulation potential – log K_{ow}	potentiometric method	2.84 (logD at pH 5: -0.95 logD at pH 9: 2.6)	Potential PBT: N
PBT-assessment			
A PBT assessment has not been conducted as the screening criterion is not met			
PBT-statement	Eliglustat is considered not PBT, nor vPvB		
Phase I			
Calculation	**Value**	**Unit**	**Conclusion**
PEC $_{surfacewater}$	0.0025	µg/L	< 0.01 threshold

Log Kow of eliglustat is below the B screening criterion (log Kow >4.5). Eliglustat is not PBT (persistent,bioaccumulative and toxic), nor vPvB (very persistent and very bioaccumulative). After refinement of the Fpen, the PECsurface water is 0.0025 µg/L, which is below the action limit of 0.01 µg/L, further assessment is not deemed necessary.

In conclusion, eliglustat is not expected to pose a risk to the environment.

2.3.6. Discussion on non-clinical aspects

Pharmacology

Primary pharmacodynamics and secondary pharmacology

Eliglustat showed a high potency and efficacy in a number of in vitro cell systems. In an in vivo mouse Gaucher disease model, eliglustat reduced GL-1 levels up to 80% in liver, lung and spleen. A few secondary target receptors, like dopamine and serotonin receptors, might be affected at high concentrations of eliglustat in the gut. However, the use of GL-1 as a biomarker in plasma of non-clinical species was questioned, but since a clinical dose dependent reduction of plasma GL-1 was demonstrated, further discussion was not considered necessary by the CHMP.

Safety pharmacology

Eliglustat showed no effects on CNS parameters in rats. A reversible decrease in respiratory rate was seen in rats treated with 400 mg/kg. Effects were also seen in the renal study at this dose, namely a reversible increase in urine pH, and a decrease in potassium and chloride urinary excretion. The poor status of the animals due to dosing above the MTD was the likely cause of these effects in the opinion of the CHMP. C_{max} values in these animals are likely to be much higher than clinical C_{max} values, and therefore clinical relevance is unlikely.

Severe effects on gastrointestinal transit in rats are probably caused by high local concentrations of eliglustat.

In dogs, eliglustat caused several cardiovascular effects. These are likely to be the result of a block in cardiac sodium channels, possibly in combination with inhibition of the *Ikr* current that may lead to changes in ECG and cardiac conduction at concentrations that appear to be above clinical C_{max} values. However, in the clinical trials, problems with cardiac output in combination with bradycardia have been observed, whereas a thorough QT study in healthy volunteers (GZGD01707) did not reveal clinically relevant prolongations of QT in plasma levels below the 500 ng/ml. Based on the analysis of clinical data a causal relation of bradycardia/cardiac output and eliglustat could not be established. The pre-clinical results might be of relevance for human safety. Differences in active concentrations might be due to the difference in protein binding of eliglustat between pre-clinical species and humans. The cardiovascular effects are further discussed in the clinical part of the AR.

Pharmacokinetics

Absorption, distribution, metabolism and excretion

Eliglustat is a highly permeable drug and is rapidly absorbed and the high volumes of distribution across the non-clinical species indicate extensive tissue distribution. However, at clinically relevant concentrations, the free fraction of eliglustat is significant lower in the non-clinical species than in humans. This has consequences for the interpretation of the toxicity safety margins.

Eliglustat is extensively metabolised and in a different manner between species. All circulating human metabolites are observed in at least one of the non-clinical species, but the systemic exposure of some of these metabolites appears to be very low in the respective species compared to humans. The human systemic exposure to the major metabolite, M24, is not achieved via repeated oral administration in the non-clinical species at the NOAEL dose. Therefore, M24 has been tested separately in 13-week rat study and genotoxicity studies, with an exposure margin of 3-4. All other metabolites are less than 10% of total drug related exposures and further characterization of the

metabolites is not considered necessary. As metabolite Genz-399240 (M24) does not contribute to pharmacological activity and does not exhibit major off-target effects, characterization of its transporter substrate specificity was considered not warranted.

Toxicology

Single and repeat dose toxicity studies

Acute doses of eliglustat above clinically relevant concentrations are well tolerated in animals. Gastrointestinal System (GI) effects were observed in all nonclinical species in the repeat dose studies. This effect however, appears to be less relevant for humans, as little or no GI-tract adverse effects were seen in the clinical trials. Effects on reproduction organs and spermatogenesis are also seen at high doses in carcinogenicity studies and reproduction toxicity studies. These effects were adequately reflected in the SmPC. Lymphoid atrophy of the thymus and lymph nodes seen in dogs after 4 weeks was not apparent in the 13 weeks and 52 weeks studies, which could indicate an adaptive response after chronic dosing. As is stated by the applicant, it cannot be ruled out that the observed effect in thymus is treatment related. However, as there appears to be no symptoms observed in clinical trials that could be related to lymphoid depletion, and the thymus has no major role in an adult human, it is unlikely that lymphoid depletion has any clinical consequence.

Several differences in the ADME of eliglustat exist among the pre-clinical species and between the preclinical species and humans. Important is the difference in free fraction between the preclinical species and humans. When this is taken into account, the margins of safety are non-existent. The safety margins, including the free fraction related ones, have been adequately presented in the SmpC. This was considered by the CHMP when evaluating safety of eliglustat from clinical development program.

Genotoxicity and carcinogenicity

In the mouse carcinogenicity study, the plasma levels after 13 weeks of dosing were generally below the limit of quantification. The applicant has attempted to demonstrate drug exposure by measuring plasma GL-1 levels. Although these levels are slightly lower in the dosed groups as compared to the controls, the difference is marginal and there is no dose response. Overall, drug exposure can be assumed to be very low in the mouse carcinogenicity study, and is low in the rat study. Dose levels for both studies were based on adverse effects seen in other studies, and it was agreed that higher doses were not appropriate. Therefore, it must be concluded that the relevance of the studies is low, but the risk of a carcinogenic effect of eliglustat is also low considering all the available data.

Reproductive and developmental toxicity

Some effects of eliglustat on testes and spermatogenesis were seen in rats during repeat dose and reproductive toxicity studies. Also, minor effects on fetuses of rats were seen at maternal toxic, but clinically relevant doses of eliglustat. Dilated brain ventricles were noted in rats at the high dose, and in rabbits but limited to foetuses of the mid dose group and not observed in foetuses of the high dose group.
Regarding juvenile toxicity, persistence inflammatory cell foci in the epididymis were seen after the recovery period in juvenile animals. It is recommended the juvenile toxicity to be discussed at the time of a potential future indication for children.

Metabolites and impurities

No additional toxicities of metabolites or impurities have been found. Metabolite Genz-399240 (M24) and impurities Genz-256146 and Genz-684453 are found not genotoxic.

2.3.7. Conclusion on the non-clinical aspects

Overall, the primary pharmacodynamic studies provided adequate evidence that Cerdelga is a potent and specific inhibitor of glucosylceramide synthase. From the pharmacokinetic point of view, the main findings were the differences in metabolite forming and protein binding in all species, including humans. The toxicology programme revealed susceptibility of GI-tract, cardiovascular system and reproductive organs where relevance for humans cannot be excluded. This information has been included in the agreed SmPC.

2.4. Clinical aspects

2.4.1. Introduction

Each capsule contains 84.4 mg eliglustat free base (equivalent to 100 mg of eliglustat tartrate). The doses mentioned in this part of the dossier are declared as tartrate. The clinical development programme for eliglustat presented in this application consists of 13 Phase 1 studies (including multiple drug-drug interaction studies, because of eliglustat's extensive metabolism via CYP450 liver enzymes), one Phase 2 study (GZGD00304), two controlled Phase 3 pivotal studies (ENGAGE [Study GZGD02507] and ENCORE [Study GZGD02607]), and one Phase 3b study (EDGE [Study GZGD03109]).
The Phase 2 study and Phase 3 studies: ENGAGE, and ENCORE, which have completed their primary analysis periods (PAPs) but have ongoing long-term treatment periods, provide efficacy and safety data in support of the marketing authorization applications for GD1, while the ongoing Phase 3b study (EDGE) provides additional safety data. These studies are listed below:

- GZGD00304: A Phase 2, Open-Label, Multi-Center Study Evaluating the Efficacy, Safety and Pharmacokinetics of Genz-112638 in Gaucher Type 1 Patients
- GZGD02507: A Phase 3, Randomized, Double-Blind, Placebo-Controlled, Multi-Center Study Confirming the Efficacy and Safety of Genz-112638 in Patients with Gaucher Disease Type 1 (ENGAGE)
- GZGD02607: A Phase 3, Randomized, Multi-Center, Multi-National, Open-Label, Active Comparator Study to Evaluate the Efficacy and Safety of Genz-112638 in Patients with Gaucher Disease Type 1 who have Reached Therapeutic Goals with Enzyme Replacement Therapy (ENCORE)

GCP
The Clinical trials were performed in accordance with GCP as claimed by the applicant.

The applicant has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

FDA GCP inspections were conducted in the period December 2013 to March 2014 (for the two clinical studies GZGD02607 and GZGD02507). Further, an inspection of the sponsor was conducted. No critical or major violations were noted, only minor regulatory issues. The studies appear to have been conducted adequately and the data generated by these studies appear acceptable in support of the respective indications.

- Tabular overview of clinical studies

Study	Phase Blind Type of Control	Number patients treated	Study treatment	Key Efficacy Endpoints	Primary analysis period Total length of study
Treatment-naïve patients					
GZGD02507 (ENGAGE)	Phase 3 Double-blind, placebo-controlled	40 (20 eliglustat/20 placebo)	Eliglustat or placebo 50 mg BID (initial dose) Potential eliglustat dose adjustment up to 100 mg BID at 4 weeks[a] and up to 150 mg after 47 weeks	Primary: % change in spleen volume with eliglustat as compared to placebo at Week 39 Secondary: At Week 39: absolute changes in haemoglobin level; % changes in liver volume ; % changes in platelet count For patients treated with eliglustat: within-patient change for % change in spleen volume; absolute change in haemoglobin level, % change in liver volume, and % change in platelet count Other: Biomarkers, bone disease assessments, Gaucher assessments; and QOL questionnaires	39 weeks (9 months) Long-term treatment period for a total of up to 6 years on study
GZGD00304 (Phase 2)	Phase 2 open-label	26	Eliglustat (open label) 50 mg BID (initial dose) Potential dose adjustment up to 100 mg BID at Day 20[a] and up to 150 mg after at least 18 to 24 months of treatment	Primary: the proportion of patient with a meaningful clinical response. For a patient to be considered to have demonstrated a clinically meaningful response to treatment with eliglustat, a response in at least 2 of the 3 main parameters (haemoglobin level [increase ≥0.5 g/dL], platelet count [increase ≥15%], and spleen volume [decrease ≥15% in MN]), if abnormal	52 weeks (1 year), [extended followup analysed at 48 months (4 years)] Long-term treatment until study termination

				at Baseline, must be observed. Secondary: Change in haemoglobin level, platelet count, spleen volume, and liver volume from Baseline to Month 48. Other: Biomarkers, Gaucher assessments, bone disease assessments, and QOL questionnaires	
Patients switching from ERT					
GZGD02607 (ENCORE)	Phase 3 open-label, active controlled	159 (106 eliglustat/ 53 Imiglucerase) (in PPS, 99 eliglustat/ 47 Imiglucerase)	Eliglustat 50 mg BID (initial dose) or Imiglucerase Potential eliglustat dose adjustment up to 100 mg at 4 weeks and up to 150 mg at 8 weeks[a]	Primary: Non-inferiority: % of patients who remain stable for 52 weeks. Patients must have remained stable in haematological parameters (haemoglobin level does not decrease > 1.5 g/dL from Baseline AND platelet count does not decrease > 25% from Baseline), and organ volumes (spleen volume (in MN) does not increase > 25% from Baseline, if applicable, AND liver volume (in MN) does not increase > 20% from Baseline FDA-recommended non-inferiority: the % change in spleen volume (MN) Secondary: At Week 52: total T- and Z-scores for bone mineral density (DXA) of femur and lumbar spine, haemoglobin level, platelet count, and spleen and liver volumes (in MN)	52 weeks (1 year) Long-term treatment period for a total of up to 5.5 years on study

				(assessed by MRI) Other: Biomarkers, bone disease, Gaucher, and QOL assessments, and treatment preference (oral vs IV therapy)	

2.4.2. Pharmacokinetics

Thirteen studies in healthy subjects and 3 studies in GD1 patients were submitted to support the pharmacokinetics of eliglustat. A total of 291 healthy subjects and 343 GD1 patients were included in these studies. In addition, 22 reports covering *in vitro* data and 6 reports with simulation data are submitted.

Genotyping for CYP2D6 allelic variants classified patients into one of 4 CYP2D6 phenotypes (PM, IM, EM, or URM).

Solubility data showed that eliglustat has a solubility of about 200 mg/ml at pH 1.0 and 4.5, which decreased at higher pH, however remained above 2 mg/ml. Considering the maximal indicated recommended dose in the SmPC of 100 mg BID, eliglustat is a highly soluble drug. Although the data indicate that eliglustat seems to be completely absorbed, metabolic profiling of eliglustat and its metabolites in faeces is lacking. Therefore, it cannot be concluded that the whole administered dose is absorbed and that the recovery of labelled drug in faeces is absorbed drug which is excreted back into the GI-tract as metabolites. Therefore, eliglustat should conservatively be considered a BCS Class III drug, i.e. high solubility and low permeability (<85% absorbed).

Analytical methods

In principle, one analytical LC-MS/MS method has been applied for the analysis of eliglustat in plasma, as clean-up procedures were almost identical. Validation proved that the method was specific, precise and accurate. Stability was shown covering study sample handling and storage. Transferring the method to 2 other analytical laboratories did not affect accuracy and precision, as proven by cross-over validation.
Also for the analysis of eliglustat in urine, validation showed that the method was precise and accurate and stability was sufficiently shown over the sampling and storage conditions.

Absorption

After oral administration, maximum eliglustat plasma concentrations are observed after about 2 h. The absolute bioavailability of eliglustat is 4.49% ± 4.13%. A high fat, high caloric meal delayed absorption of eliglustat by about 1 h, resulting in a 15% lower C_{max}. The extent of absorption (AUC) was not affected. Food has no clinically relevant effect on the pharmacokinetics of eliglustat and eliglustat can be taken with or without food, as recommended in the SmPC.

Two capsule formulations have been used in the clinical studies, i.e. capsules with a high load of microcrystalline cellulose (about 39%) and a low load (about 15 – 17%). Bioequivalence has been demonstrated between these two capsule formulations. Considering the qualitative and quantitative composition of the Phase 1b, 2 and 3 formulations, the dissolution data and the results of the bioequivalence study, no significant differences in pharmacokinetics are expected after administration of these formulations.

Although in healthy subjects a more than dose proportional increase was observed over the dose range of 50 – 150 mg BID (6-fold increase), GD1 patients showed a proportional increase, possibly related to a difference in Vc and Cl in GD1 patients compared to healthy subjects. However, as eliglustat tartrate is dosed at one dose level i.e. 100 mg BID in IM and EM patients and 100 mg QD in PM patients, this issue is not further pursued as considered not relevant.

Despite its short half-life of eliglustat, an approximately 3-fold accumulation is observed. Furthermore, steady state is achieved at about day 4. This is considered due to an increase in oral bioavailability after chronic dosing due to auto-inhibition of its CYP2D6 mediated metabolism.

Steady state for the metabolites appeared to be achieved within 10 days of dosing. A similar accumulation was observed for some metabolites.

GD1 patients had almost a 1.7-fold higher exposure compared to healthy subjects. A starting dose of 50 mg b.i.d. was selected for the Phase 2 study based in part on pharmacokinetic data in healthy subjects showing that eliglustat maximum observed C_{max} was at or near the in vitro half-maximal inhibitory concentration (IC_{50}) for glucosylceramide synthase inhibition (approximately 10 ng/ml). In later studies the target was a C_{trough} concentration > 5 ng/ml and a C_{max} <150 ng/ml. The patient's dose therefore varied from 50 mg once daily to 150 mg BID. A 100 mg b.i.d. dose to CYP2D6 IM and EM patients was considered the recommended (SPC) dose as mean trough values were >5 ng/ml, and only a few maximal concentrations were observed >150 ng/ml. It is noted that a high variability is observed in the trough values. Applying this dose resulted in acceptable efficacy and safety.

With regard to the CYP2D6 URM subjects, PBPK simulated data predicted that even at a dose of 150 mg b.i.d., at 12 h trough values above 5 ng/ml were not reached. However, eliglustat plasma concentrations above 5 ng/ml were achieved over the dose-interval, from which patients may benefit. Only limited data were obtained in URM patients, therefore no dose recommendation is given. Based upon PBPK simulation data, a 100 mg q.d. dose in PM patients is predicted to result in comparable daily exposures that were observed in the clinical development program in IM and EM patients. Although limited data in PM patients is available, a 100 mg q.d. dose is recommended for PM patients. Further data will be obtained post-authorisation in URM and PM groups to further substantiate a dose recommendation.

Eliglustat pharmacokinetics shows a high between-subject variability of about 50 – 75%. This high variability can be considered due to the metabolism, which is CYP2D6 dependent, an enzyme known to be subject to polymorphism. However, intra-subject variability was shown to be below 30% in CYP2D6 EM subjects.

Distribution

Eliglustat is moderately bound to plasma proteins and drug-drug interactions due to protein displacement are not expected with eliglustat. Based upon animal data, eliglustat is widely distributed to body tissues and it may cross the blood-brain barrier.

Metabolism

Eliglustat is extensively metabolised and twenty-one metabolites were identified in plasma. Oxidation of the octanoyl moiety, oxidation at the 2,3-dihydro-1,4-benzodioxane moiety and the metabolism of the pyrrolidine moiety are considered the metabolic pathways. Eliglustat is a substrate of CYP2D6, a cytochrome P450 isoform that is genetically controlled. CYP2D6 is, the main enzyme involved in the metabolism. In addition, CYP3A4 contributes to a minor part, however this metabolic pathway becomes the prominent pathway in CYP2D6 poor metabolisers (hence patients who are CYP2D6 PMs taking a strong CYP3A inhibitor are contraindicated in the SmPC). CYP2D6 is also involved in the metabolism of several metabolites. Plasma exposure of several structurally identified metabolites was significantly higher than parent compound. Still, due to the lower affinity of these metabolites, these metabolites do not contribute to the pharmacological activity of eliglustat.

Elimination

The plasma elimination half-life of eliglustat is about 6 h in CYP2D6 IM and EM subjects and increased in CYP2D6 PM subjects (9-10h). GD1 patients showed a higher clearance compared to healthy subjects, possibly due to an altered metabolism as a result of the disease state. CL/F at steady state in GD1 patients was about 700 - 800 l/h. Population pharmacokinetic analysis indicated a clearance of about 56 l/h. Cl/F was lower at steady state compared to single dose and lower in CYP2D6 PM subjects compared to IM and EM subjects. Mean recovery of total radioactivity in urine was 41.8% and in

faeces 51.4% (total recovery 93.2%). Total combined recovery of unchanged eliglustat in urine and faeces was less than 1%. Additional metabolites were identified in urine, however, the urine metabolite profile of eliglustat is considered consistent with that observed in systemic circulation. Metabolite profiling was not carried out in faeces samples. The elimination of about 50% of the drug is not well characterised in humans, however it is considered that eliglustat is well absorbed, the metabolic profile in plasma is well established and in line with *in vitro* data, so no unexpected metabolites are foreseen in faeces.

Special patient groups

PopPK modelling included only the 405 subjects / patients with a known CYP2D6 phenotype. The PopPK analysis indicated that the absolute bioavailability was predicted to be approximately 20 times greater for CYP2D6 PMs compared with CYP2D6 EMs. In addition, after repeated 100 mg b.i.d. doses, C_{max} and AUC_{0-12} in CYP2D6 PMs were 10-fold higher compared to CYP2D6 EMs, while C_{max} and AUC_{0-12} in CYP2D6 IMs were about ~2.8-fold higher than CYP2D6 EMs and C_{max} and AUC0-12 in CYP2D6 URMs were 46% lower than CYP2D6 EMs. $T_{1/2}$ was similar for CYP2D6 IMs, EMs and URMs and was 1.2-fold higher in CYP2D6 PMs. For PM subjects a lower dose is recommended, i.e. 100 mg q.d..

After multiple dosing, based upon population pharmacokinetic analysis no effect of gender, age, body weight and race on the clearance of eliglustat is observed.

No data were submitted regarding evaluation of pharmacokinetics in patients with renal or hepatic impairment. Therefore, the SmPC states only that Cerdelga has not been studied in patients with hepatic or renal impairment. Post approval studies are planned in these groups of patients, and the results will be submitted for the assessment.

Pharmacokinetic interaction studies

Eliglustat is a substrate of CYP2D6, 3A4 and P-gp, which may be affected by inhibition of induction. No induction has been observed by eliglustat. Inhibition of CYP2D6 (time-dependent, Ki 5.8 µM (2350 ng/ml) and P-gp (22 µM (8900 ng/ml) by eliglustat may be expected. Eliglustat is considered not to inhibit CYP3A4 in the intestine.

In vivo studies confirmed the interaction potential of eliglustat:

- Inhibition of CYP2D6 by paroxetine (30 mg q.d.) resulted in a 7.3-fold increase in C_{max} and in a 8.9-fold increase in AUC_{0-12h} of eliglustat in non-PM healthy subjects receiving 100 mg b.i.d. eliglustat. Use of a strong CYP2D6 inhibitor (e.g. paroxetine, fluoxetine, quinidine) with Cerdelga is not recommended.
- Inhibition of CYP3A4 and P-gp by ketoconazole (400 mg q.d.) resulted in a 3.8-fold increase in C_{max} and in a 4.3-fold increase in AUC_{0-12h} of eliglustat in healthy non-PM subjects receiving 100 mg b.i.d. eliglustat. Caution is advised in case of use with strong CYP3A4 inhibitors, which is agreed.
- Induction of CYP3A4 and P-gp by rifampin (600 mg q.d.) resulted in a 95% decrease in C_{max} and in a 96% decrease in AUC_{0-12h} of eliglustat in healthy PM subjects receiving 100 mg b.i.d. eliglustat and in a 84% decrease in C_{max} and 85% decrease in AUC_{0-12h} of eliglustat in healthy non-PM subjects receiving 150 mg b.i.d. eliglustat. Use of strong inducers is not recommended.
- No effect on the pharmacokinetics of eliglustat was observed due to pH modifying drugs (Maalox, calcium carbonate and pantoprazole).
    - Inhibition of P-gp by eliglustat (150 mg b.i.d. non-PM and 100 mg b.i.d. PM) resulted in a 50% increase in digoxin exposure (0.25 mg single dose). This may warrant a lower dose of digoxin, as indicated in the SmPC.
    - Inhibition of CYP2D6 by eliglustat (150 mg b.i.d. non-PM) resulted in a 110% increase in metoprolol exposure (50 mg single dose). For EM the effect was more pronounced that for IM

(130% increase) compared with IMs (60% increase). This may warrant a lower dose, as indicated in the SmPC.

- Eliglustat (100 mg b.i.d.) did not affect the pharmacokinetics of norethindrone or ethinyl estradiol (Ortho-Novum 1/35, given as the standard cycle).

These interactions have been adequately described in the SmPC.

Additional simulations using Physiologically-Based Pharmacokinetic Modelling with SimCYP® were carried out to cover additional interactions. The model was validated using the data from the interaction studies with paroxetine and ketoconazole and showed good estimates of the effect.

Based upon these simulations, it is predicted that inhibition of CYP2D6 and CYP3A4 may increase eliglustat C_{max} and AUC by 17- and 25-fold, respectively. Based upon these data, Cerdelga is contraindicated in patients taking a strong or moderate CYP2D6 inhibitor concomitantly with a strong or moderate CYP3A inhibitor, which is agreed. Furthermore, in PM patients receiving a 100 mg q.d. dose it was predicted that a strong CYP3A4 inhibitor would increase eliglustat exposure by more than 6-fold. As such, strong CYP3A4 inhibitors are contraindicated in PM subjects.

Moderate CYP2D6 inhibitors, like terbinafine, would increase eliglustat exposure approximately 4-fold. Therefore, caution is advised in the SmPC.

Moderate CYP3A4 inhibitors, like fluconazole, would increase eliglustat exposure approximately 3-fold. Therefore, Caution is advised in the SmPC which is agreed. For PM subjects receiving a 100 mg q.d. dose, moderate CYP3A4 inhibitors are predicted to increase exposure by 3-fold. Very limited data is available for this patient group and the use of moderate CYP3A4 inhibitors is not recommended.

Dose proportionality and time dependencies

Although in healthy subjects a more than dose proportional increase was observed over the dose range of 50 – 150 mg b.i.d., GD1 patients showed a proportional increase, possibly related to a difference in Vc and Cl in GD1 patients. As eliglustat tartrate is dosed at one dose level i.e. 100 mg b.i.d (100 mg q.d. for PM), this issue is not further pursued. Despite its short half-life of eliglustat, an approximately 3-fold accumulation is observed. Furthermore, steady state is achieved at about day 4. This is considered due to an increase in oral bioavailability after chronic dosing due to auto-inhibition of its metabolism. Steady state for the metabolites appeared to be achieved within 10 days of dosing. A similar accumulation was observed for some metabolites.

2.4.3. Pharmacodynamics

Mechanism of action

Eliglustat is a potent and specific inhibitor of glucosylceramide synthase, and acts as a substrate reduction therapy (SRT) for GD1. SRT aims to reduce the rate of synthesis of the major substrate glucosylceramide (GL-1) to match its impaired rate of catabolism in patients with GD1, thereby preventing glucosylceramide accumulation and alleviating clinical manifestations.

Primary and Secondary pharmacology

Several biomarkers (GL-1, GM3, ceramide, sphingomyelin) related to the pharmacological activity of eliglustat were evaluated throughout the clinical program in GD1 patients, and the results support that eliglustat has its intended biological effect as an SRT without causing abnormal depletion or accumulation of other physiologically relevant lipids.

Plasma levels of GL-1 and GM3 (a downstream ganglioside derived from GL-1), which are typically elevated in GD1 patients, were significantly reduced following repeated oral administration of eliglustat 50 mg to 150 mg BID, consistent with inhibition of GL-1 synthesis. Moreover, a majority of patients achieved normal levels of these biomarkers by the end of the primary analysis period of each study. The maintenance of normal to near-normal GM3 levels further indicates that inhibition of glucosylceramide synthase by eliglustat is unlikely to cause abnormal depletion of physiologically important lipids in the GL-1-dependent synthetic pathway.

Plasma levels of ceramide, which are typically normal in GD1 patients, did not change significantly with repeated dosing of eliglustat 50 mg to 150 mg BID, and were normal for all patients in Phase 2 and ENGAGE study and normal or not clinically significant for all patients in ENCORE study at the end of the respective primary analysis periods. Plasma sphingomyelin levels, which are also typically normal in GD1 patients, increased during eliglustat treatment but remained below the upper limit of normal in all patients at the end of the primary analysis periods of each study. These results indicate that inhibition of GL-1 synthesis by eliglustat is unlikely to cause an abnormal accumulation of either the precursor substrate of GL-1 synthesis (ceramide) or physiologically important lipids synthesized from ceramide via GL-1-independent pathways.

In treatment-naïve patients who received eliglustat, large median reductions in chitotriosidase were noted in both ENGAGE study and the Phase 2 study, with all patients exhibiting reductions by the end of the primary analysis periods (PAP), while in patients in the ENCORE study, smaller median reductions in chitotriosidase were seen in both treatment arms, with some individual patients having increases and others having decreases. The median percentage reductions in chitotriosidase that occurred in treatment-naïve patients (-39.06% [mean -39.20%; see ENGAGE CSR] at the end of the 9-month ENGAGE PAP and -51.3% [mean -49.9%; see Phase 2 Study CSR] at the end of the 12-month Phase 2 study PAP) are comparable to reductions seen with ERT, where the mean decrease in 12 months was 32% (range, 0–82%) and 78% of patients had a decrease of more than 15%. The reductions of the various biomarkers were dose depended with effects demonstrated for the lowest plasma levels (<5 ng/ml).

2.4.4. Discussion on clinical pharmacology

Analysis of the exposure-response relationship between eliglustat PK and key clinical outcomes suggested that CYP2D6 IMs and EMs receiving eliglustat 100 mg BID would be expected to achieve an eliglustat exposure within the range observed to provide efficacy and acceptable safety. Moreover clinical relevant effects are observed at all dose levels. Therefore the cut-off for efficacy defined as C_{trough} levels above 5 ng/ml should be considered relative, i.e. meaningful differences can be obtained with C_{trough} levels below 5 ng/ml. Further analysis of the applicant showed that no lower threshold for efficacy could be defined. Although a more general relation between plasma concentration and effect on PD measures (i.e. spleen volume) can be identified it should be concluded that the practical range is rather broad.

Eliglustat treatment resulted in significantly decreased plasma levels of GL-1 and GM3, consistent with its mechanism of action, and did not result in abnormal accumulation of either ceramide or sphingomyelin, confirming that inhibition of GL-1 synthesis by eliglustat did not result in abnormal accumulation of either the substrate from which GL-1 is derived (ceramide) or another sphingolipid synthesised from ceramide and phosphorylcholine via a GL-1-independent synthetic pathway (sphingomyelin).

Additional analysis of the applicant showed that the plasma concentration of sphingomyelin increased from low normal levels to high normal levels. This combined with the reports of neuropathy and the important role these lipids play in signal conduction may introduce a safety concern. However as an

increase in sphingolipids is also observed in patients on ERT no serious or acute safety risk is to be expected. Long term follow-up was considered necessary by the CHMP and this is reflected in the agreed RMP.

2.4.5. Conclusions on clinical pharmacology

Pharmacokinetics

The pharmacokinetics of eliglustat has been studied extensively. All aspects have been sufficient covered. No major issues have been identified. The CHMP recommended that two analytical reports for studies GZGD02507 and GZGD02607 should be provided post-authorisation when completed. Pharmacokinetic studies in patients with hepatic or renal impairment will be carried out post approval and the results submitted in Q3 2017.

Pharmacodynamics

Overall, the improvements in biomarkers of substrate storage, macrophage proliferation, and Gaucher cell burden provides additional pathophysiological support demonstrating that eliglustat treatment is exerting its intended biological effect as an SRT for GD1, and support the improvements observed in organ volume (liver and spleen), haematologic parameters (haemoglobin and platelets), and skeletal imaging (BMD and bone marrow infiltration).

Long term follow-up of the plasma sphingolipids level is necessary. The relation with the reported neuropathy should be determined. Neuropathy has currently been included in the agreed RMP as an important potential risk. Long term safety (including peripheral neuropathy) will be followed-up in the extension studies GZGD00304, GZGD02507, GZGD02607, GZGD03109 that were included in the agreed RMP.

2.5. Clinical efficacy

The clinical development programme for eliglustat presented in this application consisted of 13 Phase 1 studies (including multiple drug-drug interaction studies, because of eliglustat's extensive metabolism via CYP450 liver enzymes), one Phase 2 study (GZGD00304), two Phase 3 pivotal studies (ENGAGE [Study GZGD02507] and ENCORE [Study GZGD02607]), and one Phase 3b study (EDGE [Study GZGD03109]). The Phase 2 study, ENGAGE, and ENCORE, which have completed their primary analysis periods (PAPs) but have ongoing long-term treatment periods, provide efficacy and safety data in support of the marketing authorization applications for GD1, while the ongoing Phase 3b study (EDGE) provides additional safety data. These studies are listed below:

- GZGD00304: A Phase 2, Open-Label, Multi-Center Study Evaluating the Efficacy, Safety and Pharmacokinetics of Genz-112638 in Gaucher Type 1 Patients

- GZGD02507: A Phase 3, Randomized, Double-Blind, Placebo-Controlled, Multi- Center Study Confirming the Efficacy and Safety of Genz-112638 in Patients with Gaucher Disease Type 1 (ENGAGE)

- GZGD02607: A Phase 3, Randomized, Multi-Center, Multi-National, Open- Label, Active Comparator Study to Evaluate the Efficacy and Safety of Genz-112638 in Patients with Gaucher Disease Type 1 who have Reached Therapeutic Goals with Enzyme Replacement Therapy (ENCORE)

- GZGD03109: A Phase 3, Randomized, Multi-Center, Multi-National, Double- Blind Study to Evaluate the Efficacy, Safety, and Pharmacokinetics of Once Daily versus Twice Daily Dosing of Genz-112638 in Patients with Gaucher Disease Type 1 who have Demonstrated Clinical Stability on a Twice Daily Dose of Genz-112638 (EDGE)

The eliglustat programme is the largest clinical development programme conducted to date in Gaucher disease, with almost 400 patients enrolled, in an ultra-orphan population.

2.5.1. Dose response studies

No specific dose finding studies were performed.

2.5.2. Main studies

Design and conduct of clinical studies

The efficacy data were collected in two studies in treatment-naïve patients with GD1 (a 1:1 randomised, double-blind, placebo-controlled Phase 3 study [Study GZGD02507, ENGAGE] and an open-label, long-term Phase 2 study [Study GZGD00304]), and a 2:1 randomised, open-label, non-inferiority, active-control Phase 3 study in patients switching from ERT [Study GZGD02607, ENCORE]).

Each of the studies providing efficacy information for the application consists of a screening period, a dose-adjustment period for those receiving eliglustat (allowing doses up to 100 mg BID during the PAP for Phase 2 and ENGAGE and doses up to 150 mg BID in ENCORE), a primary analysis period (PAP; 39 weeks for ENGAGE and 52 weeks for the Phase 2 study and ENCORE), and an open-label long-term treatment period during which those patients initially assigned to the control treatment in ENGAGE and ENCORE can receive eliglustat and patients initially assigned to eliglustat treatment can continue to receive eliglustat.

In the Phase 2 study (Study GZGD00304) treatment was started with 50 mg BID, if a patient's PK results at Day 10 (to ensure steady-state) indicated the C_{trough} of Genz-99067 was <5 ng/mL, the patient's dose was increased to 100 mg BID starting on Day 20 and then maintained at that dose level through the remainder of the PAP. If the C_{trough} value was ≥5 ng/mL, the patient remained on 50 mg BID for the remainder of the PAP.

In the PAP of the two pivotal Phase 3 studies, ENGAGE and ENCORE, dosing also started at eliglustat 50 mg BID. At Week 4, patients randomised to eliglustat could have their dose titrated up to 100 mg BID if the patient's Genz-99067 C_{trough} was <5 ng/mL at Week 2. In ENCORE, but not ENGAGE, if the patient's C_{trough} remained at <5 ng/mL at Week 6, dosing could be titrated up further to 150 mg BID at Week 8.

The primary endpoint of ENGAGE trial was the percentage change in spleen volume (in MN) from Baseline to 39 weeks of treatment with eliglustat as compared to placebo. In the Phase 2 study, the primary efficacy endpoint was the proportion of patients demonstrating a meaningful clinical response to eliglustat, as defined by pre-specified, objective improvements in 2 or more of the 3 main efficacy parameters (haemoglobin level increase ≥0.5 g/dL, platelet count increase ≥15%, and spleen volume reduction ≥15% in MN) from Baseline to Week 52 in values that were abnormal at Baseline for each patient.

ENCORE was designed to evaluate whether the percentage of patients who maintained stability after switching from ERT to eliglustat treatment was non-inferior to the percentage of patients who maintained stability when continued on imiglucerase treatment after 52 weeks of treatment. The criteria for maintaining stability for the primary efficacy analysis in ENCORE required that a patient be stable in all 4 domains of a composite endpoint, including 2 haematologic parameters (haemoglobin

level does not decrease >1.5 g/dL from Baseline and platelet count does not decrease >25% from Baseline) and 2 organ volume measures (spleen volume [in MN] does not increase >25% from Baseline [in patients who have not had total splenectomy], and liver volume [in MN] does not increase >20% from Baseline). A non-inferiority margin of 25% was selected for this study based on considerations of an imiglucerase response rate of 95% for the defined composite primary endpoint for measuring stability, and assuming a response rate of 85% for eliglustat based on Phase 2 data. In the EMA advice it was advised to set the non-inferiority margin at 20%.

Study GZD02507

A Phase 3, Randomized, Double-Blind, Placebo-Controlled, Multi- Center Study Confirming the Efficacy and Safety of Genz-112638 in Patients with Gaucher Disease Type 1 (ENGAGE)

Methods

This multi-center, multinational Phase 3 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. Patients who met all eligibility criteria based on Screening assessments were randomized to receive treatment with eliglustat or placebo during the 39-week Primary Analysis Period. Randomization was stratified based on the patient's Baseline spleen volume (≤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 (BID) from Day 2 to Week 4; thereafter, patients received a dose of either 50 or 100 mg BID through Week 39, depending on a patient's trough plasma concentration of eliglustat at Week 2.

Patients entered the Long-term Treatment Period following completion of their Week 39 assessments. In this period, all patients received eliglustat at an initial dose of 50 mg BID from post-Week 39 (Day 1 of the Long-term Treatment Period) through Week 43. Thereafter, patients received a dose of 50 or 100 mg BID through Week 47 and a dose of 50, 100, or 150 mg BID from post-Week 47 through study completion, depending on their trough plasma concentration of eliglustat at Week 41 and Week 45, respectively. The Long-term Treatment Period is ongoing; each patient may continue to receive treatment for a total duration of up to 6 years.

These analyses include safety, efficacy, and PK data collected through Week 39 for all patients, as well as selected efficacy data collected during the initial 39 weeks of open-label eliglustat therapy for patients who were originally randomized to placebo and completed the Week 78 visit as of the data cutoff date of 18 July 2012.

Study Participants

Patients met all protocol-defined eligibility criteria, including (but not limited to) the following key criteria:

- Age ≥16 years at the time of randomization.
- Tanner Stage ≥4 prior to randomization.
- Diagnosis of GD1 confirmed by a documented deficiency of acid β-glucosidase activity by enzyme assay.
- Symptoms of Gaucher disease present during the Screening period, including:
- Hemoglobin level of 8.0 to 11.0 g/dL (females) or 8.0 to 12.0 g/dL (males) AND/OR platelet count of 50,000 to 130,000/mm3, based on the mean of 2 Screening measurements obtained at least 24 hours apart.

- Splenomegaly, defined as a spleen volume of 6 to 30 MN.
- If hepatomegaly was present, liver volume <2.5 MN.
- Consented to provide a blood sample for genotyping for Gaucher disease, chitotriosidase, and CYP2D6, if these genotyping results were not already available.
- No treatment with substrate reduction therapy within 6 months prior to randomization or enzyme replacement therapy within 9 months prior to randomization.
- No treatment with any of the following medications within 30 days prior to randomization:
- Investigational products
- Medications that may cause QTc interval prolongation
- Inducers of cytochrome P450 (CYP) 3A4
- Strong inhibitors of CYP3A4, if the patient was a CYP2D6 poor metabolizer or an indeterminate metabolizer with neither allele known to be active.
- Strong inhibitors of CYP3A4 or CYP2D6, if the patient was not a CYP2D6 poor or indeterminate metabolizer, except where a patient had chronically received either medication (but not both) for at least 30 days prior to randomization and was continuing the same dosing regimen during the primary analysis period of this study.
- No history of splenectomy (partial or total), no evidence of neurologic or pulmonary involvement related to Gaucher disease, and no current symptomatic bone disease and no bone crises within 12 months prior to randomization.
- The patient was not transfusion-dependent, and did not have anemia from causes other than Gaucher disease that was untreated or not stabilized on treatment within 3 months prior to randomization.
- No documented prior esophageal varices or liver infarction, and no current results for alanine aminotransferase (ALT), aspartate aminotransferase (AST) and total bilirubin >2 times the upper limit of normal, unless the patient had a diagnosis of Gilbert Syndrome.

The included patient population is comparable with the population intended to be treated. The in- and exclusion criteria are typical for studies evaluating the effects on patients suffering from Gaucher disease.

Treatments

Patients were treated with doses ranging from 100mg to 300mg daily. Dose will be titrated based on the C_{trough} as found after at least 2 weeks of treatment. The lower limit (5 ng/ml)is based on the IC_{50} for GL-1 inhibition as demonstrated in the *in vitro* studies. The upper limit of 150 ng/ml is based on available safety data from Phase 3 studies. This information indicates a higher-than-expected level of exposure in certain patients; these patients may benefit from lower doses of eliglustat; therefore, if a post-dose plasma level of Genz-99067 ≥150 ng/mL is seen, a provision is included in the protocol for dose reduction (the lowest dose allowed in the study was 50 mg once daily (QD)). On other places the applicant argues that there are safety issues to be expected above the 150 ng/ml. In hindsight this upper limit of safety was based on preliminary data and over-concerned concern for patient safety.

Patients received treatment for 39 weeks in the Primary Analysis Period. For patients originally randomized to placebo who completed the Week 78 visit by the data cutoff (18 July 2012), this CSR also includes selected efficacy data for the initial 39 weeks of treatment with eliglustat in the Long-term Treatment Period. All patients who remain on study are now in the Long-term Treatment Period, and these patients may continue to receive open-label eliglustat therapy until they have completed up to 6 years of study treatment or until the study is terminated by the Sponsor.

Objectives

The primary objective of this study was to confirm the efficacy and safety of eliglustat (after 39 weeks of treatment in patients with Gaucher disease type 1 (GD1).

The secondary objective of this study was to determine the long-term efficacy, safety, and pharmacokinetics (PK) of eliglustat in patients with GD1.

Outcomes/endpoints

All data from the Long-term Treatment Period will be analysed and presented in a final report upon completion of the study. Central readers were used for all imaging data (liver and spleen volume, bone mineral density [BMD], bone marrow burden [BMB]), 12-lead electrocardiogram (ECGs), and dual-lead Holter.

Efficacy:

The primary efficacy endpoint was the percentage change in spleen volume from Baseline to Week 39 for eliglustat, relative to placebo. Secondary efficacy endpoints included the percentage change in liver volume, percentage change in platelet count, and absolute change in hemoglobin level from Baseline to Week 39, as well as within-patient analyses of each of the above clinical outcomes over a 39-week treatment with eliglustat, including both patients randomized to eliglustat and patients randomized to placebo who completed 39 weeks of open-label eliglustat treatment as of the data cutoff for this report.

Additional tertiary and exploratory efficacy endpoints included percentage changes in disease-related biomarkers (chitotriosidase and chemokine CC motif ligand 18 [CCL18]), spine and femur total BMD, and exploratory biomarkers (glucosylceramide [GL-1] in dried blood spot [DBS] and GL-1, GM3, macrophage inflammatory protein 1 beta [MIP-1â], ceramide, and sphingomyelin in plasma), and absolute changes in spine and femur T and Z-scores, spine, femur, and total BMB scores, Gaucher disease assessments (mobility, bone crisis, and bone pain), quality of life scores (brief pain inventory [BPI], fatigue severity scale [FSS], 36-item short form health survey [SF-36]), and Gaucher disease severity scoring system [DS3] scores from Baseline to Week 39. At Week 39, the number of patients who were at the 1-year therapeutic goals previously established for Cerezyme (Pastores, 2004, Semin Hematol; Weinreb, 2008, Am J Hematol) was also evaluated.

Safety:

Safety was assessed by adverse events (AEs), serious adverse events (SAEs), and medical events of interest (MEOIs) reported from the time of informed consent through completion of the safety follow-up period (30-37 days after the patient last dose of study drug); concomitant medications; pregnancies in female subjects or female partners of male subjects; chest X-rays (at Screening only); and 12-lead ECGs, 24-hour dual-lead Holter monitoring, echocardiograms, physical examinations, body weight, body mass index (BMI), vital sign measurements, neurological examinations, the Mini Mental State Examination (MMSE), and standard clinical laboratory tests (hematology, serum chemistry, urinalysis) obtained during the Primary Analysis Period. Medical events of interest were defined as clinically significant cardiac arrhythmias that were detected by electrophysiological monitoring and did not meet SAE criteria, and syncope from any cause.

The endpoints as presented by the applicant are typical for studies in patients suffering from Gaucher disease. Hence the intended comparison with results obtained with imiglucerase (Pastores, 2004). Most important in the analysis of the effect is the effect seen on liver, spleen, haemoglobin, platelets and bone.. As known from other published studies these endpoints should be more or less equally affected by treatment. The other endpoints are considered useful for they give additional information on the patient's perceived benefit of the treatment.

Sample size/Randomisation

A total of 40 patients were randomized and treated with eliglustat (n=20) or placebo (n=20). All 40 patients were included in the analyses for efficacy, safety, and PK (for sample size calculation see paragraph on statistical methods). The number of patients is very small. However given the rarity of the disease and the availability of other (effective) treatments it is not to be expected that significant more patients could be enrolled.

Given the small number of patients a 1:1 randomisation appears the only acceptable ratio.

Statistical methods

Power and Sample Size:

The planned enrolment of approximately 36 patients was expected to yield at least 28 evaluable patients at the end of the Primary Analysis Period, allowing for a dropout rate of 20%. Twenty-eight patients was estimated to provide 92% power to detect a treatment difference between eliglustat and placebo in the primary efficacy endpoint, based on a 2-sided, 2-sample t-test with a 5% level of significance, and assuming mean percentage decreases in spleen volume from Baseline to Week 39 of 25% and 5% for eliglustat and placebo, respectively, and a standard deviation of 15%.

Results

Participant flow and Recruitment

Table 1 summarizes the disposition of all randomized patients. In total, 40 patients were randomized and treated with eliglustat (20 patients) or placebo (20 patients) across 17 study centers. Thirty-nine patients completed the study through Week 39. One patient (#5303) elected to withdraw from the study after 166 days on study treatment (eliglustat), and did not complete Week 39 assessments.

An additional 32 patients were screened for the study, but were not randomized because they failed to complete screening procedures, did not meet all eligibility criteria, or chose to withdraw prior to randomization. The eligibility criteria that most commonly were not met were spleen size (6 to 30 MN) and platelet count (50,000 to 130,000/mm^3). Eight study centers screened patients, but did not identify any qualified patients for randomization.

Table 1: Patient Disposition: All Randomized Patients

	Eliglustat (N=20)	**Placebo (N=20)**
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) a	0
Wishes to Withdraw	1 (5) a	0

a - Patient 5303, who received treatment with eliglustat 50 mg BID through Week 4 and thereafter received an escalated dose of 100 mg BID, withdrew consent on Day 166.

After screening 72 patients 40 were eligible for randomisation. In this time frame with various effective treatment modalities for this rare disease it is not surprisingly that patients are identified at an early stage. And thus not meeting the criteria related to the seriousness of the disease.

Conduct of the study

The mean time on study treatment was 274.5 days (SD=19.94) overall and was similar in the 2 treatment groups. The majority of patients (75%-92%) in the eliglustat group received 100 mg BID, with the remaining patients receiving 50 mg BID.

Baseline data

Table 2 summarizes demographic characteristics for the 40 patients in the FAS (Full Analysis Set). The population included equivalent numbers of males and females, predominantly white (98%) and of non-Jewish descent (73%), who ranged in age from 16.1 to 62.9 years (mean = 31.8 years) on the date of the first dose of study drug. Demographic characteristics were generally similar between treatment groups, although the eliglustat group had slightly lower proportions of male patients (40%) and patients of Jewish descent (15%) compared with placebo (60% and 40%, respectively).

Table 2: Summary of Demographics: Full Analysis Set

Parameter	Eliglustat (N=20)	Placebo (N=20)	All Patients (N=40)
Sex, n (%)			
Male	8 (40)	12 (60)	20 (50)
Female	12 (60)	8 (40)	20 (50)
Race, n (%)			
White	19 (95)	20 (100)	39 (98)
Asian	1 (5)	0	1 (3)
Jewish Descent, n (%)			
Yes[a]	3 (15)	8 (40)	11 (28)
No	17 (85)	12 (60)	29 (73)
Ethnicity, n (%)			
Not Hispanic or Latino	18 (90)	20 (100)	38 (95)
Hispanic or Latino	2 (10)	0	2 (5)
Age at Day 1 (years)			
Mean (SD)	31.6 (11.55)	32.1 (11.26)	31.8 (11.26)
Min, Max	16.6, 62.9	16.1, 59.3	16.1, 62.9
Baseline Weight (kg)			
Mean (SD)	64.8 (11.74)	68.6 (17.17)	66.7 (14.65)
Min, Max	40.0, 81.7	46.0, 102.2	40.0, 102.2
Baseline Height (cm)			
Mean (SD)	166.2 (9.91)	170.0 (12.02)	168.1 (11.05)
Min, Max	149.0, 184.0	147.9, 192.0	147.9, 192.0
Baseline BMI (kg/m^2)			
Mean (SD)	23.3 (2.74)	23.4 (3.54)	23.4 (3.13)
Min, Max	18.0, 27.7	18.4, 30.9	18.0, 30.9
Smoking Status, n (%)			
None	12 (60)	13 (65)	25 (63)
Current Smoker	1 (5)	2 (10)	3 (8)
Past Smoker	7 (35)	5 (25)	12 (30)
CYP2D6 Metabolizer Status, n (%)			
Poor	0	0	0
Intermediate	1 (5)	2 (10)	3 (8)
Extensive	18 (90)	18 (90)	36 (90)
Ultra-rapid	1 (5)	0	1 (3)

SD = standard deviation; BMI = Body mass index, calculated as ([weight in kg]/[height in cm*0.01]2).
a - Includes Ashkenazi and Sephardic Jews

Numbers analysed

Forty patients were randomized to treatment with eliglustat (n=20) or placebo (n=20). In the eliglustat group, 17 (85%) patients received a dose escalation to 100 mg BID at Week 4, and 3 (15%) patients continued to receive 50 mg BID for the duration of the Primary Analysis Period. Thirty-nine patients completed the Primary Analysis Period. One patient in the eliglustat treatment group withdrew consent after Week 13.

Analysis Sets:

The Full Analysis Set (FAS) included all 40 patients who signed informed consent and received at least 1 dose of study drug (placebo or eliglustat), and is equivalent to the intent-to-treat population referenced in the protocol. The Per Protocol Set (PPS) included the 38 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 Statistical Analysis Plan, and did not exhibit hematological decline as a result of medically determined etiologies other than Gaucher disease. The Week 39 Completer Analysis Set included the 39 patients in the FAS who completed 39 weeks of treatment and had non-missing assessments at Baseline and Week 39. The Safety Analysis Set was equivalent to the FAS. The PK Analysis Set included all 20 patients who received at least 1 dose of eliglustat and had measurable drug concentrations.

Outcomes and estimation

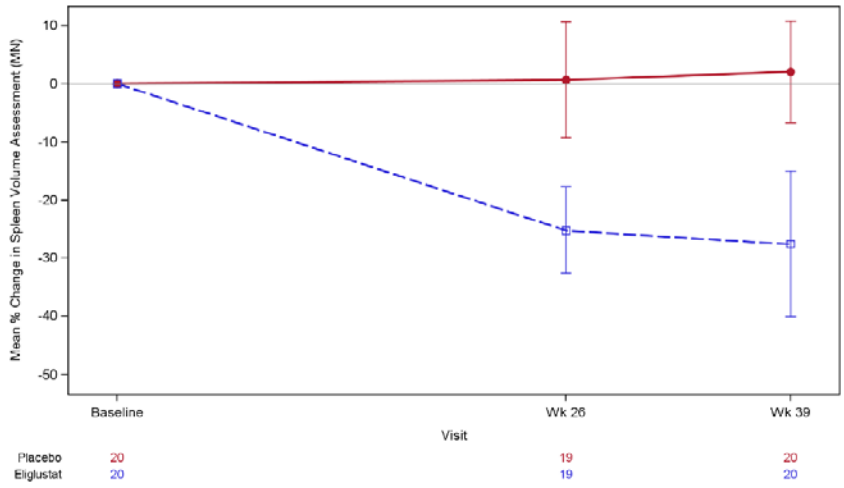
Primary efficacy endpoint

Eliglustat demonstrated superior efficacy compared to placebo on the primary efficacy endpoint, the percentage reduction in spleen volume from Baseline to Week 39. Over this 39-week period, the least squares (LS) mean percentage decrease in spleen volume (in MN) was -27.77% for the eliglustat treatment group compared with an increase of +2.26% for the placebo group, resulting in a statistically significant treatment difference of -30.03% ($p<0.0001$).

The percentage reduction in spleen volume with eliglustat therapy was not correlated with a patient's Baseline spleen volume. Overall, 15 of 20 patients in the eliglustat treatment group showed a clinically meaningful response for spleen volume, defined as >20% reduction from Baseline to Week 39, whereas only 1 of 20 placebo patients met this definition of a responder. An evaluation of eliglustat treated patients did not suggest a clear relationship between treatment response and acid β-glucosidase genotype (i.e., mutations associated with a mild [N370S] versus severe [L444P] pathology).

All patients in the study presented with splenomegaly at Baseline, with mean spleen volumes of 13.89 MN for eliglustat treatment group and 12.50 MN for the placebo group. The eliglustat treatment group showed a marked percentage reduction in spleen volume (MN) by the first post-Baseline assessment at Week 26 (mean = -25.16%), and a continued reduction in spleen volume through Week 39 (mean = -27.58%). In contrast, the placebo group showed small mean percentage increases in spleen volume at both time points (mean = 0.73% and 2.07%, respectively). Mean (SD) spleen volumes and mean percentage changes from Baseline are plotted over time for each treatment group in Fig 1, respectively.

Figure 1 Mean Percentage Change (±SD) from Baseline in Spleen Volume (MN) Over Time: Full Analysis Set



MN = multiples of normal; SD = standard deviation
Note: Percentage changes are calculated only for patients who have data at Baseline and the specified time point. Baseline refers to the last assessment prior to the first dose of study drug on Day 1.

Note: 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

Secondary Efficacy Endpoints

Eliglustat demonstrated superior efficacy compared to placebo on all secondary efficacy endpoints, including absolute change in hemoglobin levels, percentage change in liver volume, and percentage change in platelet counts from Baseline to Week 39.

Statistically significant within-patient changes were observed for the mean percentage reduction in spleen volume in MN (-28.99%, p<0.0001), mean percentage reduction in liver volume (-5.06%, p=0.0017), absolute increase in haemoglobin level (+0.9 g/dL, p=0.0003), and mean percentage increase in platelet count (29.77%, p<0.0001).

Nineteen (19) of 20 patients in the eliglustat treatment group met one (n=8), two (n=9), or three (n=2) of the 1-year therapeutic goals (as previously established for Gaucher patients on imiglucerase; Pastores, 2004, Semin Hematol; Weinreb, 2008, Am J Hematol), including goals for hemoglobin level, spleen volume, and/or platelet count. These 19 patients either attained ormaintained these goals relative to their Baseline status. Liver volume, which was already <1.5 MN in the majority (70%) patients at Baseline, was further reduced by Week 39 in 84% of patients receiving eliglustat, although none of these patients achieved the 1-year goal of a ≥20% reduction from Baseline. In contrast, for patients in the placebo group, haemoglobin was the only 1-year therapeutic goal that was met at Week 39 (in 14 of 20 patients), and 3 fewer patients met this goal at Week 39 than at Baseline.

All 40 patients in this study had Baseline total BMB scores indicative of moderate or marked-to-severe bone marrow infiltration with Gaucher cells. At Week 39, a statistically significant reversal of this infiltration was observed in both the spine BMB score (LS mean treatment difference = -0.6, p=0.0024) and femur BMB score (LS mean treatment difference = -0.4, p=0.0255), as well as the total BMB score (LS mean treatment difference = -1.1, p=0.0021). In the eliglustat group, total BMB score decreased for 15 (79%) of the 19 patients with data at Baseline and Week 39, with 5 patients having at least a 2-point reduction in total BMB score, and 3 patients having a shift in BMB category from marked-to-severe to moderate bone marrow infiltration. In the placebo group, 17 of 20 patients had minimal (<1 point) increases or decreases or no change in total BMB score, 2 patients had an

increase of at least 1 point, and 1 patient had a reduction of at least 1 point; no shifts in BMB category were observed for any patient in the placebo group.

Eliglustat also showed a positive trend on BMD in the lumbar spine, including a mean increase in total treatment difference = 0.2, p= p=0.0604). Eliglustat did not have an effect on femur total BMD, T- or Z-scores during the initial 39 weeks of treatment in this study. Statistically significant reductions in plasma MIP-1β, which is considered to be a biomarker of active bone disease, were observed with eliglustat compared with placebo (LS mean treatment difference = -43.5 pg/mL, p<0.0001).

Statistically significant reductions (p<0.0001) were also observed for the disease-related biomarker chitotriosidase, which are believed to reflect Gaucher cell burden, and for several biomarkers of eliglustat pharmacological activity (plasma and DBS GL-1, plasma GM3), with the majority of eliglustat-treated patients achieving normal GL-1 and GM3 levels by Week 39. Sphingomyelin and ceramide remained within normal range for all patients during the Primary Analysis Period, indicating that inhibition of GL-1 synthesis did not result in abnormal accumulation of the precursor substrate (ceramide) or another glycosphingolipid synthesized from that substrate (sphingomyelin). These effects are discussed further under pharmacodynamics.

Total Gaucher DS3 score, which measures the degree of GD1 disease burden across 3 domains (visceral, bone, and haematological) was significantly reduced with eliglustat treatment, relative to placebo (LS mean treatment difference = -0.3, p=0.0452).

Small, non-statistically significant but consistent improvements in the SF-36 version 2 physical component summary and its 4 scales were observed with eliglustat treatment, including a statistically significant treatment difference over placebo for the physical functioning scale. No consistent trends were observed for the SF-36 mental component summary and its 4 scales. Eliglustat had no meaningful effect on the patients' perception of fatigue (FSS) and pain severity or interference with daily activities (BPI); in general, patients in the study reported little to no fatigue or pain at Baseline, and remained stable at Week 39.

Gaucher assessments of mobility, bone pain, and bone crises were generally unremarkable; most patients had unrestricted mobility and minimal or no bone pain throughout the study, and only 1 patient (placebo group) had a reported bone crisis.

Summary of main study ENGAGE

The following table summarise the efficacy results from the main study ENGAGE supporting the present application. This summary should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment.

Table 3 Summary of efficacy for trial GZGD02507 (ENGAGE)

	Title: A Phase 3, Randomized, Double-Blind, Placebo-Controlled, Multi-Center Study Confirming the Efficacy and Safety of Genz-112638 in Patients with Gaucher Disease Type 1 (ENGAGE)				
Study identifier		GZGD02507			
Design		This multi-center, multinational Phase 3 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.			
		Duration of main phase:	39 weeks		
		Duration of Run-in phase:	not applicable		
		Duration of Extension phase:	From week 39 to week 78		
Hypothesis		Superiority			
Treatments groups		Eliglustat group	Eliglustat up to 78 weeks, 20 patients randomized		
		placebo	placebo. Up to 39 weeks, 20 patients randomized		
Endpoints and definitions	Primary endpoint	percentage change in spleen volume			
	Secondary	percentage change in liver volume			
	Secondary	percentage change in platelet count			
	Secondary	absolute change in hemoglobin level			
Database lock		The last patient visit for the Primary Analysis Period occurred on 12 July 2012, and the data cut-off date for this report was 18 July 2012.			
	Results and Analysis				
Analysis description		**Primary Analysis**			
Analysis population and time point description		Intent to treat			
Descriptive statistics and estimate variability	Treatment group	Statistic	Eliglustat	Placebo	Treatment Difference (Eliglustat-Placebo)
	Number of subject		20	20	
	Percentage	LS Mean (SEM)	-27.77 (2.37)	2.26 (2.37)	-30.03 (3.35)

	Change in Spleen Volume (MN)	95% CI	-32.57, -22.97	-2.54, 7.06	-36.82, -23.24
		p-value			<0.0001
	Change in Hemoglobin (g/dL)	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			0.0006
	Percentage Change in Liver Volume (MN)	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			0.0072
	Percentage Change in Platelet Count ($x10^9$/L)	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			<0.0001

GZGD02607: A Phase 3, Randomized, Multi-Center, Multi-National, Open- Label, Active Comparator Study to Evaluate the Efficacy and Safety of Genz-112638 in Patients with Gaucher Disease Type 1 who have Reached Therapeutic Goals with Enzyme Replacement Therapy (ENCORE)

Methods

This multi-center, multinational Phase 3 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 patient's last dose of study medication).

Patients who met all eligibility criteria based on screening assessments were randomized to receive treatment with eliglustat or Cerezyme during the 52-week Primary Analysis Period. The randomization was stratified based on the patient's every 2 weeks (q2w) equivalent ERT dose (<35 U/kg/q2w or ≥35 U/kg/q2w) prior to any unanticipated treatment interruption, dose reduction, or regimen change. Within each stratum patients were randomized in a 2:1 ratio to receive eliglustat or Cerezyme, respectively for 52 weeks (the primary analysis treatment period). All patients randomized to eliglustat received a dose of 50 mg BID from Day 1 to Week 4; thereafter, patients received a dose of either 50 or 100 mg BID through Week 8, depending on their trough plasma concentration of Eliglustat at Week 2. Post-Week 8, patients randomized to eliglustat received a dose of either 50, 100 or 150 mg BID through Week 52, depending on their trough plasma concentration of Eliglustat at Week 6 (see Dose/Route/Regimen for details).

This CSR includes results of all pre-specified analyses for the Primary Analysis Period. These analyses include safety, efficacy, and PK data collected through Week 52 for all patients as of the data cutoff date of 09 November 2012.

Study Participants

Randomized patients met all protocol-defined eligibility criteria, including (but not limited to) the following key criteria:

- Age ≥18 years at the time of randomization.
- Tanner Stage ≥4 prior to randomization.
- Diagnosis of GD1 confirmed by a documented deficiency of acid â-glucosidase activity by enzyme assay.
- Received treatment with ERT for at least 3 years. For at least 6 of the 9 months prior to randomization, the patient had received a total monthly dose of 30 to 130 U/kg of ERT that had received approval by at least 1 regulatory authority by the time of randomization.
- Reached Gaucher disease therapeutic goals prior to randomization. Gaucher disease therapeutic goals were defined as a patient with all of the following:

  A.No bone crisis and free of symptomatic bone disease such as bone pain attributable to osteonecrosis and/or pathological fractures within the last year.

  B.Mean hemoglobin level of ≥11 g/dL if female and ≥12 g/dL if male at the time of screening.

  C.Mean platelet count ≥100,000/mm^3 at the time of screening.
- Spleen volume <10 times Normal or total splenectomy (provided the splenectomy occurred >3 years prior to randomization).
- Liver volume <1.5 times Normal.
- No treatment with substrate reduction therapy within 6 months prior to randomization.
- No treatment with any of the following medications within 30 days prior to randomization:
- Investigational products
- Medications that may cause QTc interval prolongation Exception: Diphenhydramine (Benadryl) or other medications used as premedication for ERT infusions were allowed up to 7 days prior to randomization.
- Inducers of CYP3A4 with the exception of premedications for ERT infusion, which were allowed up to 7 days prior to randomization.
- Strong inhibitors of CYP3A4, if the patient was a CYP2D6 poor or indeterminate metabolizer
- Strong inhibitors of CYP3A4 or CYP2D6, if the patient was not a CYP2D6 poor or indeterminate metabolizer, except where a patient had chronically received either medication (but not both) for at least 30 days prior to randomization and was continuing the same dosing regimen during the primary analysis period of this study.
- The patient was not transfusion-dependent
- No documented prior esophageal varices or liver infarction, and no current results for alanine aminotransferase (ALT), aspartate aminotransferase (AST) and total bilirubin >2 times the upper limit of normal (ULN), unless the patient had a diagnosis of Gilbert Syndrome.
- No history of partial or total splenectomy within 3 years prior to randomization.
- No known hypersensitivity to Cerezyme.

Except for the criteria used for CYP 3A4 and CYP 2D6 this population is typical for a population suffering from Gaucher disease.

Treatments

Eliglustat was supplied as 50 mg, 100 mg and 150 mg capsules. All doses of eliglustat were taken orally with water. Cerezyme was administered as an intravenous (IV) infusion, in a q2w regimen equivalent to the patient's ERT dose prior to any unanticipated treatment interruption, dose reduction, or regimen change.

The approach to optimise the eliglustat dose is comparable with the method in study GZGD02507. $C_{through}$ concentration should be above 5 ng/ml while the peak plasma concentration should not exceed the 150 ng/ml. The lower limit is based on the IC_{50} for GL-1 inhibition in vitro. The upper limit is to ensure that patients avoid a level of Genz-99067 that does not allow an adequate safety margin in the case of an unexpected concomitant medication that interacts with eliglustat. This method is not the advised dose regimen in the SmPC.

Treatment with imiglucerase was according to the regimen advised in the imiglucerase SmPC.
Following a 45-day Screening period, each patient was treated with eliglustat or imiglucerase for 52 weeks. After the 52-week primary analysis treatment period, all patients were treated with eliglustat. Each patient's total duration of participation in this study will be at least 104 weeks, and participation may continue for a total of up to 5.5 years or until the study is terminated by the Sponsor. The study duration was considered to be sufficient to observe any change in the mayor endpoints (spleen, liver, bone marrow).

Objectives

Primary Objective: To assess the efficacy and safety of eliglustat compared with (imiglucerase) after 52 weeks of treatment in patients with Gaucher disease type 1 (GD1) who have reached therapeutic goals with enzyme replacement therapy (ERT).

Secondary Objective: To demonstrate that, in patients with GD1 who have reached therapeutic goals with ERT, the majority of patients who receive eliglustat remain stable after 52 weeks of treatment.

Tertiary Objective: To evaluate the long-term efficacy, safety, and pharmacokinetics (PK) of eliglustat in patients with GD1 who have reached therapeutic goals with ERT.

Outcomes/endpoints

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 a difference between the two treatment groups. For a patient to be considered to have demonstrated a clinically meaningful response to treatment with eliglustat or Cerezyme, patients must remain stable in hematological parameters (hemoglobin levels and platelet counts), and organ volumes (spleen, when applicable, and liver volumes in multiples of normal [MN]). A blinded Independent Adjudication Board (IAB) reviewed and confirmed that failure to meet the primary endpoint was attributed to a decline in Gaucher disease.

The secondary efficacy endpoints included the following: Total T- and Z-scores for bone mineral density (dualenergy X-ray absorptiometry [DXA]) of femur and lumbar spine, hemoglobin level, platelet count, and spleen and liver volumes (in MN) (assessed by magnetic resonance imaging [MRI]).

The tertiary efficacy endpoints included the following: Biomarkers (chemokine CC motif ligand 18 [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 vs intravenous therapy). Exploratory endpoints include Gaucher disease Severity Score System (DS3) and the percent changes from Baseline in investigational biomarkers including glucosylceramide (GL-1) assayed from dried blood spots (DBS) on filter paper and from plasma, as well as GM3, ceramide, high-sensitivity C-reactive protein (hsCRP), apolipoprotein-B-100, sphingomyelin, and macrophage inflammatory protein 1 beta (MIP-1β) (assayed from plasma).

The endpoints as presented by the applicant were considered by the CHMP as typical for studies in patients suffering from Gaucher disease. Most important in the analysis is the effect seen on liver, spleen and bone marrow. As known from other published studies these endpoints should be more or less equally affected by treatment. The other endpoints are considered useful as they give additional information on the patient's perceived benefit of the treatment or the pharmacodynamic effect of the SRT.

Sample size and Randomisation

It was planned that approximately 150 patients would be randomized in order to yield at least 120 evaluable patients at the end of 52 weeks (the primary analysis treatment period). Patients were randomized 2:1 to receive eliglustat or Cerezyme. A total of 160 patients were randomized to treatment with eliglustat (n=106) or Cerezyme (n=54). One patient randomized to the Cerezyme group was not treated. All treated patients were included in the analyses for efficacy, safety, and pharmacokinetics. The number of patients is very small. However given the rarity of the disease and the availability of other (effective) treatments it is not to be expected that significant more patients could be enrolled. Given the small number of patients a 2:1 randomisation (eliglustat : imiglucerase) appears the only acceptable ratio.

Blinding (masking)

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. A blinded Independent Adjudication Board (IAB) reviewed and confirmed instances of failure to meet the primary endpoint.

Statistical methods

Power and Sample Size:

The sample size for this non-inferiority study was based on expected stability rates of 95% for the Cerezyme treatment group (active-comparator) and 85% for the eliglustat treatment group (test treatment), power of 85%, a one-sided significance level of 0.025, a non-inferiority margin of 25%, and a 20% non-evaluable/drop-out rate.

Analysis Sets:

The Full Analysis Set (FAS) included all patients who signed informed consent and received at least 1 dose of study drug (eliglustat or imiglucerase), and is equivalent to the intent-to-treat population referenced in the protocol. The Per Protocol Set (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 Statistical Analysis Plan, and did not exhibit hematological decline as a result of medically determined etiologies other than Gaucher disease. Patients receiving eliglustat who transitioned back to Cerezyme due to clinical decline were included in the PPS and considered treatment failures regardless of their Week 52 assessments. The PPS was determined prior to database lock.

The Week 52 Completer Analysis Set included patients in the FAS who completed 52 weeks of treatment and had non-missing assessments at Baseline and Week 52. The Safety Set was equivalent to the FAS. The PK Analysis Set included all patients who received at least 1 dose of eliglustat and had measurable drug concentrations.

The statistical analysis was considered by the CHMP to be standard with respect to the arbitrary established type I and II errors (type I < 5% and a type II > 80%) to be respected. If the lower-bound

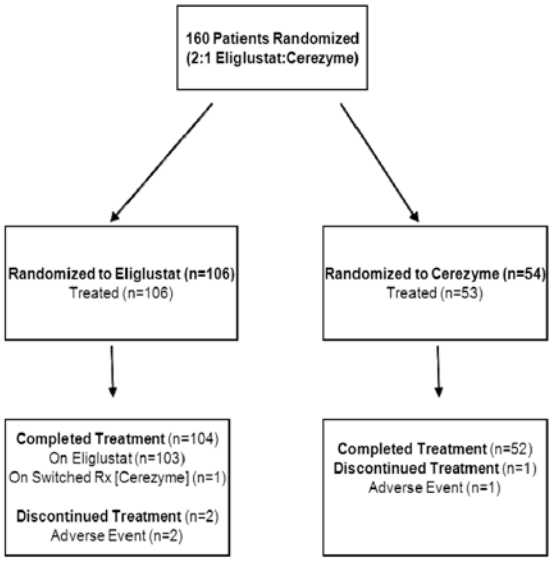
of the 95% CI for the difference was within the non-inferiority margin of 25%, then eliglustat treatment was declared non-inferior to Cerezyme treatment. This non-inferiority margin is considered too broad. As mentioned in the EMA SA (2009 and 2011) with the applicant a margin of 20% or even less is acceptable.

Results

Recruitment and Participant flow

Patient enrolment in this study was conducted from 15 September 2009 to 04 November 2011.
Patient disposition for all randomized patients is shown in
Table 4. One hundred sixty (160) patients were randomized in a 2:1 ratio to treatment with eliglustat (n=106) or Cerezyme (n=54). One patient in the Cerezyme group was randomized but did not receive study treatment. One patient in the eliglustat group switched to Cerezyme treatment and completed the 52-week primary analysis period. Two patients in the eliglustat group and 1 patient in the Cerezyme group did not complete the primary analysis period due to adverse events.

Table 4: Patient Disposition - All Randomized Patients



In total, 206 patients were screened at 39 study centers. Five study centers screened patients but did not identify any patients that qualified for randomization.

Conduct of the study

Due to dose titration the eliglustat dose varied between the various patients. At the end of the protocol-defined titration period the percentage of patients receiving the 3 possible eliglustat doses was: 50 mg BID (20%; 21/106), 100 mg BID (32%; 34/106) and 150 mg BID (48%; 51/106).
The mean number of Cerezyme infusions per patient during the Primary Analysis Period was 24.6 (±3.4) consistent with the q2w dosing interval employed in this study.

Baseline data

Demographic characteristics for the PPS are summarized in
Table. The patient population included more females (56%) than males (44%); most patients were White (93%) and of non-Jewish descent (73%). The mean age of patients enrolled was 38 years (age range from 18 to 69 years on the date of the first dose of study drug). Demographic characteristics, including ERT dose at study entry, were balanced across the treatment groups. Demographic characteristics in the FAS were similar.

Table: Summary of Demographics: Per Protocol Set

Parameter	Eliglustat (N=99)	Cerezyme (N=47)	Total (N=146)
Gender, n (%)			
Male	43 (43)	21 (45)	64 (44)
Female	56 (57)	26 (55)	82 (56)
Race, n (%)			
White	91 (92)	45 (96)	136 (93)
Black or African American	6 (6)	2 (4)	8 (5)
Asian	1 (1)	0 (0)	1 (1)
White/American Indian	1 (1)	0 (0)	1 (1)
Jewish Descent, n (%)			
Yes[a]	25 (25)	13 (28)	38 (26)
No	73 (74)	34 (72)	107 (73)
Ethnicity, n (%)			
Hispanic or Latino	40 (40)	17 (36)	57 (39)
Not Hispanic or Latino	59 (60)	30 (64)	89 (61)
Age at Day 1 (years)			
Mean (SD)	37.2 (14.0)	38.6 (15.2)	37.6 (14.4)
Min, Max	18.1, 69.3	18.2, 66.2	18.1, 69.3
Baseline Weight (kg)			
Mean (SD)	70.8 (17.3)	67.5 (15.0)	69.7 (16.6)
Min, Max	43.1, 136.0	40.6, 101.1	40.6, 136.0
Baseline Height (cm)			
Mean (SD)	167.4 (10.10)	166.1 (9.95)	167.0 (10.04)
Min, Max	144.9, 188.0	142.5, 183.0	142.5, 188.0
Baseline BMI (kg/m^2)			
Mean (SD)	25.2 (5.33)	24.4 (4.65)	24.9 (5.12)
Min, Max	16.8, 49.4	17.1, 38.2	16.8, 49.4
Randomization Stratification Groups, n (%)			
ERT <35 U/kg/q2w	38 (38)	18 (38)	56 (38)
ERT ≥35 U/kg/q2w	61 (62)	29 (62)	90 (62)
Smoking Status, n (%)			
None	71 (72)	36 (77)	107 (73)
Current Smoker	13 (13)	4 (9)	17 (12)
Past Smoker	15 (15)	7 (15)	22 (15)

SD = standard deviation; BMI = Body mass index, calculated as ([weight in kg]/[height in cm*0.01]2).
a - Includes Ashkenazi and Sephardic Jews

A total of 146 patients were included in this study. Overall the population included is comparable with those included in other studies of this kind. The patients enrolled are comparable with the patient population intended for treatment.

Numbers analysed

Outcomes and estimation

Based on the aggregate data from all doses tested in this study, eliglustat met the criteria set by the applicant in this study to be declared non-inferior to imiglucerase in maintaining patient stability. After 12 months of treatment, the percentage of patients meeting the primary composite endpoint was 84.8% ([95% confidence interval 76.2% - 91.3%] for the eliglustat group compared to 93.6% [95% confidence interval 82.5% - 98.7 %] for the imiglucerase group. The lower bound of the 95% CI in the difference in percentage (-18.6%) was within the threshold of -25%, as defined by the applicant.

Furthermore, eliglustat met the criteria to be declared non-inferior to imiglucerase for the FDA-recommended efficacy endpoint of percentage change in spleen volume. The least squares (LS) mean percentage change in spleen volume (MN) from Baseline to Week 52 in the eliglustat group was

-5.96% compared to -3.21% in the imiglucerase group. The upper bound of the 95% CI in the difference of the estimated mean change (2.62%) was less than the pre-specified threshold of 15%.

Table: Changes from baseline to Month 12 (primary analysis period) in patients with GD1 switching to Cerdelga in study 02607

	Cerezyme (N=47) Mean [95% CI]	Cerdelga (N=99) Mean [95% CI]
Spleen volume		
Percentage of Patients with stable spleen volume*[a]	100%	95.8%
Percentage Change in Spleen Volume MN (%)*	-3.01 [-6.41, 0.40]	-6.17 [-9.54, -2.79]
Haemoglobin Level		
Percentage of Patients with stable haemoglobin level[a]	100%	94.9%
Absolute Change in Haemoglobin Level (g/dL)	0.038 [-0.16, 0.23]	-0.21 [-0.35, -0.07]
Liver Volume		
Percentage of Patients with stable liver volume[a]	93.6%	96.0%
Percentage Change in Liver Volume MN (%)	3.57 [0.57, 6.58]	1.78 [-0.15, 3.71]
Platelet Count		
Percentage of Patients with stable platelet count[a]	100%	92.9%
Percentage Change in Platelet Count (%)	2.93 [-0.56, 6.42]	3.79 [0.01, 7.57]

MN = Multiples of Normal, CI = confidence interval
* Excludes patients with a total splenectomy.
[a] The stability criteria based on changes between baseline and 12 months: haemoglobin level ≤1.5 g/dL decrease, platelet count ≤25% decrease, liver volume ≤20% increase, and spleen volume ≤25% increase.

The data from the ICGG registry, which the applicant refers to support the choice of the 25% NI margin of the applicant in this aspect. However, in clinical practice margins of 15 to 20% are used to define stability/success of treatment. The NI of 20%, as recommended by CHMP, provides assurance on the efficacy of eliglustat to maintain stability, which should be based on historical data. Results from the ENCORE study show that for 85% of the patient treated stability was observed after one year of treatment. For the remaining patients alternative treatment should be considered. Given the reversibility of the deterioration this can be considered a reasonable approach (knowledge gained from the imiglucerase shortage).

At Week 52, the proportion of patients that met the stability criteria for the individual components of the composite endpoint was: hemoglobin (94.9% eliglustat; 100% imiglucerase), platelet count (92.9% eliglustat; 100% imiglucerase), spleen volume (95.8% eliglustat; 100% imiglucerase), and liver volume (96.0% eliglustat; 93.6% imiglucerase).

Absolute change from baseline in hemoglobin values was the only component of the composite endpoint that showed a statistically significant difference favouring imiglucerase after 52 weeks (-0.28 mg/dL, p=0.0253), but the amount of change observed was not clinically meaningful. BMD values were within the normal range for the majority of patients upon study entry and were

maintained over 52 weeks of treatment with both eliglustat and imiglucerase. There was no significant difference in mean change from baseline in BMD values between treatments.

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-1β and sphingomyelin concentrations). Substantial reductions in the plasma concentrations of GL-1 and GM3 with eliglustat, but not imiglucerase, 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. The continued stabilisation in 94% of the patients remaining on the ERT (imiglucerase) provides reassurance that this study has sufficient assay sensitivity

Summary of main study ENCORE

The following tables summarise the efficacy results from the main study supporting the present application. This summary should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table Summary of efficacy for trial GZGD02607 (ENCORE)

	Title: A Phase 3, Randomized, Multi-Center, Multi-National, Open-Label, Active Comparator Study to Evaluate the Efficacy and Safety of Genz-112638 in Patients with Gaucher Disease Type 1 who have Reached Therapeutic Goals with Enzyme Replacement Therapy (ENCORE)				
Study identifier		GZGD02607			
Design		This multi-center, multinational Phase 3 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 patient's last dose of study medication).			
		Duration of main phase: Duration of Run-in phase: Duration of Extension phase:	52 weeks not applicable not applicable		
Hypothesis		Non-inferiority			
Treatments groups		eliglustat	52 weeks; 106 patients randomized		
		imiglucerase	52 weeks; 54 patients randomized		
Endpoints and definitions	Primary endpoint	composite endpoint, including hemoglobin and platelet values and spleen and liver volumes			
	Secondary	Hemoglobin Criteria at 52 Weeks			
	Secondary	Platelets Criteria			
	Secondary	Spleen Volume Criteria			
	Secondary	Liver Volume Criteria			
Database lock		09 November 2012			
	Results and Analysis				
Analysis description		**Primary Analysis**			
Analysis population and time point description		Per protocol			
Descriptive statistics and estimate variability	Treatment group		eliglustat	imiglucerase	difference
	Number of subject		99	47	
	composite endpoint Patients Stable for 52 Weeks	N (%)	84 (84.8)	44 (93.6)	-8.8
		95% CI	(76.2, 91.3)	(82.5, 98.7)	(-17.6, 4.2)
	Patients Meeting Hemoglobin Criteria at 52 Weeks	n (%)	94 (94.9)	47 (100.0)	
		95% CI	(0.886, 0.983)	--	

	Patients Meeting Platelets Criteria	**n (%)**	**92 (92.9)**	**47 (100.0)**	
		95% CI	(0.860, 0.971)	--	
	Patients Meeting Spleen Volume Criteria	n (%)	68 (95.8)	39 (100.0)	
		95% CI	(0.881, 0.991)		
	Patients Meeting Liver Volume Criteria	n (%)	95 (96.0)	44 (93.6)	
		95% CI	(0.900, 0.989)	(0.825, 0.987)	

Bone effects

In the patients enrolled in Study GZGD00304 at least some dark marrow (Gaucher cells) was present at baseline in the femurs of nearly all enrolled patients at Baseline. Long-term results in the 18 patients with data at Baseline and Year 4 show that after 4 years of treatment, 56% of patients showed improvement in 1 to 6 zones, while the other 44% patients remained stable.

In the Phase 2 study, 76% of the 25 patients with evaluable DXA at Baseline had evidence of bone loss: 11 with osteopenia and 8 with osteoporosis. The total lumbar spine BMD increased by a mean (SD) of 4.4% (6.7%). This increase in mean (SD) BMD from 0.97 (0.16) to 1.01 (0.16) g/cm2 corresponded to increases in mean (SD) T-score from-1.75 (1.07) to -1.43 (1.02), both in the osteopenia range, for a mean increase of 0.33, p=0.0073, and Z score from -1.37 (0.94) to -1.09 (0.95) for a mean increase of 0.29 (0.46); p=0.012. In the 15 patients with data at Baseline and Year 4, lumbar spine BMD (g/cm2) increased significantly (p=0.02) by a mean (SD) of 9.9% (14.2%); the mean lumbar spine T-score of -1.6 (SD 1.1) at Baseline, in the osteopenic range, reached the normal range after 4 years of treatment at -0.9 (SD 1.3), representing a mean change of 0.8 (SD 1.0; p=0.0139); and the mean Z-score increased from 1.2 (SD 0.9) at Baseline to -0.5 (SD 1.1), representing a mean change of 0.7 (0.8; p=0.0044) after 4 years. The major gains in BMD occurred among osteoporotic patients and osteopenic patients with little change among patients with normal BMD T-scores. The ENGAGE study further strengthened these observations.

In ENGAGE, at Baseline, patients had mean total BMB scores in the marked-to-severe marrow infiltration range. After 9 months, eliglustat-treated patients showed a 1.1-point decrease in total BMB score, with similar contributions from the femur and spine BMB sub-scores, and 5/19 (26%) eliglustat-treated patients with data had at least a 2-point decrease in total BMB score. By comparison, the placebo group showed no change in mean total BMB score from Baseline to Month 9 (treatment difference p-value=0.0021). In ENCORE, BMB scores were essentially unchanged in both treatment groups over the 52-week Primary Analysis Period.

There was no significant difference in mean change from Baseline in lumbar spine and femur BMD, T-scores, or Z-scores between treatments in the ENCORE study, an expected result given that the goal of the study was to measure maintenance of stability in these patients.

Patient-Reported Outcomes

Patient-reported outcomes, including the Gaucher Disease Severity Scoring System and various measures of Quality of life (QOL), were assessed in the efficacy studies. Small but consistent improvements in some measures were noted, and in ENGAGE, statistically significant and clinically meaningful treatment difference of eliglustat over placebo was observed for the physical functioning

scale of the Medical Outcomes Study 36-item Short Form (SF-36; ***LS*** Mean difference=13.2, p=0.0110).
In ENCORE (the only study where this was possible), all treated patients completed a questionnaire at screening that evaluated treatment preference (oral vs IV), reasons for treatment preference, and overall satisfaction with treatment. The questionnaire was administered again at Week 52 (if randomised to eliglustat). Ninety-four percent of patients in the eliglustat group and 93% in the imiglucerase group indicated an a priori preference for oral treatment. Following 52 weeks of treatment the proportion of eliglustat patients who confirmed preference for an oral treatment was 94%. The most frequent reasons given for the preference of oral therapy were: more convenient, taken at home, given by tablets, and felt better after treatment.

2.5.3. Discussion on clinical efficacy

Dosing and design of clinical studies

In the clinical development of eliglustat dosing was based on plasma levels of eliglustat. In the primary analysis periods (PAP) of the two pivotal Phase 3 studies, ENGAGE and ENCORE, dosing started at eliglustat 50 mg BID. At Week 4, patients randomised to eliglustat could have their dose titrated up to 100 mg BID if the patient's Genz-99067 C_{trough} was <5 ng/mL at Week 2. In ENCORE, but not ENGAGE, if the patient's C_{trough} remained at <5 ng/mL at Week 6, dosing could be titrated further up to 150 mg BID at Week 8. In case the C_{max} was >150 ng/ml the dose was lowered or if necessary stopped temporarily. The currently proposed standard dose of 100 mg BID for IM and EM patients is derived from these data and based on modelling of PK/PD data by CYP2D6 genotype. For patients who are poor metabolizers (PM) a 100mg QD dose is advised based on physiologically-based pharmacokinetic (PBPK) simulations (see also PK part). Ultra-rapid metabolisers (URM) were not recommended for this treatment due to limited data.

The mean endpoints were changes in liver and spleen volume, haemoglobin level and platelet count. Other endpoints were biomarkers (GL-1, GM3, ceramide, sphingomyelin), QoL and bone mineral density. These clinical measures represent the more common manifestations of GD that may be responsive to treatment in the short term, and have been investigated in previous studies of ERT or SRT in patients with GD1. Therefore, the measurements that have been carried out are considered clinically relevant.

Because eliglustat is an oral therapy and the comparator therapy in ENCORE, imiglucerase, is administered via iv infusion, ENCORE was designed as an open-label study. While an open-label design is considered to be less rigorous than a blinded design, the potential for patient and/or physician bias with respect to efficacy was considered to be low because all four components of the primary composite endpoint (spleen and liver volumes and haemoglobin level and platelet count), are objective measurements, and the organ volume assessments were centrally read by independent organization, blinded to treatment. Therefore the open label design is acceptable.

Selection of patients

The majority of the patients in the studies were white, approximately 25% were Jewish, and most were young adults. Approximately 28% of ENCORE patients had total splenectomies and 1% had partial splenectomies, compared to none in the treatment naïve studies, which is a consequence of different exclusion criteria for the different studies. CYP2D6 phenotype was fairly consistent across studies. Approximately 82% of patients were CYP2D6 EMs, 10% were IMs, and 3% each were PMs and URMs, in accordance with population estimates.

Further analysis for a trend by ethnicity did not lead to conclusions as a non-Caucasian population as these were virtually not included.

A high percentage of patients in all studies completed the PAP (97.5% completed 39 weeks in ENGAGE; 85% completed 52 weeks in the Phase 2 study; and 98% completed 52 weeks in ENCORE). Additionally, in the Phase 2 study, 19 patients (73%) completed Month 48.

Efficacy data and additional analyses

Treatment-Naïve Patients

Both studies in treatment-naïve patients met their primary endpoint. In ENGAGE, there was a statistically significant mean reduction in spleen volume between the eliglustat and placebo groups after 9 months (-30.03%; 95% CI -36.82 to -23.24; p <0.0001). Most (75%) of the eliglustat-treated patients achieved a clinically meaningful reduction of at least 20% in spleen volume compared to only 5% of placebo treated patients. In addition, all secondary endpoints showed statistically significant and clinically meaningful changes, including 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). In the Phase 2 study (treatment naïve patients), 77% of all treated patients and 91% of all study completers met the composite primary efficacy endpoint after one year of eliglustat treatment. Furthermore, statistically significant improvements in all 4 organ volume and haematology parameters were observed at Week 52 and were maintained or continued to improve through Month 48.

The lack of data on comparison of eliglustat with imiglucerase (or other ERT) in treatment naïve patients was noted by the CHMP. The applicant explored the possibility of a non-inferiority study for such a study that would address the issue of the efficacy of eliglustat compared to imiglucerase in the best possible way. However such a study would need at least 76 patients to gain sufficient power. The CHMP agreed that given the rareness of the disease this is not considered feasible. Further the short timeframe available limits the possibility of such study.

Indirect comparison of efficacy data of eliglustat with imiglucerase (ICGG database) indicate that comparable treatment effects are seen for the most important endpoints during the 4 years of treatment. Further, continued improvement with eliglustat from 39 weeks of treatment to 78 weeks (1.5 years) in Phase 3 treatment-naïve patients (ENGAGE) is shown on established clinical treatment outcomes for GD1, in addition to clinically meaningful effects on bone disease. Given the indirect comparison it can be concluded that a reasonable percentage of patients treated with eliglustat will achieve comparable results as are to be expected for the already registered ERT. Consequently a minority should not reach sufficient effectiveness (as expressed in criteria used in the Phase 2 study: in decrease in liver and spleen volume <15%, increase in thrombocytes <15% Hb increase <0.5 g/dl after one year of treatment). Reinstitution of enzyme replacement therapy or an alternative treatment modality should be considered in individual patients who have a sub-optimal response and this was included in the SmPC. The convenience of oral use of eliglustat as compared to the bi-weekly imiglucerase infusions (and consequent infusion related reactions) was noted by the CHMP.

Patients Switching from ERT

Based on the aggregate data from all doses tested in this study, eliglustat met the criteria set in this study to be declared non-inferior to imiglucerase in maintaining patient stability. The primary composite endpoint required maintenance of stability based on changes in the haemoglobin level, platelet count, and spleen and liver volumes that could not exceed pre-specified thresholds for any of the 4 components, and the primary efficacy analysis was conducted using the per-protocol population, which included 99 eliglustat-treated patients and 47 imiglucerase-treated patients. After 52 weeks of treatment, the composite endpoint was maintained in only 85% of patients in the eliglustat group compared to 94% of patients in the imiglucerase group. This was considered of major concern and therefore the long-term sustainability of eliglustat's effect in comparison with the approved ERT. The lower bound of the 95% exact CI for the eliglustat group (75.1%) supports the

claim that the majority of eliglustat-treated patients maintained stability after 52 weeks of treatment. In case patients show a clinical deterioration during SRT (increase in liver and spleen volume >25%, increase in thrombocyte count > 25% and Hb decrease >1.5 g/dL after one year of treatment) the patients and the treating physician should consider to switch to other treatment options (ERT) which may be more beneficial to the particular individual. This is adequately mentioned in the SmPC.

The lower bound of the 95% CI for the difference between treatment groups (-17.6%) was within the non-inferiority margin of -25% as pre-specified by the applicant. However, both the choice of the non-inferiority margin (-25% defined by the applicant versus -20% defined by the CHMP during the Protocol Assistance procedure) and the method used to calculate the confidence interval for evaluation of non-inferiority were questioned by the CHMP. Based on strict statistics, the pre-specified primary analysis has an inflated type I error, therefore does not fulfill the regulatory requirements hence was considered not acceptable. Upon request by CHMP, the applicant provided further efficacy analysis for 95% confidence intervals using various recognized methods from major statistical journals and major statistical software packages. In view of the CHMP the noninferiority with a margin of -20% was not demonstrated as the lower bound of the 95% CI did not exclude -20% for all methods that may have been considered a reasonable choice for the primary analysis method at time of planning of the study. Therefore, the CHMP considered, non-inferiority of the proposed regimen (200mg daily for EM and IM only) to the ERT was not comprehensively demonstrated. However the benefit-risk of eliglustat in treatment experienced patients is considered positive. The PI is updated to mention the somewhat higher failure rate compared to ERT and the percentages of patients meeting the primary composite endpoint on eliglustat and imiglucerase in the ENCORE study are reflected in the SmPC.

Bone marrow data

Overall these data demonstrate an improvement in bone marrow infiltration and BMD with eliglustat treatment in treatment-naïve patients, particularly those with more severe bone disease at baseline, and maintenance of stable bone disease in patients switched from ERT to eliglustat.

Proposed CYP2D6 Phenotype-Based Dosing Regimen

In the Phase 2 and Phase 3 clinical studies, patients initially received eliglustat 50 mg BID, with the potential for subsequent dose increases based on trough plasma concentrations (C_{trough}). According to the applicant, this approach would be complicated by the need for the repeat testing of Genz-99067 plasma levels in the setting of potentially large fluctuations in exposure. These analyses could only be conducted at a limited number of laboratory sites and would require the patient to precisely time the last dose so that the plasma level could be accurately interpreted.

A population pharmacokinetic (PopPK) analysis using data from healthy subjects and GD1 patients showed that CYP2D6 phenotype (PM, IM, EM, or URM) was the most significant determinant of exposure to eliglustat. Therefore, a dosing regimen based on CYP2D6 phenotype is proposed for post-marketing use. The recommended use of eliglustat will be only acceptable for the PM, IM and EM patients (which is expected to constitute approximately 97% of patients) using a single dosing regimen of 100 mg BID (IM and EM patients) or QD (PM patients).

As claimed by the applicant, simplifying the eliglustat dosing regimen by targeting PMs, IMs and EMs only, with a single dose strength, reduces the complexity surrounding the management of concomitant medications via labelling, guidance and education that would need to be provided for each CYP2D6 phenotypic subgroup. Nevertheless, it should be considered that in the ENCORE study about 48 % of patients received eliglustat 150 mg BID. Further about 20% received 50 mg BID, leaving 32% of the patient treated with the proposed 100mg BID. The variation in treatment regimens was the result of individual dose titration in the ENCORE and ENGAGE studies. Additional analysis of the ENCORE study results showed that the thresholds used to titrate the dose individually

did not hold. Below the lower efficacy margin (5 ng/ml) patients were identified with acceptable efficacy. The upper safety limit (150 ng/ml) could be raised to 500 ng/ml based on the QT study results.

The popPK/PD model showed a relation between AUC and effect on spleen volume. Using this model it can be calculated that the expected loss of efficacy in patients treated with 100 mg bid (IM and EM patients) or 100mg QD (PM patients) is clinically negligible. This is justified by the actual data that do not show a difference between EM patients treated with 100 or 150 mg BID. Notwithstanding, a considerable portion of the patients falls without the 95% CI of the PopPK predictions, therefore the Patients should be closely monitored and in case of deterioration other treatment options should be considered. This is included in the SmPC.

The initial exclusion of PM and URM from the proposed indication was also questioned by the CHMP. During the procedure physiologically-based pharmacokinetic (PBPK) simulations were conducted by the applicant, the outcome of these simulations lead to a recommendation for dosing in PM patients. In PM patients, a dosing regimen of 100mg QD is advised. In addition the CHMP recommended the submission of a full report including the underlying data of the physiologically-based pharmacokinetic (PBPK) simulations conducted to support the dose recommendation in PM patients to be provided post-authorisation.

For the URM the C_{max} using a 150 mg BID regimen is 22.6 (24.3) ng/ml (mean [SD]). It is therefore to be expected that URM patients will have some benefit from treatment with eliglustat. This is further strengthened by the observation that in some patients benefit from C_{trough} levels below 5ng/ml. Despite this the CHMP agreed that the available data for URMs are currently too limited to draw definite conclusions. The applicant agreed to collect more data in patients who are CYP2D6 URM and PM post-authorisation. A comprehensive review of the data on PMs and URMs including analysis of the data from additional 5 PM patients and 4 URM patients from the extension periods of the Phase 2 study, ENGAGE and ENCORE, as well as the EDGE study together with the PKPB simulations will be provided post-authorisation and was included in the RMP.

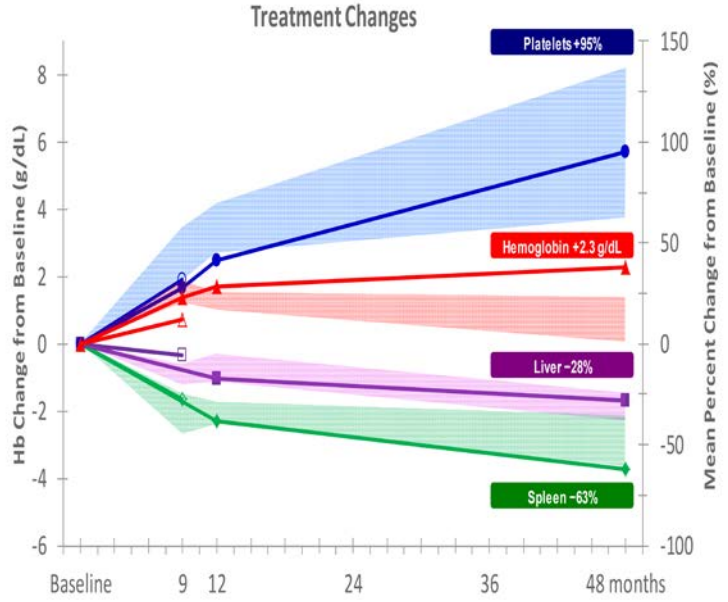
Results in Sub-Populations

Efficacy results were analysed by gender, age group, race, baseline disease severity, and GD genotype. Some small, clinically insignificant differences were noted in the studies.

Comparison of Efficacy Results with Currently Approved Therapies

In the ICGG Gaucher Registry analyses, selection criteria based on the inclusion and exclusion criteria from ENGAGE and the Phase 2 study were used to select imiglucerase-treated patients from the ICGG Gaucher Registry who had received at least 15 U/kg/2 weeks for comparison with visceral, haematological, and skeletal outcomes. The registry analysis showed that the visceral and haematological changes observed with eliglustat treatment in treatment-naïve patients after 9 months of treatment (in ENGAGE) and 4 years of treatment (in the Phase 2 study) were similar to those observed in imiglucerase-treated patients from the ICGG Gaucher Registry (Figure 1).

Figure 1: Comparison of efficacy data of eliglustat (Phase 2 data) with Imiglucerase (Data from ICGG Gaucher Registry; matched)



Eliglustat – Solid lines; closed markers: phase 2, open markers: ENGAGE
Cerezyme – Shaded areas: Upper and Lower 95% Confidence Interval around Mean

Eliglustat and imiglucerase were compared directly in ENCORE, which studied maintenance of stability in patients who had already reached pre-specified therapeutic goals with ERT. Results from this study demonstrated that eliglustat is an efficacious agent in maintaining stability in GD1 patients who have reached therapeutic goals with ERT. However the applicant proposes a different dosing regimen in the SmPC. The proposed regimen is not considered non inferior to the ERT in terms of maintenance in the opinion of the CHMP but the data indicate that the majority of the patients are adequately treated with a minority showing insufficient response. These patients should be identified based on clinical observations and other treatment which may be more beneficial to the particular individual should be considered (ERT).

Miglustat is the only currently approved treatment with a comparable mode of action. It is a second-line therapy indicated in adult patients with mild to moderate GD1 for whom ERT is not a therapeutic option. Results obtained with miglustat in treatment naïve patients showed a mean reduction in liver volume of 17.5% after 36 months. The mean reduction in spleen volume from baseline was 29.6% after 36 months. Also after 36 months treatment increase in mean haemoglobin concentration from baseline was 0.95 g/dl. At 36 months, the mean increase in mean platelet count in patients remaining on therapy was 22.2×10^9/l. However, eliglustat is approximately 1000-fold more potent for its target than miglustat (Platt, 1994, J Biol Chem; McEachern, 2007, Mol Genet Metab) and although only an indirect comparison is possible, the results obtained with eliglustat appear more beneficial than those reported for miglustat in the treatment naïve patients.

2.5.4. Conclusions on the clinical efficacy

It can be concluded that eliglustat constitutes a treatment option for GD patients in the treatment naïve patients given the clinically meaningful changes observed.

Although, based on the aggregate data from all doses tested in this study, eliglustat met the criteria set in this study to be declared non-inferior to imiglucerase in maintaining patient stability, based on strict statistics, the pre-specified primary analysis has an inflated type I error, therefore does not

fulfill the regulatory requirements. The CHMP considered that the noninferiority with a margin of -20% was not comprehensively demonstrated. Still, the CHMP agreed that eliglustat can be considered an alternative for imiglucerase in stabilized patients when needed for the clinical results in most patients (over 80%) are comparable irrespective of treatment. Nevertheless, the recommendation was included in the SmPC that in case of insufficient effectiveness with eliglustat alternative treatment options (ERT) should be considered.

The initial exclusion of PM and URM from the proposed indication was questioned by the CHMP. During the procedure physiologically-based pharmacokinetic (PBPK) simulations were conducted, the outcome of which was submitted to the CHMP and lead to a possible dosing for PM patients. For patients who are PM a dosing regimen of 100mg QD is advised. In addition the CHMP recommended the submission of a full report with the underlying data of the physiologically-based pharmacokinetic (PBPK) simulations conducted to the support the dose recommendation in PM patients post-authorisation.

For the URM the C_{max} using a 150 mg BID regimen is 22.6 (24.3) ng/ml (mean [SD]). It is therefore to be expected that URM patients will have some benefit from treatment with eliglustat. This is further strengthened by the observation that in some patients benefit from $C_{through}$ levels below 5ng/ml. Despite this the CHMP agreed that the available data for URMs are currently too limited to draw conclusions from. The applicant agreed to collect more data in patients who are CYP2D6 URM and PM post-authorisation. A comprehensive review of the data on PMs and URMs including analysis of the data from additional 5 PM patients and 4 URM patients from the extension periods of the Phase 2, ENGAGE and ENCORE, as well as the EDGE studies together with the PKPB simulations will be provided post-authorisation.

Furthermore, the CHMP recommended the development of the lower dosage strengths (21 and/or 42 mg eliglustat). Also, a single- and multiple dose pharmacokinetics study in healthy subjects is recommended to be conducted to characterize dose proportionality of 21, 42, and 84 mg eliglustat to accommodate various situations requiring further dosage adjustments.

Based on the review of the efficacy data the CHMP was of the opinion that this oral treatment is a valuable addition to the treatment options for patients with GD type 1.

2.6. Clinical safety

Patient exposure

The pooled Eliglustat Safety Set contains 393 patients: 26 patients from the Phase 2 study, 40 patients from ENGAGE, 157 patients from ENCORE, and 170 patients from EDGE. Eliglustat safety data from both the PAPs and the Long-term Treatment Periods from ENGAGE and ENCORE up to the database cut-off date (31 January 2013). In the pooled Eliglustat Safety Set, the mean (±SD) duration of treatment was 1.4 (±1.19) years, and the total duration was 535.0 patient-years. The minimum and maximum exposure both occurred in the Phase 2 study. The minimum duration was <1 day (2 patients received only one 50-mg dose), and maximum duration of treatment was 6.5 years.

Adverse events

Overall, 334/393 of eliglustat-treated patients (85%) experienced a TEAE (2,340 events; 437 events per 100 person-years). Events in the majority of patients were considered unrelated to eliglustat treatment by the Investigators (312/334; 79%). Most of the TEAEs experienced were mild or moderate in severity (78% and 44% of patients, respectively), while 45 patients (11%) experienced 68 TEAEs which were considered severe.

The most frequent TEAEs (those occurring in ≥10% of all patients who received eliglustat) were: Headache (17%), arthralgia (14%), nasopharyngitis (13%), upper respiratory tract infection (11%), diarrhoea (10%), and dizziness (10%). The proportions of patients with each of these events decreased over time. In general, the most frequently affected SOCs and the most frequent Preferred Terms (PTs) were similar in treatment-naïve patients (ENGAGE and Phase 2 study), in patients switching from ERT (ENCORE), and in the pooled patient population (including the EDGE lead-in period), with some of the reported PTs in the Musculoskeletal and connective tissue disorders SOC also being known symptoms of GD (e.g. arthralgia and bone pain).

A higher overall incidence of TEAEs was reported for eliglustat compared to imiglucerase, including TEAEs considered related to study drug by the investigator, but this result was not unexpected in this open-label study, considering this was a previously treated population of patients who had been receiving imiglucerase for a mean of almost 10 years prior to study entry. Most AEs related to imiglucerase would have been expected to occur during the first few months of treatment.

Serious adverse event / deaths / other significant events

No treatment-emergent deaths have been reported in the pooled eliglustat safety set through the database cut-off date of 31 January 2013. Across the programme, a total of 5 deaths were reported. In all cases, the events leading to the deaths were considered not related to eliglustat, and 3 of the deaths were not during treatment. Two 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 Jan 2013 cut-off date and after completion of the lead-in period; both were considered unrelated to study drug treatment).

A total of 42 SAEs occurred in 35 patients (9%) in the Pooled Eliglustat Safety SetThe majority of SAEs were due to hospitalizations for intercurrent illnesses (e.g., appendicitis) and underlying diseases for which GD patients are at increased risk (e.g., femur fracture, joint dislocation [Deegan, 2011, Medicine], hepatocellular carcinoma [Weinreb, 2013, Crit Rev Oncogen], and cholecystitis.

The most frequently reported SAE was syncope (5 patients). The serious syncopal events were vasovagal in nature with predisposing risk factors (i.e., blood draw, fasting conditions and pain), and none of these events led to permanent discontinuation from the study. Unscheduled ECGs, obtained as part of post-event diagnostic testing, did not reveal any cardiac arrhythmias or increase in ECG intervals as the potential cause for these syncopal events. SAEs of Syncope were severe in 4 patients, and were considered at least possibly related to eliglustat in 3 patients. SAEs (other than syncope) occurring in more than one patient included myocardial infarction in 4 patients, one of which was changed to Angina in late-breaking safety reports. All of these patients had pre-existing risk factors for myocardial infarction. In each case the investigator assessed these events as not related or as remote/unlikely related to eliglustat.

Discontinuations

A total of 12/393 patients (3%) had at least 1 TEAE that led to permanent discontinuation of eliglustat treatment. These events included ventricular tachycardia in 2 patients, 2 patients with myocardial infarction prior to the database cut-off of 31 Jan 2013 and another after this date, and other events occurring in one patient each. No pattern or trend was noted regarding the timing of these events relative to the start of study drug or time on treatment (the onset ranged from the day of first dose to 382 days after the first dose). TEAEs leading to permanent eliglustat discontinuation and study withdrawal that were considered possibly or probably related to eliglustat included ventricular tachycardia; lethargy and exfoliative rash in the same patient; upper abdominal pain; palpitations; and nausea, headache, and anaemia in the same patient.

Clinical Laboratory Evaluations and Vital Signs

Changes in hematology and chemistry laboratory parameters over time were small and no clinically relevant trends were observed. Overall, there were no clinically meaningful changes in mean vital sign measurements from Baseline to any post Baseline time point.

A Phase 1 Thorough QT (TQT) study in healthy volunteers (GZGD01707) tested the effect of a single dose of 200 mg or 800 mg eliglustat on cardiac repolarization. The mean C_{max} at the 200-mg dose was 26.5 ng/mL (geometric mean 16.7 ng/mL); the maximum C_{max} at the 200-mg dose was 142 ng/mL. The mean C_{max} at the 800-mg dose was 299 ng/mL (geometric mean 237 ng/mL); the maximum C_{max} was 761 ng/mL. PR, QRS, and QTcF intervals all increased from Baseline in a dose-dependent manner.

The upper limit of the 95% confidence interval of the QTcF change from Baseline did not exceed 10 msec at any time point at either the 200 mg or 800 mg dose, and therefore it was a negative study per ICH E14 guidance and at most a mild increase in QTcF at the supratherapeutic dose. The prolongation of PR (average 7 msec) at the higher dose is considered a mild increase. The small prolongation of the QRS (average 2 msec) at the higher dose is of unclear clinical significance.

There is a concentration-dependent increase in QT, PR, and QRS intervals with increased eliglustat exposure. However, the results shown above demonstrate that even at an eliglustat C_{max} of 500 ng/mL clinically significant ECG interval increases are not expected. This is higher than that expected with therapeutic doses even in the presence of concomitant medications inhibiting CYP2D6 and CYP3A, To date, patients taking eliglustat on any of the regimens evaluated in the clinical trials have not had reported plasma levels in the range predicted to cause clinically meaningful changes in ECG intervals. Furthermore, there were no clinically significant prolongations of the QTcF, PR, or QRS interval observed in clinical studies, despite extensive ongoing Holter and ECG monitoring in the trials, and findings of cardiac conduction disorders did not appear to be outside of the published range of events in normal subjects.

Safety in special populations

CYP 2D6 status

In the pooled Eliglustat Safety Set, no increase in the overall incidence of TEAEs was seen for patients identified as poor metabolizers (79%) compared with patients identified as intermediate metabolizers (73%). The proportions of patients in the poor and intermediate metabolizer groups who experienced TEAEs at any dose (79% and 73%, respectively) was lower than that observed for extensive metabolizers (88%).

Upper limit in clinical studies

In the clinical studies an upper limit of 150ng/ml was defined. This upper limit was introduced based on very preliminary data and an abundance of caution. The QT study indicated that levels up to 500 ng/ml can be considered safe from the QT perspective.

Safety of drug-drug interactions

Interactions have been studied and findings are sufficient worded in the SmPC. Besides some in vitro and modelling issues which need to be clarified, no clinical concerns are raised. The lack of the discussion is not further pursued.

Post marketing experience

N/A

2.6.1. Discussion on clinical safety

As to be expected from an orphan drug the overall safety database is small (N= 393) and the duration of treatment is short (one year) for most patients with a selected group generating 4 years data. This is considered acceptable. Nevertheless, an obligation to set up and maintain a sub registry of the ICGG was agreed and is described in the RMP. This will allow collection of further safety data post authorisation.

Eliglustat was generally well tolerated across the clinical programme. Few patients (12/393, 3%) withdrew due to TEAEs. These events includedventricular tachycardia in 2 patients, 2 patients with myocardial infarction. The most frequent TEAEs (those occurring in ⩾10% of all patients who received eliglustat) were: headache (17%), arthralgia (14%), nasopharyngitis (13%), upper respiratory tract infection (11%), diarrhoea (10%), and dizziness (10%). The gastrointestinal AE' s decreased in time.

Across the clinical programme, diarrhoea was reported in 9% of eliglustat-treated patients, and weight loss in <2%. This might be explained by the observed difference in binding to intestinal disaccharidase enzymes between miglustat and eliglustat. Compared to miglustat, the safety profile of eliglustat appears to be less severe, although direct comparison is lacking. The safety profile of patients on ERT, in particular imiglucerase was different (mainly infusion related reactions and antibody formation in case of imiglucerase).

There were no treatment-emergent deaths in the pooled Eliglustat Safety Set. Across the programme, a total of 5 deaths were reported, and the events leading to the deaths were considered not related to eliglustat. A total of 42 SAEs have occurred in 35 patients (9%). The majority of SAEs reported were due to hospitalizations for intercurrent illnesses and underlying diseases for which Gaucher patients are at increased risk. SAEs occurring in more than one patient included myocardial infarction (4 patients) and syncope (5 patients). Most AE were mild or moderate and only a small number of patients withdrawn due to AE the adverse events profile of eliglustat can be considered acceptable.

A thorough QT/QTc study in healthy volunteers (GZGD01707) did not reveal clinically relevant prolongations of QT in plasma levels below the 500 ng/ml. There was a theoretical concern considering the combination of bradycardia and adverse events possibly related to a decreased cardiac output (fatigue, cough, dizziness, syncope and oedema). Based on the analysis of the available data a causal relation of bradycardia and eliglustat could not be established. Further bradycardia was not associated with a decrease in cardiac output. No relation between various forms of arrhythmias and other conductive disorders and the use of eliglustat was established. The QT study further indicated that the QT prolongation is only relevant in patients with plasma levels above the 500ng/ml, which are not reached in these studies. Due to the lack of detailed information on patients with pre-existing cardiac conditions the applicant included a warning in the SmPC section 4.4. to avoid treatment with eliglustat in patients with cardiac disease, long QT syndrome and in combination with class IA and III antiarrhythmic medicinal products.

2.6.2. Conclusions on the clinical safety

The safety database is limited both with regards to the number of patients and time on treatment. This is acceptable and expected given the orphan nature of the disease. Particularly, drug related AEs

occurring with a low frequency might be not reported yet. Overall, the adverse effects profile of eliglustat appears manageable. The AEs currently identified were mostly mild and reversible. Most remarkable AEs were cardiovascular disorders including syncope and palpitations, infections predominately of the upper respiratory tract, gastrointestinal disorders including diarrhoea, nervous system disorders, fatigue and asthenia. The available data allow no robust conclusion on long term safety. Based on the analysis of the available data from a causal relation of the observed bradycardia and eliglustat could not be established. Further bradycardia was not associated with a decrease in cardiac output. No relation between various forms of arrhythmias and other conductive disorders and the use of eliglustat could be established.

In conclusion, the CHMP agreed that the available safety data are sufficient but require a careful follow-up post authorisation to continue characterisation of the safety profile.

The CHMP considers the following measure necessary to address the long term safety profile in the context of a MA:

Description	Due date
In order to investigate the long-term safety of eliglustat in patients prescribed eliglustat, the MAH is to create a sub-registry to the International Collaborative Gaucher Group (ICGG) Gaucher Registry to collect safety data according to an agreed protocol.	Reports from the sub-registry are to be submitted with each PSUR.

2.7. Pharmacovigilance

Detailed description of the pharmacovigilance system

The CHMP considered that the Pharmacovigilance system as described by the applicant fulfils the legislative requirements.

2.8. Risk Management Plan

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

The PRAC considered that the risk management plan version 1.4 could be acceptable if the applicant implements the changes to the RMP as described in the PRAC endorsed PRAC Rapporteur assessment report.

The CHMP endorsed this advice without changes.

The applicant implemented the changes in the RMP as requested by PRAC.

The CHMP endorsed the Risk Management Plan version 1.6 with the following content:

Safety concerns

The applicant identified the following safety concerns in the RMP:

Important identified risks	None
Important potential risks	Drug-drug interactions – Use with cytochrome P450 (CYP)2D6 and/or CYP3A inhibitors– Use with strong CYP3A inducers – Use with P-gp or CYP2D6 substrates
	Use of eliglustat in patients who are CYP2D6 indeterminate metabolisers or non-genotyped patients
	Cardiac conduction disorders and arrhythmias
	Vasovagal syncope
	Off-label use in Gaucher disease type 2 and 3
	Peripheral neuropathy
Missing information	Use in patients with a history of or current cardiac ischaemia or heart failure, clinically significant arrhythmias or conduction findings
	Use in patients with hepatic impairment
	Use in children
	Use during pregnancy and lactation
	Safety in long-term treatment use
	Use in patients who are CYP2D6 ultra-rapid metabolisers
	Use in patients with renal impairment

Pharmacovigilance plan

Ongoing and planned studies in the PhV development plan

Study/activity Type, title and category (1-3)	Objectives	Safety concerns addressed	Status	Date for submission of interim or final reports
Prospective ICGG safety sub-registry (cat 1)	To characterize the long-term safety profile of eliglustat in real-world clinical practice To describe the patients characteristics and utilization patterns	Safety in long-term treatment use Off-label use in Gaucher disease type 2 and 3 Use of eliglustat in patients who are CYP2D6 indeterminate metabolisers or non-genotyped patients Use of eliglustat in patients who are ultra-rapid metabolisers	Planned	Concept protocol will be submitted within 3 months after approval. Milestones will be reported in PSURs Re-evaluation at 5 year after first eliglustat patient has been entered
Paediatric study Open label, 2 cohorts (with and without imiglucerase), multicenter, historical-controlled study to evaluate pharmacokinetics, safety, and efficacy of eliglustat in paediatric patients with GD1 and GD3 (cat. 3)	To evaluate pharmacokinetics, safety, and efficacy of eliglustat in paediatric patients with GD1 and GD3	Use in children	Planned	Planned final report Q4 2021
Pharmacokinetics of Oral Single-Dose Eliglustat in Subjects with Hepatic Dysfunction (cat. 3)	To evaluate the pharmacokinetics of eliglustat in patients with hepatic impairment	Use in patients with hepatic impairment	Planned	Planned final report Q3 2017
Pharmacokinetics of Oral Single-Dose Eliglustat in Subjects with Renal Impairment	To evaluate the pharmacokinetics of eliglustat in patients with renal impairment	Use in patients with renal impairment	Planned	Planned final report Q3 2017
Drug utilisation study of eliglustat in Europe using electronic healthcare records (cat. 3)	To assess compliance/adherence to the labeling with regard to DDI	Drug-drug interaction	Planned	Pilot study report Q3 2014 Annual reports starting 1 year after launch in EU Final report 4 years after launch

Study/activity Type, title and category (1-3)	Objectives	Safety concerns addressed	Status	Date for submission of interim or final reports
Drug utilisation study of eliglustat in the US population using the MarketScan database (cat. 3)	To assess compliance/adherence to the labeling with regard to DDI To assess compliance/adherence to the labeling with regard to genotyping assessment	Drug-drug interaction Use in CYP2D6 poor metabolisers, indeterminate metabolisers or non-genotyped patients Use in patients who are CYP2D6 ultra-rapid metabolisers	Planned	Annual reports starting 1 year after launch in US Final report 4 years after launch in US
Phase 2 open-label, uncontrolled study in patients with GD1 who were untreated or had not been treated in preceding 12 months (GZGD00304) (cat. 3)	To assess long-term safety	Safety in long-term treatment use	Ongoing	Aug 2016
Phase 3, randomised, double-blind, placebo-controlled study in patients with GD1 who were untreated or had not been treated in preceding 9 months (GZGD02507) (cat. 3)	To assess long-term safety	Safety in long-term treatment use	Ongoing	Jul 2016
Phase 3, randomised, open-label, active comparator study in patients with GD1 who achieved therapeutic goals with long-term ERT (GZGD02607) (cat. 3)	To assess long-term safety	Safety in long-term treatment use	Ongoing	Nov 2015
Phase 3 randomised, double-blind, study to evaluate QD vs BID dosing in patients with GD1 who demonstrate clinical stability on BID dosing (GZGD03109) (cat 3)	To assess long-term safety	Safety in long-term treatment use	Ongoing	Mar 2016
Aggregate report of adverse events from the studies GZGD00304, GZGD02507, GZGD02607, GZGD03109 (cat 3)	To assess long-term safety	Safety in long-term treatment use	Planned	Statistical Analysis Plan Q4 2015 Submission of final report Q4 2016

Risk minimisation measures

Safety concern	Routine risk minimisation activities	Additional risk minimisation activities
Important potential risks		
Drug-drug interaction: Use with CYP2D6 and/or CYP3A inhibitors– Use with strong CYP3A inducers – Use with P-gp or CYP2D6 substrates	SmPC: «4.3 Contraindication section» and «4.4 Special warnings and precautions for use section» mention that Cerdelga is contraindicated in IM and EM patients taking a strong or moderate CYP2D6 inhibitor concomitantly with a strong or moderate CYP3A inhibitor and in patients who are CYP2D6 poor metabolisers (PMs) taking a strong CYP3A inhibitor. «4.5 Interaction with other medicinal products and other forms of interaction section» provides additional information on other drug-drug interactions (concomitant use with strong CYP2D6 inhibitors, or strong and moderate or weak CYP3A inhibitors, or strong CYP3A inducers, or P-gp and 2D6 substrates	Guide for Prescriber Patient Alert Card
Use of eliglustat in patients who are indeterminate metabolisers or non-genotyped patients	SmPC : Therapeutic indication section and section 4.2 "Posology and method of administration" specify Gaucher patients who are eligible for Cerdelga; Section 5.2 "Pharmacokinetic properties" provides additional warning on patient's management based on phenotype	Guide for Prescriber
Cardiac conduction disorders and arrhythmias	SmPC : Section 4.4 "Special warnings and precautions for use" mentions that the use of Cerdelga should be avoided in patients with cardiac disease (congestive heart failure, recent acute myocardial infarction, bradycardia, heart block, ventricular arrhythmia), long QT syndrome, and in combination with Class IA (e.g. quinidine) and Class III (e.g. amiodarone, sotalol) antiarrhythmic medications	None proposed
Vasovagal Syncope	SmPC: Section 4.8 specifies that syncope were reported in clinical studies, associated with predisposing risk factors and that they appeared to be vasovagal in nature	None proposed
Off-label use in Gaucher disease type 2 and 3	SmPC: Therapeutic indication section specifies Gaucher patients who are eligible for Cerdelga	Guide for Prescriber
Peripheral neuropathy	None proposed	None proposed
Missing information		

Safety concern	Routine risk minimisation activities	Additional risk minimisation activities
Use in patients with high cardiovascular risk (history of or current cardiac ischaemia or heart failure, clinically significant arrhythmias or conduction findings)	SmPC: Section 4.4 "Special warnings and precautions for use" mentions that use of Cerdelga in patients with pre-existing cardiac conditions has not been studied during clinical trials	None proposed
Use in patients with hepatic impairment	SmPC: Section 4.2 "Posology and method of administration" mentions that Cerdelga has not been studied in patients with hepatic impairment and that no dose recommendations can be made	None proposed
Use in children	SmPC : Section 4.2 "Posology and method of administration" mentions that the safety and efficacy of Cerdelga in children under the age of 18 years has not been established.	None proposed
Use during pregnancy and lactation	SmPC: Section 4.6 "Fertility, pregnancy and lactation" informs that there are no or limited amount of data from the use of Cerdelga in pregnant and breast feeding women and that it is preferable to avoid the use of Cerdelga during pregnancy and breast feeding.	None proposed
Safety in long-term treatment use	None	None proposed
Use in patients who are CYP2D6 ultra-rapid metabolisers	SmPC : Therapeutic indication section and section 4.2 "Posology and method of administration" specify Gaucher patients who are eligible for Cerdelga; Section 5.2 "Pharmacokinetic properties" provides additional warning on patient's management based on phenotype	None proposed
Use in patients with renal impairment	SmPC : Section 4.2 "Posology and method of administration" mentions that Cerdelga has not been studied in patients with renal impairment and that no dose recommendations can be made	None proposed

2.9. Product information

2.9.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

3. Benefit-Risk Balance

Benefits

Beneficial effects

The effects of eliglustat were evaluated in three studies, a phase 2 study (GZGD00304) and 2 phases 3 ENCORE, ENGAGE. ENGAGE (placebo controlled study) and the Phase 2 open, non-controlled study were designed to assess the ability of eliglustat to improve clinical manifestations in treatment naïve patients, whereas ENCORE (open, imiglucerase controlled study) assessed the ability of eliglustat to maintain the clinical status of patients who had stabilized on ERT.

In *treatment-naïve patients (*ENGAGE), there was a statistically significant mean reduction in spleen volume between the eliglustat and placebo groups after 9 months (-30.03%; 95% CI -36.82 to -23.24; p <0.0001). Most (75%) of the eliglustat-treated patients achieved a clinically meaningful reduction of at least 20% in spleen volume compared to only 5% of placebo treated patients. In addition, all secondary endpoints showed statistically significant and clinically meaningful changes, including 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). In the open phase 2 study statistically significant improvements in all 4 organs volume and haematology parameters were observed at Week 52 and were maintained or continued to improve through Month 48.

In *patients switching from ERT (*ENCORE), the composite endpoint, indicating continuing stability of the patient (expressed as no change in liver, spleen, haemoglobin and platelet count), was maintained in 85% of patients in the eliglustat group and 94% in the imiglucerase group after 52 weeks of treatment. The lower bound of the 95% CI for the difference between treatment groups (-17.6%) was within the pre-specified by the applicant non-inferiority margin of -25%.

Other endpoints for both naïve and stabilized patients were: biomarkers (GL-1, GM3, ceramide, sphingomyelin), QoL and bone mineral density. These clinical measures represent the more common manifestations of GD that may be responsive to treatment in the short term, and have been investigated in previous studies of ERT or SRT in patients with GD1. The results obtained with these endpoints support the results observed for the primary endpoints and most important secondary endpoints.

Efficacy results were analysed by gender, age group, race, baseline disease severity, geographical location and GD genotype. Some small, clinically insignificant differences were noted in the studies. A population pharmacokinetic analysis using data from healthy subjects and GD1 patients showed that CYP2D6 phenotype (PM, IM, EM, or URM) was the most significant determinant of exposure to eliglustat.

Uncertainty in the knowledge about the beneficial effects.

Based on strict statistics, the unstratified Agresti-Caffo method in the ENCORE study has an inflated type I error, therefore does not fulfil the regulatory requirements. The CHMP considered that the statement that eliglustat is non-inferior to ERT (imiglucerase) was not comprehensively demonstrated. The SmPC was updated to mention the higher failure rate compared to ERT: the defined disease stability criterion in the composite endpoint including haemoglobin and platelet values and spleen and liver volumes was maintained in only 84.8% of patients on eliglustat compared to 94% on imiglucerase after 52 weeks of treatment. The secondary endpoints showed a similar trend. In practice this means that the majority of the patients can switch to eliglustat without loss of efficacy. A minority of patients (about 15%) does not remain stable on eliglustat and should receive alternative therapy.

The number of patients in the clinical development was 393. This relatively small number of patients exposed led to broad variations of the various endpoints and reduced the sensitivity of the studies. Notwithstanding this low sensitivity, statistically significant results were obtained for the primary endpoints.

The currently proposed fixed posology for IM and EM patients (100 mg BID) and PM patients (100 mg QD) is different from the exposure adjusted one used in pivotal studies and is based on popPK/PD studies for IMs/EMs and modelling of PBPK data for PMs. Further analysis in EM patients showed that the fixed dose regimen can be used without the risk of under treatment in the majority of the patients. Therefore, eliglustat is indicated in PM, IM and EM patients using a single dosing regimen of 100 mg BID (IM and EM patients) or 100 mg QD (PM patients).

Before initiation of treatment with Cerdelga, patients should be genotyped for CYP2D6 to determine the CYP2D6 metaboliser status. However, genotyping for CYP2D6 is generally available in the specialised centres that treat GD patients and the test can be performed in most hospitals.

Only about 3% of the GD population are URM and are excluded currently from the treatment with eliglustat. The efficacy in this subgroup can only be estimated by using PK modelling and *in vitro* studies and not by a direct interpretation of efficacy results. A higher dosage of 150 mg of eliglustat or more may be required as indicated by the observed plasma levels in these patients. Further data in URM patients are required to be provided post-marketing. This is reflected in the agreed RMP.

Risks

Unfavourable effects

The pooled Eliglustat Safety Set consists of 393 patients. In the pooled Eliglustat Safety Set, the mean (±SD) duration of treatment was 1.4 (±1.19) years, and the total duration was 535.0 patient-years. Overall, 334/393 of eliglustat-treated patients (85%) experienced a TEAE (2,340 events; 437 events per 100 person-years). The most frequent TEAEs (those occurring in ≥10% of all patients who received eliglustat) were: headache (17%), arthralgia (14%), nasopharyngitis (13%), upper respiratory tract infection (11%), diarrhoea (10%), and dizziness (10%). The proportions of patients with each of these events decreased over time.

Eliglustat is a substrate of CYP2D6, CYP3A4 and P-gp. Inhibition of these pathways may lead to a 9-fold increase in eliglustat exposure. Moreover, simultaneous inhibition of the CYP2D6 and 3A4 pathway may lead even up to a 25-fold increase in exposure, which may raise a safety concern. In addition, due to induction exposure may be about 95% decreased, which may lead to efficacy problems.

No unfavourable clinically relevant pharmacodynamic interactions were observed.

A Phase 1 Thorough QT study in healthy volunteers tested the effect of a single dose of 200 mg or 800 mg eliglustat on cardiac repolarization. The upper limit of the 95% confidence interval of the QTcF change from baseline did not exceed 10 msec at any time point at either the 200 mg or 800 mg dose, and therefore this study was considered negative according to the ICH E14 Guidance.

In the pooled Eliglustat Safety Set, no increase in the overall incidence of TEAEs was seen for patients identified as PM (79%) compared with patients identified as IM (73%). The proportions of patients in the poor and intermediate metabolizer groups who experienced TEAEs at any dose (79% and 73%, respectively) were lower than that observed for extensive metabolizers (88%).

Uncertainty in the knowledge about the unfavourable effects

Given eliglustat is an orphan medicinal product the overall safety database is small (N= 393) and the duration of treatment is short (one year) for most patients with a selected group generating 4 years

data. An adequate RMP to gain sufficient safety information after registration was agreed during the procedure.

The combination of bradycardia and adverse reactions like fatigue, cough, dizziness, syncope and oedema could be possibly related to a decreased cardiac output. Analysis of the available data indicates that a causal relation of the observed bradycardia and eliglustat could not be established. Further bradycardia was not associated with a decrease in cardiac output. No relation between various forms of arrhythmias and other conductive disorders and the use of eliglustat could be established.

Due to the lack of detailed information on patients with pre-existing cardiac conditions a warning in the SmPC section 4.4. was included to avoid treatment with eliglustat in patients with cardiac disease, long QT syndrome and in combination with class IA and III antiarrhythmic medicinal products.

The safety data in PMs are limited. Dose recommendation is based on popPK/PBPK analysis and further safety data from the sub-registry of ICGG and from the extension studies (ENGAGE, ENCORE and EDGE) are to be provided post-authorisation.

Benefit-risk balance

Importance of favourable and unfavourable effects

The main endpoints in pivotal studies were changes in liver and spleen volume, haemoglobin level and platelet count. Other endpoints were biomarkers (GL-1, GM3, ceramide, sphingomyelin), quality of life (QoL) and bone mineral density and these endpoints are considered “surrogate endpoints” for treatment although no formal relation with the clinical importance or patients perceived improvements was demonstrated.

In the phase 3 ENGAGE study, most (75%) of the treatment-naïve eliglustat-treated patients achieved a clinically meaningful reduction of at least 20% in spleen volume compared to only 5% of placebo treated patients. Comparable changes were observed in all secondary endpoints. In the open phase 2 study statistically significant improvements in all 4 organ volume and haematology parameters were observed at Week 52 and were maintained or continued to improve through Month 48.

In the phase 3 ENCORE study, the composite endpoint (indicating stabilisation) was maintained in 85% of patients in the eliglustat group and 94% in the imiglucerase group after 52 weeks of treatment. The lower bound of the 95% CI for the difference between treatment groups (-17.6%) was within the pre-specified non-inferiority margin of -25%, but not within the -20% non-inferiority margin, that was advised by CHMP via the scientific advice procedure, for all methods that may have been considered a reasonable choice for the primary analysis method at time of planning of the study. These findings were considered clinically important. Therefore, the CHMP considered that the statement that eliglustat is non-inferior to ERT (imiglucerase) has not been comprehensively demonstrated. However, the demonstrated superiority over placebo and the ease of the orally-administered treatment (as compared to ERT) justifies eliglustat as a first line treatment. Patients who fail to reach accepted treatment goals or maintain a stabilisation need to be identified and other treatment options should be considered. The SmPC gives a recommendation for the identification of the above mentioned patients. The reversibility of the deterioration in ERT stable patients further concur with this approach.

In study GZGD02607 (ENCORE) the majority of patients (48%) received eliglustat 150 mg BID. Therefore some concerns were raised regarding “under treatment” with the proposed fixed dosing of 100 mg BID. Analysis using the popPK/PD model showed that there is a relation between AUC and effect on spleen volume. Using this model it can be calculated that the loss of efficacy is clinically negligible in patients switching from 150 mg BID to 100 mg BID. This conclusion is justified by the actual data that do not show a difference between EM patients treated with 100 or 150 mg BID.

However, a considerable portion of patients falls outside the 95% CI of the popPK model, therefore the patients should be monitored closely and in case of deterioration other treatment options should be considered.

In most patients efficacy of eliglustat appears comparable to ERT, with a different safety profile, both in treatment-naïve patients and in patients switching from ERT. The oral route of administration for the eliglustat capsules can be considered more convenient than the iv administration of imiglucerase.

Safety profile was considered acceptable by the CHMP. The most frequent TEAEs (those occurring in ≥10% of all patients who received eliglustat) were: headache (17%), arthralgia (14%), nasopharyngitis (13%), upper respiratory tract infection (11%), diarrhoea (10%), and dizziness (10%). The proportions of patients with each of these events decreased over time.

There were no treatment-emergent deaths in the pooled Eliglustat Safety Set as of 31 January 2013. Across the programme, a total of 5 deaths were reported, and the events leading to the deaths were considered not related to eliglustat. A total of 42 SAEs have occurred in 35 patients (9%). The majority of SAEs reported were due to hospitalizations for intercurrent illnesses and underlying diseases for which Gaucher disease patients are at increased risk. SAEs occurring in more than one patient included myocardial infarction (4 patients) and syncope (5 patients). Number of discontinuations was low (3%).

A thorough QT/QTc study in healthy volunteers (GZGD01707) did not reveal clinically relevant prolongations of QT. There remains, however, a theoretical concern considering the combination of bradycardia and adverse reactions possibly related to a decreased cardiac output (fatigue, cough, dizziness, syncope and oedema). After analysis of the available data a causal relation of the observed bradycardia and eliglustat could not established. Further bradycardia was not associated with a decrease in cardiac output. No relation between various forms of arrhythmias and other conductive disorders and the use of eliglustat could be established.

Due to the lack of detailed information on patients with pre-existing cardiac conditions a warning was added to the SmPC.

Benefit-risk balance

The efficacy of eliglustat in the treatment of GD, both in treatment-naïve patients and patients who are switched from ERT has been demonstrated with clinically relevant effects. Eliglustat is generally well tolerated and its safety profile is considered acceptable.

Discussion on the benefit-risk balance

The CHMP considered that the statement that eliglustat is non-inferior to ERT (imiglucerase) was not comprehensively demonstrated. However the benefit-risk of eliglustat in treatment experienced patients is considered positive. The PI is updated to mention the somewhat higher failure rate compared to ERT and the percentages of patients meeting the primary composite endpoint on eliglustat and imiglucerase in the ENCORE study are reflected in the SmPC.

The majority of patients (48%) in the ENCORE study received eliglustat 150 mg BID. Based on an analysis using the popPK/PD model it can be calculated that the loss of efficacy is clinically negligible in most patients switching from 150 mg BID to 100 mg BID. This conclusion is justified by the actual data that do not show a difference in response between EM patients treated with 100 or 150 mg/ml.

However, still a considerable proportion of the patients (15%) showed sub-optimal clinical results (less than 20% improvement in treatment naïve patient) after nine months of treatment. For these patients an alternative treatment modality should be considered. For patients with stable disease who switch from ERT to eliglustat, close monitoring for disease progression (e.g. at least at 6 months

interval) should be performed for all disease domains to evaluate disease stability. In case of deterioration, reinstitution of ERT should be considered in line with a warning included in the SmPC.

The MAH also made a commitment to design a sub-registry for the follow-up of the patients.

4. Recommendations

Similarity with authorised orphan medicinal products

The CHMP by consensus is of the opinion that Cerdelga is not similar to Vpriv within the meaning of Article 3 of Commission Regulation (EC) No. 847/200.

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the risk-benefit balance of Cerdelga in the long-term treatment of adult patients with Gaucher disease type 1 (GD1), who are CYP2D6 poor metabolisers (PMs), intermediate metabolisers (IMs) or extensive metabolisers (EMs) is favourable and therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

Conditions and requirements of the Marketing Authorisation

- **Periodic Safety Update Reports**

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation. Subsequently, the marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Risk Management Plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreeed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time.

- **Additional risk minimisation measures**

Prior to launch of Cerdelga in each Member State the Marketing Authorisation Holder (MAH) must agree the content and format of the educational programme, including communication media, distribution modalities, and any other aspects of the programme, with the National Competent Authority.

The MAH shall ensure that in each Member State where Cerdelga is marketed, all healthcare professionals who are expected to prescribe Cerdelga are provided with a prescriber guide.

The prescriber guide shall contain the following key elements:

o Cerdelga is indicated for the long-term treatment of adult patients with Gaucher disease type 1 (GD1). ***It is not intended to be used*** in patients with Gaucher disease type 2 or type 3 (GD2 or GD3).

o Before initiation of treatment with Cerdelga, patients should be genotyped for CYP2D6 to determine the CYP2D6 metaboliser status. Cerdelga is indicated in patients who are CYP2D6 poor metabolisers (PMs), intermediate metabolisers (IMs) or extensive metabolisers (EMs).

o The recommended dose is 84 mg eliglustat twice daily in CYP2D6 intermediate metabolisers (IMs) and extensive metabolisers (EMs). The recommended dose is 84 mg eliglustat once daily in CYP2D6 poor metabolisers (PMs).

o Patients should be informed that consumption of grapefruit or its juice should be avoided

o Eliglustat is contraindicated in patients who are CYP2D6 Intermediate Metabolisers or Extensive Metabolisers who are taking a strong or moderate CYP2D6 inhibitor concomitantly with a strong or moderate CYP3A inhibitor. Eliglustat is also contraindicated in patients who are CYP2D6 poor metabolisers taking a strong CYP3A inhibitor. Use of eliglustat under these conditions results in substantially elevated plasma concentrations of eliglustat. This may cause mild increases in the PR, QRS, and QTc intervals.

o Use of eliglustat with strong CYP3A inducers substantially decreases the exposure to eliglustat, which may reduce the therapeutic effectiveness; therefore concomitant administration is not recommended.

The MAH shall ensure that in each Member State where Cerdelga is marketed, all patients who are prescribed Cerdelga are provided with a patient alert card. The patient alert card shall contain the following key elements:

Information for healthcare professionals:

o This patient is using eliglustat (Cerdelga) for the treatment of Gaucher Disease type 1.

o Eliglustat should not be used concomitantly with medicines that may have an impact on liver enzymes that play a role in the metabolism of eliglustat.

o Using eliglustat together with such products may either make eliglustat less effective, or it may increase the eliglustat levels in the patient's blood.

Information for the patient:

o Always consult the doctor who prescribed eliglustat before you start using other medicines

o Do not consume grapefruit products.

- **Obligation to complete post-authorisation measure**

The MAH shall complete, within the stated timeframe, the below measure:

Description	Due date
In order to investigate the long-term safety of eliglustat in patients prescribed eliglustat, the MAH is to create a sub-registry to the International Collaborative Gaucher Group (ICGG) Gaucher Registry to collect safety data according to an agreed protocol.	Reports from the sub-registry are to be submitted with each PSUR.

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States.

Not applicable.

New Active Substance Status

Based on the CHMP review of data on the quality properties of the active substance, the CHMP considers that eliglustat (as tartrate) is qualified as a new active substance.