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RESEARCH**

APPLICATION NUMBER:

205494Orig1s000

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	August 18, 2014
From	Lara Dimick-Santos, MD, FACS
Subject	Cross-Discipline Team Leader Review
NDA #	205-494
Supplement#	Original - NME
Applicant	Genzyme
Date of Submission	September 20 th , 2013
PDUFA Goal Date	May 10 th , 2014
IND # used for development	67-589
Proprietary Name / Established (USAN) names	Cerdelga eliglustat tartrate
Dosage forms / Strength	84 mg capsules
Proposed Indication(s)	Long term treatment of adult patients with Type 1 Gaucher Disease who are CYP2D6 poor, intermediate or extensive metabolizers
Recommended:	Approval

Material Reviewed/Consulted	Names of Discipline Reviewers
Clinical Review - DGIEP	Karyn Berry, MD
Clinical Pharmacology Reviewers:	
Office Clinical Pharmacology - primary - in vitro study - team leader	Elizabeth Shang, PhD, RPh Sandhya Apparaju, PhD Sue-Chih Lee, PhD
Pharmacometrics Reviewers - team leader	Anshu Marathe, PhD & Justin Earp, PhD Nitin Mehrotra, PhD
GTT Reviewer - team leader	Sarah Dorff, PhD Michael Pacanowski, PharmD, MPH
PBPK Reviewer - team leader	Yuzhuo Pan, PhD Ping Zhao, PhD
Biostatistics Reviewer - team leader	Benjamin P Vali, MS Freda Cooner, PhD
Bone Review (DBRUP)	John T Stinson, MD
Maternal and Pediatrics - PMHS	Carol Kasten, MD
Labeling Reviewers	Monica Calderon, PharmD, BCPS Adewale Adeleye, PharmD, MBA Nathan Caulk, MS, BSN, RN
Nonclinical Reviewers - team leader	Tamal Chakraborti, PhD Sruthi Tallapragada King, PhD Sushanta Chakder, PhD
Compliance Reviewer - DSI	Susan Leibenhaut, MD
CDRH Reviewer	Lynn Filpi, MD
CMC reviewers	Yichun Sun, PhD Tarun Mehta, PhD Hamid Shafiei, PhD
Biopharmaceuticals Reviewer	Albert Chen, PhD
Microbiology Reviewer	Robert Mello, PhD
QT—IRT Reviewer	Monica Fiszman, MD, PhD
Project Manager	Jessica Benjamin

Cross Discipline Team Leader Review

1. Introduction

The current submission is the original NDA for eliglustat for the proposed indication of “long-term treatment of adult patients with Gaucher disease type 1 (GD1)”.

Gaucher disease is a rare, autosomal recessive lysosomal storage disorder caused by a deficiency in the lysosomal enzyme glucocerebrosidase (or acid- β glucosidase), which catalyzes the hydrolysis of glucosylceramide (or GL-1) to glucose and ceramide. This enzyme deficiency results in the accumulation of GL-1, especially in the liver, spleen, and bone marrow. Eliglustat is a selective glucosylceramide synthase inhibitor for substrate reduction therapy (SRT) to reduce the synthesis and hence the accumulation of GL-1.

Significant issues identified during the review of this application were the significant differences in PK and thus in systemic exposure to eliglustat based on the CYP2D6 enzyme metabolizer status of patients and the need to identify CYP2D6 metabolizer status (i.e., Ultra-rapid, Extensive, Intermediate, Indeterminate or Poor) to determine appropriate dosing. This issue was complicated by the fact that development of the testing to identify CYP2D6 metabolizer status was ongoing during drug development. At the late cycle meeting the applicant noted that updates available in testing for CYP2D6 metabolizer status would reclassify some of the patients as a different CYP type. The applicant subsequently submitted the data with the reclassifications and this data was reviewed by the clinical pharmacology team after the submission of their original review. (See Section 5 - Clinical Pharmacology)

Another significant safety issue with this application is the potential for QT interval prolongation with high systemic exposures. These high exposures could potentially be achieved in clinical practice in situations of drug-drug interactions. CYP2D6 status also would determine the risk for drug-drug interactions to cause clinically significant exposures.

The review of this Application was also complicated by the fact that the phase 3 trial designs required dose adjustment based on steady-state (SS) serum eliglustat levels, (b) (4)

The sponsor’s proposed labeling (b) (4)

See Section 13 – risk Benefit Assessment for full discussion of the issues pertaining to this application.

Regulatory History

The first pre IND meeting was held December 15th, 2003, with Agency input obtained for phase 1 trials and dose selection.

On September 17th, 2007 an advice letter notified the Applicant that that Genz-112638 tested positive for QT prolongation in safety pharmacology studies, and both nonclinical and clinical studies indicate that Genz-112638 is likely to prolong the QT interval. Division recommended that Applicant conduct a thorough QT study (TQT) in healthy subjects prior to initiating any other clinical studies under the IND.

On February 5th, 2009 at an end-of-phase 2 meeting the Agency discussed with the Applicant that even though their TQT trial is a negative study as defined by ICH E14, their drug clearly prolonged the QTc and PR intervals in a concentration dependent manner. The Agency recommended that the Applicant conduct additional ECG monitoring after multiple dose administrations at T_{max} in Phase 3 trials.

It was agreed that the phase 3 efficacy and safety study GZGD02507 (ENGAGE) would be the main basis for the efficacy assessments of eliglustat. This study was designed as a multinational (with a total of 12 participating countries), multicenter (with a total of 18 participating sites), randomized, double-blind, placebo-controlled, parallel group trial evaluating the efficacy and safety of eliglustat in treatment-naïve patients with Gaucher Disease Type 1 (GD1). The Division recommended change in spleen volume as the primary endpoint. The Division recommended change in hemoglobin concentration, change in platelet count and change in liver volume as secondary endpoints using a step down approach.

For trial GZGD02607 (ENCORE), the Agency agreed with the Applicant's proposed primary endpoint of a composite of spleen volume, hemoglobin levels and platelet count. Liver volume could be a component of the primary endpoint or a secondary endpoint. The Division did not agree with the Applicant's (b) (4)

The original ENGAGE trial protocol was finalized after the EOP2 meeting on March 31, 2009, and the trial was subsequently started on November 5, 2009. The original protocol incorporated all important suggestions and comments from DGIEP at the EOP2 meeting. These suggestions and comments included the design of the study itself, the control to be used (i.e., placebo), and the endpoints to be measured and subsequently analyzed. The study has been amended seven times since the original protocol, and the final amendment was made on February 5, 2013. All of the protocol amendments were either administrative or contained minor changes which had no notable impact on the originally pre-specified study endpoints and corresponding analyses.

At an April 12, 2011, a critical face-to-face Type C advice meeting was held between Genzyme and DGIEP. Genzyme was having difficulties in recruiting patients for the ENGAGE study. At

the time of the Type C advice meeting, there had been five previous products approved by the FDA for the treatment of GD1, and four of these products were still on the market. The Division continued to recommend that ENGAGE trial be primarily relied upon to establish efficacy of the drug product and ENCORE data should be supportive, and that Genzyme continue to recruit as best as possible.

Genzyme, however, stated that they would amend the ENGAGE trial design to include inferential within-treatment group analyses for eliglustat patients in case patient recruitment continued to stall. The division understood the applicant's proposition; however, the division clearly stated that these within-treatment group analyses for eliglustat patients would be deemed as exploratory, and that the originally pre-specified comparative analyses between eliglustat and placebo would still be considered confirmatory. Genzyme subsequently amended the ENGAGE protocol (amendment five) on July 12, 2011, while making the corresponding amendment to the SAP on August 11, 2011, to include these within-treatment group analyses for eliglustat patients. Fortunately, the patient recruitment issue for ENGAGE did not seem to negatively impact the study or the development program. Subsequently, a total of 40 patients were recruited, which surpassed the original 36 patient recruiting target.

In February 17, 2012, meeting preliminary responses (the applicant cancelled the meeting), Eliglustat was determined to be a BCS Class I drug and BE and food effects studies would not be required. Clinical pharmacology comments on drug-drug interactions were conveyed.

At the May 21, 2013, meeting the Agency did not agree with the selected non-inferiority margin of 25% for spleen volume changes in the ENCORE trial design. 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.

There was also discussion of CYP2D6 genotyping and the need to adequately power the subgroups. The Agency stated that adequate data was not presented to assess if dosing based on trough levels was appropriate. It was agreed that if a FDA approved reliable test was available for genotype testing it would not require the development of a separate companion diagnostic. *(Note: there are FDA approved genotype tests available on the market)*

The Agency also again expressed concerns that the thorough Q-T study did not adequately address the risk of Q-T interval prolongation in special populations and that further investigation would be necessary to address this issue.

The Applicant agreed to conduct renal and hepatic impairment PK studies post approval.

2. Background

Description of Disease

Gaucher Disease

Gaucher disease is a rare disease, but 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.

The clinical expression of Gaucher disease is variable within all three subtypes, especially within type 1 Gaucher disease. Pediatric type 1 Gaucher disease is common, with more than 50% of type 1 Gaucher cases in the International Collaborative Gaucher Group (ICGG) Gaucher Registry reporting an onset of disease manifestations in childhood or adolescence. Infants with type 1 Gaucher disease are clinically normal; in severe cases, organomegaly becomes evident after the first year or two of life, and may progress for some years after. The primary clinical manifestations of the disease, hepatomegaly, anemia, and thrombocytopenia, have been related to splenic dysfunction. In an analysis of 1028 type 1 Gaucher patients in the ICGG Gaucher Registry, 637/677 (94%) patients “with spleen” (i.e., had an intact spleen) had hepatomegaly, anemia, or thrombocytopenia (or a combination of these three abnormalities), compared with 172 (62%) of the 277 patients who had undergone splenectomy ($P < 0.01$). Systematic follow-up of a number of patients over age 15 years shows that Gaucher disease-related changes in untreated patients, if they occur at all, are noted over decades. Hematologic measures of anemia and decreased platelet counts as well as spleen and liver sizes exhibit little or no change. Progressive osteopenia and occasional development of new fractures may be observed; however, bone disease usually occurs later than visceral disease. Pediatric-onset disease may represent a more aggressive form of type 1 Gaucher disease. In adults, rapid progression of previously quiescent disease is unusual. In an analysis of survival data of type 1 Gaucher patients enrolled in the

ICGG Gaucher Registry, the estimated life expectancy at birth for type 1 Gaucher patients was about 9 years less than the general US population.

Current Therapy

Patients with GD1 have a partial deficiency in the activity of the lysosomal enzyme acid B-glucosidase, which catalyses the hydrolysis of glucosylceramide (GL-1) to glucose and ceramide. Consequently, GL-1, lyso-GL-1, and other complex glycosphingolipids accumulate in lysosomes.

Two treatment approaches aimed at lowering GL-1 levels are currently available for GD1: 1) ERT with recombinant acid β -glucosidase, which augments the deficient enzyme activity in patients and catabolizes stored GL-1 in lysosomes, and 2) substrate reduction therapy (SRT), which acts by partially inhibiting the enzyme glucosylceramide synthase, thereby reducing rate of synthesis of GL-1 to better match the impaired rate of catabolism in patients. Most research effort to date has focused on strategies for augmenting enzyme levels to compensate for the underlying enzyme deficiency. These strategies include bone marrow transplantation (BMT), gene therapy, substrate reduction therapy (SRT), chaperone-mediated enzyme enhancement therapy, and enzyme replacement therapy (ERT).

Currently, ERT is the first-line treatment of Gaucher type 1 disease, and reverses or improves important disease manifestations. SRT is an alternative therapy for patients who do not tolerate ERT. Zavesca (miglustat), an inhibitor of glucosylceramide production, is currently the only approved SRT for Gaucher disease. Supportive care for all Gaucher patients may include blood transfusions for severe anemia and bleeding, analgesics for bone pain, joint replacement or other orthopedic intervention for chronic pain and restoration of skeletal function, and bisphosphonates and calcium for osteopenia.

The majority of patients (90%) achieve normal hemoglobin levels within two years of initiation of ERT. Treatment of bone disease in Gaucher patients remains an unmet need. Although ERT has been demonstrated to reduce bone pain, other manifestations of bone involvement have been more refractory to ERT. Similarly, certain pulmonary manifestations of Gaucher disease (interstitial lung disease) are not responsive to ERT.

Three ERT's are currently approved Cerezyme (imiglucerase), VPRIV (velaglucerase alfa) and Elelyso (taliglucerase alfa) for the treatment of Gaucher type 1. ERT must be given intravenously, every two weeks and there is risk hypersensitivity and infusion-associated reactions. A small percentage of patients treated with Cerezyme may develop antibodies to the enzyme during the first year of treatment, but seldom after 12 months of therapy (Starzyk, 2007, Mol Gen Metab). Rarely, the antibodies can be neutralizing or associated with anaphylactic reactions (Cerezyme USPI and SmPC).

Zavesca (miglustat) is the only currently approved SRT product for Gaucher Disease. It is a second-line drug indicated for the treatment of adult patients with mild to moderate type 1 Gaucher disease for whom enzyme replacement therapy is not a therapeutic option (e.g. due to constraints such as allergy, hypersensitivity, or poor venous access). There is a warning for

potential development of peripheral neuropathy. Patients receiving Zavesca should have neurological evaluations every six months. Other precautions from product labeling include tremor, diarrhea and weight loss, and effect on male fertility.

CDTL Comment:

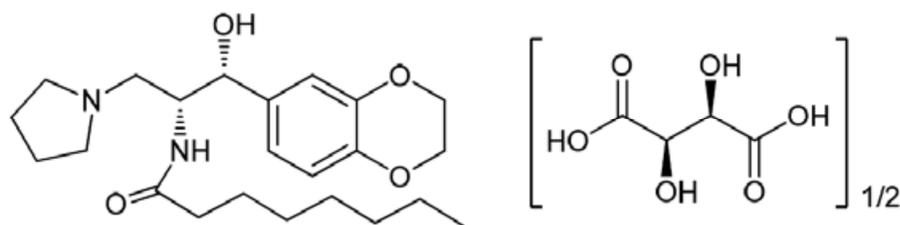
Because ERTs must be given intravenously and carries the risk of hypersensitivity reactions and the only other oral treatment Zavesca is restricted secondary to the potential for development of peripheral neuropathy, eliglustat represents a potential for improvement in patient care.

3. CMC

Drug Product

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. 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. 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.

Figure 1: Eliglustat tartrate chemical structure



Proposed trade name: Cerdelga

Pharmacological class: Glucosylceramide (GL-1) synthase inhibitors

Manufacturer: Genzyme

Chemical Name: N-((1R,2R)-1-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)octanamide (2R,3R)-2,3- dihydroxysuccinate

Molecular formula: $C_{23}H_{36}N_2O_4 + \frac{1}{2} (C_4H_6O_6)$

The CMC review was conducted by Dr. Yichun Sun, Dr. Tarun Mehta and Dr. Hamid Shafiei. From CMC perspective the NDA was not ready for approval until identified issues had been resolved.

See addendum to CMC review by Yichun Sun, PhD, dated [redacted] (b) (4). The drug substance was found that [redacted] (b) (4) levels were very low and routine testing was not necessary. The drug product specifications for removing the microbial limit testing response were satisfactory. All labeling issues were satisfactorily resolved. The office of compliance provided and Overall Acceptable recommendation for the facilities involved in the manufacture and test of the drug substance and drug product. ONDQA recommended Approval.

4. Nonclinical Pharmacology/Toxicology

The nonclinical safety assessment was conducted by Dr. Tamal Chakraborti. No significant issues were identified by Dr. Chakraborti. Dr. Chakraborti recommended approval from a nonclinical standpoint. See his full review dated May 5, 2014 for further details.

The carcinogenicity assessment was conducted by Dr. Sruthi King. There were no outstanding issues to preclude approval from her perspective.

5. Clinical Pharmacology

Mechanism of Action

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

Summary

The pharmacology review was conducted by the following reviewers:

OCP Reviewers:	Elizabeth Shang, Ph.D., Sue-Chih Lee, PhD. (Primary) Sandhya Apparaju, Ph.D. (<i>In vitro</i> 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 clinical pharmacologists found the application acceptable for approval. This approval though is based on the outcome of the ongoing negotiations with the Applicant. Clinical Pharmacology has recommended changes to:

- 1) The proposed dosing regimen, for 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).

The excerpts from the Executive Summary and Summary from the Clinical Pharmacology Review is copied below please refer to the full Clinical Pharmacology review dated June 16, 2014 in DARRTS under the name of Elizabeth Shang for details.

“The sponsor is proposing a fixed oral dosing regimen of 84 mg (free base; equivalent to 100 mg tartrate salt) twice daily (BID) in patients who are CYP2D6 extensive metabolizers (EMs) or intermediate metabolizers (IMs). The sponsor intends to exclude use of eliglustat in CYP2D6 (b) (4) ultra-rapid metabolizers (URMs). The to-be-marketed product is eliglustat capsules 84 mg, each containing eliglustat tartrate 100 mg. Hereafter, the eliglustat dose refers to the salt form unless otherwise specified since that was the designation used by the sponsor during their drug development.

To support the approval of this NDA, the sponsor conducted an array of clinical pharmacology-related studies. A total of twenty-four in vitro studies were performed to facilitate the mechanistic understanding in the absorption, distribution and metabolism characteristics and CYP enzyme- and transporter-mediated drug-drug interaction (DDI) potentials of eliglustat. The phase 1 studies evaluated in healthy subjects the eliglustat pharmacokinetics (PK) and short term safety, mass balance, pharmacodynamics (PD), clinical DDIs, QT prolongation potential (thorough QT study), relative and absolute bioavailability, and food-effect on eliglustat PK. In addition, population PK, exposure-response for efficacy and safety, and physiologically-based pharmacokinetics (PBPK) modeling and simulations were performed. Validated analytical methods were employed for assay of eliglustat concentrations in plasma and urine samples across studies.

The clinical studies conducted in GD1 patients consist of one phase 2 and two phase 3 trials (ENGAGE and ENCORE). Status of CYP2D6 phenotype of each patient was determined before the administration of eliglustat using FDA cleared tests. In all three studies, patients were started with eliglustat tartrate 50 mg PO BID and a dose titration strategy was employed in an attempt to ascertain that the individual trough concentration of eliglustat at steady-state (SS) would not be below 5 ng/mL. The titration involved one step increase to 100 mg BID for the Phase 2 and ENGAGE studies while the ENCORE trial allowed one further dose increase to 150 mg BID. All the CYP2D6 PMs (N=5) were dosed at 50 mg BID without the need for dose increase based upon their trough concentrations. For efficacy, the ENGAGE study demonstrated that eliglustat treatment was superior to placebo and the ENCORE study showed that eliglustat treatment was non-inferior to Cerezyme.

Eliglustat is primarily metabolized by CYP2D6 and, therefore, CYP2D6 genotype/phenotype greatly impacts the PK of eliglustat. Four key questions were raised during the review of this NDA, which are given below along with the current positions on these issues:

1. Is the sponsor’s proposed one fixed oral dosing regimen (100 mg BID) for both CYP2D6 EMs and IMs acceptable? Is therapeutic drug monitoring (i.e., assessment of eliglustat trough concentrations) necessary?

In terms of efficacy, one fixed dosing regimen of 100 mg BID for both EMs and IMs is considered acceptable and there is no need to measure and maintain trough eliglustat

concentrations at or above 5 ng/mL. Although pharmacometrics analyses revealed an exposure-response (E-R) relationship for efficacy, patients who had trough concentrations below 5 ng/mL appeared to demonstrate clinical benefit notwithstanding the small sample size available for analysis. (Sections 1.3.1, 1.3.2, and 2.3.4 of clinical pharmacology review). The patients in ENGAGE and Phase 2 study were treated successfully at doses of 100 mg BID or lower. Regarding safety considerations, please refer to Question #3 below.

2. *Can we recommend a dose for patients who are CYP2D6 PMs?*

OCP recommends a dosing regimen of 100 mg once daily (QD) for PMs. The sponsor is prepared to market only one strength (i.e., eliglustat tartrate 100 mg), limiting the dosing regimens that can be considered. At the dose of 100 mg BID proposed for EMs and IMs, PMs would have approximately 6- to 7-fold higher AUC and C_{max} compared to EMs, and 2- to 3-fold higher AUC and C_{max} compared to IMs. A dosing regimen of 100 mg every other day can bring the eliglustat AUC to a level between EMs and IMs given 100 mg BID. This dosing regimen, however, is considered impractical in terms of patient compliance and no further assessment was made. Based on the observed data and PBPK predictions, a 100 mg QD regimen will likely result in a C_{max} of approximately 80 ng/mL, which is lower than 250 ng/mL and is likely not to result in any QT related safety concerns. For a C_{max} of 250 ng/mL, the mean (upper 90% CI) of $\Delta\Delta QTcF$ are predicted to be 6.4 (9.4) ms, which is below the regulatory threshold set as the upper limit based on the thorough QT study. For other aspects of safety considerations, refer to Question #3 below.

3. *To guide dosing in CYP2D6 IMs and PMs and dose adjustment in DDI scenarios, what is the maximum systemic exposure that is considered safe based on the clinical safety database?*

Because of the dose titration design and restrictions in concomitant medications in the Phase 2 and Phase 3 studies, the systemic exposures in these studies were relatively low and few patients experienced the higher systemic exposures expected for IMs given 100 mg BID or PMs given 100 mg QD as compared to EMs given 100 mg BID (Section 2.3.5.1.2, Figure 17 and Figure 18 of clinical pharmacology review). On the other hand, eliglustat does not appear to have a narrow therapeutic index in view of the current safety database.

Based on discussions with the clinical team, no major safety concerns have been identified for eliglustat in Phase 2 and Phase 3 studies. No meaningful E-R relationship for adverse reactions was observed except for nervous system disorders, which was primarily driven by headaches. Overall the incidence rates for adverse events were low (see Section 2.3.4.4 of clinical pharmacology review). Thus exposures achieved in the Phase 2 and Phase 3 studies are considered safe. Including the available exposure data from the ongoing phase 3b (EDGE) study, the highest individual exposure (AUC_{0-24h}) achieved is 1984 ng×hr/mL, with 20 patients with AUC_{0-24h} > 800 ng×hr/mL and 7 patients with AUC_{0-24h} > 1100 ng×hr/mL. The mean AUC_{0-24h} for IMs at 100 mg BID and PMs at 100 mg QD are expected to lie within 800-1100 ng×hr/mL.

The Clinical Pharmacology Review Team met with the Clinical Review Team on May 7, 2014 to discuss the maximum systemic exposure that will be safe in patients. The clinical team

considered that the exposures expected at 100 mg BID for IMs and 100 mg QD for PMs are acceptable in view of the clinical experience with eliglustat in terms of systemic exposure and safety data gathered from the Phase 2 and Phase 3 studies. The mean AUC_{0-24h} of 1100 ng×hr/mL also serves as the threshold mean exposure to guide dosage adjustment in DDI scenarios as the safety at higher exposures is uncertain, taking into consideration the intersubject variability in PK parameters.

4. *CYP2D6 genotyping of patients is essential for dosing of eliglustat. Is this feasible without concurrent approval of a test kit by the Center for Devices and Radiological Health (CDRH)?*

In clinical studies of eliglustat, CYP2D6 genotype and phenotype were determined using FDA-cleared assays. As the FDA proposed use of eliglustat is limited to patients who are CYP2D6 EMs, IMs and PMs (e.g., not indicated in indeterminate metabolizers), CYP2D6 genotype testing is essential for the safe and effective use of eliglustat. FDA-cleared tests are available for genotyping CYP2D6. CDRH was consulted regarding use of available tests as a companion diagnostic for eliglustat; CDRH has recommended that the available tests are suitable to identify candidates for eliglustat therapy and that labeling should reference use of an FDA-cleared test to identify the indicated populations. The CDRH review by Denise Johnson-Lyles, dated 7/21/14, comments on the possibility of patients being misclassified by one of the two cleared CYP2D6 tests, which are in 98% agreement with the reference test (sequencing).

CDTL Comment: Team discussion noted that because of the rarity of Gaucher Disease and the accuracy of the test, the incidence of patients receiving the incorrect CYP2D6 classification would be low.

Note that the applicant provided information at the end of the review cycle that reclassified the CYP2D6 metabolizer status of some of the patients in the data set. This reclassification was performed with updated testing now available. The clinical pharmacology team reviewed this data and the overall recommendations for dosing did not change as a result of the reanalyze; however some of the recommendations for dosing in drug-drug interactions scenarios did change.

Dose Recommendations

- CYP2D6 EMs and IMs: 100 mg BID
- CYP2D6 PMs: 100 mg QD
- CYP2D6 URM: A safe and effective dose has not been determined.

The sponsor's proposed eliglustat dose of 100 mg PO BID in patients who are CYP2D6 EMs or IMs is acceptable as described above (see Section 1 of clinical pharmacology review). The proposed exclusion of CYP2D6 URM is also acceptable because even at a high dose of 200 mg BID, the exposure in URM are ~57% and ~82% lower than the exposures for EMs and IMs at 100 mg BID, respectively. The local safety, e.g. gastrointestinal tolerability, and potential toxicity due to high metabolite concentrations at a higher dose (in order to match systemic exposure in URM to EMs or IMs) is unknown.

(b) (4)

(b) (4) (b) (4) Eliglustat 100 mg PO QD may be used in patients who are CYP2D6 PMs. Limited data are available; five PMs (one in Phase 2 study and four in ENCORE) received eliglustat 50 mg BID for at least one year with acceptable adverse event (AE) profiles. At 100 mg QD, the predicted C_{max} is less than 250 ng/mL. Thus, the likelihood for QT-related safety concerns is low. At 100 mg QD, the AUC in PMs will be within the exposures achieved in the study (Section 2.3.4.5 of clinical pharmacology review). Based on the clinical database, the safety at the expected exposure is deemed acceptable by the clinical team. Additionally, no clinically meaningful E-R relationship was observed for AEs except for nervous system disorders.

See addendum to Clinical Pharmacology Review by Elizabeth Shang, PhD.:

During the Late Cycle Meeting of June 18, 2014, Genzyme informed the Agency that CYP2D6 phenotypes in subjects genotyped by the (b) (4) were reclassified after the original NDA submission to harmonize the data with phenotypes obtained from studies genotyped by (b) (4). As a result, the PK of eliglustat stratified by the CYP2D6 phenotype and the dose adjustment for various DDI scenarios were affected.

(b) (4)

See Late Cycle Communication by Jessica Benjamin, project manager, dated 8/12/2014:

The sponsor also proposed during the late cycle meeting to present information on (b) (4)

(b) (4)

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 efficacy summary will be presented first followed by the details of the phase 3 trials.

Efficacy Summary

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.

It was noted by the statistical reviewer, Benjamin Vali, MS that “overall, the designs of both the ENGAGE and ENCORE trials were deemed adequate from a statistical perspective for the proposed indication, and the applicant’s corresponding statistical analysis plans deemed appropriate. One issue pertaining to the ENCORE trial (the supportive trial) is 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. See below details of the design of the ENCORE trial for further details.

The CYP2D6 metabolizer status distribution in the US and in the drug trial population was primarily extensive metabolizers, followed by intermediate metabolizers and then very few of the other subtypes. The efficacy data was showed less of a treatment response in the few intermediate metabolizers studied, however the numbers were too small to make conclusions and the modeling done by clinical pharmacology supports efficacy at the recommended dose.

See Section 13 – Risk Benefit Assessment, for discussion of other issues pertaining to the efficacy review of this application.

Sources of Clinical Data

The clinical development program for Eliglustat consisted of 13 Phase 1 trials (including modified TQT trial and drug-drug interaction studies, because of eliglustat’s extensive metabolism via CYP450 liver enzymes), one Phase 2 trial (GZGD00304), two Phase 3 trials GZGD02507 (ENGAGE) and GZGD02607 (ENCORE) and one Phase 3b trial GZGD03109 (EDGE). The Phase 3 trials, ENGAGE and ENCORE have completed their primary analysis periods (PAPS), and have ongoing long-term treatment periods. The Applicant has not submitted efficacy data for the EDGE trial for this review cycle. To date, no pediatric patients < 16 years of age have been enrolled in any of the clinical trials. Trial design and efficacy results for the two Phase 3 trials (ENGAGE and ENCORE) and the one Phase 2 trial were reviewed for

the efficacy evaluation of this submission. Safety data reviewed included all exposed patients, including data from the ongoing Phase 3b trial (EDGE).

Efficacy parameters evaluated in the clinical trials included liver and spleen volume and hemoglobin and platelet counts. Normal organ volumes are a function of body weight. Thus, normal organ volumes differ by age and gender. The normal liver and spleen volumes are approximately 2.5% and 0.2% of body weight (kg), respectively. In published literature on Gaucher disease, organ volumes commonly are described in terms of multiples of normal (MN) and percent of body weight in kilograms (%BW) rather than by the specific volume measurement in milliliters.

GZGD02507 (ENGAGE) – Phase 3 Treatment Naïve Patients

General Design and Objectives

It was agreed at the EOP2 meeting on February 5, 2009 that the phase 3 efficacy and safety study GZGD02507 (ENGAGE) would be the main basis for the efficacy assessments of eliglustat. This study was designed as a multinational (with a total of 12 participating countries), multicenter (with a total of 18 participating sites), randomized, double-blind, placebo-controlled, parallel group trial evaluating the efficacy and safety of eliglustat in treatment-naïve patients with GD1.

This was a randomized, placebo controlled, double-blind, multi-center, multinational Phase 3 trial. The trial consisted of a Primary Analysis Period (Day 1 to Week 39), an open label long-term treatment period (post Week 39 through trial completion) and a follow-up phone call approximately 30 to 37 days after the last dose of trial medication.

The trial was conducted at a total of 26 sites in South America, US, Canada, Middle East, Northern Africa, India and Europe. All total of 40 patients, aged ≥ 16 years, were randomized and treated with eliglustat (n=20) or placebo. The trial period was from November 5, 2009 to July 18, 2012 (data cut-off date).

The primary objective of the trial was to confirm the efficacy and safety of eliglustat after 39 weeks of treatment in patients with Gaucher disease type 1. The secondary objectives were to determine the long-term efficacy, safety and pharmacokinetics (PK) of eliglustat in patients with GD1.

Patients who met all eligibility criteria based on screening assessments were randomized to receive treatment with eliglustat or placebo during the 39-week Primary Analysis Period. Randomization was stratified based on the patient's baseline spleen volume (≤ 20 multiples of normal [MN] or >20 MN), and within each stratum patients were randomized in a 1:1 ratio to each treatment group. All patients randomized to eliglustat received a single 50-mg dose on Day 1 and repeat doses of 50 mg twice daily (BID) from Day 2 to Week 4; thereafter, patients received a dose of either 50 or 100 mg BID through Week 39, depending on a patient's trough plasma concentration of Genz-99067 at Week 2.

Patients entered the Long-term Treatment Period following completion of their Week 39 assessments. In this period, all patients received eliglustat at an initial dose of 50 mg BID from post-Week 39 (Day 1 of the Long-term Treatment Period) through Week 43. Thereafter, patients received a dose of 50 or 100 mg BID through Week 47 and a dose of 50, 100, or 150 mg BID from post-Week 47 through study completion, depending on their trough plasma concentration of Genz-99067 at Week 41 and Week 45, respectively.

The potential for subjective bias was minimized by use of a core laboratory for central blinded analysis of imaging data, including the primary efficacy endpoint (percentage change in spleen volume from Baseline in MN). In addition, randomization was stratified by a patient's spleen volume at Baseline (in MN) to achieve balance between the treatment groups.

The trial population was chosen to select for patients who had major clinical manifestations of GD1 (e.g., anemia, thrombocytopenia, and hepatosplenomegaly) and had either not previously received treatment with ERT or SRT or had been off treatment for an extended duration of 6 months or 9 months, respectively. See clinical review by Karyn Berry, MD for full details of inclusion/exclusion criteria.

The primary efficacy endpoint was the percentage change in spleen volume from Baseline to Week 39 for eliglustat, relative to placebo.

Secondary efficacy endpoints included the percentage change in liver volume, percentage change in platelet count, and absolute change in hemoglobin level from Baseline to Week 39, as well as within-patient analyses of each of the above clinical outcomes over a 39 week treatment with eliglustat, including patients randomized to eliglustat and patients randomized to placebo who completed 39 weeks of open-label eliglustat treatment as of the data cut-off date.

MRI scans for assessment of Spleen and Liver Volumes without contrast agent were obtained from patients who had been fasting for at least 6 hours prior to the procedure. Central readers at (b) (4) evaluated the digital images to determine spleen and liver volumes and calculated MN using the following formula:

$$\begin{aligned}\text{Spleen MN} &= \text{volume in cc} / (\text{weight in kg} * 2) \\ \text{Liver MN} &= \text{volume in cc} / (\text{weight in kg} * 25)\end{aligned}$$

If a patient's spleen or liver volume (in MN) increased > 30% above the patient's baseline value, a repeat organ volume measurement was obtained within approximately 4 weeks and this repeat measurement was used in the study analyses.

At Week 26, a subset of patients each had 2 MRIs to measure the variability of volumetric MRIs. These MRIs were obtained on the same day or within 3 days of each other at approximately the same time of day. For these patients the average of the 2 values at Week 26 was used in the study analyses.

Primary Analysis Period

Patients randomized to active therapy received double-blind treatment with eliglustat for 39 weeks. Eliglustat was administered to each patient as a single 50-mg dose on Day 1, and as repeat doses of 50 mg BID from the morning of Day 2 through the evening prior to the Week 4 visit. From the morning of Week 4 through Week 39, patients who had a Genz-99067 trough concentration ≥ 5 ng/mL at Week 2 continued to receive 50 mg BID and patients who had a Genz-99067 trough concentration < 5 ng/mL at Week 2 received an increased dose of 100 mg BID. Patients randomized to placebo received placebo capsules on the morning of Day 1 and BID from the morning of Day 2 through Week 39.

Long-term Treatment Period

All patients received open-label treatment with eliglustat from post-Week 39 (Day 1 of the Long-term Treatment Period) until study completion. Each patient received an eliglustat dosing regimen of 50 mg BID from post-Week 39 through the evening prior to the Week 43 visit. From the morning of Week 43 through the evening prior to the Week 47 visit, patients who had a trough concentration ≥ 5 ng/mL continued to receive 50 mg BID and patients who had a trough concentration < 5 ng/mL received an increased dose of 100 mg BID. From the morning of Week 47 through study completion, patients who had a Genz-99067 trough concentration ≥ 5 ng/mL continued to receive their same dose of eliglustat and patients who had a Genz-99067 trough concentration < 5 ng/mL received an increased dose of either 100 mg BID (for patients who had been receiving 50 mg BID) or 150 mg BID (for patients who had been receiving 100 mg BID).

Dose Modification

As of approval of Amendment 5 (dated 12 July 2011), any patient who experienced a peak Genz-99067 plasma concentration ≥ 150 ng/mL, in either period of the study, would have been temporarily discontinued from treatment and, if applicable, removed from the Primary Analysis Period. Following completion of additional protocol specified evaluations, the patient would have been permitted to initiate/resume open-label eliglustat therapy, either at a reduced dose or at his/her current BID dose (prior to treatment discontinuation), depending on the patient's peak plasma concentration and the treatment period in which it was reported, any concurrent safety findings, and any adjustments of concomitant medications. Subsequent dose decreases or increases would have been permitted based on continued evaluation of the patient's data, in consultation with the Sponsor.

During the Long-term Treatment Period, dose decreases were permitted in the event of poor tolerability, and were managed in consultation with the Sponsor and, as appropriate, the DMC.

The lowest dose allowed in this study (either period) was 50 mg once daily (QD), and the highest dose allowed was 100 mg BID in the Primary Analysis Period and 150 mg BID in the Long-term Treatment Period.

Twenty-two (55%) patients were receiving 1 or more prior medications to initiation of study treatment, many of which were being administered chronically or on an as needed basis for the management of symptoms and complications of GD1. The more commonly administered prior medications included paracetamol and other aniline analgesics, non-steroidal anti-inflammatory

drugs (NSAIDs), nutritional supplements, and antihistamines. These medications were generally continued during the patient's participation in the study

Use of strong inhibitors of CYP2D6 and CYP3A4 and inducers of CYP3A4, which have the potential to alter Genz-99067 metabolism, was closely monitored and controlled throughout the trial. Medications that might cause QT interval prolongation were prohibited throughout the study, with exceptions permitted for temporary (i.e., ≤ 1 week) but not chronic use.

Given the potential for eliglustat to increase the exposure of other P-glycoprotein (P-gp) substrate drugs, Investigators were also advised to closely monitor the levels of any coadministered P-gp substrate drugs with narrow therapeutic indices (e.g., digoxin, phenytoin) and drugs that required titration when administered with P-gp inhibitors (e.g., tolvaptan, colchicine).

Medical Reviewer's comments:

Thirty-one (78%) patients received one or more concomitant medications during treatment in the Primary Analysis Period, most commonly (>10%) including aniline analgesics, NSAIDs, antibiotics and/or extended spectrum penicillins, corticosteroids, antihistamines, and various nutritional supplements.

Two patients in the eliglustat treatment group had a prohibited change in a nutritional supplement during the Primary Analysis Period. Seven patients in the eliglustat treatment group received 1 or more concomitant medications that are known to have the potential to cause a drug-drug interaction with eliglustat.

Analysis Population

This was a superiority trial. Efficacy analyses were performed on the Full Analysis (FA) Set, the Per Protocol (PP) Set and Week 39 Completer Analysis Set as applicable.

Full Analysis Set (FAS): The FAS included all patients who signed informed consent and received at least 1 dose of study drug (placebo or eliglustat). The FAS is equivalent to the intent-to-treat population.

Per Protocol Set (PPS): The PPS included patients in the FAS who were at least 80% compliant with treatment during the Primary Analysis Period, had no major protocol deviations expected to interfere with the assessment of efficacy and did not exhibit hematological decline as a result of medically determined etiologies other than Gaucher disease.

Week 39 Completer Analysis Set: This analysis set included patients in the FAS who completed 39 weeks of treatment and had non-missing assessments at Baseline and Week 39.

Safety Set: This analysis set included all patients who received at least 1 dose of study drug and is equivalent to the FAS.

In order to control the overall study-wise type I error rate, a step-down/closed sequential testing procedure was pre-specified by the applicant to adjust for the multiple comparisons on the study endpoints presented in the order as presented.

The original statistical analysis plan (SAP) was finalized on October 28, 2010. An amendment to the SAP was made on August 11, 2011. This amendment incorporated additional inferential analyses for assessing the change from baseline at Week 39 in the four efficacy parameters of interest (i.e., spleen volume, hemoglobin concentration, liver volume, and platelet count) exclusively within the eliglustat treatment group without comparison to the placebo group. These additional analyses were deemed exploratory by the review team. The SAP, along with the amendment, was submitted, and all relevant analyses were finalized before the Double-Blind Treatment Period (see below in Section 3.2.1.1) was completed on July 18, 2012. Database hard-lock for the Double-Blind Treatment Period was on August 17, 2012, and the study was officially unblinded on September 17, 2012.

Although LOCF may not be an acceptable missing data handling strategy for the primary analyses, there was only one patient in the eliglustat group who dropped out of the ENGAGE study. Consequently, the study results and conclusions were not dependent on the missing data handling strategy.

CDTL Comment:

The statistical reviewer found the overall design of the ENGAGE study and its image evaluation plan was deemed adequate from a statistical perspective, and the estimated sample size was appropriate given the assumptions on the anticipated treatment effect.

Results for ENGAGE

Table 1: ENGAGE Analysis Populations

Analysis Population	Placebo (N=20)	Eliglustat (N=20)	Total (N=40)
ENGAGE FAS, n (%)	20 (100)	20 (100)	40 (100)
ENGAGE Safety Set, n (%)	20 (100)	20 (100)	40 (100)
ENGAGE PPS, n (%)	20 (100)	18 (90)	38 (95)
Patients excluded	0	2 (10)	2 (5)
Dosing compliance <80%; withdrew prior to wk 39	0	1 (5)	1 (3)
Missed evening doses prior to wk 2 PK sample collection	0	1 (5)	1 (3)

Table 2: ENGAGE Trial Demographic Characteristics

Parameter	Eliglustat (N=20)	Placebo (N=20)	All Patients (N=40)
Sex, n (%)			
Male	8 (40)	12 (60)	20 (50)
Female	12 (60)	8 (40)	20 (50)
Race, n (%)			
White	19 (95)	20 (100)	39 (98)
Asian	1 (5)	0	1 (3)
Jewish Descent, n (%)			
Yes ^a	3 (15)	8 (40)	11 (28)
No	17 (85)	12 (60)	29 (73)
Ethnicity, n (%)			
Not Hispanic or Latino	18 (90)	20 (100)	38 (95)
Hispanic or Latino	2 (10)	0	2 (5)
Age at Day 1 (years)			
Mean (SD)	31.6 (11.55)	32.1 (11.26)	31.8 (11.26)
Min, Max	16.6, 62.9	16.1, 59.3	16.1, 62.9
CYP2D6 Metabolizer Status, n (%)			
Poor	0	0	0
Intermediate	1 (5)	2 (10)	3 (8)
Extensive	18 (90)	18 (90)	36 (90)
Ultra-rapid	1 (5)	0	1 (3)

CDTL Comment:

There was no significant imbalance between the treatment groups regarding the presented demographic and baseline characteristics.

Major protocol deviations, which were pre-defined as deviations "expected to impact the scientific soundness of the study or the rights, safety, or welfare of human subjects," were reported for 23 patients. The MO and statistical reviewers did not think they compromised the results of the trial.

Compliance was at least 90% for the all patients with the exception of 2 patients in the placebo group and 1 patient in the eliglustat group, and was evenly distributed among subgroups.

The mean time on study treatment was 274.5 days (standard deviation [SD] =19.94) overall and was similar in the 2 treatment groups, regardless of sex or age subgroup.

Patient Disposition: In total, 40 patients were randomized and treated with eliglustat (20 patients) or placebo (20 patients) across 17 study centers. Thirty-nine patients completed the study through Week 39. One patient (#5303) withdrew from the study after 166 days on study treatment (eliglustat), and did not complete Week 39 assessments.

Primary Efficacy Analysis

As previously noted, the primary efficacy endpoint for eliglustat in the ENGAGE trial was the percentage change in spleen volume from Baseline to Week 39 compared to placebo. All patients in the study presented with splenomegaly at Baseline, with mean spleen volumes of 13.89 MN for eliglustat treatment group and 12.50 MN for the placebo group. The eliglustat treatment group showed a percentage reduction in spleen volume (MN) by the first post-Baseline assessment at Week 26 (mean = -25.16%), and a reduction in spleen volume through Week 39 (mean = -27.58%). In contrast, the placebo group showed small mean percentage increases in spleen volume at both time points (mean = 0.73% and 2.07%, respectively).

All 19 patients in the eliglustat treatment group with post Baseline data achieved a reduction in spleen volume at both Week 26 and Week 39 of the Primary Analysis Period, with percentage reductions from Baseline to Week 39 ranging from -7.68% to -51.52%. In the placebo group, 13 patients had increases in spleen volume during the PAP (range: 0.14% to 13.68%); 6 patients had reductions in spleen volume (range: -2.78 to -8.96%) and one patient in the placebo group had a reduction in spleen volume of -20.91%.

Table 3: Comparison of Organ Volume and Hematology Results from ENGAGE (FAS) and the Phase 2 Study (ITT)

	ENGAGE*		Phase 2 Study Eliglustat (N=26)
	Eliglustat (N=20)	Placebo (N=20)	
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]

CDTL Comment:

From the statistical review by Benjamin Vali, MS:

“Eliglustat showed superior improvement in the percentage change from baseline for spleen volume at Week 39 when compared to placebo. It should be noted that the ANCOVA model assumptions, i.e., normality and constant variance of residuals, were appropriate based on graphically observing residuals along with the pertinent normal quantile-quantile plot. This analysis was repeated utilizing the PP and Week-39- Completer analysis sets, and the conclusions were consistent. From the 40 patients who were originally randomized, there was only one dropout, and a sensitivity analysis consequently showed that this dropout did not impact the study conclusions. It is important to note that no single site influenced or drove the overall study results. There were no patients who were designated as outliers (i.e., by having studentized residual values greater than three). An additional sensitivity analysis was conducted by replacing the baseline spleen severity category (i.e., less than or equal to 20 MN or greater than 20 MN), a factor in the original ANCOVA model, with the covariate of baseline spleen volume (in MN). The study conclusion from this additional sensitivity analysis was consistent with the findings from the primary analysis.”

Table 4: ENGAGE- Primary and Secondary Endpoints

	Statistic	Eliglustat (N=20)	Placebo (N=20)	Treatment Difference (Eliglustat-Placebo)
Percentage Change in Spleen Volume (MN) from Baseline to Week 39	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	NA	NA	<0.0001
Change in Hemoglobin (g/dL) from Baseline to Week 39	LS Mean (SEM)	0.69 (0.23)	-0.54 (0.23)	1.22 (0.32)
	95% CI	0.23, 1.14	-1.00, -0.08	0.57, 1.88
	p-value	NA	NA	0.0006
Percentage Change in Liver Volume (MN) from Baseline to Week 39	LS Mean (SEM)	-5.20 (1.64)	1.44 (1.64)	-6.64 (2.33)
	95% CI	-8.53, -1.87	-1.89, 4.78	-11.37, -1.91
	p-value	NA	NA	0.0072
Percentage Change in Platelet Count (x10 ⁹ /L) from Baseline to Week 39	LS Mean (SEM)	32.00 (5.95)	-9.06 (5.95)	41.06 (8.44)
	95% CI	19.94, 44.06	-21.12, 3.00	23.95, 58.17
	p-value	NA	NA	<0.0001

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

ENGAGE

No conclusions can be drawn from BMD efficacy data. The trial enrolled an inadequate number of patients to effectively compare eliglustat to placebo for lumbar BMD efficacy. For such a study to be adequately powered, approximately 4 times as many patients would need to be enrolled. This appears impractical given the rarity of GD 1.

While positive trends were noted, percentage changes in total BMD and absolute changes in Z-scores in the lumbar spine did not reach statistical significance and the trial was not adequately powered to assess a meaningful difference in treatment effect on BMD. The restrictions of the 39 week Primary Analysis Period and bone exclusion criteria may be contributory. Data from the long term treatment period should provide further clarity on the BMD efficacy of eliglustat in GD 1.

GZGD02607 (ENCORE) – Phase 3 Switchover of patients from imiglucerase

General Design and Objectives

It was agreed at the EOP2 meeting on February 5, 2009 that phase 3 efficacy and safety study GZGD02607 (ENCORE) would provide the key supportive evidence for the efficacy assessments of eliglustat, specifically for patients who were previously ERT-exposed. This study was designed as a multinational (with a total of 12 participating countries), multicenter (with a total of 34 participating sites), randomized, open-label, active-controlled, parallel group non-

inferiority trial to evaluate the efficacy and safety of eliglustat in patients with GD1 who had been treated with ERT for at least three years and were currently stabilized on it.

This was a Phase 3, randomized, multi-center, multi-national, open-label, active comparator trial that evaluated the efficacy and safety of eliglustat in patients with Gaucher Disease type 1 who had been treated with enzyme replacement therapy for at least 3 years and had reached therapeutic goals.

The trial included a screening period (Days -45 to -1), a primary analysis treatment period (Day 1 to Week 52), a long-term treatment period (post-Week 52 through study completion), and a safety follow up period (30 to 37 days after the patient's last dose of study medication).

The trial was conducted at a total of 39 sites in Latin America, the United States (US), Canada, Australia, Middle East and Europe. A total of 160 patients were randomized to treatment with eliglustat (n=106) or Cerezyme (n=54). The trial period was from 15 September 2009 to 09 November 2012 (data cut-off date for the Primary Analysis Period).

The primary objective of the trial was to assess the efficacy and safety of eliglustat compared with Cerezyme® (imiglucerase) after 52 weeks of treatment in patients with Gaucher disease type 1 (GD1) who have reached therapeutic goals with enzyme replacement therapy (ERT).

The secondary objective was to demonstrate that, in patients with GD1 who have reached therapeutic goals with ERT, the majority of patients who receive eliglustat remain stable after 52 weeks of treatment.

The tertiary objective was to evaluate the long-term efficacy, safety, and pharmacokinetics (PK) of eliglustat in patients with GD1 who have reached therapeutic goals with ERT.

This trial included a screening period (Days -45 to -1), a primary analysis treatment period (Day 1 to Week 52), a long-term treatment period (post-Week 52 through study completion), and a safety follow up period (30 to 37 days after the patient's last dose of study medication). Patients who met all eligibility criteria based on screening assessments were randomized to receive treatment with eliglustat or Cerezyme during the 52-week Primary Analysis Period.

The randomization was stratified based on the patient's every 2 weeks (q2w) equivalent ERT dose (<35 U/kg/q2w or ≥ 35 U/kg/q2w) prior to any unanticipated treatment interruption, dose reduction, or regimen change. Within each stratum patients were randomized in a 2:1 ratio to receive eliglustat or Cerezyme, respectively for 52 weeks (the primary analysis treatment period). All patients randomized to eliglustat received a dose of 50 mg BID from Day 1 to Week 4; thereafter, patients received a dose of either 50 or 100 mg BID through Week 8, depending on their trough plasma concentration of Genz-99067 at Week 2. Post-Week 8, patients randomized to eliglustat received a dose of either 50, 100 or 150 mg BID through Week 52, depending on their trough plasma concentration of Genz-99067 at Week 6.

After the 52-week primary analysis treatment period, all patients who remain on-study are receiving eliglustat therapy in the Long-term Treatment Period. Each patient's total duration of

participation in this study will be at least 104 weeks, and participation may continue for a total of up to 5.5 years.

The Inclusion and Exclusion criteria were deemed appropriated by the MO. They required patients to have been on ERT for at least 3 years and to have reached Gaucher disease therapeutic goals prior to randomization. Gaucher disease therapeutic goals were defined as a patient with all of the following:

- A. No bone crisis and free of symptomatic bone disease such as bone pain attributable to osteonecrosis and/or pathological fractures within the last year.
- B. Mean hemoglobin level of ≥ 11 g/dL if female and ≥ 12 g/dL if male at the time of screening.
- C. Mean platelet count $\geq 100,000/\text{mm}^3$ at the time of screening.

Spleen volume must have been < 10 times normal or total splenectomy (provided the splenectomy occurred > 3 years prior to randomization), and liver volume must have been < 1.5 times normal.

The primary efficacy endpoint for analysis (FDA-recommended efficacy endpoint) is the percentage change in spleen volume (MN) from baseline to Week 52. This endpoint was used to evaluate the non-inferiority of eliglustat compared to Cerezyme. Eliglustat treatment was declared non-inferior to Cerezyme treatment if the lower-bound of the 95% CI for the difference was within the non-inferiority margin of 15%.

CDTL Comment:

From the statistical review by Benjamin Vali, MS:

“One issue pertaining to the ENCORE trial (the supportive trial) is 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 CERZYME. Note that a placebo-controlled trial with CERZYME has never been conducted. In addition, the aforementioned hypothetical placebo-controlled trial with CERZYME 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.”

While the noninferiority margin was not ideal, the overall results of the trial supported the efficacy of eliglustat in previously treated GD1 patients.

The alternate primary efficacy endpoint was the percentage (%) of patients who remained stable for 52 weeks (the primary analysis period) assessed for both treatment groups separately along with a difference between the 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]).

Criteria for success included:

Stable Hematological Parameters

- Hemoglobin level does not decrease > 1.5 g/dL from Baseline.

AND

- Platelet count does not decrease $> 25\%$ from Baseline.
- Stable Organ Volume

Spleen volume (in MN) does not increase $> 25\%$ from Baseline, if applicable.

AND

Liver volume (in MN) does not increase $> 20\%$ from Baseline.

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

Treatment

Primary Analysis Period

On Day 1 (within 7 days after randomization), patients randomized to receive eliglustat received 50 mg of eliglustat BID. Dose adjustments could occur at Week 4 based on plasma trough and 2-hour (peak) concentrations of Genz-99067 collected during the Week 2 PK. For patients with a Genz-99067 plasma trough concentration of < 5 ng/mL at Week 2, the eliglustat dose was increased at Week 4 to 100 mg of eliglustat BID.

Patients who had a Genz-99067 plasma trough concentration of ≥ 5 ng/mL continued to receive 50 mg of eliglustat BID. Plasma trough and peak concentrations of Genz-99067 were also collected at Week 6. For patients with a Genz-99067 plasma trough concentration of < 5 ng/mL at Week 6, the eliglustat dose was increased at Week 8. For patients on 50 mg of eliglustat BID whose plasma trough concentration was < 5 ng/mL, the dose was increased to 100 mg BID. For patients on 100 mg of eliglustat BID whose plasma trough concentration was < 5 ng/mL, the dose was increased to 150 mg BID through Week 52. Patients receiving 50 mg or 100 mg of eliglustat with a Genz-99067 plasma trough concentration of ≥ 5 ng/mL at Week 6 continued to receive 50 mg or 100 mg of eliglustat BID through Week 52.

Patients randomized to receive Cerezyme in the primary analysis treatment period received treatment through Week 52 in a q2w regimen equivalent to their ERT dose prior to any unanticipated treatment interruption, dose reduction, or regimen change. The first infusion of Cerezyme occurred within 14 days of randomization.

Dose Modification

As of approval of Amendment 5 (dated 06 July 2011), any patient who experienced a peak Genz-99067 plasma concentration ≥ 150 ng/mL, in either period of the study, would have been temporarily discontinued from treatment and, if applicable, removed from the Primary Analysis Period. Following completion of additional protocol-specified evaluations, the patient would have been permitted to initiate/resume open-label eliglustat therapy, either at a reduced dose or at his/her current BID dose (prior to treatment discontinuation), depending on the patient's peak plasma concentration and the treatment period in which it was reported, any concurrent safety findings, and any adjustments of concomitant medications. Subsequent dose decreases or increases would have been permitted based on continued evaluation of the patient's data, in consultation with the Sponsor.

During the Long-term Treatment Period, dose decreases were also permitted in the event of poor tolerability, and were managed in consultation with the Sponsor and, as appropriate, the DMC. The lowest dose allowed in this study (either period) was 50 mg once daily, and the highest dose allowed (either period) was 150 mg BID.

Analysis Population

As noted earlier, this was a non-inferiority trial with a non-inferiority margin of 15%. Full Analysis Set (FAS): The FAS included all patients who signed informed consent and received at least 1 dose of study drug (Cerezyme or eliglustat). The FAS is equivalent to the intent-to-treat (ITT) population referenced in the protocol.

Per Protocol Set (PPS): The PPS included patients in the FAS who were at least 80% compliant with treatment during the Primary Analysis Period, had no major protocol deviations expected to interfere with the assessment of efficacy and did not exhibit hematological decline as a result of medically determined etiologies other than Gaucher disease. Eliglustat patients who transitioned back to ERT (Cerezyme) due to a decline in Gaucher disease were included in the PPS and were considered treatment failures regardless of their Week 52 assessments.

The original statistical analysis plan (SAP) was finalized on November 19, 2010. An amendment to the SAP was made on August 11, 2011. Note that this SAP amendment occurred on the same day as that of the ENGAGE SAP amendment. This amendment incorporated an additional non-inferiority analysis (as recommended by DGIEP in its responses to questions for the April 12, 2011 Type C advice meeting), which specifically assessed the difference in the percentage change from baseline at Week 52 in spleen volume between the eliglustat and CERZYME treatment groups. Although this additional analysis was requested by DGIEP, its result should be considered exploratory and supportive only. The SAP, along with the amendment, was submitted, and all relevant analyses were finalized in advance of the Primary Analysis Treatment Period completion which was on November 9, 2012. Database hard-lock for the Primary Analysis Treatment Period was on December 7, 2012.

CDTL Comment:

Although 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.

Results of ENCORE

Table 5: ENCORE Analysis Populations

	Eliglustat (N=106)	Cerezyme (N=54)
Randomized, n (%)	106 (100)	54 (100)
Safety/Full Analysis Set, n (%)	106 (100)	53 (98)
Patients Excluded, n (%)	0	1 (2)
Patient not treated	0	1 (2)
Per Protocol Set, n (%)	99 (93)	47 (87)
Patients Excluded, n (%)	7 (7)	7 (13)
Did not reach Week 52	2 (2)	1 (2)
Dosing compliance <80%	2 (2)	3 (6)
Mismatch between randomized dose stratum and actual pre-study Cerezyme dose	2 (2)	2 (4)
Missing Baseline and/or Week 52 platelet count or hemoglobin value	1 (1)	0
Randomized but not dosed	0	1 (2)

Fourteen patients (7 eliglustat; 7 Cerezyme) were excluded from the PPS. The most frequent reasons for exclusion from the PPS were dosing compliance <80% (2 eliglustat; 3 Cerezyme) and a mismatch between the randomized dose stratum and the actual Cerezyme dose received prior to randomization (2 patients in each treatment group).

Patient Disposition

One hundred sixty (160) patients were randomized in a 2:1 ratio to treatment with eliglustat (n=106) or Cerezyme (n=54). One patient in the Cerezyme group was randomized but did not receive study treatment. One patient in the eliglustat group switched to Cerezyme treatment and completed the 52-week primary analysis period. Two patients in the eliglustat group and 1 patient in the Cerezyme group did not complete the primary analysis period due to adverse events.

Study drug compliance was at least 80% for all patients with the exception of 2 patients in the eliglustat group and 4 patients in the Cerezyme group. Patients with compliance rates <80% in the Primary Analysis Period were excluded from the PPS.

The mean \pm SD number of days on study treatment was 361.5 ± 24.28 in the eliglustat group and 347.2 ± 38.80 days in the Cerezyme treatment group.

Table 6: ENCORE Trial Summary of Demographic:

Parameter	Eliglustat (N=106)	Cerezyme (N=53)	Total (N=159)
Sex, n (%)			
Male	47 (44)	25 (47)	72 (45)
Female	59 (56)	28 (53)	87 (55)
Race, n (%)			
White	98 (92)	48 (91)	146 (92)
Black/African-American	6 (6)	4 (8)	10 (6)
Asian	1 (1)	1 (2)	2 (1)
Jewish Descent, n (%)			
Yes ^a	29 (27)	14 (26)	43 (27)
No	76 (72)	39 (74)	115 (72)
Ethnicity, n (%)			
Not Hispanic or Latino	64 (60)	34 (64)	98 (62)
Hispanic or Latino	42 (40)	19 (36)	61 (38)
Age at Day 1 (years)			
Mean (SD)	37.6 (14.17)	37.5 (14.92)	37.5 (14.37)
Min, Max	18.1, 69.3	18.2, 66.2)	18.1, 69.3
Randomization stratification,			
ERT<35U/kg/q2wks	43 (41)	22 (42)	65 (41)
ERT≥35U/kg/q2wks	63 (59)	31 (58)	94 (59)
CYP2D6 Metabolizer Status, n (%)			
Poor	4	2 (4)	6
Intermediate	10 (10)	8 (17)	18 (12)
Extensive	79 (80)	33 (70)	112 (77)
Ultra-rapid	4 (4)	1 (2)	5 (3)
Indeterminate	0	2 (4)	2 (1)

Medical Reviewer's comments:

There were a greater percentage of extensive CYP2D6 metabolizers in the Eliglustat treatment group than the Cerezyme treatment group. Other than CYP2D6 metabolizer status, demographic characteristics were balanced across the treatment groups.

CDTL Comment:

This distribution reflects that of the general US population. Because of the low number of patients in the poor and intermediate groups, actual experience is limited in these populations.

Prior and concomitant meds did not appear to affect the efficacy analysis.

Primary Efficacy Analysis:

Percentage Change in Spleen Volume (FDA-Recommended Efficacy Endpoint)

The least squares (LS) mean percentage change in spleen volume (MN) from Baseline to Week 52 in the eliglustat group was -5.96% compared to -3.21% in the Cerezyme group. The upper bound of the 95% CI in the difference of the estimated mean change (2.62%) was less than the pre-specified threshold of 15%.

Table 7: 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) (-
	95% CI	(-9.12, -2.80)	(-7.47, 1.06)	8.12, 2.62)
	p-value	NA	NA	0.3118

Source: Applicant's table from ENCORE CSR

Medical Reviewer's Comments:

Both treatment groups demonstrated a percentage change in spleen volume from baseline to 52 weeks (Least square Mean of -5.96% in the eliglustat group versus Least square mean of -3.21% in the Cerezyme group).

Stability in the composite endpoint, including hemoglobin and platelet values and spleen and liver volumes, was maintained after 52 weeks of treatment in 84% of patients in the eliglustat group and 94% in the Cerezyme group. The lower bound of the 95% CI in the difference in percentage (-18.6%) was within the pre-specified threshold of -25%.

Table 8: 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)

Medical Reviewer's Comments:

For the alternate primary endpoint, while the Applicant met the stated non-inferiority margin, the percentage of patients in the eliglustat treatment group who remained stable at 52 weeks was approximately 10% less than the Cerezyme treatment group (84% versus 94%). The results of the long term treatment arm of this trial will be important to determine if treatment with oral SRT over time will be similar to ERT.

Greater than 92% of patients in both treatment groups met the stability criteria for each individual component of the composite endpoint: 92.9% to 96.0% for eliglustat versus 93.6% to 100% for Cerezyme. In 3 of the 4 components (i.e., hemoglobin, platelet count, and spleen volume) 100% of Cerezyme-treated patients were stable at Week 52 and the percentage of patients meeting the stability criteria for these components was numerically greater compared to eliglustat.

Nineteen patients (16/99 eliglustat and 3/47 Cerezyme) did not meet the composite endpoint for stability at Week 52. One eliglustat patient failed to remain stable in 2 clinical parameters (i.e., spleen volume and platelet count), while the remaining 18 patients failed to remain stable in only 1 of 4 clinical parameters.

In the 19 patients who failed to meet the composite endpoint at Week 52, the patient's age ranged from 18 to 62 years, 53% (10/19) were female. In the eliglustat group there was an equal

number of patients with average Genz-99067 trough plasma concentrations < 5ng/mL (n=8) and ≥ 5 ng/mL (n=8).

Secondary Endpoints Analysis

Because the applicant did not pre-specify a multiplicity adjustment method for controlling the overall study-wise significance level, the secondary efficacy endpoints were only summarized descriptively by treatment group at Baseline and at Week 52. Specifically, change and/or percentage change from baseline values were summarized.

Hemoglobin level

Hemoglobin was normal at baseline in both treatment groups, with mean values of 13.6 g/dL (range: 11.1 g/dL to 17.3 g/dL) among patients randomized to eliglustat and 13.8 g/dL (range: 11.2 to 16.0 g/dL) for Cerezyme patients. The eliglustat treatment group showed an initial decrease in hemoglobin level of -0.4 g/dL at Week 13 followed by a return towards baseline values after Week 13. At Week 52 the proportion of patients meeting the stability criteria for hemoglobin level was 95% for the eliglustat group and 100% for the Cerezyme group.

A statistically significant increase in hemoglobin was observed following 52 weeks of treatment with Cerezyme, relative to eliglustat. For the PPS, the least squares mean absolute change in hemoglobin from Baseline to Week 52 was -0.22 g/dL for the eliglustat treatment group compared with 0.05 g/dL for the Cerezyme group, resulting in a significant difference (eliglustat - Cerezyme) of -0.28 g/dL (p=0.0253).

Platelet Count

Platelet counts were similar at baseline in both treatment groups, with mean values of 206.8 x 10⁹/L (range: 100.5 to 511.0 x 10⁹/L) in patients randomized to eliglustat and 192.3 x 10⁹/L (range: 102.0 to 339.5 x 10⁹/L) for Cerezyme patients. Mean percentage change from baseline in platelet count was not different between treatments after 52 weeks (p=0.6674). At Week 52, the proportion of patients meeting the stability criteria for platelet counts was 93% for the eliglustat group and 100% for the Cerezyme, group.

Liver Volume

Most patients had normal liver volumes at Baseline, with mean liver volumes of 0.95 MN in the eliglustat group and 0.91 MN in the Cerezyme group. At Week 52 mean liver volumes were essentially unchanged from baseline (0.96 and 0.94 MN for eliglustat and Cerezyme, respectively). At Week 52, the proportion of patients meeting the stability criteria for liver volume was 96.0% for the eliglustat group and 93.6% for the Cerezyme, group.

Bone Mineral Density (DXA)

Study eligibility criteria required a minimum of 3 years of treatment with ERT and excluded patients with symptomatic bone disease (e.g., bone pain attributable to osteonecrosis and/or pathological fractures) within the year prior to study entry. Bone mineral density (BMD) was normal for the vast majority of patients in both treatment groups at study entry, as measured by total BMD, T-scores (peak density) and Z-scores (age-adjusted density) for the total lumbar spine and total femur. This was maintained following 52 weeks of treatment in the Primary Analysis Period, with both eliglustat and Cerezyme.

The percentage of patients with T-scores indicating normal bone density (i.e., T-score >-1) in the lumbar spine and femur at Baseline ranged from 57 to 78% in the eliglustat group and 64 to 73% in the Cerezyme group. Most other patients presented with osteopenia in both bone regions (T-score -2.5 to ≤-1); 3 patients in each treatment group had osteoporosis at baseline (T-score ≤-2.5). For the 28 eliglustat patients with Baseline osteopenia (lumbar spine T-score -2.5 to ≤-1), 20 patients remained in the osteopenia category at Week 52, 5 patients improved to a normal T-score, and 3 patients worsened.

CDTL Comment:

From statistical review by Benjamin Vali, MS: “It is important to note that no single site influenced or drove the overall study results. It was observed that sites #27 (Investigator Martins), #28 (Investigator Drelichman), and #29 (Investigator Cravo) had a larger number of successes/responders than the other sites. A sensitivity analysis was conducted by removing all patients from these sites from the overall analysis, and the subsequent results and conclusions stood. The Office of Scientific Investigation’s (OSI) did not identify any deviations from regulations from these sites/investigators and issued NAI for each of these sites after inspection during the review cycle.”

Bone Data Evaluation



From Dr. Stinson’s review, “The single-arm phase 2 study 0304 showed a 4.4 % increase in lumbar L1-L4 BMD (g/cm²) at 12 months with eliglustat therapy in 20 patients and an increase of 7.3% at 48 months in 15 patients with evaluable DXA data. Improvement in lumbar Z-scores observed after 52 weeks and 48 months respectively were 0.3 and 0.7%.

In Trial 2507, no conclusions can be drawn from BMD efficacy data. While positive trends were noted, percentage changes in total BMD and absolute changes in Z-scores in the lumbar spine did not reach statistical significance and the trial was not adequately powered to assess a meaningful difference in treatment effect on BMD. The restrictions of the 39 week Primary Analysis Period and bone exclusion criteria may be contributory.

In Trial 2607, BMD values for L1-L4 were within the normal range for the majority of patients upon study entry and were maintained over 52 weeks of treatment with both eliglustat and Cerezyme. There were insignificant differences in BMD (g/cm² and Z-scores) between both groups at Baseline and at Week 52, and minimal changes in both groups for these parameters at Week 52”. See the full review dated April 24, 2014.

Medical Reviewer's comments: This reviewer concurs with Dr. Stinson's assessment that while positive trends for BMD increase were noted in the Phase 2 trial and ENGAGE and no significant BMD difference between eliglustat and Cerezyme were found in ENCORE, there is uncertainty regarding the validity of BMD as an indicator for risk of skeletal complications in Gaucher Disease Type 1. The relationship between BMD and bone clinical outcomes such as fracture in GD Type 1 has not been established. There is no evidence that therapeutically increasing BMD in these patients reduces fracture risk or improves any other Type I GD-associated bone-related pathology.

Special Subgroups Analysis by CYP2D6 Metabolizer Status

The special subgroup population of clinical interest was the CYP2D6 metabolizer status at baseline (i.e., poor, intermediate, extensive, ultra-rapid, or unknown). The results of this subgroup analysis for the primary endpoint in both ENGAGE and ENCORE are presented within this section. The study participants for ENGAGE were primarily extensive metabolizers.

Table 10: Summary of Percentage Change from Baseline to Week 39 in Spleen Volume (MN) by Gender – ENGAGE

Timepoint/ Treatment Group	n	Mean	SD	Median	Min	Max
<i>Intermediate</i>						
Baseline Spleen Volume (MN)						
Eliglustat	1	5.94		5.94	5.9	5.9
Placebo	2	13.63	5.848	13.63	9.5	17.8
Week 39 Spleen Volume (MN)						
Eliglustat	1	4.12		4.12	4.1	4.1
Placebo	2	12.72	5.763	12.72	8.6	16.8
Absolute Change from Baseline to Week 39						
Eliglustat	1	-1.82		-1.82	-1.8	-1.8
Placebo	2	-0.91	0.0849	-0.91	-1.0	-0.9
% Change from Baseline to Week 39						
Eliglustat	1	-30.64		-30.64	-30.6	-30.6
Placebo	2	-7.21	2.475	-7.21	-9.0	-5.5
<i>Extensive</i>						
Baseline Spleen Volume (MN)						
Eliglustat	18	13.99	5.766	12.09	7.6	28.4
Placebo	18	12.37	6.125	11.05	6.3	25.3
Week 39 Spleen Volume (MN)						
Eliglustat	18	10.08	4.800	8.34	5.2	21.9
Placebo	18	12.86	6.615	10.97	6.6	26.2
Absolute Change from Baseline to Week 39						
Eliglustat	18	-3.91	2.439	-3.36	-9.1	0.0
Placebo	18	0.49	1.012	0.55	-1.8	2.3
% Change from Baseline to Week 39						
Eliglustat	18	-28.30	12.681	-29.03	-51.5	0.0
Placebo	18	3.10	8.630	4.86	-20.9	13.7
<i>Ultra-Rapid</i>						
Baseline Spleen Volume (MN)						
Eliglustat	1	20.16		20.16	20.2	20.2
Placebo	0					
Week 39 Spleen Volume (MN)						
Eliglustat	1	17.85		17.85	17.9	17.9
Placebo	0					
Absolute Change from Baseline to Week 39						
Eliglustat	1	-2.31		-2.31	-2.3	-2.3
Placebo	0					
% Change from Baseline to Week 39						
Eliglustat	1	-11.46		-11.46	-11.5	-11.5
Placebo	0					

From statistical review of Benjamin Vali, MS

Table 11: Summary of Proportion of Patients who were Stable at Week 52 by CYP2D6 Metabolizer Status – ENCORE (FAS)

Gender	Eliglustat (N = 106)	CEREZYME (N = 53)
<i>Poor</i>		
<i>n</i>	4	2
<i>n (%)</i>	3 (75.0%)	2 (100%)
<i>Intermediate</i>		
<i>n</i>	12	9
<i>n (%)</i>	8 (66.7%)	9 (100%)
<i>Extensive</i>		
<i>n</i>	84	38
<i>n (%)</i>	71 (84.5%)	34 (89.5%)
<i>Ultra-Rapid</i>		
<i>n</i>	4	1
<i>n (%)</i>	4 (100%)	1 (100%)
<i>Unknown</i>		
<i>n</i>	2	3
<i>n (%)</i>	1 (50.0%)	2 (66.7%)

Source: Benjamin Vali, Statistical Reviewer's Table.

Note: Denominators for percentages are n.

CDTL Comment:

This data appears to show that intermediate metabolizers (IMs) may not respond as well as extensive metabolizers; however the numbers of IMs is small and therefore conclusions cannot be made. In addition, the modeling for efficacy done by the clinical pharmacology team predicts adequate efficacy for this population. Therefore, I agree with the dosing recommendation for the IM population.

Safety

Safety Summary

The overall safety assessment of eliglustat in this population is favorable for approval. Exposures were adequate to assess safety considering the rarity of the disease. There were no deaths. The overall incidence of SAEs was 9%, with syncopal events reported in 5 patients (1%) 3 of which were thought to be treatment related by the investigators.

The major safety risk for eliglustat is the potential for QTc or PR interval prolongation. This risk is only likely to be clinically significant in scenarios of drug-drug interactions (CYP2D6 pathway) or overdose. Therefore, adequate information in the labeling and Medication Guide is necessary to avoid drug-drug combinations that could lead to high systemic exposures and the potential for cardiac arrhythmias.

Common adverse events reported for all eliglustat patients' were diarrhea 39 patients (10%), headache 66 patients (77%), dizziness 38 patients (10%), syncope 8 patients (2%), and arthralgia 55 patients (14%).

The potential for QTc or P-R interval prolongation with high systemic exposures prompted safety assessments for neurologic and cardiac events.

No sudden cardiac deaths, Torsade 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. This reviewer agrees with the Applicant's assignment of causality. 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 $\geq 25\%$. 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.

All cardiac arrhythmias deemed clinically significant by the investigator (first or second degree AV block) were detected either during scheduled Holter monitoring or extensive, routine ECG monitoring as required by the protocol. All cardiac arrhythmias were A-V nodal in origin (Atrioventricular block second degree [n=3]; Atrioventricular block first degree [n=1]) and none were associated with clinical symptoms. When reviewed by a cardiac adjudicator as well as a cardiologist serving on the DMC, none of the arrhythmias were considered clinically significant.

Safety Analysis

The clinical safety database supporting this application (pooled Eliglustat Safety Set) contains data from 393 patients with GD1 who received eliglustat in 4 Genzyme sponsored clinical studies as of the database cut-off date of 31 January 2013. This includes 26 patients treated for up to 4 years in the ongoing Phase 2 study (1-year Primary Analysis Period in addition to a 3-year follow-up period), 197 patients treated in the 2 ongoing, controlled Phase 3 studies: 40 patients in ENGAGE (treatment naïve patients), and 157 patients in ENCORE (patients

switching from ERT). Eliglustat safety data from both the Primary Analysis Periods and the Long-term Treatment Periods from ENGAGE and ENCORE up to the database cut-off date (31 January 2013) are included in the pooled Eliglustat Safety Set data.

As of 31 January 2013, 170 patients were enrolled in an ongoing double-blinded Phase 3b study (EDGE) comparing once daily (QD) with twice-daily (BID) administration of eliglustat. Safety data for 170 patients who received eliglustat in the open-label lead-in BID dosing period of this study as of the cut-off date are described separately and are also included in the pooled safety analysis.

For the pooled Eliglustat Safety Set, subgroup analyses of exposure duration by dose were performed by sex, race, age group, region, recent prior ERT exposure, CYP2D6 metabolizer status, and GD genotype categories.

Exposure

As January 31, 2013, the safety database included 393 patients with GD1 (treatment naïve or switching from imiglucerase or miglustat) who have received at least one dose of eliglustat 50 mg in phase 2 or phase 3 trials. Among these 393 patients, 349/393 patients (89%) received eliglustat for at least 6 months, 204/393 patients (52%) received eliglustat for at least 12 months, 62/393 patients (16%) have received eliglustat for at least 24 months, and 19/393 (5%) have received eliglustat for at least 60 months. The duration of eliglustat treatment has been between 0 and 36 months for 373/393 patients (95%).

In the pooled Eliglustat Safety Set, 319/393 patients (81%) received eliglustat 100 mg BID. 198 patients have been treated for at least 6 months, 81 patients have been treated for at least 12 months, 31 patients have been treated for at least 24 months, and 14 patients have been treated for at least 60 months.

A total of 391/393 patients (99%) received eliglustat 50 mg BID (Two patients did not receive 50 mg BID because they withdrew from the trial after receiving only one 50-mg dose). 67 patients have been treated for at least 6 months, 36 patients have been treated for at least 12 months, 10 patients have been treated for at least 24 months, and 3 patients have been treated for at least 60 months.

A total of 98/393 patients (25%) received eliglustat 150 mg BID. At 150 mg BID, 81 patients have been treated for at least 6 months, 57 patients have been treated for at least 12 months, and 16 patients have been treated for 24 to 36 months.

Table 12: Cumulative Eliglustat Exposure – Eliglustat Safety Set

Duration (months)	Eliglustat Dose		
	50 mg BID n (%)	100 mg BID n (%)	150 mg BID n (%)
>0 to <2	292 (74)	76 (19)	9 (2)
≥2 to <6	32 (8)	45 (11)	8 (2)
≥6 to <12	31 (8)	117 (30)	24 (6)
≥12 to <18	19 (5)	40 (10)	25 (6)
≥18 to <24	7 (2)	10 (3)	16 (4)
≥24 to <36	7 (2)	16 (4)	16 (4)
≥36 to <48	0	0	0
≥48 to <60	0	1 (0)	0
≥60 to <72	3 (1)	10 (3)	0
≥72 to <84	0	4 (1)	0
Total Patients (any duration)	391 ^a	319	98

Source: Applicant's table

Demographics

In the pooled Eliglustat Safety Set, 49% of patients were male and 51% were female. Most patients were White (82%), not of Jewish descent (78%), and not Hispanic or Latino (72%). The mean weight was 68.2 (±16.06) kg, and the mean BMI was 24.1 (±4.60) kg/m². Most patients (89%) were not current smokers. The mean age (± SD) was 37.1 (±14.40) years (range 16.6 to 75.1 years), and most patients were in the >30-65 year age group (58%) or the 16-30 year age group (40%). Ten patients (3%) were >65 years old. Two patients (< 1%) were <18 years old. Demographic characteristics were similar across the studies with a few exceptions.

Major Safety Results

The major safety results reviewed in this section are from the 4 clinical trials in GD1 patients. Overall, 334/393 of eliglustat-treated patients (85%) experienced a TEAE (2,340 events), the majority of patients had events which were considered not related to eliglustat treatment by the Investigators (312/334; 79%). Most of the TEAEs experienced were mild or moderate in severity (78% and 44% of patients, respectively). Forty-five patients (11%) experienced 68 TEAEs which were considered severe. A total of 35 patients (35/393; 9%) experienced 42 events that were treatment-emergent serious adverse events (SAEs), the majority of which were also considered not related to eliglustat treatment by the Investigators (31 patients [89%]; 36 SAEs). Five patients (1%) had SAEs that were considered related to eliglustat treatment.

Deaths

There were no deaths that occurred in the pooled Eliglustat Safety Set within the period covered by the ISS and as of the database cut-off date of 31 January 2013. Two deaths were reported in the Phase 1 clinical program while the patients were not taking eliglustat. Three additional deaths occurred, one in the Phase 2 study (occurring after study withdrawal) and two after the EDGE Lead-in Period. The MO agreed with the Applicant that the deaths were unrelated to study drug.

Nonfatal Serious Adverse Events

Serious adverse events were reported for 35/393 patients (9%) treated with eliglustat (42 events). By study, for patients in the pooled Eliglustat Safety Set, 4/26 (15%) patients in the Phase 2 Study experienced an SAE, 1/40 (3%) in ENGAGE, 18/157 (11%) in ENCORE, and 12/170 (7%) in EDGE. For the pooled Eliglustat Safety Set, there were no SOCs with > 2% of patients experiencing an SAE, and there was no single PT reported for >2% of patients.

The 3 most frequently affected SOCs for SAEs were Nervous system disorders (8/393 patients [2%]), Cardiac disorders (6/393 [2%]), and Injury, Poisoning and Procedural complications (6/393 [2%]). The most frequently reported SAE within the Nervous system disorders SOC was Syncope, experienced by 5 (1%) of eliglustat-treated patients. The syncopal events for 3 patients were considered related to eliglustat treatment (2 possibly related, 1 definitely related). The serious syncopal events occurring in the ENCORE study were vasovagal in nature with predisposing risk factors (i.e., blood draw, fasting conditions and pain), and none of these events led to permanent discontinuation from the study. Unscheduled ECGs, obtained as part of post-event diagnostic testing, did not reveal any cardiac arrhythmias as the potential cause for these syncopal events.

One patient (GZGD03109/32806) experienced a seizure requiring hospitalization and one (1) patient (GZGD03109/31610) experienced dizziness and a fall. Patient GZGD03109/34501 experienced an ischemic stroke which did not require hospitalization and was treated with medication.

In the Cardiac disorders SOC, 3 patients experienced Myocardial infarctions, and an additional patient had Acute myocardial infarction (PT; Verbatim term: non-ST-elevating myocardial infarction), all considered to be not related to study drug by the Investigators (Statistical Listing 6.4). The event of Myocardial infarction for Patient GZGD03109/34601 was updated by the Applicant to 'Angina' per follow-up information received from the investigational site after the database cut-off date. In all cases the patients had risk factors for these events.

One patient experienced Ventricular tachycardia (PT; Verbatim term: short run of ventricular tachycardia) on the first day of dosing while at the hospital and remained hospitalized to complete evaluation, and like all other ventricular tachycardia PTs reported in the Eliglustat Safety Set, was a case of non-sustained monomorphic ventricular tachycardia. This event was assessed as possibly related to treatment by the Investigator. An additional patient experienced atrioventricular block and atrioventricular block second degree that resulted in hospitalization for additional cardiac evaluations. This event was assessed as probably related to treatment by the investigator. Two patients had SAEs of neoplasms that required hospitalization and surgical treatment; both were considered not related to eliglustat treatment. Patient GZGD02607/7001 had a Hepatic neoplasm malignant, which was retrospectively identified as present at Baseline. Patient GZGD02607/5957 had a uterine leiomyoma, which is not a malignant finding.

Medical Reviewer's Comments:

A review of all SAEs narratives was conducted. The majority of SAEs were due to hospitalization for intercurrent illnesses (i.e., device malfunction, appendicitis, mammoplasty). After reviewing of narratives for cardiac and neurologic SAEs this reviewer agrees with the

Applicant's assessment of relationship of AEs to study drug for SOC Nervous system disorders and Cardiac disorders.

Dropouts and/or Discontinuations

In the pooled Eliglustat Safety Set, 393 patients received eliglustat treatment, and 92% were still receiving eliglustat as of the data cut-off date of 31 January 2013. Among the patients who discontinued eliglustat treatment, the most frequent reasons were AE (12 patients [3%]) and patient wished to withdraw (10 patients [3%]), followed by pregnancy (5 patients [1%]), "other" (5 patients [1%]), and noncompliance (<1%). For 3 of the patients whose reason for discontinuation was "other," the more specific reason was pregnancy; therefore, a total of 8 patients withdrew due to pregnancy. The number of discontinued patients was highest in the Phase 2 study

Significant Adverse Events

Because of results of TQT trial, cardiac and neurologic event, specifically syncopal episodes, dizziness and headache were considered medical events of interest and were further assessed.

Treatment Emergent Cardiac Arrhythmia Adverse Events by MedDRA High Level Term and Preferred Term by Study and Overall

Fifteen (15) of 393 patients in the pooled Eliglustat Safety Set reported cardiac arrhythmia events by HLT or HLT. The HLT in which events were most frequently reported included Cardiac conduction disorders (6/393 patients [1%]), Supraventricular arrhythmias (4/393 patients [1%]), and Ventricular arrhythmias and cardiac arrest (4/393 patients [1%]); one patient reported a TEAE in the HLT Rate and rhythm disorders not elsewhere classified (NEC). The TEAEs considered related to study drug by the investigators were: Atrioventricular block second degree (3/393 patients [1%]); Ventricular tachycardia (2/393 patients [1%]); and Supraventricular tachycardia (2/393 patients [1%]). One patient temporarily discontinued study drug but remained in the study (GZGD02507/4905; a dose adjustment was made afterward) and 2 patients (GZGD0304/0302 and GZGD0304/0202) withdrew from the study due to a cardiovascular event, and 6 patients (2%) experienced SAEs in the Cardiac disorders SOC.

Please see MO review by Karyn Berry MD for full details of cardiac adverse events review. All cardiac arrhythmias deemed clinically significant by the investigator (first or second degree AV block) were detected either during scheduled Holter monitoring or extensive, routine ECG monitoring as required by the protocol. All cardiac arrhythmias were A-V nodal in origin (Atrioventricular block second degree [n=3]; Atrioventricular block first degree [n=1]) and none were associated with clinical symptoms. When reviewed by a cardiac adjudicator as well as a cardiologist serving on the DMC, none of the arrhythmias were considered clinically significant.

Submission Specific Primary Safety Concerns

Submission specific primary safety concerns with this application include CYP2D6 metabolizer status and its relationship to drug-drug interactions and adverse events.

For the pooled Eliglustat Safety Set, subgroup analyses of exposure duration by dose were performed by CYP2D6 metabolizer status. Most patients were Extensive or Intermediate CYP2D6 metabolizers. The majority of patients in the Extensive Metabolizer group were

escalated to 100 mg BID doses, and approximately a third also were escalated to 150 mg BID. In the Intermediate Metabolizer group, approximately a third were also escalated to 100 mg BID and 1 was escalated to 150 mg BID.

Among the Ultra-Rapid Metabolizers (n=9), all were escalated to 100 mg BID and approximately two-thirds were also escalated to 150 mg BID. Among patients with Indeterminate Metabolizer status (n=5), 3 were escalated to 100 mg BID, and 1 was also escalated to 150 mg BID. The patients in the Poor Metabolizer group (n=14) received only eliglustat 50 mg BID and did not require dose escalation to achieve the target trough concentration.

Common Adverse Events

A total of 334 eliglustat-treated patients experienced 1 or more TEAE (334/393 patients, 85%). The 3 most frequently affected SOCs were Infections and infestations (184/393 patients [47%]), Gastrointestinal disorders (163/393 [41%]), and Nervous system disorders (126/393 patients [32%]). The most frequent TEAEs (those occurring in $\geq 10\%$ of all patients who received eliglustat) were: Headache (17%), Arthralgia (14%), Nasopharyngitis (13%), Upper respiratory tract infection (11%), Diarrhea (10%), and Dizziness (10%). Overall, TEAEs in the Cardiac SOC were reported for 41/393 (10%) of patients. Palpitations were reported for 20 patients (5%) and Syncope was reported for 8 patients (2%).

Medical Reviewer's Comments:

The most frequently affected SOCs observed in the pooled Eliglustat Safety Set were generally the same as those seen across the individual clinical studies (Phase 2, ENGAGE, and ENCORE). For all eliglustat patient's highest rates of AEs were the following: diarrhea 39 patients (10%); headache 66 patients (77%); dizziness 38 patients (10%); syncope 8 patients (2%); arthralgia 55 patients (14%).

Comparison to AEs reported in the Zavesca review: The most common AEs included GI-diarrhea 91%, flatulence 46%, abdominal pain 44%, nausea 19%, constipation 15% and vomiting 14%; Metabolic & Nutritional – weight decrease 70%; Central & Peripheral Nervous System – headache 36%; tremor 33%; dizziness 19%; paresthesia 13%; neuropathy 5%.

For 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 ($\geq 10\%$) 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 $\geq 10\%$ compared to Cerezyme rates were nausea (12% versus 0%), abdominal pain upper (10% versus 0%), headache (13% versus 2%), and fatigue (14% versus 2%).

Laboratory Findings

Hematology

For most hematology parameters, the majority of patients in the pooled Eliglustat Safety Set remained in the same category (low, normal, or high), and there did not appear to be a trend of worsening over time for any parameter. There was a shift in values for lymphocyte/leucocyte ratio. At Week 26, 5% had shifts from normal to low values for lymphocyte/leucocyte ratio and 12% had shifts from normal to high values. At Week 52, the proportion of patients with shifts from normal to high values had decreased (6%), and the proportion of patients with shifts from normal to low values was similar to that observed at Week 26 (5%). At Week 78, the proportions of patients with either shifts from normal to low values or normal to high values were similar (5% and 6%, respectively).

CDTL Comment:

These shifts in lymphocyte counts appear not to be clinically significant.

Chemistry

For most clinical chemistry parameters, the majority of patients in the pooled Eliglustat Safety Set remained in the same category (low, normal, or high), and there did not appear to be a tendency towards worsening values over time for any parameter. For most chemistry parameters, a majority of eliglustat-treated patients were in the normal category at Baseline and remained in the normal category through Week 104. Of the clinical chemistry parameters of interest (ALT, AST, GGT, total bilirubin, fasting glucose, CK, and cholesterol), there was only 1 notable shift from Baseline values. At Week 104, 11% of patients had shifts from normal to high values for fasting glucose.

Overall, there were no clinically meaningful changes in mean vital sign measurements from Baseline to any post-Baseline time point.

Electrocardiograms (ECGs)

Even though the applicant's TQT trial was a negative study as defined by ICH E14, eliglustat prolongs the QTc and PR intervals in a concentration dependent manner. Therefore, the Agency recommended that the Applicant conduct additional ECG monitoring and 24 hour Holter monitoring after multiple dose administrations at Tmax in Phase 2 and 3 trials. The effects of eliglustat on ECG parameters were assessed in adult GD1 patients after repeated dosing at 50, 100 or 150 mg twice a day during these trials.

With the exception of EDGE, all ECGs were centrally read by a core laboratory. EGDE had machine read ECGs.

Among the 389 patients treated with eliglustat and with ECG evaluations in the Phase 2 and 3 trials, 28 patients overall (7.2%) had presented, as of the January 31, 2013 cut-off date, at least one PR, QRS and/or QTcF PCSA leading to a safety narrative. The following incidences were observed in each trial: no patients in the Phase 2, 2 patients in ENGAGE (5.0% of the study population), 5 patients in ENCORE (3.2% of the study population), and 21 patients in EDGE (12.4% of the study population).

Two (2) patients had a new QTcF > 480 msec (QTcF > 480 msec post-Baseline and Baseline ≤ 480 msec), both in EDGE. Six (6) patients had a QTcF change from Baseline >60 msec, all also in EDGE. All QTcF liability cases came from the EDGE study and involved in all but 1 patient had 1 or 2 occurrences among multiple visits and 4 hour post-dose follow-up (corresponding to 4 time points) at each visit while in the setting of continued drug therapy.

Seven (7) patients overall treated with eliglustat met the PR outlier criterion (PR >200 msec and increase from Baseline ≥25%): no patients in the Phase 2 and ENGAGE studies up to cut-off date, 4 patients in ENCORE up to cut-off date (2.6% of the study population; all during the PAP, none during the extension period), and 3 patients in EDGE (2% of the study population). Apart from an ENCORE patient, none of these patients had any episodes of 2nd Degree or higher AV Block. An ENCORE patient who had elevated PR values during the entire study (highest reported PR interval at 568 msec; Baseline = 398 msec), had episodes of Mobitz I and 2:1 AV Block on the Week 13 Holter. The central reader considered this patient to have severe pre-existing AV conduction system disease, as evidenced by the extremely long Baseline PR interval, and judged unclear if eliglustat treatment contributed to further prolongation of the PR interval and episodes of AV block noted at Week 13.

Eighteen (18) patients overall treated with eliglustat had a QRS ≥120 msec: none in the Phase 2 up to cut-off date, 2 patients in ENGAGE up to cut-off date (5.0% of the study population), both with less than 25% increase from Baseline (in ENGAGE during the PAP and again during the extension period; and during the extension period only), 1 patient in ENCORE up to cut-off date (0.6% of the study population) with a less than 25% increase from Baseline (during the PAP and the extension as well), and 15 patients in EDGE Lead-In Period (8.8% of the study population). For ENCORE, the ECG review by the central reader revealed no significant change in QRS morphology and appeared to be of no clinical significance. These QRS values ≥120 msec represented a greater than 25% increase from Baseline in 4/18 (22%) of the patients in the EDGE trial.

Holter monitor findings across all patient trials (PAP and Long Term Treatment Periods) were reviewed. The findings were observed on Holter monitor and were not necessarily associated with an AE in the clinical database. No patient receiving eliglustat had any episodes of sustained ventricular tachycardia. Five (5) patients treated with eliglustat had non-sustained ventricular tachycardia (the longest ventricular run was of 7 beats). Some cases of non-sustained ventricular tachycardia were also observed during placebo and Cerezyme treatments and during the Screening/Baseline visit. Six patients had Mobitz I second degree atrioventricular block. No episodes of Mobitz II or higher degree heart block were documented in any patients treated with eliglustat.

Medical Reviewer's Comments:

The Phase 2 and Phase 3 trials included repeat dosing over an extended period of time. No sudden cardiac deaths, Torsade 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. This reviewer agrees with the Applicant's assignment of causality. 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 $\geq 25\%$. 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.

Thorough QTc Trial

The relationship between eliglustat plasma concentrations and electrocardiogram (ECG) parameters (e.g., QTc, PR, QRS, and/or heart rate [HR]) was investigated in a single dose thorough QTc (TQT) study in healthy subjects (GZGD01707), as well as in other clinical studies in healthy subjects and patients with Type 1 GD.

Under IND 67,589, the Applicant conducted a randomized, double-blinded, four-way crossover study, 47 subjects received Genz-112638 200 mg, Genz-112638 800 mg, placebo, and moxifloxacin 400 mg. Forty-two (42) subjects completed the study and were used in the analysis. The largest lower bound of the two-sided 90% CI for the $\Delta\Delta$ QTcF for moxifloxacin was greater than 5 ms. This study was reviewed by the Interdisciplinary Review Team (IRT) for QT Studies.

The IRT concluded that Genz-112638 increased the QTc and PR intervals in a dose- and concentration-dependent manner. For QTcF, the largest upper bounds of the 2-sided 90% CI for the mean difference between GENZ-112638 (200 mg and 800 mg) and placebo were below 10 ms, the threshold for regulatory concern as described in ICH E14 guidance. For PR, the largest upper limits of the 2-sided 90% CI for the mean difference between Genz-112638 (200 mg and 800 mg) and placebo were 5.8 ms and 16.4 ms, respectively. Two subjects whose baseline PR was under 200 ms experienced a maximum change of 18 ms. No patients had a QTcF ≥ 480 msec or a QTcF change from Baseline >60 msec. No patients met the PR outlier criterion (PR >200 msec and increase from Baseline $\geq 25\%$) or had a QRS ≥ 120 msec.

The IRT determined that even though the suprathreshold dose (800 mg) produced a geometric mean C_{max} value 14-fold higher than the geometric mean C_{max} for the therapeutic dose (200 mg), these concentrations may not be sufficient to cover the high clinical exposure scenario (e.g., drug interaction with CYP2D6 inhibitor, elderly, and hepatic impairment). They noted that data are not available to determine the impact of CYP2D6 phenotype status, metabolic inhibition with

CYP3A4 inhibitor, Pgp inhibition, hepatic impairment, and renal impairment on the exposure to Genz-112838.

At the time of submission of the NDA, the QT-IRT conducted further analysis with datasets of the TQT study. The results show no pro-arrhythmia risk at the predicted steady-state C_{max} achieved (44 ng/ml) for the GD1 patients with CYP2D6 phenotype. They note that QT_c, PR and QRS prolongation are expected at steady-state supratherapeutic scenario C_{max} (e.g., more than 10 ms mean change in QT_{cF} may be expected when mean C_{max} is higher than 250 ng/mL) (Table 1). The PR effect size is unlikely to be clinically meaningful in healthy subjects. In patients with pre-existing AV nodal disease and/or being co-administered agents that block the AV node, the PR prolongation may become clinically important. QRS effect size is not clinically meaningful in healthy subjects and probably not in patients. See full QT-IRT review dated February 5, 2009.

Medical Reviewer's Comments:

Though the result of the TQT study were "negative", eliglustat increased the QT_c and PR intervals in a concentration dependent manner. Based on the concentration QT relationship, there appears to be no QT_c related safety concerns for drug concentrations below 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.

Adverse event analysis by severity showed no clinically significant trends.

Dose Dependency for Adverse Events Analysis

A total of 334/393 patients (85%) experienced one or more TEAEs while receiving any dose of eliglustat. A lower proportion of patients experienced TEAEs while receiving the 50 mg BID dose (181/391 [46%]) or the 100 mg BID dose (225/319 [71%]) compared with those taking the 150 mg BID dose (78/98 [80%]).

Time Dependency for Adverse Events

Overall, the incidence of TEAEs decreased steadily over time relative to length of eliglustat treatment. The proportions of patients with TEAEs in the Infections and infestations, gastrointestinal disorders, musculoskeletal and connective tissue disorders, nervous system disorders, and cardiac disorders SOCs all decreased over time. The proportions of patients with PTs of Headache, Arthralgia, Nasopharyngitis, Upper respiratory tract infection, Diarrhea, and Dizziness also decreased over time.

The incidence of TEAEs considered related to eliglustat treatment also decreased steadily over time. Eliglustat-related events in the Gastrointestinal disorders, Musculoskeletal and Connective tissue disorders, Nervous system disorders, and Cardiac disorders SOCs decreased over time, similar to the pattern observed for all TEAEs. The incidence of the PTs Headache, Diarrhea, and Dizziness considered related to eliglustat treatment all decreased over time.

Subgroup analysis

There were no clinically significant trends in relation to age or gender by analysis of adverse events.

Drug-Disease Interactions

Dose level at the time of event and CYP2D6 metabolizer status

No increase in the overall incidence of TEAEs was seen for patients identified as Poor Metabolizers Eliglustat. (11/14 [79%]) compared with patients identified as Intermediate Metabolizers (36/49 [73%]). Both the Poor and Intermediate Metabolizer groups had a lower incidence of TEAEs than that observed for Extensive Metabolizers (272/310 patients [88%]). Low numbers of patients in the Ultra-Rapid and Indeterminate metabolizer status categories precluded meaningful comparisons for these groups.

TEAEs were tabulated by the patient's dose level at the time of the AE, not the highest dose achieved by the patient at any time during the study. For this reason, the same patient could appear in all 3 dose columns, as patients all started at 50 mg BID and could have titrated up to 100 mg BID and to 150 mg BID per protocol (Section 4). Importantly, a patient's dose also could be down titrated, i.e., they titrated up to a dose level of 150 mg BID but then subsequently had a dose reduction to 100 mg BID per protocol.

Drug-Drug Interactions

In vitro, CYP2D6 and to a lesser degree CYP3A4 are involved in eliglustat metabolism. Consequently, the use of strong and moderate CYP2D6 inhibitors or CYP3A inhibitors and CYP3A inducers during eliglustat treatment are of interest because these medications are known to alter the exposure of eliglustat.

In vitro, eliglustat is a substrate of the efflux transporter P-gp, but not of breast cancer resistance protein or the organic anion transport polypeptides (OATP1B1 and OATP1B3) uptake transporters.

In vivo, eliglustat was found to be an inhibitor of P-gp (1.49-fold increase in digoxin AUC_{0-last}) and a moderate inhibitor of CYP2D6 (2.09-fold in metoprolol AUC_{0-last}), consistent with in vitro data showing eliglustat to be a direct and time-dependent inhibitor of CYP2D6 and an inhibitor of P-gp. Eliglustat had no effect on ethinylestradiol and norethindrone exposure.

The use of QT prolonging medications during eliglustat treatment was also of interest. Therefore, the Phase 2 and Phase 3 trials had specific guidance to investigators on the management of such drug categories, including the allowed duration of treatment (i.e., temporary or chronic use) and administration according to CYP2D6 metabolizer phenotype. The guidance was revised during the course of the trials based on information from concurrent clinical DDI studies.

In the pooled Eliglustat Safety Set, 181/393 patients (46%) took at least 1 medication of special interest during eliglustat treatment. The most frequently used of these medications were QT prolonging medications (86/393 patients, 22%), weak CYP2D6 inhibitors (71/393 patients, 18%), and weak CYP3A inhibitors (95/393 patients, 24%).

CYP2D6 inhibitors were used by 79/393 patients (20%) during eliglustat treatment. Two moderate CYP2D6 inhibitors were used by 5/393 patients (1%); the moderate CYP2D6 inhibitors used were duloxetine hydrochloride (4/393, 1%) and terbinafine (1/393, <1%). The duration of use for the moderate inhibitors was not recorded. Strong CYP2D6 inhibitors were used by 11/393 patients (3%), and the most frequently used strong CYP2D6 inhibitor was bupropion or bupropion hydrochloride (7/393 [2%], combined). Among the patients who used strong CYP2D6 inhibitors, the duration of use was known for 2 patients. Two patients used paroxetine for >15 days: GZGD02607/1909 (01 Oct 2011 to 06 Feb 2012; 129 days), and GZGD03109/30804 (12 Jan 2011 to 08 Jan 2012; 362 days). Both patients were receiving eliglustat 50 mg BID,

In the pooled Eliglustat Safety Set, QT prolonging medications were used by 86/393 patients (22%) during eliglustat treatment. The most frequently used of these medications were azithromycin (17/393, 4%); ciprofloxacin (6/393, 2%); ondansetron (6/393, 2%); and clarithromycin, diphenhydramine hydrochloride, famotidine, levofloxacin, Medinite, pseudoephedrine hydrochloride, and Vicks Formula 44M (5/393, 1% each).

CDTL Comment:

There was no correlation with AR's with patients on CYP2D6 inhibitors, likely because eliglustat levels were monitored closely and dose adjustments were made during the trials.

Additional Safety Evaluations

Nerve conduction evaluations were performed in the Phase 2 study and the ENCORE Study. In the ENCORE study, 8 patients had TEAEs of Neuropathy peripheral or similar TEAEs (5 Neuropathy peripheral and 1 patient each Ulnar nerve injury, Sensory loss, and Decreased vibratory sense). The TEAEs were mild except 1 event of Neuropathy peripheral (moderate), all were nonserious, and 3 were considered by the Investigator to be possibly related to eliglustat treatment (Ulnar nerve injury, Neuropathy peripheral, Decreased vibratory sense).

As of the database cut-off of 31 January 2013, 4 patients in the Phase 2 study had TEAEs of abnormal nerve conduction studies; 2 of these patients also had other neuropathy TEAEs. One additional patient had a TEAE of Neuropathy peripheral reported through a neurological examination. 3 were considered by the Investigator to be possibly related to eliglustat treatment (2 Nerve conduction studies abnormal, 1 Neuropathy peripheral).

Human Reproduction and Pregnancy Data

Eliglustat has a Pregnancy category C, as does Zavesca. Previously, the Zavesca label carried a warning statement about male fertility based on studies in the rat suggested that miglustat may adversely affect male fertility. However, post-marketing human data failed to demonstrate effects on male fertility and this warning was removed from the Zavesca labeling.

No adequate and well-controlled clinical studies of eliglustat in pregnant or lactating women have been conducted; however, pregnancies have been reported in the Phase 2 and Phase 3 trials. As of the database cut-off date of 31 January 2013, the Applicant reported 10 pregnancies in 9 eliglustat-treated female patients and 7 pregnancies in female partners of 6 male patients. The female patient pregnancies have resulted in 2 live births, 3 elective terminations, 1 spontaneous

abortion, 1 tubal pregnancy, 1 in-utero death, and 2 unknown outcomes. The partner pregnancies have resulted in 4 live births, 1 spontaneous abortion, and 2 unknown outcomes.

In the Phase 2 trial, Patient 0503, a 27 year old, had two pregnancies while on eliglustat 100 mg bid. The patient was on eliglustat 100 mg BID. The first event was a spontaneous abortion at 4 weeks and the second pregnancy involved in-utero death at 37 weeks. During the second pregnancy, the patient had a fetal ultrasound at 29.6 weeks which was normal and had hypertension at 34 weeks which required hospitalization and treatment with methyldopa. Dr. Carol Kasten, the Maternal Health Team reviewer recommended label changes to the sections 8.1 Pregnancy and 8.3 Nursing Mothers based on her review.

Medical Reviewer's Comments:

The Applicant has reported all the spontaneous abortion seen in the narrative above as unrelated to the study drug. The Applicant has reported the in-utero death at 37 weeks also in the narrative above as unlikely related to study drug and the spontaneous abortion (x2) in female partner of male study patient who was on placebo as remote/unlikely related to study drug. From the narrative for the patient who was on eliglustat it is difficult to determine if the spontaneous abortion/in-utero death were related to eliglustat.

Overdose, Drug Abuse Potential, Withdrawal and Rebound

The Applicant reports that to date, there has been a single known occurrence of accidental eliglustat overdose in humans which occurred in the ENCORE trial. The patient (GZGD02607/2914) was a 20-year-old white woman receiving 150 mg eliglustat BID who inadvertently took 450 mg (150 mg capsules × 3) on a single occasion prior to the Week 52 blood draws. The observed C_{max} at Week 52 was 261 ng/mL, no AEs were noted at the Week 52 visit, and ECG results were normal. The only TEAE the patient experienced was vaginitis approximately one month prior to the Week 52 visit that was treated with metronidazole.

There have been no reports of patient abuse of or dependence on eliglustat. Nonclinical studies suggest that eliglustat has limited to no ability to cross the blood brain barrier.

No formal studies for withdrawal or rebound effects associated with eliglustat treatment have been conducted.

8. Advisory Committee Meeting

None

9. Pediatrics

The Drug was granted Orphan status and therefore is exempt from the requirement for pediatric drug development. (b) (4)

No patients under 16 years of age were included in the present eliglustat safety database. See also Section 12 - Risk Benefit Assessment.

10. Other Relevant Regulatory Issues

Submission Quality and Integrity

This was an electronic submission. The overall quality of the data submitted by the applicant was adequate for a comprehensive review of the data.

Compliance with Good Clinical Practices

The Applicant stated that the trials were conducted in accordance with Good Clinical Practice (GCP) as defined by the International Conference on Harmonization (ICH), the principles defined in the Declaration of Helsinki and its amendments, and all applicable national and international laws.

The Division of Scientific Investigations (DSI) was consulted to determine the reliability of data by evaluating clinical sites with most enrolled patients and sites that had unusually high responder rates. Site 49 of Study 2507 located in Tunis, Tunisia was identified as a site that enrolled a high number of subjects, six, but the FDA was unable to schedule an inspection of this site due to international safety concerns. Six clinical investigator sites and the sponsor were inspected. 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. See Susan Leibenhaut's, MD, full review dated May 15, 2014 for further details.

Financial Disclosures

While there were some financial payments to some of the investigators in the trials, their did not appear to be an impact on the integrity of the trials as there were no discrepancies in the conduct or the results of the trials noted by the MO.

11. Labeling

Extensive modifications were made to the applicant's original proposed labeling that included almost all sections of the initially proposed labeling. The two major areas of note were the (b) (4) and the inclusion of dosing modification recommendations for drug-drug interaction scenarios. Please see the discussion below in Section 13 – Risk Benefit Assessment.

12. Recommendations/Risk Benefit Assessment

- **Risk Benefit Assessment**

The overall assessment of this marketing application favors approval. Eliglustat, an SRT, appears to have similar efficacy to the comparator ERT (imiglucerase) and demonstrates superiority to placebo in a well-designed clinical trial. Eliglustat offers an advantage to patients in that all ERTs are intravenous and Eliglustat in an oral one or two times daily dose form. The only other oral medication for Gaucher Disease is Zavesca, an SRT that is restricted to patients intolerant to ERTs secondary to adverse events of peripheral neuropathy.

The applicant submitted the results from the ENGAGE and ENCORE trials to support the efficacy of CERDELGA (eliglustat), a novel substrate reduction therapy (SRT), for the treatment of Gaucher Disease Type 1 (GD1) in adult patients (the proposed indication). Overall, the designs of both the ENGAGE and ENCORE trials were deemed adequate from a statistical perspective for the proposed indication, and the applicant's corresponding statistical analysis plans deemed appropriate.

The Division had requested the applicant to perform the ENGAGE (treatment naïve patient's) as the primary efficacy trial against placebo. The applicant initially had difficulty enrolling in this trial and requested to allow submission of the ENCORE (previously treated patients) trial as the pivotal trial. However, the Division disagreed with this approach and subsequently the applicant was able to successfully able to enroll and complete the ENGAGE trial against placebo.

In the pivotal ENGAGE trial, eliglustat was demonstrated to be superior to placebo with respect to the Week 39 change from baseline in spleen volume, hemoglobin level, liver volume, and platelet count, respectively. The currently ongoing Open- Label Treatment Period suggests a sustained efficacy profile with respect to the aforementioned four parameters.

The key supportive ENCORE trial (in previously treated patients) demonstrated that patients who had reached therapeutic goals with enzyme replacement therapy (ERT) CEREZYME®, the most widely used ERT for treating adults with GD1, remained stable 52 weeks after switching to oral treatment with eliglustat. Stability in the composite endpoint, including hemoglobin and platelet values and spleen and liver volumes, was maintained after 52 weeks of treatment in 84% of patients in the eliglustat group and 94% in the Cerezyme group. The ongoing Long-Term Treatment Period suggests that this maintained clinical response is durable.

One issue pertaining to the ENCORE trial is 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. However, the results of each component of the composite endpoint, which show stability in spleen volume, liver volume, platelet count and Hemoglobin, support the efficacy of eliglustat. The ongoing long term trial results will be important in determining the long-term stability of Gaucher patients.

The safety of eliglustat was assessed by the review team and found to be acceptable with a relatively low incidence of serious adverse events. The major risk associate with this drug is the potential for QTc and PR interval prolongation with suprathapeutic systemic exposures. This risk is compounded by the potential for many drug-drug interactions. There were no clinically significant events of QTc interval prolongation reported in the clinical trials. However, the potential for high systemic exposures with the possibility of clinically significant cardiac arrhythmias will be present when this drug is used in the clinical setting. The team discussed the clinical implications of holding the eliglustat for short periods, during need for other medications such as some antibiotics and we felt that short term holing of eliglustat did not present a significant safety risk and was acceptable. To mitigate the risk for high systemic exposures and

the potential for cardiac arrhythmias, labeling for dose adjustment and holding the dose during use of some drug-drug combinations has been performed. In addition a medication guide has been developed to warn patients of the potential for cardiac adverse events with combined use of eliglustat with certain other medications. Because of the significant advantage to patients of an oral treatment, it was felt by the team that the potential cardiac risk from drug-drug interactions was acceptable.

There was no signal of peripheral neuropathy in the clinical trials however because of the history of this event with Zavesca, the other SRT approved for this indication. Post-marketing surveillance should include assessment for evidence of peripheral neuropathy.

A issue that complicated this review was that fact that the dosing for the clinical trials was based on adjustment of dose by trough level, however the dosing proposed for the labeling was a fixed dose of 84 mg of eliglustat two times daily in Extensive and Intermediate metabolizers (b) (4). The applicant has stated that the trough levels must be timed exactly with the dose to be accurate and they do not think that obtaining accurate levels will be practical in a clinical setting. After analysis of the data and discussions with the applicant, the review team has agreed with the applicant's proposal for a fixed dose (84 mg two times daily) in the Extensible and Intermediate Metabolizers. (b) (4) the review team also recommended a fixed dose regime (eliglustat tartrate 84 mg one time daily) for Poor Metabolizers. After discussion with the applicant and presentation of the data analysis the applicant agreed with the proposal for dosing in Poor Metabolizers.

A caution with the data analysis is the fact that the majority of the patients, both in the general population in the US and in the clinical trials are EMs, therefore the actual clinical data in the IMs and PMs is limited and the recommendation especially for PMs are based mostly on modeling.

The applicant has agreed to a post-marketing commitment to produce lower strength formulations of eliglustat which may improve the ability to dose populations with hepatic or renal impairment and to adjust doses for drug-drug interactions.

Another major issue with this review was the applicant's proposal to (b) (4). The team felt that appropriate PK/PD modeling could allow dose adjustments in many of the drug-drug inaction scenarios. Subsequently, after extensive analysis of the data by the clinical pharmacology team, and review of the data by the entire team, recommendations for drug-drug interaction dosing was proposed to the applicant. The applicant agreed with making recommendation for dose adjustments in drug-drug interaction scenarios; (b) (4) clinical pharmacology review team (b) (4) outlined separate recommendations for each genotype, EMs, IMs, and PMs. However, after further discussion and review of the data the applicant accepted the review team's proposals for separate recommendations for labeling for drug-drug interactions for each metabolizer status.

Another issue that complicated this review was the applicant's submission of new data that reassessed the metabolizer status in some patients late in the review cycle. Genzyme informed the Agency that CYP2D6 phenotypes in subjects genotyped by the (b) (4) were reclassified

after the original NDA submission to harmonize the data with phenotypes obtained from studies genotyped by (b) (4). As a result, the PK of eliglustat stratified by the CYP2D6 phenotype and the dose adjustment for various DDI scenarios were affected. This issue was first introduced by the sponsor at the late cycle meeting June 18th, 2014 and subsequently required review of the proposed reclassification of CYP2D6 phenotypes on healthy subjects, 2) the assessment of the impact of the reclassification on the characterizing eliglustat pharmacokinetics (PK) in CYP2D6 extensive metabolizers (EMs) and intermediate metabolizers (IMs), and subsequently dose adjustment of eliglustat in various drug-drug interaction (DDI) scenarios, (b) (4)

(b) (4) in the original Clinical Pharmacology Review. See the addendum to the Clinical Pharmacology Review in DARRTS by Elizabeth Shang, PhD.

Because this is an Orphan Indication the applicant is not required to perform pediatric trials, (b) (4)

(b) (4) There is significant risk for off label use of this drug in the older pediatric population at this time (b) (4)

(b) (4) There is no evidence at this time to conclude that there would be a safety issue in pediatric patients, (b) (4)

However, the overall risk vs. benefit evaluation for eliglustat in the population of Gaucher Disease type 1 favors the approval of this product with the changes to the labeling as agreed on by the sponsor.

- **Recommendation for Postmarketing Risk Evaluation and Management Strategies**
Routine post-marketing surveillance should include monitoring for adverse reactions as related to QcT and/or PR interval changes and other cardiac events. In addition, while there was no safety signal for peripheral neuropathy in this application, because of the peripheral neuropathy seen with Zavesca (miglustat), the other marketed SRT for this indication, surveillance should include monitoring of peripheral neuropathy.
- **Recommendation for other Postmarketing Requirements and Commitments**

PMR 1 Conduct a clinical study to evaluate the effects of hepatic impairment on eliglustat PK.

Final protocol submission:	June 2015
Study completion date:	January 2017
Final report submission:	July 2017

PMR 2 Conduct a study to evaluate the effect of renal impairment on eliglustat pharmacokinetics. A reduced design may be used.

Final protocol submission:	June 2015
Study completion date:	January 2017
Final report submission	July 2017

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 PK study in healthy subjects to characterize dose proportionality of 21, 42, and 84 mg dose strengths.

Final Report Submission: 12/2018

These PMC and PMRs were accepted by Genzyme.

- **Recommended Comments to Applicant**
None

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

/s/

LARA DIMICK-SANTOS
08/18/2014