17 October 2024
EMA/516361/2024
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Cerdelga

International non-proprietary name: Eliglustat

Procedure No. EMEA/H/C/003724/X/0036/G

Note

Variation assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
Send us a question Go to www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000

Table of contents

List of abbreviations

AE:	adverse event
AUC0-τ:	area under the plasma concentration curve from time 0 to T hours during a dose interval
BID:	twice a day
BMB:	bone marrow burden
BMD:	bone mineral density
CEP	Certificate of Suitability of the EP
CHMP	Committee for Medicinal Products for Human use
COC	Cyclic Olefin Copolymer
CYP:	cytochrome P450
DXA:	dual-energy absorptiometry
ELIKIDS:	EFC13738
EM:	extensive metabolizer
EP:	extension period
ERT:	enzyme replacement therapy
FAS:	full analysis
FDA:	Food and Drug Administration
GCS:	glucosylceramide synthase
GD:	Gaucher disease
GD1:	Gaucher disease type 1
GD2:	Gaucher disease type 2
GD3:	Gaucher disease type 3
GMP	Good Manufacturing Practice
GL-1:	glucosylceramide
GSL:	glycosphingolipid
HPLC	High performance liquid chromatography
IAR:	infusion associated reaction
ICGG:	international collaborative Gaucher group
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IM:	intermediate metabolizer
LE	Line Extension
LTP:	long-term period
LoQ	List of Questions
lyso-GL-1:	glucosylsphingosine
MAH:	Marketing Authorization Holder
MN:	multiples of normal
PAP:	primary analysis period
PCSA:	potentially clinically significant abnormality
PCTFE	Polychlorotrifluorethylene
PETG	Glycollated Polyethylene Terapthalate
Ph. Eur.	European Pharmacopoeia
PIP:	Pediatric Investigational Plan
PM:	poor metabolizer
PT:	preferred term
QC	Quality Control
QD:	once a day
SAE:	serious adverse event

SmpC	Summary of Product Characteristics
SOC:	system organ class
SRT:	substrate reduction therapy
TEAE:	treatment-emergent adverse event
t_{max}:	time to reach maximum plasma concentration
UV	Ultraviolet

1. Background information on the procedure

1.1. Submission of the dossier

Sanofi B.V. submitted on 23 November 2023 a group of variation(s) consisting of an extension of the marketing authorisation and the following variation(s):

Variation(s) requested		Type
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	II

Extension application to introduce a new strength (21 mg capsule, hard) grouped with an extension of indication to include treatment of paediatric patients with GD1 who are 6 years and older with a minimum body weight of 15 kg, who have been previously treated with enzyme replacement therapy (ERT), and who are CYP2D6 poor metabolisers (PMs), intermediate metabolisers (IMs) or extensive metabolisers (EMs) for Cerdelga, based on interim results from study EFC13738 (Open label, two cohort (with and without imiglucerase), multicenter study to evaluate pharmacokinetics, safety, and efficacy of eliglustat in paediatric patients with Gaucher disease type 1 and type 3). As a consequence, sections 4.1, 4.2, 4.8, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet is updated in accordance. In addition, the MAH took this opportunity to introduce editorial changes to the PI. The RMP version 8.0 has also been submitted.

1.2. Legal basis, dossier content

The legal basis for this application refers to:

Article 7.2 of Commission Regulation (EC) No 1234/2008 – Group of variations

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

The new indication, which is the subject of this application, falls within the above-mentioned orphan designation.

The Committee for Orphan Medicinal Products (COMP) was of the view that the scope of this procedure does not raise justified and serious doubts in respect to the fulfilment of the orphan designation criteria.

1.3. Information on Paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) P/0440/2022 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0440/2022 was completed.

The PDCO issued an opinion on compliance for the PIP P/0440/2022.

1.4. Information relating to orphan market exclusivity

1.4.1. Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the MAH did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

1.5. Protocol assistance

The MAH received Protocol assistance from the CHMP on the development for the indication from the CHMP on 23 June 2016 (EMEA/H/SA/1370/2/2016/PA/PED/II) and 16 December 2021 (EMA/SA/0000073298). The Protocol assistance pertained to quality and clinical aspects.

1.6. Steps taken for the assessment of the product

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

Rapporteur: Patrick Vrijlandt Co-Rapporteur: N/A

CHMP Peer reviewer(s): N/A

The Rapporteur appointed by the PRAC was:

PRAC Rapporteur: Maria del Pilar Rayon

The application was received by the EMA on	23 November 2023
The procedure started on	28 December 2023
The CHMP Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	14 March 2024
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC and CHMP members on	26 March 2024
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	14 April 2024
The CHMP agreed on the consolidated List of Questions to be sent to the MAH during the meeting on	25 April 2024
The MAH submitted the responses to the CHMP consolidated List of Questions on	24 May 2024
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Questions to all CHMP and PRAC members on	28 June 2024

The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	11 July 2024
The CHMP agreed on a list of outstanding issues to be sent to the MAH on	25 July 2024
The MAH submitted the responses to the CHMP List of Outstanding Issues on	17 September 2024
The CHMP Rapporteurs circulated the Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP and PRAC members on	2 October 2024
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	3 October 2024
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 on	17 October 2024

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

Gaucher disease (GD) is a rare autosomal recessive lysosomal storage disorder. Three major clinical subtypes of Gaucher disease (types 1, 2, and 3) are classically recognized. The clinical manifestations of the different GD types are extremely heterogeneous, including variable type and severity of symptoms, the presence or absence of classically reported neurological findings, age at onset of clinical signs and symptoms, and disease progression. Hematologic abnormalities, in the form of thrombocytopenia and anaemia, are a common clinical feature. Painless splenomegaly is often the earliest sign of the disease in all 3 types. Hepatomegaly, another frequent sign of GD, is usually milder than splenomegaly and liver function is maintained. Skeletal disease is another major aspect of GD, reported to affect more than 80% of GD type 1 (GD1) patients. GD1 is considered the mildest form of the disease. Type 2 (GD2), the acute neuronopathic form, and GD3, the sub-acute or chronic neuronopathic form, also exhibit neurological symptoms in addition to the non-neurological GD manifestations.

2.1.2. Epidemiology

GD is a pan-ethnic disorder that is inherited in an autosomal recessive manner. There is limited data on the frequency of GD because of the rarity of this disease and the long observation period necessary to collect sufficient cases to make reliable frequency estimations.

GD1 is the most common subtype and is estimated to affect more than 20 000 patients worldwide, with certain populations exhibiting a higher prevalence. In populations from Western Europe or of Western European descent, birth prevalence rates of symptomatic GD of between 1:57 000 and 1:111 000 have been reported, which translate into overall population prevalence rates in the order of 1 in 100 000. In the Ashkenazi Jewish population, GD1 has an estimated incidence of 1 in 855 births. The estimated prevalence estimates in this particular population range between 1:400 and 1:2500; however, a considerable proportion of patients homozygous for the most common mutation, N370S (a missense mutation associated with a high amount of residual enzyme activity), do not show clinically overt symptoms, or at least not until adulthood.

2.1.3. Aetiology and pathogenesis

Gaucher is a storage disorder that results from a deficient activity of the enzyme acid β-glucosidase (also known as glucocerebrosidase), due to mutations in the *GBA* gene encoding acid β-glucosidase. The major natural substrate for acid β-glucosidase is glucosylceramide (GL-1), an intermediate metabolite in the synthesis and catabolism of more complex glycosphingolipids (GSLs). Gaucher disease is characterized by accumulation of GL-1 and glucosylsphingosine (lyso-GL-1; a minor substrate) in the reticuloendothelial system, due to impaired GL-1 hydrolysis secondary to the deficiency of acid β-glucosidase. In patients with GD, the liver, spleen, bone marrow, and brain show increases in GL-1 concentration.

2.1.4. Clinical presentation, diagnosis and prognosis

GD1, the most common and traditionally considered the mildest form of the disease, is characterised by the absence of neuronopathic involvement seen in GD 2 and 3. Hematologic abnormalities, in the form of thrombocytopenia and anaemia, are a common clinical feature in all 3 GD types. These abnormalities result from splenic sequestration of cells and Gaucher cell (glucosylceramide-laden macrophages) infiltration of bone marrow, which causes displacement of hematopoietic elements. Painless splenomegaly is often the earliest sign of the disease in all 3 types. Hepatomegaly, another frequent sign of GD, is usually milder than splenomegaly and liver function is generally maintained. Hepatomegaly can in rare cases progress towards fibrosis followed by cirrhosis. Skeletal disease is another major aspect of GD, reported to affect more than 80% of GD1 participants. The skeletal manifestations include bone marrow infiltration, osteonecrosis, bone pain and bone crises, osteopenia and osteoporosis, and pathological fractures.

The neuronopathic variants (types 2 and 3) of GD are characterized by onset in infancy to early childhood. GD2 is the acute neuronopathic variant, frequently presenting with early development of oculomotor abnormalities and other neurological symptoms, including retroflexion of the neck, bulbar signs, and seizures. GD2 is further characterized by rapid progression and death by about 2 years of age due to severe CNS involvement. GD3 is the subacute neuronopathic variant with a later onset than the acute neuronopathic variant, with neurological symptoms typically appearing before the age of 2 years in about half of the patients. The vast majority of GD3 patients exhibit CNS manifestations in the latter part of the first decade of life. Nonclinical studies have shown that eliglustat has limited to no ability to cross the blood brain barrier and has no clinically relevant access to brain tissue; therefore, it is highly unlikely that eliglustat will have a beneficial effect on the central nervous system (CNS) disease.

Although clinical manifestations of this GD1 can occur at any age, the presence of symptoms during childhood or adolescence typically proclaims a more aggressive and severe disease with a more rapid rate of progression compared with one of later onset. A review of 887 paediatric GD1 participants enrolled in the International Collaborative Gaucher Group (ICGG) Gaucher Registry revealed that the most common signs

and symptoms are splenomegaly (95%), hepatomegaly (87%), radiologic bone disease (81%), thrombocytopenia (50%), anaemia (40%), growth retardation (34%), bone pain (27%), and bone crisis (9%). Anaemia and more severe splenomegaly and hepatomegaly are observed more frequently in younger participants, whereas skeletal manifestations are found more often in adolescents. When the skeleton is affected in a child who is not fully grown, often growth retardation occurs. Children with GD1 often also present with delays in pubertal development. Although certain disease manifestations may occur more commonly in children than in adults, the ranges of abnormalities are similar.

Due to the rarity and heterogenic presentation of the disease there is often a diagnostic delay. Diagnostic methods involve ultrasound and magnetic resonance imaging or computed tomography to detect bone disease and measure the size of the liver and spleen. Formal diagnosis of the disease is determined by measuring the amount of glucocerebrosidase in circulating leukocytes. Genotyping can confirm the diagnosis. In rare cases, genotyping may be of prognostic value: a patient with a homozygous N370S mutation in the *GBA* gene will not develop neurological disease.

Patients with GD1 are estimated to have a decreased life span of about 9 years compared to the reference population. The functional prognosis can be affected by sometimes serious bone complications.

2.1.5. Management

Two treatment approaches aimed at lowering GL-1 levels are currently available:

- Enzyme replacement therapy (ERT) with recombinant acid β-glucosidase, augments the deficient enzyme activity in participants and catabolizes stored GL-1 in lysosomes (Imiglucerase under the tradename Cerezyme, Velaglucerase alfa under the tradename Vpriv).
- Substrate reduction therapy (SRT), acts by partially inhibiting the enzyme glucosylceramide synthase (GCS), thereby reducing the rate of synthesis of GL-1 to better match the impaired rate of catabolism. (Miglustat under the tradename Zavesca)

Currently, ERT is the standard of care for pediatric participants with GD; no SRT is currently approved for pediatric use.

Besides these treatment options many patients also require adjunctive medication or intervention, eg, bisphosphonates for osteopenia; pain relief, orthopedic surgery, and physical therapy for pre-existent irreversible skeletal complications; specific therapies to ameliorate portal hypertension; and vasodilator treatment for pulmonary hypertension.

The heterogeneity of Gaucher disease requires an individualized approach to treatment. Therapeutic goals include amongst others improving anemia (increase hemoglobin levels and eliminate the need for blood transfusions) and thrombocytopenia (increase platelet count), reducing liver and spleen volumes, lessen or eliminate bone pain and prevent bone crises. For paediatric patients, a therapeutic goal is to normalize growth and achieve normal onset of puberty [1].

There is a need for a more practical route of administration as ERT requires regular intravenous (IV) infusions (generally every 2 weeks) for the duration of a patient's lifetime. ERT also has the associated risk of developing hypersensitivity and infusion reactions. Furthermore, maintenance of intravenous access that is

[1] Pastores GM, et al. Therapeutic goals in the treatment of Gaucher disease. Semin Hematol 2004;41: 4e14.

required for ERT, can be difficult in children. Pediatric patients who require central venous access devices for long-term venous access are at risk of complications such as infection and device failure.

There is an unmet clinical therapeutic need for paediatric patients with neurological involvement (Types II and III), as current ERT therapy only impacts visceral disease pathology and not neurologic manifestations. However, non-clinical studies have shown that eliglustat has limited to no ability to cross the blood brain barrier and has no clinically relevant access to brain tissue; therefore, it is highly unlikely that eliglustat will have a beneficial effect on the central nervous system (CNS) disease.

2.2. About the product

Cerdelga is a substrate reduction therapy to reduce the synthesis of GL-1 and GL-1-based glycosphingolipids, thereby allowing for a better match between the production of substrate and the impaired rate of catabolism in order to prevent GL-1 accumulation and allow for accumulated GL-1 to be metabolized.

Cerdelga 84 mg is currently indicated for the long-term treatment of adult patients with GD1, who are CYP2D6 poor metabolisers (PMs), intermediate metabolisers (IMs) or extensive metabolisers (EMs).

The proposed indication:

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 poor metabolisers (PMs), intermediate metabolisers (IMs) or extensive metabolisers (EMs).

Proposed posology:

Paediatric population (from 6 to 18 years) 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

Thus, the existing 84 mg strength (marketed) and the new 21 mg strength are both pharmaceutical forms for use in the paediatric patient population. Cerdelga is to be taken orally in children who can swallow intact capsule.

2.3. The development programme/compliance with guidance/scientific advice

Protocol assistance

The MAH has sought protocol assistance twice. In April 2016, the MAH requested advice (EMEA/H/SA/1370/2/2016/PA/PED/II) to obtain feedback on whether the study EFC13738 as described in the PIP is sufficient to expand the Cerdelga indication to include paediatric GD1 and GD3 patients aged 2 to <18 years (treated with eliglustat as monotherapy). Two new formulations: a 21 mg capsule and a liquid formulation 5 mg/ml were proposed.

The CHMP did not agree with the MAH that the BCS status could be the basis for eligibility to a biowaiver for bioequivalence between the new formulations and the registered one. To confirm eligibility to waiving a bioavailability study, the current case could be covered by the general biowaiver requirements as detailed in the guideline on the investigation of bioequivalence (strength to be investigated), which detailed the following 4 requirements that should be met: same manufacturing process, homothetic formulations, same dissolution profiles and linearity of PK within the corresponding doses range.

The proposed dose selection, study population as well as the endpoints for cohort 1 were generally endorsed.

In October 2021, the MAH requested advice (EMA/SA/0000073298) regarding quality and clinical aspects. The proposed strategy to use the 21 mg capsule strength was considered acceptable for use in children down to 2 years of age provided that the handling is safe and sufficient acceptability, palatability and stability within suitable liquids are demonstrated within the proposed age groups. It was noted that in the approved SmPC, it is stated that the capsules should be swallowed whole, preferably with water and should not be crushed, dissolved or opened.

Provided that opening the capsules is possible, the proposal to use the 84 mg capsules for creating a suspension to be used for children requiring doses below 21 mg might be acceptable. The complete composition of the vehicle has to be known and suitable for the proposed age group. The use of a commercialized vehicle with limited knowledge about the composition was not considered acceptable. Additional efforts to develop an oral powder or granules for suspension with a suitable suspending liquid should be done if not lower strengths of the capsule formulation can be developed.

Although dosing with single capsules is the most favourable, the use of the 21 mg strength for dosing 42 mg could be considered acceptable, taking into account the few patients expected in the lowest weight cohort. Considering the need on dosing flexibility for patients who cannot swallow capsules, due to young age or motor incoordination, and/or patients requiring a dose of <21 mg, it was the CHMP opinion that the availability of a commercial eliglustat 844 mg powder for oral suspension formulation would clearly favour these patient's compliance and reduce associated errors to the preparation of a suspension by opening the capsule and mixing the contents with drink.

The main proposed update was the number of patients enrolled in the on-going ELIKIDS study will be reduced from 60 to approximately 52 which was not endorsed. In particular, it was considered important not to recruit fewer patients with GD3 as compared to what was previously planned (n=10) and not fewer subjects in the age group 2-<6 years (n=6). Regarding GD3, every effort should be made to collect additional data in this subgroup, as extrapolation of efficacy and safety through PK-matching may not be sufficient. A modelling and simulation approach to support the extension of indication was agreed with, and primarily the applicant was advised to use population PK modelling analysis, however insufficient PK data in children 2-6 years old might result in a restricted indication to children above 6 years/15 kg.

Effects on growth rate, puberty and development are not amenable to extrapolation. The ELIKIDS study is too limited in duration and size to provide this data and lacks a control group. Although it is acknowledged that also for other drugs used for Gaucher disease, data on the effects on these manifestations may be lacking, the future application would need to thoroughly discuss these aspects and how the data gaps may be addressed.

Further, although 1-year data (complemented with the available beyond 52 week-data) may be sufficient to support a paediatric approval, a thorough post-marketing follow-up would in that case need to be planned. The proposed safety package for the paediatric indication may otherwise suffice, should the safety profile be

mostly similar to the adult population and not raise particular concerns regarding developmental milestones or learning abilities.

2.4. Quality aspects

2.4.1. Introduction

The finished product subject of this line extension (LE) is presented as hard capsules containing 21 mg of eliglustat as active substance, which correspond to 25 mg of eliglustat tartrate. This LE also concerns the extension of the indication in the treatment of 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.

Other ingredients for the capsule contents are: microcrystalline cellulose, lactose monohydrate, hypromellose and glycerol dibehenate.

Other ingredients for the capsule shell are: gelatin, potassium aluminium silicate (E555) and titanium dioxide (E171).

Other ingredients for the printing ink are: shellac, black iron oxide (E172), propylene glycol and ammonia solution, concentrated.

The product is available in PETG/COC.PETG/PCTFE-aluminium blister as described in section 6.5 of the SmPC.

2.4.2. Active Substance

No new information on the active substance eliglustat tartrate has been provided with this line extension. The hard capsules, subject of this LE, contain eliglustat tartrate of the same quality as the active substance used in the approved presentations. The active substance is manufactured by the approved manufacturing sites.

The approved specification of the active substance is acceptable for manufacturing of the finished product and no additional tests are required.

2.4.3. Finished Medicinal Product

2.4.3.1. Description of the product and pharmaceutical development

The finished product is presented as a hard capsule. The capsules are size 4 (dimensions 14 x 5 mm) with a pearl white opaque cap and pearl white opaque body with "GZ04" printed in black on the capsule. The capsules are filled with a white to off-white powder.

The new strength can be distinguished from the currently approved one by the colour of the cap, imprint and by size.

The pharmaceutical development includes adequate discussion on the suitability of the excipients in paediatric preparations, patient acceptability and on the safety profile of the selected excipients. The suitability of the dosage form in the intended paediatric population was considered, a small capsule size was selected in relation to the proposed target population.

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 formulation does not require the use of an overage.

The dissolution method proposed for the 21 mg strength is the same method approved and utilised for testing of the 84 mg capsules. The discriminatory power of the dissolution method has been demonstrated.

The Applicant initially proposed an alternative method of administration for children unable to swallow the capsules. This option entailed the compounding by local pharmacies of an oral suspension (4.2 mg/ml) from Cerdelga capsules using commercial suspension vehicles. As the data package in support of this option was incomplete and the SmPC had not been revised accordingly to cover the relevant information on this extemporaneous formulation and alternative method of administration, a major objection (MO) was raised. Additionally, as the proposed commercial suspension vehicles would not be co-packed, are not available in all EU countries and taking into account that local pharmacies in several countries might not be able to perform this type of extemporaneous preparations, the Applicant was also asked to investigate the option of opening the capsules and mixing its content with food or drinks. No data demonstrating the feasibility of this option was provided. The Applicant withdrew the option of pharmacy compounding for an oral suspension of eliglustat and/or any other method of administration for children who cannot swallow an intact capsule during the ongoing procedure. This is acceptable and the initially raised MO is no longer applicable as the proposed product is indicated in children above 6 years of age and no issues are expected with the capsule size in this target age group. Furthermore, the proposed indication is for paediatric patients with GD1, 6 years old and above, who have been stable on ERT, therefore, children unable to swallow capsules can remain on available ERT treatment. Section 4.2 of the SmPC has been revised to add that the medicinal product is to be taken orally in children who can swallow an intact capsule.

The manufacturing process is based on the manufacturing process used for the authorised 84 mg strength. The new strength of 21 mg hard capsule is manufactured from the same common blend utilised for the commercial 84 mg capsule, and no changes have been proposed to the active substance, excipients, or common blend, with the only change in the manufacturing process being the adjustment of the fill weight from the common blend formulation. The Applicant has provided acceptable reference to the relevant supporting data in the approved 84 mg strength dossier.

An overview of the batches used in the clinical studies has been provided. As the manufacturing site of the primary stability batches and future commercial batches is different than the site responsible for the manufacturing of the pivotal 21 mg clinical batches a comparative dissolution study was performed. Similarity between batches manufactured at the commercial manufacturing site and the pivotal clinical batches was confirmed.

The primary packaging is PETG/COC.PETG/PCTFE-aluminium blister. The choice and rationale for selection of the container closure system in view of the difference in size of the capsule proposed for the 21 mg strength compared to the approved 84 mg strength was discussed. The selected blister includes a smaller cavity; except for this difference, no other change to the primary packaging currently approved for the 84 mg strength is proposed.

The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

2.4.3.2. Manufacture of the product and process controls

The manufacturing process consists of eight main steps: Dispensing (Step 1), Mixing and Granulation (Step 2), Milling and Sub-batch blending (Step 3), Drying, Milling and Final blending (Step 4), De-lumping of final blend (Step 5), Encapsulation (Step 6), Weight sorting (Step 7) and Packaging (Step 8). The manufacturing process is considered to be a standard process.

Critical steps identified during the manufacture of the finished product were presented including in-process controls, applied test methods and acceptance criteria. Operating ranges and acceptance criteria were discussed and justified.

Bulk holding times have been clearly stated and are supported by data.

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.

2.4.3.3. Product specification

The finished product release specifications include appropriate tests for this kind of dosage form: appearance of contents and capsule (visual), identification (HPLC, UV), assay (HPLC), degradation products (HPLC), dissolution, uniformity of dosage units (mass variation), microbial contamination.

The finished product specification was set according to ICH Q6A and is acceptable.

The specification limit for dissolution was initially not set in line with the requirements of the reflection paper on the dissolution specification for generic solid oral immediate release products with systemic action (EMA/CHMP/CVMP/QWP/336031/2017) and a MO was raised by the CHMP. The Applicant was requested in this MO to tighten the specification in line with the provided dissolution data of the biobatch. The MO was satisfactorily resolved by tightening the dissolution limit of the finished product.

The analytical methods used have been adequately described and appropriately validated in accordance with the ICH guidelines. Compliance with the revised acceptance criteria for dissolution has been demonstrated. Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

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

2.4.3.4. Stability of the product

Stability data from 3 commercial scale batches of finished product stored for up to 12 months under long term conditions (30 ºC / 75% RH) 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. The long-term stability results demonstrate compliance with the proposed specification and no significant changes at accelerated storage conditions.

Samples were tested for appearance of contents and capsule (visual), assay (HPLC), degradation products (HPLC), dissolution, microbial contamination. The analytical procedures used are stability indicating. At long term and accelerated conditions, the results remained within the specification limits and no significant trend was observed.

In accordance with EU GMP guidelines[2], any confirmed out-of-specification result, or significant negative trend, should be reported to the Rapporteur and EMA.

In addition, the Applicant referred to the approved 84 mg dossier in which photostability data are provided for 3 batches as defined in the ICH Guideline on Photostability Testing of New Drug Substances and Products.

Based on available stability data obtained from the 3 primary stability batches for 21 mg capsules and 36 months stability data of already approved 84 mg capsules, the proposed shelf-life of 24 months without specific storage conditions as stated in the SmPC (section 6.3) is acceptable.

2.4.3.5. 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.

Gelatine obtained from bovine sources is used in the product. Valid TSE CEP from the suppliers of the gelatine used in the manufacture is provided.

2.4.4. 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.

Two MOs were raised following the initial assessment. The first MO related to the need to tighten the QC dissolution limit in line with the biobatch performance. The Applicant has resolved the MO by tightening the QC dissolution limit.

The second MO was raised regarding the Applicant's proposal of pharmacy compounding for an oral suspension of eliglustat and alternative method of administration of the medicinal product. The Applicant has decided to withdraw this proposal of extemporaneous formulation for an oral suspension of eliglustat and/or any other method of administration for children who cannot swallow an intact capsule. In addition, the issue of this MO is considered as not no longer applicable in view of the target age group, the capsules size and the fact that alternative treatment (i.e. ERT) is available for children unable to swallow capsules.

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.

[2] 6.32 of Vol. 4 Part I of the Rules Governing Medicinal products in the European Union

2.4.5. 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.

2.4.6. Recommendation(s) for future quality development

Not applicable.

2.5. Non-clinical aspects

2.5.1. Introduction

All relevant non-clinical information in relation to eliglustat in paediatric patients has been submitted previously (e.g. studies GT-157-TX-47 and GT-157-TX-48). There were no new pharmacology/pharmacokinetic/toxicology studies undertaken in support of the current application, which is agreed.

All the pivotal pre-clinical safety studies were conducted in compliance with GLP. Dose range finding studies do not all claim GLP compliance but were conducted in a GLP-compliant facility. The juvenile studies re-assessed as part of this application were GLP-compliant.

2.5.2. Pharmacology

No new pharmacology studies were provided in this application, which is acceptable. The pharmacology of Cerdelga has therefore not been re-assessed.

2.5.3. Pharmacokinetics

No new pharmacokinetics studies were provided in this application, which is acceptable. The pharmacokinetics of Cerdelga have therefore not been re-assessed.

2.5.4. Toxicology

No new toxicology studies were provided in this application, which is acceptable. Previously submitted juvenile animal studies relevant to this application were re-assessed, while other toxicity studies were not.

Studies in which the offspring (juvenile animals) are dosed and/or further evaluated

Table: Juvenile animal studies

Study details Species treatment period Route GLP status (Study ID)	**No: Sex/ Group**	**Dose** (mg/kg/ BID)	**Exposure**				**Major (alt salient) findings & NOAEL**
			Day	Sex (n)	Cmax ng/ml	AUC ng/ml/h	
Juvenile animal toxicity studies			**(NOAELs highlighted)**				
Rat (Sprague-Dawley) PND 22-49 (4 weeks) oral gavage, BID GLP (GT-157-TX-47)	Main study: 10M and 10F /dose group TK (PND22 and PND49): 27M and 27F /dose group	0	-		-		30: 3 animals died after dosing (cause undetermined), delayed sexual maturity in females 50: 8 animals died after dosing (cause undetermined), delayed sexual maturity in females, ↑ inorganic phosphorus (F), ↑ ALT (F), ↓ prostate weight (M)
		15	PND22	M (3)	223	751	
				F (3)	294	824	
			PND49	M (3)	87.5	110	
				F (3)	77	170	
		30	PND22	M (3)	561	1476	
				F (3)	973	2364	
			PND49	M (3)	359	384	
				F (3)	500	786	
		50	PND22	M (3)	760	3960	
				F (3)	665	3241	
			PND49	M (3)	605	1115	
				F (3)	719	1816	
Rat (Sprague-Dawley) PND 22-91 (10 weeks) oral gavage, BID GLP (GT-157-TX-48)	Main study: 10M and 10F /dose group Fertility: 20M and 20F /dose group TK (PND22 only): 3M and 3F /dose group	0	N.D.		Cmax or AUC N.D.		5: 1f died PND 30 (lung cyst) 15: 1M died PND 88 (cause undetermined), ↑ RBC (F), ↓ mean platelet volume (M), ↑ glucose, ↑ inorganic phosphorus, ↑ urine volume (M) 25: ↑ RBC (F), ↑ neutrophils and lymphocytes (F), ↓ platelet distribution width (M), ↓ potassium, ↑ glucose , ↑ creatinine (M), ↑ urea (M), ↑ Glucose, ↑ urine volume (M), lymphoid hyperplasia and histiocytic foci, ↑ enlarged mandibular lymph nodes (F), ↑ liver weight (F), trend towards delayed sexual maturity in females but not significant, ↑ inflammatory cell foci in epididymis and prostate (M) 25 Recovery: ↑ enlarged mandibular lymph nodes (F), partial reversal of lymphoid hyperplasia and histiocytic foci, ↑ weight seminal vesicle (M), ↑ inflammatory cell foci epididymis (M)
		5	*Plasma conc. 1h post-dose* M (3): 12.4 F (3): 11.6				
		15	M (3): 81 F (3): 55.8				
		25	M (3): 273.7 F (3): 187.3				

A 4-week dose range-finding (DRF) study in rats (PND 22-49) identified 25 mg/kg BID as a suitable high dose for a 10-week toxicity study in the juvenile rat, due to excessive mortality at doses above 25 mg/kg

BID. In the surviving animals that were given the high dose, there was a slight increase in plasma inorganic phosphorous concentration and ALT (significant in females, trend in males), and decreased prostate weight in males. From the low dose of 15 mg/kg BID, a delay in female sexual maturation (as measured by vaginal opening) was noted.

In the pivotal study, rats were dosed twice daily by oral gavage, from 22 to 91 days of age. This dosing period corresponds to the proposed paediatric age range for eliglustat of ≥2 to <18 years. In this study, animals were assigned to a fertility group or a main toxicology group. There were eight deaths during the study, which were either caused by gavage dosing errors or were otherwise not treatment-related.

Delayed completion of vaginal opening in treated females from the toxicity group was observed, which was not statistically significant in the fertility group. In the 10-week study, an increase in inflammatory cell foci in prostate and epididymis was found at 25 mg/kg BID (<4.8x estimated safety margin based on DRF study), which was not resolved in epididymis after recovery. In contrast, there were no findings in epididymis of mature rats.

At 25 mg/kg BID, partially reversible histopathological changes were observed in the mandibular lymph nodes in both sexes, showing lymphoid hyperplasia and histiocytic foci. Females also had enlarged mandibular lymph nodes. These findings are potentially related to traumatic injury to the buccal area and local exposure to test article. Repeated dosing of mature rats did not lead to any findings in the mandibular lymph nodes.

The kinetics of eliglustat suggest that exposure was generally greater in female animals than in males. Exposure reduced over the study period and, as a consequence, the exposure at PND49 was up to 6x lower than the exposure at PND22. Decreased plasma GL-1 levels of 26-38% confirmed pharmacological activity in the DRF study. However, in the pivotal study, no decrease in GL-1 levels was observed suggesting an absence of pharmacological activity.

The NOAEL for the pivotal juvenile study is 15 mg/kg BID. This exposure is estimated to be clinically relevant (≤2.7x safety margin in the DRF study). Non-adverse disturbances in haematology and blood chemistry were observed from this dose level onwards.

2.5.5. Ecotoxicity/environmental risk assessment

Summary of main study results

PECsurfacewater for eliglustat is below the action limit of 0.01 µg/L and eliglustat is not a PBT substance as log Kow does not exceed 4.5.

Eliglustat is already used in existing marketed products and no significant increase in environmental exposure is anticipated.

2.5.6. Discussion on non-clinical aspects

Compared to adult rats, juvenile rats appeared to be more sensitive to effects of eliglustat based on increased mortality in the JAS DRF study at comparable doses and adverse effects on male reproductive organs. No mortality was observed at doses that did not affect GL-1 levels in juvenile animals. The Applicant explained that the mortalities occurred mostly within 1 min after dosing, suggesting a gavage error rather

than a pharmacological effect. Furthermore, the rapid clearance and associated short half-life of eliglustat made it difficult to derive a strong PK/PD relationship in rodents.

Due to the reduction in exposure over the study period, safety margins were particularly low at PND49 (≤ 0.55x for the NOAEL) in the pivotal juvenile rat study. Given that PND35-42 corresponds to the onset of rat puberty, the exposure at this developmental stage was rather low. The Applicant explained that the NOAEL was chosen based on the findings in the mandibular lymph nodes, which can be considered of low toxicological concern. At the higher dose used in the pivotal juvenile rat study, a more clinically relevant exposure was achieved and no effect of treatment on developmental parameters, including fertility, was found. Also in the 4-week DRF juvenile study, in which adequate safety margins (at least 5.6x) were achieved, no particular risks were identified.

Inflammation in the epididymis was observed at clinically relevant exposures in juvenile rats. The incidence of males with inflammatory cell foci in the epididymis was further increased at the end of the recovery period. The Applicant noted that the severity of these findings was graded minimal and that no functional effect on fertility was found. The inflammatory cell foci in the epididymis of juvenile rats were therefore considered non-adverse and not compound-related. The Applicant also noted that there were no findings in the epididymis in the 4-week and 26-week "adult" rat studies as well as the carcinogenicity study, which were initiated in young rats starting approximately PND 42, which corresponds to the peripubertal stage. Given these non-clinical results, and the available human experience from the paediatric trial, the reproductive toxicity risk for paediatric patients is considered sufficiently evaluated.

Both the DRF and pivotal juvenile study suggested a dose-related trend towards delayed sexual maturation in females at clinically relevant exposures. However, the Applicant performed a new, more robust, evaluation of the effect of eliglustat on female maturation in the pivotal juvenile study (combining the main/recovery and fertility groups), and found no significance. Moreover, the dose-related trend observed in the DRF study was not considered biologically meaningful.

2.5.7. Conclusion on the non-clinical aspects

The non-clinical data provided are considered sufficient, and an approval of the application is recommended from a non-clinical viewpoint. Relevant non-clinical data are reflected in sections 4.6 and 5.3 of the SmPC as well as in the RMP.

2.6. Clinical aspects

2.6.1. Introduction

GCP aspects

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

The MAH 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.

- **Tabular overview of clinical studies**

Study identifier	Study design	Population (incl number of subjects, healthy vs patient and gender ratio)	Dosing regimen	Main PK parameters
PKM14187	a single-center, open-label, non-randomized study	healthy adult subjects (n=6)	mouth wash with 42 mg eliglustat solution at 8.4 mg/ml for 3 times, separated by 2-hour intervals	AUC and C_{max}
PKM14281	3-sequence, three-period, cross-over, randomized, single and multiple dose administration	adult healthy CYP2D6 EM and PM participants (n=18)	dose intervals in each period: EM participants: single dose (days 1 and 7), BID (days 2 to 6) PM participants: QD (days 1 to 7)	AUC and C_{max}
EFC13738 (ELIkids)	Phase 3, open-label, two-cohort, multicenter study	paediatric GD1 and GD3 patients (n=57, 51 in Cohort 1 and 6 Cohort 2), CYP2D6 EM, IM and PM	Eliglustat adjusted dosing regimen after planned interim PK analysis: *EM/IM participants:* <u>12 to <18 years</u> ≥50 kg: 84 mg BID 25 - <50 kg: 84 mg BID <u>2 to <12 years</u> 25 - <50 kg: 84 mg BID 15 - <25 kg: 42 mg BID 10 - <15 kg: 12.6 mg BID (no data) *PM participants:* <u>12 to <18 years</u> ≥50 kg: 42 mg QD 25 - <50 kg: 21 mg QD (no data) <u>2 to <12 years:</u> 25 - <50 kg: 21 mg QD (no data)	AUC and C_{max}

			15 - <25 kg: 12.6 mg QD (no data) 10 - <15 kg: 8.4 mg QD (no data)	

BID = twice daily; EM = extensive metabolizer; IM = intermediate metabolizer: PM = poor metabolizer; QD = once daily

2.6.2. Clinical pharmacology

2.6.2.1. Pharmacokinetics

Analytical methods

Two validated methods were applied in the analysis of eliglustat in plasma. Both methods have been submitted/applied in previous applications. Validation proved that the methods were specific, precise and accurate. Stability was shown covering study sample handling and storage.

Within study validation data showed that the method performed within normal criteria. Incurred sample reanalysis showed reproducible results for both methods.

For the PD biomarkers GL-1, lyso-GL-1 and chitotriosidase, validated methods were applied. Validation proved that the methods were precise and accurate. Stability was shown covering study sample handling and storage. For the biomarker ACE, a diagnostic laboratory developed test.

Within study validation data showed that the methods performed within normal criteria.

Evaluation and qualification of models

Two popPK analyses were submitted, i.e. SIM0218, a PopPK analysis to characterize absorption of eliglustat via oral mucosa in adult and paediatric populations, and POH0969, a PopPK analysis of eliglustat using data from paediatric participants with GD.

For SIM0218, basic diagnostic plots revealed that the model was consistent with the observed data and no systemic bias was evident for each study, this was corroborated by various other diagnostic plots: CWRES standard normal QQ and CWRES vs. PRED plots, individual plots of observed, PRED and IPRED vs time.

For POH0969, the evaluation of all goodness of fit did not reveal a major bias in both EM/IM and PM models. PK variabilities and median concentrations were well predicted for all CYP2D6 phenotypes in both sub models, and the pcVPCs showed that a majority of the observed concentrations were included within the range (5^{th} to 95^{th} percentiles).

Next to the 2 popPK analyses, 2 PBPK analyses were submitted, i.e. SIM0351, a PBPK modelling to predict eliglustat pharmacokinetics and support dose selection in paediatric population with Gaucher disease, and PBM0142, a PBPK analysis to characterize eliglustat PK in paediatric participants with GD (for the primary analysis period).

The PBPK model performance of SIM0351 was validated using observed eliglustat PK data in adults. Although SIM0351 simulated eliglustat exposure in the paediatric population at the recommended dosing regimen were comparable with the simulated exposures in adults, based on the results of subgroup PK analyses in paediatrics in EFC13738, the 90% CIs of the geometric mean of C_{max} and AUC were below the target

exposure predicted by the previous PBPK model SIM0351 in the 2 to <12 year age group, suggesting that the previous PBPK model overestimated the PK exposure in the younger paediatric population at the specific dose regimen initially selected in study EFC13738. The paediatric PBPK model was updated and was qualified using the observed paediatric PK data from study EFC13738. The model was subsequently employed to simulate the eliglustat PK for different dosing regimens in various subgroups of paediatric patients, stratified by CYP2D6 phenotypes and BW ranges. Simulated eliglustat exposures in paediatric populations at the recommended doses were comparable with the simulated exposures in adult EM and IM populations at the approved therapeutic dose of 84 mg BID, and in adult PM population at the approved dose of 84 mg QD. However, regarding the PM model, only 1 subject could be included. Considering that the model seems to underpredict the exposure, this fact indicates that the model is not sufficiently appropriate. Therefore, the model can be considered not convincingly qualified to be fit-for-purpose for simulating exposure in paediatric PMs.

Absorption

As an oral suspension to be given to paediatric patients was initially proposed as an alternative method of administration as part of this application, the possible extent of absorption through the buccal and sublingual mucosa has been evaluated. After dosing adult subjects with 42 mg eliglustat solution at 8.4 mg/ml for 3 times, separated by 2-hour intervals over the course of 1 day, using SyrSpend SF cherry flavor syrup as the vehicle, and holding the solution 30 seconds in the mouth, it was shown that eliglustat is absorbed through the buccal and sublingual mucosa. It was predicted that this would lead to an increase in $AUC_{0\text{-}24h}$, Cmax, and C_{trough} by about 24, 14, and 38%, respectively, in paediatrics ((2 to 6 years of age, 16.5 kg body weight and CYP2D6 EM) when dosed at 21 mg BID of eliglustat in oral suspension and held for at least 30 seconds in the mouth before ingestion). However, holding the suspension in the mouth for 30 seconds will give an overestimation of the additional absorption, as in clinical practise the suspension will be directly swallowed. So, no clinically relevant effect is expected.

It should be noted that the proposed alternative method of administration (oral suspension) was withdrawn by the MAH following the CHMP assessment of all available data. Cerdelga is to be taken orally in children who can swallow intact capsule.

Eliglustat pharmacokinetics shows a high between-subject variability of about 50 – 75%, due to the CYP2D6 metabolism, an enzyme known to be subject to polymorphism. Variability is comparable in the paediatric population.

Bioavailability/bioequivalence

The oral bioavailability estimated by the final Pop PK analysis is approximately 6.4% in paediatric CYP2D6 EMs and IMs, similar to the observed absolute oral bioavailability in adults (about 4.5%) (presented in the initial marketing authorisation application (MAA) for adults (study GZGD02107)).

In the clinical trials included in the current application, eliglustat capsules of 21 mg, 42 mg, and 84 mg were used. The 21 and 42 mg capsules contain the same blend as used for the 84 mg capsule. To support the comparable bioavailability, *in vitro* dissolution data using 900 ml media pH 1.2, 4.5 and 6.8, paddle apparatus 50 rpm or basket apparatus 100 rpm, for the 21 mg and 42 mg capsule versus the 84 mg capsule should have been provided. However, considering that eliglustat is a highly soluble drug substance, and considering that for the 21, 42 and 84 mg capsules the same blend has been used, and considering the very

rapid dissolution of the 21 and 84 mg strength, it is expected that similar results will be obtained for the 42 mg strength. Furthermore, dose proportional pharmacokinetics is observed over the 21 -84 mg dose range, using 21 mg, 42 mg and 84 mg capsules.

Eliglustat was also made available as an oral suspension for the paediatric clinical trial EFC13738 for subjects who were unable to swallow capsules or for any other subjects requiring a dose <21 mg. Eliglustat 844 mg powder (the same blend as used for the capsules) was reconstituted at a concentration of 4.2 mg/mL (equivalent to 5 mg/ml of eliglustat tartrate) as an oral suspension. In the European Union, eliglustat oral suspension was provided to the EFC13738 study sites in the form of powder for oral suspension with a suspending agent, SyrSpend SF Cherry. For the non-EU study sites, pharmacy compounding of eliglustat capsules with the suspending agent, SyrSpend, was allowed.

Dissolution data (900 ml of medium at 37°C, paddle apparatus at 75 rpm) between the oral suspension and the 84 mg capsule showed very rapid dissolution (>85% within 15 min). It is demonstrated that at pH 1.2, very rapid dissolution is observed for the 84 mg capsule and SyrSpend suspension. Considering that eliglustat is a highly soluble drug substance, comparable results are expected at pH 4.5 and 6.8. This also accounts for the Ora-Plus/Ora-Sweet suspension.

No bioavailability study is carried out with the suspension. As the suspension is prepared from the same blend as the capsules, a pronounced effect is not expected. PopPK analysis showed that the suspension resulted in a 33% and 10% higher exposure in EM and IM subjects, respectively. The applicant indicated that buccal and sublingual mucosal absorption may be a factor contributing to the higher exposure. Buccal and sublingual mucosal absorption of eliglustat will escape from the first pass metabolism. In IM subjects this increase is smaller, due to the less pronounced first pass metabolism compared to EM subjects. However, as concluded before, it seems unlikely that mucosal absorption is the main factor, as the contact time is limited. As indicated by the applicant, other factors may have also contributed, like the fact that the simulation results were based upon only 6 subjects receiving the suspension. In addition, a formulation effect cannot be excluded either. However, eliglustat exposures with the oral suspension are expected to be within the overall exposure range observed in the adult population.

However, it should be noted that the proposed alternative method of administration (oral suspension) was withdrawn by the MAH following the CHMP assessment of all available data. Cerdelga is to be taken orally in children who can swallow intact capsule.

Distribution

Based on the PopPK model, the BW normalized volume of distribution in the paediatric participants is assumed to be about 10.7 L/kg.

Elimination

From the initial MAA it is known that 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.

Dose proportionality and time dependencies

Eliglustat displayed non-linear PK for doses higher than 84 mg. It was not known what the behaviour is for the lower dose range of 21 mg to 84 mg. This study investigated the dose proportionality for eliglustat in the lower dose range. It assessed dose proportionality for three doses of eliglustat (21 mg, 42 mg, and 84 mg capsules) after single and repeated (twice daily for CYP2D6 EMs and once daily for CYP2D6 PMs) administration in healthy adults.

Metabolism is the primary elimination pathway for eliglustat and renal clearance (5.27 l/h) represents only about 6% of total systemic clearance (85.8 l/h). Eliglustat is mainly metabolized by CYP2D6 and to a lesser extent by CYP3A4. In healthy EM subjects, after oral administration of single and repeated doses of 42 mg to 127 mg eliglustat b.i.d., C_{max} and AUC values increased in a more than dose proportional manner over the entire dose range.

Several factors might contribute to the non-linear kinetics of eliglustat. Eliglustat is both a competitive and time-dependent inhibitor of CYP2D6 as well as a substrate of CYP2D6. From previous studies it is known that after repeated doses, C_{max} and $AUC_{0\text{-}12h}$ values increased in only a slightly more than dose-proportional manner for a two-fold increase in eliglustat dose from 42 to 84 mg BID (2.37-fold and 2.75-fold, respectively), and in a more than dose-proportional manner for a 1.5-fold increase in eliglustat dose from 84 to 127 mg b.i.d. (increases of 2.73-fold and 3.06-fold, respectively). The observed supra-dose proportionality after oral administration is plausibly related to auto-inhibition of CYP2D6.

The current study confirmed the non-proportional PK in EM subjects. Supra-dose-proportionality of C_{max} and AUC on Day 7 appeared to be stronger than those on Day 1 based on beta estimates, and this is in accordance with the fact that eliglustat is both a substrate and a mechanism-based inhibitor of CYP2D6, thus could auto- inhibit its own metabolism, and the extent of auto-inhibition accumulates with time.

In PM subjects a dose proportional increase is observed after single as well as after multiple doses. This can be explained by the fact that PM subjects have less CYP2D6 activity compared to CYP2D6 EMs, and thus auto-inhibition of CYP2D6 plays a lesser role.

The accumulation ratio and the time required to reach steady state and day for eliglustat appear to be comparable between paediatric and adult populations.

Special populations

This application concerns an extension of the indication to the paediatric population.

Physiologically based PK simulations (report SIM0351) were performed in a virtual population of 500 or 1000 paediatric participants to identify the appropriate dose regimens for the 2 age groups (2 to <12 years old and 12 to <18 years old) and 3 CYP2D6 phenotype groups (EM, IM, and PM). These doses were applied in study EFC13738. Dose verification was conducted at an individual as well as subgroup level based on PK at week 2. It appeared that for participants in the 12 to <18-year age group with a BW ≥25 kg, the results showed that the dosing regimen of 84 mg BID achieved the desired target exposure. However, in the 2 to <12-year age group, the 90% CI of the geometric mean of both PK parameters (C_{max} and $AUC_{0\text{-}tau}$) were outside the 5^{th} to 95^{th} percentile of the target exposure. Therefore, the eliglustat doses were increased from 21 mg BID to 42 mg BID and from 42 mg BID to 84 mg BID for CYP2D6 EM and IM participants with BW of 15 to <25 kg in the 2 to <12-year age group, and 25 to <50 kg in both 2 to <12-year and 12 to <18-year age groups, respectively.

Week 52 confirmed that appropriateness of the revised dose regimen. The revised dose regimens applied for CYP2D6 EM/IM participants were the same as the final recommendation doses and have been shown to be safe and efficacious in the corresponding paediatric population. The observed eliglustat PK exposure in paediatric CYP2D6 EM participants at the recommended doses was comparable to those in adult participants at approved dose of 84 mg BID and were also generally within the target exposure which was pre-defined in the study protocol (within the target exposure 5^{th} - 95^{th} percentile of PBPK-predicted exposure in adults at steady state). As limited PK data was collected in paediatric participants who were CYP2D6 PMs and IMs, the recommended doses were primarily justified by PopPK and PBPK modelling and simulation using the PK exposure matching approach.

Although the data show comparable exposures, the PK exposures observed in CYP2D6 EM participants are confounded by the dose-titration design employed in the adult Phase 2/3 studies. Therefore, additional simulations were performed using the Pop PK model (POH0969) to compare PK exposures in virtual CYP2D6 EM adults receiving 84 mg BID and virtual CYP2D6 paediatric patients following the recommended dose regimens. The results show that in virtual paediatric CYP2D6 PM patients, simulated PK exposures at 84 mg QD with BW ≥50 kg matched the adult PK exposure at 84 mg QD (approved dose). The simulated median PK parameters (i.e. C_{max} and $AUC_{0\text{-}tau}$) at 42 mg QD with BW 25 to <50 kg and at 21 mg QD with BW 15 to <25 kg were slightly lower than the adult PK exposure at 84 mg by about 16% to 18% and 33% to 35%, respectively. However, eliglustat exposures in paediatric PM patients were generally within the overall exposure range simulated in the adult PM population.

Furthermore, as indicated before, the PM model was based upon inclusion of data from 1 subject and has not been convincingly qualified to be fit-for-purpose for simulating exposure in paediatric PMs. It is expected there will be no further ongoing CYP2D6 enzyme maturation in children ≥ 6 years of age. Therefore, the most reasonable dosing recommendation is to use the same approach as in heavier children (≥25kg) and adults where the dose amount is kept in PMs and only the dosing interval is extended (QD instead of BID). However, it is argued that although only 1 PM patient was included and uncertainties may arise considering the qualification of the model, the overall model, which included EM and IM data, performed well. The model predicts an up to 71% higher exposure applying the suggested higher doses, which may raise concerns regarding safety. As this is the only data to support the dosing, the more conservative approach is acceptable.

Table: Final recommended dose regimens for paediatric patients with GD1

Weight	EMs and IMs	PMs
≥50 kg	84 mg BID	84 mg QD
25 - <50 kg	84 mg BID	42 mg QD
15 - <25 kg	42 mg BID	21 mg QD

Abbreviations: GD1 = Gaucher disease type 1; BID = twice daily; EM = extensive metabolizer; IM = intermediate metabolizer: PM = poor metabolizer; QD = once daily.

No dose regimen can be recommended for GD1 patients below the age of 6 years or <15 kg BW or GD3 paediatric patients, due to the limited available clinical data.

Further, it should be noted that the proposed alternative method of administration (oral suspension) was withdrawn by the MAH following the CHMP assessment of all available data. Cerdelga is to be taken orally in children who can swallow intact capsule.

2.6.2.2. Pharmacodynamics

Mechanism of action

Gaucher disease is caused by a deficiency of the lysosomal enzyme, β-glucosidase (also known as glucocerebrosidase), that results in the accumulation of its major natural substrate, glucosylceramide, especially in the liver, spleen, and bone marrow. 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

In clinical trials in treatment-naïve GD1 patients, plasma GL-1 levels were elevated in the majority of these patients and decreased upon Cerdelga 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 Cerdelga treatment), plasma GL-1 levels were normal in most patients and decreased upon Cerdelga treatment. In line with this, paediatric participants who received eliglustat monotherapy after being stabilized on ERT in the ELIkids study had a decrease in GL-1 levels from baseline through Week 52 and Week 104.

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.

Thus the use of eliglustat in combination with Class IA and Class III antiarrhythmic medications was prohibited in the ELIkids study.

A standard 12-lead ECG was conducted at screening to evaluate exclusion criterion. Holter monitoring was conducted only for patients aged 12 years to <18 years. It was determined, following the planned interim subgroup PK analysis in the 12 to <18-year age group, that Holter monitoring was not necessary to be conducted in participants in the 2 to <12-year age group.

PCSA criteria were evaluated for heart rate, PR interval, QRS interval, QT interval, QTcB and QTcF.

In one participant, although interpreted as not clinically significant by the central reader, ECG abnormalities observed at Week 52 Holter were deemed clinically significant by the investigator and reported as AESI (sinus tachycardia)(see Clinical Safety below).

PK/PD

Exploratory PK/PD analyses showed that out of the 4 main efficacy endpoints, a linear relationship was observed for percent change in platelet count and absolute change in haemoglobin level with higher eliglustat exposure resulting in an increase in percent change in platelet count and absolute change in haemoglobin level. The effect of eliglustat exposure on haemoglobin level was minimal (~0.2 g/dL increase with a 10-fold increase in eliglustat exposure) and was not considered to be relevant. The effect was more apparent between eliglustat exposure and percent change in platelet count. However, the observed exposure

dependency with platelet count was also not considered to be clinically relevant as >96% of participants maintained platelet counts within the prespecified therapeutic goal. No apparent PK/PD relationship was observed for percent change in spleen volume (multiples of normal [MN]) and liver volume (MN) from baseline at Week 52 over the exposure range.

2.6.3. Discussion on clinical pharmacology

The new strength 21 mg capsule is dose proportional with the 84 mg capsule.

PopPK and PBPK modelling was used to support the dose posology in paediatric patients in study EFC13738. An initial dose recommendation was based upon modelling from adult data and scaling factors, which should result in an exposure within the target exposure 5^{th} - 95^{th} percentile of PBPK-predicted exposure in adults at steady state. After dose verification at week 2, it appeared that in the 2 to <12-year age group the target exposure was not obtained, and the model needed to be updated with paediatric PK data. The new suggested dose recommendations were applied and at week 52, the data were used to confirm the appropriateness of the revised dose regimens. As PK exposure was confounded in the study by dose titration, additional simulations were carried out to support the dose regimen in paediatric patients. It is expected there will be no further ongoing CYP2D6 enzyme maturation in children ≥ 6 years of age. Therefore, it is recommended to apply a comparable dosing strategy as those for adults and EM/IM patients, and instead of BID, apply a QD regimen.

No dose regimen can be recommended for GD1 patients below the age of 6 years or <15 kg BW or GD3 paediatric patients, due to the limited available clinical data.

It should also be noted that the initially proposed alternative method of administration (oral suspension) was withdrawn by the MAH following the CHMP assessment of all available data. Cerdelga is to be taken orally in children who can swallow intact capsule.

The pharmacodynamic endpoints GL-1 and GM3 were included as supportive and exploratory endpoints in the ELIkids study. Modest decreases/maintenance of GL-1 and GM3 levels were observed as can be expected for patients who are stable and well managed on ERT.

Exploratory PK/PD analysis were conducted, a linear relationship was observed for percent change in platelet count and absolute change in haemoglobin level with higher eliglustat exposure resulting in an increase in percent change in platelet count and absolute change in haemoglobin level. However, as the majority of patients remained within their therapeutic goals after the switch to eliglustat, the dose-response relationship is not considered relevant.

2.6.4. Conclusions on clinical pharmacology

The PK is sufficiently evaluated. Simulations supported the proposed posology. Furthermore, the PD and PK/PD analysis support the proposed posology and paediatric indication.

2.6.5. Clinical efficacy

2.6.5.1. Dose response study

There was no dedicated dose finding study in paediatric patients. The proposed dosing regimen is mainly based on PK analysis.

2.6.5.2. Main study

Study EFC13738, ELIKIDS

Methods

This was a Phase 3, open-label, two-cohort, multicenter study to evaluate the safety, pharmacokinetics (PK) and efficacy of eliglustat alone or in combination with imiglucerase in pediatric participants aged 2 to less than 18 years old with GD1 and GD3.

The study includes:

- A screening period that can extend from Day -60 to Day-1.
- A primary analysis treatment period (PAP) from Day 1 to Week 52.
- A long-term treatment period from Week 53 to Week 104.
- An extension period from Week 104 to the end of study.

The study enrolled 2 age groups in a sequential manner:

- The first age group consisted of patients aged 12 to <18 years.
- The second age group consisted of patients aged 2 to <12 years (with at least 6 patients aged 2 to <6 years).

The younger age group started enrollment once 10 patients in the older age group had reached 6 months of treatment with eliglustat and no safety concerns had been identified by the Sponsor and the Data Monitoring Committee (DMC).

Study Participants

Male and female participants ages 2 to <18 years who were clinically diagnosed with GD1 or GD3 with documented deficiency of acid β-glucosidase activity by enzyme assay and *GBA* genotype were enrolled in this study.

In addition, participants needed to be CYP2D6 EM, IM, or PM and not have clinically significant disease(s) other than GD or neurological symptoms other than oculomotor apraxia at study entry.

Cohort 1 enrolled GD1 and GD3 participants who reached prespecified therapeutic goals, as defined by:

a) Haemoglobin level for ages 2 to <12 years: ⩾11.0 g/dL; for ages 12 to <18 years: ⩾11.0 g/dL for females and ⩾12.0 g/dL for males, and

b) Platelet count ⩾100 000/mm^3, and

c) Spleen volume <10.0 multiples of normal (MN) and d) Liver volume <1.5 MN, and

In addition, this cohort enrolled patients who did not have Gaucher-related pulmonary disease, severe bone disease, or persistent thrombocytopenia, and had been receiving ERT for at least 24 months with treatment ongoing at the time of enrollment.

Cohort 2 enrolled GD1 and GD3 participants who, despite adequate/optimal treatment with ERT for at least 36 months prior to enrollment and ongoing at the time of enrollment, had prespecified severe clinical manifestations of GD (pulmonary disease, symptomatic bone disease, or persistent thrombocytopenia).

Given the proposed indication, the primary focus of assessment in this procedure is on GD1 patients, > 6 years of age from Cohort 1 (eliglustat monotherapy).

Treatments

Eliglustat was the investigational medicinal product (IMP), or primary study treatment used in Cohort 1 as a monotherapy.

- The eliglustat doses included: 21, 42, and 84 mg hard gelatin capsules. Each capsule contained respectively 25, 50, and 100 mg eliglustat tartrate, which was equivalent to 21, 42, and 84 mg of eliglustat (free base). Eliglustat was administered daily (QD) for PM participants or twice daily (BID) for non-PM participants, orally with water.
- Eliglustat was made available as pharmacy-prepared eliglustat oral suspension only for participants who were unable to swallow capsules. No participants required oral suspension for dosing less than 21 mg, given that there was no participant less than 15 kg during the study, and based on metabolizer status. Of note, in the EU, eliglustat oral suspension was provided to study sites in the form of eliglustat powder for oral suspension with suspending agent, SyrSpend, while non-EU study sites were allowed pharmacy compounding of eliglustat capsule with the suspending agent, SyrSpend. The appropriate pharmacy instructions were provided to the respective sites.

The eliglustat dose regimen for participants was commensurate with their CYP2D6 metabolizer status and bodyweight at baseline. The initial dose regimen was adjusted after the planned interim analysis. The interim subgroup PK analysis of the first 10 EM participants in the 2 to <12-year age group showed that the lower bound of the 90% CI of geometric mean of both C_{max} and $AUC_{0-\tau}$ were lower than the 5th percentile of PK target exposure. As a result, the dose regimen in the weight categories of ≥15 kg to <25 kg (21 mg BID → 42 mg BID), and ≥25 kg to <50 kg (42 mg BID → 84 mg BID) in all age groups was subsequently adjusted to the next higher dose level for EMs and IMs. This dose adjustment was also implemented for all participants entering the study as of July 2021. All participants in both age groups who either initiated treatment or continued treatment received doses aligned with the Revised Dose Regimen. Of note, no participants were enrolled weighing ≥10 to <15 kg.

Table: Revised Dose Regimen – Post interim Subgroup PK analysis

Age Group	Weight	EMs and IMs	PMs
12 to < 18 years	≥50 kg	84 mg BID	42 mg QD
	25 - <50 kg	84 mg BID	21 mg QD
2 to < 12 years	25 - <50 kg	84 mg BID	21 mg QD
	15 - <25 kg	42 mg BID	12.6 mg QD
	10 - <15 kg	12.6 mg BID	8.4 mg QD

BID = twice daily; EM = extensive metabolizer; IM = intermediate metabolizer: PM = poor metabolizer; QD = once daily.

Concomitant therapies

Information on all concomitant medications (defined as all prescription and non-prescription medications, herbal supplements, traditional medications, etc.) were recorded on the Medication eCRF. Concomitant medications are those the participants used at any time from the first administration of IMP up to the last IMP intake + 5 days.

During the study, use of medications affecting CYP2D6 or CYP3A4 activity (i.e. CYP2D6/CYP3A inhibitors and CYP3A strong inducers), which alter eliglustat plasma concentrations, and Class IA and Class III antiarrhythmic medications, which are known to prolong QTc interval, were restricted or prohibited. An overview of the allowed and prohibited inhibitors and inducers as determined by the patient's CYP2D6 phenotype is provided in the study protocol. Investigators were provided with a list of prohibited drugs.

Rescue therapy

Step 1: During the study PAP or LTP, patients in Cohort 1 who met at least one of the following rescue criteria due to a decline in GD status (after other causes had been eliminated, and treatment compliance of at least 90% had been demonstrated) could be switched from eliglustat monotherapy to imiglucerase monotherapy (60 U/kg/2 weeks) through Week 104.

- The patient’s haemoglobin level falls below 8.0 g/dL and remains below 8.0 g/dL when testing is repeated at least 2 weeks later.
- The patient’s platelet count falls below 45 000/mm3 and remains below 45 000/mm3 when testing is repeated at least 2 weeks later.
- The patient experiences a clinically significant bleeding episode assessed by the Investigator as related to a low platelet count.
- The patient’s spleen volume in MN increases by 35% compared to baseline volume and the increase is confirmed at least 4 weeks later.
- The patient’s liver volume in MN increases by 35% compared to baseline volume and the increase is confirmed at least 4 weeks later.
- Any other decline in GD status, which in the opinion of the Investigator warrants treatment with ERT.

It is important to note, guidelines for rescue therapy do not account for individual participant's baseline values. As such, it was possible to qualify for rescue therapy due to the magnitude of change from baseline while maintaining values within the prespecified therapeutic goals.

Imiglucerase was administered intravenously according to the SmPC.

Step 2: Patients who, after 6 months of rescue therapy with imiglucerase monotherapy (60 U/kg/2 weeks), did not show improvement (according to the criteria below) in the parameter(s) that led to the switch from eliglustat to imiglucerase, would then receive combination therapy with eliglustat until the end of the long-term treatment period.

Objectives

The primary objectives of this study is to evaluate the safety and pharmacokinetics (PK) of eliglustat in paediatric patients (≥2 to <18 years old). The secondary objective of this study is to evaluate the efficacy of eliglustat and quality of life in paediatric patients (≥2 to <18 years old).

One of the exploratory efficacy objectives of this study is to evaluate the efficacy of eliglustat relative to ERT with imiglucerase using historical control data in paediatric participants from the ICGG Gaucher Registry.

Outcomes/endpoints

The primary safety endpoints included:

- Type, frequency, rate, severity, seriousness and relationship to study treatment of any AEs;
- Drug discontinuation due to AE;
- Laboratory tests (chemistry, haematology and urinalysis) and pregnancy;
- Vital signs;
- Cardiac electrophysiology assessments (including 24-hour 12-lead Holter recording and extracted ECGs, all centrally read) only for participants aged 12 to <18 years;
- The abnormalities of physical examination (including sexual maturation [pubertal status; Tanner stage], asthenia, gastro-intestinal, and clinical neurologic examinations);
- Neuropsychological testing by age-appropriate scales;
- Echocardiogram (ECHO) with Doppler only for GD3 patients or patients with known pulmonary artery hypertension (PAH);
- Brain magnetic resonance imaging;
- Hearing test (audiometry or electro-acoustical emissions depending on age);
- Electroencephalograms in participants with a clinical diagnosis of GD3 and in participants carrying mutations other than N370S;
- Nerve conduction velocity, performed for cause in all GD patients and at screening and Week 104 in GD3 patients and repeated as clinically indicated at experienced sites (with electromyography if clinically indicated).

The primary PK endpoints included:

- C_{max} at Week 2, Week 13, Week 26 and Week 52;
- $AUC_{0-\tau}$ at Week 2 and Week 52.

The key secondary endpoints related to evaluating the efficacy included:

- Mean absolute change from baseline of haemoglobin (g/dL and mmol/L) at Week 52;
- Mean percentage change from baseline of platelets (mm^3) at Week 52;
- Mean percentage change from baseline of spleen volume (MN) at Week 52;
- Mean percentage change from baseline of liver volume (MN) at Week 52;
- To evaluate the quality of life in paediatric participants (2 to <18 years old).

Growth rate (height, height Z-score, weight, BMI), was a supportive efficacy endpoint.

Exploratory endpoints will evaluate: descriptive statistics of the absolute change from baseline of haemoglobin, the percentage changes from baseline of platelets, spleen volume (MN) and liver volume (MN) at Week 52 will be provided. The differences between eliglustat treated participants in Cohort 1 and matched imiglucerase treated Registry participants will be calculated, along with 95% confidence intervals.

Sample size

At least 60 patients were expected to be enrolled. The sample size determination was not based on statistical power consideration, but rather was based on empirical results from eliglustat clinical pharmacology studies in adults that provided descriptive information on eliglustat PK.

The study was planned to include at least 40 GD1 patients and at least 6 GD3 patients with approximately 20 patients in each age group (2 to <12 years and 12 to <18 years) in Cohort 1.

In Cohort 1 and Cohort 2 combined, at least 3 patients with a predicted phenotype of cytochrome P450 (CYP) 2D6 Poor Metabolizer (PM) and at least 10 GD3 patients were planned to be recruited.

Randomisation and blinding (masking)

This study was an open-label, two cohort design without randomization. No blinding procedures were applicable.

Statistical methods

Defined population sets:

Pharmacokinetic Set

All patients exposed to at least one dose of study drug with no major or critical deviations related to study drug administration, and for whom the primary PK data was considered sufficient and interpretable, were included in the PK population.

Safety Set

All patients who were exposed to study drugs (eliglustat and imiglucerase), regardless of the amount of treatment administered, were included in the summaries of safety.

Full Analysis Set (FAS)

Efficacy endpoints will be analysed using the FAS. The FAS is the same as the safety set, including all patients enrolled in the study who received at least one dose of study medication.

Primary endpoint (safety)

Safety and PK analysis were performed in the safety population and PK population respectively.

The overview of TEAEs were presented, summarizing number (%) of participants with any of the following conditions overall and by cohort and treatment phases. The overview of TEAEs was also presented by dose regimen and weight category.

Key secondary endpoints (efficacy)

Efficacy endpoints were analyzed in the FAS. No hypothesis testing will be performed. Efficacy endpoints were summarized descriptively. The main efficacy analysis was evaluated at Week 52, whereas a descriptive summary was also provided at other visits through Week 104.

The absolute change of haemoglobin (g/dL and mmol/L) and percentage change of platelets ($\times 10^9$/L), liver volume (MN), and spleen volume (MN) from baseline to Week 52 were summarized using the number of observations available, mean, SD, median, Q1, Q3, minimum, and maximum. The 95% confidence interval of the change from baseline was calculated.

Two blood samples collected 12-36 hours apart at screening, and Week 26, 52 and 104 visits were used in efficacy analyses. The average of the two values at each scheduled visit for each parameter was used as efficacy endpoints. If one of the two assessments was missing, the single assessment result was used. Spleen and liver volumes were measured from the abdominal MRI which were performed at screening, and Week 26, 52 and 104.

The primary analyses were performed once all the patients completed the PAP.

If patients switch to rescue therapy before Week 52, the last available values of efficacy endpoints during the eliglustat monotherapy will be used for the efficacy analyses at Week 52. If patients have missing results at Week 52 or patients discontinue the study before Week 52, the last available values of efficacy endpoints will be used for the efficacy analyses at Week 52. For the efficacy analyses at other visits, only the patients who have the non-missing values at corresponding visits will be included into the analyses.

Quality of life and pubertal development

Health-related quality of life status were evaluated by the PedsQL™ questionnaires. PedsQL evaluation consisted of participant self-assessment of the generic core scale, fatigue, and pain report categories of questions and parental assessment of the generic core scale, fatigue, pain report, and family impact.

Tanner scale was used to define physical measurements of growth and development based on external primary and secondary sex characteristics, such as the size of the breasts, genitalia, and development of pubic hair. Tanner staging was performed at screening, and every 26 weeks up to Week 104.

ICGG Historical control

Historical control data from the ICGG Gaucher Registry sponsored by Genzyme were used to evaluate the main efficacy endpoints of eliglustat relative to ERT with imiglucerase. Enzyme replacement therapy is the standard of care for paediatric with GD1. For patients participating in the eliglustat paediatric study, patients with similar baseline characteristics were selected from the registry in order to evaluate eliglustat treatment relative to imiglucerase treatment as described below. Thus, eliglustat-treated patients aged 2 to <18 years were matched with registry imiglucerase-treated patients aged 2 to <18 years. All data submission is voluntary and there are no pre-determined follow-up periods. The physicians determine the frequency and nature of follow-up assessments for each patient.

Matching of study and Registry participants were performed for Cohort 1 and Cohort 2 participants separately. Depending on the number of eligible participants from the ICGG Gaucher Registry, 1: k matching or variable ratio matching may be applied. Participants were matched without replacement with a 1:1 ratio and using optimal matching on the logit of the propensity score (LPS) with exact matching on GD type. Registry participants whose propensity scores lie in the region of the logit of propensity scores for study participants in the treated group were selected to match participants in the clinical study.

Unlike clinical trial participants, ICGG Gaucher Registry participants may have more than one possible enrolment time. For Registry participants, eligibility will be assessed using enrolment periods defined using an incremental 6-month shift during the period when the participant meets eligibility criteria. If a patient has more than one possible enrolment time, the window with the most recent enrolment time (i.e. most recent calendar time) will be selected so that the enrolment time of the ICGG Gaucher Registry participants will be closer to the enrolment time of the trial participants, as the trial was initiated after most Registry participants had initiated ERT. For trial participants, endpoints at Week 52 will be analyzed. For Registry participants, endpoints at the assessment closest to Week 52 during follow-up (but at least 11 months after enrolment) will be analyzed.

The SAP specifies that logistic regression will be used to generate a propensity score for the patients in Cohort 1 and the selected ICGG Gaucher Registry patients. In Cohort 1, treatment received (eliglustat or imiglucerase) will be used as the dependent variable of the logistic regression, where the independent variables include: disease type (GD1 or GD3), weight, gender, age at GD diagnosis (years), age at enrolment (years), time on ERT treatment (years), baseline value of spleen volume (MN), liver volume (MN), platelet count (mm^3), and haemoglobin (g/dL). Matching with replacement may be used to increase the balance if the overlap between the two groups is insufficient. If there is poor balance between the two groups, the logistic model and/or matching method will be adjusted, e.g. modifying the specification of the logistic model (for example, by introducing nonlinear terms for the continuous variables or by adding interactions) or modifying the matching criteria or choosing another matching method.

The protocol, specifies that at a minimum, matching will take into account disease type (GD1 or GD3), age at the achievement of prespecified TGs on Cerezyme treatment or age at the beginning of ERT treatment (±1 year), time on ERT treatment, and baseline value of the following parameters: Cohort 1: Haemoglobin ±1 g/dL, Platelet count ±10 000/mm^3, Spleen volume ±3 MN, Liver volume ±0.3 MN.

After matching, the standardized mean differences (SMD) and variance ratio (VR) of baseline characteristics and LPS were summarized and compared between participants in the study and Registry participants. The acceptable range was <0.25 for SMD and 0.5-2.0 for VR.

The differences between eliglustat treated participants in Cohort 1 and matched imiglucerase treated Registry participants were calculated, along with 95% confidence intervals.

Results

Participant flow

In total, 72 participants were screened. Of these, 57 (79.2%) participants were enrolled, 51 in Cohort 1 and 6 in Cohort 2. Participants that were screened for the study but did not meet all inclusion criteria or met one or more of the exclusion criteria (n = 15; 20.8%).

Recruitment

Participant enrolment in this study was conducted from 06 June 2018 to 05 July 2022 at 21 sites in 10 countries (Argentina, Canada, France, Italy, Japan, Russia, Spain, Sweden, Turkey and United Kingdom).

Conduct of the study

Protocol deviations

One critical deviation occurred as of the cut-off date. Due to an incorrect weight measurement at baseline, a participant in Cohort 1 was assigned to an incorrect initial dose. The deviation was classified as investigational medicinal product (IMP) administered but not as per protocol. All other deviations reported were major.

In Cohort 1, 25 of the 51 (49.0%) participants had at least one major deviation. In Cohort 2, 4 (66.7%) participants had at least one major deviation. Overall, assessments/procedures were the main contributor to major deviations. In Cohort 1, 10 of 51 participants (19.6%) had a major deviation related to assessments/procedures (of these, 1 [2.0%] was COVID-19 related).

One participant was incorrectly enrolled in Cohort 1; discrete reticulonodular signs were identified by chest X-ray at screening. A second participant was enrolled in Cohort 1 but did not meet Inclusion Criteria 08; the participant had received a higher dose of ERT than allowed. Both participants qualified for rescue therapy during the PAP. In Cohort 2, 3 of 6 participants (50%) had similar deviations due to assessments/procedures.

Other major protocol deviation did not impact the safety of the participants in the study; no adverse events resulted from the deviations. Additionally, no major protocol deviations were expected to interfere with the assessment of efficacy as defined in the SAP.

Baseline data

Fifty-one participants were enrolled in Cohort 1, 18 participants in the 2 to <12-year age group, with only 3 being <6 years of age, and 33 participants in the 12 to <18-year age group. On average, the age of diagnosis was 4.9 years (range: 0.15 to 13.54 years). Forty-six participants (90.2%) were classified as GD1; 5 participants (9.8%) were classified as GD3. One participant was a PM and one an IM; all other participants in Cohort 1 were EMs. No participants enrolled weighed <15 kg.

Table: Demographics and participant/subject characteristics at baseline by cohort – Safety population

	Cohort 1 (N=51)	Cohort 2 (N=6)	All (N=57)
Age (years)			
Number	51	6	57
Mean (SD)	12.2 (3.4)	10.2 (4.5)	12.0 (3.5)
Median	12.0	9.5	12.0
Q1 ; Q3	10.0 ; 15.0	6.0 ; 13.0	10.0 ; 14.0
Min ; Max	3 ; 17	6 ; 17	3 ; 17
Age Group (years) [n(%)]			
Number	51	6	57
Children (2 to < 12)	18 (35.3)	3 (50.0)	21 (36.8)
Younger Children (2 to < 6)	3 (5.9)	0	3 (5.3)
Older Children (6 to < 12)	15 (29.4)	3 (50.0)	18 (31.6)
Adolescents (12 to < 18)	33 (64.7)	3 (50.0)	36 (63.2)
Gender [n(%)]			
Number	51	6	57
Male	25 (49.0)	4 (66.7)	29 (50.9)
Female	26 (51.0)	2 (33.3)	28 (49.1)
Race [n (%)]			
Number	51	6	57
White	45 (88.2)	5 (83.3)	50 (87.7)
Middle-Eastern	2 (3.9)	1 (16.7)	3 (5.3)
North Africa	3 (5.9)	0	3 (5.3)
Black or African American	0	0	0
Asian	3 (5.9)	1 (16.7)	4 (7.0)
Native Hawaiian or Other Pacific Islander	0	0	0
American Indian or Alaska Native	0	0	0
Not Reported	3 (5.9)	0	3 (5.3)
Unknown	0	0	0
Ethnicity [n (%)]			
Number	51	6	57
Hispanic or Latino	11 (21.6)	2 (33.3)	13 (22.8)
Not Hispanic or Latino	39 (76.5)	4 (66.7)	43 (75.4)
Ashkenazi Jew	1 (2.0)	0	1 (1.8)
Not reported	0	0	0
Weight (kg)			
Number	51	6	57
Mean (SD)	47.70 (15.63)	35.98 (19.96)	46.47 (16.34)
Median	49.10	32.20	47.00
Q1 ; Q3	34.00 ; 56.70	20.00 ; 43.30	33.70 ; 56.60
Min ; Max	15.2 ; 88.1	18.7 ; 69.5	15.2 ; 88.1
Height (cm)			
Number	51	6	57
Mean (SD)	151.90 (17.92)	138.55 (26.99)	150.49 (19.21)

	Cohort 1 (N=51)	Cohort 2 (N=6)	All (N=57)
Median	157.00	135.40	156.00
Q1 ; Q3	141.50 ; 164.00	115.00 ; 162.00	137.00 ; 164.00
Min ; Max	99.0 ; 183.0	111.0 ; 172.5	99.0 ; 183.0

For Cohort 1, Primary study treatment is eliglustat monotherapy; For Cohort 2, Primary study treatment is eliglustat plus imiglucerase combination therapy.

Overall, the population was well balanced between males and females (50.9% males versus 49.1% females) and was predominately White (87.7%) and of non-Hispanic/Latino descent (75.4%) in Cohort 1.

Participants' GD classification was based on clinical presentation and not genotype. GD classification was retained throughout the study regardless of the appearance of subsequent manifestations indicative of neuronopathic GD. Several participants enrolled in the study and classified as GD1 carried two severe GBA gene mutations commonly associated with neuronopathic GD (i.e. L444P in the homozygous state and L444P in combination with another severe mutation such as D409H).

Participants in Cohort 1 entered the study with haematologic values (i.e. haemoglobin level and platelet count) and organ volumes (i.e. liver and spleen) that met the prespecified therapeutic goals (see Study Participants for the inclusion criteria). At baseline, all 51 participants had haemoglobin levels and 47 participants had platelet counts within normal limits, respectively; 4 (7.8%) participants had mild thrombocytopenia (120 to <150 × 10^9/L). All participants had liver and spleen volumes in the normal or mild hepatomegaly and splenomegaly range except 4 (7.8%) who had moderate hepatomegaly (>1.25 to <2.5 MN) and 8 (15.8%) with moderate splenomegaly (>5.0 MN to <15.0 MN). Four of 44 participants (9.1%) having a DXA at baseline had total body Z-scores within the normal range; all other participants had scores consistent with osteopenia or osteoporosis (⩽-1 SD to >-2.5 SD and ⩽-2.5 SD, respectively). Two (4%) participants had a BMB score in the normal/mild range; all other participants had BMB scores in the moderate or severe range (moderate: 5 to 8; marked to severe: 9 to 16). No participant had a history of bone crisis within 12 months of enrolment, but 2 (3.9%) participants had a history of very mild bone pain within 4 weeks of enrolment. Chitotriosidase activity and lyso-GL-1 levels were elevated indicating active disease.

Table: Summary of baseline disease characteristics by cohort - Safety population

	Cohort 1 (N=51)	Cohort 2 (N=6)	All (N=57)
Gaucher Disease type [n (%)]			
Number	51	6	57
GD1	46 (90.2)	3 (50.0)	49 (86.0)
GD3	5 (9.8)	3 (50.0)	8 (14.0)
CYP2D6 metabolizer status [n (%)]			
Number	51	6	57
EM (aka NM)	49 (96.1)	6 (100)	55 (96.5)
IM	1 (2.0)	0	1 (1.8)
PM	1 (2.0)	0	1 (1.8)
Age at diagnosis (years)			
Number	51	6	57
Mean (SD)	4.938 (3.279)	2.324 (2.844)	4.663 (3.313)

	Cohort 1 (N=51)	Cohort 2 (N=6)	All (N=57)
Median	3.795	1.355	3.633
Q1 ; Q3	2.919 ; 7.351	0.849 ; 2.004	2.324 ; 7.296
Min ; Max	0.15 ; 13.54	0.38 ; 8.00	0.15 ; 13.54
Time on ERT prior to enrolment (years)			
Number	51	6	57
Mean (SD)	7.200 (3.752)	4.920 (1.249)	6.960 (3.634)
Median	6.984	4.908	6.075
Q1 ; Q3	3.997 ; 10.125	3.773 ; 6.075	3.997 ; 10.084
Min ; Max	2.00 ; 14.88	3.46 ; 6.40	2.00 ; 14.88
Spleen volume (MN)			
Number	51	5	56
Mean (SD)	3.364 (1.536)	3.670 (1.401)	3.391 (1.515)
Median	3.041	3.779	3.068
Q1 ; Q3	2.256 ; 3.933	2.981 ; 4.410	2.289 ; 4.162
Min ; Max	1.22 ; 7.95	1.75 ; 5.43	1.22 ; 7.95
Liver volume (MN)			
Number	51	6	57
Mean (SD)	0.977 (0.189)	1.110 (0.283)	0.991 (0.202)
Median	0.951	1.079	0.951
Q1 ; Q3	0.857 ; 1.062	0.866 ; 1.421	0.863 ; 1.124
Min ; Max	0.66 ; 1.50	0.80 ; 1.42	0.66 ; 1.50
Platelet Count (10^9/L)			
Number	51	6	57
Mean (SD)	213.692 (51.287)	251.667 (75.867)	217.689 (54.778)
Median	202.000	219.000	203.000
Q1 ; Q3	179.000 ; 251.300	192.000 ; 336.000	181.000 ; 251.300
Min ; Max	123.00 ; 338.00	185.00 ; 359.00	123.00 ; 359.00
Haemoglobin level (g/dL)			
Number	51	6	57
Mean (SD)	8.45 (0.65)	13.433 (1.542)	13.596 (1.099)
Median	8.50	13.600	13.700
Q1 ; Q3	7.94 ; 8.937	11.900 ; 13.900	12.800 ; 14.300
Min ; Max	7.09 ; 9.56	11.70 ; 15.90	11.40 ; 15.90

PM: Poor Metabolizer; NM: Normal Metabolizer; IM: Intermediate Metabolizer; EM: Extensive Metabolizer; NM=EM;
For Cohort 1, Primary study treatment is eliglustat monotherapy; For Cohort 2, Primary study treatment is eliglustat plus imiglucerase combination therapy

Numbers analysed

The table below summarizes the disposition of all enrolled participants in the study by cohort, age group and GD type.

Table: Number of Participants in Cohorts 1 and 2

Cohort	Age group	GD1	GD3	Total
Cohort 1	12 to <18 years	30	3	33
	2 to <12 years[a]	16	2	18
	(2 to <6 years)	(2)	(1)	(3)
	Total	46	5	51
Cohort 2	12 to <18 years	1	2	3
	2 to <12 years[a]	2	1	3
	(2 to <6 years)	(0)	(0)	(0)
	Total	3	3	6
Total		49	8	57

a This group includes the 2 to <6 years age group.

Most participants were more than 90% compliant overall during the PAP. Four participants in Cohort 1 (in the 12- <18 year of age category) had a compliance rate for eliglustat between 80% and 90%.

Of 51 patients, 3 patients discontinued the PAP, 2 on primary study treatment and one on rescue therapy step 1. Forty-eight patients finished the PAP, of which 46 on eliglustat treatment and 2 on rescue therapy step 1. Five patients permanently discontinued eliglustat.

Outcomes and estimation

The primary objective is to evaluate the safety and PK of eliglustat in paediatric patients.

The secondary objective is to evaluate the efficacy of eliglustat and quality of life in paediatric patients (⩾2 to <18 years old).

Key efficacy endpoints

The key efficacy endpoints assessed included absolute change in haemoglobin level (g/dL and mmol/L) and percent change for platelet count (x10^9/L), spleen volume (MN), and liver volume (MN), these are discussed individually below. Change from baseline in the different age groups of Cohort 1 for the haemoglobin, platelet, spleen and liver volume are summarized in the table below.

Table: 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] GD1: n = 2 GD3: n = 1	Haemoglobin Level (g/dL) (mmol/L)	12.25 (0.76) 7.61 (0.47)	11.93 (0.60) 7.41 (0.37)	-0.32 g/dL (0.20) -0.25 mmol/L (0.01)
	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] GD1: n = 14 GD3: n = 1	Haemoglobin Level (g/dL) (mmol/L)	13.70 (1.17) 8.51 (0.73)	13.21 (1.22) 8.20 (0.76)	-0.49 g/dL (1.17) -0.30 mmol/L (0.73)
	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] GD1: n = 30 GD3: n = 3	Haemoglobin Level (g/dL) (mmol/L)	13.75 (0.97) 8.54 (0.60)	13.37 (1.20) 8.30 (0.75)	-0.38 g/dL (1.01) -0.24 mmol/L (0.63)
	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)

Haemoglobin level

Forty-nine (96%) participants sustained haemoglobin levels above the prespecified therapeutic goal (see the Study Participants section for the TGs) for haemoglobin at Week 52.

During the PAP, the mean haemoglobin level at baseline for participants who received eliglustat monotherapy was 8.47 mmol/L (0.66). At Week 52, the mean (SD) haemoglobin level for participants in Cohort 1 was 8.22 mmol/L (0.75). The mean (SD) absolute change from baseline to Week 52 was -0.26 mmol/L (0.63).

Mean changes from baseline at 52 weeks were similar for the 6 to <12-year subgroup (-0.30 mmol/L (0.73)) and the 12 to <18 year subgroup (-0.24 mmol/L (0.63)).

Two participants that received eliglustat monotherapy had a decrease in haemoglobin levels to the level of anaemia (GD1, one 2 to <12-year age group, one 12 to <18-year age group) (anaemia: age >2 years to ⩽ 12 years: <10.5 g/dL; males aged >12 years: <12 g/dL; females aged >12 years: <11 g/dL). Both participants experienced declines in the other main efficacy parameters as well. Both participants completed the PAP and continued on treatment in the LTP.

Long term extension

The mean (SD) absolute change in haemoglobin for the participants who received eliglustat monotherapy (n=36) from baseline to Week 104 was -0.13 mmol/L (0.60) for a mean level of 8.41 mmol/L (0.73).

Of the two participants who had anaemia during the PAP, the older participant qualified for rescue therapy during the LTP for another reason. The second participant was receiving eliglustat monotherapy in the LTP. No additional participants who completed the LTP had haemoglobin levels below normal limits.

Platelet count

All but one participant (98%) sustained values at or above the prespecified therapeutic goal for platelet count (see the Study Participants section for the TGs).

At baseline, the mean (SD) platelet count for participants in the cohort was 215.33 × 10^9/L. (51.6). Four participants entered into the study with levels consistent with mild thrombocytopenia (120 to <150 × 10^9/L). At Week 52, the mean (SD) platelet count was 196.25 × 10^9/L (64.12). The mean (SD) percentage change from baseline was -7.87% (22.71).

There was an increase in the mean percent change from baseline at 52 weeks observed for the 6 to <12 year subgroup (7.25% (20.50)), while there was a decrease observed for the 12 to <18 year subgroup (-14.36% (20.67).

One participant (GD1, 2 to <12-year age group) with mild thrombocytopenia at baseline experienced an improvement in platelet counts into the normal range by Week 52. Six participants (5 GD1 and 1 GD3; 12 to <18-year age group) with normal platelet counts at baseline had mild thrombocytopenia at Week 52.

One participant (GD1, 12 to <18-year age group) with mild thrombocytopenia at baseline had moderate thrombocytopenia (⩾60 × 10^9/L to <120 × 10^9/L) at Week 52. A second participant (GD1, 12 to <18-year age group) had platelet counts within normal limits at baseline and moderate thrombocytopenia at Week 52. The latter patient is also discussion in section on haemoglobin levels.

Long-term extension

At Week 104, the mean (SD) platelet count of the 36 participants in the LTP that received eliglustat monotherapy changed by -5.04% (19.76) from baseline for a mean count of 193.36 × 10^9/L (61.60).

Three participants (GD1, 12 to <18-year age group) who were mildly thrombocytopenic in the PAP had counts increase into the normal range by Week 104. Two participants (GD1, 12 to <18-year age group) remained mildly thrombocytopenic from PAP through Week 104. One participant (GD1, 12 to <18-year age group) with mild thrombocytopenia levels in the PAP had counts in the mild range at Week 104. Three additional participants (one 2 to <12-year age group, two 12 to <18-year age group) with normal counts at Week 52 had mild thrombocytopenia at Week 104.

Liver volume

At baseline, the mean (SD) liver volume in MN for the participants who received eliglustat monotherapy was 0.98 MN (0.19). Forty-seven participants had values within the normal to mild hepatomegaly range at baseline (none/mild: <1.25 MN), while 4 participants had moderate hepatomegaly (>1.25 to <2.5 MN). At Week 52, the mean (SD) liver volume in MN of the participants was 0.98 (0.21). The mean (SD) percentage change from baseline in liver volume was 0.95% (13.45).

Mean percent changes from baseline at 52 weeks were similar for the 6 to <12 year subgroup (2.22 % (13.86)) and the 12 to <18 year subgroup (-1.47% (10.39)).

All 51 participants sustained values at or below the prespecified therapeutic goal for liver volume (<1.5 MN) at Week 52. One participant experienced an increased liver volume (MN) outside of the prespecified therapeutic goal during the PAP which returned within range by Week 52. This participant qualified for rescue therapy but not based on liver volume.

Long-term extension

At Week 104, the mean (SD) liver volumes of the participants changed by -3.07% (11.53) from baseline for a mean volume of 0.92 MN (0.17).

One participant (GD1, 2 to <12-year age group) with moderate hepatomegaly in the PAP had a volume in the normal/mild range at Week 104. Two participants (GD1, one 2 to <12-year age group, one 12 to <18-year age group) maintained liver volumes in the moderate range.

Spleen volume

The mean (SD) baseline spleen volume for the cohort was 3.36 MN (1.54). Most participants had normal to mild splenomegaly at baseline (<5.0 MN), 6 participants had moderate splenomegaly (>5.0 MN to <15.0 MN). Over the 52-week period, mean (SD) spleen volumes of the participants changed by 3.67% (25.47) for a mean volume of 3.40 (1.60).

Mean percent changes from baseline at 52 weeks were similar for the 6 to <12-year subgroup (0.11% (19.52)) and the 12 to <18 year subgroup (1.79% (26.11)).

Three participants (GD1, 12 to <18-year age group) with moderate splenomegaly at baseline experienced improvement in spleen volume and had levels in the no/mild splenomegaly range at Week 52. Two participants (GD1, one 2 to <12-year age group, one 12 to 18-year age group) with no/mild splenomegaly at baseline had increases in volume to the level of moderate splenomegaly at Week 52. Five participants (3 with GD1, 2 with GD3, one from the 2 to <12-year age group, four from the 12 to < 8-year age group) with moderate splenomegaly at baseline maintained values within this range at Week 52.

All participants sustained values at or below the prespecified therapeutic goal for spleen volume (<10.0 MN) at Week 52.

Long-term extension

Over the 104-week period, the mean (SD) spleen volumes of the participants changed by -5.96% (18.52) from baseline for a mean volume of 3.09 MN (1.40).

One participant (GD1, 12 to <18-year age group) with moderate splenomegaly in the PAP had a decrease in spleen volume to the no/mild range by Week 104. Two participants (GD1, 12 to <18-year age group) maintained spleen volumes in the moderate splenomegaly range through the LTP. One participant (GD1, 12 to <18-year age group) with a spleen volume increase to the moderate range at Week 52 was ongoing in the LTP.

Concomitant and rescue therapy

Overall, 84.2% of participants (48 of 57) received 1 or more concomitant medications during treatment, most commonly dermatological products (60.8%), alimentary tract and metabolism products (56.9%), and respiratory system products (56.9%). No participants were reported to have received either strong or moderate CYP2D6 inhibitors or strong CYP3A4 inducers. Two participants were reported to have received either strong or moderate CYP3A4 inhibitors. Use of these medications in the 2 participants were permitted as the medication was administered topically and after Week 2 per protocol. Additionally, no participants were reported to have received Class IA antiarrhythmic medication, Class III antiarrhythmic medication, P-gp substrate, or any other ERT or SRT during the study.

During the PAP, no participant qualified for rescue therapy due to a decrease in haemoglobin levels, decrease in platelet count or based on increasing liver volume. However, three participants (1 GD1, 2 GD 3, two 2 to

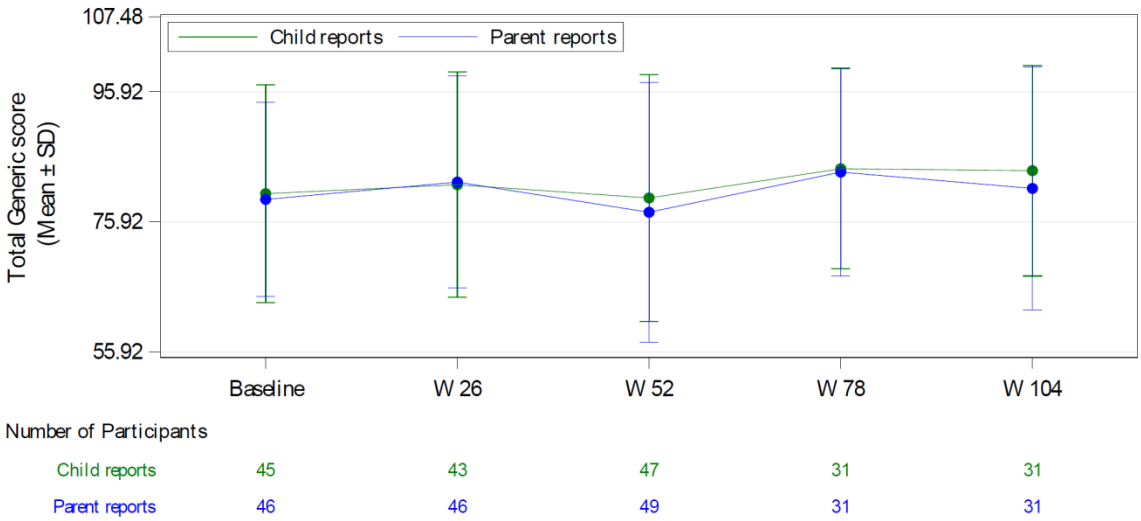
<12-year age group, one 12 to <18-year age group) qualified for rescue therapy (Step 1) based on spleen volume (MN) (spleen volume in MN increases by ⩾35% compared to baseline volume) prior to Week 52. While all participants maintained spleen volumes (MN) within therapeutic goals from baseline to Week 52 (<10.0 MN).

During the LTP, two participants continued on rescue therapy from the PAP into the LTP. Two additional participants (GD1, 12 to <18-year age group) qualified for rescue therapy (Step 1) due to "Any other decline in GD status, which in the opinion of the Investigator warrants combination therapy", one in the PAP and the other in the LTP. The consideration for this decline in GD status was due to, in part, a decrease in platelet count but platelet counts did not reach the threshold for rescue therapy. One additional participant (GD3, 12 to <18-year age group) qualified for rescue therapy due to increased spleen volume.

No participant qualified for rescue therapy Step 2 during the PAP or LTP.

Quality of Life

Figure: Mean absolute value of Generic Core Scales total score (child report and parent report) over time in Cohort 1 – FAS



Different age-based versions of the PedsQL scales were completed by patients ages 5-7, 8-12, and 13-17. The baseline values for the Overall QOL child reports in Cohort 1 were 95.3 (age 5-7), 76.4 (age 8-12), and 81.8 (age 13-17) on the 0-100 scale, where higher scores indicate better quality of life. At Week 52, the average changes on the Overall QOL score on the child reports from Cohort 1 were [mean (SD)] -14.4 (8.1) in the 5-7 age group, 1.9 (9.9) in the 8-12 age group, and -2.0 (10.6) in the 13-17 age group. The parent report scores were rather similar to the child report scores. Figure 1 shows the average of the child report scores and the parent report scores of all age groups combined. The pattern of scores on the other PedsQL Generic Core scales (Psychosocial Health, Physical Health, Emotional Functioning, Social Functioning, School Functioning) were similar with some scales at the targeted time intervals showing increases and others decreasing through Week 52. In the Cohort 1 FAS, numeric increases from baseline were observed at later time intervals (Weeks 78 and 104).

Growth and pubertal development

Growth was assessed by height Z-score for both male and female participants. At baseline, the mean (SD) height Z-score for male participants that received eliglustat monotherapy (n=25) was 2.19 (8.84). At Week 52, the mean (SD) height Z-score for male participants changed by -0.11 (1.23) [mean (SD) of 2.09 (7.74)].

The mean (SD) height Z-score for female participants that received eliglustat monotherapy (n=26) was 1.96 (8.83) at baseline. At Week 52, the mean (SD) height Z-score for female participants changed by -0.23 (0.78) [mean (SD) of 1.73 (8.32)].

An increase in the assessed Tanner stage over the course of the study in some individuals was seen, as would be anticipated.

Matching historical controls

There were 289 participants from the ICGG Gaucher Registry who met the inclusion and exclusion criteria and had non-missing values in baseline characteristics and post-baseline efficacy endpoints.

Matching took into account disease type (GD1 or GD3), age at the achievement of prespecified TGs on imiglucerase treatment or age at the beginning of eliglustat treatment (±1 year), time on ERT treatment, and baseline value of the following parameters for Cohort 1: haemoglobin ±1 g/dL, platelet count ±10 000/mm3, spleen volume ±3 MN, liver volume ±0.3 MN.

The logit of propensity score and all the covariates had good balance between Cohort 1 participants and matched Registry participants.

After matching, 51 participants from the ICGG Registry were selected automatically by using propensity score matching method to match the 51 participants in Cohort 1. Results are summarized in the table below.

Table: Results and Analysis Main in matched ICGG participants and Cohort 1- FAS

Endpoint	Definition	Cohort 1 N=51	ICGG matched controls receiving continued ERT with imiglucerase N=51
Change in haemoglobin level from baseline to Week 52	Absolute change (mmol/L) (mean [SD]) Percentage change	-0.26 (0.63) -2.86% (7.37)	0.15 (0.58) 2.09% (7.26)
Change in platelet count from baseline to Week 52	Absolute change ($x10^9$/L) (mean [SD]) Percentage change	-19.08 (54.45) -7.87% (22.71)	0.57 (45.22) 1.48% (20.97)
Change in liver volume from baseline to Week 52	Absolute change (MN) (mean [SD]) Percentage change	0.01 (0.13) 0.95% (13.45)	-0.02 (0.19) 0.25% (22.67)

Endpoint	Definition	Cohort 1 N=51	ICGG matched controls receiving continued ERT with imiglucerase N=51
Change in spleen volume from baseline to Week 52	Absolute change (MN) (mean [SD]) Percentage change	0.03 (0.94) 3.67% (25.47)	-0.58 (0.98) -14.16% (21.54)

Note For study participants, endpoints at Week 52 will be analysed. For Registry participants, endpoints at the assessment closest to Week 52 during follow-up (but at least 11 months after enrolment) will be analysed.

Ancillary analyses

N/A

Summary of main efficacy results

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries 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 EFC13738, ELIKIDS

Title: Open label, two cohort (with and without imiglucerase), multicenter study to evaluate pharmacokinetics, safety, and efficacy of eliglustat in pediatric patients with Gaucher disease type 1 and type 3		
Study identifier	Study Number: EFC13738 EudraCT/EU trial number: 2016-000301-37 NCT: NCT03485677 WHO: U1111-1172-2950 AMENDED CLINICAL TRIAL PROTOCOL NO. 04 Pediatric investigational plan number: EMEA-000461-PIP02-11-M05	
Design	Phase 3, open-label, two-cohort, multicenter	
	Duration of main phase: Duration of Run-in phase: Duration of Extension phases:	52 weeks Not applicable Long-term period: 52 weeks Extension Period: Week 104 to the end of study
Hypothesis	Exploratory	

Treatments groups	Eliglustat monotherapy (Cohort 1)	51 participants GD1: 46, GD3: 5 12 to <18-years: 33 2 to <12-years: 18 (including 3 in the 2 to <6-year age group)
Database Lock	07 July 2023	

Results and Analysis of Main Efficacy Endpoints of Cohort 1 (monotherapy)

Treatment Group	Endpoint	Definition	Result (mean [SD])	Mean (SD) at: Baseline Week 52
Monotherapy	Change in haemoglobin level from baseline to Week 52	Absolute change Mmol/L	-0.26 (0.63)	8.47 mmol/L (0.66)8.22 mmol/L (0.75)
	Change in platelet count from baseline to Week 52	Percent change $x10^9$/L	-7.87% (22.71)	215.33 (51.16) 196.25 (64.12)
	Change in liver volume from baseline to Week 52	Percent change MN	0.95% (13.45)	0.98 (0.19) 0.98 (0.21)
	Change in spleen volume from baseline to Week 52	Percent change MN	3.67% (25.47)	3.36 (1.54) 3.40 (1.60)

2.6.5.3. Clinical studies in special populations

N/A

2.6.5.4. In vitro biomarker test for patient selection for efficacy

N/A

2.6.5.5. Analysis performed across trials (pooled analyses and meta-analysis)

The clinical package supporting the efficacy of eliglustat in paediatric participants with Gaucher disease consists of 1 study, EFC13738.

2.6.5.6. Supportive study(ies)

N/A

2.6.6. Discussion on clinical efficacy

Design and conduct of clinical studies

Efficacy of eliglustat in paediatric GD1 patients is based on an open-label, two-cohort study, to primarily evaluate the safety and PK and secondarily evaluate efficacy of eliglustat alone or in combination with imiglucerase in paediatric participants 2 to <18 years old with GD1 and GD3. An RCT study design with an imiglucerase-only control group would have been preferred for determining efficacy. However, the open-label two cohort design was agreed in the PIP, in view of the unmet need, urgency to collect PK/PD data and the rarity of the disease.

Eliglustat is currently authorized for the long-term treatment of adults patients with GD1. As the underlying biology of Gaucher disease is the same in adults and children it is therefore acceptable to extrapolate based on the PK bridge. The adults efficacy on haematologic and visceral features of the disease can be extrapolated to paediatric patients. In contrast, effects of SRT on specific paediatric manifestations (e.g. growth, puberty and development) are not amenable to extrapolation. Efficacy data provided in this study is regarded as supportive in the assessment. The design, with limitations for efficacy, is therefore acceptable.

The study population included male and female participants between 2-18 years of age, diagnosed with GD1 or GD3. Patients were eligible for Cohort 1, the eliglustat monotherapy group, in case therapeutic goals for GD (for haemoglobin levels, platelet counts, liver and spleen volume) were reached after a minimum of 24 months of ERT. It was noted that the inclusion criterium (<10 MN) regarding spleen volume was less strict than formulated in treatment guidelines (<8 MN), in order to increase paediatric enrolment. Patients who are indeterminate or ultra-rapid CYP2D6 metabolisers were excluded. The eligibility criteria are considered appropriate.

There were no randomization and blinding procedures in place as expected with an open-label, two-cohort study design.

The proposed indication is as follows: *GD1 patients who are 6 years and older with a minimum body weight of 15 kg, who are stable on enzyme replacement therapy (ERT), and who are CYP2D6 poor metabolisers (PMs), intermediate metabolisers (IMs) or extensive metabolisers (Ems).*

The indication is narrower than the included patient population. Therefore, the primary focus of assessment in this procedure is on GD1 patients, >6 years of age from Cohort 1.

As initially formulated, the indication included any paediatric GD1 patient (of 6 years and older with a minimum body weight of 15 kg, and who are CYP2D6 PMs, IMs or EMs) on ERT regardless of how well the disease is managed by enzyme replace therapy can be switched to eliglustat treatment. Upon request during the procedure, the MAH has amended the indication to reflect that patients should be stable on ERT, to reflect the studied population.

The dosing regimen for the paediatric population was based on body weight and on CYP2D6 metabolizer status and estimated using PopPK and PBPK analyses. Following a planned interim assessment after 2 weeks, the dose regimen was increased for the two weight categories of ⩾15 - <25 kg and ⩾25 - <50 kg to the next higher dose level for EMs and IMs. All participants in these age groups who either initiated treatment or continued treatment received doses aligned with this revised regimen. This is acceptable.

Furthermore, 42 mg capsules were used during the clinical study, while not applied for in this line extension. With only the 21 mg capsules commercially available, some patients will be required to take 2 capsules twice

a day (EM and IM paediatric patients of ⩾15 - <25 kg) based on the proposed dose regimen. Dosing with single capsules is the most favourable, especially in young children. Thus commercialisation of the 42 mg capsules would be favourable. The MAH has considered this however, the MAH has no intention of manufacturing 42 mg capsules. The MAH is of opinion that the burden of manufacturing, storing and dispensing the 42 mg capsule does not outway the benefit for the limited number of patients that require 42 mg capsules.

In case of insufficient response to eliglustat monotherapy, patients were given imiglucerase as a rescue therapy. The thresholds for insufficient response enabled the determination of a possible decline in disease status (ineffective treatment) while forming a safe level to timely treat patients who require rescue therapy. Guidelines for rescue therapy do not account for individual participant's baseline values. As such, it was possible to qualify for rescue therapy due to the magnitude of change from baseline while maintaining values within the prespecified therapeutic goals.

The secondary objective of the study was to evaluate efficacy and quality of life in paediatric patients. The key efficacy endpoints were analysed as the change from baseline in haemoglobin levels, platelet count, spleen and liver volume at week 52 in the full analysis set. PedsQL Inventory was used to determine quality of life over the course of the study. These endpoints are acceptable since splenomegaly, hepatomegaly, thrombocytopenia and anaemia are amongst the most common signs and symptoms of GD1. The time span is considered sufficient for the assessment of the primary endpoint (PK and safety) and the key efficacy endpoints. Duration is also considered sufficient for the assessment of for instance haematologic parameters (anaemia, fatigue, easy bruising) that would impact quality of life. Data of the long-term extension will be informative for efficacy and safety assessments on the long-term. Considering that paediatric patients who have reached therapeutic goals while being on ERT treatment were included and who switched to eliglustat treatment upon study enrolment, a maintenance of their hematologic and visceral measures is considered acceptable.

Key intercurrent events were not pre-specified as such, however from the investigational plan and SAP it can be deduced that important key intercurrent events were: study treatment non-compliance, discontinuation of study treatment due to an adverse event, discontinuation of study treatment due to lack of efficacy, start of rescue therapy, initiation of concomitant medication. The frequency of the intercurrent events were described.

For Cohort 1, if patients switch to rescue therapy before Week 52, the last available values of efficacy endpoints during the eliglustat monotherapy will be used for the efficacy analyses at Week 52, carrying those values forward to Week 52 assumes those patients would not have further deteriorated. Provided patients are monitored, this is a reasonable assumption, but does affect the interpretation of the results. If patients have missing results at Week 52 or patients discontinue the study before Week 52, the last available values of efficacy endpoints will be used for the efficacy analyses at Week 52.

Growth and pubertal development are of importance to paediatric Gaucher patients, as some patients exhibit growth retardation and delayed puberty and since these paediatric manifestations are not amenable to extrapolation from adult patients. Tanner staging is a widely used tool for the assessment of pubertal development. Both parameters are sufficiently addressed in the study. However, the study lacks a control group and is considered too limited in duration and sample size to enable an assessment of growth and pubertal development and impossible to determine efficacy of eliglustat in this respect.

The study was designed to assess PK and safety and secondarily efficacy. A total sample size of 60 patients was estimated to provide a 95% probability of observing at least one patient with an AE if the true rate of

such an event is 5%. The planned subgroup analyses are considered relevant; however, overall numbers and numbers within subgroups are small and therefore preclude drawing robust conclusions.

As this was not a randomized comparison study, historical control data from the ICGG Gaucher Registry were used to evaluate the main efficacy endpoints of eliglustat relative to ERT with imiglucerase. A matching plan based on a propensity score method to ensure comparable population between Cohort 1 vs. historical cohort has been accepted. Matching took into account important prognostic variables. As the trial was initiated after most registry participants had initiated ERT, enrolment will not be fully concurrent. Selection of the start of enrolment time in the control group may be an additional source of (immortal time) bias, which was mitigated by selecting the window with the most recent enrolment time.

Efficacy data and additional analyses

Fifty-one patients, 46 GD1 and 5 GD3 patients, were included in Cohort 1. As the visceral manifestations of the disease are a common feature of GD1 and GD3, it is not expected that efficacy on visceral symptoms is different for these two subtypes. Therefore, the entire Cohort 1 is taken along in the efficacy assessment. There were 15/51 patients in the 6 - <12 years group and 33/51 in the 12 - <18 years group (three patients were in the age category of 2 -<6 years of age). There was a high treatment compliance. The amount of included patients is lower than planned. However, considering the proposed indication (not including GD3 and children below the age of 6) this is not considered an issue. Numbers are considered sufficient for the assessment of PK and safety in GD1 patients between 6 - <18 years of age. Of 51 patients included 48 finished the PAP (94%), of which 46 (90%) on eliglustat. Five patients permanently discontinued eliglustat.

The levels for the four efficacy endpoints remained stable in the majority of patients. The SD remained the same during the course of the study for all four endpoints. There was one GD1 patient with an increase in liver and spleen volume during the PAP. Liver size returned within range by the end of the PAP, while spleen volume in MN increased ⩾35% compared to baseline volume because of which this patient qualified for rescue therapy (while this patient was still within therapeutic goals). There were no relevant differences between age groups in change in haemoglobin levels nor in change of liver and spleen volume from baseline up to 52 weeks. There was a difference observed in platelet counts between age groups in mean percent changes from baseline; the 6 to <12-year subgroup (7.25% (20.50)) showed an increase in platelet counts while for the 12 to <18-year subgroup (-14.36% (20.67)) a decrease in platelet count was observed after 52 weeks. Some patients had mild thrombocytopenia at baseline other developed mild-moderate thrombocytopenia during the study, some improved, some remained around the same level. While there were fluctuations, platelet counts did not fall below 45 000/mm^3 nor did one of the patients experience a significant bleeding episode (which were criteria for rescue therapy). Mild thrombocytopenia is a common symptom of the disease, these differences are therefore not considered as clinically relevant differences.

No patients reported to have received either strong or moderate CYP2D6 inhibitors or strong CYP3A4 inducers. Two participants received topical strong or moderate CYP3A4 inhibitors, which was permitted. Therefore, the impact of received concomitant therapy on the assessment of clinical efficacy is expected to be limited.

There were three patients (1 GD1 and 2 GD3 patient) that required rescue therapy during the PAP and three (2 GD1 and 1 GD3) additional patient that required rescue therapy during the LTP. Reasons for qualifying for rescue therapy during the PAP were an increase in spleen volume, while all participants maintained spleen volumes within the therapeutic goals. During the LTP, one participant required rescue therapy due to spleen size. The other two due to a decline in GD status, which was in part ascribed to a decrease in platelet count

while the counts did not reach the threshold for rescue therapy. Switching to imiglucerase monotherapy (step 1) was sufficient as no patients were required to switch to combination therapy (imiglucerase + eliglustat, rescue therapy step 2). This approach regarding rescue therapy is in agreement with the SmPC section 4.4; it is stated that after switching from ERT to eliglustat patients should be monitored to evaluate disease stability and that reinstitution of ERT should be considered in case of sub-optimal response.

Scores of quality of life (total score and the different individual scores) remained rather constant. Numerical differences in height (z-scores) were observed from baseline to 52 weeks. Pubertal development assessed by Tanner scale, showed an increase in some of the patients as anticipated. The suboptimal study design precludes an accurate assessment of the effect of eliglustat treatment on these paediatric specific manifestations, however no aberrant or alarming results with respect to quality of life, growth and pubertal development were observed.

There were 51 participants from the ICGG Registry selected to match participants from Cohort 1. The four key efficacy endpoints were compared between participants from Cohort 1 and ICGG matched controls receiving continued ERT with imiglucerase. Numerical differences were observed, which are slightly in favour of continued ERT treatment. Although balance was achieved between the groups with regard to the matching factors, residual confounding cannot be excluded. While the data are dispersed, patients remain within therapeutic goals and this comparison does not indicate that switching from ERT to eliglustat leads to clinically meaningful reductions in efficacy for GD1 patients. Taking into account the convenience of taking capsules instead of IV infusions, and the possibility to switch back to ERT if indicated, eliglustat is considered a suitable treatment approach for paediatric GD1 patients of 6-18 years once they have reached therapeutic goals on ERT.

2.6.7. Conclusions on the clinical efficacy

In conclusion, the presented efficacy data for the haematologic and visceral components of the disease are in line with results in adult Gaucher patients. The design precludes drawing conclusions on the paediatric manifestations of the disease. The submitted data supports an extension of the indication to paediatric GD1 patients, of 6 years and older with a minimum body weight of 15 kg, who are stable on ERT and who are CYP2D6 PMs, IMs or EMs. Cerdelga is to be taken orally in children who can swallow intact capsule.

2.6.8. Clinical safety

The assessment of clinical safety is based on the data analysis of the Phase 3 paediatric study EFC13738. This study consisted of a 52-week PAP, followed by a long-term treatment period up to week 104. The data cut-off is 21 June 2023.

Patients were continuously monitored for the occurrence of AEs and SAEs up to week 104. After week 104 and up to end of study, safety was monitored by monthly phone call.

Because eliglustat was predicted to cause mild increases in ECG intervals (PR, QTc, and QRS) at substantially elevated eliglustat plasma concentrations, an interim analysis was conducted to assess potential cardiac effects of eliglustat in the paediatric participants after the tenth participant in the 12 to <18 years age group completed their 2-week visit. Twenty-four-hour Holter monitoring was conducted and the ECG data extracted was independently reviewed. In addition, this interim analysis included global safety information from 6 months of treatment with eliglustat in the first 10 participants in the older age group (12 to <18 years), including AE profile and PK data, and was performed before the younger age group started enrolment.

A subgroup PK analysis of the first 10 EM participants in each age group (2 to <12 years and 12 to <18 years) was performed at Week 2 (steady state) to evaluate eliglustat exposure and allow a new dose regimen to the target exposure, if needed.

2.6.8.1. Patient exposure

In Cohort 1, 51 patients were enrolled and exposed. Forty-eight patients finished the PAP, of which 46 on eliglustat treatment. All 48 patients were enrolled in the LTP, 38 had finished on the LTP and 9 patients are still ongoing. One patient has discontinued the LTP.

Table: Patient exposure in the PAP (up to week 52) (21 June 2023)

	Cohort 1 (N=51)	**Cohort 2 (N=6)**	**Total (N=57)**
Enrolled	51 (100)	6 (100)	57 (100)
Enrolled and exposed	51 (100)	6 (100)	57 (100)
Completed the PAP	48 (94.1)	6 (100)	54 (94.7)
Completed on Primary study treatment	46 (90.2)	6 (100)	52 (91.2)
Completed on Rescue Step 1	2 (3.9)	n/a	2 (3.9)
Completed on Rescue Step 2	0	n/a	0
Discontinued the PAP	3 (5.9)	0	3 (5.3)
Discontinued on Primary study treatment	2 (3.9)	0	2 (3.5)
Discontinued on Rescue Step 1	1 (2.0)	n/a	1 (2.0)
Discontinued on Rescue Step 2	0	n/a	0
Reason for permanent Eliglustat discontinuation	5 (9.8)	0	5 (8.8)
Adverse Events	4 (7.8)	0	4 (7.0)
Progressive Disease	0	0	0
Lack of Efficacy	0	0	0
Poor Compliance to Protocol	0	0	0
Withdrawal by Subject	0	0	0
Other	1 (2.0)	0	1 (1.8)

PAP = Primary Analysis Period, from W0/Day 1-W52. In Cohort 1, Primary study treatment: eliglustat monotherapy; Rescue step 1: imiglucerase monotherapy; Rescue step 2: eliglustat plus imiglucerase combination therapy. In Cohort 2, Primary study treatment: eliglustat plus imiglucerase combination therapy

Table: Patient exposure in the long term treatment period (cut off)

	Cohort 1 (N=48)	**Cohort 2 (N=6)**	**Total (N=54)**
Enrolled	48 (100)	6 (100)	54 (100)
Enrolled and exposed	48 (100)	6 (100)	54 (100)
Still in the LTP	9 (18.8)	0	9 (16.7)
Ongoing Primary study treatment	7 (14.6)	0	7 (13.0)
Ongoing Rescue Step 1	2 (4.2)	n/a	2 (4.2)
Ongoing Rescue Step 2	0	n/a	0
Switched to Eliglustat Monotherapy	n/a	0	0

	Cohort 1 (N=48)	Cohort 2 (N=6)	Total (N=54)
Completed the LTP	38 (79.2)	6 (100)	44 (81.5)
Completed on Primary study treatment	36 (75.0)	4 (66.7)	40 (74.1)
Completed on Rescue Step 1	2 (4.2)	n/a	2 (4.2)
Completed on Rescue Step 2	0	n/a	0
Completed Eliglustat Monotherapy	n/a	2 (33.3)	2 (33.3)
Discontinued the LTP	1 (2.1)	0	1 (1.9)
Discontinued on Primary study treatment	0	0	0
Discontinued on Rescue Step 1	1 (2.1)	n/a	1 (2.1)
Discontinued on Rescue Step 2	0	n/a	0
Discontinued on Eliglustat Monotherapy	n/a	0	0
Reason for permanent Eliglustat discontinuation	3 (6.3)	0	3 (5.6)
Adverse Events	3 (6.3)	0	3 (5.6)
Progressive Disease	0	0	0
Lack of Efficacy	0	0	0
Poor Compliance to Protocol	0	0	0
Withdrawal by Subject	0	0	0
Other	0	0	0

Thirty-one participants entered the EP from Cohort 1. Of those, 22 (71.0%) were continuing in the study as of the cut-off date, and 9 (29.0%) participants completed the study on eliglustat monotherapy including those who turned 18 years of age during the EP.

Participants in Cohort 1 received eliglustat monotherapy and dosing was based on their CYP2D6 metabolizer status and bodyweight at baseline.

The first 49 enrolled participants (43 in Cohort 1 and 6 in Cohort 2) received eliglustat based on the Initial Regimen. There were no participants in the 10 to <15 kg weight category or other participants that required a dose less than 21 mg.

The last 8 participants who entered the study after July 2021 (all in Cohort 1) received doses based on the Revised Dose Regimen. No participants received a dose less than 42 mg BID after the dose regimen change as no participants weighing between 10 and <15 kg and no PMs weighing <50 kg had been enrolled.

Twenty-nine of 57 (50.8%) participants maintained a consistent dose of eliglustat during the PAP, 28 participants in Cohort 1 and 1 participant in Cohort 2. Twenty-eight participants had at least one dose increase during the PAP including two participants in Cohort 1 that had dose increases at Week 52.

Five participants (3 in Cohort 1 and 2 in Cohort 2) had dose increases during the LTP; the dose change for the two participants in Cohort 2 was the second dose increase for those participants.

Table: Extent of exposure to Eliglustat capsule by dose regimen in Cohort 1 - Safety population

	42 mg BID (N=21)	84 mg BID (N=46)	126 mg BID (N=4)	42 mg QD (N=1)
Cumulative exposure to treatment (Participant years)	16.03	87.74	8.75	3.57
Duration of study treatment (Weeks)				
Number	21	46	4	1
Mean (SD)	39.8 (21.4)	99.5 (59.6)	114.1 (67.6)	186.4 (NC)
Median	46.6	84.9	128.4	186.4
Min ; Max	2 ; 77	14 ; 209	29 ; 171	186 ; 186
Duration of study treatment by category [n (%)]				
1 day to 52 weeks	14 (66.7)	10 (21.7)	1 (25.0)	0
53 to 104 weeks	7 (33.3)	16 (34.8)	1 (25.0)	0
> 104 weeks	0	20 (43.5)	2 (50.0)	1 (100)
Cumulative duration of study treatment by category [n (%)]				
≥ 1 day	21 (100)	46 (100)	4 (100)	1 (100)
> 52 weeks	7 (33.3)	36 (78.3)	3 (75.0)	1 (100)
> 104 weeks	0	20 (43.5)	2 (50.0)	1 (100)

Note: Treatment period includes a primary analysis treatment period (Day 1 to Week 52) and a long-term treatment period (Week 53 to Week 104) and an extension period (from Week 105 to EOS).
A participant may be counted in multiple dose regimen groups due to possible dose adjustment during the study. NC = not calculated.

For patients who were unable to swallow the tablets, a pharmacy-prepared oral suspension was available. In total, 1 patients received the oral suspension for the 21 mg BID dose, 3 patients for the 42 mg BID dose and 2 patients for the 84 mg BID dose. The duration of treatment with the oral suspension was between 1 day and 52 weeks for all patients.

2.6.8.2. Adverse events

Over the course of the study (see table below), 53 participants (93.0%) experienced at least one treatment-emergent adverse event (TEAE), with a total number of 360 TEAEs reported and an event rate of 2.67 events per participant-year regardless of the study treatment received.

There were no deaths during the study.

Table: Overview of adverse event profile: TEAE(s) by cohort and treatment phases - Safety population

	Cohort 1 (N=51)		Cohort 2 (N=6)		Total (N=57)	
n(%)	**n**	**E(R)**	**n**	**E(R)**	**n**	**E(R)**
Overall TEAE study treatment						
Number of participants	51 (100)		6 (100)		57 (100)	
Total participant years		121.80		13.17		134.96
- any TEAE	48 (94.1)	284 (2.33)	5 (83.3)	76 (5.77)	53 (93.0)	360 (2.67)
- any Severe TEAE	4 (7.8)	5 (0.04)	0	0	4 (7.0)	5 (0.04)
- any treatment emergent SAE	6 (11.8)	9 (0.07)	0	0	6 (10.5)	9 (0.07)
- any treatment emergent AESI	3 (5.9)	5 (0.04)	0	0	3 (5.3)	5 (0.04)
- any Eliglustat-related TEAE	17 (33.3)	31 (0.25)	3 (50.0)	4 (0.30)	20 (35.1)	35 (0.26)
- any Imiglucerase-related TEAE	0	0	0	0	0	0
- any TEAE leading to death	0	0	0	0	0	0
- any TEAE leading to permanent treatment discontinuation	7 (13.7)	8 (0.07)	0	0	7 (12.3)	8 (0.06)
Primary study treatment						
Number of participants	51 (100)		6 (100)		57 (100)	
Total participant years		119.09		10.74		129.83
- any TEAE	48 (94.1)	280 (2.35)	5 (83.3)	73 (6.80)	53 (93.0)	353 (2.72)
- any Severe TEAE	4 (7.8)	5 (0.04)	0	0	4 (7.0)	5 (0.04)
- any treatment emergent SAE	5 (9.8)	8 (0.07)	0	0	5 (8.8)	8 (0.06)
- any treatment emergent AESI	3 (5.9)	5 (0.04)	0	0	3 (5.3)	5 (0.04)
- any Eliglustat-related TEAE	17 (33.3)	31 (0.26)	3 (50.0)	4 (0.37)	20 (35.1)	35 (0.27)
- any Imiglucerase-related TEAE	0	0	0	0	0	0
- any TEAE leading to permanent treatment discontinuation	7 (13.7)	8 (0.07)	0	0	7 (12.3)	8 (0.06)
Rescue Step 1						
Number of participants	6 (100)		n/a	n/a	6 (100)	
Total participant years		2.72				2.72
- any TEAE	2 (33.3)	4 (1.47)			2 (33.3)	4 (1.47)
- any Severe TEAE	0	0			0	0
- any treatment emergent SAE	1 (16.7)	1 (0.37)			1 (16.7)	1 (0.37)
- any treatment emergent AESI	0	0			0	0
- any Eliglustat-related TEAE	0	0			0	0
- any Imiglucerase-related TEAE	0	0			0	0
Monotherapy						
Number of participants	n/a	n/a	2 (100)		2 (100)	
Total participant years				2.43		2.43
- any TEAE			1 (50.0)	3 (1.23)	1 (50.0)	3 (1.23)

TEAE: Treatment emergent adverse event, SAE: Serious adverse event, AESI: Adverse event with special interest. n (%) = number and percentage of participants with at least one TEAE. Note: TEAEs are defined as AEs that developed or worsened or became serious during the treatment-emergent period. For Cohort 1, Primary study treatment is eliglustat monotherapy; Rescue Step 1 is imiglucerase monotherapy; Rescue Step 2 is imiglucerase + eliglustat combination therapy; For Cohort 2, Primary study treatment is eliglustat plus imiglucerase combination therapy; Monotherapy is eliglustat.

The table below summarizes the incidence of TEAEs reported in at least 2 participants by cohort and treatment phases, by SOC and PT during the study.

In Cohort 1, the most frequently reported TEAEs were in the SOCs infections and infestations (64.7%), gastrointestinal disorders (43.1%), and musculoskeletal and connective tissue disorders (29.4%). The most

frequent PTs (in ≥10% of participants) were nasopharyngitis (23.5%), COVID-19 (21.6%), headache (13.7%), arthralgia (13.7%), dyspepsia (13.7%), pharyngitis (11.8%), and vomiting (11.8%).

Table: Number (%) of participants with TEAE(s) on primary study treatment in at least two participants by cohort and by Primary SOC and PT - Safety population

	Cohort 1 (N=51)	**Cohort 2 (N=6)**	**Total (n=57)**
Treatment phases Primary System Organ Class Preferred Term n(%)	**n**	**n**	**n**
Primary study treatment			
Number of participants	51	6	57
Total participant years			
Any Class	45 (88.2)	5 (83.3)	50 (87.7)
INFECTIONS AND INFESTATIONS			
Nasopharyngitis	12 (23.5)	2 (33.3)	14 (24.6)
COVID-19	11 (21.6)	2 (33.3)	13 (22.8)
Pharyngitis	6 (11.8)	0	6 (10.5)
Upper respiratory tract infection	3 (5.9)	0	3 (5.3)
Bronchitis	2 (3.9)	0	2 (3.5)
Gastroenteritis	2 (3.9)	0	2 (3.5)
Otitis externa	0	2 (33.3)	2 (3.5)
BLOOD AND LYMPHATIC SYSTEM DISORDERS			
Splenomegaly	5 (9.8)	0	5 (8.8)
Iron deficiency anaemia	3 (5.9)	0	3 (5.3)
METABOLISM AND NUTRITION DISORDERS			
Vitamin D deficiency	5 (9.8)	0	5 (8.8)
Decreased appetite	2 (3.9)	0	2 (3.5)
Obesity	2 (3.9)	0	2 (3.5)
Vitamin B12 deficiency	2 (3.9)	0	2 (3.5)
PSYCHIATRIC DISORDERS			
Insomnia	2 (3.9)	0	2 (3.5)
Nervousness	2 (3.9)	0	2 (3.5)
NERVOUS SYSTEM DISORDERS			
Headache	7 (13.7)	1 (16.7)	8 (14.0)
Tension headache	2 (3.9)	0	2 (3.5)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS			
Epistaxis	3 (5.9)	1 (16.7)	4 (7.0)
Cough	2 (3.9)	1 (16.7)	3 (5.3)
Oropharyngeal pain	2 (3.9)	0	2 (3.5)
GASTROINTESTINAL DISORDERS			
Dyspepsia	7 (13.7)	1 (16.7)	8 (14.0)
Vomiting	6 (11.8)	2 (33.3)	8 (14.0)

	Cohort 1 (N=51)	Cohort 2 (N=6)	Total (n=57)
Treatment phases Primary System Organ Class Preferred Term n(%)	**n**	**n**	**n**
Nausea	4 (7.8)	1 (16.7)	5 (8.8)
Abdominal pain	3 (5.9)	1 (16.7)	4 (7.0)
Diarrhoea	2 (3.9)	2 (33.3)	4 (7.0)
Abdominal pain upper	2 (3.9)	1 (16.7)	3 (5.3)
Constipation	3 (5.9)	0	3 (5.3)
Toothache	2 (3.9)	0	2 (3.5)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS			
Dry skin	3 (5.9)	0	3 (5.3)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS			
Arthralgia	7 (13.7)	1 (16.7)	8 (14.0)
Pain in extremity	3 (5.9)	2 (33.3)	5 (8.8)
Bone pain	2 (3.9)	1 (16.7)	3 (5.3)
Groin pain	2 (3.9)	1 (16.7)	3 (5.3)
Back pain	2 (3.9)	0	2 (3.5)
Osteochondrosis	2 (3.9)	0	2 (3.5)
REPRODUCTIVE SYSTEM AND BREAST DISORDERS			
Dysmenorrhoea	3 (5.9)	0	3 (5.3)
CONGENITAL, FAMILIAL AND GENETIC DISORDERS			
Gaucher's disease	1 (2.0)	1 (16.7)	2 (3.5)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
Pyrexia	4 (7.8)	1 (16.7)	5 (8.8)
Fatigue	2 (3.9)	1 (16.7)	3 (5.3)
INVESTIGATIONS			
Chitotriosidase increased	2 (3.9)	0	2 (3.5)
Platelet count decreased	2 (3.9)	0	2 (3.5)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS			
Fall	4 (7.8)	0	4 (7.0)
Ligament sprain	2 (3.9)	1 (16.7)	3 (5.3)
Accidental overdose	2 (3.9)	0	2 (3.5)

Most participants experienced mild to moderate TEAEs and 4 participants in Cohort 1 had severe TEAEs which were isolated events. By PT, the severe events were pneumonia, constipation, arthralgia, fall, and lower limb fracture, of which, only arthralgia was assessed as related to eliglustat.

Adverse drug reactions

An overview of the number of participants with TEAE(s) reported by the Investigator as related to eliglustat by cohort and treatment phases by Primary SOC and PT is provided in the table below.

Overall, the most frequently reported related TEAEs were in the gastrointestinal disorders SOC with dyspepsia reported in 6 participants (10.5%). Splenomegaly, headache, fatigue, and dry skin were the only other related TEAEs reported in more than 1 participant.

Table: Number (%) of participants on primary study treatment with TEAE(s) related to Eliglustat by cohort and primary SOC and PT - Safety population

	Cohort 1 (N=51)	**Cohort 2 (N=6)**	**Total (n=57)**
Treatment phases Primary System Organ Class Preferred Term n(%)	**n**	**n**	**n**
Primary study treatment			
Number of participants	51	6	57
Total participant years			
Any Class	17 (33.3)	3 (50.0)	20 (35.1)
BLOOD AND LYMPHATIC SYSTEM DISORDERS	3 (5.9)	0	3 (5.3)
Splenomegaly	3 (5.9)	0	3 (5.3)
NERVOUS SYSTEM DISORDERS	1 (2.0)	1 (16.7)	2 (3.5)
Headache	1 (2.0)	1 (16.7)	2 (3.5)
EYE DISORDERS	1 (2.0)	0	1 (1.8)
Dry eye	1 (2.0)	0	1 (1.8)
CARDIAC DISORDERS	1 (2.0)	0	1 (1.8)
Sinus tachycardia	1 (2.0)	0	1 (1.8)
VASCULAR DISORDERS	1 (2.0)	0	1 (1.8)
Haematoma	1 (2.0)	0	1 (1.8)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	2 (3.9)	0	2 (3.5)
Epistaxis	1 (2.0)	0	1 (1.8)
Throat irritation	1 (2.0)	0	1 (1.8)
GASTROINTESTINAL DISORDERS	7 (13.7)	2 (33.3)	9 (15.8)
Dyspepsia	5 (9.8)	1 (16.7)	6 (10.5)
Abdominal pain	1 (2.0)	0	1 (1.8)
Abdominal pain upper	1 (2.0)	0	1 (1.8)
Constipation	1 (2.0)	0	1 (1.8)
Gastritis	0	1 (16.7)	1 (1.8)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	4 (7.8)	0	4 (7.0)
Dry skin	2 (3.9)	0	2 (3.5)
Eczema asteatotic	1 (2.0)	0	1 (1.8)
Lichen planus	1 (2.0)	0	1 (1.8)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	1 (2.0)	0	1 (1.8)
Arthralgia	1 (2.0)	0	1 (1.8)

	Cohort 1 (N=51)	Cohort 2 (N=6)	Total (n=57)
Treatment phases Primary System Organ Class Preferred Term n(%)	**n**	**n**	**n**
REPRODUCTIVE SYSTEM AND BREAST DISORDERS	1 (2.0)	0	1 (1.8)
Pelvic pain	1 (2.0)	0	1 (1.8)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	2 (3.9)	1 (16.7)	3 (5.3)
Fatigue	1 (2.0)	1 (16.7)	2 (3.5)
Chest pain	1 (2.0)	0	1 (1.8)
Non-cardiac chest pain	1 (2.0)	0	1 (1.8)
INVESTIGATIONS	2 (3.9)	0	2 (3.5)
Chitotriosidase increased	1 (2.0)	0	1 (1.8)
Platelet count decreased	1 (2.0)	0	1 (1.8)

2.6.8.3. Serious adverse event/deaths/other significant events

An overview of the number of participants with SAEs is provided in the table below. SAEs were only reported in Cohort 1: 6 (11.8%) participants experienced 9 treatment-emergent SAE.

There were no deaths during the study.

Table: Number (%) of participants on primary study treatment with Treatment-emergent SAE(s) by cohort and by Primary SOC and PT - Safety population

	Cohort 1 (N=51)	
Treatment phases Primary System Organ Class Preferred Term n(%)	**n**	**E**
Total participant years		121.80
Any All Class	6 (11.8)	9
Primary study treatment		
Number of participants	51	
Total participant years		119.09
Any Class	5 (9.8)	8
INFECTIONS AND INFESTATIONS	1 (2.0)	1
Pneumonia	1 (2.0)	1
BLOOD AND LYMPHATIC SYSTEM DISORDERS	1 (2.0)	1

	Cohort 1 (N=51)	
Treatment phases Primary System Organ Class Preferred Term n(%)	**n**	**E**
Splenomegaly	1 (2.0)	1
HEPATOBILIARY DISORDERS	1 (2.0)	1
Hepatomegaly	1 (2.0)	1
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	1 (2.0)	2
Arthralgia	1 (2.0)	2
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	2 (3.9)	3
Facial bones fracture	1 (2.0)	1
Fall	1 (2.0)	1
Lower limb fracture	1 (2.0)	1
Rescue Step 1		
Number of participants	6	
Total participant years		2.72
Any Class	1 (16.7)	1
INFECTIONS AND INFESTATIONS	1 (16.7)	1
COVID-19	1 (16.7)	1

AESI

Per the study protocol, the following events were defined as adverse event of special interest (AESI):

• Pregnancy of a female patient entered in a study as well as pregnancy occurring in a female partner of a male patient entered in a study with IMP(s).

• Symptomatic overdose (serious or non-serious) with IMP(s). Defined as at least twice the intended dose within the intended therapeutic interval.

• Other project specific AESI(s):

- Syncope from any cause;
- Clinically significant cardiac arrhythmias (detected by electrophysiological monitoring such as ECG); this is based on nonclinical findings;

- Peripheral neuropathy;
- Infusion associated reactions (IARs).

The incidence of AESIs was low, and AESIs were reported in Cohort 1 only. Three (5.9%) participants experienced 5 treatment-emergent AESIs. These included 1 (2.0%) incidence of each of the following events: syncope, sinus tachycardia, and accidental overdose (3 events in 1 participant).

ADRs of special interest, serious ADRs and deaths causally related to the medicinal product.

The applicant did not submit an analysis of relatedness to the drug for the SAE's/AESI's.

Review of the case narratives showed that from the SAE's, the following were considered related to the study drug by the investigator:

- Two events of moderate/severe arthralgia were reported in the same patient. This patient experienced various events of mild hip pain during the course of treatment with eliglustat.

One patient experienced SAEs of hepatomegaly and splenomegaly: In the narrative it is described that the relationship with the study drug could not be established due to the active growth of the study participant, frequent omissions of drugs and the peculiarities of the metabolism of the drug in the study participant.

Review of the case narratives showed that from the AESI's, the following was deemed related to the study drug by the investigator:

- On Day 364 of the study, an adverse event of special interest (AESI) of sinus tachycardia (moderate) was reported. On that day, a Holter monitor was performed at Week 52 which was interpreted by the independent central cardiac reader as "abnormal not clinically significant" with the comment "sinus rhythm with periods of sinus tachycardia few supraventricular beats few ventricular beats". The investigator considered the Holter finding as clinically significant and reported as AESI. No corrective treatment was given, and no action was taken with eliglustat due to the event of sinus tachycardia.sinus tachycardia.

The accidental overdoses were deemed related to the study procedures, and the case of syncope was deemed not related to the study drug but to the patient experiencing a traumatic event.

2.6.8.4. Laboratory findings

No clinically significant changes were observed with respect to laboratory findings.

In one participant, although interpreted as not clinically significant by the central reader ECG abnormalities observed at Week 52 Holter were deemed clinically significant by the Investigator and reported as AESI (sinus tachycardia).

2.6.8.5. In vitro biomarker test for patient selection for safety

N/A

2.6.8.6. Safety in special populations

Safety was assessed in subgroups for age, CYP2D6 metabolizer status and GD phenotype.

Meaningful conclusions cannot be drawn from these subgroup analyses since the number of GD3 patients and patients who were not extensive metabolizers were very small. There were no meaningful differences between the age groups.

2.6.8.7. Immunological events

N/A

2.6.8.8. Safety related to drug-drug interactions and other interactions

During the study, use of medications affecting CYP2D6 or CYP3A4 activity (i.e. CYP2D6/CYP3A inhibitors and CYP3A strong inducers), which alter eliglustat plasma concentrations, and Class IA and Class III antiarrhythmic medications, which are known to prolong QTc interval, were restricted or prohibited.

No participants were reported to have received either strong or moderate CYP2D6 inhibitors or strong CYP3A4 inducers. Two participants were reported to have received either strong or moderate CYP3A4 inhibitors both of which were topical medications.

2.6.8.9. Discontinuation due to adverse events

Seven (13.7%) participants in Cohort 1 (4 GD1 and 3 GD3) experienced TEAEs leading to permanent treatment discontinuation. In 4 out of these 7 participants, a confirmatory abdominal MRI showed a spleen volume increase in MN > 35% compared to baseline that qualified the respective participants for rescue therapy and which led to permanent eliglustat treatment discontinuation.

2.6.8.10. Post marketing experience

A cumulative search up to 07 July 2023 performed in the Applicant's global pharmacovigilance database for all cases of eliglustat reported in the paediatric population retrieved 71 cases (21 serious cases, 50 non-serious cases) with 180 adverse events, including 28 cases that were participants in the ICGG Gaucher registry.

The most frequent adverse events (reported 3 times or more) were reported for off-label use [15], product use issue [5], dyspepsia [5], gastroesophageal reflux disease [4], product prescribing issue [4], pyrexia [4], weight increased [4], cough, diarrhoea, dyspnoea, fatigue, gastrointestinal disorder, nausea, pneumonia, weight decreased, and wrong technique in product usage process [all 3].

There were no AEs indicative of a potential drug-drug interaction between eliglustat and other compounds; no AEs were reported related to cardiac conduction disorders or arrhythmias, or related to an unknown status of the liver metabolism.

2.6.9. Discussion on clinical safety

Safety was a primary objective of the ELIkids study. Continuous monitoring was in place for the study duration of 104 weeks, which is appropriate.

Safety can be extrapolated from adults to paediatric patients with GD1, nevertheless, the study provides support for the safety in the proposed indication. From a safety perspective, cohort 1 (eliglustat monotherapy) provides the most relevant safety information and is used for the safety assessment.

In Cohort 1, 51 patients were enrolled. The majority were GD1 patients (n=46) and 5 were GD3 patients. It is not expected that the safety profile is different for GD1 and GD3 patients and hence, Cohort 1 can be used integrally to establish the safety profile in children with GD aged 6-18 years of age. 49 patients were extensive metabolisers (EM), therefore the safety profile for IM and PM has to be extrapolated. This is acceptable, as the dose regimen is based on PK modelling.

In Cohort 1, 48 patients finished the primary study part of 52 weeks, of whom 46 on study treatment and 2 patients required rescue treatment. Of the 48 patients, 38 finished the long-term extension study of 104 weeks, 36 on study treatment and 2 switched to rescue therapy during the LTP.

In line with the guidance in the updated SmPC, the majority of patients received 84 mg BID, being between 25-50 kg and EM. Four patients received 126 mg BID for an extensive period of time (29-171 weeks). This is not part of the proposed dosing regimen in the SmPC but was an option in the study protocol for patients above 50 kg in the 12-18 years group based on individual week 2 PK results. The applicant was requested to clarify why 126 mg BID is not an option in the SmPC for patients aged 12-18 year of age and with a BW above 50 kg. Simulated PK parameters from the PopPK model in a virtual paediatric CYP2D6 EM and IM patient population at 126 mg BID with BW $\geqslant$50 kg were higher than the simulated PK exposures in adults at the approved dose of 84 mg BID. The higher dose of 126 mg BID dose is not expected to provide any further meaningful clinical benefit.

Of 51 patients in Cohort 1, 28 received a stable dose of eliglustat during the study, for the other patients the dose was increased during the study. The main reasons for dose changes during the PAP were amendments based on the assessment of PK exposure after 2 weeks (n=11), weight change resulting in change in weight band (n=6) or as a consequence of the planned PK subgroup analysis resulting in the revised dose regimen (n=11). It is indicated that the proposed dose adjustments on the basis of these week 2 data were also the final dose recommendations. New patients were dosed according these dose recommendations.

For participants unable to swallow the study medication, eliglustat was initially proposed to be available as a pharmacy-prepared suspension. The exposure to the oral suspension is limited, 1 patient received 21 mg BID, 3 patients 42 mg BID and 2 patients 84 mg BID via oral suspension. Six unique patients received eliglustat via oral suspension, of which four in Cohort 1. Among these four, there were three GD3 and one GD1 patient. Under the proposed indication, none of these participants would qualify for eliglustat treatment. Safety data was not provided separately for the patients receiving the oral suspension, but if it was, patient numbers would be so low that the data would not allow for conclusions.

It should also be noted that the initially proposed alternative method of administration (oral suspension) was withdrawn by the MAH following the CHMP assessment of all available data. Cerdelga is only to be used in children who can swallow an intact capsule.

Overall, the safety database is considered sufficient to support the safety of the proposed dosing regimen in paediatric patients. The length of follow-up is sufficient to conclude on the safety in long-term treatment.

In Cohort 1, 94% of patients experienced a total of 284 TEAEs. In the pooled cohort, 93% of patients experienced in total 360 TEAEs. The majority of the events were mild to moderate. Four severe events were reported, of which one was related to study treatment (arthralgia).

In Cohort 1, the most frequently reported TEAEs were in the SOCs infections and infestations (64.7%), gastrointestinal disorders (43.1%), and musculoskeletal and connective tissue disorders (29.4%). The most frequent PTs (in ⩾10% of participants) were nasopharyngitis (23.5%), COVID-19 (21.6%), headache (13.7%), arthralgia (13.7%), dyspepsia (13.7%), pharyngitis (11.8%), and vomiting (11.8%).

The TEAEs in the SOC infections and infestations are reported as being unrelated to study treatment. This is agreed, since these AEs are expected to occur frequently in the paediatric study population.

In Cohort 1, 33% of TEAE were judged as being related to study treatment by the investigator. Overall, the most frequently reported related TEAEs were in the gastrointestinal disorders SOC with dyspepsia reported in 6 participants (10.5%). Splenomegaly, headache, fatigue, and dry skin were the only other related TEAEs reported in more than 1 participant.

All reported ADRs occurring in more than 1 patient are included in the SmPC.

Chitotriosidase increased, platelet count decreased and splenomegaly are considered as consequences of Gaucher disease and are more reflective of inadequate disease management and not indicative of safety concern, therefore, inclusion in the SmPC is not warranted.

Few SAE's were reported. One patient experienced two drug related SAE's of arthralgia. The causality assessment of the investigator is supported. As arthralgia is already included in section 4.8 as ADR, no further action in necessary.

With regard to the AESI's, 5 events were reported. The events of syncope (1) and accidental overdose (3) are not considered ADRs. One AESI of sinus tachycardia was reported, which is reported as related to study treatment. A causal relationship is considered possible, but since "Cardiac conduction disorders and arrhythmias" is included as important potential risk in the RMP, action is not considered necessary at this point.

Seven patients discontinued treatment due to AEs, of which 4 patients discontinuation was due to being eligible to rescue treatment based on spleen size. Hence, for these 4 patients, the discontinuation not so much indicates a safety issue but inadequate disease management on eliglustat. No safety concerns arise from the discontinuations.

The safety profile was analysed based on age, metaboliser status and GD subtype. However, these subpopulations all consisted of limited number of patients. The size of the safety database does not allow for firm conclusions on subsets of patients.

No clinically relevant changes were observed in the laboratory parameters.

Specific attention was paid to cardiac safety, after 2 weeks in the 12-18 years age group and at the week 52 interim analysis. Besides the one incident of sinus tachycardia, no clinically meaningful findings were recorded. Cardiac safety remains to be monitored via the RMP as an important potential risk.

The Applicant retrieved 71 case reports reporting 180 adverse events through a safety database search of eliglustat use in the paediatric population. It is agreed that the provided post-marketing data do not suggest a safety issue in the paediatric population: the most frequently reported adverse events are in line with use in the paediatric population [off label use], the known safety profile of eliglustat, or may be expected in the paediatric treatment population. Additionally, 'Use in children' is monitored in the eliglustat PSURs. In the most recent eliglustat PSUR assessment [PSUSA/00010351/202208], the PRAC concluded that no new safety concern was identified regarding eliglustat use in children.

Product information

The MAH does not propose any changes to the ADR table in the SmPC section 4.8. This is agreed. The observed safety profile in paediatric patients is in line with the known safety profile of eliglustat in adults.

2.6.10. Conclusions on the clinical safety

The safety profile in paediatric patients is in line with that in adults. The submitted safety data supports the proposed extension of indication.

2.7. Risk Management Plan

2.7.1. Safety concerns

Table: Summary of safety concerns

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

2.7.2. Pharmacovigilance plan

Table: Summary of on-going and planned additional pharmacovigilance activities

Study status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorization (key to benefit risk)				
Prospective ICGG safety	To characterize the long-term safety profile of eliglustat in	• Safety in long-term treatment use	Concept protocol	Submitted within 3 months after approval.

Study status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
sub-registry (OBS14099) Ongoing	real-world clinical practice.	• Use of eliglustat in patients who are CYP2D6 indeterminate metabolizers or non-genotyped patients • Use of eliglustat in patients who are ultra-rapid metabolizers	Final Protocol approval	Protocol dated 23-Aug-2016 approved by EMA on 01-Dec-2016. Start date of data collection: 18-Apr-2018.
	To describe the patient's characteristics and utilization patterns		Report	Progress reports will be reported in PSURs. Latest progress report submitted in the PBRER covering the period 20-Aug-2020 to 19-Aug-2022.
			Interim report	An interim analysis of study results will be performed two years after the last CERDELGA patient has been enrolled in the study, and an interim analyses report was submitted to EMA on 07-July 2023.
			End of data collections	Four years after the last CERDELGA patient has been enrolled in the study.
			Final report of study results	Q3 2025
Category 3 - Required additional pharmacovigilance activities (by the competent Authority)				
Study Status	**Summary of objectives**	**Safety concerns addressed**	**Milestones**	**Due dates**
Drug utilization study of eliglustat in Europe using electronic healthcare records. (ELIGLC06913) Ongoing	To assess compliance/adherence to the labeling with regard to DDI.	Drug-Drug Interaction	Pilot study report	Q4 2014
			Submission of final protocol[a]	May-2015
			Submission of final report	Q4 2024

a The revised EU drug utilization study protocol was submitted to PRAC in Nov-2015 and approved in Feb-2016.

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

2.7.3. Risk minimisation measures

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

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

Safety concern	Risk minimization measures	Pharmacovigilance activities
arrhythmias or conduction findings	**Additional risk minimization measures:** None	**Additional pharmacovigilance activities:** None
Use during pregnancy and lactation	**Routine risk minimization measures:** • Labeled in section 4.6 of SmPC. • Labeled in section 2 of PIL. **Additional risk minimization measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** None
Safety in long-term treatment use	**Routine risk minimization measures:** None **Additional risk minimization measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** Prospective ICGG safety sub-registry.
Use in patients who are CYP2D6 ultra-rapid metabolizers	**Routine risk minimization measures:** • Labeled in sections 4.2 and 4.4 of SmPC. • Labeled in section 2 of PIL. **Additional risk minimization measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** Prospective ICGG safety sub-registry.

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

2.7.4. Conclusion

The CHMP considered that the risk management plan version 8.3 is acceptable.

2.8. Pharmacovigilance

2.8.1. Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the MAH fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

2.8.2. Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

2.9. Product information

2.9.1. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the MAH and has been found acceptable, as the proposed dosing schedule in the proposed population is written in language understandable for the patient, and additional testing to the user test performed at the time of the initial MAA is not considered necessary.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

The extension of the indication includes long-term treatment of paediatric patients with Gaucher disease type 1 (GD1) who are 6 years and older with a minimum body weight of 15 kg, who are stable on enzyme replacement therapy (ERT), and who are CYP2D6 poor metabolisers (PMs), intermediate metabolisers (IMs) or extensive metabolisers (EMs). Further, Cerdelga is only to be used in children who can swallow an intact capsule.

Gaucher disease (GD) is a rare autosomal recessive lysosomal storage disorder that results from a deficient activity of the enzyme acid β-glucosidase (also known as glucocerebrosidase). The major natural substrate for acid β-glucosidase is glucosylceramide (GL-1), an intermediate metabolite in the synthesis and catabolism of more complex glycosphingolipids (GSLs). GD is characterized by accumulation of GL-1 in the reticuloendothelial system, due to impaired GL-1 hydrolysis secondary to the deficiency of acid β-glucosidase.

Three major clinical subtypes of Gaucher disease (types 1, 2, and 3) are classically recognized. Gaucher disease type 1 (GD1, non-neuronopathic form), the most common form of the condition, does not involve the central nervous system (brain and spinal cord). Common features of GD1 relevant for the proposed indication are thrombocytopenia, anaemia, and an abnormally enlarged liver and/or spleen (hepatosplenomegaly).

3.1.2. Available therapies and unmet medical need

Currently, ERT with recombinant acid β-glucosidase is the standard of care for paediatric participants with Gaucher disease. ERT requires regular lifelong intravenous (IV) infusions (generally every 2 weeks) and has the associated risk of developing hypersensitivity and infusion reactions. Maintenance of IV access can be difficult in children. Thus, there is a need for a less burdensome and more practical route of administration.

Substrate reduction therapy (SRT), with eliglustat, works by partially inhibiting the enzyme glucosylceramide synthase (GCS), thereby reducing the rate of synthesis of GL-1 to better match the impaired rate of catabolism. No SRT is currently approved for paediatric use. Eliglustat is an oral treatment and currently approved for the long-term treatment of adult GD1 patients, who are CYP2D6 PMs, IMs or EMs.

3.1.3. Main clinical studies

The clinical programme consisted of one phase 3, open-label, two-cohort, multicenter study (Study EFC13738, ELIKIDS) to evaluate the safety, PK and efficacy of eliglustat alone (cohort 1, n=51) or in combination with ERT imiglucerase (cohort 2, n=6) in paediatric participants 2 to <18 years old with GD1 and GD3.

Considering the proposed paediatric indication, the primary focus of assessment in this procedure is on patients of >6 years of age on eliglustat monotherapy (Cohort 1). As the visceral manifestations of the disease are a common feature of GD1 and GD3, it is not expected that safety and efficacy on visceral symptoms is different for these two subtypes. Therefore, the entire Cohort 1 is taken along in the safety and efficacy assessment.

Cohort 1 enrolled 51 male and female GD1 (n=46) and GD3 (n=5) participants, between 2 - <18 years of age (3/51 were 2 - <6 years of age; 15/51 were 6 - <12 years of age; 33/51 were 12 - <18 years of age), who reached prespecified therapeutic goals for haemoglobin level, platelet count and spleen and liver volume while receiving ERT for at least 24 months with ongoing treatment at time of enrolment. In addition, this cohort enrolled patients who were CYP2D6 EM, IM, or PM and did not have Gaucher-related pulmonary disease, severe bone disease, nor persistent thrombocytopenia.

The primary objectives of the study were safety and PK. PopPK and PBPK analyses were used to predict eliglustat pharmacokinetics and support dose selection in the paediatric population with GD, and to characterize eliglustat PK in paediatric participants with GD (for the primary analysis period (PAP)).

Efficacy variables included the change from baseline in haemoglobin levels, platelet count, spleen and liver volume after 52 weeks of treatment. In the current procedure where patients switch from ERT to SRT, the aim of the treatment is to maintain patients within therapeutic goals with regards to haemoglobin levels, platelet counts, liver and spleen volume, while minimising toxicity.

3.2. Favourable effects

Forty-nine (96%) participants sustained haemoglobin levels above the prespecified therapeutic goal for haemoglobin at Week 52. The mean (SD) absolute change in haemoglobin levels from baseline to Week 52 was -0.41 g/dL (1.02).

Fifty (98%) participants sustained values at or above the prespecified therapeutic goal for platelet count at Week 52. The mean (SD) percentage change in platelet count from baseline to Week 52 was -7.87% (22.71).

All participants sustained values at or below the prespecified therapeutic goal for liver volume (<1.5 multiples of normal (MN)) at Week 52. The mean (SD) percentage change in liver volume from baseline to Week 52 was 0.95% (13.45).

All participants sustained values at or below the prespecified therapeutic goal for spleen volume (<10.0 MN) at Week 52. The mean (SD) percentage change in spleen volume from baseline to Week 52 was 3.67% (25.47).

There were no relevant differences between age groups in change in haemoglobin levels, platelet count, nor in change of liver and spleen volume from baseline up to 52 weeks.

Data of 36 participants from Cohort 1 were available from the long-term treatment period (LTP; week 53-104) of the study. Similar effects were observed regarding mean (SD) change from baseline to Week 104 for haemoglobin levels (-0.21 g/dL (0.97)), platelet counts (-5.04% (19.76)), liver (-3.07% (11.53)) and spleen volume (-5.96% (18.52)).

Quality of life scores, with large variation, remained rather constant. There were numerical differences in height Z-scores. Tanner staging, the assessment for pubertal development, showed an increase in some of the patients as would be expected.

Participants from the ICGG Registry, receiving continued ERT with imiglucerase, were selected to match participants from Cohort 1. Numerical differences were observed for the four key endpoints (haemoglobin levels, platelet count, spleen and liver volume) which are slightly in favor of ERT treatment.

3.3. Uncertainties and limitations about favourable effects

The patient population included in this study is limited in size and the study lacks a control group, therefore the design precludes drawing robust conclusions regarding efficacy.

Within Cohort 1, there were three (1 GD1 and 2 GD3) participants that required rescue therapy (switch to ERT imiglucerase) during the PAP based on increasing spleen size and three (2 GD1 and 1 GD3) additional participants that required rescue therapy during the LTP due to spleen size (n=1) and a decline in GD status (n=2). Spleen volume remained below the prespecified therapeutic goal for all participants through the PAP and LTP.

Participants of the ICGG Gaucher Registry were matched to participants from Cohort 1 however, this is not a randomized comparison and residual confounding cannot be excluded.

3.4. Unfavourable effects

In Cohort 1, 48/51 patients experienced at least one TEAE.

The most frequent PTs (in ≥10% of participants) were nasopharyngitis (23.5%), COVID-19 (21.6%), headache (13.7%), arthralgia (13.7%), dyspepsia (13.7%), pharyngitis (11.8%), and vomiting (11.8%).

Approximately one-third of AEs was considered related to the study treatment (ADRs). Overall, the most frequently reported related TEAEs were in the gastrointestinal disorders SOC with dyspepsia reported in 6 participants (10.5%). Splenomegaly, headache, fatigue, and dry skin were the only other related TEAEs reported in more than 1 participant. All AEs were mild to moderate, except for a severe event of arthralgia which was assessed as related to eliglustat.

In Cohort 1, 6/51 participants experienced 9 treatment-emergent SAEs. From these SAEs, two events of arthralgia were considered ADRs.

Three (5.9%) participants experienced 5 treatment-emergent AESIs. These included 1 (2.0%) incidence of each of the following events: syncope, sinus tachycardia, and accidental overdose (3 events in 1 participant). Of the AESIs, only the event of sinus tachycardia was considered related to study treatment.

Seven (13.7%) participants in Cohort 1 (4 GD1 and 3 GD3) experienced TEAEs leading to permanent treatment discontinuation. In 4 out of these 7 participants, a confirmatory abdominal MRI showed a spleen volume increase in MN >35% compared to baseline that qualified the respective participants for rescue therapy.

There were no deaths in the study.

3.5. Uncertainties and limitations about unfavourable effects

The paediatric patient population included in this study is relatively small and there is no comparator arm in this study. This hampers the conclusions that can be drawn on safety.

3.6. Effects Table

Table: Effects Table for Cerdelga for paediatric patients with GD1 who are 6 years and older with a minimum body weight of 15 kg, who have been previously treated with enzyme replacement therapy (ERT) based on Study EFC13738 (data cut-off: 21 June 2023)

Effect	Short Description	Unit	Eliglustat Mean (SD) change	Control	Uncertainties/ Strength of evidence
Favourable Effects					
Haemoglobin levels	Mean change from baseline to week 52	mmol/L g/dL	-0.26 (0.63) -0.41 (1.02)	n/a	SoE: No relevant differences between age categories
Platelet count	% change from baseline to week 52	%	-7.87% (22.71)	n/a	SoE: No relevant differences between age categories
Liver volume	% change from baseline to week 52	%	0.95% (13.45)	n/a	SoE: No relevant differences between age categories
Spleen volume	% change from baseline to week 52	%	3.67% (25.47)	n/a	SoE: No relevant differences between age categories
Unfavourable Effects					
Gastrointestinal AEs	Incidence in cohort 1 patients	%	13.7	n/a	Known ADR of eliglustat in adults.
Arthralgia	Incidence in cohort 1 patients	%	13.7	n/a	Known ADR of eliglustat in adults.

Abbreviations: AEs, adverse events, ADR, adverse drug reaction

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

Efficacy of eliglustat on haematologic and visceral features of the disease can be extrapolated from adult to paediatric GD1 patients based on the PK bridge. The bridge was based on simulations targeting the exposure within the exposure 5th - 95th percentile of PBPK-predicted exposure in adults at steady state. As the study was not designed to confirm efficacy, the limitations of the study design (duration, size and lack of a control group) preclude drawing robust conclusions. As extrapolation has been agreed on in the context of discussions regarding the PIP and previous protocol assistance/scientific advice, this approach is considered acceptable and efficacy data will be regarded as supportive.

Most paediatric patients on eliglustat treatment for 52 weeks remain on therapeutic goals with regards to liver and spleen volume, haemoglobin levels and platelet count after switching from ERT. These endpoints are considered important and clinically relevant in the context of GD.

The enrolled study population included paediatric patients who have been treated for minimally 24 months with ERT and have reached therapeutic goals. No efficacy data are available in treatment naïve paediatric patients.

Manifestations of GD that are specific for children (growth retardation and delayed pubertal development) are not amenable to extrapolation. Growth and pubertal development were assessed in this study. Although no alarming results were observed, the limited study size and duration and lack of control group preclude assessing efficacy of eliglustat in this respect.

There is data available in some patients at 104 Weeks, which support the maintenance of the effect observed at 52 weeks and support the proposed indication.

When paediatric patients on eliglustat treatment were compared to matched external controls from the ICGG Registry who were on ERT, data did not indicate that switching from ERT to eliglustat leads to clinically meaningful reductions in efficacy for GD1 patients. However, this is not a randomized comparison and residual confounding cannot be excluded. Therefore, these data is considered supportive only.

Overall, the proposed paediatric posology is sufficiently justified by the PK data.

Eliglustat treatment is a daily oral treatment which is a less burdensome and more practical route of administration than bi-weekly IV infusions. This is considered important especially for the paediatric population.

Cerdelga is only to be used in children who can swallow an intact capsule. The proposed posology initially included also an alternative method of administration with compounding of an oral suspension (4.2 mg/ml) from Cerdelga capsules by local pharmacies using commercial suspension vehicles. However, following the assessment of all available data this proposed alternative approach is not acceptable to the CHMP due to several limitations. In addition to possible unavailability of the proposed commercial vehicles, local pharmacies in several countries might not be able to prepare the oral suspension. However, as the current indication is from 6 years of age and above, it is not expected that many patients have difficulty swallowing capsules. Of the four participants of Cohort 1 who received eliglustat via oral suspension during the clinical study, none would qualify for eliglustat treatment under the proposed indication as these participants were either too young (<6 year of age) or had GD3.

With regard to safety, the reported safety profile is in line with what is known for eliglustat. Safety of eliglustat can be extrapolated from adults to children with GD1. Therefore, although the studied patient population is limited, the submitted data are sufficient to assess the safety profile of eliglustat in paediatric patients with GD1 and are supportive of the proposed extension of the indication.

No new adverse reactions are added to 4.8 of the SmPC and no changes to the safety specifications are proposed. This is acceptable as no new safety findings arose from the paediatric study.

3.7.2. Balance of benefits and risks

Eliglustat efficacy and safety can be extrapolated from adults with GD1 based on a PK bridge. The provided safety and efficacy data of eliglustat treatment in paediatric GD1 patients of 6 - <18 year of age support the

extrapolation. Most paediatric patients, who were stable on ERT, maintained therapeutic goals for haemoglobin levels, platelet count and liver and spleen volume after switching to eliglustat treatment. Meanwhile, the safety profile in paediatric patients is in line with what is seen in adults.

The proposed 21 mg capsules strength is acceptable from a quality point of view.

From a clinical perspective, the favourable effects outweigh the unfavourable effects in the proposed paediatric indication. The benefit risk of Cerdelga is positive.

3.7.3. Additional considerations on the benefit-risk balance

The convenience of taking capsules instead of IV infusion (ERT) is considered an additional benefit.

3.8. Conclusions

The overall benefit/risk balance of Cerdelga is positive, subject to the conditions stated in section 'Recommendations'.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Cerdelga 21 mg hard capsules is favourable in the following indication(s):

> 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 poor metabolisers (PMs), intermediate metabolisers (IMs) or extensive metabolisers (EMs).

The CHMP therefore recommends the extension(s) of the marketing authorisation for Cerdelga 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 requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates 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 Marketing authorisation holder (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

agreed 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.

Additional risk minimisation measures

Prior to the launch of Cerdelga in each Member State the Marketing Authorisation Holder (MAH) must agree about 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 educational programme is aimed at minimizing specific safety concerns.

The MAH shall ensure that in each Member State where Cerdelga is marketed, all healthcare professionals who are expected to prescribe Cerdelga have access to/are provided with the physician educational material:

1. Physician educational material:

- The Summary of Product Characteristics
- Guide for prescriber
- Patient card

The **prescriber guide** shall contain the following key elements:

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

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

- Patients should be informed that consumption of grapefruit or its juice should be avoided.
- Eliglustat is contraindicated in patients who are CYP2D6 IMs or EMs who are taking a strong or moderate CYP2D6 inhibitor concomitantly with a strong or moderate CYP3A inhibitor. Eliglustat is also contraindicated in patients who are CYP2D6 PMs taking a strong CYP3A inhibitor. Use of

eliglustat under these conditions results in substantially elevated plasma concentrations of eliglustat. This may cause mild increases in the PR, QRS, and QTc intervals.

- Use of eliglustat with strong CYP3A inducers substantially decreases the exposure to eliglustat, which may reduce the therapeutic effectiveness; therefore, concomitant administration is not recommended. Use of a moderate CYP3A inhibitor with eliglustat is not recommended in PMs.
- A once daily dose of eliglustat is recommended when a strong CYP2D6 inhibitor is used concomitantly in IMs and EMs.
- Caution should be used with moderate CYP2D6 inhibitors in IMs and EMs. Caution should be used with strong or moderate CYP3A inhibitors in IMs and EMs. Caution should be used with weak CYP3A inhibitors in PMs.
- In CYP2D6 EMs with severe hepatic impairment, Cerdelga is contraindicated. In CYP2D6 EMs with mild or moderate hepatic impairment taking a strong or moderate CYP2D6 inhibitor, Cerdelga is contraindicated.
- In CYP2D6 EMs with mild hepatic impairment taking a weak CYP2D6 inhibitor or a strong, moderate or weak CYP3A inhibitor, a once daily dose of eliglustat is recommended.
- In CYP2D6 IMs or PMs with any degree of hepatic impairment, Cerdelga is not recommended.

The MAH shall ensure that in each Member State where Cerdelga is marketed, all patients/caregivers who are expected to use Cerdelga have access to/are provided with the patient information pack.

2**.** Patient information pack

- Patient information leaflet
- Patient card

The **patient card** shall contain the following key elements:

Information for healthcare professionals:

- This patient is using eliglustat (Cerdelga) for the treatment of Gaucher disease type 1.
- Eliglustat should not be used concomitantly with medicines that may have an impact on liver enzymes that play a role in the metabolism of eliglustat. In addition, patient's hepatic or renal status may have an impact on the metabolism of eliglustat.
- Using eliglustat together with such products or in patients with hepatic or renal impairment may either make eliglustat less effective, or it may increase the eliglustat levels in the patient's blood.

Information for the patient/ caregiver:

- Always consult the doctor who prescribed eliglustat before you start using other medicines.
- Do not consume grapefruit products.

Obligation to conduct post-authorisation measures

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.	Q3 2025

Paediatric data

Furthermore, the CHMP reviewed the available paediatric data of studies subject to the agreed Paediatric Investigation Plan P/0440/2022 and the results of these studies are reflected in the Summary of Product Characteristics (SmPC) and, as appropriate, the Package Leaflet.

In addition, CHMP recommends the variation(s) to the terms of the marketing authorisation, concerning the following change(s):

Variations requested		Type	Annexes affected
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I, II, IIIA and IIIB

Extension application to introduce a new strength (21 mg capsule, hard) grouped with an extension of indication (C.I.6.a) to include treatment of paediatric patients with GD1 who are 6 years and older with a minimum body weight of 15 kg, who are stable on enzyme replacement therapy (ERT), and who are CYP2D6 poor metabolisers (PMs), intermediate metabolisers (IMs) or extensive metabolisers (EMs), based on interim results from study EFC13738 (Open label, two cohort (with and without imiglucerase), multicenter study to evaluate pharmacokinetics, safety, and efficacy of eliglustat in paediatric patients with Gaucher disease type 1 and type 3). The above indication is approved for the new strength (21 mg) and the existing strength (84 mg) and as a consequence, sections 4.1, 4.2, 4.8, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet is updated in accordance. In addition, the MAH took this opportunity to introduce editorial changes and to align the product information with the latest version of the QRD guideline. The RMP version 8.3 was agreed during the procedure.