# CENTER FOR DRUG EVALUATION AND RESEARCH

***APPLICATION NUMBER:***

# 205494Orig1s000

# SUMMARY REVIEW

# Summary Review for Regulatory Action

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|---|---|
| **Date** | August 19, 2014 |
| **From** | Andrew E. Mulberg, MD, FAAP, CPI |
| **Subject** | Division Deputy Director Summary Review |
| **NDA/BLA #**<br>**Supplement #** | 205494 |
| **Applicant Name** | Genzyme |
| **Date of Submission** | September 20, 2013 |
| **PDUFA Goal Date** | August 10, 2014 |
| **Proprietary Name / Established (USAN) Name** | Cerdelga/eliglustat tartrate |
| **Dosage Forms / Strength** | Oral/84 mg bid |
| **Proposed Indication(s)** | Long-term treatment of adult patients with Gaucher disease type 1 who are CYP2D6 extensive metabolizers (EMs), intermediate metabolizers (IMs), or poor metabolizers (PMs) as detected by an FDA-cleared test |
| **Action/Recommended Action for NME:** | **Approval** |

| **Material Reviewed/Consulted**<br>OND Action Package, including: | **Names of discipline reviewers** |
|---|---|
| Medical Officer Review | Karen Berry, MD |
| CDTL Reviews: | Lara Dimick, MD |
| Statistical review | Ben Vali, MS<br>Freda Cooner, PhD |
| Nonclinical Reviewer | Tamal Chakraborti, PhD<br>Sushanta Chakder, PhD |
| Biopharmaceutics reviewer | Albert Chen, PhD |
| Clinical Pharmacology | Elizabeth Shang, Ph.D. (Primary)<br>Sandhya Apparaju, Ph.D. (In vitro study review)<br>Sue Chih-Lee, PhD |
| PBPK reviewer | Yuzhuo Pan, Ph.D.<br>Ping Zhao, PhD |
| Labeling reviews | Monica Calderon, PharmD<br>Nathan Caulk, MS, BSN<br>Adewale Adeleye, PharmD |
| PMHS | Carol Kasten, MD |
| Bone review | John Stinson, MD |

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|---|---|
| Genomics | Sarah Dorff, Ph.D.<br>Michael Pacanowski, PhD |
| CMC Review | Yichun Sun, PhD<br>Tarun Mehta, PhD<br>Hamid Shafiei, PhD |
| QT-IRT Review | Monica Fiszman, MD, PhD |
| Microbiology Reviewer | Robert Mello, PhD |
| Pharmacometrics | Anshu Marathe, Ph.D.<br>Justin Earp, Ph.D.<br>Nitin Mehrotra, PhD |

OND=Office of New Drugs
DDMAC=Division of Drug Marketing, Advertising and Communication
OSE= Office of Surveillance and Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
DSI=Division of Scientific Investigations
DRISK=Division of Risk Management
CDTL=Cross-Discipline Team Leader

# Signatory Authority Review Template

## 1. Introduction

Genzyme has submitted the NDA for Cerdelga (eliglustat tartrate) for the following indication:

1) Long term treatment of adult patients with Type 1 Gaucher Disease who are CYP2D6 poor, intermediate or extensive metabolizers**.**

This submission was comprised of multiple clinical trials delineated below in Table 1. The substantial evidence of efficacy and safety was based on two phase 3 trials (GZGD02507-ENGAGE, GZGD02607–ENCORE) and one phase 2 trial (GZGD00304) and safety based on three phase 3 trials (GZGD02507- ENGAGE, GZGD02607–ENCORE and GZGD03109 - EDGE) and one phase 2 trial (GZGD00304).These trials are described below in Table 1.

**Table 1: Studies/Clinical Trials for Eliglustat**

| Trial | Phase | N | Design | Dosing | Study population | Duration | Primary Efficacy Evaluation |
|---|---|---|---|---|---|---|---|
| **GZGD02507 (ENGAGE)** | 3 | Total 40 (20 placebo 20 eliglustat) | R, DB, PC, Efficacy Safety PK | Elglustat 50 mg bid, 100 mg bid based on plasma trough concentration | Gaucher type 1 patients ≥16 years old who have not had treatment with SRT within 6 months prior to randomization or ERT within 9 months prior to randomization | PAP- Day 1 to wk 39 | (%) change in spleen volume from Baseline to Wk 39<br><br>Long term trial ongling |
| **GZGD02607 (ENCORE)** | 3 | 106 eliglustat 54 Cerezyme | R, OL, AC, Efficacy Safety PK | Elglustat 50 mg bid, 100 mg bid or 150 mg bid based on plasma trough concentration Cerezyme: q 2 wk regimen equivalent to their ERT dose | Gaucher type 1 patients ≥18 years old who have reached therapeutic goals with ERT | PAP- Day 1 to wk 52 | (%) of pts who remain stable in Hgb levels, platelet counts & organ vol (spleen, liver)<br><br>Long term ongoing |
| **GZGD00304** | 2 | 26 | OL, MC Efficacy Safety, PK | Eliglustat 50 mg bid or 100 mg bid based on plasma trough concentration | Gaucher type 1 patients 18 to 65 years old who have not received miglustat or ERT within 12 months prior to enrollment | PAP- Day 1 to wk 52 | Response in at least 2 of the 3 main parameters (hemoglobin, platelets, and spleen)<br><br>Long term ongoing |
| **GZGD03109 (EDGE )** | 3b | 170 | R, MC, DB Evaluate QD dosing vs. BID dosing | Eliglustat Lead-in/Longterm /extended treatment period: Capsule (oral); 50-mg, 100-mg, and 150-mg | Gaucher type 1 patients ≥ 18 years old who demonstrate stability on BID dosing | 6-18M Lead in Period,followed by 52 wk PAP Longterm ex-tended treatment period up to 42 month | (%) of pts who remain stable through R-Week 52 (the PAP) assessed for both dosing regimens<br><br>Ongoing |

Reviewer' table
R- Randomized, DB-Double-blind, PC- Placebo controlled, OL-Open label, AC-Active comparator, MC-Multi-center, PK-Pharmacokinetics

**Table reproduced from Medical review, Dr. Karyn Berry**

I have concluded that there is sufficient evidence of clinical benefit to justify acceptance of this NDA as evidence of efficacy and safety, as fulfilled. I do agree that the indication for Cerdelga should be labeled accordingly, as: Long-term treatment of adult patients with Gaucher disease type 1 who are CYP2D6 extensive metabolizers (EMs), intermediate metabolizers (IMs), or poor metabolizers (PMs) as detected by an FDA-cleared test. My

review will focus on the salient issues related to this risk/benefit assessment as a recommendation to the Signatory, Dr. Amy Egan.

## 2. Background

Gaucher disease is the most common of the lysosomal storage diseases. It is inherited as an autosomal recessive trait and is caused by a deficiency of β-glucocerebrosidase activity. This enzyme deficiency results in accumulation of glucosylceramide in tissue macrophages, particularly in the liver, spleen, bone marrow, and lungs. These lipid-filled macrophages are the so-called "Gaucher cells" characteristic of the disease. Gaucher disease is a clinically heterogeneous disorder, with three main phenotypes based on the presence or absence of primary neurologic disease and severity of neurologic disease. Type 1 Gaucher disease is the most common variant and accounts for about 94% of all Gaucher cases. Type 1 Gaucher disease does not involve the CNS. Typical manifestations of type 1 Gaucher disease include hepatomegaly, splenomegaly, thrombocytopenia, bleeding tendencies, anemia, hypermetabolism, skeletal pathology, growth retardation, pulmonary disease, and decreased quality of life. The estimated worldwide incidence of type 1 Gaucher disease is 1 in 50,000 to 100,000. Further details of the indication can be accessed through the Medical Review summary.

Cerdelga (eliglustat tartrate), a SRT, is a new molecular entity. It is a member of a novel class of glucosylceramide (GL-1) synthase inhibitors that resembles the ceramide substrate for the enzyme (Figure 1).

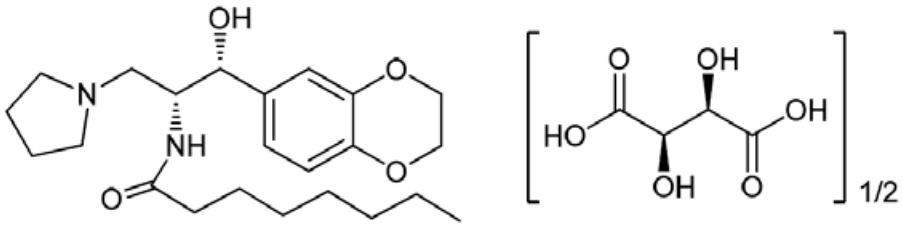


**Figure 1: Eliglustat tartrate chemical structure**

**Pharmacological class: Glucosylceramide (GL-1) synthase inhibitors**

Eliglustat is a potent and specific inhibitor of glucosylceramide synthase. Inhibition of glucosylceramide synthase by eliglustat results in a reduction of the accumulation of glucosylceramide, thereby allowing the patient's residual endogenous acid β -glucosidase levels to clear the substrate. This biochemical pathway is reproduced below (**Figure 2**) demonstrating the critical interaction between glucocerebrosidase and the GL-1 synthase involved in reformation of GL-1.

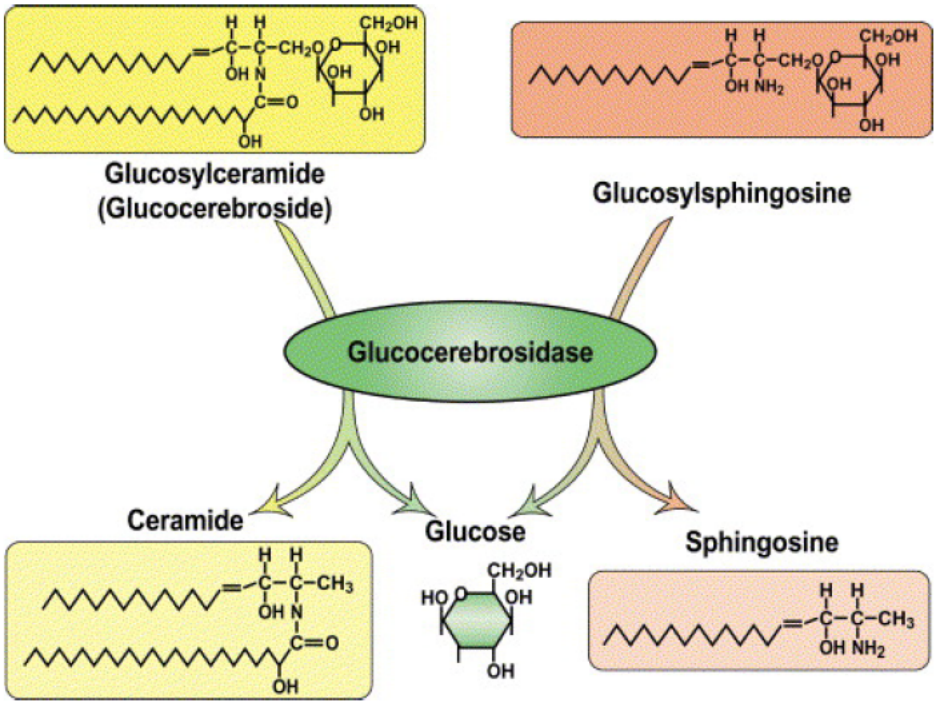


**Figure 2: Biochemical Pathway of Synthesis and Metabolism of Gl-1**

The goal of this approach is to reduce the rate of synthesis of glucosylceramide to match its impaired rate of catabolism in patients with GD1, thereby preventing glucosylceramide accumulation and alleviating clinical manifestations. Cerdelga is supplied as 84 mg hard capsules and contains standard excipients. 84 mg of eliglustat is equivalent to 100 mg of eliglustat tartrate. Other currently available treatments for Gaucher disease including use of enzyme replacement therapies that have been approved are listed in **Table 2** below:

**Table 2: Currently Available Treatments for Proposed Indications**

| **Enzyme replacement therapy (ERT) products** | | | | |
|---|---|---|---|---|
| **Drug** | **Year Approved** | **Formulation** | **Indication** | **Dosage** |
| **Cerezyme** (imiglucerase) | 1991 | IV formulation of recombinant DNA using CHO cells culture | Long-term ERT for pediatric and adult patients with type 1 Gaucher with anemia, thrombocytopenia, bone disease, or hepatomegaly or splenomegaly | 2.5 U/kg three times per week to 60 U/kg every two weeks |
| **VPRIV** (velaglucerase alfa) | 2010 | IV formulation of recombinant DNA using human | Long-term ERT for pediatric and adult patients with type 1 | 60 Units/kg every other week |

| | | | | |
|---|---|---|---|---|
| | | fibroblast cells | Gaucher | |
| **Elelyso** (taliglucerase alfa) | 2012 | IV formulation of recombinant DNA using carrot cells | Long-term ERT for adult patients with type 1 Gaucher | 60 Units/kg every other week |
| **Substrate reduction therapy (SRT) products** | | | | |
| **Drug** | **Year Approved** | **Formulation** | **Indication** | **Dosage** |
| **Zavesca** (miglustat) | 2003 | Capsule for oral administration | Treatment of adult type 1 Gaucher patients for whom ERT is not an option. | 100 mg three times daily |

## 3. CMC

The CMC review was conducted by Dr. Yichun Sun, Dr. Tarun Mehta and Dr. Hamid Shafiei. From CMC perspective the NDA was approvable. Further details are provided in their individual reviews.

## 4. Nonclinical Pharmacology/Toxicology

There are no new nonclinical issues that were raised with this application and were deemed approvable. The reader is referred to previous reviews by Tamal Ckakraborti, PhD. Of particular note though is related to the mechanism of action of Eliglustat which was shown to inhibit ($IC_{50}$ = 10 ng/mL) glucosylceramide synthase (GCS) in human K562 cells or human A375 cell-derived microsomes. In animal efficacy studies, eliglustat decreased GL-1 levels in peripheral tissues and plasma of normal rats and dogs following oral administration. In the D409V/null mouse model of GD1, eliglustat decreased the accumulation of GL-1 in tissues. In addition eliglustat caused an inhibition of hERG channels expressed in HEK-293 cells with an $IC_{50}$ value of 0.35 µg/mL, indicating a potential to cause QT prolongation. Eliglustat also inhibited sodium and calcium channels with $IC_{50}$ values of 5.2 and 10.4 µg/mL. This inhibition becomes clinically relevant as one interprets the impact of the CYP2D6 metabolizer status and Drug-Drug interactions that become clinically relevant and discussed for labeling implications. Eliglustat is a substrate for CYP2D6, CYP3A4 and P-glycoprotein transporter. Metabolism of eliglustat was predominantly mediated by CYP2D6 and to a lesser extent CYP3A4. Overall, more than ten metabolites of eliglustat have been identified, seven of which were formed via CYP2D6 in in vitro studies. These issues are discussed below in sections of Clinical pharmacology and Clinical/Safety.

## 5. Clinical Pharmacology

The pharmacology review was conducted by the following reviewers:

| | |
|---|---|
| OCP Reviewers: | Elizabeth Shang, Ph.D., Sue-Chih Lee, PhD. (Primary)<br>Sandhya Apparaju, Ph.D. (In vitro study review) |
| Pharmacometrics Reviewers: | Anshu Marathe, Ph.D. & Justin Earp, Ph.D. |
| GTT Reviewers: | Sarah Dorff, Ph.D., Michael Pacanowski, PharmD, MPH |

PBPK Reviewer: Yuzhuo Pan, Ph.D., Ping Zhao, PhD

Overall, the application was found to be acceptable for approval recommendation to Dr. Egan. This approval though is based on the outcome of the ongoing negotiations with the Applicant concerning the labeling of Cerdelga. Clinical Pharmacology has recommended changes to:

1) The proposed dosing regimen, for Partial metabolizers (PMs)
2) Labeling revisions, especially related to drug-drug interactions; and
3) Post-marketing requirements/commitments that assess hepatic and renal impairment on eliglustat PK (see Section 13 - Recommendations/Risk Benefit Assessment).

**1. Effect of CYP2D6 Genotype on Cerdelga Metabolism and QTc Effects:**

One of the major issues with this application centered on the CYP2D6 genotype metabolizer status of the patients as the metabolism of Cerdelga is intimately associated with this polymorphism. This genotype status also impacted the cardiovascular effects specifically on the QtC interval. A key safety concern for Cerdelga is the potential for significant drug-drug interactions. Though the result of the TQT was "negative", eliglustat increased the QTc and PR intervals in a concentration dependent manner. Based on the concentration QT relationship, there appears to be no QTc related safety concerns for drug concentrations below 250 ng/ml. As noted in the QTc evaluation here was a concentration dependent increase in QTc. An increase in ΔΔ QTcF is observed with increasing drug concentration. The mean (upper 90% CI) predicted ΔΔQTcF at the mean Cmax of 16.7 ng/ml and 237 ng/ml for the 200 mg and 800 mg doses achieved in the QT study are 0.18 (1.7) ms and 6.06 (8.9) ms. For a Cmax of 250 ng/mL, the mean (upper 90% CI) of ΔΔQTcF are predicted to be 6.4 (9.4) ms, which is below the regulatory threshold (Table 9). Thus based on the concentration-QT relationship, clinical pharmacology reviewers identified no QT related safety concerns for drug concentrations below 250 ng/mL (**Tables 3 and 4, below**)

**Table 3: Predicted change of ΔΔQTcF interval at geometric mean Cmax of eliglustat observed in the thorough QT study**

| Dose Group | Predicted change in ΔΔ QTcF interval (ms) | |
|---|---|---|
| | Mean | 90% Confidence Interval |
| **200 mg Genz-112638** | | |
| Geometric Mean $C_{max}$ (16.7 ng/mL) | 0.176 | (-1.35; 1.7) |
| **800 mg Genz-112638** | | |
| Geometric Mean $C_{max}$ (237 ng/mL) | 6.06 | (3.24; 8.88) |

**Table 4: Predicted QT prolongations at the steady state mean Cmax of 250 ng/mL**

| **Predicted mean (90%CI, ms) change in** | At mean Cmax of 250 ng/mL |
|---|---|
| **QTcF** | **6.4 (3.4, 9.4)** |
| **PR** | **11.2 (8.9, 13.4)** |
| **QRS** | **3.5 (1.9, 5.1)** |

**Source: Clinical Pharmacology review**

## 2. Implication of Genotype and Drug-Drug Interactions

PD/PK modeling suggests that there is a potential for prolongation at concentrations that could be achieved with significant drug-drug interactions. Drug-drug interactions and pre-existing cardiac disease, specifically AV nodal disease will be important considerations in dosing patients to minimize risk of adverse reactions. These will need to be clearly described in the product label. The reader is referred to the Clinical Pharmacology reviews for further details.

The label will reflect appropriate dosing recommendation for each of the metabolizer genotypes. As a result of new data presented at the late cycle meeting, the sponsor indicated that several study subjects originally classified as CYP2D6 intermediate metabolizers (IMs) have been reclassified as extensive metabolizers (EMs) (see Dr. Shang's clinical pharmacology review addendum for details on reclassification and studies being affected by this reclassification). Because the reclassification does not affect datasets used for model development, simulation results remain unchanged. However, observed PK values used for comparison with simulated values in several figures and tables should be updated with new information which is available in Dr. Shang's review.

The final dose recommendations for all CYP2D6 metabolizer status are reflected below in **Tables 5-7:**

**Table 5: Effect of various CYP inhibitors on systemic exposure to Eliglustat and dose recommendations in CYP2D6 EMs:**

**Table 6: Effect of various CYP inhibitors on systemic exposure to Eliglustat and dose recommendations in CYP2D6 IMs:**

(b) (4)

**Table 7: Effect of various CYP inhibitors on systemic exposure to Eliglustat and dose recommendations in CYP2D6 PMs:**

| CYP Inhibitors | (b) (4) | Dosing Recommendation |
|---|---|---|
| Ketoconazole (Strong CYP3A4 inhibitors) | | Contraindicate |
| Fluconazole (Moderate CYP3A4 inhibitors | | Not recommended |
| Ranitidine (Weak CYP3A4 inhibitors) | | Not recommended |

The reader is referred to the final label for further details as it delineates clearly in **Sections 8 and 12** regarding these issues as well as the Reviewer Addendum of Elizabeth Shang for details.

3. **Impact of CYP2D6 Metabolism on Renal and Hepatic Impairment**:
The main route of eliglustat metabolism is by CYP450 enzymes, predominantly CYP2D6 and to a lesser extent CYP3A, which are largely expressed in liver. Eliglustat also moderately

inhibits CYP2D6, leading to higher than predicted dose-proportional eliglustat exposure levels. Therefore, patients with hepatic impairment are expected to have higher eliglustat levels than patients without hepatic impairment. While it is unknown to what extent partial hepatic impairment will affect eliglustat levels, patients with severe hepatic impairment are expected to have very little CYP2D6 and CYP3A activity, which would be similar to administering eliglustat with both strong CYP2D6 and CYP3A inhibitors concomitantly; a drug-drug interaction scenario that is contraindicated per the CERDELGA USPI.

Liver failure is a very rare complication of GD1, which itself is an orphan disease. The number of patients with GD1 and liver failure of any cause is still expected to be extremely small, and patients with severe hepatic impairment would be better served by enzyme replacement therapy. Considering the remote likelihood in which a GD1 patient with severe hepatic impairment would use CERDELGA, Genzyme proposes to (b) (4)

The PMR discussed below will be to conduct this PMR study initially in "healthy" (non-GD1) subjects with moderate hepatic impairment, with provisions in the study protocol to enroll a cohort of subjects with mild hepatic impairment only if the results in subjects with moderate hepatic impairment show a substantial effect of reduced hepatic function on eliglustat PK compared to the control subjects. This "reduced design" would mimic the renal impairment study design in PMR 2 which is discussed separately below.

## 6. Clinical Microbiology

The Microbiology review was conducted by Dr. Robert Mello, Senior Review Microbiologist. Dr. Mello stated that the in process controls and microbial limits testing within the ongoing stability program provided adequate assurance of the microbial control of the manufacturing process. See his full review dated January 2, 2014 for further details.

## 7. Clinical/Statistical-Efficacy

The reader is referred to the Clinical review of Dr. Berry for further information on clinical trial specific information. Table 1 referenced above in Introduction describes the datasets used for the determination of efficacy and safety for Cerdelga in adults. This submission was comprised of multiple clinical trials delineated below in Table 1. The substantial evidence of efficacy and safety was based on two phase 3 trials (GZGD02507- ENGAGE, GZGD02607–ENCORE) and one phase 2 trial (GZGD00304) and safety based on three phase 3 trials (GZGD02507- ENGAGE, GZGD02607–ENCORE and GZGD03109 - EDGE) and one phase 2 trial (GZGD00304). The reader is referred to the study design and specific details outlined in Table 1 for further details.

I concur with Dr. Dimick who notes that the "results from the ENGAGE and ENCORE trials collectively support the efficacy of eliglustat. Efficacy was established by the ENGAGE trial in treatment naïve patients, and in which demonstrated that eliglustat was superior to placebo with respect to the Week 39 change from baseline in (separately) spleen volume, hemoglobin

level, liver volume, and platelet count. The currently ongoing Open-Label Treatment Period suggests a sustained efficacy profile with respect to the aforementioned four parameters.

Efficacy was further supported by the ENCORE trial (in previously treated patients), which demonstrated that patients who had reached therapeutic goals with CEREZYME remained stable 52 weeks after switching to oral treatment with eliglustat. The currently ongoing Long-Term Treatment Period suggests that this maintained clinical response is durable in the long run." The Statistical Reviewer, Benjamin Vali supported the adequacy of the ENGAGE trial to support approvability. Primary and secondary endpoints in the ENGAGE trial were statistically significantly different. Please see statistical review for further details.

## 1. GZGD02507 (ENGAGE)-Phase 3 Treatment Naïve Patients

**Table 8: Comparison of Organ Volume and Hematology Results from ENGAGE and the Phase 2 Trial**

| | ENGAGE* | | Phase 2 Study |
|---|---|---|---|
| | Eliglustat (N=20) | Placebo (N=20) | Eliglustat (N=26) |
| **Spleen Volume, mean (SD)** | | | |
| Baseline, MN | 13.89 (5.929) [N=20] | 12.50 (5.959) [N=20] | 20.04 (12.798) [N=26] |
| 6 Months, % change | -25.16 (7.511) [N=19] | 0.73 (9.972) [N=19] | -24.3 (11.76) [N=23] |
| 9 Months, % change | -27.58 (12.591) [N=20] | 2.07 (8.777) [N=20] | -- |
| 12 Months, % change | -- | -- | -38.5 (11.41) [N=22] |
| **Haemoglobin, mean (SD)** | | | |
| Baseline, g/dL | 12.05 (1.186) [N=20] | 12.75 (1.629) [N=20] | 11.10 (1.674) [N=26] |
| 3 Months, g/dL change | -0.02 (0.776) [N=20] | -0.17 (0.811) [N=19] | 0.34 (0.798) [N=24] |
| 6 Months, g/dL change | 0.72 (0.909) [N=19] | -0.51 (0.999) [N=20] | 0.98 (0.710) [N=20] |
| 9 Months, g/dL change | 0.73 (1.093) [N=20] | -0.58 (0.890) [N=20] | 1.39 (0.893) [N=19] |
| 12 Months, g/dL change | -- | -- | 1.70 (1.274) [N=22] |
| **Liver volume (MN), mean (SD)** | | | |
| Baseline, MN | 1.44 (0.354) [N=20] | 1.36 (0.280) [N=20] | 1.77 (0.633) [N=26] |
| 6 Months, % change | -2.97 (8.019) [N=19] | 1.25 (7.383) [N=19] | -11.2 (11.51) [N=23] |
| 9 Months, % change | -5.45 (6.886) [N=20] | 1.70 (8.004) [N=20] | -- |
| 12 Months, % change | -- | -- | -16.9 (10.48) [N=22] |
| **Platelets, mean (SD)** | | | |
| Baseline, $x10^9/L$ | 75.05 (14.095) [N=20] | 78.48 (22.611) [N=20] | 66.423 (20.1413) [N=26] |
| 3 Months, % change | 3.47 (16.282) [N=20] | -7.56 (18.200) [N=19] | 12.7 (32.37) [N=23] |
| 6 Months, % change | 14.61 (26.202) [N=19] | -10.63 (16.601) [N=20] | 23.1 (33.61) [N=19] |
| 9 Months, % change | 31.71 (31.801) [N=20] | -8.77 (19.187) [N=20] | 27.9 (36.68) [N=17] |
| 12 Months, % change | -- | -- | 41.3 (36.95) [N=22] |

**Reproduced from CDTL review, Dr. Dimick**

Importantly, the issue of impact of Cerdelga on Bone Mineral Density and Marrow Burden changes was not deemed to be clinically meaningful and used non-validated measurement assessments. Further details are described in review of Drs. Berry and Dimick.

**2. GZGD02607 (ENCORE)-Phase 3 Switchover of patients from Imiglucerase (Cerezyme):**

Concerns were raised by Benjamin Vali concerning the ENCORE trial (the supportive trial) related to the non- inferiority margin of 25% that was pre-specified for the primary efficacy assessment. This margin was deemed clinically unacceptable by the clinical review team. There was also no agreement on the non-inferiority margin of 15%, proposed for the additionally requested assessment of percentage change from baseline in spleen volume. Benjamin Vali notes that the "non- inferiority margin of 25% that was pre-specified for the primary efficacy assessment. This margin was deemed clinically unacceptable by the clinical review team. There was also no agreement on the non-inferiority margin of 15%, proposed for the additionally requested assessment of percentage change from baseline in spleen volume. Neither of these margins was acceptable from a statistical perspective. Each margin was chosen by the applicant based on the data from phase 2 study GZGD00304, which was an open-label study in 26 treatment-naïve adult GD1 patients who received monotherapy with eliglustat. It was not feasible to assess assay sensitivity when evaluating the proposed non-inferiority margins without a placebo-controlled trial with CEREZYME. Note that a placebo-controlled trial with CEREZYME has never been conducted. In addition, the aforementioned hypothetical placebo-controlled trial with CEREZYME would have to utilize the same trial design and also be in the same population of patients as those studied in ENCORE to ensure constancy. The differences between the GZGD00304 and ENCORE study designs and patient populations ultimately precluded the constancy assumption from being met." Dr. Dimick states that "While the noninferiority margin was not ideal, the overall results of the trial supported the efficacy of eliglustat in previously treated GD1 patients." Dr. Dimick and the Clinical team based this on the analysis of an alternate primary efficacy endpoint which was the percentage (%) of patients who remained stable for 52 weeks (the primary analysis period) assessed for both treatment groups separately along with a difference between the 2 treatment groups. For a patient to be considered to have demonstrated a clinically meaningful response to treatment with eliglustat or Cerezyme, patients must have remained stable in hematological parameters (hemoglobin levels and platelet counts), and organ volumes (spleen, when applicable, and liver volumes in multiples of normal [MN]). As she notes that ENCORE was an open-label study, the design was appropriate per the measurement/evaluation of the endpoint values based on the blinded image evaluations and objective laboratory measures which would not be expected to introduce bias. In addition, a double-blinded study would have been difficult to conduct because a double-dummy (i.e., additional placebo IV QOW for patients randomized to receive eliglustat or additional placebo capsules BID for patients randomized to receive CEREZYME) would have to be instituted in order to ensure study blinding.

Tables 9 and 10 below reflect the data analyses from this trial supporting efficacy and durability of response of Cerdelga in the treatment of adult Gaucher disease.

**Table 9: Summary of Values and Percentage Change in Spleen Volume (MN) from Baseline to Week 52: Per Protocol Set**

| Time Point / Change | Statistic | Eliglustat (N=99) | Cerezyme (N=47) | Treatment Difference (Eliglustat-Cerezyme) |
|---|---|---|---|---|
| Baseline | n | 70 | 39 | -- |
| | Mean (SD) | 3.23 (1.37) | 2.62 (1.08) | -- |
| | Median Min, | 2.87 | 2.23 | -- |
| | Max | 1.06, 7.43 | 1.14, 5.34 | -- |
| Week 52 | n | 70 | 39 | -- |
| | Mean (SD) | 3.07 (1.39) | 2.53 (0.99) | -- |
| | Median Min, | 2.95 | 2.31 | -- |
| | Max | 0.85, 7.59 | 1.13, 4.88 | -- |
| % Change from Baseline to Week 52 | Mean (SD) | -6.07 (14.35) | -3.01 (10.50) | -- |
| | Median Min, | -6.65 | -5.20 | -- |
| | Max | -48.7, 31.8 | -22.1, 20.1 | -- |
| | LS Mean (SEM) | -5.96 (1.59) | -3.21(2.15) | -2.75 (2.71) (-8.12, 2.62) |
| | 95% CI | (-9.12, -2.80) | (-7.47, 1.06) | |
| | p-value | NA | NA | 0.3118 |

**Reproduced from CDTL summary, Dr. Dimick**

**Table 10: Summary of Percentage of Patients who remained stable for 52 Weeks: Composite Endpoint: per Protocol set**

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

**Reproduced from CDTL summary, Dr. Dimick**

Specific details regarding bone density results and metabolizer status are discussed by the Medical reviewer and summarized in the CDTL memorandum. The labeling implications for these issues reflects the absence of specific bone related effects of Cerdelga and the DDI

concerns of Cerdelga with recommended dosing adjustments described below. I agree with these assumptions and data analysis to support an approval recommendation for Cerdelga.

# 8. Safety

The reader is referred to the Safety analysis of Dr. Berry, Medical officer. Particular issues worthy of comment are related to the analyses of safety related to potential of cardiac events related to the potential effects of DDI. Concerns of cardiac specific ADRs were reviewed, in light of the results of the TQT study which were deemed "negative" (**see Clinical Pharmacology Section 5.1**). According to the medical reviewer, eliglustat increased the QTc and PR intervals in a concentration dependent manner. Based on the concentration QT relationship, there appears to be no QTc related safety concerns for drug concentrations <250 ng/ml. PK/PD modeling suggests that there is a potential for prolongation at concentrations that could be achieved with significant drug-drug interactions. Drug-drug interactions and pre-existing cardiac disease, specifically AV nodal disease will be important considerations in dosing patients to minimize risk of adverse reactions. These issues have been discussed above in Clinical Pharmacology and had labeling implications for DDI.

Dr. Berry notes, "The Phase 2 and Phase 3 trials included repeat dosing over an extended period of time. No sudden cardiac deaths, torsades de pointes or clinically meaningful AV-block cases were reported in the eliglustat Safety Set. One subject was withdrawn from the study after the first dose of eliglustat due to a ventricular tachycardia episode that required hospitalization and was considered by the investigator to be possibly related to eliglustat. Three patients had non-sustained ventricular tachycardia episodes that were asymptomatic. Four patients reported 2nd-degree AV block that were asymptomatic and taken from unscheduled Holter monitoring. Data reported from electrocardiogram monitoring during phase 2 and 3 studies showed no clinically relevant changes in QTcF. Seven subjects had PR intervals > 200 ms and increase from Baseline of ≥ 25%. One had a clinically meaningful PR prolongation. Eighteen subjects had a post-baseline QRS ≥ 120 ms; two of them had post baseline increases of 30 and 50%, which were considered clinically meaningful. While some changes were observed in ECG and Holter monitor parameters with eliglustat, most patients were asymptomatic and continued treatment. As noted in the Table 45, some cases of cardiac arrhythmias were also observed at baseline screenings and in patients who received placebo or Cerezyme."

Pooled data from the Eliglustat Safety Set were generally the same as those seen across the individual clinical studies (Phase 2, ENGAGE, and ENCORE). For all eliglustat patients, the highest rates of AEs included: diarrhea 39 patients (10%); headache 66 patients (77%); dizziness 38 patients (10%); syncope 8 patients (2%); arthralgia 55 patients (14%). According to Dr. Berry, in the ENGAGE trial, a total of 18 (90%) of patients in the eliglustat group and 14 (80%) of patients in the placebo group had at least 1 TEAE. The most frequent TEAEs were headache and arthralgias. Both of these TEAEs occurred more frequently in the eliglustat group compared to the placebo group. Arthralgia occurred in 9 patients (45%) in the eliglustat group for a total of 11 events, and 2 patients (10%) in the placebo group for a total of 4 events. Headache occurred in 8 patients (40%) in the eliglustat for a total of 23 events, and 6 patients (30%) in the placebo group for a total of 13 events. Combining headache, tension

headache, and migraine (unique patients only), the incidence in the eliglustat group was 10 patients (50%) for a total of 27 events versus 30% in the placebo group (no patients in the placebo group had migraine or tension headache). Otherwise, the AEs profile was similar in both treatment groups.

For the ENCORE trial, the most frequently reported TEAE was arthralgia (16%), which occurred at a similar frequency in the eliglustat group (15%) and the Cerezyme group (17%). The most common TEAEs (≥10%) in the eliglustat group were arthralgia (15%), fatigue (14%), headache (13%), back pain (12%), diarrhea (12%), nausea (12%), pain in extremity (11%), abdominal pain upper (10%), nasopharyngitis (10%), upper respiratory tract infection (10%), and sinusitis (10%). TEAEs occurring more frequently with eliglustat and at an incidence ≥10% compared to Cerezyme rates were nausea (12% versus 0%), abdominal pain upper (10% versus 0%), headache (13% versus 2%), and fatigue (14% versus 2%).

The issue of appropriate patient counseling in section 17 of the label is required to ensure that new signs or symptoms consistent with cardiac adverse events are reported. The label will reflect these considerations.

## 9. Advisory Committee Meeting

During this review cycle, an advisory committee meeting was not convened to discuss the current supplement

## 10. Pediatrics

This application concerns an orphan indication and therefore the Sponsor is not bound by PREA regulation. (b) (4)

GD can present at any age, though approximately 55–60% of type 1 patients are diagnosed before 20 years of age, and ~30% of these patients are diagnosed before age 10. The underlying pathophysiology of GD is the same in adults and children, and the scope of disease manifestations, particularly organ enlargement, hematologic abnormalities, and bone involvement, is similar across age groups.

## 11. Other Relevant Regulatory Issues

**A. DSI audits**

As per Dr. Dimick, DSI reported that all clinical sites had the classification of NAI with only minor regulatory violations noted. For the sponsor inspection, the preliminary classification is NAI. The studies appear to have been conducted adequately, and the data generated by these studies appear acceptable in support of the respective indications

## 12. Labeling

Distinct recommendations for the CYP2D6 metabolizer status were a focus for labeling negotiations and reflected in the label and also discussed definitively in **Section 5** Clinical Pharmacology. Specific details are referred to the CDTL memorandum. Of note is the

requirement for a FDA cleared test to be used for pharmacogenomics analysis of genotype associated with CYP2D6 isoforms which are related to Benefit-Risk assessment of Cerdelga for individual patients, as discussed above in several aspects of this review. Furthermore, extensive labeling detailing the DDI is detailed in multiple sections of the labeling in sections 5.1 and 7.1, including the following specific details:

- Eliglustat is a CYP2D6 and CYP3A substrate. Co-administration of CERDELGA with drugs that inhibit CYP2D6 and CYP3A may significantly increase the exposure to eliglustat and result in prolongation of the PR, QTc, and/or QRS cardiac interval, which could result in cardiac arrhythmias. Consider potential drug interactions prior to and during therapy (5.1, 7.1)
- CYP2D6 IMs and PMs taking moderate CYP3A inhibitors: not recommended (7.1)
- CYP2D6 PMs taking weak CYP3A inhibitors: not recommended (7.1)
- CYP2D6 EMs and IMs taking strong or moderate CYP2D6 inhibitors and CYP2D6 EMs taking strong or moderate CYP3A inhibitors: reduce the dosage to 84 mg once daily (2.2, 7.1)
- Eliglustat is an inhibitor of P-gp and CYP2D6. Co-administration with drugs that are substrates for P-gp or CYP2D6 may result in increased concentrations of the other drug (7.2)
- See Full Prescribing Information for a list of clinically significant drug interactions (7.1, 7.2)

# 13. Decision/Action/Risk Benefit Assessment

**13.1 Regulatory Action**:
All of the review disciplines recommended the product for approval pending approved labeling specifying the revisions. This Signatory concurs with the approval recommendation as discussed above specifying the indication of Long term treatment of adult patients with Type 1 Gaucher Disease who are CYP2D6 poor, intermediate or extensive metabolizers.

**13.2 Risk Benefit Assessment**:
I concur with the CDTL recommendation that the benefit and risk of Cerdelga in adult patients with Gaucher disease and provide an alternative to the management of this orphan disease. With full knowledge of the DDI with multiple medications, the safety profile is acceptable based on what was found in the clinical trials of Cerdelga. The experimental clinical trial data focus on cardiovascular safety and determination of the CYP2D6 metabolizer status. These issues are well documented in labeling of Cerdelga.

**Recommendation for Postmarketing Risk Evaluation and Mitigation Strategies:**
There are no requirements for postmarketing risk evaluation and mitigation strategies.

**Recommendation for other Postmarketing Requirements and Commitments**

**POSTMARKETING REQUIREMENTS UNDER 505(o)**

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to assess the known serious risk

of high systemic exposure to eliglustat in patients with renal or hepatic impairment that could result in prolongation of PR and QTc and cardiac intervals and the potential for cardiac arrhythmias. .

Furthermore, the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) of the FDCA will not be sufficient to assess this serious risk.

Finally, we have determined that only a clinical trial (rather than a nonclinical or observational study) will be sufficient to assess this serious risk. Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following:

2766-1 Conduct a clinical trial to evaluate the effect of renal impairment on eliglustat pharmacokinetics. A reduced design may be used.

The timetable you submitted on August 11, 2014, states that you will conduct this trial according to the following schedule:

| | |
|---|---|
| Final Protocol Submission: | 06/15 |
| Trial Completion: | 01/17 |
| Final Report Submission: | 07/17 |

2766-2 Conduct a clinical trial to evaluate the effects of hepatic impairment on eliglustat pharmacokinetics.

The timetable you submitted on August 11, 2014, states that you will conduct this trial according to the following schedule:

| | |
|---|---|
| Final Protocol Submission: | 06/15 |
| Trial Completion: | 01/17 |
| Final Report Submission: | 07/17 |

**POSTMARKETING COMMITMENTS NOT SUBJECT TO THE REPORTING REQUIREMENTS UNDER SECTION 506B**

2766-3 Develop 21-mg and/or 42-mg dosage strength(s) to accommodate various situations requiring further dosage adjustments. Conduct a single- and multiple-dose pharmacokinetics study in healthy subjects to characterize dose proportionality of 21, 42, and 84 mg dose strengths.

The timetable you submitted on August 11, 2014, states that you will conduct this study according to the following schedule:

| | |
|---|---|
| Final Report Submission: | 12/18 |

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**

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/s/

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ANDREW E MULBERG
08/19/2014
Division Deputy Director Summary review