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APPLICATION NUMBER:

205494Orig1s000

OFFICE DIRECTOR MEMO

Office Deputy Director (acting) Decisional Memo

Date	August 19, 2014
From	Amy G. Egan, MD, MPH
Subject	Office Deputy Director (acting) Decisional Memo
NDA/BLA #	NDA 205494
Applicant Name	Genzyme Corporation
Date of Submission	September 20, 2013
PDUFA Goal Date	August 20, 2014
Proprietary Name / Established (USAN) Name	Cerdelga (eliglustat)
Dosage Forms / Strength	Capsules/84 mg
Proposed Indication(s)	For the 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:	Approval

Summary

Gaucher disease is a rare autosomal recessive lysosomal storage disorder caused by a deficiency of the enzyme, β -glucocerebrosidase. This enzyme is necessary to break down glucocerebroside, a glycosphingolipid. The enzyme deficiency results in the accumulation of glucosylceramide in the lysosomes of macrophages in the liver, spleen and bone marrow. These swollen macrophages are referred to as “Gaucher cells”. Gaucher disease is estimated to occur in 1 in 100,000 births.

Gaucher disease type 1 (GD1) is the most common variant, accounting for approximately 94% of all Gaucher cases. GD1 patients typically present in later childhood or early adulthood; the central nervous system is generally spared permitting these patients to have normal intellect. The disease is compatible with a long life span, albeit with a decreased quality of life. Typical manifestations of the disease include hepatomegaly, splenomegaly, anemia, thrombocytopenia, bleeding tendencies, skeletal pathology, growth retardation, and pulmonary disease. There are estimated to be ~5700 GD1 patients in the U.S.

Currently available therapies for GD1 include intravenous enzyme replacement therapies (Cerezyme®, VPRIV™, and Elelyso™) and oral substrate reduction therapy (Zavesca™). Zavesca is only approved in adults for whom enzyme replacement therapy is not a viable option; it is associated with a high discontinuation rate due to adverse effects of nausea and weight loss.

The subject of this NDA, Cerdelga (eliglustat), is a small molecule inhibitor of glucosylceramide synthase that resembles the ceramide substrate for the enzyme, and is intended to reduce the rate of synthesis of glucosylceramide to match its impaired rate of catabolism in GD1 patients. The molecular weight is 479.59.

This memo documents my concurrence with the Division of Gastrointestinal and Inborn Errors Products’ approval recommendation for Cerdelga (eliglustat) for the 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.

Dosing

Cerdelga is available as a hard gelatin capsule containing 100 mg of eliglustat tartrate, which is equivalent to 84 mg of eliglustat. The proposed dose is:

- 84 mg twice daily in patients who are CYP2D6 extensive metabolizers (EMs) and intermediate metabolizers (IMs)
- 84 mg once daily in patients who are CYP2D6 poor metabolizers (PMs)

Capsules should be swallowed whole, preferably with water, and can be taken with or without food. Grapefruit juice consumption should be avoided in patients taking Cerdelga. It is suggested that patients currently treated with enzyme replacement therapy (ERT) may initiate Cerdelga dosing approximately 24 hours after the last dose of ERT.

Because Cerdelga is a substrate of CYP2D6 and CYP3A4, it is contraindicated in EM and IM patients taking a strong or moderate CYP2D6 inhibitor with a strong or moderate CYP3A inhibitor, and in IM and PM patients taking a strong CYP3A inhibitor, due to the risk of significantly increased eliglustat plasma concentrations which may result in prolongation of the PR and/or QTc cardiac intervals. Co-administration of Cerdelga with other CYP2D6 and CYP3A inhibitors may require dose adjustment depending on the patient's metabolizer status. These dosing recommendations will be detailed in the package insert (PI).

The Office of Clinical Pharmacology (OCP) noted that an exposure-response (E-R) relationship for efficacy was demonstrated in treatment naïve subjects between eliglustat and the endpoints of spleen and liver volume, hemoglobin, and platelets; however, no clinically relevant E-R relationship was observed in treatment experienced subjects. An E-R relationship for adverse reactions was not observed, with the exception of an increased frequency of headaches.

OCP notes that CYP2D6 genotyping is essential for the safe and effective use of eliglustat. OCP agreed with the applicant's proposed dose of 84 mg twice daily for both EMs and IMs, without the need for therapeutic drug monitoring. (b) (4)

OCP has recommended a dosing regimen of 84 mg once daily for PMs. OCP agrees with the applicant's proposal to not recommend dosing for ultra-rapid metabolizers (URMs), as these patients may not achieve adequate concentrations of Cerdelga to achieve a therapeutic effect, and indeterminate metabolizers, as a specific dose cannot be determined.

Regulatory History

A pre-IND meeting was held on December 15, 2003 to discuss non-clinical and cardiovascular safety-related issues. IND 067589 was opened on December 31, 2003.

FDA issued an advice letter on September 17, 2007 notifying the applicant that eliglustat tested positive for QT prolongation in safety pharmacology studies and recommending that the applicant conduct a thorough QT trial in healthy subjects prior to initiating additional clinical trials.

A Type C meeting was held on July 17, 2008 to discuss the thorough QT clinical trial and the clinical development program. A clinical End-of-Phase 2 meeting was held on February 5, 2009 to discuss the planned Phase 3 clinical trials. At that meeting, FDA recommended the applicant conduct additional ECG monitoring during the Phase 3 trials. A separate CMC End-

of-Phase 2 meeting was held on May 26, 2010. A Type C meeting was held on April 12, 2011 to discuss clinical trial enrollment challenges and alternate filing strategies. A Pre-NDA meeting was held on May 21, 2013. At that meeting, FDA agreed that hepatic and renal impairment trials could be conducted as Post-Marketing Requirements (PMRs).

NDA 205494 for Cerdelga (eliglustat) was submitted on September 20, 2013 and granted a priority review; however, multiple submissions received in November and December 2013 constituted a major amendment resulting in an extension of the user fee goal date to August 20, 2014.

Eliglustat is currently under review by the European Medicines Agency's Committee for Medicinal Products for Human Use.

Product Quality Considerations

All information related to the manufacturing, controls, and stability of the drug substance was reviewed by the Office of New Drug Quality Assurance (ONDQA) Chemistry Manufacturing and Controls (CMC) and was deemed acceptable; however, the potential presence of residual (b) (4) was not accounted for in the specifications. The applicant was asked to revise the drug substance specification and propose a limit to control the (b) (4). The applicant provided the (b) (4) analysis data on July 15, 2014. These data show that the (b) (4) resulting in insignificant levels. ONDQA-CMC determined that based on these data, routine testing for (b) (4) is not necessary. ONDQA-CMC has determined that stability data support an expiration dating period of (b) (4) months for drug substance when stored in the commercial packaging configuration under the long-term storage condition.

ONDQA determined that the drug product specification is adequate to ensure the identity, purity, strength and quality of the drug product. An expiration dating period of 24 months when stored at 68-77°F (20-25°C) with excursions permitted between 59-86°F (15-30°C) was granted.

ONDQA-CMC submitted a Methods Validation Request to the Division of Pharmaceutical Analysis (DPA). DPA determined that the HPLC Purity/Assay for the drug substance was acceptable for quality control and regulatory purposes. DPA further determined that the HPLC chiral purity, and gradient HPLC method for ID, Assay, Purity and Content for the drug product were acceptable for quality control and regulatory purposes with the following comments:

1. The equation for calculating chiral purity should be added.
2. DPA observed that detection and quantification were improved using a wavelength of (b) (4) nm. Solvent absorbance at (b) (4) nm results in a noisy baseline. DPA recommends

- use of (b) (4) nm or (b) (4) nm instead of (b) (4) nm. When using (b) (4) nm instead of (b) (4) nm, the relative response factor for the peak observed at approximately 14 minutes increases.
3. Drug substance impurities (b) (4) were observed in this test method. DPA suggests that drug substance impurity retention times should be noted in the method to remove them from consideration during calculation of unspecified degradation products.

In response to DPA's methods validation, ONDQA noted that (b) (4) is a known related substance specified in the drug substance specification at or less than (b) (4)%. Therefore, the level of (b) (4) detected in the drug product is not a concern.

On September 12, 2013, the Office of Pharmaceutical Science in ONDQA concurred with the applicant's request for a categorical exclusion from environmental assessment under 21 CFR 25.31(b).

ONDQA Biopharmaceutics determined the dissolution method and the dissolution acceptance criterion for eliglustat immediate-release 100 mg capsule to be acceptable. Eliglustat is a Biopharmaceutics Classification System (BCS) Class I drug. The *in vitro* dissolution study showed that the dissolution is > (b) (4) % in (b) (4) minutes.

On July 8, 2014, the Office of Compliance, Division of Good Manufacturing Practice Assessment (OC-DGMPA) provided an Overall Acceptable recommendation for the facilities involved in the manufacture and test of the drug substance and drug product.

No CMC or Biopharmaceutics post-marketing commitments (PMCs) have been recommended.

Microbiology Product Quality Considerations

No microbiology product quality issues were identified. The New Drug Microbiology Staff within the Office of Pharmaceutical Science determined that the in-process controls and the microbial limits testing within the ongoing stability program provide adequate assurance of microbial control of the manufacturing process.

Non-clinical Considerations

Pharmacology studies demonstrated that eliglustat inhibits glucosylceramide synthase *in vitro*. Eliglustat decreased glucosylceramide levels in peripheral tissues and plasma of normal rats and dogs following oral administration. Eliglustat was demonstrated to have a potential to cause QT prolongation at doses 8-fold over the mean clinical C_{max} of 44.3 ng/mL.

Chronic oral toxicology studies were conducted in rats (6 months) and dogs (1 year). There were no significant treatment-related histopathological findings in any organ or tissue in rats. The NOAEL identified in rats is approximately 8 to 12 times higher than the proposed clinical

dose based on area under the curve (AUC). Histopathological changes were observed in the lung, heart, and testes of Beagle dogs; however, no dose response was observed and the heart findings were observed in females only. The NOAEL identified in dogs is approximately 10 to 15 times higher than the proposed clinical dose based on AUC.

An oral gavage study in juvenile rats was conducted and demonstrated histopathological changes in the lymph node (increased incidence/severity of lymphoid hyperplasia in the mandibular lymph nodes) and eye (minimal grade unilateral neuropathy in the optic nerve of two animals). The NOAEL was considered to be 15 mg/kg twice daily.

A 28-day oral study was conducted in male rats to evaluate specific effects on male reproductive organs and spermatogenesis. At 200 mg/kg/day (about 10 times the recommended human dose), microscopic changes in the testis and epididymis were observed and did not reverse during the 14-week treatment-free recovery period. To confirm these effects, a 4-week oral study in mature Cynomolgus monkeys was conducted. There were no significant treatment-related effects on any of the measured sperm parameters in the monkey study.

A fertility and early embryonic development study in rats was conducted. Eliglustat increased pre-implantation loss at exposures 1.5 and 5 times the recommended human oral dose based on body surface area. Maternal toxicity was observed at 120 mg/kg/day (6 times the recommended human dose). Also observed at 120 mg/kg/day was an increase in the number of late resorptions, dead fetuses, mean post-implantation loss, and reduced fetal body weight. At 120 mg/kg/day, fetal visceral variations (dilated cerebral ventricles), fetal skeletal malformations (abnormal number of ribs or lumbar vertebra) and fetal skeletal variations (poor bone ossification) were observed. Cerdelga will be labeled as Pregnancy Category C and should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

An oral embryofetal development study was conducted in rabbits. No significant treatment-related adverse effects on embryofetal development were observed in rabbits at dose levels 10 times the recommended human dose.

In a pre- and post-natal development study in rats, eliglustat did not appear to cause any significant adverse effects on pre- and post-natal development at doses 5 times the recommended human oral dose based on body surface area.

Eliglustat was non-genotoxic *in vitro* in the Ames test, chromosome aberration assay using human peripheral blood lymphocytes (HPBL), mouse lymphoma gene mutation assay and *in vivo* in the oral mouse micronucleus test. In addition, Genz-399240, a human metabolite of eliglustat, was non-genotoxic *in vitro* in the Ames test and chromosome aberration assay using HPBL.

The carcinogenic potential of eliglustat tartrate was assessed in 2-year carcinogenicity studies in Sprague-Dawley rats and CD-1 mice. No treatment-related neoplasms were observed in male rats dosed to 3.6 times the recommended human daily dose of 84 mg twice daily based on body surface area, or in female rats dosed to 2.4 times the recommended human daily dose, or in male and female mice dosed to 1.8 times the recommended human daily dose.

Clinical Pharmacology Considerations

Because eliglustat is a BCS Class I drug, a bioequivalence study was not required to link the to-be-marketed formulation to other formulations in the clinical study. However, the sponsor conducted a study to evaluate the relative bioavailability of the commercial formulation (b) (4) to the Phase 3 formulation ((b) (4) capsules) in healthy subjects. The results indicated that there was no difference between the to-be-marketed formulation and the Phase 3 formulation.

The PK characteristics of eliglustat were determined in healthy subjects and in GD1 subjects across the four CYP2D6 phenotypes. The absolute oral bioavailability of eliglustat is very low due to high first-pass metabolism. Bioavailability was predicted to be 18.8 and 3.3 times greater for PMs and IMs, respectively, relative to EMs, in whom bioavailability was estimated to be 4.17%. In EMs, median time to reach maximum plasma concentration (T_{max}) occurs between 1.5 to 2 hours following multiple doses of eliglustat 84 mg twice daily. In IMs and PMs, median T_{max} occurs at 2 and 3 hours, respectively. Eliglustat systemic exposure increased up to 2-fold at steady state compared to after the first dose. Compared to EMs, the systemic exposure following 84 mg twice daily at steady state is 7- to 9-fold higher in PMs. Food does not have a clinically relevant effect on eliglustat PK.

Eliglustat is a substrate for CYP2D6, CYP3A4 and P-glycoprotein transporter. Metabolism of eliglustat is mediated predominantly by CYP2D6 and to a lesser extent CYP3A4. The excretion of the drug is through both liver (51.4%) and kidney (41.8%), mainly as metabolites. Following multiple oral doses of eliglustat 84 mg twice daily, the terminal elimination was approximately 6.5 hours in EMs and 9 hours in PMs.

- No significant impact of sex, body weight, age, race, and serum creatinine clearance on eliglustat PK was identified.
- Gastric pH-modifying agents did not have a clinically relevant effect on eliglustat exposure.
- Cerdelga has not been studied in GD1 subjects with renal or hepatic impairment. Patients with hepatic impairment are expected to have higher eliglustat systemic exposure 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 achieve unacceptably high eliglustat exposures and should not be studied. As liver failure is rare in GD1 patients, the number of patients with severe hepatic impairment is estimated to be very low, and these patients would be better candidates for ERT.

The applicant will be required to address the safety of Cerdelga in patients with renal or hepatic impairment who may experience increased systemic exposure to eliglustat due to their renal/hepatic impairment, as a PMR.

The *in vivo* drug-drug interaction potential of eliglustat was assessed and demonstrated eliglustat systemic exposure in the presence of different types of CYP inhibitors. Drugs that inhibit CYP2D6 and CYP3A pathways may significantly increase the systemic exposure to eliglustat and result in prolongation of the PR, QTc, and/or QRS cardiac intervals. OCP has recommended various dosing modifications, including contraindications, based on CYP2D6 metabolizer status and concomitant administration of CYP3A and CYP2D6 inhibitors. These recommendations will be conveyed in Sections 2, 4 and 7 of product labeling.

To allow for flexibility in dosing in PMs in various drug-drug interaction scenarios, OCP has recommended that the applicant develop a lower strength capsule as a PMC.

PMC 1: 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 effect of eliglustat as a perpetrator drug was assessed. Product labeling will provide clinical recommendations regarding dosing and monitoring of therapeutic drug concentrations based on effects seen with digoxin and metoprolol. Monitoring of therapeutic drug concentrations will also be recommended for other P-gp substrates (e.g., phenytoin, colchicine, dabigatran etexilate) and CYP2D6 substrates (e.g., tricyclic antidepressants, phenothiazines, and Type 1 C antiarrhythmics)

A thorough QT/QTc study was performed for eliglustat and was reviewed by the Interdisciplinary Review Team (IRT) for QT Studies. The study doses included a therapeutic dose (200 mg) and a suprathreshold dose (800 mg) which covered a margin of up to a 14-fold increase in the mean C_{max} over the therapeutic dose. For QTcF, the largest upper bounds of the 90% 2-sided confidence interval for the mean differences between eliglustat (200 mg and 800 mg) and placebo were below 10 msec. For PR, the largest upper limits of the 2-sided 90% CI for the mean differences between eliglustat (200 mg and 800 mg) and placebo were 5.8 msec and 16.4 msec, respectively. The QT-IRT expressed concern that the 14-fold higher C_{max} obtained with the suprathreshold dose may not be sufficient to cover a high clinical exposure scenario (e.g., drug interaction with CYP2D6 inhibitor, elderly, and hepatic impairment). Further analyses were conducted by the QT-IRT and results demonstrated no proarrhythmia risk at the predicted steady-state C_{max} achieved for the GD1 subjects with CYP2D6 phenotype; however, PR, QTc and QRS prolongation are expected at steady-state suprathreshold C_{max} (e.g., greater than 10 msec mean change in QTcF may be expected when

the mean C_{max} is higher than 250 ng/mL). QT-IRT concluded that the PR effect size is unlikely to be clinically meaningful in healthy subjects; however, in patients with pre-existing AV nodal disease and/or receiving co-administered agents that block the AV node, the PR prolongation may become clinically important. The QRS effect size was not considered to be clinically meaningful.

Efficacy

The efficacy of Cerdelga was assessed in three clinical trials in subjects with GD1 - an open-label dose-finding Phase 2 trial in treatment-naïve adult GD1 subjects; a randomized, double-blind, placebo-controlled trial in GD1 treatment-naïve subjects (Trial 1); and a randomized, open-label, active-controlled, non-inferiority trial in GD1 subjects previously stabilized with ERT (Trial 2). Trial 1 was considered the pivotal trial, and Trial 2 was considered the key supportive trial. A third Phase 3 trial is ongoing.

Trial 1 was conducted in 40 treatment-naïve GD1 subjects age 16 years or older with pre-existing splenomegaly and hematological abnormalities. Subjects were stratified by spleen severity score – low (≤ 20 multiples of normal [MN]) and high (> 20 MN). The primary endpoint was the percent change in spleen volume (in MN) from baseline at Week 39, comparing Cerdelga to placebo. Trial 2 was conducted in 159 GD1 subjects age 18 years or older who had reached therapeutic goals with ERT. Subjects were stratified based on stable ERT dose prior to randomization – low (< 35 U/kg/every other week [QOW]) and high (≥ 35 U/kg/QOW). The primary endpoint was a composite of stability on four component domains (hemoglobin level, platelet count, liver volume, and spleen volume) based on changes between baseline and Week 52, comparing Cerdelga to active comparator. The Phase 2 trial was conducted in 26 treatment-naïve GD1 subjects age 18 years or older. The primary endpoint was a “clinically meaningful response” from baseline to Week 52, defined as achievement of at least two of the following parameters: an increase of ≥ 0.5 mg/dL in hemoglobin; an increase of $\geq 15\%$ in platelets; and a reduction of $\geq 15\%$ in total spleen volume.

The median age of enrolled subjects in Trial 1 was 30.4 years. An equal number of males and females were enrolled. The majority of subjects were Caucasian (97.5%), CYP2D6 EMs (90%), and in the low spleen severity group (82.5%). Of enrolled subjects, 32.5% were from North America and 37.5% were from Europe.

In Trial 1, 40 subjects were randomized 1:1 to receive Cerdelga (n=20) or placebo (n=20) for 39 weeks.

In Trial 1, the percent change in spleen volume from baseline to week 39 was -27.58 in the Cerdelga group versus 2.07 for the placebo group. The estimated treatment difference between Cerdelga and placebo was -30.03% (95% CI: -36.82, -23.24; $p < 0.0001$).

Table 1: Trial 1 – Percent change from baseline to Week 39 in spleen volume*

Percent change from baseline to Week 39	Cerdelga N=20 n (%)	Placebo N=20 n (%)	Treatment difference
Mean (SD)	-27.58 (12.591)	2.07 (8.777)	
Median	-29.03	4.20	
Min, Max	-51.5, 0.0	-20.9, 13.7	
LS Mean (SEM)	-27.77 (2.37)	2.26 (2.37)	-30.03 (3.35)
95% CI	-32.57, -22.97	-2.54, 7.06	-36.82, -23.24
p-value			<0.0001

*Source: Adapted from Table 5 of the Statistical Review.

FDA statistical reviewers conducted sensitivity analyses and concluded that no single site influenced or drove the overall study results; the single dropout did not impact the study conclusions; and there were no subjects who were designated as outliers. Furthermore, a sensitivity analysis was conducted replacing the baseline spleen severity category from the original analysis model with the covariate of baseline spleen volume. The study conclusion from this analysis was consistent with the findings from the primary analysis.

Subgroup analyses were conducted for gender and geographic region. There were no apparent treatment differences in these subgroups.

Cerdelga also demonstrated superior improvement in the following secondary endpoints:

- absolute change from baseline in hemoglobin level at Week 39 compared to placebo (p=0.0006);
- percentage change from baseline in liver volume at Week 39 compared to placebo (p=0.0072); and
- percentage change from baseline in platelet count at Week 39 compared to placebo (p<0.0001).

The median age of enrolled subjects in Trial 2 was 36.7 years. Fifty-five percent of enrolled subjects were female and 45% were male. The majority of subjects were Caucasian (91.9%), CYP2D6 EMs (76.9%), and in the high pre-study CERZYME dose group (59.4%). Of enrolled subjects, 45.3% were from North America and 16.4% were from Europe.

In Trial 2, 150 subjects were randomized 2:1 to receive Cerdelga (n=106) or CERZYME (n=53) at their current stable ERT dose for 52 weeks.

In Trial 2, the percentage of subjects stable at Week 52 in the per-protocol population was 84.8% in the Cerdelga group versus 93.6% in the CERZYME group. The estimated treatment difference between Cerdelga and CERZYME was -8.8% (95% CI: -17.6, 3.3). The lower bound of the 95% CI was above the pre-specified non-inferiority margin of -25%. Therefore, Cerdelga is non-inferior to CERZYME.

Table 2: Trial 2 – Proportion of subjects who were stable at Week 52 (Per Protocol population)*

	Cerdelga			CEREZYME		
	Pre-study CEREZYME <35 U/kg/QOW N=38	Pre-study CEREZYME ≥35 U/kg/QOW N=61	Overall N=99	Pre-study CEREZYME <35 U/kg/QOW N=18	Pre-study CEREZYME ≥35 U/kg/QOW N=29	Overall N=47
Subjects stable at Week 52 n (%)	32 (84.2)	52 (85.2)	84 (84.8)	17 (94.4)	27 (93.1)	44 (93.6)
Difference in proportion stable at Week 52 (Cerdelga-CEREZYME, %)	-10.2	-9.5	-8.8			
95% CI of difference in proportion stable, %	(-25.2, 10.2)	(-21.8, 6.2)	(-17.6, 3.3)			

*Source: Adapted from Table 11 of the Statistical Review

FDA statistical reviewers repeated the analyses utilizing the Full Analysis Set, Week 52 Completer and All-Randomized analysis sets and conclusions were consistent. FDA statistical reviewers conducted sensitivity analyses and concluded that no single site influenced or drove the overall study results, and the four dropouts did not impact the study conclusions.

Subgroup analyses were conducted for gender and geographic region. There were no apparent treatment differences in these subgroups.

Secondary endpoints should be considered exploratory because they did not control the overall Type I error rate. They suggest that platelet counts remained reasonably stable in both treatment groups at Week 52, 92.9% and 100% for Cerdelga and CEREZYME, respectively; liver volume remained reasonably stable for both treatment groups at Week 52, 96.0% and 93.6% for Cerdelga and CEREZYME, respectively; hemoglobin levels remained fairly stable for both treatment groups at Week 52, 94.9% and 100% for Cerdelga and CEREZYME, respectively; and spleen volume change from baseline at Week 52 (FDA’s preferred primary efficacy endpoint) was below the pre-specified non-inferiority margin of 15%, -6.2%, (95% CI: -9.5, -2.8).

The mean age of enrolled subjects in the Phase 2 trial was 34.5 years. Sixty-two percent of subjects were female and 38% were male. The majority of subjects were Caucasian (73%) and CYP2D6 EMs (96%). Of enrolled subjects, 46% were from Russia and 7.8% were from the U.S.

In the Phase 2 trial, 26 subjects were treated with either Cerdelga 50 mg BID (n=8) or Cerdelga 100 mg BID (n=18) for 52 weeks.

In the Phase 2 trial, 20 Cerdelga-treated subjects (77%) met the primary composite for success. The individual components of hemoglobin criteria for success, platelet criteria for success and spleen criteria for success were achieved in 90%, 68%, and 85%, of Cerdelga-treated subjects, respectively. The Phase 2 trial also demonstrated persistence of efficacy of Cerdelga in 19 subjects who continued to receive Cerdelga for at least 48 months after completion of the 52-week primary analysis period.

The Office of Scientific Investigations (OSI) conducted inspections of six clinical sites, and the sponsor, Genzyme Corporation. All sites were classified as NAI. OSI concluded that the data generated by the clinical sites appear adequate for use in support of the proposed indication.

Safety

Safety data were obtained from approximately 393 GD1 subjects exposed to Cerdelga at dosages of 50 mg, 100 mg, or 150 mg in Phase 2 or 3 clinical trials. In the pooled safety dataset, 89% of subjects received Cerdelga for at least 6 months, and 52% for at least one year. The mean duration of treatment was 1.4 years, and the total exposure was 535.0 patient-years.

The proportion of subjects with at least one adverse event was 85% for Cerdelga (all doses and Phase 2 and 3 trials pooled), 70% for placebo (from Trial 1) and 79% for CEREZYME (from Trial 2). The most common adverse reactions were fatigue, headache, nausea, diarrhea, back pain, pain in extremities, and upper abdominal pain.

No deaths occurred in the Cerdelga clinical development program.

Serious adverse events (SAEs) were reported in 35 (9%) Cerdelga-treated subjects (one [3%] subject from Trial 1 and 18 [11%] subjects from Trial 2), no placebo-treated subject and no CEREZYME-treated subject. The most frequently reported SAE was syncope which was reported in five (1%) subjects; three of the cases were considered to be treatment-related. Six (2%) subjects experienced SAEs in the Cardiac disorders System Organ Class, including one case of non-sustained monomorphic ventricular tachycardia, one case of 2° AV block, and one case of 1° AV block.

Adverse events leading to discontinuation occurred in 12 (3%) Cerdelga-treated subjects, no placebo-treated subject, and 1 (2%) CEREZYME-treated subject. Discontinuations due to cardiac disorders occurred in 5 (1%) Cerdelga-treated subjects and no CEREZYME-treated subject. Cardiac disorders leading to discontinuation among Cerdelga-treated subjects included ventricular tachycardia in two subjects, myocardial infarction in two subjects, and palpitations in one subject.

Because of the potential for Cerdelga to prolong ECG intervals (PR, QTc and/or QRS), safety assessments included monitoring for clinically significant cardiac arrhythmias or syncope of any cause. Syncope occurred in eight (2%) Cerdelga-treated subjects, no placebo-treated subject, and no CEREZYME-treated subject. Five of the syncopal events were SAEs, three of which were considered treatment related. All syncopal events occurring in Cerdelga-treated subjects were determined to be vasovagal in nature, with the exception of one of unknown etiology. According to the applicant, the occurrence of syncope was not associated with cardiac conduction defect or arrhythmia. Cardiac arrhythmias occurred in 15 (4%) Cerdelga-treated subjects, one (5%) placebo-treated subject, and no CEREZYME-treated subject. All cardiac arrhythmia events were detected either during scheduled Holter or ECG monitoring, and among Cerdelga-treated subjects, included 6 (2%) subjects with cardiac conduction disorders (4 with 2° AV block, 1 with AV block, 1 with 1° AV block and 1 with sinoatrial block), 4 (1%) subjects with supraventricular arrhythmias, and 4 (1%) subjects with ventricular arrhythmias (3 with ventricular tachycardia and 1 with ventricular extra-systoles), and 1 subject with rate and rhythm disorders (tachycardia). Non-sustained ventricular tachycardia occurred in one placebo-treated subject.

Treatment-emergent cardiac adverse events determined to be drug-related included three (1%) subjects with 2° AV block; 2 (1%) subjects with ventricular tachycardia; and 2 (1%) subjects with supraventricular tachycardia, among Cerdelga-treated subjects. No treatment-emergent drug-related cardiac adverse events were observed in placebo-treated or CEREZYME-treated subjects.

Electrocardiogram findings included two (<1%) Cerdelga-treated subjects with new QTcF >480 msec, and 6 (2%) subjects with QTcF change from baseline >60 msec versus no placebo-treated subject, and no CEREZYME-treated subject. Seven (2%) Cerdelga-treated subjects met the PR outlier criterion (PR >200 msec and increase from baseline \geq 25%), one of whom had a clinically meaningful PR prolongation, versus no placebo-treated subject, and no CEREZYME-treated subject. Eighteen (5%) Cerdelga-treated subjects had a QRS \geq 120 msec, two of whom had increases of 30% and 50%, which are considered clinically meaningful, versus no placebo-treated subject, and one (2%) CEREZYME-treated subject. There did not appear to be any TEAE findings that could be related to the potentially clinically significant ECG outliers.

Holter monitoring did not show evidence of sustained ventricular tachycardia in any subject. Five (1%) Cerdelga-treated subjects had non-sustained ventricular tachycardia versus one (5%) placebo-treated subject, and one (2%) CEREZYME-treated subject. Six (2%) Cerdelga-treated subjects had Mobitz I 2° AV block versus no placebo-treated subject and no CEREZYME-treated subject.

Because Cerdelga has not been studied in subjects with pre-existing cardiac conditions, and because Cerdelga is predicted to cause increases in cardiac intervals at substantially elevated

eliglustat plasma concentrations, labeling will caution that the use of Cerdelga is not recommended in patients with pre-existing cardiac disease, e.g., congestive heart failure, recent acute myocardial infarction, bradycardia, heart block, long QT syndrome, or in combination with Class IA and Class III antiarrhythmic medications.

No increase in the overall incidence of TEAEs was observed in subjects classified as PMs (79%) relative to IMs (73%). TEAEs were slightly higher in subjects classified as EMs (88%).

The impact of concomitant medication use, specifically CYP2D6 and CYP3A inhibitors, on the incidence of TEAEs could not be assessed as eliglustat levels were monitored closely during the clinical trials and dose adjustments were made accordingly.

Nerve conduction evaluations were performed in 2 trials, the Phase 2 trial and Trial 2. In Trial 2, 8 (6%) Cerdelga-treated subjects had TEAEs consistent with peripheral neuropathy (5 neuropathy peripheral and 1 patient each with ulnar nerve injury, sensory loss, and decreased vibratory sense) versus no CEREZYME-treated subject. Three were considered by the Investigator to be possibly related to Cerdelga treatment (ulnar nerve injury, neuropathy peripheral, and decreased vibratory sense).

Four (3%) Cerdelga-treated subjects had TEAEs of abnormal nerve conduction studies versus no CEREZYME-treated subject; two of these subjects also had other neuropathy TEAEs. One (<1%) additional subject had a TEAE of neuropathy peripheral reported through a neurological examination. Three were considered by the investigator to be possibly related to Cerdelga treatment (2 nerve conduction studies abnormal, 1 neuropathy peripheral).

Pediatric Considerations

Eliglustat for the treatment of GD1 was granted orphan status and therefore is exempt from the requirement for pediatric studies under the Pediatric Research Equity Act. No subjects under the age of 16 have been studied to date; (b) (4)

Tradename Review

DMEPA, in consultation with the Office of Prescription Drug Products, has concluded that the applicant's proposed proprietary name "Cerdelga" is acceptable from both a promotional and safety perspective. In a letter dated November 21, 2013, FDA notified Genzyme Corporation that the proposed propriety name was acceptable.

Advisory Committee

No Advisory Committee input was sought on this application.

Consults

Division of Bone, Reproductive and Urologic Products (DBRUP)

DGIEP consulted DBRUP to review bone marrow density (BMD) data submitted by the applicant [REDACTED] (b) (4)

DBRUP's review noted that the degree and type of bone involvement in GD1 is variable, although low bone mass is common regardless of disease severity. The cause of low bone mass is believed to be due to increased osteoclastic bone resorption and impaired osteoblast function associated with accumulating lipids. Low bone mass has been identified as a predictor of fracture in GD1; however, there are no data linking improvement in BMD with improved bone health in GD1.

The applicant submitted efficacy data from two trials in 66 treatment-naïve GD1 subjects and one trial in 160 GD1 subjects stabilized on ERT. The effect of Cerdelga on skeletal pathology was assessed using BMD as determined by dual energy x-ray absorptiometry. DBRUP concluded:

The three studies are neither powered nor designed to detect meaningful treatment effect of eliglustat on BMD, and no conclusions may be drawn regarding BMD efficacy.

Even if BMD efficacy were to be demonstrated, a corresponding reduction in fracture risk or any of the other bone pathologies associated with Type I GD cannot be assumed.

Center for Devices and Radiological Health (CDRH)

Because CYP2D6 genotype testing will be recommended prior to initiation of Cerdelga to ensure its safe and effective use, CDRH was asked to provide input on FDA-cleared diagnostics. There are currently two cleared devices for genotyping CYP2D6, Luminex Molecular Diagnostics xTAG CYP2D6 Kit v3 [REDACTED] (b) (4) and Roche AmpliChip CYP450 microarray. Both devices demonstrate over 98% agreement with the reference method; however, CDRH acknowledges that not all CYP2D6 alleles are identified by these two devices. CDRH and the clinical review team agreed that given the rarity of GD1 and the accuracy of these tests, the chances of a patient being placed into the incorrect metabolizer status are very low and if such an event were to occur it would likely not cause an adverse effect, but rather would delay treatment. Therefore, CDRH recommended use of an FDA-cleared genotyping test to identify the CYP2D6 genotype, and with a medical professional's care, to determine if the patient is a candidate for Cerdelga. This will be conveyed in product labeling.

Division of Risk Management (DRISK)

DRISK evaluated the Cerdelga application to determine if a Risk Evaluation and Mitigation Strategy is necessary to ensure the benefits of Cerdelga outweigh its risks. DRISK concluded that the benefit-risk profile for Cerdelga is favorable and the identified risks (drug-drug interactions and QTc prolongation) can be mitigated through professional labeling. No additional risk mitigation measures were recommended.

Postmarketing Requirements under 505(o)

Section 505(o)(3) of the Food, Drug and Cosmetic Act (FDCA) authorizes FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute.

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 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, the applicant will be required to conduct the following:

- PMR 1: Conduct a clinical trial to evaluate the effect of renal impairment on eliglustat pharmacokinetics. A reduced design may be used.
- PMR 2: Conduct a clinical trial to evaluate the effect of hepatic impairment on eliglustat pharmacokinetics.

Conclusions

Gaucher disease is a rare lysosomal storage disease that has significant impact on a patient's morbidity and quality of life. Available therapies exist; however, enzyme replacement therapy requires intravenous infusions, and the only currently approved oral substrate reduction therapy is associated with a high discontinuation rate due to adverse effects of nausea and weight loss. Cerdelga (eliglustat) provides an additional oral treatment option.

Treatment with Cerdelga 84 mg BID demonstrated superiority to placebo in treatment-naïve GD1 subjects and was non-inferior to CERZYME in GD1 subjects who had reached therapeutic goals with ERT.

The safety of Cerdelga has been adequately characterized. Physician and patient labeling will convey the known and potential safety concerns, including higher eliglustat systemic exposure due to CYP2D6 metabolizer status and drug-drug interactions resulting in the potential to increase the PR, QTc, and/or QRS cardiac intervals.

DGIEP has recommended approval of NDA 205494 for Cerdelga (eliglustat) for the 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. I concur with DGIEP's recommendation for approval, the PMRs/PMC detailed in this memo, and the agreed upon labeling. Cerdelga will fill an unmet medical need in providing an additional treatment option for GD1 patients.

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

/s/

AMY G EGAN
08/19/2014