SUMMARY OF PRODUCT CHARACTERISTICS

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1 NAME OF THE MEDICINAL PRODUCT

Cerdelga 84 mg hard capsules

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains 84.4 mg of eliglustat (as tartrate).

Excipient(s) with known effect:
Each capsule contains 106 mg of lactose (as monohydrate).

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Hard capsule

Capsule with pearl blue-green opaque cap and pearl white opaque body with "GZ02" printed in black on the body of the capsule. The size of the capsule is 'size 2' (dimensions 18 x 6.4 mm).

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Adults
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).

Paediatric population (from 6 to <18 years of age) weighing ≥15 kg
Cerdelga is indicated for paediatric patients with GD1 who are 6 years and older with a minimum body weight of 15 kg, who are stable on enzyme replacement therapy (ERT), and who are CYP2D6 PMs, IMs or EMs.

4.2 Posology and method of administration

Therapy with Cerdelga should be initiated and supervised by a physician knowledgeable in the management of Gaucher disease.

Patient selection
Before initiation of treatment with Cerdelga, patients must be genotyped for CYP2D6 to determine the CYP2D6 metaboliser status.

Eliglustat should not be used in patients who are CYP2D6 ultra-rapid metabolisers (URMs) or indeterminate metabolisers (see section 4.4).

Posology

Adults
The recommended dose is 84 mg eliglustat twice daily in CYP2D6 IMs and EMs.
The recommended dose is 84 mg eliglustat once daily in CYP2D6 PMs.

Paediatric population (from 6 to <18 years of age) weighing ≥15 kg
Table 1: Paediatric population (from 6 to <18 years of age) weighing ≥15 kg

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

Cerdelga is to be taken orally in children who can swallow the intact capsule.

Missed dose
If a dose is missed, the prescribed dose should be taken at the next scheduled time; the next dose should not be doubled.

Special populations

Elderly
There is limited experience in the treatment of elderly with eliglustat. Data indicates that no dose adjustment is considered necessary (see sections 5.1 and 5.2).

Patients with hepatic impairment
Table 2: Patients with hepatic impairment

CYP2D6 metaboliser type	Hepatic Impairment	Inhibitors	Dose Adjustment
EM	Mild (Child-Pugh Class A)	Eliglustat alone	No dose adjustment required
	Moderate (Child-Pugh Class B)	Eliglustat alone	Not recommended (see section 5.2)
	Severe (Child-	Eliglustat alone	Contraindicated

	Pugh Class C)	Eliglustat + Any CYP inhibitor	(see sections 4.3 and 5.2)
	Mild (Child-Pugh Class A) or moderate (Child-Pugh Class B)	Eliglustat + strong or moderate inhibitor of CYP2D6	Contraindicated (see sections 4.3 and 5.2)
	Mild (Child-Pugh Class A)	Eliglustat + weak inhibitor of CYP2D6; or strong, moderate or weak inhibitor of CYP3A	Once daily dose should be considered (see sections 4.4 and 5.2)
IM or PM	Any	N/A	Not recommended (see section 5.2)

Patients with renal impairment
Table 3: Patients with renal impairment

CYP2D6 metaboliser type	**Renal Impairment**	**Dose Adjustment**
EM	Mild, moderate or severe	No dose adjustment required (see sections 4.4 and 5.2)
	End stage renal disease (ESRD)	Not recommended (see sections 4.4 and 5.2)
IM or PM	Mild, moderate or severe, or ESRD	Not recommended (see sections 4.4 and 5.2)

Paediatric population (<6 years of age) weighing <15 kg
Safety and efficacy data of eliglustat are limited in paediatric patients below the age of 6 years. There are no data to support the use of eliglustat in children weighing less than 15 kg. Currently available data are described in section 5.1.

Method of administration
Cerdelga is to be taken orally. The capsules should be swallowed whole, preferably with water, and must not be crushed or dissolved.

The capsules may be taken with or without food. Consumption of grapefruit or its juice should be avoided (see section 4.5).

Mixing the content of the capsule (eliglustat powder) into food or drinks has not been studied.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Cerdelga is contraindicated in patients who are CYP2D6 IMs or EMs taking a strong or moderate CYP2D6 inhibitor concomitantly with a strong or moderate CYP3A inhibitor, and patients who are CYP2D6 PMs taking a strong CYP3A inhibitor (see section 4.5).

Cerdelga is contraindicated in CYP2D6 EMs with severe hepatic impairment and in CYP2D6 EMs with mild or moderate hepatic impairment taking a strong or moderate CYP2D6 inhibitor (see sections 4.2 and 5.2).

4.4 Special warnings and precautions for use

Patients with pre-existing cardiac conditions
Use of eliglustat in patients with pre-existing cardiac conditions has not been studied during clinical trials. Because eliglustat is predicted to cause mild increases in ECG intervals at substantially elevated plasma concentrations, use of eliglustat 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 medicinal products.

Patients with hepatic impairment and concomitant use with other medicinal products
Concomitant use of eliglustat with CYP2D6 or CYP3A4 inhibitors in CYP2D6 EMs with mild hepatic impairment can result in further elevation of eliglustat plasma concentrations, with the magnitude of the effect depending on the enzyme inhibited and the potency of the inhibitor. In CYP2D6 EMs with mild hepatic impairment taking a weak CYP2D6 inhibitor or strong, moderate or weak CYP3A inhibitor, a once daily dose is recommended (e.g. if a dose of 84 mg eliglustat is taken twice daily, it should be adjusted to 84 mg eliglustat once daily) (see sections 4.2 and 5.2).

Patients with renal impairment
Limited or no data are available in CYP2D6 EMs, IMs or PMs with ESRD and in CYP2D6 IMs or PMs with mild, moderate, or severe renal impairment; use of eliglustat in these patients is not recommended (see sections 4.2 and 5.2).

Monitoring of clinical response
Some treatment-naïve patients showed less than 20% spleen volume reduction (sub-optimal results) after 9 months of treatment (see section 5.1). For these patients, monitoring for further improvement or an alternative treatment modality should be considered.

For patients with stable disease who switch from enzyme replacement therapy to eliglustat, monitoring for disease progression (e.g. after 6 months with regular monitoring thereafter) should be performed for all disease domains to evaluate disease stability. Reinstitution of enzyme replacement therapy or an alternative treatment modality should be considered in individual patients who have a sub-optimal response.

Lactose
Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

Eliglustat is metabolised primarily by CYP2D6 and to a lesser extent by CYP3A4. Concomitant administration of substances affecting CYP2D6 or CYP3A4 activity may alter eliglustat plasma concentrations. Eliglustat is an inhibitor of P-gp and CYP2D6 *in vitro;* concomitant administration of eliglustat with P-gp or CYP2D6 substrate substances may increase the plasma concentration of those substances.

The list of substances in section 4.5 is not an inclusive list and the prescriber is advised to consult the SmPC of all other prescribed medicinal products for potential drug-drug interactions with eliglustat.

Agents that may increase eliglustat exposure

Cerdelga is contraindicated in patients who are CYP2D6 IMs or EMs taking a strong or moderate CYP2D6 inhibitor concomitantly with a strong or moderate CYP3A inhibitor, and in patients who are CYP2D6 PMs taking a strong CYP3A inhibitor (see section 4.3). Use of eliglustat under these conditions results in substantially elevated eliglustat plasma concentrations.

CYP2D6 inhibitors in IMs and EMs
After repeated 84 mg twice daily doses of eliglustat in non-PMs, concomitant administration with repeated 30 mg once daily doses of paroxetine, a strong inhibitor of CYP2D6, resulted in a 7.3- and 8.9-fold increase in eliglustat C_{max} and AUC_{0-12}, respectively. Once a day dosing of eliglustat for EMs and IMs is recommended when a strong CYP2D6 inhibitor (e.g. paroxetine, fluoxetine, quinidine, bupropion) is used concomitantly in IMs and EMs.

At 84 mg twice daily dosing with eliglustat in non-PMs, it is predicted that concomitant use of moderate CYP2D6 inhibitors (e.g. duloxetine, terbinafine, moclobemide, mirabegron, cinacalcet, dronedarone) would increase eliglustat exposure approximately up to 4-fold. Caution should be used with moderate CYP2D6 inhibitors in IMs and EMs.

CYP2D6 inhibitors in EMs with mild or moderate hepatic impairment
See sections 4.2, 4.3 and 4.4.

CYP2D6 inhibitors in EMs with severe hepatic impairment
See sections 4.2 and 4.3.

CYP3A inhibitors in IMs and EMs
After repeated 84 mg twice daily doses of eliglustat in non-PMs, concomitant administration with repeated 400 mg once daily doses of ketoconazole, a strong inhibitor of CYP3A, resulted in a 3.8 and 4.3-fold increase in eliglustat C_{max} and AUC_{0-12}, respectively; similar effects would be expected for other strong inhibitors of CYP3A (e.g. clarithromycin, ketoconazole, itraconazole, cobicistat,

indinavir, lopinavir, ritonavir, saquinavir, telaprevir, tipranavir, posaconazole, voriconazole, telithromycin, conivaptan, boceprevir). Caution should be used with strong CYP3A inhibitors in IMs and EMs.

At 84 mg twice daily dosing with eliglustat in non-PMs, it is predicted that concomitant use of moderate CYP3A inhibitors (e.g. erythromycin, ciprofloxacin, fluconazole, diltiazem, verapamil, aprepitant, atazanavir, darunavir, fosamprenavir, imatinib, cimetidine) would increase eliglustat exposure approximately up to 3-fold. Caution should be used with moderate CYP3A inhibitors in IMs and EMs.

CYP3A inhibitors in EMs with mild hepatic impairment
See sections 4.2 and 4.4.

CYP3A inhibitors in EMs with moderate or severe hepatic impairment
See sections 4.2 and 4.3.

CYP3A inhibitors in PMs
At 84 mg once daily dosing with eliglustat in PMs, it is predicted that concomitant use of strong CYP3A inhibitors (e.g. ketoconazole, clarithromycin, itraconazole, cobicistat, indinavir, lopinavir, ritonavir, saquinavir, telaprevir, tipranavir, posaconazole, voriconazole, telithromycin, conivaptan, boceprevir) would increase the C_{max} and AUC_{0-24} of eliglustat 4.3- and 6.2-fold. The use of strong CYP3A inhibitors is contraindicated in PMs.

At 84 mg once daily dosing with eliglustat in PMs, it is predicted that concomitant use of moderate CYP3A inhibitors (e.g. erythromycin, ciprofloxacin, fluconazole, diltiazem, verapamil, aprepitant, atazanavir, darunavir, fosamprenavir, imatinib, cimetidine) would increase the C_{max} and AUC_{0-24} of eliglustat 2.4- and 3.0-fold, respectively. Use of a moderate CYP3A inhibitor with eliglustat is not recommended in PMs.

Caution should be used with weak CYP3A inhibitors (e.g. amlodipine, cilostazol, fluvoxamine, goldenseal, isoniazid, ranitidine, ranolazine) in PMs.

CYP2D6 inhibitors used simultaneously with CYP3A inhibitors in IMs and EMs
At 84 mg twice daily dosing with eliglustat in non-PMs, it is predicted that the concomitant use of strong or moderate CYP2D6 inhibitors and strong or moderate CYP3A inhibitors would increase C_{max} and AUC_{0-12} up to 17- and 25-fold, respectively. The use of a strong or moderate CYP2D6 inhibitor concomitantly with a strong or moderate CYP3A inhibitor is contraindicated in IMs and EMs.

Grapefruit products contain one or more components that inhibit CYP3A and can increase plasma concentrations of eliglustat. Consumption of grapefruit or its juice should be avoided.

<u>Agents that may decrease eliglustat exposure</u>

Strong CYP3A inducers

After repeated 127 mg twice daily doses of eliglustat in non-PMs, concomitant administration of repeated 600 mg once daily doses of rifampicin (a strong inducer of CYP3A as well as the efflux transporter P-gp) resulted in an approximately 85% decrease in eliglustat exposure. After repeated 84 mg twice daily doses of eliglustat in PMs, concomitant administration of repeated 600 mg once daily doses of rifampicin resulted in an approximately 95% decrease in eliglustat exposure. Use of a strong CYP3A inducer (e.g. rifampicin, carbamazepine, phenobarbital, phenytoin, rifabutin and St. John's wort) with eliglustat is not recommended in IMs, EMs and PMs.

Agents whose exposure may be increased by eliglustat

P-gp substrates
After a single 0.25 mg dose of digoxin, a P-gp substrate, concomitant administration of 127 mg twice daily doses of eliglustat resulted in a 1.7- and 1.5-fold increase in digoxin C_{max} and AUC_{last}, respectively. Lower doses of substances which are P-gp substrates (e.g. digoxin, colchicine, dabigatran, phenytoin, pravastatin) may be required.

CYP2D6 substrates
After a single 50 mg dose of metoprolol, a CYP2D6 substrate, concomitant administration of repeated 127 mg twice daily doses of eliglustat resulted in a 1.5- and 2.1-fold increase in metoprolol C_{max} and AUC, respectively. Lower doses of medicinal products that are CYP2D6 substrates may be required. These include certain antidepressants (tricyclic antidepressants, e.g. nortriptyline, amitriptyline, imipramine, and desipramine), phenothiazines, dextromethorphan and atomoxetine).

4.6 Fertility, pregnancy and lactation

Pregnancy
There are no or limited amount of data from the use of eliglustat in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity (see section 5.3). As a precautionary measure, it is recommended to avoid the use of Cerdelga during pregnancy.

Breast-feeding
It is unknown whether eliglustat metabolites are excreted in human milk. Available pharmacodynamic/toxicological data in animals have shown excretion of eliglustat in milk (see section 5.3). A risk to the newborns/infants cannot be excluded. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from Cerdelga therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

Fertility
Effects on testes and reversible inhibition of spermatogenesis were observed in rats (see section 5.3). The relevance of these findings for humans is not known.

4.7 Effects on ability to drive and use machines

Cerdelga may affect the ability to drive and use machines in patients who experience dizziness after its administration.

4.8 Undesirable effects

Summary of the safety profile

The most frequently reported adverse reaction with eliglustat is dyspepsia, reported in approximately 6% of the pooled adult clinical trial patients, and in 10.5% (for both cohorts) of paediatric patients from the ELIKIDS study. Overall, the safety profile of eliglustat in paediatric patients observed in clinical development setting was consistent with the established safety profile in adults.

Tabulated list of adverse reactions
Adverse reactions are ranked by system organ class and frequency ([very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000)]). Adverse reactions from long term clinical trial data reported in at least 4 patients are presented in Table 4. Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Table 4: Tabulated list of adverse reactions

System organ class	**Common**
Nervous system disorders	Headache*, dizziness*, dysgeusia
Cardiac disorders	Palpitations
Respiratory, thoracic and mediastinal disorders	Throat irritation, cough
Gastrointestinal disorders	Dyspepsia, abdominal pain upper*, diarrhoea*, nausea, constipation, abdominal pain*, gastroesophageal reflux disease, abdominal distension*, gastritis, dysphagia, vomiting*, dry mouth, flatulence
Skin and subcutaneous tissue disorders	Dry skin, urticaria*
Musculoskeletal and connective tissue disorders	Arthralgia, pain in extremity*, back pain*
General disorders and administration site conditions	Fatigue

* The incidence of the adverse reaction was the same or higher with placebo than with eliglustat in the placebo-controlled pivotal study.

Paediatric population
In the ELIKIDS paediatric study Cohort 1 (eliglustat monotherapy), the most common adverse reactions were dyspepsia (9.8%) and dry skin (3.6%). In Cohort 2 (eliglustat/imiglucerase combination therapy), the most common adverse reactions were headache, dyspepsia, gastritis, and fatigue (each

experienced by 16.7% (1/6) of the patients). Of 57 enrolled patients 53 (93%, 48/51 in Cohort 1) experienced at least one treatment-emergent adverse event (TEAE) with no meaningful difference by age group, gender, or GD type. No patients permanently discontinued treatment due to TEAE.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme at: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

The highest eliglustat plasma concentration observed to date occurred in a Phase 1 single-dose dose escalation study in healthy subjects, in a subject taking a dose equivalent to approximately 21 times the recommended dose for GD1 patients. At the time of the highest plasma concentration (59-fold higher than normal therapeutic conditions), the subject experienced dizziness marked by disequilibrium, hypotension, bradycardia, nausea, and vomiting.

In the event of acute overdose, the patient should be carefully observed and given symptomatic treatment and supportive care.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Other alimentary tract and metabolism products, various alimentary tract and metabolism products, ATC code: A16AX10.

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.

Pharmacodynamic effects
In clinical trials in treatment-naïve GD1 patients, plasma GL-1 levels were elevated in the majority of these patients and decreased upon eliglustat treatment. Additionally, in a clinical trial in GD1 patients stabilised on enzyme replacement therapy (ERT) (i.e. having already achieved therapeutic goals on ERT prior to initiating eliglustat treatment), plasma GL-1 levels were normal in most patients and decreased upon eliglustat treatment.

Clinical efficacy and safety

The recommended dosing regimens (see section 4.2) are based on modelling, either of PK/PD data from the dose-titration regimens applied in the clinical studies for IMs and EMs, or physiologically-based PK data for PMs.

Pivotal study of eliglustat in treatment-naïve GD1 patients – study 02507(ENGAGE)

Study 02507 was a randomized, double-blind, placebo-controlled, multicentre clinical study in 40 patients with GD1. In the eliglustat group 3 (15%) patients received a starting dose of 42 mg eliglustat twice daily during the 9-month primary analysis period and 17 (85%) patients received a dose escalation to 84 mg twice daily based on plasma trough concentration.

Table 5: Change from baseline to month 9 (primary analysis period) in treatment-naïve patients with GD1 receiving treatment with eliglustat in study 02507

		Placebo* (n=20) [a]	Eliglustat (n=20) [a]	Difference (Eliglustat – Placebo) [95% CI]	p value[b]
Percentage change in spleen volume MN (%) (primary endpoint)		2.26	-27.77	-30.0 [-36.8, -23.2]	<0.0001
Absolute change in haemoglobin level (secondary endpoint)	(g/dL)	-0.54	0.69	1.22 [0.57, 1.88]	0.0006
	(mmol/L)	-0.34	0.43	0.76 [0.35, 1.17]	
Percentage change in liver volume MN (%) (secondary endpoint)		1.44	-5.20	-6.64 [-11.37, -1.91]	0.0072
Percentage change in platelet count (%) (secondary endpoint)		-9.06	32.00	41.06 [23.95, 58.17]	<0.0001

MN = Multiples of Normal, CI = confidence interval

[a] At baseline, mean spleen volumes were 12.5 and 13.9 MN in the placebo and eliglustat groups, respectively, and mean liver volumes were 1.4 MN for both groups. Mean haemoglobin levels were 12.8 g/dL (7.954 mmol/L) and 12.1 g/dL (7.51 mmol/L), and platelet counts were 78.5 and 75.1 x 10^9/L, respectively.

[b] Estimates and p-values are based on an ANCOVA model

* All patients transitioned to eliglustat treatment after month 9.

During the open-label long term treatment period with eliglustat (extension phase), all patients with complete data who continued to receive eliglustat showed further improvements throughout the extension phase. Results (change from baseline) after 18 months, 30 months and 4.5 years of exposure to eliglustat on the following endpoints were: absolute change in haemoglobin level 1.1 g/dL (1.03) [0.68 mmol/L (0.64); n=39], 1.4 g/dL (0.93) [0.87 mmol/L (0.58); n=35], and 1.4 g/dL (1.31) [0.87 mmol/L (0.81); n=12]; mean increase in platelet count (mm^3) 58. 5% (40.57%) [n=39], 74.6% (49.57%) [n=35], and 86.8% (54.20%) [n=12]; mean reduction in spleen volume (MN)

46.5% (9.75%) [n=38], 54.2% (9.51%) [n=32], and 65.6% (7.43%) [n=13]; and mean reduction in liver volume (MN) 13.7% (10.65%) [n=38], 18.5% (11.22%) [n=32], and 23.4% (10.59%) [n=13].

Long-term clinical outcomes in treatment-naïve GD1 patients – study 304
Study 304 was a single-arm, open-label, multicentre study of eliglustat in 26 patients of which 19 completed 4 years of treatment. Of these patients, 15 (79%) received a dose escalation to 84 mg eliglustat twice daily; 4 (21%) patients continued to receive 42 mg twice daily.

In the study, 18 patients completed 8 years of treatment. Of these 18 patients, one (6%) received a further dose escalation to 127 mg twice daily; 14 (78%) continued on 84 mg eliglustat twice daily; 3 (17%) patients continued to receive 42 mg twice daily. At year 8, 16 patients had an efficacy endpoint assessment.

Eliglustat showed sustained improvements in organ volume and haematological parameters over the 8 year treatment period (see Table 6).

Table 6: Change from baseline to year 8 in study 304

		N	Baseline value (Mean)	Change from baseline (Mean)	Standard deviation
Spleen volume (MN)		15	17.34	-67.9%	17.11
Haemoglobin level	(g/dL)	16	11.33	2.08	1.75
	(mmol/L)		7.04	1.29	1.09
Liver volume (MN)		15	1.60	-31.0%	13.51
Platelet count ($x10^9$/L)		16	67.53	109.8%	114.73

MN = Multiples of Normal

Pivotal study of eliglustat in GD1 patients switching from ERT– Study 02607 (ENCORE)
Study 02607 was a randomized, open-label, active-controlled, non-inferiority, multicentre clinical study in 159 patients previously stabilised with ERT. In the eliglustat group 34 (32%) patients received a dose escalation to 84 mg eliglustat twice daily and 51 (48%) to 127 mg twice daily during the 12-month primary analysis period, and 21 (20%) patients continued to receive 42 mg twice daily.

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. After 12 months of treatment, the percentage of patients meeting the primary composite endpoint (composed of all four components mentioned in Table 7) 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. Of the patients who did not meet stability criteria for the individual components, 12 of 15 eliglustat patients and 3 of 3 imiglucerase patients remained within therapeutic goals for GD1.

There were no clinically meaningful differences between groups for any of the four individual disease parameters (see Table 7).

Table 7: Changes from baseline to month 12 (primary analysis period) in patients with GD1 switching to eliglustat in study 02607

		Imiglucerase (N=47)** Mean [95% CI]	Eliglustat (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]
	(mmol/L)	0.024 [-0.099, 0.14]	-0.13 [-0.22, -0.043]
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.
** All patients transitioned to Eliglustat treatment after 52 weeks
[a] The stability criteria based on changes between baseline and 12 months: haemoglobin level ≤1.5 g/dL (0.93 mmol/L) decrease, platelet count ≤25% decrease, liver volume ≤20% increase, and spleen volume ≤25% increase.
All patient number (N)= Per Protocol Population

During the open-label long term treatment period with eliglustat (extension phase) the percentage of patients with complete data meeting the composite stability endpoint was maintained at 84.6% (n=136) after 2 years, 84.4% (n=109) after 3 years and 91.1% (n=45) after 4 years. The majority of extension phase discontinuations were due to transition to commercial product from year 3 onwards. Individual disease parameters of spleen volume, liver volume, haemoglobin levels and platelet count remained stable through 4 years (see Table 8).

Table 8: Changes from month 12 (primary analysis period) to month 48 in patients with GD1 in the long-term treatment period on eliglustat in study 02607

		Year 2		Year 3		Year 4	
		Imiglucerase/ Eliglustat[a] Mean [95% CI]	Eliglustat[b] Mean [95% CI])	Imiglucerase/ Eliglustat[a] Mean [95% CI]	Eliglustat[b] Mean [95% CI]	Imiglucerase/ Eliglustat[a] Mean [95% CI]	Eliglustat[b] Mean [95% CI]
Patients at start of year (N)		51	101	46	98	42	96
Patients at end of year (N)		46	98	42	96	21	44
Patients with available data (N)		39	97	16	93	3	42
Spleen volume							
Patients with stable spleen volume (%)*		31/33 (93.9) [0.798, 0.993]	69/72 (95.8) [0.883, 0.991]	12/12 (100.0) [0.735, 1.000]	65/68 (95.6) [0.876, 0.991]	2/2 (100.0) [0.158, 1.000]	28/30 (93.3) [0.779, 0.992]
Change in spleen volume MN (%)*		-3.946[-8.80, 0.91]	-6.814[-10.61, -3.02]	-10.267[-20.12, -0.42]	-7.126[-11.70, -2.55]	-27.530[-89.28, 34.22]	-13.945[-20.61, -7.28]
Haemoglobin level							
Patients with stable haemoglobin level (%)		38/39 (97.4) [0.865, 0.999]	95/97 (97.9) [0.927, 0.997]	16/16 (100.0) [0.794, 1.000]	90/93 (96.8) [0.909, 0.993]	3/3 (100.0) (0.292, 1.000]	42/42 (100.0) [0.916, 1.000]
Change from baseline in haemoglobin level	(g/dL)	0.034[-0.31, 0.38]	-0.112[-0.26, 0.04]	0.363[-0.01, 0.74]	-0.103[-0.27, 0.07]	0.383[-1.62, 2.39]	0.290[0.06, 0.53]
	(mmol/L)	.0.021[-0.19, 0.24]	-0.077[-0.16, 0.025]	0.23[-0.006, 0.46]	-0.064[-0.17, 0.043]	0.24 [-1.01, 1.48]	.0.18 [0.0374, 0.33]
Liver volume							
Patients with stable liver volume (%)		38/39 (97.4) (0.865, 0.999)	94/97 (96.9) (0.912, 0.994)	15/16 (93.8) [0.698, 0.998]	87/93 (93.5) (0.865, 0.976)	3/3 (100.0) [0.292, 1.000]	40/42 (95.2) [0.838, 0.994]
Change from baseline in liver volume MN (%)		0.080[-3.02, 3.18]	2.486[0.50, 4.47]	-4.908[-11.53, 1.71]	3.018[0.52, 5.52]	-14.410[-61.25, 32.43]	-1.503[-5.27, 2.26]
Platelet count							
Patients with stable platelet count (%)		33/39 (84.6) [0.695, 0.941]	92/97 (94.8) [0.884, 0.983]	13/16 (81.3) [0.544, 0.960]	87/93 (93.5) [0.865, 0.976]	3/3 (100.0) [0.292, 1.000]	40/42 (95.2) [0.838, 0.994]
Change in platelet count (%)		-0.363[-6.60, 5.88]	2.216[-1.31, 5.74]	0.719[-8.20, 9.63]	5.403[1.28, 9.52]	-0.163[-35.97, 35.64]	7.501[1.01, 13.99]
Composite stability endpoint							
Patients who are stable on eliglustat (%)		30/39 (76.9) [0.607, 0.889]	85/97 (87.6) [0.794, 0.934]	12/16 (75.0) [0.476, 0.927]	80/93 (86.0) [0.773, 0.923]	3/3 (100.0) [0.292, 1.000]	38/42 (90.5) [0.774, 0.973]

MN = Multiples of Normal, CI = confidence interval

* Excludes patients with a total splenectomy.

a Imiglucerase/Eliglustat - Originally randomised to imiglucerase

b Eliglustat - Originally Randomised to eliglustat

Clinical experience in CYP2D6 PMs and URMs
There is limited experience with eliglustat treatment of patients who are PMs or URMs. In the primary analysis periods of the three clinical studies, a total of 5 PMs and 5 URMs were treated with eliglustat. All PMs received 42 mg eliglustat twice daily, and four of these (80%) had an adequate clinical response. The majority of URMs (80%) received a dose escalation to 127 mg eliglustat twice daily, all of which had adequate clinical responses. The one URM who received 84 mg twice daily did not have an adequate response.

The predicted exposures with 84 mg eliglustat once daily in patients who are PMs are expected to be similar to exposures observed with 84 mg eliglustat twice daily in CYP2D6 IMs. Patients who are URMs may not achieve adequate concentrations to achieve a therapeutic effect. No dosing recommendation for URMs can be given.

Effects on skeletal pathology
After 9 months of treatment, in Study 02507, bone marrow infiltration by Gaucher cells, as determined by the total Bone Marrow Burden (BMB) score (assessed by MRI in lumbar spine and femur) decreased by a mean of 1.1 points in eliglustat treated patients (n=19) compared to no change in patients receiving placebo (n=20). Five eliglustat-treated patients (26%) achieved a reduction of at least 2 points in the BMB score.

After 18 and 30 months of treatment, BMB score had decreased by a mean 2.2 points (n=18) and 2.7 (n=15), respectively for the patients originally randomised to eliglustat, compared to a mean decrease of 1 point (n=20) and 0.8 (n=16) in those originally randomised to placebo.

After 18 months of eliglustat treatment in the open-label extension phase, the mean (SD) lumbar spine Bone Mineral Density T-score increased from -1.14 (1.0118) at Baseline (n=34) to -0.918 (1.1601) (n=33) in the normal range. After 30 months and 4.5 years of treatment, the T-score further increased to -0.722 (1.1250) (n=27) and -0.533 (0.8031) (n=9), respectively.

Results of study 304 indicate that skeletal improvements are maintained or continue to improve during at least 8 years of treatment with eliglustat.

In study 02607, lumbar spine and femur BMD T- and Z-scores were maintained within the normal range in patients treated with eliglustat for up to 4 years.

Electrocardiographic evaluation
No clinically significant QTc prolonging effect of eliglustat was observed for single doses up to 675 mg.

Heart-rate corrected QT interval using Fridericia's correction (QTcF) was evaluated in a randomized, placebo and active (moxifloxacin 400 mg) controlled cross-over, single-dose study in 47 healthy subjects. In this trial with demonstrated ability to detect small effects, the upper bound of the one-

sided 95% confidence interval for the largest placebo-adjusted, baseline-corrected QTcF was below 10 msec, the threshold for regulatory concern. While there was no apparent effect on heart rate, concentration-related increases were observed for the placebo corrected change from baseline in the PR, QRS, and QTc intervals. Based on PK/PD modelling, eliglustat plasma concentrations 11-fold the predicted human C_{max} are expected to cause mean (upper bound of the 95% confidence interval) increases in the PR, QRS, and QTcF intervals of 18.8 (20.4), 6.2 (7.1), and 12.3 (14.2) msec, respectively.

Elderly

A limited number of patients aged 65 years (n=10) and over were enrolled in clinical trials. No significant differences were found in the efficacy and safety profiles of elderly patients and younger patients.

Paediatric population

Paediatric patients (2 to <18 years of age)

Study EFC13738 (ELIKIDS) is an ongoing Phase 3, open-label, two-cohort, multicentre study to evaluate the safety and pharmacokinetics (PK) of eliglustat alone (Cohort 1) or in combination with imiglucerase (Cohort 2) in paediatric patients aged 2 to less than 18 years old with GD1 and GD3. Cohort 1 enrolled GD1 and GD3 patients who were receiving ERT for at least 24 months and reached prespecified therapeutic goals with respect to their haemoglobin level (ages 2 to <12 years: ≥11.0 g/dL (6.827 mmol/L); for ages 12 to <18 years: ≥11.0 g/dL (6.827 mmol/L) for females and ≥12.0 g/dL (7.452 mmol/L) for males), platelet count (≥100,000/mm^3), and spleen volume (<10.0 MN) and liver volume (<1.5 MN), and had absence of Gaucher-related pulmonary disease, severe bone disease, or persistent thrombocytopenia. Cohort 2 enrolled GD1 and GD3 patients who, despite ongoing treatment with ERT for ≥36 months, were having at least one severe clinical manifestation of GD (e.g. pulmonary disease, symptomatic bone disease, or persistent thrombocytopenia).

There were 51 patients in Cohort 1 (n=46 GD1 and n=5 GD3) and 6 in Cohort 2 (n=3 GD1 and n=3 GD3). Patients were dosed according to their CYP2D6 predicted phenotype (EM, IM, PM) and weight category with potential dose increase due to increased body weight and lower PK exposure (based on the results of individual and subgroup PK analyses). No patient below 15 kg at baseline was enrolled into the study. During the 52 week period, 28 patients (49.2%) had at least one dose increase.

The safety profile of eliglustat seen in this study is consistent with the safety profile of eliglustat in adults and no new adverse reactions were identified (see section 4.8).

The main efficacy endpoints for Cohort 1 included change from baseline to 52-weeks (primary analysis period) for haemoglobin (g/dL), platelets (%), spleen volume (%), and liver volume (%). The majority of study patients (96%) on eliglustat monotherapy maintained their Gaucher-related clinical parameters (Table 9) within the pre-specified therapeutic goals for study entry.

Of the 3 patients below the age of 6 years on eliglustat monotherapy, 2 switched to imiglucerase.

Out of 51 patients, 47 in Cohort 1 were maintained on eliglustat monotherapy through 52 weeks.

Four patients (n=2 GD1, n=2 GD3) required a switch to imiglucerase due to decline in Gaucher-related clinical parameters. Of the 4 patients, one (GD3) discontinued the study and 3 initiated rescue therapy treatment. Further, one (GD1) of the 3 patients who initiated rescue therapy withdrew from the study during the primary analysis period.

Of the five patients with GD3 on eliglustat monotherapy one discontinued the study due to Covid-19 and 2 patients qualified for rescue therapy; of the two who qualified for rescue therapy, one patient discontinued the study and one completed the PAP on rescue therapy as stated above. The efficacy data of eliglustat as monotherapy in paediatric patients below the age of 6 years (n=3) and with GD3 (n=5) are limited; no clinically meaningful conclusion can be drawn.

The main efficacy endpoint for patients in Cohort 2 was the percentage of patients with improvement in the severe manifestation(s) that made the patient eligible for inclusion in Cohort 2 after 52 weeks of treatment. For efficacy of combination therapy, 4 out of 6 patients did not meet the main endpoint; no conclusion can be drawn as to the use of combination therapy in the paediatric population.

Table 9: Changes from baseline to 52 weeks (primary analysis period) in patients with GD on eliglustat monotherapy (Cohort 1) in study EFC13738

Age (years) [n]	Gaucher-related clinical parameters	Mean (SD) at baseline	Mean (SD) at week 52	Mean change (SD)
2 to < 6 [n = 3]	Haemoglobin level (g/dL)	12.25 (0.76)	11.93 (0.60)	-0.32 g/dL (0.20)
	(mmol/L)	7.61 (0.47)	7.41 (0.37)	-0.25 mmol/L (0.01)
GD1: n = 2 GD3: n = 1	Platelet count ($x10^9$/L)	261.50 (59.33)	229.33 (90.97)	-12.19% (26.05)
	Spleen volume (MN)	3.84 (1.37)	5.61 (2.56)	42.12% (16.64)
	Liver volume (MN)	1.22 (0.27)	1.43 (0.02)	21.23% (26.97)
6 to < 12 [n = 15]	Haemoglobin level (g/dL)	13.70 (1.17)	13.21 (1.22)	-0.49 g/dL (1.17)
	(mmol/L)	8.51 (0.73)	8.2 (0.76)	-0.3 mmol/L (0.73)
GD1: n = 14 GD3: n = 1	Platelet count ($x10^9$/L)	216.40 (51.80)	231.73 (71.62)	7.25% (20.50)
	Spleen volume (MN)	3.01 (0.86)	2.93 (0.82)	0.11% (19.52)
	Liver volume (MN)	1.02 (0.20)	1.03 (0.16)	2.22% (13.86)
12 to < 18 [n = 33]	Haemoglobin level (g/dL)	13.75 (0.97)	13.37 (1.20)	-0.38 g/dL (1.01)

Age (years) [n]	Gaucher-related clinical parameters	Mean (SD) at baseline	Mean (SD) at week 52	Mean change (SD)
	(mmol/L)	8.54 (0.60)	8.3 (0.75)	-0.24 mmol/L (0.63)
GD1: n = 30 GD3: n = 3	Platelet count ($x10^9$/L)	210.64 (49.73)	177.11 (50.92)	-14.36% (20.67)
	Spleen volume (MN)	3.48 (1.78)	3.41 (1.65)	1.79% (26.11)
	Liver volume (MN)	0.93 (0.16)	0.92 (0.18)	-1.47% (10.39)

The European Medicines Agency has waived the obligation to submit the results of studies with eliglustat in all subsets of the paediatric population in Gaucher disease type 2 (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

Absorption
Median time to reach maximum plasma concentrations occurs between 1.5 to 6 hours after dosing, with low oral bioavailability (<5%) due to significant first-pass metabolism. Eliglustat is a substrate of the efflux transporter P-gp. Food does not have a clinically relevant effect on eliglustat pharmacokinetics. Following repeated dosing of eliglustat 84 mg twice daily in non-PMs and once daily in PMs, steady state was reached by 4 days, with an accumulation ratio of 3-fold or less.

Distribution
Eliglustat is moderately bound to human plasma proteins (76 to 83%) and is mainly distributed in plasma. After intravenous administration, the volume of distribution was 816 L, suggesting wide distribution to tissues in humans. Nonclinical studies demonstrated a wide distribution of eliglustat to tissues, including bone marrow.

Biotransformation
Eliglustat is extensively metabolized with high clearance, mainly by CYP2D6 and to a lesser extent CYP3A4. Primary metabolic pathways of eliglustat involve sequential oxidation of the octanoyl moiety followed by oxidation of the 2,3-dihydro-1,4-benzodioxane moiety, or a combination of the two pathways, resulting in multiple oxidative metabolites.

Elimination
After oral administration, the majority of the administered dose is excreted in urine (41.8%) and faeces (51.4%), mainly as metabolites. After intravenous administration, eliglustat total body clearance was 86 L/h. After repeated oral doses of 84 mg eliglustat twice daily, eliglustat elimination half-life is approximately 4-7 hours in non-PMs and 9 hours in PMs.

Characteristics in specific groups

CYP2D6 phenotype
Population pharmacokinetic analysis shows that the CYP2D6 predicted phenotype based on genotype is the most important factor affecting pharmacokinetic variability. Individuals with a CYP2D6 poor metaboliser predicted phenotype (approximately 5 to 10% of the population) exhibit higher eliglustat concentrations than intermediate or extensive CYP2D6 metabolisers.

Gender, body weight, age, and race
Based on the population pharmacokinetic analysis, gender, body weight, age, and race had limited or no impact on the pharmacokinetics of eliglustat.

Paediatric population
In paediatric patients treated with body-weight tiered dosing regimens (see section 4.2), steady state exposures (C_{max} and AUC) were comparable and within the observed range in adult patients.

Hepatic impairment
Effects of mild and moderate hepatic impairment were evaluated in a single dose phase 1 study. After a single 84 mg dose, eliglustat C_{max} and AUC were 1.2- and 1.2-fold higher in CYP2D6 EMs with mild hepatic impairment, and 2.8- and 5.2-fold higher in CYP2D6 EMs with moderate hepatic impairment compared to healthy CYP2D6 EMs.

After repeated 84 mg twice daily doses of eliglustat, C_{max} and AUC_{0-12} are predicted to be 2.4- and 2.9-fold higher in CYP2D6 EMs with mild hepatic impairment and 6.4- and 8.9-fold higher in CYP2D6 EMs with moderate hepatic impairment compared to healthy CYP2D6 EMs.

After repeated 84 mg once daily doses of eliglustat, C_{max} and AUC_{0-24} are predicted to be 3.1- and 3.2-fold higher in CYP2D6 EMs with moderate hepatic impairment compared to healthy CYP2D6 EMs receiving eliglustat 84 mg twice daily (see sections 4.2 and 4.4).

Steady state PK exposure could not be predicted in CYP2D6 IMs and PMs with mild and moderate hepatic impairment due to limited or no single-dose data. The effect of severe hepatic impairment was not studied in subjects with any CYP2D6 phenotype (see sections 4.2, 4.3 and 4.4).

Renal impairment
Effect of severe renal impairment was evaluated in a single dose phase 1 study. After a single 84 mg dose, eliglustat C_{max} and AUC were similar in CYP2D6 EMs with severe renal impairment and healthy CYP2D6 EMs.

Limited or no data were available in patients with ESRD and in CYP2D6 IMs or PMs with severe renal impairment (see section 4.2).

5.3 Preclinical safety data

The principal target organs for eliglustat in toxicology studies are the gastrointestinal (GI) tract, lymphoid organs, the liver in rat only and, in the male rat only, the reproductive system. Effects of eliglustat in toxicology studies were reversible and exhibited no evidence of delayed or recurring toxicity. Safety margins for the chronic rat and dog studies ranged between 8-fold and 15-fold using total plasma exposure and 1- to 2-fold using unbound (free fraction) plasma exposures.

Eliglustat did not have effects on central nervous system (CNS) or respiratory functions. Concentration-dependent cardiac effects were observed in non-clinical studies: inhibition of human cardiac ion channels, including potassium, sodium, and calcium, at concentrations ≥7-fold of predicted human C_{max}; sodium ion channel-mediated effects in an ex-vivo electrophysiology study in dog Purkinje fibres (2-fold of predicted human unbound plasma C_{max}); and increases in QRS and PR intervals in dog telemetry and cardiac conduction studies in anaesthetised dogs, with effects seen at concentrations 14-fold of predicted human total plasma C_{max}, or 2-fold of predicted human unbound plasma C_{max}.

Eliglustat was not mutagenic in a standard battery of genotoxicity tests and did not show any carcinogenic potential in standard lifetime bioassays in mice and rats. Exposures in the carcinogenicity studies were approximately 4-fold and 3-fold greater in mice and rats, respectively, than the mean predicted human eliglustat total plasma exposure, or less than 1-fold using unbound plasma exposure.

In mature male rats, no effects on sperm parameters were observed at systemically non-toxic doses. Reversible inhibition of spermatogenesis was observed in the rat at 10-fold of predicted human exposure based on AUC, a systemically toxic dose. In rat repeated dose toxicity studies, seminiferous epithelial degeneration and segmental hypoplasia of the testes was seen at 10-fold of predicted human exposure based on AUC.

Placental transfer of eliglustat and its metabolites was shown in the rat. At 2 and 24 hours post-dose, 0.034 % and 0.013 % of labelled dose was detected in foetal tissue, respectively.

At maternal toxic doses in rats, foetuses showed a higher incidence of dilated cerebral ventricles, abnormal number of ribs or lumbar vertebrae, and many bones showed poor ossification. Embryofoetal development in rats and rabbits was not affected up to clinically relevant exposure (based on AUC).

A lactation study in the rat showed that 0.23% of labelled dose was transferred to pups during 24 hours post-dose, indicating milk excretion of eliglustat and/or its related materials.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule contents
Cellulose, microcrystalline (E460)
Lactose monohydrate
Hypromellose 15 mPa.S, 2910
Glycerol dibehenate

Capsule shell
Gelatin
Potassium aluminium silicate (E555)
Titanium dioxide (E171)
Yellow iron oxide (E172)
Indigotine (E132)

Printing ink
Shellac
Black iron oxide (E172)
Propylene glycol (E1520)
Ammonia solution, concentrated (E527)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

PETG/COC.PETG/PCTFE-aluminium blister

Each blister wallet contains 14 hard capsules.
Each pack contains 14, 56 or 196 hard capsules.

Pack size: 14 hard capsules in 1 blister wallet, 56 hard capsules in 4 blister wallets of 14 capsules each or 196 hard capsules in 14 blister wallets of 14 capsules each.

6.6 Special precautions for disposal

Any unused product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

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8 MARKETING AUTHORISATION NUMBER(S)

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9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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10 DATE OF REVISION OF THE TEXT

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