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RESEARCH**

*APPLICATION NUMBER:*

**205494Orig1s000**

**MEDICAL REVIEW(S)**

## CLINICAL REVIEW

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Review Completion Date	August 15, 2014
Established Name	eliglustat tartrate
(Proposed) Trade Name	Cerdelga
Therapeutic Class	Substrate Reduction Therapy
Applicant	Genzyme
Formulation(s)	Oral
Dosing Regimen	84 mg capsule to be taken twice a day
Indication(s)	Long term treatment of adult patients with Type 1 Gaucher
Intended Population(s)	Adults with Type 1 Gaucher Disease who are intermediate or extensive CYP2D6

# metabolizers

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## 1 Recommendations/Risk Benefit Assessment

### 1.1 Recommendation on Regulatory Action

From the clinical standpoint, the submitted clinical data are adequate to support the recommendation of US marketing approval for CERDELGA for the indication of treatment of type 1 Gaucher disease in adult patients who are poor, intermediate or extensive CYP2D6 metabolizers at the recommended dose of 84 mg once a day (QD) for poor metabolizers (PM) and 84 mg twice a day (BID) for intermediate metabolizers (IM) and extensive metabolizers (EM).

There is sufficient evidence of efficacy based on two phase 3 trials (GZGD02507-ENGAGE, GZGD02607-ENCORE) and one phase 2 trial (GZGD00304) and safety based on three phase 3 trials (GZGD02507-ENGAGE, GZGD02607-ENCORE and GZGD03109 - EDGE) and one phase 2 trial (GZGD00304).

### 1.2 Risk Benefit Assessment

Review of the current application reveals that the benefit of Cerdelga (eliglustat tartrate) for the treatment of type 1 Gaucher disease in adult patients who are poor, intermediate or extensive CYP2D6 metabolizers outweighs the risk of Cerdelga in this patient population.

Treatment with Cerdelga appears to have resulted in clinically and statistically significant improvements in major clinical features of Type 1 Gaucher disease in adult patients. The efficacy data from the pivotal Phase 3 ENGAGE trial indicated that spleen volume, liver volume, hemoglobin count and platelet count parameters in treatment naïve type 1 Gaucher disease patients improved following treatment with eliglustat for 9 months. Data from the supportive Phase 3 ENCORE trial demonstrated that patients switched from imiglucerase to eliglustat maintained clinical stability for these parameters up through 52 weeks of treatment. The Applicant's Phase 2 trial also demonstrated improvements in organ volume and hematologic parameters.

(b) (4) Based on the observed data and PBPK predictions performed by reviewers in the Office of Clinical Pharmacology, it was determined that a 84 mg QD regimen will likely result in a exposure response that is not likely to result in QT related safety concerns. Therefore, the Agency has recommended a dosing regimen of 84 mg once daily (QD) for PMs. At the end of cycle review meeting, the Applicant agreed to include this dosing for PMs in the label.

Evidence of long-term efficacy is based on the efficacy results to date of the open label treatment period of ENGAGE, ENCORE and Phase 2 trial. The Applicant provided efficacy data for up to 78 weeks for 38 patients in the ENGAGE trial and efficacy data for up to 104 weeks for 143 patients in the ENCORE trial. Patients in the ENGAGE and ENCORE trials are can continue in their respective trials for a total of 6 years for ENGAGE and a total of 5.5 years for ENCORE. In the Phase 2 trial, 18 patients received Cerdelga for 4 years. Patients in all trials continued improving in all four efficacy parameters, spleen volume, liver volume, hemoglobin count and platelet count.

A key safety concern for Cerdelga is the potential for significant drug-drug interactions. Though the result of the TQT study were “negative” eliglustat increased the QTc and PR intervals in a concentration dependent manner. Based on the concentration QT relationship, there appears to be no QTc related safety concerns for drug concentrations below 250 ng/ml. PD/PK modeling suggests that there is a potential for prolongation at concentrations that could be achieved with significant drug-drug interactions. The Phase 2 and Phase 3 clinical trials had specific guidance to investigators regarding the management of concomitant medication use of CYP2D6 and CYP3A inhibitors during the trials, including allowed duration of treatment (i.e. temporary or chronic use) and adjustment of eliglustat dosing according to CYP2D6 phenotype. A review of the available adverse reaction data for CYP2D6 concomitant medication use did not identify any significant adverse reaction trends.

Drug-drug interactions and pre-existing cardiac disease, specifically AV nodal disease and long QT syndrome, will be important considerations in dosing patients to minimize the risk of adverse reactions. The potential for drug-drug interactions status will need to be clearly described in the product labeling.

Another concern discussed during the review of Cerdelga was assessing the need for an assay to measure drug concentration levels. Drug trough levels were used for drug dosing in the Phase 2 and Phase 3 clinical trials. In the clinical trials, dosing was titrated and adjusted based on drug concentrations lower or higher than 5 ng/mL. While sample sizes are limited, treatment naïve patients in study GZGD00304 with drug concentrations lower than 5 ng/ml showed clinically meaningful effects with respect to changes in spleen volume, liver volume and hemoglobin level. The Agency has determined that a 5 ng/mL concentration threshold may not be necessary for successful treatment. Therefore, measurement of drug concentration levels as was done in clinical trials is not required.

### 1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

The primary postmarketing risk to be managed is the potential for drug-drug interactions. Specifically, those interactions that have the potential to increase eliglustat plasma concentrations beyond what is expected at proposed doses. This risk can be mitigated through guidance in the drug label drug-drug interactions section and minimizing the use of concomitant medications with the potential to interact with Cerdelga.

An additional recommendation, specifically to educate and guide patients, is the use of a medication guide that cautions patients about drug-drug interactions and instructs them to discuss medications and supplements with their healthcare providers.

### 1.4 Recommendations for Postmarket Requirements and Commitments

The following are postmarket requirements and commitments to be conducted by the Applicant.

#### PMRs

Conduct a study to assess the impact of hepatic impairment on the eliglustat pharmacokinetics. Use the Child-Pugh classification to define the degree of hepatic impairment. (Eliglustat is substantially metabolized through CYP2D6 and CYP3A4 in the liver. Total combined recovery of unchanged eliglustat in the urine and feces was less than 1% in the mass balance study).

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

Conduct a dedicated study to assess the effect of renal impairment on eliglustat pharmacokinetics. A reduced design may be used. Renal function may be estimated by either Cockcroft-Gault equation or glomerular filtration rate (eGFR). PK study in subjects with moderate renal impairment may be needed if significant changes in systemic exposure of eliglustat in subjects with severe renal impairment are observed compared to those with normal renal function. Eliglustat is intended for chronic use. Renal impairment can inhibit some pathways of hepatic and gut drug metabolism and transport.

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

### PMC

Develop 21-mg and/or 42-mg dosage strength(s) to accommodate various situations requiring further dosage adjustments. Conduct a single- and multiple-dose pharmacokinetics study in healthy subjects to characterize dose proportionality of 21, 42, and 84 mg dose strengths. This is because both dosing regimens appear to be viable options for patients who are CYP2D6 PMs and may relax some restrictions on concomitant medications that are CYP3A inhibitors in these patients.

Final Report Submission: 12/18

## 2 Introduction and Regulatory Background

### A. Gaucher Disease

Gaucher disease is the most common of the lysosomal storage diseases. It is inherited as an autosomal recessive trait and is caused by a deficiency of  $\beta$ -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.<sup>1</sup>

Patients with type 2 and type 3 Gaucher disease have neurologic disease in addition to hematologic, visceral, and bone disease. Patients with type 2 Gaucher disease present with acute neurological deterioration; death usually occurs by two years of age. Neurologic findings include spasticity, head retraction, and oculomotor palsy. Type 3 disease typically follows a more subacute neurological course, with progression occurring over three to four decades. Neurologic findings include horizontal nuclear palsy, ataxia, dementia, and spasticity. The different types of Gaucher disease are summarized in [Table 1](#):

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<sup>1</sup> Cox TM, Aerts JMFG et al., Management of non-neuronopathic Gaucher disease with special reference to pregnancy, splenectomy, bisphosphonate therapy, use of biomarkers and bone disease monitoring, *J. Inherit Metab Dis* 2008; 31:319-336.

**Table 1: Clinical features of the three types of Gaucher disease**

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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).<sup>2</sup>

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. Although ERT and SRT are not approved in the US for treatment of neuronopathic Gaucher disease, current expert consensus treatment guidelines recommend ERT treatment for type 3 Gaucher patients with symptomatic hematologic and/or visceral disease (supportive care alone is recommended for type 2 Gaucher patients).<sup>3</sup> For patients with severe Gaucher disease, primarily those with chronic neurologic involvement (type 3 Gaucher), bone marrow transplantation can be of benefit. However, with the advent of ERT, bone marrow transplantation plays a limited role in the treatment of patients with type 1 Gaucher disease due to its high risk of morbidity and mortality. 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.

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2 Pastores GM, Barnett NL, Current and emerging therapies for the lysosomal storage disorders, *Expert Opin Emerging Drugs* 2005; 10(4):891-902.

3 Kaplan P, Baris H et al., Revised recommendations for the management of Gaucher disease in children, *Eur J Pediatr* 2013; 172(4): 447-458.

Prior to the availability of ERT, splenectomy was a common procedure to treat patients with massive splenomegaly and thrombocytopenia. Due to the effectiveness of ERT in the reduction of organomegaly, splenectomy is rarely indicated in treated patients.<sup>4</sup> Similarly, a majority of patients (90%) achieve normal hemoglobin levels within two years of initiation of ERT.<sup>5</sup> 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.

### **B. Natural History of Type 1 Gaucher Disease**

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 ( $P < 0.01$ ).<sup>6</sup> 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. However, 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.<sup>7</sup>

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4 Cox TM, Aerts JMFG et al., Management of non-neuronopathic Gaucher disease with special reference to pregnancy, splenectomy, bisphosphonate therapy, use of biomarkers and bone disease monitoring, *J Inherit Metab Dis* 2008; 31:319-36.

5 Weinreb NJ, Charrow J et al., Effectiveness of enzyme replacement therapy in 1028 patients with type 1 Gaucher disease after 2 to 5 years of treatment: a report from the Gaucher Registry. *Am J Med* 2002; 113: 112–9.

6 Ibid.

7 Weinreb NJ, Deegan P et al., Life expectancy in Gaucher disease type 1, *Am J Hematol* 2008;83:896-900.

### **Hematologic Effects**

Anemia and thrombocytopenia are almost universal in untreated Gaucher disease and may present together or separately in the course of the disease. The pattern of anemia and thrombocytopenia in Gaucher disease is dependent on the degree of splenic dysfunction. Thrombocytopenia is the most common peripheral blood abnormality in patients with Gaucher disease and may result from hypersplenism, splenic pooling of platelets, or marrow infiltration or infarction. Early in the course of the disease, it is usually due to splenic sequestration of platelets and responds to splenectomy. Later, replacement of the marrow by Gaucher cells may be more important etiologically in patients who have undergone splenectomy. Thrombocytopenia may be associated with easy bruising or overt bleeding, particularly with trauma, surgery, or pregnancy.

Anemia may result from hypersplenism. In advanced disease, decreased erythropoiesis is a result of bone marrow failure from Gaucher cell infiltration or medullary infarction. As a result, hemoglobin concentrations and platelet counts are routinely monitored in patients to determine disease burden. Leukopenia is rarely severe enough to require treatment.

### **Organomegaly**

Enlargement of the liver is a hallmark in Gaucher patients. In severe cases, the liver may fill the entire abdomen. Minor abnormalities of liver enzymes, consisting of increases in plasma transaminase and gammaglutyl transferase activities, are commonly present, even in mildly affected patients. Similarly, splenic enlargement is present in all but the most mildly affected patients with type 1 Gaucher disease. In patients who are otherwise asymptomatic, splenic enlargement is commonly the presenting sign. As with other diseases where splenomegaly occurs, splenic infarctions frequently result. In an analysis of 400 patients in the ICGG Gaucher Registry, 116 patients with data available prior to ERT had a mean enlargement of the spleen 19-fold normal. Liver and spleen size /volume are also routine measures of disease burden in patients. Changes over time in liver occur very slowly, with a slight downward trend in untreated patients with type 1 Gaucher disease.

### **Bone disease**

Bone involvement results in skeletal abnormalities and deformities (including osteonecrosis, lytic lesions, and fractures), bone pain crises, and is a frequent presenting feature of Gaucher disease in children. Of 1698 patient with Gaucher disease in the ICGG Gaucher Registry, 94% were reported to have radiological evidence of bone disease.<sup>8</sup> Bone marrow infiltration and splenic sequestration lead to clinically significant anemia and thrombocytopenia respectively. Bone disease occurs in 70-100% of patients with type 1 Gaucher disease and is the greatest source of morbidity and long-term disability. Bone pain and bone crises were reported by 63%

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<sup>8</sup> Pastores GM, Weinreb NJ et al., Therapeutic goals in the treatment of Gaucher disease, *Semin Hematol* 2004; 41: 4-14.

and 33% respectively in all Gaucher patients with available information from the ICGG Gaucher Registry. Bone disease may not correlate with the severity of hematologic or visceral involvement. Skeletal abnormalities secondary to bone disease contribute to the chronic growth failure observed in children with inadequately treated disease. The pathophysiology of bone abnormalities and bone pain in Gaucher patients has not been fully delineated and likely is multifactorial.<sup>9</sup>

### **Lung disease**

Only 1-2 % of type 1 Gaucher patients exhibit lung disease, which manifests as interstitial lung disease, pulmonary hypertension, or hepatopulmonary syndrome. Pulmonary hypertension is an important cause of early mortality in type 1 Gaucher disease; development of pulmonary hypertension may be prevented by avoidance of splenectomy. The spleen serves as the primary reservoir of Gaucher storage cells. Removal of the spleen promotes migration of storage cells to other tissue macrophage pools, including the lungs, liver, and bones. The pathophysiology of interstitial lung disease in Gaucher patients is unclear.<sup>10</sup>

### **C. Treatment**

Patients with GD1 have a partial deficiency in the activity of the lysosomal enzyme acidB-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  $\beta$ -glucosidase, which augments the deficient enzyme activity in patients and catabolises 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.

ERT requires regular intravenous (IV) infusions (generally every 2 weeks) for the duration of a patient's lifetime, and some patients are unable or unwilling to receive ERT. Adverse events associated with ERT include hypersensitivity and infusion-associated reactions (Cerezyme USPI and SmPC). 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).

### **2.1 Drug Product Information**

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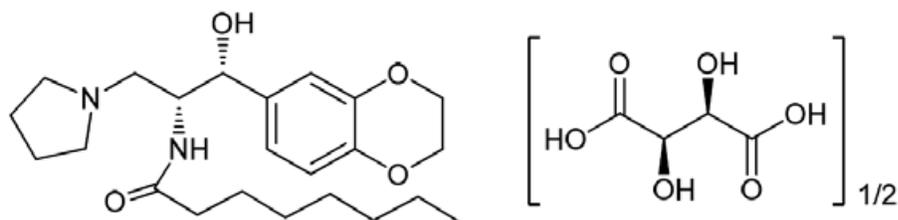
9 Mikosch P, Gaucher disease and bone, *Best Pract Res Clin Rheumatol* 2011; 25: 665-681.

10 Mistry PK, Sirrs S et al., Pulmonary hypertension in type 1 Gaucher's disease: genetic and epigenetic determinants of phenotype and response to therapy, *Mol Genet Metab* 2002; 77:91-98.

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  $\beta$ -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.

The chemical structure of eliglustat tartrate is shown in Figure 1.

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

**Proposed indication:** Long-term treatment of adult patients with Gaucher disease Type 1 who are CYP2D6 intermediate (IM) or extensive (EM) metabolizer phenotypes.

**Proposed aged groups:** Adults

**Dosing and Administration:** Proposed fixed oral dosing regimen of 84 mg (free base; equivalent to 100 mg tartrate salt) twice a day in patients who are CYP2D6 extensive metabolizers (EMs) or intermediate metabolizers (IMs).

## 2.2 Tables of Currently Available Treatments for Proposed Indications

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

<b>Enzyme replacement therapy (ERT) products</b>				
<b>Drug</b>	<b>Year Approved</b>	<b>Formulation</b>	<b>Indication</b>	<b>Dosage</b>
<b>Cerezyme</b> (imiglucerase)	1991	IV formulation of recombinant DNA using CHO cells culture	Long-term ERT for pediatric and adult patients with type 1 Gaucher with anemia, thrombocytopenia, bone disease, or hepatomegaly or splenomegaly	2.5 U/kg three times per week to 60 U/kg every two weeks
<b>VPRIV</b> (velaglucerase alfa)	2010	IV formulation of recombinant DNA using human fibroblast cells	Long-term ERT for pediatric and adult patients with type 1 Gaucher	60 Units/kg every other week
<b>Elelyso</b> (taliglucerase alfa)	2012	IV formulation of recombinant DNA using carrot cells	Long-term ERT for adult patients with type 1 Gaucher	60 Units/kg every other week
<b>Substrate reduction therapy (SRT) products</b>				
<b>Drug</b>	<b>Year Approved</b>	<b>Formulation</b>	<b>Indication</b>	<b>Dosage</b>
<b>Zavesca</b> (miglustat)	2003	Capsule for oral administration	Treatment of adult type 1 Gaucher patients for whom ERT is not an option.	100 mg three times daily

### **Cerezyme (imiglucerase)**

ERT has been commercially available for the treatment of type 1 Gaucher disease since 1991, when Ceredase (alglucerase), placentally-derived GCB, received approval as the first enzyme for the treatment of Gaucher disease. Cerezyme (imiglucerase), a recombinant product, received approval in the U.S. for the treatment of Gaucher

disease in 1994 and subsequently replaced Ceredase<sup>11</sup>. Warning information for Cerezyme includes hypersensitivity and anaphylactic reactions. There are also precautions related to pulmonary hypertension and pneumonia. The pregnancy category is C.

#### **VPRIV (velaglucerase alfa)**

Velaglucerase alfa was approved in February 2010 for the treatment of type 1 Gaucher disease. Velaglucerase is a human recombinant form of glucocerebrosidase and differs from Cerezyme by [REDACTED] (b) (4). Warning information for VPRIV includes hypersensitivity and anaphylactic reactions. The pregnancy category is B.

#### **ElELYso (taliglucerase alfa)**

Taliglucerase alfa was approved in May 2012 for the treatment of type 1 Gaucher disease. Taliglucerase is a plant-cell expressed recombinant form of glucocerebrosidase that differs from Cerezyme by [REDACTED] (b) (4). Warning information for ElELYso includes hypersensitivity and anaphylactic reactions. The pregnancy category is B.

#### **Zavesca (miglustat)**

Zavesca 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).

Zavesca is an inhibitor of the enzyme glucosylceramide synthase, which is a glucosyl transferase enzyme responsible for the first step in the synthesis of glucosylceramide and other glycosphingolipids. 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. Other common adverse events are: flatulence, abdominal pain, headache, and influenza-like symptoms. The pregnancy category is C.

### 2.3 Availability of Proposed Active Ingredient in the United States

There are currently three approved ERT products for type 1 Gaucher disease in the U.S.: Cerezyme (imiglucerase), ElELYso (taliglucerase) and VPRIV (velaglucerase). There is one approved SRT product approved in the US: Zavesca (miglustat).

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<sup>11</sup> In April 2012, the FDA approved a request by the manufacturer (Genzyme) to voluntarily withdraw Ceredase due to the product no longer being marketing. Genzyme is the manufacturer of Ceredase and Cerezyme.

## 2.4 Important Safety Issues With Consideration to Related Drugs

The labeling for Zavesca notes the following:

1. The most common serious AR reported with Zavesca was peripheral neuropathy. Label warning to perform baseline and follow-up neurological evaluations at 6 month intervals in all patients.
2. The most common AR requiring intervention were diarrhea and tremor. Label warning to reduce dose to ameliorate tremor or discontinue treatment if it doesn't resolve within days of dose reduction.

The labeling for Cerezyme notes the following:

1. Approximately 14% of patients experienced AEs related to Cerezyme administration.
2. Some of the AEs were related to the route of administration such as discomfort, pruritus, burning, swelling, or sterile abscess at the site of venipuncture (each reported in <1% of the patient population).
3. Anaphylactoid reaction has been reported in <1% of the patient population. Further treatment with imiglucerase should be conducted with caution. Most patients have successfully continued therapy after a reduction in rate of infusion and pretreatment with antihistamines and/or corticosteroids.
4. Symptoms suggestive of hypersensitivity (e.g., pruritus, flushing, urticaria, angioedema, chest discomfort, dyspnea, coughing, cyanosis, and hypotension) have been noted in approximately 6.6% of patients. (Onset of such symptoms has occurred during or shortly after infusions.)
5. Approximately 15% of patients treated and tested have developed IgG antibody to Cerezyme during the first year of therapy. Patients who developed IgG antibody did so largely within 6 months of treatment, and rarely developed antibodies to Cerezyme after 12 months of therapy.
6. Approximately 46% of patients with detectable IgG antibodies experienced symptoms of hypersensitivity. Patients with antibody to Cerezyme have a higher risk of hypersensitivity, but not all patients with symptoms of hypersensitivity have detectable IgG antibody.

The labeling for Ceredase also notes AEs related to route of administration, symptoms suggestive of hypersensitivity, and a higher risk of hypersensitivity reactions in patients

with antibody to Ceredase. As per the Ceredase labeling, approximately 13% of patients treated and tested developed antibody to Ceredase.

The labeling for VPRIV notes the following:

1. The most serious AEs in patients treated with VPRIV were hypersensitivity reactions.
2. The most commonly reported AEs were infusion reactions. Approximately 52% of treatment-naïve patients and 23% of patients previously treated with Cerezyme experienced infusion reactions.
3. Other AEs affecting more than one patient (>3% of treatment-naïve patients and >2% of patients switched from Cerezyme) were bone pain, tachycardia, rash, urticaria, flushing, hypertension, and hypotension.
4. Adverse reactions more commonly seen in pediatric patients compared to adult patients include (>10% difference): upper respiratory tract infection, rash, aPTT prolonged, and pyrexia.
5. 1 of 54 (2%) treatment-naïve patients treated with VPRIV developed IgG class antibodies to VPRIV. Antibodies were neutralizing in this patient. No infusion-related reactions were reported for this patient.
6. In treatment-naïve patients, onset of infusion-related reactions occurred mostly during the first 6 months of treatment and tended to occur less frequently with time.

The labeling for Elelyso notes the following:

1. The most commonly reported AEs were infusion reactions (44%-46% of patients).
2. Anaphylaxis has been observed in some patients treated with Elelyso.
3. One patient experienced a Type III immune-mediated skin reaction.
4. 17 of 32 (53%) treatment-naïve patients and 4 of 28 (14%) patient switched from imiglucerase developed IgG antibodies to Elelyso. Three patients (2 treatment-naïve patients and 1 patient switched from imiglucerase) developed neutralizing antibodies. There was no demonstrated association between positive neutralizing antibodies and therapeutic response for these patients.
5. Other AEs affecting 10% or greater of patients included upper respiratory tract infection/nasopharyngitis, pharyngitis, throat infection, headache, arthralgia, influenza/flu, upper urinary tract infection/pyelonephritis, back pain, and extremity pain.

## 2.5 Summary of Presubmission Regulatory Activity Related to Submission

### **May 21, 2013 (Type B Meeting-pre-NDA):**

Discussion on adequacy of the Applicant's current clinical and nonclinical data packages to support an NDA filing of eliglustat for the proposed indication in Gaucher disease.

### **February 17, 2012 (Type C Meeting):**

Applicant informed that eliglustat was determined to be a BCS Class 1 drug. Renal impairment on PK of eliglustat to be evaluated post-approval. Planned drug-drug interaction studies were reasonable. The Agency also recommended that the Applicant address drug-drug interaction potential of eliglustat with moderate CYP3A4 inhibitors and with moderate CYP2D6 inhibitors. Hepatic impairment PK study agreed to be conducted post-approval.

### **April 12, 2011 (Type C Meeting):**

Discussion of enrollment issues and proposed alternative NDA filing plans. The Division responded that the Applicant's proposal to use the ENCORE trial (active comparator) GZGD02607 as the pivotal registration and to submit the ENGAGE trial as a post marketing study due to enrollment issues was not acceptable. The Division recommended that ENGAGE trial be primarily relied upon to establish efficacy of the drug product and ENCORE data would be supportive. The Agency discussed concerns and recommendations related to: amendments to change entry criteria to allow enrollment of patients who are not clinically stable, selected non-inferiority margin of 25%,

### **February 5, 2009 (End of Phase 2 Meeting):**

Discussion of Phase 1 and Phase 2 data and planned Phase 3 trials. Division recommended that the Applicant submit a Special Protocol Assessment (SPA) for their proposed trial in patients currently not receiving treatment (GZGD02507) for review and concurrence before initiating trial. 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 Tmax in Phase 3 trials. Regarding Phase 3 trial endpoints, the Division did not agree with the (b) (4)

for trial GZGD02507. 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, 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 [REDACTED] (b) (4)

The Division also recommended that at least one Phase 3 trial be conducted in prior ERT treated patients and that both add –on-therapy and and switch therapy and the comparator arm which would be a continuation of ERT alone.

In addition, clinical pharmacology comments regarding drug-drug interaction were discussed with the Applicant.

**September 17, 2008:**

Eliglustat granted orphan designation for the indication of Gaucher Disease

**July 17, 2008 (Type C Meeting):**

Discussion of TQT study submission and development of clinical program.

The Applicant proposed that data collected from their current ongoing single dose TQT study in combination with cardiac data available from Phase 1 and Phase 2 trials will provide adequate cardiac safety profile to permit initiation of Phase 3 trials. The Agency responded that the data from the single dose TQT trial would need to be reviewed to assess adequacy. The Agency recommended that the Applicant not proceed with planned Phase 3 trials until this data has been reviewed.

**September 17, 2007 (Advice Letter):**

The Applicant was notified 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. In addition, Division recommended that patients currently receiving Genz-112638 in ongoing clinical studies should not be exposed to drugs known to prolong the QT interval and/or drugs that will increase serum concentrations of Genz-112638 and patients with a history of risk factors for torsade de pointes (TdP), such as long QT syndrome, baseline prolongation of the QT interval, hypokalemia, hypomagnesemia, left ventricular dysfunction, or heart failure (among others), should be excluded from studies of Genz-112638. The Division also recommended that the Applicant provide a cardiac safety evaluation by a specialist in electrophysiology on the relationship between Genz-112638 and the ventricular arrhythmias noted to date in the Genz-112638 clinical studies.

**July 7, 2006 (Advice Letter):**

The partial clinical hold was lifted.

**June 6, 2006 (Partial Clinical Hold):**

The Applicant's IND was placed on partial clinical hold for protocol GZG00304 (phase 2, open-label, multi-center trial evaluating the efficacy, safety and PK of Genz112638 in Type 1 Gaucher patients) due to insufficient information to assess risks to human subjects. The application was deficient for non-clinical toxicology data (9 month oral gavage study in dogs and an in vivo oral bone marrow cell micronucleus assay).

**December 15, 2005 (Type B Meeting- Pre-IND):**

Agency provided cardiology and non cardiology related recommendations to the Applicant, such as monitor heart rate and ECGs, standardization of ECG in regard to time of day (eg peak concentration time and not just trough), relationship to meals, exploration of effect of highest serum concentration on cardiac conduction and repolarization. Extensive neurological monitoring should be incorporated into Phase 2 and 3 trials.

**October 13, 2005:**

The Applicant was notified that due to an Agency re-organization, their application was transferred from the Division of Metabolism and Endocrinology to the Division of Gastroenterology

**January 29, 2004:**

The Agency reviewed the Initial protocol for IND 67,589 for Genz-112638 for the treatment of Gaucher Disease.

**December 15, 2003 (Type B, Pre-IND Meeting):**

The Applicant requested this meeting to provide the Agency with an overview of the clinical development plan for Genz 112638 and to obtain Agency input regarding selection of doses and subject monitoring in the Phase 1 program. Based on pre-clinical data, cardiology recommendations were conveyed to the Applicant. These included, monitoring of heart rate and ECGs, specifically PR, QRS and QTc intervals, standardizing ECGs and performing ECGs at peak concentration times and exploring effect of highest serum concentration on cardiac conduction.

2.6 Other Relevant Background Information

### 3 Ethics and Good Clinical Practices

3.1 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.

### 3.2 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 clinical trials ENGAGE and ENCORE were also registered on [clinicaltrials.gov](http://clinicaltrials.gov) under identification number NCT00891202 (ENGAGE), NCT00943111(ENCORE).

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 Dr. Susan Leibenhaut's full review dated May 15, 2014 for further details.

### 3.3 Financial Disclosures

Genzyme disclosed financial arrangements with 13 investigators (see [Table 3](#)). The Applicant reported that they were unable to obtain complete financial disclosure information for 7 clinical investigators. All other clinical investigators were reported as having no disclosable financial interest. Refer to Section 9.4.

**Table 3: Financial Disclosures**

Site/Investigator	Financial Compensation (Description)
(b) (6)	Received indirect, unrestricted award from Genzyme unrelated to this clinical trial Total amount not disclosed
(b) (6)	\$202,753 (Payments for an investigator sponsored study and honorarium)
(b) (6)	\$226,135 (Payments for honoraria and ISS)

Site/Investigator	Financial Compensation (Description)
(b) (6)	\$60,801 (Payments for honoraria and consultant fees)
	\$223,425 (Payments for honoraria and ISS)
	\$23,991 (Payments for honoraria)
	\$769,756 (Payments for honoraria and to (b) (6) for Pompe Disease) Additional \$1,239,632 to be paid by 2015
	\$34,555 (Payments for reigstry services, honoraria, etc.) \$951,700 (Payment to (b) (6) for study Gaucher Disease). Remaining amt of \$1,306,711 to be paid to (b) (6) in 2015
	\$6,570 (Payments for honoraria, registry, etc) \$39,142 (Payment to (b) (6) for ISS)
	\$128,750 (Payments for grants and honoraria)
	\$18,025 (Payment for honoraria, speaking, etc) \$1,160,767 (Payment to (b) (6) for Lysosomal Storage Disease for ISS – \$168,600 to be paid by 2014
	\$47,445 (Payments for honoraria, consults, registry)

Site/Investigator	Financial Compensation (Description)
(b) (6)	\$30,000 (Payment for honoraria)

**Medical Reviewer's comments:** *The financial arrangements do not appear to have impacted the integrity of the trials as there were no discrepancies in the conduct or results of the trials noted.*

## 4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

### 4.1 Chemistry Manufacturing and Controls

Eliglustat (Cerdelga) is a synthetic small molecule. Eliglustat tartrate is the (b) (4) Genz- 99067. Eliglustat tartrate contains two chiral centers, in addition to the salt chirality. Eliglustat is supplied as 84 mg hard gelatin capsules for oral administration. Each capsule contains eliglustat tartrate, microcrystalline cellulose, lactose monohydrate, hypromellose and glyceryl behenate (b) (4)

Eliglustat tartrate Drug Substance (DS) is a (b) (4) powder, which is highly soluble in water and meets the minimum dose-based solubility requirements for a BCS Class 1 compound ( $\geq 2$  mg/mL) at physiologic pH (pH =1.0, 4.5, 6.8 and 7.5) and 37 °C. The DS is soluble in methanol, methylene chloride and ethanol at concentrations greater than 40 mg/mL and slightly soluble (<5 mg/mL) in acetone, acetonitrile, 1,4-dioxane, ethyl acetate, isopropyl alcohol, tert-butyl methyl ether, tetrahydrofuran and toluene. The pH of eliglustat tartrate in a 2.5% wt/volume solution in water is 5.8-7.3. The pK of the free base (Genz-99067) was determined to be  $8.79 \pm 0.03$ .

The CMC review was conducted by Dr. Yichun Sun, Dr. Tarun Mehta and Dr. Hamid Shafiei. From CMC perspective the NDA is ready for approval.

See the full CMC review dated May 21, 2014 for further details.

### 4.2 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.

#### 4.3 Preclinical Pharmacology/Toxicology

##### Nonclinical Safety Assessment

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.

Eliglustat was shown to inhibit ( $IC_{50} = 10$  ng/mL) glucosylceramide synthase (GCS) in human K562 cells or human A375 cell-derived microsomes. In animal efficacy studies, eliglustat decreased GL-1 levels in peripheral tissues and plasma of normal rats and dogs following oral administration. In the D409V/null mouse model of GD1, eliglustat decreased the accumulation of GL-1 in tissues.

Eliglustat caused an inhibition of hERG channels expressed in HEK-293 cells with an  $IC_{50}$  value of  $0.35$   $\mu$ g/mL, indicating a potential to cause QT prolongation. Eliglustat also inhibited sodium and calcium channels with  $IC_{50}$  values of  $5.2$  and  $10.4$   $\mu$ g/mL.

The recommended human dose for eliglustat tartrate is  $100$  mg BID (free base: equivalent to  $84$  mg of eliglustat) or  $200$  mg/day ( $3.33$  mg/kg/day). The NOAEL in rats ( $50$  mg/kg/day) in the 6-month toxicity study was approximately 2.4 times the recommended human dose of  $100$  mg BID based on body surface area. The exposure (AUC) at the NOAEL of  $50$  mg/kg/day in rats is approximately 8 to 12 times higher than the mean predicted  $AUC_{0-12h}$  of  $307$  ng.hr/mL. The NOAEL in dogs ( $10$  mg/kg/day) in the 12-month toxicity study was approximately 1.6 times the recommended human dose of  $100$  mg BID based on body surface area. The exposure (AUC) at the NOAEL of  $10$  mg/kg/day in dogs is approximately 10 to 15 times higher than the mean predicted  $AUC_{0-12h}$  of  $307$  ng.hr/mL.

A 28-day oral study (GT-157-TX-28) was conducted in male rats to evaluate specific effects of Genz-112638 on male reproductive organs and spermatogenesis. No effects on sperm count or motility were seen at  $15$  and  $50$  mg/kg BID doses. A follow-up 4-week oral study (GT-157-TX-31) was conducted at  $36$  mg/kg BID ( $72$  mg/kg/day) in mature Cynomolgus monkeys to confirm the above effects of Genz-112638 on spermatogenesis in nonhuman primates. There were no significant treatment-related effects on any of the measured sperm parameters in this monkey study.

Reproduction studies were performed in pregnant rats at oral doses up to  $120$  mg/kg/day (about 6 times the recommended human dose based on body surface area) and in pregnant rabbits at oral doses up to  $100$  mg/kg/day (about 10 times the

recommended human dose based on body surface area). In rats, at 120 mg/kg/day (about 6 times the recommended human dose based on body surface area), eliglustat increased the number of late resorptions, dead fetuses and post implantation loss, reduced fetal body weight, and caused fetal visceral variations (dilated cerebral ventricles), fetal skeletal variations (poor bone ossification) and fetal skeletal malformations (abnormal number of ribs or lumbar vertebra). Eliglustat did not cause fetal harm in rabbits at oral doses up to 100 mg/kg/day (about 10 times the recommended human dose based on body surface area). In a pre and postnatal development study in rats, eliglustat did not show any significant adverse effects on pre and postnatal development at doses up to 100 mg/kg/day (about 5 times the recommended human dose based on body surface area).

Animal reproduction study with eliglustat in rats produced a spectrum of anomalies at doses 6 times the recommended human dose. No fetal harm was observed with oral administration of eliglustat to pregnant rabbits at dose levels 10 times the recommended human dose. The nonclinical reviewer therefore recommends a Pregnancy Category C for eliglustat. The drug should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

#### Carcinogenicity assessment

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

The Applicant conducted a 2-year carcinogenicity study in mice and a 2-year carcinogenicity study in rats. There were no drug related neoplastic findings in male or female mice/rats at any dose tested. Refer to Dr. King's full review dated April 15, 2014 for further details.

#### 4.4 Clinical Pharmacology

To support the approval of this NDA, the sponsor conducted a number of clinical pharmacology-related studies. A total of twenty-four in vitro studies were performed to facilitate the fundamental 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 also performed. Validated analytical methods were employed for assay of eliglustat concentrations in plasma and urine samples across studies.

The pharmacology review was conducted by the following primary reviewers.

OCP Reviewers: Elizabeth Shang, Ph.D. (Primary)  
Sandhya Apparaju, Ph.D. (In vitro study review)  
Pharmacometrics Reviewers: Anshu Marathe, Ph.D. & Justin Earp, Ph.D.  
GTT Reviewer: Sarah Dorff, Ph.D.  
PBPK Reviewer: Yuzhuo Pan, Ph.D.

Overall, the clinical pharmacologists found the application acceptable for approval. This approval though is based on 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; development of a 25 mg or 50 mg formulation for potential 50 mg QD or 25 mg BID dosing in PMs; and establishment of a safe and effective eliglustat dose for URM.

Refer to the full Clinical Pharmacology review dated June 16, 2014 for further details.

#### 4.4.1 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.

#### 4.4.2 Pharmacodynamics

##### Electrocardiographic Evaluation

QTc interval prolongation was studied in a double-blind, single dose, placebo- and positive-controlled crossover study in 42 healthy subjects. Concentration-related increases were observed for the placebo-corrected change from baseline in the PR, QRS, and QTc intervals. Based on PK/PD modeling, eliglustat plasma concentrations of about 490 ng/mL are predicted to cause mean (upper bound of the 95% one-sided confidence interval) increases in the PR, QRS, and QTcF intervals of 22 (26), 7 (10), and 13 (19) msec, respectively. At the highest geometric mean concentrations of 237 ng/mL following a single suprathreshold dose tested in the QT study, Cerdelga did not prolong the QT/QTc interval to any clinically relevant extent.

#### 4.4.3 Pharmacokinetics

Eliglustat PK is highly dependent on CYP2D6 phenotype. In CYP2D6 EMs and IMs, the eliglustat PK is time-dependent and the systemic exposure increases are more than proportional to dose. The PK of eliglustat in CYP2D6 PMs appears to be linear and time-independent.

### *Absorption*

Eliglustat is a highly permeable drug based on *in vitro* studies. Eliglustat exhibited high bidirectional permeability which was higher at all tested concentrations (12.5, 125, and 1250 $\mu$ M) than the internal high permeability standard labetalol. It is formally classified as a Biopharmaceutics Classification System (BCS) Class I drug. In CYP2D6 EMs, median time to reach maximum plasma concentration (T<sub>max</sub>) occurs between 1.5 to 2 hours following multiple doses of eliglustat tartrate 100 mg BID. In IMs and PMs, median T<sub>max</sub> occurs at 2 and 3 hours, respectively.

### *Food Effect*

Food does not have a clinically relevant effect on eliglustat PK.

### *Distribution*

Eliglustat is moderately bound to human plasma proteins (76 to 83%). Eliglustat exhibited low *in vitro* red blood cell partitioning. After intravenous (IV) administration in EMs, the volume of distribution of eliglustat was 835 L, suggesting wide distribution to tissues.

### *Metabolism & Elimination*

Eliglustat is a substrate for CYP2D6, CYP3A4 and P-glycoprotein transporter. Metabolism of eliglustat was predominantly mediated by CYP2D6 and to a lesser extent CYP3A4. Overall, more than ten metabolites of eliglustat have been identified, seven of which were formed via CYP2D6 in *in vitro* studies

The primary metabolic pathways of eliglustat involve sequential oxidation of the octanoyl moiety followed by oxidation of the 2,3-dihydro-1,4-benzodioxane moiety, or a combination of the two pathways, resulting in multiple oxidative metabolites. None of the identified metabolites are active against glucosylceramide synthase activity.

After oral administration of 100 mg [<sup>14</sup>C]-eliglustat, the majority of the administered dose is excreted in urine (41.8%) and feces (51.4%), mainly as metabolites. After 50 mg IV administration, mean eliglustat total body clearance was 88 L/hr in CYP2D6 EMs. Following multiple oral doses of 84 mg eliglustat BID, terminal elimination half-life (T<sub>1/2</sub>) was approximately 6.5 hours in EMs and 9 hours in PMs

**Table 4: Mean (CV%) of plasma PK parameters on Day 1 and at Week 52 (Phase 2, ENCORE) or Week 39 (ENGAGE) in patients who are CYP2D6 EMs.**

Study ID	Dose	50 mg	50 mg BID	100 mg BID	150 mg BID
Phase 2	Visit	Day 1	Week 52	Week 52	
	N	25	4	17	
	C <sub>max</sub> (ng/mL)	8.372 (71.17)	22.06 (50.61)	19.07 (57.52)	
	Median T <sub>max</sub> (hr)	1.5 [1, 4]	2.05 [1, 3]	2.9 [1, 3.1]	
	AUC <sub>tau</sub> (ng.hr/mL)	N/A	159.7 (44.05)	140.5 (63.17)*	
ENGAGE	Visit	Day 1	Week 39	Week 39	
	N	18	2	13	
	C <sub>max</sub> (ng/mL)	6.40 (96.2)	20.6 (15.1)	23.7 (76.3)	
	Median T <sub>max</sub> (hr) (Min - Max)	1.74 (0.92 - 4.00)	2.09 (2.00 - 2.17)	2.00 (1.00 - 4.00)	
	AUC <sub>tau</sub> (ng.hr/mL)	N/A	143 (6.92)	128 (85.7)	
ENCORE	Visit	Day 1	Week 52	Week 52	Week 52
	N	84	9	30	41
	C <sub>max</sub> (ng/mL)	6.03 (105)	26.8 (74.4)	35.1 (60.7)	38.1 (80.7)
	Median T <sub>max</sub> (hr) (Min - Max)	1.99 (0.70 - 4.58)	2.50 (1.00 - 4.07)	2.02 (1.00 - 4.08)	1.98 (0.98 - 4.00)
	AUC <sub>tau</sub> (ng.hr/mL)	N/A	214 (91.3)	201 (58.7)**	195 (64.3)***

\*N=16; \*\*N=29; \*\*\*N=40

Source: Clinical Pharmacology review

**Table 5: Mean (CV%) of plasma PK parameters on Day 1 and at Week 52 (ENCORE) or Week 39 (ENGAGE) in patients who are CYP2D6 IMs.**

Study ID	Dose	50 mg	50 mg BID	100 mg BID	150 mg BID
ENGAGE	Visit	Day 1	Week 39	Week 39	
	N	1	1		
	C <sub>max</sub> (ng/mL)	11.7	13.1		
	T <sub>max</sub> (hr)	2.00	2.08		
	AUC <sub>tau</sub> (ng.hr/mL)	N/A	87.1		
ENCORE	Visit	Day 1	Week 52	Week 52	Week 52
	N	12	5	4	1
	C <sub>max</sub> (ng/mL)	13.7 (69.9)	34.9 (23.2)	58.7 (55.7)	2.94
	Median T <sub>max</sub> (hr) (Min - Max)	2.00 (1.00 – 4.48)	2.00 (1.00 - 4.05)	1.51 (1.02 - 2.02)	3.00
	AUC <sub>tau</sub> (ng.hr/mL)	N/A	200 (27.1)	400 (71.6)	24.24

Source: Clinical Pharmacology review

**Table 6: Mean (CV%) of plasma PK parameters on Day 1 and at Week 52 (Phase 2, ENCORE) in patients who are CYP2D6 PMs.**

Study ID	Dose	50 mg	50 mg BID
	Visit	Day 1	Week 52
Phase 2	N	1	1
	C <sub>max</sub> (ng/mL)	22.41	40.13
	T <sub>max</sub> (hr)	1.5	2
	AUC <sub>tau</sub> (ng.hr/mL)	N/A	322.84
	AUC <sub>inf</sub> (ng.hr/mL)	271.86	--
	T <sub>1/2</sub> (hr)	9.32	–
ENCORE	N	4	4
	C <sub>max</sub> (ng/mL)	40.1 (33.3)	78.5 (48.9)
	Median T <sub>max</sub> (hr) (Min - Max)	3.51 (2.00 – 4.00)	3.00 (1.83 - 4.18)
	AUC <sub>tau</sub> (ng.hr/mL)	N/A	648 (35.6)

Source: Clinical Pharmacology Review

The pharmacology review team found the Applicant's proposed dose of eliglustat 100 mg BID acceptable in patients who are CYP2D6 IMs or EMs. They also found the proposed exclusion of CYP2D6 URM to be acceptable because at doses as high 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 pharmacology reviewers also note that the local safety, e.g. gastrointestinal tolerability and potential toxicity due to high metabolite concentrations at a higher dose, in order to match systemic exposures in URM to EMs or IMs, is unknown.

Eliglustat is primarily metabolized by CYP2D6 and, therefore, CYP2D6 genotype/phenotype greatly impacts the PK of eliglustat. Four key questions addressed by the pharmacology review team during the review of this NDA were:

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?
2. Can the Agency recommend a dose for patients who are CYP2D6 PMs?
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?
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 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 (as was done in clinical trials). 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. The patients in ENGAGE and Phase 2 study were treated successfully at doses of 100 mg BID or lower.

Office of Clinical Pharmacology recommended a dosing regimen of 100 mg once daily (QD) for PMs. The Applicant 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<sub>max</sub> compared to EMs, and 2-to 3-fold higher AUC and C<sub>max</sub> 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, clinical pharmacology reviewers determined that a 100 mg QD regimen will likely result in a C<sub>max</sub> 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<sub>max</sub> of 250 ng/mL, the mean (upper 90% CI) of  $\Delta\Delta\text{QTcF}$  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.

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. On the other hand, eliglustat does not appear to have a narrow therapeutic index in view of the current safety database.

Based on clinical and clinical pharmacology team discussions, no major safety concerns were identified for eliglustat in Phase 2 and Phase 3 trials. 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. Thus exposures achieved in the Phase 2 and Phase 3 trials were considered safe. Including the available exposure data from the ongoing phase 3b (EDGE) study, the highest individual exposure (AUC<sub>0-24h</sub>) achieved was 1984 ng×hr/mL, with 20 patients with AUC<sub>0-24h</sub> > 800 ng×hr/mL and 7 patients with AUC<sub>0-24h</sub> > 1100 ng×hr/mL. The mean AUC<sub>0-24h</sub> 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 would be acceptable in patients. The review teams 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<sub>0-24h</sub> of 1100 ng×hr/mL also served 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 variabilities in PK parameters.

In clinical trials 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 and ultra rapid 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 provisionally 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. Refer to the CDRH review.

Postmarketing requirements/commitments recommended by the Office of Clinical Pharmacology are:

- Conduct a study to assess the impact of hepatic impairment on the eliglustat PK. Use the Child-Pugh classification to define the degree of hepatic impairment. Eliglustat is almost exclusively eliminated through metabolism via CYP2D6 and CYP3A4 in the liver. A hepatic impairment study can inform appropriate dosing in these patients.
- Conduct a dedicated study to assess the effect of renal impairment on eliglustat PK. A reduced design may be used. Renal function may be estimated by either Cockcroft-Gault equation or estimated glomerular filtration rate (eGFR) from the Modification of Diet in Renal Disease (MDRD) Study. PK study in subjects with moderate renal impairment may be needed if significant changes in systemic exposure of eliglustat in subjects with severe renal impairment are observed compared to those with normal renal function. Eliglustat is intended for chronic use. Although eliglustat is minimally eliminated through renal excretion, a renal impairment study is necessary because renal impairment can indirectly impact drug metabolism.
- Develop a 25- or 50-mg strength of the product for 50 mg QD or 25 mg BID dosing in CYP2D6 poor metabolizers and addressing dose adjustment in drug interactions. This is because both dosing regimens appear to be viable options for patients who are CYP2D6 PMs and a lower strength will allow removal of some restrictions on concomitant medications in patients of various CYP2D6 phenotypes.
- A safe and effective dose of eliglustat has not been determined for patients who are CYP2D6 URM. A possible PMC to establish appropriate dosing regimen or dosing approach is under discussion. If such a PMC is determined to be necessary at a later time, the review will be amended in this regard.

#### *Exposure-Response*

There is a trend for increase in response (decline in spleen and liver volume from baseline, increase in hemoglobin levels and platelet count from baseline) with increasing steady state average trough concentrations of the drug as evidenced in treatment naïve subjects in both Phase 2 (GZGD00304) and ENGAGE study. However, for treatment experienced patients (who were switched from ERT to eliglustat), there was no clinically relevant E-R relationship observed.

#### *Measuring drug concentration and maintaining patients above 5 ng/mL*

In the Phase 3 and Phase 2 clinical trials, dosing was titrated and adjusted based on drug concentrations lower or higher than 5 ng/mL. OCP has determined that a 5 ng/mL concentration threshold may not be necessary for successful treatment. While sample sizes are limited, treatment naïve patients in study GZGD00304 with drug concentrations lower than 5 ng/ml showed clinically meaningful effects with respect to changes in spleen volume, liver volume and hemoglobin level (for details see Pharmacometrics review).

For subjects with drug concentrations lower than 5 ng/ml, the spleen volume decreased from 12.3 MN at baseline to 5.3 MN after 4 years of treatment. For subjects with drug concentrations greater than 5 ng/ml, the spleen volume decreased from 20.5 MN at baseline to 6.6 MN., The spleen volumes were comparable after 4 years. For subjects with drug concentrations lower and greater than 5 ng/ml, the liver volume was 1.1 MN and 1.2 MN respectively after 4 years of treatment. The hemoglobin levels in the two groups were 13.5 and 13.6 g/dL. While the platelet count did not achieve normal levels and were lower in the <5 ng/ml group (106x10<sup>9</sup>/L) compared to ≥5 ng/mL group (139x10<sup>9</sup>/L), the value in the lower concentration group were above the threshold of clinical concern.

*QTc evaluation*

There was a concentration dependent increase in QTc. An increase in  $\Delta\Delta$  QTcF is observed with increasing drug concentration. The mean (upper 90% CI) predicted  $\Delta\Delta$ QTcF at the mean C<sub>max</sub> of 16.7 ng/ml and 237 ng/ml for the 200 mg and 800 mg doses achieved in the QT study are 0.18 (1.7) ms and 6.06 (8.9) ms. For a C<sub>max</sub> 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 (Table 9). Thus based on the concentration-QT relationship, clinical pharmacology reviewers identified no QT related safety concerns for drug concentrations below 250 ng/mL.

**Table 7: Predicted change of  $\Delta\Delta$ QTcF interval at geometric mean C<sub>max</sub> of eliglustat observed in the thorough QT study**

Dose Group	Predicted change in $\Delta\Delta$ QTcF interval (ms)	
	Mean	90% Confidence Interval
<b>200 mg Genz-112638</b>		
Geometric Mean C <sub>max</sub> (16.7 ng/mL)	0.176	(-1.35; 1.7)
<b>800 mg Genz-112638</b>		
Geometric Mean C <sub>max</sub> (237 ng/mL)	6.06	(3.24; 8.88)

Source: Clinical Pharmacology review

**Table 8: Predicted QT prolongation at the steady state mean Cmax of 250 ng/mL**

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

Source: Clinical Pharmacology review

#### *Intrinsic Factors*

Based on population PK analysis there was no effect on age, sex, race or weight and thus no dose adjustment is needed. Population PK analysis comprised of 59% males and 41% females. The PopPK analysis included 65% Caucasians, 9% African-Americans, 9% Jewish, 7% Hispanics, 7% Asians, and 3% others. Population PK included body weights ranging from 41 to 136 kg.

For disease, subject status (healthy versus GD1 patients) was identified as a covariate on clearance and volume. CL and Vc were 1.95 and 1.71 times higher in healthy subjects than in patients.

Creatinine clearance was not identified as a covariate on clearance. Figure 12 shows that the inter-individual variability in clearance cannot be explained creatinine clearance. The lowest value of creatinine clearance included in the analysis was 47 mL/min. There were no subjects in the severe renal impairment category

#### 4.5 Division of Bone, Reproductive and Urologic Products (DBRUP)

(b) (4)

From Dr. Stinson's review, "The single-arm phase 2 study 0304 showed a 4.4 % increase in lumbar L1-L4 BMD (g/cm<sup>2</sup>) 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/cm<sup>2</sup> 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's 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.***

## 5 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 2 trial, ENGAGE and ENCORE have completed their primary analysis periods (PAPS), and have ongoing long-term treatment periods. The ongoing Phase 3b trial (EDGE) provides only additional safety data for this review. The Applicant has not submitted efficacy data for the EDGE trial for this review cycle.

Table 9 below summarizes the primary studies used in the review of this NDA to evaluate the efficacy and safety of eliglustat. GZGD02507 (ENGAGE) was the pivotal efficacy trial and GZGD02607 (ENCORE) and Phase 2 trial (GZGD00304) were submitted as supportive trials for this NDA for the indication of long-term treatment of adult patients with Gaucher disease type 1 (GD1). While trial GZGD03109 (EDGE) is an ongoing long-term safety and efficacy trial, the Applicant has only submitted lead-in safety data for this trial. To date, no pediatric patients < 16 years of age have been enrolled in any of the clinical trials.

**5.1 Table 9: Studies/Clinical Trials**

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

Reviewer' table

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

## 5.2 Review Strategy

A review of the pivotal trial GZGD02507 (ENGAGE) and the other supportive trials GZGD02607 (ENCORE) and Phase 2 trial (GZGD00304) was performed using the Applicant's submitted data. Each trial was reviewed individually by the medical reviewer and compared to the results reported in the sponsor's safety and efficacy reports.

The sources of clinical data used in this review are the results of the submitted clinical trials, with emphasis on the protocols and clinical trial reports, supporting eliglustat for the long-term treatment of adult patients with Gaucher disease type 1.

Other sources of clinical data consulted in this review include:

- Electronic submission of the medical section of the NDA (including narratives and case report forms)
- Electronic submitted data sets
- Literature review

## 5.3 Discussion of Individual Studies/Clinical Trials

This section discusses trial design and efficacy results for two Phase 3 trials and one Phase 2 trial reviewed in this submission. No efficacy data was provided for EDGE trial. Only safety data was provided and this data is discussed in Section 7.

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.

## 5.4 GZGD02507 (ENGAGE) – Phase 3 Treatment Naïve Patients

### A. General Design and Objectives

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  $\geq 16$  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 ( $\leq 20$  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.

## **B. Inclusion Criteria/Exclusion Criteria**

The study 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.

Eligibility criteria included the following:

- Age  $\geq 16$  years at the time of randomization.
- Tanner Stage  $\geq 4$  prior to randomization.

- Diagnosis of GD1 confirmed by a documented deficiency of acid  $\beta$ -glucosidase activity by enzyme assay.
- Symptoms of Gaucher disease present during the Screening period, including:
  - Hemoglobin level of 8.0 to 11.0 g/dL (females) or 8.0 to 12.0 g/dL (males) AND/OR platelet count of 50,000 to 130,000/mm<sup>3</sup>, based on the mean of 2 Screening measurements obtained at least 24 hours apart.
  - Splenomegaly, defined as a spleen volume of 6 to 30 MN.
  - If hepatomegaly was present, liver volume <2.5 MN.
- Consented to provide a blood sample for genotyping for Gaucher disease, chitotriosidase, and CYP2D6, if these genotyping results were not already available.
- No treatment with substrate reduction therapy within 6 months prior to randomization or enzyme replacement therapy within 9 months prior to randomization.
- No treatment with any of the following medications within 30 days prior to randomization:
  - Investigational products
  - Medications that may cause QTc interval prolongation
  - Inducers of CYP3A4
  - Strong inhibitors of CYP3A4, if the patient was a CYP2D6 poor metabolizer or an indeterminate metabolizer with neither allele known to be active.
  - Strong inhibitors of CYP3A4 or CYP2D6, if the patient was not a CYP2D6 poor or indeterminate metabolizer, except where a patient had chronically received either medication (but not both) for at least 30 days prior to randomization and was continuing the same dosing regimen during the primary analysis period of this study.
- No history of splenectomy (partial or total), no evidence of neurologic or pulmonary involvement related to Gaucher disease, and no current symptomatic bone disease and no bone crises within 12 months prior to randomization.
- The patient was not transfusion-dependent, and did not have anemia from causes other than Gaucher disease that was untreated or not stabilized on treatment within 3 months prior to randomization.
- No documented prior esophageal varices or liver infarction, and no current results for alanine aminotransferase (ALT), aspartate aminotransferase (AST) and total bilirubin >2 times the upper limit of normal, unless the patient had a diagnosis of Gilbert Syndrome.

### C. Primary Endpoints

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

## D. Secondary Endpoints

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.

## E. Tertiary and Exploratory Endpoints

Additional tertiary and exploratory efficacy endpoints included percentage changes in disease-related biomarkers (chitotriosidase and chemokine CC motif ligand 18[CCL181], spine and femur total BMD, and exploratory biomarkers (glucosylceramid [GL-1] in dried blood spot [DSB] and GL-1, GM3, macrophage inflammatory protein 1 beta [MIP-1 $\beta$ ], ceramide, and sphingomyelin in plasma), and absolute changes in spine and femur T- and Z- scores, spine, femur and total BMB scores, Gaucher disease assessments (mobility, bone crisis, and bone pain), quality of life scores (brief pain inventory [BPI], fatigue severity scale [FSS], 36 item short form health survey [SF-36], and Gaucher disease severity scoring system [DS3] scores from Baseline to Week 39.

## F. Overall Endpoint Assessment Spleen and Liver Volume by MRI

MRI scans 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.

## Platelet count and Hemoglobin level

At selected time-points, blood samples were collected at least 24 hours apart and the average of the 2 platelet counts was used in the study analyses. In the event that a

patient was missing one of two assessments at a particular time-point, then the single assessment was used in the analyses.

All patients were assessed for hemoglobin variant at Screening to rule out confounding conditions of thalassemia or sickle cell disease as a cause for anemia.

### **Bone**

Dual energy X-ray Absorptiometry (DXA): Images of the spine and bilateral femur were obtained to determine T-scores and Z-scores for each bone area, and total bone mineral density (BMD).

Bone marrow burden (BMB) score: BMB score was calculated by summing 6 MRI based scores for the lumbar spine and femur.

MRI: Coronal T1 and T2 weighted images of the entire bilateral femur and sagittal T-1 and T-2 weighted images of the lumbar spine were evaluated at baseline for dark marrow, infarctions and lytic lesions in 6 anatomical zones.

X-ray: A lateral view of the spine, including the entire cervical spine, was evaluated at Baseline for evidence of lytic lesions, infarctions, and fractures.

Gaucher Disease assessments included the following:

Mobility: The patient's current mobility status was recorded

Bone pain: The severity of the patient's bone pain was assessed, "How would you rate your bone pain during the last 4 weeks.

Bone crisis: The number of bone crises since the previous visit was recorded. A bone crisis was defined as bone pain with acute onset requiring immobilization of the affected area, narcotics for pain relief, and possibly accompanied by periosteal elevation, an elevated white blood cell count, fever and/or debilitation of > 3 days.

### **G. Treatment**

#### 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  $\geq 5$  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 Genz-99067 trough concentration  $\geq 5$  ng/mL at Week 41 continued to receive 50 mg BID and patients who had a Genz-99067 trough concentration  $< 5$  ng/mL at Week 41 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  $\geq 5$  ng/mL at Week 45 continued to receive their same dose of eliglustat and patients who had a Genz-99067 trough concentration  $< 5$  ng/mL at Week 45 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  $\geq 150$  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 are also being permitted in the event of poor tolerability, and are managed in consultation with the Sponsor and, as appropriate, the DMC.

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

#### Selection and Timing of Dose for Each Patient

A starting dose of 50 mg (per dosing occasion) was administered to all patients randomized to eliglustat in the Primary Analysis Period and all patients initiating open-label eliglustat therapy in the Long-term Treatment Period. The dose of eliglustat was

escalated in individual patients based on observed trough plasma concentrations of Genz-99067, The BID doses were administered approximately 12 hours apart.

#### **H. Prior Medications**

Information on all prior medications and therapies taken within 30 days prior to informed consent and any prior use of ERT, SRT, or pharmacological chaperone therapies was recorded in the eCRF.

Twenty-two (55%) patients were receiving 1 or more medications prior 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.

Four patients were known to be receiving supplements for folic acid, vitamin B-12, and/or iron deficiency at study entry. Three of these patients continued to receive supplementation with folic acid (#0102, eliglustat), ferrous sulfate and vitamin B-12 (#0901, eliglustat) or ferrous sulfate (#3301, placebo) during treatment in the study. A few additional patients were receiving multivitamins or vitamin complexes that are likely to have included vitamin B-12, folic acid, and/or iron; however, due to limitations of the concomitant medication reporting, the Applicant stated that it was not possible to determine the precise number of these patients who were receiving each specific supplement or the quantity received.

Five patients had received prior ERT with alglucerase or imiglucerase, including two patients randomized to eliglustat and three patients randomized to placebo. Four of the 5 patients had also received prior treatment with miglustat. As required by protocol, all patients discontinued treatment with ERT and miglustat at least 9 months and 6 months, respectively, prior to initiation of treatment in this study.

One patient was receiving bisphosphonate therapy (alendronate sodium, 70 mg by mouth [PO] weekly), but discontinued this medication prior to initiating study treatment (placebo).

One patient received a prohibited prior medication. Patient #4901 (eliglustat group) received treatment with pseudoephedrine, a medication known to prolong QTc interval, for 3 days for an episode of influenza. This medication was discontinued on the date that the patient initiated study treatment.

#### **I. Concomitant Medications**

Information on concomitant medications was recorded from the time of informed consent through the final follow-up assessment. Prohibited concomitant medications, and circumstances under which use these medications was permitted on a temporary or chronic basis.

1) 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 study.

- During the Primary Analysis Period, these medications were restricted in all patients with the exception of continuation of pre-existing chronic therapy, new temporary use of these medications, or new chronic use of strong CYP2D6 inhibitors in patients who were CYP2D6 poor metabolizers or indeterminate metabolizers with neither allele known to be active. Other new chronic use of these medications was permitted only after completion of the dose adjustment phase of the Long-term Treatment Period. Note: All patients were prohibited from simultaneously receiving strong inhibitors of both CYP2D6 and CYP3A4.
- Study treatment was interrupted in patients who temporarily (i.e.,  $\leq 2$  weeks) used a strong inhibitor of CYP2D6 or CYP3A4.
- Additional PK monitoring and/or eliglustat dose adjustments were undertaken in patients who initiated chronic use with any of these medications (excepting chronic use of strong CYP2D6 inhibitors in patients who were CYP2D6 poor metabolizers or indeterminate metabolizers with neither allele known to be active).
- The Sponsor's Medical Monitor was contacted if, at any time in the study, a patient needed to initiate treatment (acute or chronic) treatment with these medications, or was discontinuing chronic treatment with these medications.

2) Medications that might cause QT interval prolongation were prohibited throughout the study, with exceptions permitted for temporary (i.e.,  $\leq 1$  week) but not chronic use. Study treatment was interrupted in patients who temporarily used a medication that might cause QT interval prolongation (e.g., amiodarone, disopyramide, dofetilide, ibutilide, procainamide, quinidine, sotalol, thioridazine, etc).

3) 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).

4) The following concomitant medications were also prohibited during specific periods of the study:

- Calcium was prohibited for 24 hours prior to the DXA scan.

- New vitamin supplementation (e.g., supplements to correct deficiencies in iron, folate, or vitamin B-12) was prohibited during the Primary Analysis Period.

***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:***

- ***Patient #0901 was receiving intra-muscular vitamin B-12 at a dose of 1000 µg every 6 weeks and oral ferrous sulfate at a dose of 325 mg QD at Day 1. The vitamin B-12 supplementation was increased to 1000 µg every month starting on Day 28, and ferrous sulfate was increased to 325 mg BID on Day 30 and to 325 mg 3 times daily (TID) on Day 116.***
- ***Patient #0102, who was receiving folic acid at a dose of 5 mg QD at Day 1, discontinued this supplement approximately 2 weeks prior to the Week 39 hemoglobin assessment.***

***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.***

## **J. Safety Assessments**

Safety was assessed through monitoring of adverse events (including SAES) and concomitant medications, as well as through evaluation of standard clinical parameters including cardiac electrophysiology (12 lead ECG, 24 hour Holter), echocardiograms, physical examinations, vital sign measurements, neurological examinations, neuropsychological testing by Mini Mental State Examination (MMSE), standard clinical laboratory tests (hematology, serum chemistry, urinalysis) and chest X-rays. In addition, clinically significant cardiac arrhythmias that were detected by EPS monitoring and did not meet SAE criteria, and syncope from any cause, were reported as medical events of interest (MEOIs).

## **K. Analysis Population**

As noted earlier, 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.

## L. Results

**Table 10: 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)

## Patient Demographics

**Table 11: 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 <sup>a</sup>	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
Baseline Weight (kg)			
Mean (SD)	64.8 (11.74)	68.6 (17.17)	66.7 (14.65)
Min, Max	40.0, 81.7	46.0, 102.2	40.0, 102.2
Baseline Height (cm)			
Mean (SD)	166.2 (9.91)	170.0 (12.02)	168.1 (11.05)
Min, Max	149.0, 184.0	147.9, 192.0	147.9, 192.0
Baseline BMI (kg/m <sup>2</sup> )			
Mean (SD)	23.3 (2.74)	23.4 (3.54)	23.4 (3.13)
Min, Max	18.0, 27.7	18.4, 30.9	18.0, 30.9
Smoking Status, n (%)			
None	12 (60)	13 (65)	25 (63)
Current Smoker	1 (5)	2 (10)	3 (8)
Past Smoker	7 (35)	5 (25)	12 (30)
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)

**Medical Reviewer's comments: Demographic characteristics were generally similar between treatment groups, although the eliglustat group had slightly lower proportions of male patients (40%) and patients of Jewish descent (15%) compared with placebo (60% and 40%, respectively).**

### Protocol Deviations

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. Major protocol deviations reported by the Applicant included: study eligibility criteria, study procedure or assessment, excluded

concomitant medication, informed consent and study medication. The Applicant considered all other protocol deviations as minor.

**Table 12: ENGAGE Trial – Major Protocol Deviations: FAS**

Treatment Group	Type of Deviation	Patient ID	Description
Placebo	Study Eligibility Criteria	6404	Patient did not have a documented deficiency of acid $\beta$ -glucosidase activity by enzyme assay.
		0112	4-hour post-dose ECG was not performed
	Study Procedure or Assessment	3102	3- and 4-hour post-dose ECGs were not performed.
		3203	MRI procedures were not performed
		4603	1-, 3- and 4-hour post-dose ECGs were not performed during the repeat of Day 1. Less than 1 hour of Holter data was collected.
		6404	The patient's weight from Screening through Week 26 was measured on a non-calibrated scale. Left ventricular mass was not measured on ECHO Doppler
		7202	The 4-hour post-dose ECG was not performed.
Excluded Concomitant Medication	3301	Patient received Zofran, a prohibited medication, from 13 Jun 2012 to 30 Jun 2012 (3 pills) for treatment of vomiting.	
Eliglustat	Patient Info/Informed Consent	0901	Patient was re-screened and did not sign the same version of the informed consent form that she signed at the original screening.
		5303	Patient did not sign a new informed consent form prior to re-screening. The patient checked 2 contradictory boxes (accepting vs. not accepting) on the pharmacogenetics informed consent form.
		5901	Patient did not sign a new informed consent form prior to re-screening.
Eliglustat	Study Procedure or Assessment	4202	Site personnel failed to complete the accountability and dispensing log for Week 26
		4303	1-hour post-dose ECG was not performed.
		4602	The 1- and 2-hour post-dose ECGs were not performed. Only 14.5 hours of Holter data were collected.
		4701	The ECG was obtained at 07:38, prior to the time of informed consent at 08:15. The 2-hour post-dose ECG was not performed.
		4905	The 4-hour post-dose ECG was not performed.
		5303	Incomplete documentation of radiologist's review of pregnancy test results prior to imaging (no signature, date, hour). Reticulocyte number was not obtained by the local laboratory.
		5901	Core laboratory (eRT) could analyze only 8 of the 24 hours of Holter data collected at this visit.
		6403	The patient's weight from Screening through Week 26 was measured on a non-calibrated scale.
		7201	The 4-hour post-dose ECG was not performed.
Eliglustat	Study Medication	4903	Study drug was administered 4 hours outside of the time window. Pre-dose PK sample was not collected at

			the correct time relative to the preceding dose of study drug
		5601	Open label medication was dispensed at Week 39 instead of being dispensed at Week 39 +1.
		5901	Patient discarded their unused study drug, instead of returning it to the site the Week 13 visit.

### Treatment Compliance

All randomized patients received study drug, 20 patients in each treatment group. Compliance was at least 90% for the all patients with the exception of 2 patients in the placebo group (#2001 and #3301, compliance 80.3% and 86.3%, respectively) and 1 patient in the eliglustat group (#5303, compliance 61.6%).

The patients with compliance <90% were evenly distributed among sex and age subgroups so that compliance was at least 90% for almost all patients regardless of sex or age subgroup.

**Table 13: ENGAGE Trial Summary of Study Drug Exposure: Safety Set**

Parameter	Statistic	Placebo (N=20)	Eliglustat (N=20)	Total (N=40)
<b>Patients Randomized</b>				
Placebo	n (%)	20 (100)	0	20 (50)
Eliglustat 50 mg BID	n (%)	0	3 (15)	3 (8)
Eliglustat 100 mg BID	n (%)	0	17 (85)	17 (43)
<b>Total Time on Treatment (days) from Day 1 to Week 39 per patient</b>				
	n	20	20	40
	Mean (SD)	274.8 (10.05)	274.2 (26.75)	274.5 (19.94)
	Median	273.0	277.5	275.5
	Min, Max	263, 301	166, 296	166, 301
<b>Frequency of Percentage of Drug Compliance from Day 1 to Week 39</b>				
>100%	n (%)	3 (15)	5 (25)	8 (20)
≥90% to ≤100%	n (%)	15 (75)	14 (70)	29 (73)
≥80% to <90%	n (%)	2 (10)	0	2 (5)
≥70% to <80%	n (%)	0	0	0
≥60% to <70%	n (%)	0	1 (5)	1 (3)
≥50% to <60%	n (%)	0	0	0
≥40% to <50%	n (%)	0	0	0
≥30% to <40%	n (%)	0	0	0
≥20% to <30%	n (%)	0	0	0
≥10% to <20%	n (%)	0	0	0
≥0% to <10%	n (%)	0	0	0

The mean time on study treatment was 274.5 days (standard deviation [SD]=19.94) overall and was similar in the 2 treatment groups. In the eliglustat group, all patients received 50 mg QD on Day 1 and proceeded to 50 mg BID and/or 100 mg BID. The majority of patients (17 [85%]) received a dose escalation to 100 mg BID at Week 4, and 3 (15%) continued to receive 50 mg BID for the duration of the Primary Analysis Period. Although permitted by protocol, no patient received a dose reduction to 50 mg QD due to poor tolerability, or had a treatment interruption due to a peak Genz-99067 concentration  $\geq 150$  ng/mL.

Regardless of sex or age subgroup, the mean time on study treatment was similar in the 2 treatment groups, with the mean ranging between 273 and 276 days overall in the 4 subgroups (males, females,  $\leq 30.4$  years [the median age],  $> 30.4$  years). In each of the subgroups, the majority of patients (75%-92%) in the eliglustat group received 100 mg BID, with the remaining patients receiving 50 mg BID.

### 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.

An additional 32 patients were screened for the study, but were not randomized because they failed to complete screening procedures, did not meet all eligibility criteria, or chose to withdraw prior to randomization. The eligibility criteria that most commonly were not met were spleen size (6 to 30 MN) and platelet count (50,000 to 130,000/mm<sup>3</sup>).

**Table 14: ENGAGE Trial Patient Disposition: All Randomized Patients**

	<b>Eliglustat (N=20)</b>	<b>Placebo (N=20)</b>
<b>Randomized, n (%)</b>	20 (100)	20 (100)
<b>Treated, n (%)</b>	20 (100)	20 (100)
<b>Completed Week 39, n (%)</b>	19 (95)	20 (100)
<b>Withdrew prior to Week 39, n (%)</b>	1 (5)	0

### 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 15: ENGAGE: Summary of Values and Percentage Change in Spleen Volume (MN) from Baseline to Week 39: Full Analysis Set**

Time Point / Change	Statistic	Eliglustat (N=20)	Placebo (N=20)	Treatment Difference (Eliglustat-Placebo)
Baseline	n	20	20	NA
	Mean (SD)	13.89 (5.929)	12.50 (5.959)	NA
	Median	12.09	11.05	NA
	Min, Max	5.94, 28.39	6.32, 25.27	NA
Week 39	n	20	20	NA
	Mean (SD)	10.17 (5.065)	12.84 (6.395)	NA
	Median	8.34	10.97	NA
	Min, Max	4.12, 21.90	6.63, 26.17	NA
% Change from Baseline to Week 39	Mean (SD)	-27.58 (12.591)	2.07 (8.777)	NA
	Median	-29.03	4.20	NA
	Min, Max	-51.52, 0.00	-20.91, 13.68	NA
	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

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

### **A. General Design and Objectives**

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.

## **B. Inclusion Criteria/Exclusion Criteria**

### *Inclusion Criteria*

Patients must have met all of the following inclusion criteria in order to participate in this study:

1. Willing and able to provide signed informed consent prior to performance of any protocol-required procedures.
2. Age  $\geq 18$  years at the time of randomization.
3. Tanner Stage  $\geq 4$  prior to randomization.
4. Diagnosis of GD1 confirmed by a documented deficiency of acid  $\beta$  glucosidase activity by enzyme assay.
5. Consented to provide a blood sample for genotyping for Gaucher disease, chitotriosidase, and CYP2D6 (to categorize the patient's predicted rate of metabolism), if these genotyping results are not already available for the patient.
6. Received treatment with ERT for at least 3 years. For at least 6 of the 9 months prior to randomization, the patient has received a total monthly dose of 30 to 130 U/kg of ERT that has received approval by at least one regulatory authority by the time randomization.
7. 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  $\geq 11$  g/dL if female and  $\geq 12$  g/dL if male at the time of screening.
  - C. Mean platelet count  $\geq 100,000/\text{mm}^3$  at the time of screening.
8. Spleen volume  $< 10$  times Normal or total splenectomy (provided the splenectomy occurred  $> 3$  years prior to randomization).
9. Liver volume  $< 1.5$  times Normal.
10. Female patients of childbearing potential must have a documented negative pregnancy test prior to randomization. In addition, all female patients of childbearing potential must use a medically accepted form of contraception throughout the study (either a barrier method or hormonal contraceptive with ethinyl estradiol and norethindrone or similar active components).

11. Willing to abstain from consumption of grapefruit, grapefruit juice, or grapefruit products for 72 hours prior to administration of the first dose of study medication (eliglustat or Cerezyme) and, if randomized to eliglustat, for the duration of the primary analysis period.

*Exclusion criteria*

Patients were excluded from participation in this study if they met any of the following exclusion criteria:

1. Received substrate reduction therapies for Gaucher disease within 6 months prior to randomization.
2. A partial or total splenectomy within 3 years prior to randomization.
3. Any evidence of neurologic (e.g., peripheral neuropathy, tremor, seizures, Parkinsonism or cognitive impairment) or pulmonary involvement (e.g., pulmonary hypertension) as related to Gaucher disease.
4. Transfusion-dependent.
5. Documented prior esophageal varices or liver infarction or current liver enzymes (alanine aminotransferase [ALT]/aspartate aminotransferase [AST]) or total bilirubin >2 times the upper limit of normal (ULN), unless the patient has a diagnosis of Gilbert Syndrome.
6. Any clinically significant disease, other than Gaucher disease, including cardiovascular, renal, hepatic, gastrointestinal, pulmonary, neurologic, endocrine, metabolic (e.g. hypokalemia, hypomagnesemia), or psychiatric disease, other medical conditions, or serious intercurrent illnesses that may preclude participation in the study.
7. Any of the following: Clinically significant coronary artery disease including history of myocardial infarction or ongoing signs or symptoms consistent with cardiac ischemia or heart failure; or clinically significant arrhythmias or conduction defect such as 2<sup>nd</sup> or 3<sup>rd</sup> degree atrioventricular (AV) block, complete bundle branch block, prolonged QTc interval, or sustained ventricular tachycardia (VT).
8. Tested positive for the human immunodeficiency virus (HIV) antibody, Hepatitis C antibody, or Hepatitis B surface antigen.
9. Received an investigational product within 30 days prior to randomization.
10. Scheduled for in-patient hospitalization, including elective surgery, during the study.
11. A history of cancer within 5 years of randomization, with the exception of basal cell carcinoma.
12. Pregnant or lactating.
13. Received any medication that may cause QTc interval prolongation within 30 days prior to randomization. Exception: Diphenhydramine (Benadryl) or other medications used as premedication for ERT infusions are allowed up to 7 days prior to randomization.
14. Received any medication that may induce cytochrome P450 3A4 (CYP3A4) within 30 days prior to randomization, with the exception of premedications for ERT infusion, which are allowed up to 7 days prior to randomization.
15. Not a CYP2D6 poor metabolizer, or an indeterminate metabolizer with one allele identified as active, and has received any medication that is a strong inhibitor of

CYP3A4 or CYP2D6 within 30 days prior to randomization, with the exception of the following:

- premedications for ERT infusion, which are allowed up to 7 days prior to randomization;
- a strong inhibitor of CYP3A4 or a strong inhibitor of CYP2D6 (but not both medications) that has been administered chronically for at least 30 days prior to randomization and will be continued on the same dosing regimen during the primary analysis period.

16. A CYP2D6 poor metabolizer or an indeterminate metabolizer with neither allele known to be active and has received any medication that is a strong inhibitor of CYP3A4 within 30 days prior to randomization, with the exception of premedications for ERT infusion, which are allowed up to 7 days prior to randomization.

17. Unable to receive treatment with Cerezyme due to a known hypersensitivity or is unwilling to receive Cerezyme treatment q2w.

### C. Primary Endpoints

As recommended by the US Food and Drug Administration (FDA), the efficacy endpoint for the Agency's analysis (FDA-recommended efficacy endpoint) will be 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%.

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.

### D. Secondary Endpoints

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).

### **E. Tertiary and Exploratory Endpoints**

The tertiary efficacy endpoints included the following: Biomarkers (CCL18 and chitotriosidase); bone disease assessments (X-ray, MRI and bone marrow burden score); Gaucher assessments (mobility, bone crisis, and bone pain); Quality of Life (QOL) (Brief Pain Inventory [BPI], Fatigue Severity Score [FSS], Short Form-36 Health Survey [SF-36]), and treatment preference (oral vs IV therapy).

Exploratory endpoints included Gaucher disease Severity Score System (DS3) and the percentage changes from Baseline in investigational biomarkers, including GL-1 assayed from dried blood spots (DBS) on filter paper and from plasma, as well as GM3, ceramide, hsCRP, apo-B-100, sphingomyelin, and MIP-1 $\beta$  (assayed from plasma).

### **F. Overall Endpoint Assessments**

#### **Spleen and Liver Volume by MRI**

MRI scans 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:

Spleen MN = volume in cc/ (weight in kg \* 2)

Liver MN = volume in cc/ (weight in kg\* 25)

The assessment prior to randomization (Screening) was reviewed by 1 central reader, and was used as the baseline in the study analyses. The assessments at Week 26 and Week 52 were each reviewed by 2 central readers. In the event of a >5% discrepancy between readers, the value that was closest to that of an adjudicating third reader was used in the study analyses. If a patient's spleen or liver volume (in MN) increased above the patient's Baseline value (>25% and >20% for spleen and liver volume, respectively) a repeat organ volume measurement was obtained within approximately 4 weeks, and this repeat measurement was used in the trial analysis.

#### **Platelet count and Hemoglobin level**

At selected time points, 2 blood samples were collected at least 24 hours apart, and the average of the 2 platelet counts/hemoglobin values was used in the study analyses. In the event that a patient was missing 1 of the 2 assessments at a particular time point, then the single assessment was used in the analyses.

#### **Bone disease assessments**

Dual energy X-ray Absorptiometry (DXA): Images of the spine and bilateral femur were obtained to determine T-scores and Z-scores for each bone area, and total bone mineral density (BMD).

Bone marrow burden (BMB) score: BMB score was calculated by summing 6 MRI based scores for the lumbar spine and femur.

### **Gaucher Disease Assessments (Mobility, Bone Crisis, and Bone Pain)**

Gaucher Disease assessments included the following:

Mobility: The patient's current mobility status was recorded

Bone pain: The severity of the patient's bone pain was assessed, "How would you rate your bone pain during the last 4 weeks.

Bone crisis: The number of bone crises since the previous visit was recorded. A bone crisis was defined as bone pain with acute onset requiring immobilization of the affected area, narcotics for pain relief, and possibly accompanied by periosteal elevation, an elevated white blood cell count, fever and/or debilitation of > 3 days.

### **G. 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  $\geq 5$  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  $\geq 5$  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  $\geq 150$  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.

During the course of the study, if an eliglustat patient met at least 1 of the following criteria due to a decline in Gaucher disease, the Investigator was to notify the Genzyme Medical Monitor as soon as possible and Global Pharmacovigilance and Epidemiology, when appropriate (i.e., SAE notifications within 24 hours). After discussion, which may include consultation with the DMC, the patient may have transitioned to Cerezyme q2w, as study drug.

- The patient's hemoglobin level fell below 8 g/dL and remained below 8 g/dL when hematology laboratory testing was repeated within approximately 2 weeks.
- The patient's platelet count fell below 45,000/mm<sup>3</sup> and remains below 45,000/mm<sup>3</sup> when hematology laboratory testing was repeated within approximately 2 weeks, or if the patient experienced a clinically significant bleeding episode assessed by the Investigator as related to a low platelet count.
- Any other decline in Gaucher disease status which, in the opinion of the Investigator, warranted a return to ERT (Cerezyme).

Patients who transitioned from eliglustat to Cerezyme every 2 weeks continued to be followed in the study, and their data were collected on the eCRF. These patients were followed in the study until their disease had been treated to a clinically acceptable range. This was defined as a return to baseline values of objective measure(s) causing the decline (e.g., platelet count, spleen volume), or no additional occurrence or further worsening of the measure(s) causing the decline (e.g., bone crisis, bone fracture, worsening bone pain). Once the parameter(s) causing the decline were in an acceptable range, the patient was discontinued from the study

#### Selection and Timing of Dose for Each Patient

A starting dose of 50 mg (per dosing occasion) was administered to all patients randomized to eliglustat in the Primary Analysis Period and all patients initiating open-label eliglustat therapy in the Long-term Treatment Period. The dose of eliglustat was escalated in individual patients based on observed trough plasma concentrations of Genz-99067. The BID doses were administered approximately 12 hours apart.

#### **H. Prior Medications**

Information on all prior medications and therapies taken within 30 days prior to informed consent and any prior use of ERT, SRT, or pharmacological chaperone therapies was recorded in the eCRF.

### **I. Concomitant Medications**

Information on all concomitant medications (defined as all prescription and non-prescription medications, including herbal supplements) taken by the patient from the time of informed consent through the final follow-up assessment, including all premedication administered prior to Cerezyme infusions in the primary analysis period, was recorded on the patient's eCRF.

### **J. Safety Assessments**

Safety was assessed through continuous monitoring of adverse events (AEs; including SAEs) and concomitant medications, as well as through evaluation of standard clinical parameters including cardiac electrophysiology (12-lead ECG, 24-hour dual-lead Holter), echocardiograms (ECHO) with Doppler, physical examinations, vital sign measurements, neurological examinations, nerve conduction testing, neuropsychological testing by Mini-Mental State Examination (MMSE), standard clinical laboratory tests (hematology, serum chemistry, urinalysis), and chest X-rays (posterior-anterior and lateral views).

For the purpose of ongoing safety monitoring in this clinical trial, certain adverse events of special interest (serious or non-serious) were defined in the protocol. Those events were reported to the Sponsor as MEOIs and followed the timeframe and the process for reporting SAEs. In this study, MEOIs were defined as clinically significant cardiac arrhythmias detected by electrophysiological monitoring such as ECG or Holter monitoring that did not meet SAE criteria, as well as syncope from any cause, regardless of treatment group.

### **K. 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.

Week 52 Completer Analysis Set: This analysis set includes patients in the FAS who completed 52 weeks of treatment and had non-missing assessments at Baseline and Week 52.

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

## L. Results

**Table 16: ENCORE Analysis Populations**

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

**Table 17: Patients excluded from the Per Protocol Set**

<b>Treatment Group</b>	<b>Patient ID</b>	<b>Time on Treatment (days)</b>	<b>Time in Study (days)</b>	<b>Completed Week 52</b>	<b>Reason for Exclusion from Per Protocol Set</b>
Eliglustat	2101	251	321	No	Did not reach Week 52
	2701	375	534	Yes	Mismatch between randomized dose stratum and actual pre-study Cerezyme dose
	4614	371	421	Yes	Dosing Compliance <80%

	6102	366	395	Yes	Missing Baseline and/or Week 52 Platelet; Missing Baseline and/or Week 52
	6903	198	261	No	Did not reach Week 52
	8303	350	399	Yes	Mismatch between randomized dose stratum and actual pre-study Cerezyme dose
	9202	369	411	Yes	Dosing Compliance <80%
Cerezyme	1402	342	437	Yes	Dosing Compliance <80%
	2805	352	408	Yes	Mismatch between randomized dose stratum and actual pre-study Cerezyme dose
	2817	-	-	No	Randomized but not dosed
	2916	232	288	No	Did not reach Week 52
	6001	351	417	Yes	Mismatch between randomized dose stratum and actual pre-study Cerezyme dose
	6601	181	351	Yes	Dosing Compliance <80%
	6606	218	337	Yes	Dosing Compliance <80%

#### 5.5.16 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.

**Table 18: ENCORE Trial Patient Disposition: All Randomized Patients**

Clinical Review  
 Karyn L. Berry, MD, MPH  
 NDA 205494  
 Cerdelga (Eliglustat tartrate)

	Eliglustat (N=106)	Cerezyme (N=54)	Total (N=160)
Randomized, n (%)	106 (100)	54 (100)	160 (100)
Treated, n (%)	106 (100)	53 (98)	159 (99)
Completed Week 52, n (%)	104 (98)	52 (96)	156 (98)
On Treatment	103 (97)	52 (96)	155 (97)
On Switched Treatment(Cerezyme)	1 (1)	0	1 (1)
Did Not Complete Week 52, n (%)	2 (2)	2 (4)	4 (3)
ADVERSE EVENT	2 (2)	1 (2)	3 (2)
NON-COMPLIANCE WITH STUDY DRUG	0	1 (2)	1 (1)
WITHDRAWAL BY SUBJECT	0	0	0
LOST TO FOLLOW-UP	0	0	0
DECLINE IN GAUCHER DISEASE	0	0	0
TRANSITION FROM ELIGLUSTAT TO CEREZYME	0	0	0
STUDY TERMINATED BY SPONSOR	0	0	0
OTHER	0	0	0

### Treatment Compliance

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.

**Table 19: ENCORE Trial Summary of Study Drug Exposure: Safety Set**

Parameter	Statistic	Eliglustat (N=106)	Cerezyme (N=53)
<b>Duration of Study Participation (days) from Day 1 to Week 52 Per Patient</b>			
	n	106	53
	Mean (SD)	421.4 (35.23)	404.4 (33.29)
	Min, Max	261, 534	288, 483
<b>Total Time on Treatment (days) from Day 1 to Week 52 Per Patient</b>			
	n	106	53
	Mean (SD)	361.5 (24.28)	347.2 (38.80)
	Min, Max	198, 420	181, 386
<b>Eliglustat Dose Group (mg BID) at the end of the Titration Period</b>			
50	n (%)	21 (20)	--
100	n (%)	34 (32)	--
150	n (%)	51 (48)	--
<b>Number of Cerezyme infusions per patient from Day 1 to Week 52</b>			
	n	NA	53
	Mean (SD)	NA	24.6 (3.44)
	Min, Max	NA	12, 28
<b>Frequency of Percentage of Drug Compliance from Day 1 to Week 52</b>			
>100%	n (%)	3 (3)	12 (23)
≥90% to ≤100%	n (%)	93 (88)	29 (55)
≥80% to <90%	n (%)	8 (8)	8 (15)
≥70% to <80%	n (%)	1 (1)	1 (2)
≥60% to <70%	n (%)	0	1 (2)
≥50% to <60%	n (%)	0	1 (2)
≥40% to <50%	n (%)	1 (1)	1 (2)

The mean ± 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 9-6). All patients randomized to eliglustat treatment 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, eliglustat patients 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. At the end of the protocol- defined titration period the percentage of patients receiving the 3 possible eliglustat doses was: 50 mg BID (20%; 21/106), 100 mg BID (32%; 34/106) and 150 mg BID (48%; 51/106).

The mean number of Cerezyme infusions per patient during the Primary Analysis Period was 24.6 ( $\pm$ 3.4) consistent with the q2w dosing interval employed in this study.

## Demographics

**Table 20: 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 <sup>a</sup>	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.*

**Prior Medications**

Ninety-nine percent of patients (157/159) were receiving 1 or more medications prior to initiation of study treatment, many of which were being administered chronically or as needed for the management of symptoms and complications of GD1. The more commonly administered prior medications included enzymes (primarily imiglucerase), nonsteroidal anti-inflammatory drugs (NSAIDs), paracetamol and other anilides, calcium products and multivitamins. Biphos-phonate therapy was reported as a prior medication in 8% of patients in both treatment groups.

**Concomitant Medications**

Eighty-seven percent of patients (139/159) received 1 or more concomitant medications during treatment in the Primary Analysis Period, most commonly NSAIDs, paracetamol and other anilides, glucocorticosteroids, and calcium products. Bisphosphonate therapy was reported as a concomitant medication in 7% of eliglustat patients and 8% of Cerezyme patients.

When the reported medications in the eliglustat treatment group were reviewed to determine concomitant use for at least 15 consecutive days during the 52 week primary analysis period, 5 patients were reported to have received either strong or moderate inhibitors of CYP2D6, 2 patients were reported to have received inducers of CYP3A4, and no patients were reported to have received either strong or moderate inhibitors of CYP3A4. The 5 eliglustat patients receiving either strong or moderate inhibitors of CYP2D6 were all receiving treatment for chronic pre-existing conditions (i.e., depression, hypertension) and continuation of the same dosing regimen was allowed

per protocol. Nine eliglustat-treated patients were reported to have received a medication for more than 15 consecutive days with the potential to increase the QTc interval.

### 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 21: 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	2.87	2.23	--
	Min, 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	2.95	2.31	--
	Min, 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	-6.65	-5.20	--
	Min, 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 22: 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.

**Table 23: Summary of Proportion of Patients who Met Stable Hematologic and Organ Volume Criteria of the Primary Endpoint at Week 52: Per Protocol Set**

Variable	Eliglustat (N=99)	Cerezyme (N=47)
Patients Meeting Hemoglobin Criteria, n (%) Exact 95% CI	94 (94.9) (0.886, 0.983)	47 (100.0) -
Patients Meeting Platelets Criteria, n (%) Exact 95% CI	92 (92.9) (0.860, 0.971)	47 (100.0) -
Patients Meeting Spleen Volume Criteria, n (%)* Exact 95% CI	67 (94.4) (0.862, 0.984)	39 (100.0) -
Patients Meeting Liver Volume Criteria, n (%) Exact 95% CI	95 (96.0) (0.900, 0.989)	44 (93.6) (0.825, 0.987)

\* Patient percentages are based on the total number of non-splenectomized patients in the particular treatment group.

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 patients 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

### 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).

**Table 24: Summary of Values and Absolute Change in Hemoglobin (g/dL) from Baseline to Week 52: Per Protocol Set**

Time Point / Change	Statistic	Eliglustat (N=99)	Cerezyme (N=47)	Treatment Difference (Eliglustat-Cerezyme)
Baseline	n	98	47	--
	Mean (SD)	13.592 (1.2467)	13.797 (1.2234)	--
	Median	13.575	13.900	--
	Min, Max	11.05, 17.25	11.20, 16.00	--
Week 52	n	98	47	--
	Mean (SD)	13.380 (1.2840)	13.835 (1.2932)	--
	Median	13.350	13.850	--
	Min, Max	10.05, 16.35	11.05, 16.85	--
Change from Baseline to Week 52	Mean (SD)	-0.213 (0.7090)	0.038 (0.6639)	--
	Median	-0.250	0.150	--
	Min, Max	-1.95, 1.35	-1.45, 1.15	--
	LS Mean (SEM)	-0.22 (0.07)	0.05 (0.10)	-0.28 (0.12)
	95% CI	(-0.36, -0.08)	(-0.14, 0.25)	(-0.52, -0.03)
	p-value	NA	NA	0.0253

Source: Applicant's table from ENCORE CSR

### Platelet Count

Platelet counts were similar at baseline in both treatment groups, with mean values of 206.8 x 10<sup>9</sup>/L (range: 100.5 to 511.0 x 10<sup>9</sup>/L) in patients randomized to eliglstat and 192.3 x 10<sup>9</sup>/L (range: 102.0 to 339.5 x 10<sup>9</sup>/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 eliglstat group and 100% for the Cerezyme, group.

**Table 25: Summary of Values and Percentage Change in Platelet Count (10<sup>9</sup>/L) from Baseline to Week 52: Per Protocol Set**

Time Point / Change	Statistic	Eliuglstat (N=99)	Cerezyme (N=47)	Treatment Difference (Eliuglstat-Cerezyme)
Baseline	n	98	47	--
	Mean (SD)	206.750 (80.7371)	192.298 (57.3367)	--
	Median	188.250	185.000	--
	Min, Max	100.50, 511.00	102.00, 339.50	--
Week 52	n	98	47	--
	Mean (SD)	216.281 (83.9567)	198.340 (61.1593)	--
	Median	201.250	186.000	--
	Min, Max	69.50, 522.00	103.50, 367.50	--
% Change from Baseline to Week 52	Mean (SD)	3.787 (18.8507)	2.930 (11.8867)	--
	Median	4.000	2.200	--
	Min, Max	-55.70, 73.10	-20.80, 34.80	--
	LS Mean (SEM)	3.93 (1.71)	2.63 (2.47)	1.30 (3.01)
	95% CI	(0.55, 7.31)	(-2.25, 7.52)	(-4.65, 7.24)
	p-value <sup>a</sup>	NA	NA	0.6674

Source: Applicant's table from ENCORE CSR

### Liver Volume

Most patients had normal liver volumes at Baseline, with mean liver volumes of 0.95 MN in the eliglstat 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 eliglstat and Cerezyme, respectively). At Week 52, the proportion of patients meeting the stability criteria for liver volume was 96.0% for the eliglstat group and 93.6% for the Cerezyme, group.

**Table 26: Summary of Values and Percentage Change in Liver 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	98	47	--
	Mean (SD)	0.948 (0.1911)	0.911 (0.1622)	--
	Median	0.915	0.930	--
	Min, Max	0.53, 1.50	0.56, 1.25	--
Week 52	n	98	47	--
	Mean (SD)	0.963 (0.1856)	0.944 (0.1670)	--
	Median	0.945	0.940	--
	Min, Max	0.57, 1.66	0.62, 1.31	--
% Change from Baseline to Week 52	Mean (SD)	1.780 (9.6429)	3.572 (10.2364)	--
	Median	2.600	5.200	--
	Min, Max	-21.50, 30.00	-26.80, 25.30	--
	LS Mean (SEM)	1.99 (0.95)	3.13 (1.36)	-1.14 (1.66)
	95% CI	(0.10, 3.84)	(0.43, 5.83)	(-4.42, 2.15)
	p-value	NA	NA	0.4941

Source: Applicant's table from ENCORE CSR

### 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.

**Table 27: Summary of Shift in Bone Mineral Density T-Scores from Baseline to Week 52 for Centrally Reviewed DXA Assessments: Per Protocol Set**

Week 52 BMD Category
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Treatment Group	Parameter	Total n	Baseline BMD Category	Normal	Osteopenia	Osteoporosis
Eliglustat (N=99)	Lumbar Spine T-score	81	Normal	46 (57)	4 (5)	0
			Osteopenia	5 (6)	20 (25)	3 (4)
			Osteoporosis	0	0	3 (4)
	Femur T-score	80	Normal	62 (78)	0	0
			Osteopenia	3 (4)	15 (19)	0
			Osteoporosis	0	0	0
Cerezyme (N=47)	Lumbar Spine T-score	38	Normal	27 (71)	1 (3)	0
			Osteopenia	1 (3)	8 (21)	0
			Osteoporosis	0	0	1 (3)
	Femur T-score	37	Normal	23 (62)	1 (3)	0
			Osteopenia	1 (3)	9 (24)	1 (3)
			Osteoporosis	0	0	2 (5)

Source: Applicant's table ENCORE CSR

T-score bone density categories are normal (score >-1), osteopenia (score -2.5 to ≤-1), and osteoporosis (score ≤-2.5).

## 5.6 GZGD00304 (Phase 2 Trial)

### A. General Design and Objectives

This was a Phase 2, open label, multi-center trial evaluating the efficacy, safety and pharmacokinetics in Gaucher Type 1 patients.

The trial was conducted at a total of seven sites in five countries (Russia, Argentina, United States, Israel and Mexico). Twenty-six patients were treated with at least one dose of eliglustat. Twenty-two (85%) of patients completed the Week 52 assessments and 19 patients (73%) completed the month 48 assessments. Four patients (15%) discontinued prior to Week 52 and 3 additional patients (12%) discontinued prior to Month 48. The trial was initiated on June 16, 2006.

A reference therapy was not used during this open-label trial.

The primary objective of the trial was to evaluate the efficacy, safety, and PK of eliglustat, administered as an oral dose of either 50 mg BID or 100 mg BID, to patients with GD1 for 52 weeks.

The secondary objective was to determine the long-term efficacy, safety, and PK effects of eliglustat at doses of 50, 100, or 150 mg BID administered to the same patients from approximately Week 54 through trial completion.

This trial consists of several phases: Screening, dose adjustment/treatment, initial steady-state treatment, a treatment interruption period, long-term steady-state treatment, and safety follow-up. After receiving their initial dose of eliglustat on Day 1, each patient was to return to the study center at regular intervals for efficacy, safety, and PK assessments. On Day 1, each patient received an open-label 50 mg dose of

eliglustat; on Day 2, patients began receiving 50 mg eliglustat BID. Following PK sampling on Day 20, if a patient's Day-10 PK results indicated that trough plasma concentration of Genz-99067 was less than 5 ng/mL, the patient received a dose increase to 100 mg BID eliglustat for the remainder of the treatment period; if trough plasma concentration was greater than or equal to 5 ng/mL, the patient remained on 50 mg BID for the remainder of the treatment period. Patients were eligible for a further dose adjustment to 150 mg BID if they had been on treatment for at least 24 months and met certain efficacy criteria.

## **B. Key Inclusion Criteria/Exclusion Criteria**

### **Inclusion Criteria**

The main inclusion criteria for this study included:

- willingness and ability to provide written informed consent;
- a diagnosis of GD1 and a documented deficiency of acid  $\beta$ -glucosidase (glucocerebrosidase) activity by enzyme assay, along with the following signs/symptoms of GD1: hemoglobin 8.0 to 10.0 g/dL if female, or 8.0 to 11.0 g/dL if male (the mean of 2 measurements from separate blood draws taken at least 24 hours apart during Screening), platelet count 45,000 to 100,000/mm<sup>3</sup> (the mean of 2 measurements from separate blood draws taken at least 24 hours apart during Screening), and splenomegaly, by MRI or spiral computed tomography (CT), defined as spleen volume  $\geq$ 10 times normal;
- consent to provide a blood sample for genotyping for Gaucher disease, chitotriosidase, and for genetic assessment of cytochrome P450 (e.g., cytochrome P450 2D6 [CYP2D6] and other isoenzymes);

### **Exclusion criteria**

The main exclusion criteria for this study included:

- patients with partial or total splenectomy; those with evidence of any neurologic (e.g., peripheral neuropathy, tremor, seizures, Parkinsonism, or cognitive impairment) or pulmonary involvement (e.g., pulmonary hypertension); or those with new pathological bone involvement (osteonecrosis, pathological fractures, aseptic necrosis, lytic lesions; as assessed by x-ray or MRI) or bone crisis in the 12 months prior to enrollment;
- those with hemoglobin level <8.0 g/dL or platelet level <45,000/mm<sup>3</sup> (each calculated as the mean of 2 separate blood measurements taken at least 24 hours apart during Screening);
- patients who received miglustat, enzyme replacement therapy (ERT), or corticosteroids for GD1 within 12 months prior to enrollment, or who received bisphosphonates within 3 months prior to enrollment;
- patients with other serious co-morbidities (anemia due to causes other than Gaucher disease; prior bleeding varices or liver infarction; cancer; cardiovascular, renal, hepatic, gastrointestinal, pulmonary, neurologic, endocrine, metabolic, or psychiatric disease; positive for human immunodeficiency virus [HIV] antibody, hepatitis C antibody, or hepatitis B surface antigen);

- patients with cardiac functional and/or anatomical abnormalities (e.g., mitral valve prolapse, septal defects, ventricular hypertrophy) or clinically significant ECG or ECHO findings at the time of Screening;
- those who received any medication within 30 days prior to enrollment that may induce or inhibit CYP2D6, or cause QT interval prolongation.

### **C. Primary Endpoints**

The main efficacy endpoints in this Phase 2 study are the changes in hemoglobin and platelet levels and the percent change in spleen volume during the Primary Analysis Period, from baseline through Week 52. For a patient to be considered to have demonstrated a clinically meaningful response to treatment with Genz-112638, a response in at least 2 of the 3 main parameters (hemoglobin, platelets, and spleen), as defined below, must be observed.

- An increase of  $\geq 0.5$  g/dL in hemoglobin (if abnormal at baseline)
- An increase of  $\geq 15\%$  in platelets (if abnormal at baseline)
- A reduction of  $\geq 15\%$  in total spleen volume (based on MRI or spiral CT)

### **D. Additional Endpoints**

Additional efficacy endpoints are the change in liver volume from baseline to 52 weeks and biomarkers (ACE, TRAP, CCL18, and chitotriosidase), and exploratory biomarkers (e.g., GL-1, GL-3, GM3, sphingomyelin, ceramide, and HbA1c), which were assessed at various times during the study.

Changes in patient self-reported QoL (i.e., health, fatigue) will be assessed via questionnaires and summarized descriptively (Day 0 and Weeks 26 and 52). Additional endpoints also included changes in Gaucher assessments (mobility, bone crisis, and bone pain), and bone disease assessments (X-ray, DEXA, and MRI).

### **E. Prior Medications**

All medications taken by the patient from the time of informed consent to the first administration of Genz-112638 will be recorded on the eCRF.

### **F. Concomitant Medications**

All medications taken by the patient from administration of Genz-112638 through the final follow-up assessment will be recorded on the eCRF. Because Genz-112638 is a substrate for CYP450 2D6 and its' metabolism is highly variable and dependent upon the 2D6 genotype of the individual, medications known to induce or inhibit CYP450 2D6 must not be taken prior to or during the study. These medications, and those that may cause QT interval prolongation, are therefore not allowed to be taken by patients.

### **G. Doses Selected**

The doses selected for this study, 50 mg BID and 100 mg BID, were based on the safety data from 3 Phase 1 studies and the expected efficacious dose in humans from available preclinical data for Genz-112638.

## **H. Safety Assessments**

The safety of eliglustat will be assessed by evaluating the incidence of reported AEs, SAEs, and changes from Baseline in vital signs, physical examination, neurologic examination, ECG assessments (including continuous telemetry from 12 hours prior to the first dose to 24 hours after the first dose), chest X-ray, echocardiogram with Doppler, routine laboratory assessments (chemistry, hematology, and urinalysis), NCV and neuropsychological testing.

## **I. Analysis Population**

Efficacy analyses will be performed on all patients (Intent-to-treat [ITT] population) as well as a Per Protocol (PP) population. The ITT population includes all patients who have signed informed consent forms and received at least 1 dose of eliglustat. Safety analyses will be performed on the ITT population.

For the main efficacy parameters, the proportion of response and a 90% Confidence Interval (CI) will be constructed. No hypothesis testing was planned for this study. As a secondary analysis, the actual values and changes from Baseline for hemoglobin (absolute change), platelets (percent change) and spleen (percent change) to follow-up study timepoints will be summarized.

## **J. Results**

### **Patient Disposition**

A total of 26 patients (10 males and 16 females) received at least 1 dose of eliglustat. Twenty-two patients (85%) completed the Week 52 assessments, and 19 patients (73%) completed the Month 48 assessments. Four patients discontinued prior to the Week 52 assessments, and an additional 3 patients discontinued prior to the Month 48 assessments.

Two patients (0202 and 0302) were discontinued after receiving a single 50 mg dose each of eliglustat on Day 1, due to mild AEs of asymptomatic non-sustained ventricular tachycardia (NSVT) that occurred at 6 and 13 hours post-dose in patient 0202 and at 12 hours post-dose in patient 0302.

Twenty-four patients received 50 mg eliglustat BID from Day 2 through Day 20, after which doses could be adjusted. Six (25%) patients continued to receive 50 mg BID, and 18 (75%) were dose-adjusted to 100 mg BID.

**Table : Phase 2 Trial Patient Disposition: All Randomized Patients**

	Phase 2
	Eliglustat (N=26)
Randomized, n(%)	NA
Treated, n(%)	26 (100)
Completed Primary Analysis Period, n(%)	22 (85)
Withdrew prior to end of Primary Analysis Period, n (%)	4 (15)
Completed Month 48	19 (73)
Did not complete Month 48	7 (27)
Adverse Event(s)	3 (12)
Non-compliant	0
Wishes to Withdraw	1 (4)
Lost to follow-up	0
Other	3 (12)

Source: Phase 2 CSR Table

## 5.7 GZGD03109 (EDGE)

No efficacy data was submitted for this trial; only safety data was submitted

### A. General Design and Objectives

This is a Phase 3, randomized, multi-center, multi-national, double-blind trial to evaluate the efficacy, safety and PK of once daily versus twice daily dosing of Genz-112638 in patients with Gaucher Disease Type 1 who have demonstrated clinical stability on a twice daily dose of Genz-112638.

A total of approximately 170 patients will be treated in the Lead-in Period, and approximately 153 patients will be randomized into the Primary Analysis Period in order to have at least 130 evaluable patients for the noninferiority analysis powered at 88%.

The primary objective of the trial is to evaluate the efficacy and safety of once daily (QD) versus twice daily (BID) dosing of Genz-112638 (eliglustat tartrate) in patients with Gaucher disease type 1 who have demonstrated clinical stability on BID dosing of Genz-112638.

The secondary objective is to evaluate the pharmacokinetics (PK) of Genz-99067 when Genz-112638 is administered QD and BID in patients with Gaucher disease type 1 who have demonstrated clinical stability on BID dosing of Genz-112638.

The study will include a Screening period (Days -45 to -1) and an open-label BID dosing Lead-in Period of between 6 and 18 months (N-Day 1 to N-Month 18, where 'N' designates that study visits occur prior to randomization) for all patients. After the Lead-in Period, patients who meet criteria for randomization will participate in a double-blind

Primary Analysis Period (R-Day 1 to R-Week 52, where 'R' designates that study visits occur after randomization) followed by an open-label Long-term Treatment Period (after R-Week 52 through study completion). Patients who do not meet randomization criteria may continue with non-randomized treatment in an open-label Extended Treatment Period (after N-Month 18 through study completion). All patients will have a Safety Follow-up Period at 30 to 37 days after their last dose of Genz-112638.

After patients provide informed consent, each patient will undergo Screening assessments to determine study eligibility. Eligible patients will participate in a Lead-in Period in which each patient's dose of Genz-112638 will be titrated (from 50 mg BID to 100 mg BID) based on Genz-99067 plasma pre-dose (trough) and 2-hour (peak) concentrations. A dose decrease from 50 mg BID to 50 mg QD and from 50 mg QD to 50 mg once every other day (QOD) is possible for patients whose peak concentrations are too high; these patients will not enter the randomized portion of the study if they cannot make adjustments in concomitant medications (defined as all prescription and non-prescription medications, including herbal supplements) or other factors to allow for a subsequent dose increase to 50 mg BID. Patients will be assessed at N-Month 6 to determine whether they have achieved therapeutic goals, as defined by a patient meeting all of the following criteria:

- No more than 1 bone crisis and is free of other clinically symptomatic bone disease (such as bone pain attributable to osteonecrosis and/or pathological fractures) during the previous 6 months of the Lead-in Period.
- Mean hemoglobin level of  $\geq 11$  g/dL if female and  $\geq 12$  g/dL if male at the time of the assessment.
- Mean platelet count  $\geq 100,000/\text{mm}^3$  at the time of assessment.
- Spleen volume  $\leq 10$  times Normal (if applicable) at the time of the assessment.
- Liver volume  $\leq 1.5$  times Normal at the time of the assessment.

Additional randomization criteria:

- A dose of 50 mg BID or 100 mg BID for at least 4 months and
- A peak (2-hour) Genz-99067 plasma concentration  $< 50$  ng/mL.

If a patient meets the additional randomization criteria, but has not met therapeutic goals by N-Month 6, they will continue receiving BID treatment in the Lead-in Period, and will be reassessed at N-Month 12 and, if necessary, N-Month 18, to determine whether they meet therapeutic goals and additional randomization criteria at that time.

Patients who do not meet the additional randomization criteria may remain in the Lead-in Period up to N-Month 18 in case a change in concomitant medications or other factors may allow patients to attain the additional criteria. In this case, the patient must be at a 50 mg BID or 100 mg BID dose for at least 4 months.

After at least 4 months have passed, therapeutic goals and additional criteria will be assessed at the next randomization timepoint.

For patients receiving 150 mg BID in the Lead-in Period: The patient's dose will be reduced to 100 mg BID. Once the patient has been on 100 mg BID for at least 4 months, the patient will be randomized to BID or QD dosing at the next randomization timepoint (N-Month 12 or N-Month 18), provided therapeutic goals and additional randomization criteria are met.

Patients who fail to meet therapeutic goals or the additional randomization criteria by N-Month 18 will not be randomized, but may participate in an open-label Extended Treatment Period in which they will receive Genz-112638 at the same dose and regimen that they were receiving at the end of the Lead-in Period or at an adjusted dose. Non-randomized patients will have study visits every 3 months until study completion.

Patients who achieve therapeutic goals and meet additional randomization criteria during the Lead-in Period will be randomized to treatment for the 52-week Primary Analysis Period. Within each of the 2 stratification levels, patients will be randomized in a 1:1 ratio to receive one of the following Genz-112638 dosing regimens for 52 weeks (the Primary Analysis Period):

- BID full dose: Continue on the BID dose that was administered at the end of the Lead-in Period (e.g., Lead-in Period 100 mg BID → Primary Analysis Period 100 mg BID)
- QD full **dose**: Switch to QD dosing at the same total daily dose that was administered at the end of the Lead-in Period (e.g., Lead-in Period 100 mg BID → Primary Analysis Period 200 mg QD)

After completion of R-Week 52 assessments, patients will continue to receive Genz-112638 in the Long-term Treatment Period. Patients still on blinded randomized treatment will continue on their blinded randomized treatment for the first 4 weeks of the Long-term Treatment Period. During these 4 weeks, these patients will be assessed to ensure they have maintained therapeutic goals. Thereafter, patients who have maintained therapeutic goals and remained on blinded randomized treatment during the Primary Analysis Period will receive Genz-112638 at the same total daily dose as their lead-in BID dose, but administered QD (regardless of their randomized treatment) until study completion, while patients who did not maintain therapeutic goals will receive their lead-in BID dose until study completion.

If a patient meets at least one of the following criteria, the Investigator must notify the Genzyme Medical Monitor as soon as possible and the Genzyme Global Pharmacovigilance and Epidemiology Department when appropriate (i.e., serious adverse event [SAE] notifications within 24 hours).

- The patient's hemoglobin level falls below 8 g/dL and remains below 8 g/dL when hematology laboratory testing is repeated within approximately 2 weeks.

- The patient's platelet count falls below 45,000/mm<sup>3</sup> and remains below 45,000/mm<sup>3</sup> when hematology laboratory testing is repeated within approximately 2 weeks, or if the patient experiences a clinically significant bleeding episode assessed by the Investigator as related to a low platelet count.
- A decline in Gaucher disease status which, in the opinion of the Investigator, warrants discontinuation from the study.

## **B. Key Inclusion Criteria/Exclusion Criteria**

### **Inclusion Criteria**

The main inclusion criteria for this study included:

1. The patient is willing and able to provide signed informed consent prior to any study-related procedures.
2. The patient is ≥18 years of age.
3. The patient has a diagnosis of Gaucher disease type 1 confirmed by a documented deficiency of acid β-glucosidase activity by enzyme assay. The patient may be previously untreated, off prior treatment, or receiving enzyme replacement therapy (ERT) for Gaucher disease.
4. The patient meets all of the following criteria at the time of Screening:
  - Hemoglobin level ≥9 g/dL (mean of 2 measurements);
  - Platelet count ≥70,000/mm<sup>3</sup> (mean of 2 measurements);
  - Spleen volume ≤25 multiples of normal (MN);
  - Liver volume ≤2.0 MN.
5. The patient consents to provide a blood sample for genotyping for Gaucher disease and for cytochrome P450 2D6 (CYP2D6) to categorize the patient's predicted rate of metabolism, if these genotyping results are not already available for the patient.
6. Female patients of childbearing potential must have a documented negative pregnancy test prior to administration of the first dose of Genz-112638 in this study. In addition, all female patients of childbearing potential must use a medically accepted form of contraception throughout the study, i.e., either a barrier method or hormonal contraceptive with norethindrone and ethinyl estradiol or similar active components.
7. The patient is willing to abstain from consumption of grapefruit, grapefruit juice, or grapefruit products for 72 hours prior to administration of the first dose of Genz-112638 and throughout the duration of the study.

### **Exclusion criteria**

The main exclusion criteria for this study included:

1. The patient is participating in GZGD02607 study or is eligible for inclusion in GZGD02607 (while enrollment is ongoing) and has access to a physician participating in GZGD02607) or The patient is participating in GZGD02507 study or is eligible for inclusion in GZGD02507 (while enrollment is ongoing) and has access to a physician participating in GZGD02507).
2. The patient received miglustat within 6 months prior to administration of the first dose of Genz-112638 in this study.

3. The patient has had a partial or total splenectomy within 3 years prior to administration of the first dose of Genz-112638 in this study.
4. The patient has any evidence of neurologic disorder (e.g., peripheral neuropathy, tremor, seizures, Parkinsonism or cognitive impairment) or pulmonary involvement (e.g., pulmonary hypertension) as related to Gaucher disease.
5. The patient is transfusion-dependent.
6. The patient has a documented deficiency of iron, vitamin B-12, or folate that requires treatment not yet initiated or, if initiated, the patient has not been stable under treatment for at least 3 months prior to administration of the first dose of Genz-112638 in this study.
7. The patient has documented prior esophageal varices or clinically significant liver infarction or current liver enzymes (alanine transaminase [ALT]/aspartate aminotransferase [AST]) or Total Bilirubin >2 times the upper limit of normal (ULN), unless the patient has a diagnosis of Gilbert Syndrome.
8. The patient has any clinically significant disease, other than Gaucher disease, including cardiovascular, renal, hepatic, gastrointestinal (GI), pulmonary, neurologic, endocrine, metabolic (including hypokalaemia or hypomagnesemia), or psychiatric disease, other medical conditions, or serious intercurrent illnesses that may preclude participation in the study.
9. The patient is known to have any of the following: Clinically significant coronary artery disease including history of myocardial infarction [MI] or ongoing signs or symptoms consistent with cardiac ischemia or heart failure; or clinically significant arrhythmias or conduction defect such as 2nd or 3rd degree atrioventricular (AV) block, complete bundle branch block, prolonged QTc interval, or sustained ventricular tachycardia (VT).
10. The patient is known to have tested positive for the human immunodeficiency virus (HIV) antibody, Hepatitis C antibody, or Hepatitis B surface antigen.
11. The patient has received an investigational product (other than Genz-112638) within 30 days prior to administration of the first dose of Genz-112638 in this study.
12. The patient is scheduled for in-patient hospitalization, including elective surgery, during the study.
13. The patient has a history of cancer, with the exception of basal cell carcinoma, within 5 years prior to administration of the first dose of Genz-112638 in this study.
14. The patient is pregnant or lactating.
15. The patient has received any medication that may cause QTc interval prolongation within 30 days prior to the first dose of Genz-112638. Exception: Diphenhydramine (Benadryl) or other medications used as premedication for ERT infusions are allowed up to 7 days prior to the first dose of Genz-112638.
16. The patient has received for the first time (i.e., the patient is not already chronically using) any of the following medications within 30 days prior to the first dose of Genz-112638:  
Strong inhibitors of CYP2D6 or cytochrome P450 3A4 (CYP3A4)  
Inducers of CYP3A4  
Exception: Premedications for ERT infusions are allowed up to 7 days prior to the first dose of Genz-112638.

17. The patient is a CYP2D6 non-poor metabolizer or an indeterminate metabolizer with one allele identified as active who is chronically receiving both a strong competitive inhibitor of CYP2D6 and a strong competitive inhibitor of CYP3A4 and for whom no reasonable alternative medication exists.  
**OR** The patient is a CYP2D6 poor metabolizer or an indeterminate metabolizer with neither allele known to be active who is chronically receiving a strong competitive inhibitor of CYP3A4 and for whom no reasonable alternative medication exists.  
Exception for both cases: Premedications for ERT infusions are allowed up to 7 days prior to the first dose of Genz-112638.

### **C. Primary Endpoints**

The primary efficacy endpoint will be the percentage (%) of randomized patients who remain stable after treatment with Genz-112638 through R-Week 52 (the Primary Analysis Period) assessed for both dosing regimens (BID full dose, QD full dose) separately along with a difference between the two dosing regimens. This endpoint will be used to evaluate the non-inferiority of the QD regimen compared with the BID regimen.

A patient must meet all of the following (applicable) criteria in each parameter to be considered a success; the spleen volume assessments do not apply to patients who have had a total splenectomy.

#### Stable Hematological Parameters

- If the hemoglobin level does not decrease >1.5 g/dL from Baseline.  
**AND**
- If the platelet count does not decrease >25% from Baseline.  
**AND**

#### 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.

### **D. Additional Endpoints**

The secondary efficacy endpoints include the following: Hemoglobin level, platelet count, and spleen and liver volumes (in MN) (assessed by magnetic resonance imaging [MRI]); biomarkers (chemokine CC motif ligand 18 [CCL18] and chitotriosidase); bone disease assessments (dual-energy X-ray absorptiometry [DXA] and MRI); and Gaucher assessments (mobility, bone crisis, and bone pain). Exploratory endpoints include percent changes from Baseline in investigational biomarkers including glucosylceramide (GL-1) assayed from dried blood spots (DBS) on filter paper and macrophage inflammatory protein-1 beta (MIP1- $\beta$ ) assayed from plasma.

### **E. Prior Medications**

All medications taken by the patient within 30 days prior to patient providing written consent will be recorded on the eCRF. Enzyme-replacement therapy is allowed up to the day before the first dose of Genz-112638.

#### **F. Concomitant Medications**

All medications taken by the patient from administration of Genz-112638 through the final follow-up assessment will be recorded on the eCRF. Grapefruit, grapefruit juice, and grapefruit products are not permitted at any time during the study. Genz-112638 is considered a moderate inhibitor of CYP2D6 and thus may decrease the metabolism of drugs that rely on this enzyme for their clearance; there is no change in the recommended dosing for Genz-112638.

Temporary use of the following medications is permitted in any patient (regardless of CYP2D6 metabolizer status) and will be managed with respect to the duration of temporary use and actions taken (including a dose interruption of Genz-112638, where applicable):

- Medications that cause QTc interval prolongation
- CYP3A4 inducers
- Strong or moderate CYP2D6 inhibitors
- Strong or moderate CYP3A4 inhibitors

New chronic use (>2 weeks) of the following medications is permitted and will be managed as described below:

- CYP3A4 inducers
- Strong or moderate CYP2D6 inhibitors
- Strong or moderate CYP3A4 inhibitors (permitted only in patients who are CYP2D6 non-PMs, i.e., extensive, intermediate, or ultra-rapid metabolizers or indeterminate metabolizers with one allele known to be active; such patients are not permitted to chronically receive both a strong or moderate CYP3A4 inhibitor and a strong or moderate CYP2D6 inhibitor).

Patients initiating new chronic therapy with a strong or moderate inhibitor of CYP2D6 or CYP3A4 will require a dose reduction of Genz-112638 at the start of co-administration as follows:

- A patient on 300 mg daily (150 mg BID) will receive 100 mg BID;
- A patient on 200 mg daily (100 mg BID or 200 mg QD) will receive 100 mg daily (in the same dosing regimen);
- A patient on 100 mg daily (50 mg BID or 100 mg QD) will receive 50 mg QD;
- A patient on 50 mg QD will receive 50 mg every other day (QOD);
- A patient on 50 mg QOD will interrupt the dose.

#### **H. Safety Assessments**

The safety of eliglustat will be assessed by evaluating the incidence of reported AEs, SAEs, and changes from Baseline through study completion in vital signs, physical examination, bone disease assessments, electrophysiology assessments (including 24-hour Holter monitoring and 12-lead ECG and routine clinical laboratory assessments (chemistry, hematology, and urinalysis), as well as pregnancy testing for female patients of child bearing age.

## 6 Review of Efficacy

### Efficacy Summary

The statistical reviewer for this application, Benjamin Vali, MS, identified no statistical review issues that would preclude product approval. Overall, Mr. Vali found the designs of both the ENGAGE and ENCORE trials were adequate from a statistical perspective. See his full review dated July 22, 2014.

Mr. Vali stated that the results from the ENGAGE and ENCORE trials collectively support the efficacy of eliglustat. Efficacy was established by the ENGAGE trial, 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 key supportive ENCORE trial, which demonstrated that patients who had reached therapeutic goals with CERZYME 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. This reviewer agrees with the assessment of the statistical reviewer.

#### 6.1 Indication

The Applicant proposes the following indication:

“CERDELGA (eliglustat tartrate) is indicated for the long-term treatment of adult patients with Gaucher disease type 1.”

The Applicant has proposed that eliglustat (b) (4) be used in patients who are intermediate (IM) or extensive (EM) CYP2D6 metabolizers. This would prohibit dosing of patients who are (b) (4) ultra rapid metabolizers (UM).

### 6.1.1 Methods

See section 5.3

### 6.1.2 Demographics

The majority of patients in the trials were white, approximately 25% were Jewish, and most were young adults, with a mean age in the 30's (spanning from 16.1 to 69.3 years). The mean body mass index (BMI) was in the normal range, and most patients were non-smokers. Few Hispanic or Latino patients were enrolled in ENGAGE and the Phase 2 study, but 39% of patients in ENCORE had Hispanic or Latino ethnicity.

#### **Table 28: Demographics (Phase 2, ENGAGE and ENCORE)**

	Treatment-Naïve Patients			Patients Switching from ERT	
	ENGAGE		Phase 2 Eliglustat (N=26)	ENCORE	
	Eliglustat (N=20)	Placebo (N=20)		Eliglustat (N=99)	Cerezyme (N=47)
Sex, n (%)					
Male, n (%)	8 (40)	12 (60)	10 (38)	43 (43)	21 (45)
Female, n (%)	12 (60)	8 (40)	16 (62)	56 (57)	26 (55)
Race, n (%)					
White	19 (95)	20 (100)	16 (73) <sup>a</sup>	91 (92)	45 (96)
Other	0	0	10 (38) <sup>a</sup>	1 (1)	0
Asian	1 (5)	0	0	1 (1)	0
Black or African American	0	0	0	6 (6)	2 (4)
Jewish Descent, n (%)					
Yes	3 (15)	8 (40)	7 (27)	25 (25)	13 (28)
No	17 (85)	12 (60)	16 (62)	73 (74)	34 (72)
Unknown	0	0	3 (12)	0	0
Age at Day 1 (years)					
Mean (SD)	31.6 (11.55)	32.1 (11.26)	34.47 (12.960)	37.2 (14.03)	38.6 (15.19)
Min, max	16.6, 62.9	16.1, 59.3	18.6, 60.3	18.1, 69.3	18.2, 66.2
Baseline weight (kg)					
Mean (SD)	64.8 (11.74)	68.6 (17.17)	61.47 (11.018)	70.8 (17.28)	67.5 (14.96)
Min, max	40.0, 81.7	46.0, 102.2	50.5, 104.0	43.1, 136.0	40.6, 101.1
Baseline height (cm)					
Mean (SD)	166.2 (9.91)	170.0 (12.02)	165.12 (9.747)	167.4 (10.10)	166.1 (9.95)

	Treatment-Naïve Patients			Patients Switching from ERT	
	ENGAGE		Phase 2 Eliglustat (N=26)	ENCORE	
	Eliglustat (N=20)	Placebo (N=20)		Eliglustat (N=99)	Cerezyme (N=47)
Min, max	149.0, 184.0	147.9, 192.0	148.0, 186.0	144.9, 188.0	142.5, 183.0
Baseline BMI (kg/m <sup>2</sup> )					
Mean (SD)	23.3 (2.74)	23.4 (3.54)	22.56 (3.529)	25.2 (5.33)	24.4 (4.65)
Min, max	18.0, 27.7	18.4, 30.9	18.5, 36.0	16.8, 49.4	17.1, 38.2
Smoking status, n (%)					
None	12 (60)	13 (65)	N/A	71 (72)	36 (77)
Current smoker	1 (5)	2 (10)	N/A	13 (13)	4 (9)
Past smoker	7 (35)	5 (25)	N/A	15 (15)	7 (15)
Yes	N/A	N/A	1 (4)	N/A	N/A
No	N/A	N/A	25 (96)	N/A	N/A

	Treatment-Naïve Patients			Patients Switching from ERT	
	ENGAGE		Phase 2	ENCORE	
	Eliglustat (N=20)	Placebo (N=20)	Eliglustat (N=26)	Eliglustat (N=99)	Cerezyme (N=47)
Residual Acid $\beta$ -glucosidase Activity (nmol/hour/mg)					
Mean (SD)	2.29 (3.380)	2.04 (3.793)	0.467 (0.7728)	1.18 (1.35)	1.08 (0.97)
Min, Max	0.0, 15.7	0.0, 15.5	0.00, 3.79	0.0, 9.9	0.0, 5.8
Gaucher Disease Genotype, n (%)					
N370S/Other	8 (40)	8 (40)	11 (42)	31 (31)	12 (26)
N370S/N370S	5 (25)	6 (30)	3 (12)	19 (19)	11 (23)
N370S/L444P	2 (10)	4 (20)	8 (31)	35 (35)	17 (36)
L444P/Other	3 (15)	1 (5)	3 (12)	2 (2)	0
Other/Other	2 (10)	1 (5)	1 (4)	11 (11)	7 (15)
Chitotriosidase Genotyping Category, n (%)					
Normal	13 (65)	16 (80)	19 (73)	56 (57)	26 (55)
Heterozygous	6 (30)	4 (20)	5 (19)	28 (28)	18 (38)
Homozygous Mutation	1 (5)	0	2 (8)	6 (6)	1 (2)
Missing/Unknown	0	0	0	9 (9)	2 (4)
Age at first Gaucher symptom onset (year)					
Mean (SD)	16.74 (10.526)	15.22 (12.362)	11.82 (10.946)	12.3 (11.8)	15.94 (14.22)
Min, Max	3.0, 38.0	0.0, 37.0	0.6, 40.0	1.0, 59.0	0.0, 54.0
Splenectomy performed					
No	N/A	N/A	N/A	70 (71)	38 (81)
Partial	N/A	N/A	N/A	1 (1)	1 (2)

Clinical Review  
 Karyn L. Berry, MD, MPH  
 NDA 205494  
 Cerdelga (Eliglustat tartrate)

	Treatment-Naïve Patients			Patients Switching from ERT	
	ENGAGE		Phase 2	ENCORE	
	Eliglustat (N=20)	Placebo (N=20)	Eliglustat (N=26)	Eliglustat (N=99)	Cerezyme (N=47)
Total	N/A	N/A	N/A	28 ( 28)	8 ( 17)
Splenomegaly severity <sup>d</sup> , n (%)					
None/Mild	0	0	0	68 (89) <sup>e</sup>	37 (95) <sup>e</sup>
Moderate	12 (60)	15 (75)	14 (54)	8 (11) <sup>e</sup>	2 (5) <sup>e</sup>
Severe	8 (40)	5 (25)	12 (46)	0	0
Hepatomegaly severity <sup>d</sup> , n (%)					
None/mild	6 (30)	9 (45)	5 (19)	91 (92)	46 (98)
Moderate	14 (70)	11 (55)	20 (77)	8 (8)	1 (2)
Severe	0	0	1 (4)	0	0
Anaemia severity <sup>d</sup> , n(%)					
None	15 (75)	17 (85)	13 (50)	99 (100)	47 (100)
Mild	2 (10)	2 (10)	3 (12)	0	0
Moderate	2 (10)	1 (5)	6 (23)	0	0
Severe	1 (5)	0	4 (15)	0	0
Thrombocytopenia severity <sup>d</sup> , n(%)					
None	0	0	0	15 (15)	2 (4)
Mild	0	3 (15)	3 (12)	84 (85)	45 (96)
Moderate	17 (85)	13 (65)	10 (38)	0	0
Severe	3 (15)	4 (20)	13 (50)	0	0
CYP2D6 Metabolizer status, n (%)					
Poor	0	0	1 (4)	4 (4)	2 (4)

	Treatment-Naïve Patients			Patients Switching from ERT	
	ENGAGE		Phase 2	ENCORE	
	Eliglustat (N=20)	Placebo (N=20)	Eliglustat (N=26)	Eliglustat (N=99)	Cerezyme (N=47)
Intermediate	1 (5)	2 (10)	0	10 (10)	8 (17)
Extensive	18 (90)	18 (90)	25 (96)	79 (80)	33 (70)
Ultra-Rapid	1 (5)	0	0	4 (4)	1 (2)
Indeterminate	0	0	0	2 (2)	2 (4)

Source: Applicant's table

Disease severity was defined as follows: Splenomegaly: Mild: <5 MN spleen volume; Moderate: ≥5 to ≤15 MN; Severe: >15 MN. Hepatomegaly: Mild: <1.25 MN liver volume; Moderate: ≥1.25 to ≤2.50 MN; Severe: >2.50 MN. Anaemia: None: haemoglobin ≥12 g/dL (males), ≥11 g/dL (females); Mild: ≥11 to <12 g/dL (males), ≥10 to <11 g/dL (females); Moderate: ≥9 to <11 g/dL (males), ≥9 to <10 g/dL (females); Severe: <9 g/dL. Thrombocytopenia: None: platelets ≥130000 to ≤400000 /mm<sup>3</sup>; Mild: ≥100000 to <130000 /mm<sup>3</sup>; Moderate: ≥60000 to <100000 /mm<sup>3</sup>; Severe: <60000 /mm<sup>3</sup>.

**Medical Reviewer's comments: The majority of patients were CYP2D6 extensive metabolizers, while the majority of intermediate metabolizers were in the ENCORE trial. Otherwise, demographic characteristics were generally similar across the trials.**

### 6.1.3 Subject Disposition

**Table 29: Comparison of Disposition of Patients in ENGAGE, Phase 2 and ENCORE**

	Treatment-Naïve Patients			Patients Switching from ERT	
	ENGAGE		Phase 2	ENCORE (FAS)	
	Eliglustat (N=20)	Placebo (N=20)	Eliglustat (N=26)	Eliglustat (N=106)	Cerezyme (N=54)
Randomized, n(%)	20 (100)	20 (100)	N/A	106 (100)	54 (100)
Treated, n(%)	20 (100)	20 (100)	26 (100)	106 (100)	53 (98)
Completed Primary Analysis Period <sup>a</sup> , n(%)	19 (95)	20 (100)	22 (85)	104 (98)	52 (96)
Withdrew prior to end of Primary Analysis Period <sup>a</sup> , n (%)	1 (5)	0	4 (15)	2 (2)	2 (4)
Adverse Event(s)	0	0	2 (8)	2 (2)	1 (2)
Non-compliant	0	0	0	0	1 (2)
Wishes to Withdraw	1 (5)	0	0	0	0
Other	0	0	2 (8) <sup>b</sup>	0	0

ERT = enzyme replacement therapy (for Gaucher disease); FAS = Full Analysis Set

<sup>a</sup> Primary analysis period was 39 Weeks for ENGAGE and 52 weeks for Phase 2 and ENCORE.

<sup>b</sup> "Other" was pregnancy for both patients.

Applicant's table

**Medical Reviewer's comments: The majority of all patients in each trial completed the PAP (39 weeks for ENGAGE and 52 weeks for the Phase 2 trial and ENCORE).**

**Table 30: Summary of Doses Received During PAP**

Dose during PAP	Treatment-Naïve Patients		Patients Switching from
	ENGAGE Eliglustat (N=20)	Phase 2 Eliglustat (N=26)	ENCORE (FAS) Eliglustat (N=106)
50 mg BID	3 (15%)	8 (31%) <sup>a</sup>	21 (20%)
100 mg BID	17 (85%)	18 (69%)	34 (32%)
150 mg BID	NA	0	51 (48%)

Source: Applicant's table  
 BID= twice a day; ERT = enzyme replacement therapy (for Gaucher disease); FAS = Full Analysis Set; NA = not applicable; PAP = primary analysis period  
 a Includes 2 patients who received a single 50 mg dose during the dose-adjustment period and then discontinued from study

#### 6.1.4 Analysis of Primary Endpoint(s)

##### ENGAGE Trial

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 31: ENGAGE: Summary of Values and Percentage Change in Spleen Volume (MN) from Baseline to Week 39: Full Analysis Set**

Time Point / Change	Statistic	Eliglustat (N=20)	Placebo (N=20)	Treatment Difference (Eliglustat)
Baseline	n	20	20	NA
	Mean (SD)	13.89 (5.929)	12.50 (5.959)	NA
	Median	12.09	11.05	NA
	Min, Max	5.94, 28.39	6.32, 25.27	NA
Week 39	n	20	20	NA
	Mean (SD)	10.17 (5.065)	12.84 (6.395)	NA
	Median	8.34	10.97	NA
	Min, Max	4.12, 21.90	6.63, 26.17	NA

Absolute Change from Baseline to Week 39	n Mean (SD) Median Min, Max	20 3.72 (2.377) -3.02 -9.1, 0.0	20 0.35 (1.050) 0.34 -1.8, 2.3	
% Change from Baseline to Week 39	Mean (SD) Median Min, Max LS Mean (SEM) 95% CI p-value	-27.58 (12.591) -29.03 -51.52, 0.00 -27.77 (2.37) -32.57, -22.97 NA	2.07 (8.777) 4.20 -20.91, 13.68 2.26 (2.37) -2.54, 7.06 NA	NA NA NA -30.03 (3.35) -36.82, -23.24 <0.0001

Source: Statistical Review

**Medical Reviewers' comments: Based on the results above, eliglustat demonstrated superior improvement in the percentage change from baseline for spleen volume at Week 39 when compared to placebo. The statistical reviewer noted consistent conclusions when the analysis was repeated utilizing the PP and Week-39-Completer analysis sets. Mr. Vali, also noted in his review that no single site influenced or drove the overall study results and there were no patients who were designated as outliers.**

#### ENCORE Trial

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

As recommended by the US Food and Drug Administration (FDA), the efficacy endpoint for the Agency's analysis (FDA-recommended efficacy endpoint) will be 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%.

For the FAS set the least squares (LS) mean percentage change in spleen volume (MN) from Baseline to Week 52 in the eliglustat group was -5.00% compared to -3.26% in the Cerezyme group. The upper bound of the 95% CI in the difference of the estimated mean change (3.25%) was less than the pre-specified threshold of 15%.

**Table 32: ENCORE Trial -Summary of Values and Percentage Change in Spleen Volume (MN) from Baseline to Week 52: FAS**

Timepoint	Eliglustat (N=106)	Cerezyme (N=53)	Treatment Difference (Eliglustat-Cerezyme)
<b>Baseline Spleen Volume (MN)</b>			
n	106	53	-
Mean (SD)	3.17 (1.346)	2.74 (1.152)	-
Median	2.87	2.24	-
Min, Max	1.1, 7.4	1.1, 5.8	-
<b>Week 52 Spleen Volume (MN)</b>			
n	106	53	-
Mean (SD)	3.04 (1.363)	2.64 (1.059)	-
Median	2.93	2.42	-
Min, Max	0;9. 7.6	1.1, 5.2	-
<b>Absolute Change from Baseline to Week 52</b>			
n	106	53	-
Mean (SD)	-0.13 (0.470)	-0.10 (0.299)	-
Median	-0.14	-0.10	-
Min, Max	-1.7, 1.3	-0.8, 0.7	-

% Change from Baseline to Week 52			
n	106	53	-
Mean (SD)	-5.11 (14.548)	-3.06 (10.466)	-
Median	-6.00	-4.40	-
Min, Max	-48.7, 31.8	-22.1, 20.1	-
LS Mean (SEM) [1]	-5.00 (1.52)	-3.26 (1.99)	-1.73 (2.52)
95% CI [1]	-8.00, -1.99	-7.21, 0.68	-6.72, 3.25
p-value [1]	NA	NA	0.4924
LS Mean (SEM) [2]	-6.17 (1.59)	-3.21 (2.15)	-2.83 (2.71)
95% CI [2]	-9.17, -2.93	-7.47, 1.06	-8.14, 2.47
p-value [2]	NA	NA	0.2922

The alternate primary efficacy endpoint for the ENCORE trial was the percentage (%) of patients who remained stable for 52 weeks (the primary analysis period). 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]). 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 33: ENCORE - 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)

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. A numerically greater percentage of eliglustat patients met the criterion for stable liver volume compared to Cerezyme, 96.0% versus 93.6%, respectively.

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.

**Table 34: ENCORE Trial -Summary of Proportion of Patients who Met Stable Hematologic and Organ Volume Criteria of the Primary Endpoint at Week 52: Per Protocol Set**

Variable	Eliglustat (N=99)	Cerezyme (N=47)
Patients Meeting Hemoglobin Criteria, n (%)	94 (94.9)	47 (100.0)
Exact 95% CI	(0.886, 0.983)	-
Patients Meeting Platelets Criteria, n (%)	92 (92.9)	47 (100.0)
Exact 95% CI	(0.860, 0.971)	-
Patients Meeting Spleen Volume Criteria, n (%)*	67 (94.4)	39 (100.0)
Exact 95% CI	(0.862, 0.984)	-
Patients Meeting Liver Volume Criteria, n (%)	95 (96.0)	44 (93.6)
Exact 95% CI	(0.900, 0.989)	(0.825, 0.987)

\* Patient percentages are based on the total number of non-splenectomized patients in the particular treatment group.

**Medical Reviewer's comments: The Applicant successfully demonstrated non-inferiority of eliglustat in the ability to achieve maintenance of spleen volume over a 52 week period compared to Cerezyme and in the proportion of patients who were stable at 52 (based on hematologic and organ volume over a 52 week period).**

**Table 35: Comparison of Organ Volume and Hematology Results from ENGAGE (FAS) and the Phase 2 Study (ITT)**

	ENGAGE*		Phase 2 Study Eliglustat
	Eliglustat (N=20)	Placebo (N=20)	
<b>Spleen Volume, mean (SD)</b>			
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]
<b>Haemoglobin, mean (SD)</b>			
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]
<b>Liver volume (MN), mean (SD)</b>			
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]
<b>Platelets, mean (SD)</b>			
Baseline, x10 <sup>9</sup> /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]

**Table 36: Organ Volume and Hematology Results in Patients Switching from ERT in ENCORE: Per Protocol Set**

	<b>Eliglustat (N=99)</b>	<b>Cerezyme (N=47)</b>
<b>Spleen Volume, mean (SD)</b>		
Baseline, MN	3.227 (1.3692) [N=70]	2.625 (1.0763) [N=39]
6 Months, % change	-4.350 (13.5641) [N=70]	-4.100 (10.5711) [N=39]
12 Months, % change	-6.071 (14.3461) [N=70]	-3.008 (10.5009) [N=39]
<b>Hemoglobin, mean (SD)</b>		
Baseline, g/dL	13.592 (1.2467) [N=98]	13.797 (1.2234) [N=47]
3 Months, g/dL change	-0.443 (0.7464) [N=96]	0.108 (0.7138) [N=46]
6 Months, g/dL change	-0.282 (0.7044) [N=98]	0.066 (0.7402) [N=46]
9 Months, g/dL change	-0.355 (0.7990) [N=97]	0.142 (0.6607) [N=46]
12 Months, g/dL change	-0.213 (0.7090) [N=98]	0.038 (0.6639) [N=47]
<b>Platelets, mean (SD)</b>		
Baseline, x10 <sup>9</sup> /L	206.750 (80.7371) [N=98]	192.298 (57.3367) [N=47]
3 Months, % change	-3.415 (23.9430) [N=96]	0.717 (14.1613) [N=46]
6 Months, % change	0.541 (18.1696) [N=98]	1.716 (11.3966) [N=45]
9 Months, % change	-0.683 (14.5073) [N=96]	4.017 (13.5319) [N=46]
12 Months, % change	3.787 (18.8507) [N=98]	2.930 (11.8867) [N=47]
<b>Liver volume, mean (SD)</b>		
Baseline, MN	0.948 (0.1911) [N=98]	0.911 (0.1622) [N=47]
6 Months, % change	-0.493 (8.8813) [N=97]	1.879 (9.6937) [N=47]
12 Months, % change	1.780 (9.6429) [N=98]	3.572 (10.2364) [N=47]

Source: Applicant's table

**Table 37: ENGAGE - Summary of Gaucher Therapeutic Goals (FAS)**

Parameter	Statistics	Placebo (N=20)	Eliglustat (N=20)
<b>Met Hemoglobin Goal at Week 39</b>			
Yes	n (%)	14 ( 70)	18 ( 90)
No	n (%)	6 ( 30)	2 ( 10)
<b>Met Platelet Count Goal at Week 39</b>			
Yes	n (%)	0	5 ( 25)
No	n (%)	20 (100)	15 ( 75)
<b>Met Spleen Volume Goal at Week 39</b>			
Yes	n (%)	0	9 ( 45)
No	n (%)	20 (100)	11 ( 55)
<b>Met Liver Volume Goal at Week 39</b>			
Yes	n (%)	0	0
No	n (%)	20 (100)	20 (100)
<b>Met All 4 Goals at Week 39</b>			
Yes	n (%)	0	0
No	n (%)	20 (100)	20 (100)
<b>Number of Goals Met at Week 39</b>			
0	n (%)	6 ( 30)	1 ( 5)
1	n (%)	14 ( 70)	8 ( 40)
2	n (%)	0	9 ( 45)
3	n (%)	0	2 ( 10)
4	n (%)	0	0

### 6.1.5 Analysis of Secondary Endpoints(s)

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.

**Table 38: ENGAGE- Primary and Secondary Endpoints**

	Statistic	Eliglustat (N=20)	Placebo (N=20)	Treatment Difference (Eliglustat-
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 ( $\times 10^9/L$ ) 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

### 6.1.6 Other Endpoints

*Summary by trials for Bone mineral density (BMD) endpoint:*

#### Phase 2 Study 0304

This single-arm phase 2 study showed a 4.4% increase in lumbar (L1-L4) BMD (g/cm<sup>2</sup>) at 12 months with eliglustat therapy in 20 patients and an increase of 7.3% at 48 months in 15 patients over Baseline. Improvement in lumbar Z-scores observed after 52 weeks and 48 months respectively were 0.3 and 0.7. These figures are driven in part by one subject with unexplained dramatic responses in BMD efficacy and by inclusion of younger patients undergoing natural bone accrual.

#### ENGAGE

No conclusions can be drawn from BMD efficacy data in 2507. Trial 2507 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 of 2507 should provide further clarity on the BMD efficacy of eliglustat in GD 1.

#### ENCORE

BMD values 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. At Week 52, subjects in the eliglustat arm had a mean percent change at L1-L4 DXA (g/cm<sup>2</sup>) of 0.52; those in the cerezyme arm had a value of 0.76. There were insignificant differences in BMD (g/cm<sup>2</sup> and Z-scores) between both groups at Baseline and at Week 52, and minimal changes in both groups for these parameters at Week 52. BMD data showed no relationship to the stratification randomization indicator (equivalent ERT dose < 35 U/kg/q2w or  $\geq$  U/kg/q2w), or to subject age.

**Medical Reviewer's comments:** [REDACTED] (b) (4)

**Bone endpoints were either tertiary or exploratory endpoints in the ENGAGE and ENCORE trial. They were secondary endpoints in the open label Phase 2 trial.** [REDACTED] (b) (4)

**While a relationship between lower BMD and increased fracture risk in Type I GD has been shown (Khan 2012), there is no evidence that therapeutically increasing BMD in these patients reduces fracture risk or improves any other GD 1-associated bone-related pathology.**

### *Biomarkers*

Several biomarkers, including plasma GL-1, were explored during the clinical development of eliglustat. Results for some biomarkers were inconsistent among patients or studies. However, the result for plasma GL-1 was consistent among the Phase 2 and Phase 3 studies. Since GL-1 is related to the mechanism of action, the findings were reviewed by the clinical pharmacologists. In treatment naïve patients, the mean percentage reduction from baseline was 80% at week 52 in the Phase 2 trial and 75% at week 39 in patients receiving eliglustat in the ENGAGE trial. In treatment experienced patients (ENCORE), patients who switched to eliglustat had a reduction in GL-1 levels at Week 13 and maintained this decrease through Week 52, with a 61% decrease from baseline in plasma GL-1 levels. OCP found that overall, the reduction in plasma GL-1 concentration observed in patients receiving eliglustat is consistent with the mechanism of action of eliglustat as a substrate reduction therapy that inhibits glucosylceramide synthase.

### 6.1.7 Subpopulations

The study participants for both ENGAGE and ENCORE were primarily white adults between the ages of 18 and 65. Consequently, no race or age subgroup analyses were conducted. The analyses for the primary endpoint in both ENGAGE and ENCORE were re-assessed by the gender and geographic subgroup.

The statistical reviewer, Mr. Vali, found that the results were consistent across the gender subgroups and geographic subgroups in both ENGAGE and ENCORE trials. See Mr. Vali's full review.

The special subgroup population of clinical interest was the CYP2D6 metabolizer status at baseline (i.e., poor, intermediate, extensive, ultra-rapid, or unknown). The study participants for both ENGAGE and ENCORE were primarily extensive metabolizers.

**Table 39: Summary of Percentage Change from Baseline to Week 39 in Spleen Volume (MN) by CYP2D6 Metabolizer Status – ENGAGE (FAS)**

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					

Source: Statistical Reviewer's Table.

Note: MN = multiples of normal; SD = standard deviation.

**Table 40: 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: Statistical Reviewer's Table.  
 Note: Denominators for percentages are *n*.

### 6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

There is a trend for increase in response (decline in spleen and liver volume from baseline, increase in hemoglobin levels and platelet count from baseline) with increasing steady state average trough concentrations of the drug as evidenced in treatment naïve subjects in both Phase 2 (GZGD00304) and ENGAGE study. However, for treatment experienced patients (who were switched from ERT to eliglustat), there was no clinically relevant E-R relationship observed.

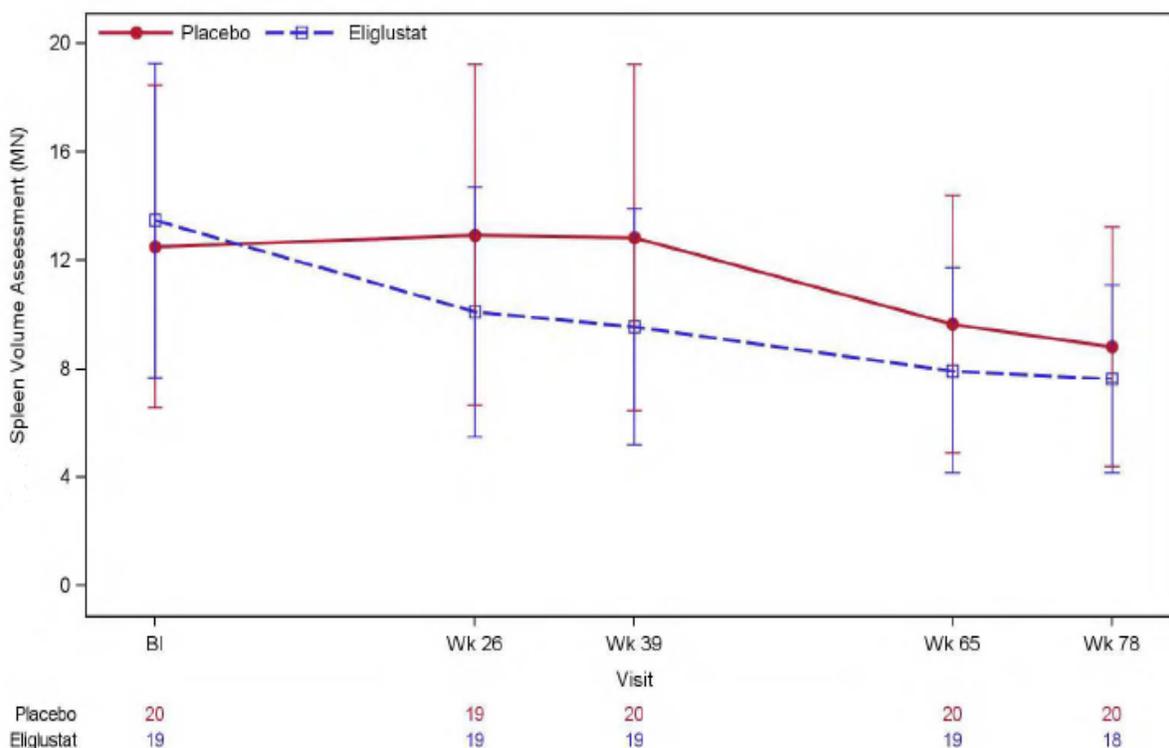
### 6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

The Applicant submitted long term data from ENGAGE, ENCORE and the Phase 2 trial.

#### ENGAGE

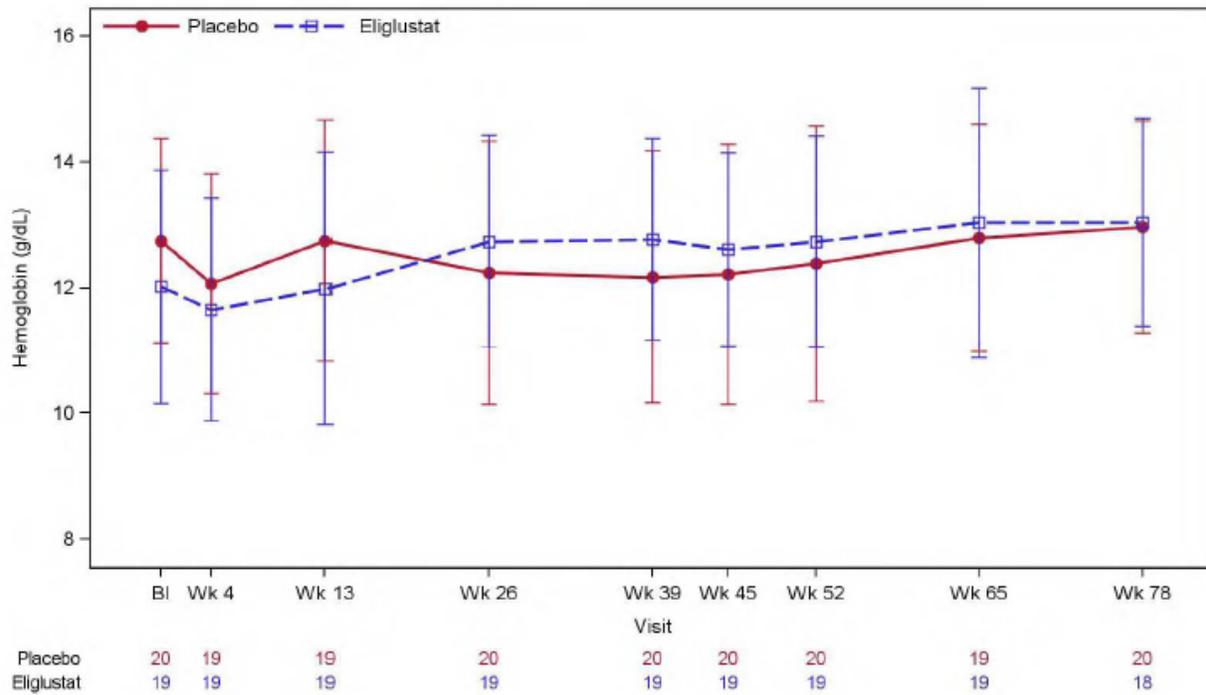
After Week 39 assessments were completed, each patient then entered the Open-Label Treatment Period where all patients received eliglustat from post-Week 39 (Day 1 of the Open-Label Treatment Period) through study completion. Each patient's total duration of participation in this study (including both the Double-Blind and Open-Label Treatment Periods) was planned to be at least 130 weeks, and each patient could continue participation for a total of up to six years. This Open-Label Treatment Period has been ongoing at the time of NDA filing, and the most up-to-date submission by the applicant includes a total exposure of 78 weeks.

**Figure 2: Mean ( $\pm$  SD) Spleen Volume (MN) over Time – ENGAGE (FAS)**



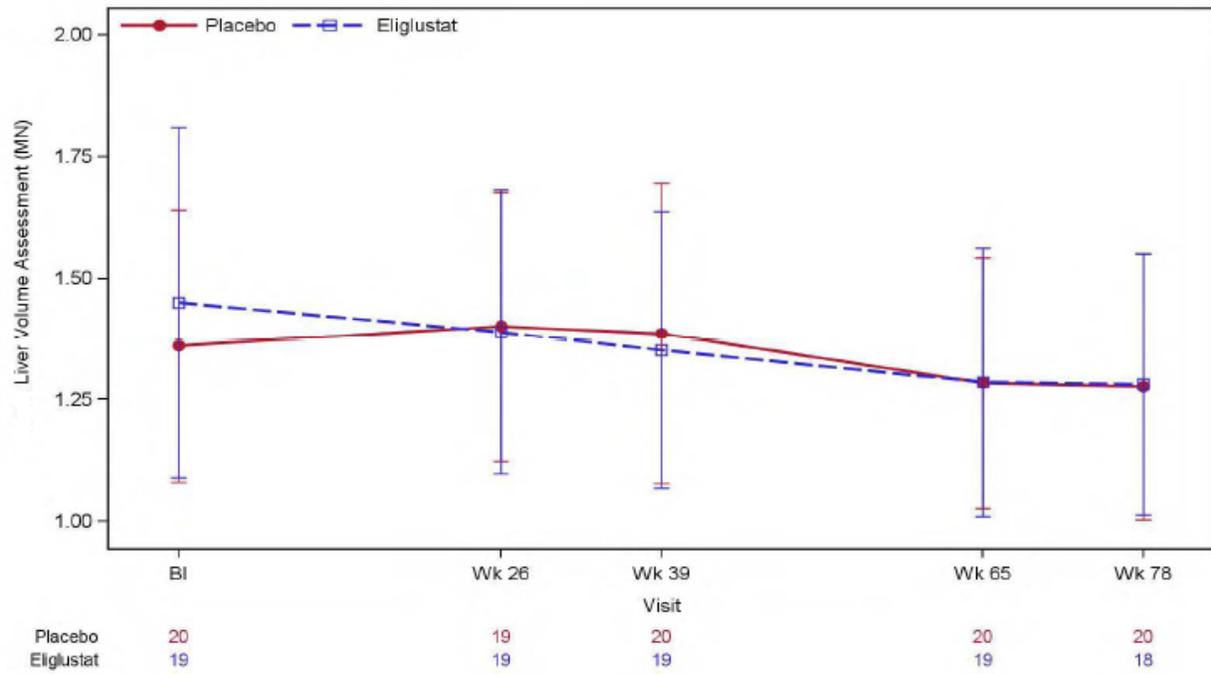
Source: Statistical review

**Figure 3: Mean ( $\pm$  SD) Hemoglobin Level (g/dL) over Time – ENGAGE (FAS)**



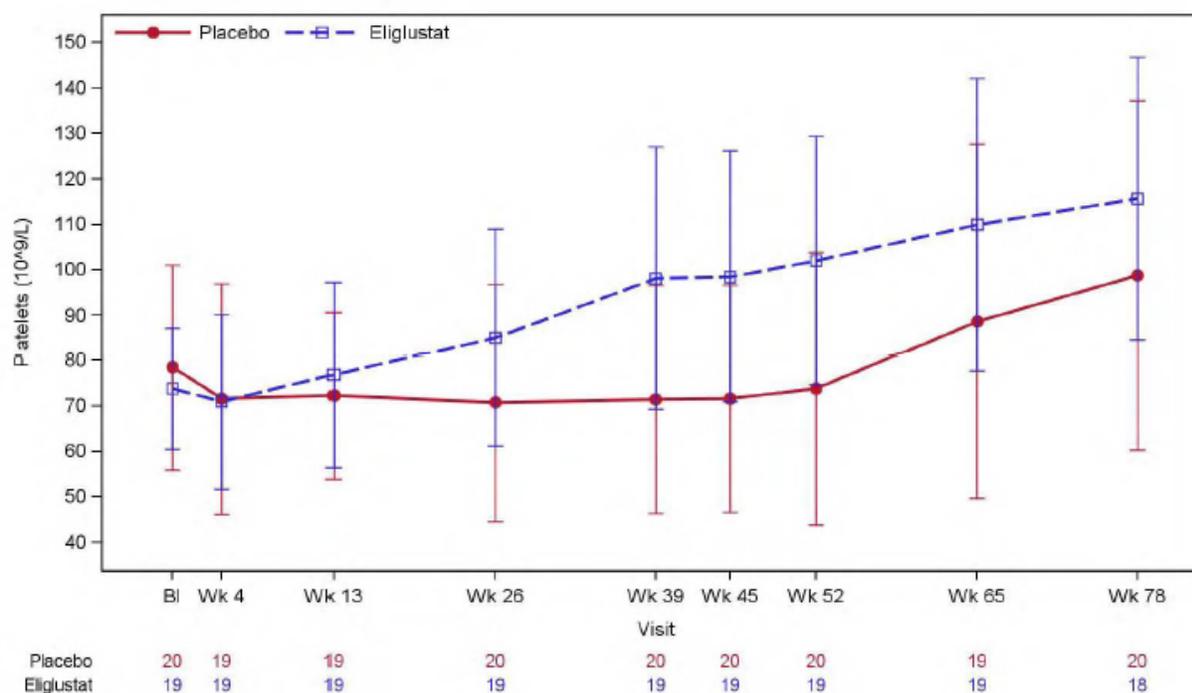
Source: Statistical review

**Figure 4: Mean ( $\pm$  SD) Liver Volume (MN) over Time – ENGAGE (FAS)**



Source: Statistical review

**Figure 5: Mean ( $\pm$  SD) Platelet Count ( $10^9/L$ ) over Time – ENGAGE (FAS)**



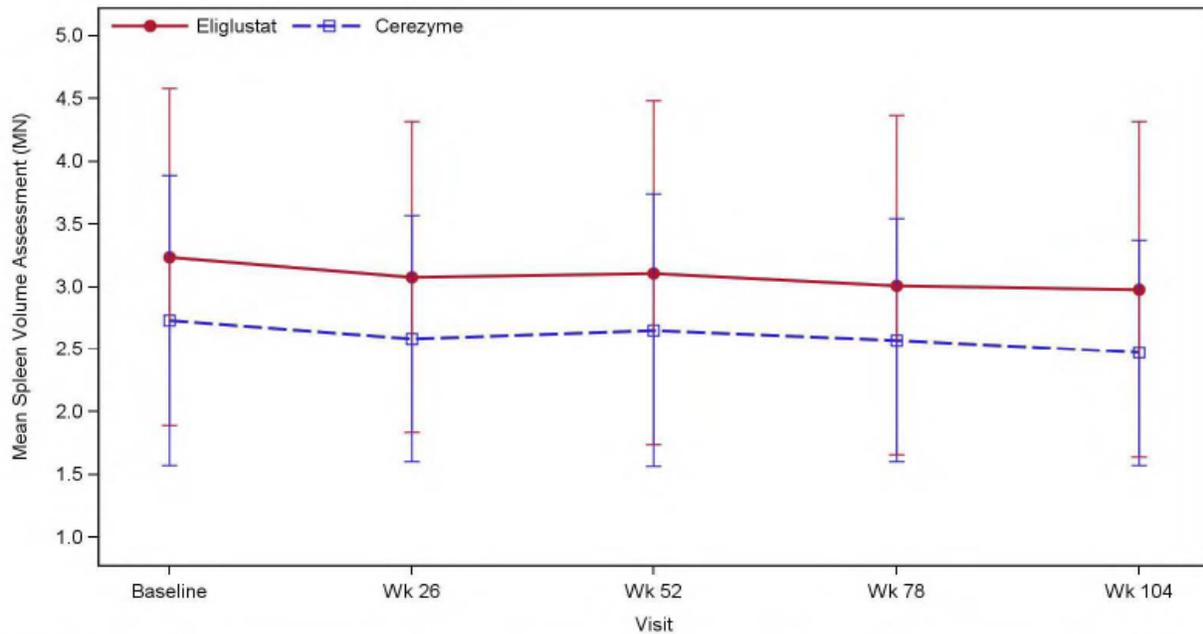
Source: Statistical review

**Medical Reviewer's comments:** *This reviewer agrees with Dr. Vali's conclusions that that patients who were randomized at Baseline to eliglustat for the Double-Blind Treatment Period continued improving in all four efficacy parameters after Week 39 and patients who were randomized at Baseline to placebo for the Double-Blind Treatment Period started improving in all four efficacy parameters after Week 39 when these patients began exclusive treatment with eliglustat.*

ENCORE

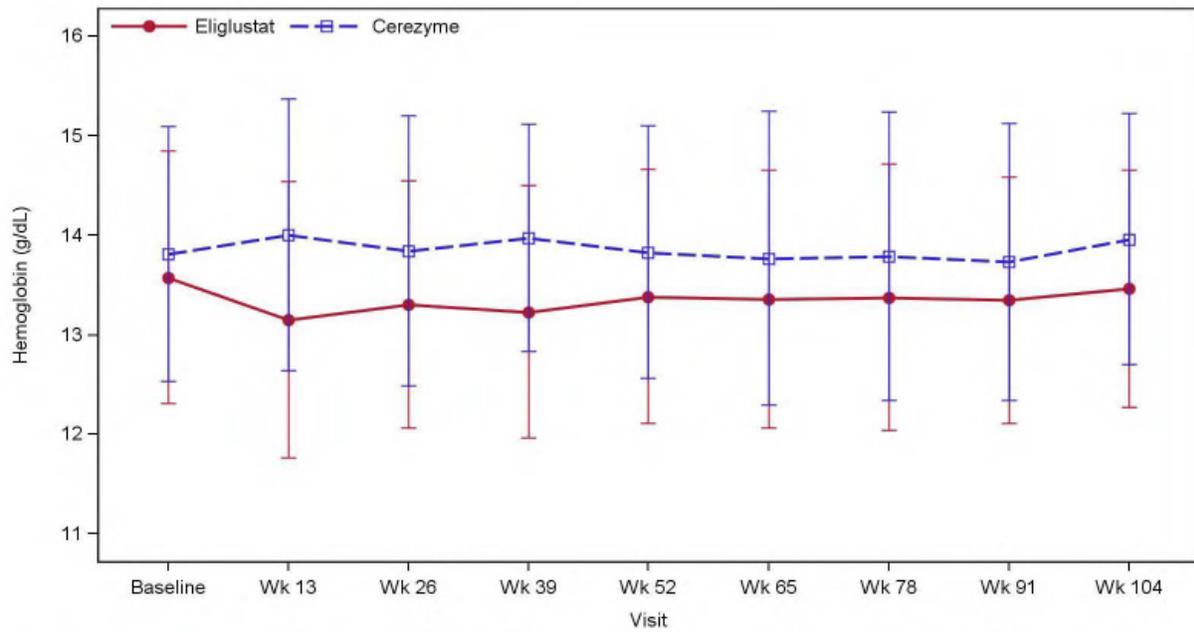
After week 52, each patient's total duration of participation in this study (including both the Primary Analysis and Long-Term Treatment Periods) was planned to be at least 104 weeks, and each patient could continue participation for a total of up to 5.5 years. This Long-Term Treatment Period has been ongoing at the time of NDA filing, and the most up-to-date submission by the applicant includes a total exposure of 104 weeks.

**Figure 6: Mean ( $\pm$  SD) Spleen Volume (MN) over Time – ENCORE (FAS)**



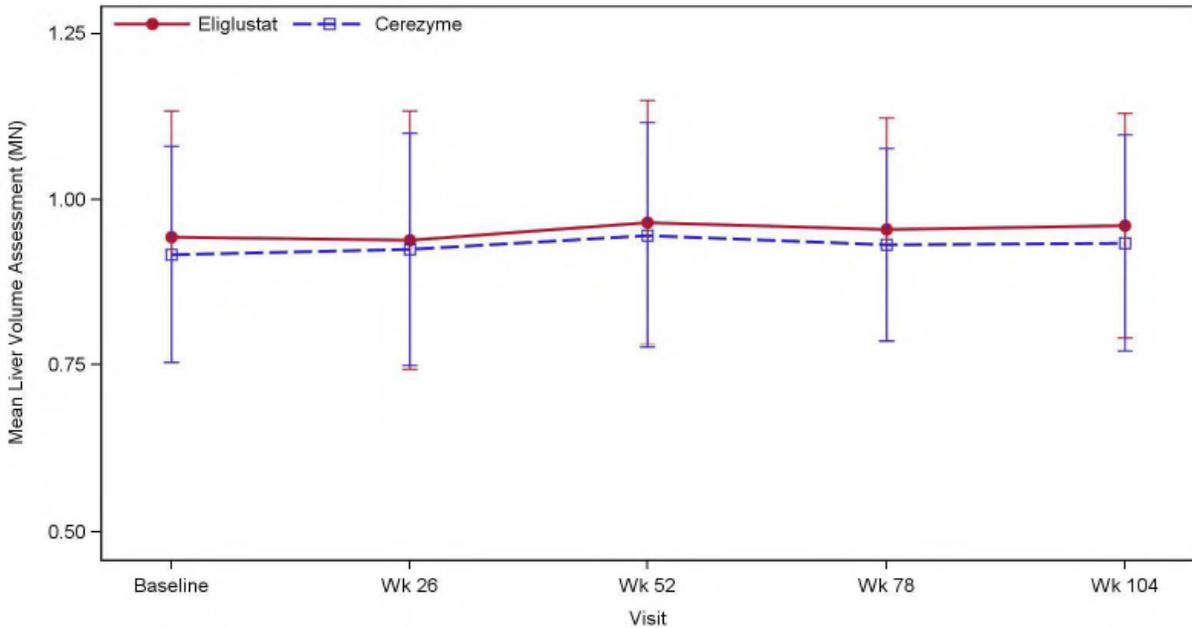
Source: Statistical Review

**Figure 7: Mean ( $\pm$  SD) Hemoglobin Level (g/dL) over Time – ENCORE (FAS)**



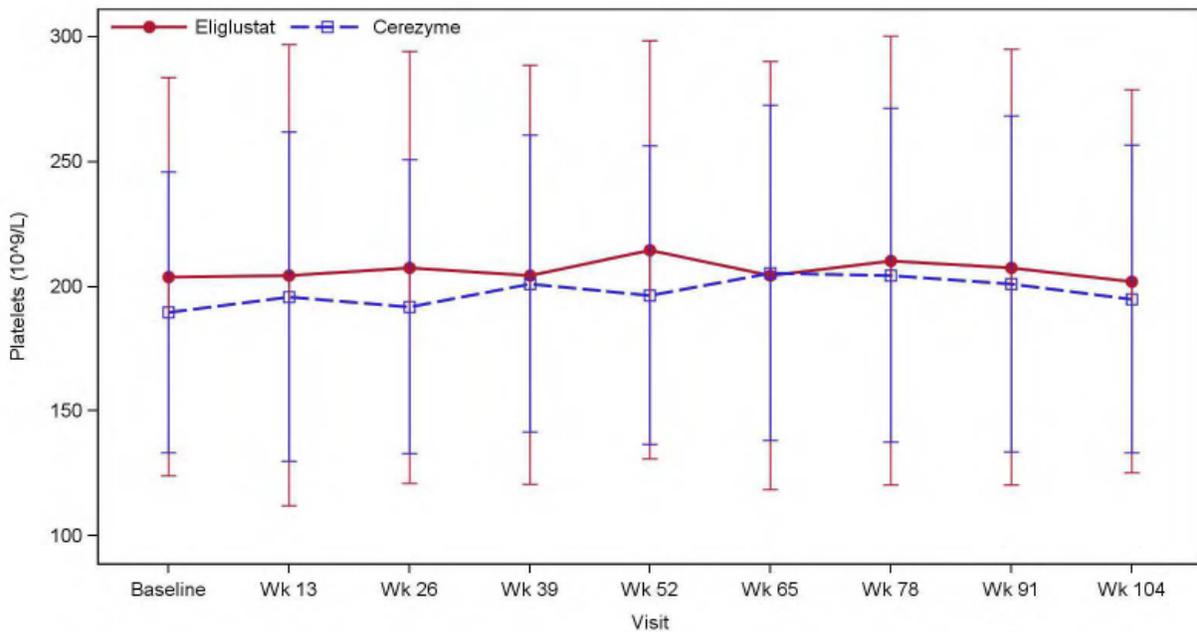
Source: Statistical Review

**Figure 8: Mean ( $\pm$  SD) Liver Volume (MN) over Time – ENCORE (FAS)**



Source: Statistical Review

**Figure 9: Mean ( $\pm$  SD) Platelet Count ( $10^9/L$ ) over Time – ENCORE (FAS)**



Source: Statistical Review

**Medical Reviewer's comments:** Based on the above tables, this reviewer agrees with Dr. Vali's assessment that patients who were randomized at Baseline to eliglustat for the Primary Analysis Treatment Period maintained their organ

***volume and hematological parameter values after Week 52. It can also be seen that patients who were randomized at Baseline to continue on CEREZYME for the Primary Analysis Treatment Period also maintained their organ volume and hematological parameter values after Week 52 when these patients began exclusive treatment with eliglustat.***

The Applicant also submitted long term data from the Phase 2 trial to demonstrate persistence of efficacy of eliglustat in patients who continued to receive eliglustat after completion of the 52 week PAP. A total of 7 treated patients discontinued prior to the Month 48 evaluations: four prior to Week 52 and 3 following Week 52, none due to efficacy reasons. These discontinuations are discussed in the context of the efficacy results in Section 5.2. At the time of data cut-off for the 48-month report, of the 19 patients who had completed at least 48 months of treatment, 4 patients were receiving 50 mg BID eliglustat and 15 patients were receiving 100 mg BID eliglustat.

**Table 41: Efficacy Results From the Phase 2 Study: Organ Volumes and Hematologic Parameters (4 Years, Change from Baseline)**

Endpoint	N	Baseline Value (Mean)	Change from Baseline (Mean)	95% Confidence Interval	p-value
Spleen Volume	18	17.32 MN	-62.5%	(-68.3, -56.7)	<0.0001
Hemoglobin	19	11.30 g/dL	2.27 g/dL	(1.57, 2.97)	<0.0001
Liver Volume	18	1.70 MN	-28.0%	(-34.9, -21.2)	<0.0001
Platelet Count	19	68.7x10 <sup>9</sup> /L	95.0	(50.7, 139.4)	0.0003

Source: Applicant's table

**Table 42: Response to ERT after 2 to 5 years in patients with abnormal values at the inception of treatment**

	Duration of Treatment (Years from Start)			
	2	3	4	5
<b>Hemoglobin (g/dL increase from baseline)</b>				
Number of pts with spleen	135	105	76	45
Mean ± SD	2.5 ± 1.7	2.6 ± 1.5	2.7±1.3	3.0 ± 1.4
Number of pts without spleen	49	33	31	14
Mean ± SD	2.4 ± 1.6	2.7 ± 1.6	2.3±1.8	2.4 ± 1.6
<b>Platelet count (% increase from baseline)</b>				
Number of pts with spleen	222	170	119	61
Mean ± SD	74 ± 77	80 ± 87	82 ± 70	104 ± 82
Number of pts without spleen	15	12	8	4
Mean ± SD	197 ± 221	236 ± 230	259 ± 247	316 ± 355
<b>Liver volume (% decrease from baseline)</b>				
Number of pts with spleen	94	56	37	17
Mean ± SD	29.4 ± 14	36 ± 15	38 ± 16	41 ± 13
Number of pts without spleen	35	21	11	10
Mean ± SD	38 ± 15	41 ± 16	50 ± 17	47 ± 13
<b>Spleen volume (% decrease from baseline)</b>				
Number of pts with spleen	96	55	36	16
Mean ± SD	49 ± 17	54 ± 18	57 ± 16	56 ± 18

Weinreb et al, Effectiveness of ERT in 1028 patients with type 1 Gaucher Disease after 2 to 5 years of treatment: A report from the Gaucher Registry, American Journal of Medicine, 2002

**Medical Reviewer's comments:** In the above tables, the results of long term treatment with eliglustat in the Phase 2 trial appear to be less than results observed with ERT, although the results appear to trend similarly to results observed in patients with abnormal values at the start of treatment after 2 to 5 years of ERT therapy.

#### 6.1.10 Additional Efficacy Issues/Analyses

Clinical trial data for eliglustat were also compared with clinical trials of Cerezyme, and VPRIV, Eleyso and Zavesca. Clinical trials for all products evaluated changes in organ volume, along with changes in hemoglobin and platelet count, as measures of treatment efficacy. The pivotal trial for Cerezyme evaluated all of these parameters as primary endpoints, the pivotal trial for VPRIV evaluated hemoglobin and platelet count as primary endpoints and organ volumes as secondary endpoints. The pivotal trial for Eleyso evaluated spleen volume as a primary endpoint and liver volume, hemoglobin level and platelet count as secondary endpoints. Zavesca's active comparator trial evaluated liver volume as the primary endpoint and spleen, hemoglobin and platelet count as secondary endpoints. The open label Zavesca trials evaluated liver, spleen, hemoglobin and platelet counts as primary endpoints.

Of this group of drug products, eliglustat is the only drug that conducted a placebo comparison trial. While comparison with other products is of interest and may be helpful in some respects to gauge the therapeutic effect of eliglustat, many of the early trials enrolled patients who were truly treatment naïve. This difference is important as the magnitude of response to treatment for Gaucher disease would depend on the patient's ability to respond. That is, patients with larger liver and spleen volumes and lower Hemoglobin and Platelet values would be expected to have a larger response to treatment than patients with smaller liver and spleen volumes and higher Hemoglobin and Platelet values at Baseline. Although, the data from the eliglustat trials are not as dramatic as those seen in the ERT trials, clinically meaningful improvements were observed in organ volume, hemoglobin concentration, and platelet count at the proposed dose of 84 (100) mg twice a day for IM and EM.

## 7 Review of Safety

### **Safety Summary**

Eliglustat tartrate was generally well tolerated in adult patients with Type 1 Gaucher disease, including treatment naïve patients and patients transitioned from imiglucerase, an enzyme replacement therapy to eliglustat. Overall, 334 of 393 of eliglustat-treated patients (85%) experienced a TEAE. 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). Three deaths were reported in Gauchers patients. Serious adverse events were reported for 35/393 patients (9%) treated with eliglustat (42 events). 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 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%).

A key safety concern for Cerdelga is the potential for significant drug-drug interactions. Though the result of the TQT were “negative”, eliglustat increased the QTc and PR intervals in a concentration dependent manner. Based on the concentration QT relationship, there appears to be no QTc related safety concerns for drug concentrations below 250 ng/ml. PD/PK modeling suggests that there is a potential for prolongation at concentrations that could be achieved with significant drug-drug interactions. The Phase 2 and Phase 3 clinical trials had specific guidance to investigators regarding the management of concomitant medication use of CYP2D6 and CYP3A inhibitors during the trials, including allowed duration of treatment (i.e. temporary or chronic use) and according to CYP2D6 phenotype. Because of the strict management of concomitant medications in the clinical trials, there is limited adverse reaction safety data. A review of the available AE data for CYP2D6 concomitant medication use did not identify any significant adverse event trends.

Drug-drug interactions and pre-existing cardiac disease, specifically AV nodal disease will be important considerations in dosing patients to minimize risk of adverse reactions. These will need to be clearly described in the product label.

## 7.1 Methods

### 7.1.1 Studies/Clinical Trials Used to Evaluate Safety

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.

### 7.1.2 Categorization of Adverse Events

The applicant coded AEs by System Organ Class (SOC) and AE preferred terms using the Medical Dictionary for Regulatory Activities (MedDRA). Reporting of adverse events included information such as classification of AE using standard medical terminology (MedDRA Version 10.1), system organ class (SOC), timing of AE in relationship to the infusion, classification of relationship to study medication, classification of severity of AE, and date of onset and resolution of AE. These appear to be adequate to assess the safety profile of eliglustat.

### 7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

Safety data was pooled for the 4 clinical trials (Phase 2, ENGAGE, ENCORE, EDGE [Phase 3 trials]) in patients with GD1.

## 7.2 Adequacy of Safety Assessments

Safety parameters for the trials reviewed included concomitant medications, 12 lead ECGs, echocardiogram, 24 hour Holter monitoring, DEXA, QCSI, standard clinical laboratory tests (serum chemistry, hematology and urinalysis), vital sign measurements, nerve conduction velocity (NCV), neuropsychological testing using the Mini Mental State Examination (MMSE). Adverse events of special interest included clinically significant cardiac arrhythmias that were detected by electrophysiological monitoring and syncope from any cause.

### 7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

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 43: 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
<b>Total Patients (any duration)</b>	391 <sup>a</sup>	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/m<sup>2</sup>. Most patients (89%) were not current smokers. The mean age (± SD)

was 37.1 ( $\pm$ 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.

By geographic region, 27% of the patients in the pooled Eliglustat Safety Set were enrolled in the US, 11% were enrolled in the EU, 3% were enrolled in Japan, and 59% were enrolled in other countries (grouped together as the Rest of the World [ROW]). In the ROW group, most of the patients were enrolled in Brazil (66/393 [17%]), the Russian Federation (43/393 [11%]), Argentina (33/393 [8%]), and China (25/393 [6%]). Other countries where a small percentage of the patients were enrolled ( $\leq$ 3% per country) were Australia, Canada, Colombia, Croatia, Egypt, India, Israel, Lebanon, Mexico, Portugal, Serbia, and Tunisia.

Demographic characteristics were similar across the studies with a few exceptions. The percentage of female patients was higher in the Phase 2 study (62%) compared with the other studies (48% to 54%). The percentage of Asian patients was higher in EDGE (23%) compared with the other studies (0-3%), and the percentage of Hispanic or Latino patients was higher in EDGE and ENCORE (27% and 38%, respectively) than in ENGAGE and the Phase 2 study (5% and 12%, respectively). By region, the percentage of patients enrolled in Japan was higher in EDGE (6%) compared with the other studies (0%) as none of the other 3 studies had sites in that country. A small number of patients > 65 years of age were enrolled, specifically 2/157 (1%) of ENCORE patients and 8/170 (5%) of EDGE patients.

**Table 44: Summary of Patient Demographics by Study and Overall – Eliglustat Safety Set**

Baseline Characteristics	GZGD00304 Phase 2 (N=26)	GZGD02507 ENGAGE (N=40)	GZGD02607 ENCORE (N=157)	GZGD03109 EDGE (N=170)	All Eliglustat (N=393)
<b>Age (years)</b>					
Mean (SD (Min, Max)	34.5 (12.96) 18.6, 60.3	32.2 (11.27) 16.6, 62.9	38.0 (14.43) 18.1, 69.3	37.8 (15.050) 18.2, 75.1	37.1 (14.40) 16.6, 75.1
<b>Sex, n (%)</b>					
Male	10 (38)	20 (50)	72 (46)	89 (52)	191 (49)
Female	16 (62)	20 (50)	85 (54)	81 (48)	202 (51)
<b>Race, n (%)</b>					
White	16 (62)	39 (98)	144 (92)	124 (73)	323 (82)
Black	0	0	10 (6)	7 (4)	17 (4)
Asian	0	1 (3)	2 (1)	39 (23)	42 (11)
Multiple	0	0	1 (1)	0	1 (<1)
Unknown	10 (38)	0	0	0	10 (3)
<b>CYP2D6 Status, n (%)</b>					
Poor	1 (4)	0	6 (4)	7 (4)	14 (4)
Intermediate	0	3 (8)	21 (13)	25 (15)	49 (12)
Extensive	25 (96)	36 (90)	120 (76)	129 (76)	310 (79)
Ultra-rapid	0	1 (3)	5 (3)	3 (2)	9 (2)
Indeterminate	0	0	2 (1)	3 (2)	5 (1)
Missing	0	0	3 (2)	3 (2)	6 (2)
<b>Splenectomy Status, n (%)</b>					
No	26 (100)	40 (100)	118 (75)	117 (69)	301 (77)
Partial	0	0	2 (1)	7 (4)	9 (2)
Total	0	0	37 (24)	46 (27)	83 (21)
<b>Recent Prior ERT Exposure, n (%)</b>					
No	26 (100)	40 (100)	0	68 (40)	134 (34)
Yes	0	0	157 (100)	102 (60)	259 (66)

### 7.2.2 Explorations for Dose Response

Relationship between dose and response was evaluated in all trials. There was no clear dose response relationship in terms of safety signals seen. See Section 4.4 and [Section 7.5.1](#) for evaluation of AEs and various dosages of eliglustat.

### 7.2.3 Special Animal and/or In Vitro Testing

Nonclinical testing was adequate to explore potential adverse reaction.

### 7.2.4 Routine Clinical Testing

Routine clinical testing was adequate. Clinical laboratory evaluations were generally performed at central laboratories, however, local laboratories could be used at the Investigator's discretion for safety monitoring (e.g., if the patient was unable to visit the study site or results were needed immediately, such as for a confirmatory blood count). Clinical laboratory evaluations were conducted for hematology, chemistry and urinalysis parameters.

### 7.2.5 Metabolic, Clearance, and Interaction Workup

For more information see the Section 4.4 Clinical Pharmacology.

### 7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

The trials were adequately designed to allow for safety analyses. The submitted trials also adequately monitored for adverse effects known to be related to SRTs and ERTs in patients with type 1 Gaucher disease. The trials did not reveal any new safety signals.

***Medical Reviewer's comments: The literature and the label for Zavesca describe peripheral neuropathy experienced by patients. In some instances this has been severe enough to cause discontinuation of the drug. To assess for this adverse event in the eliglustat treatment group, the Applicant included nerve conduction studies as a safety assessment.***

## 7.3 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.

### 7.3.1 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 3 fatal events in GD1 patients:

- Patient GZGD00304/0503 died from hypovolemic shock secondary to a lacerated spleen approximately 6.5 months following withdrawal from the Phase 2 study (withdrawal due to maternal [radiation] exposure during pregnancy). This patient had a still birth at 37 weeks gestation that occurred 2 months before she died. The patient had undergone a laparoscopic cholecystectomy 2 days prior to death and was hypersplenic secondary to her GD. The death was considered not related to eliglustat.
- Patient GZGD03109/30104 died due to multiple severe traumas following a downhill skiing accident, which was reported approximately 562 days after the patient began eliglustat treatment. At the time of death, the patient had completed the Lead-in Period and was randomized in the Primary Analysis Period. The death was considered unrelated to eliglustat treatment.
- Patient GZGD03109/30106 died from cardiac arrest due to massive blood loss. The patient was hospitalized and underwent surgery for multiple injuries caused by unspecified violence. A splenectomy was also performed on the same day. Following surgery, the patient experienced cardiac arrest due to massive blood loss more than 3 liters and subsequently died.

***Medical Reviewer's comments: This reviewer agrees with the Applicant's assessment that these deaths are unrelated to the study drug.***

### 7.3.2 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 (GZGD03109/30603, GZGD03109/33304, GZGD03109/38402) 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 (GZGD02607/2101, GZGD02607/2203, and (GZGD03109/34601) experienced Myocardial infarctions, and an additional patient (GZGD02607/6702) 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 (GZGD0304/0302) 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 (GZGD02507/4905) 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.

**Table 45: Patients With Serious Adverse Events - Eliglustat Safety Set as of 31 January 2013**

MedDRA System Organ Class	MedDRA Preferred Term	Study Subject /Patient ID	Dose at Time of Event (mg)	Relation to Study Drug	Days Since First Study Drug Dose	Action Taken with Study Drug	Outcome
Nervous system disorders	Syncope	GZGD02607/2703	150 BID	Remote/unlikely	105	Dose not changed	Recovered/ resolved
	Syncope	GZGD02607/5806	150 BID	Remote/unlikely	104	Dose adjusted	Recovered/ resolved
	Syncope	GZGD03109/30603	100 BID	Possible	332	Drug interrupted	Recovered/ resolved
	Dizziness	GZGD03109/31610	100 BID	Not related	210	Dose not changed	Recovered/ resolved
	Convulsion	GZGD03109/32806	100 BID	Not related	173	Drug interrupted	Recovered/ resolved
	Syncope	GZGD03109/33304	100 BID	Possible	205	Dose not changed	Recovered/ resolved
	Ischaemic stroke	GZGD03109/34501	100 BID	Remote/unlikely	128	Dose not changed	Recovered/ resolved
Injury, poisoning, and procedural complications	Maternal exposure during pregnancy	GZGD00304/0503	100 BID	Not related	382	Dose not changed	Recovered/ resolved
					385	Dose not changed	Recovered/ resolved
		GZGD00304/0801	100 BID	Not related	184	Dose not changed	Recovered/ resolved
	Injury	GZGD02607/3302	50 BID	Not related	366	Drug withdrawn	Not recovered/ not resolved
	Joint dislocation	GZGD02607/5954	100 BID	Not related	122	Dose not changed	Recovered/ resolved
	Femur fracture	GZGD03109/31004	50 BID	Remote/unlikely	9	Dose not changed	Recovered/ resolved
	Femur fracture		--	Remote/unlikely	29	Drug interrupted	Recovered/ resolved

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MedDRA System Organ Class	MedDRA Preferred Term	Study Subject /Patient ID	Dose at Time of Event (mg)	Relation to Study Drug	Days Since First Study Drug Dose	Action Taken with Study Drug	Outcome
	Fall	GZGD03109/31610	100 BID	Not related	210	Dose not changed	Recovered/ resolved
Cardiac disorders	Ventricular tachycardia	GZGD00304/0302	50 QD	Possible	1	Drug withdrawn	Recovered/ resolved
	AV block	GZGD02507/4905	150 BID	Probable	421	Dose adjusted	Recovered/ resolved
	AV block second degree						
	Myocardial infarction	GZGD02607/2101	50 BID	Not related	237	Drug withdrawn	Recovered/ resolved
	Myocardial infarction	GZGD02607/2203	50 BID	Remote/ Unlikely	80	Drug withdrawn	Recovered/ resolved
	Acute myocardial infarction	GZGD02607/6702	50 BID	Remote/ Unlikely	157	Dose not changed	Recovered/ resolved with sequelae
	Myocardial infarction	GZGD03109/34601	100 BID	Remote/ unlikely	309	Drug interrupted	Recovered/ resolved
General disorders and administration site conditions	Device malfunction	GZGD02607/0108	150 BID	Not related	546	Drug interrupted	Recovered/ resolved
	Pain	GZGD02607/8303	150 BID	Remote/ unlikely	363	Dose not changed	Recovered/ resolved
	Pyrexia						
	Medical device pain	GZGD03109/35703	50 BID	Not related	69	Dose not changed	Recovered/ resolved
Hepatobiliary disorders	Cholecystitis	GZGD02607/2818	150 BID	Not related	88	Drug interrupted	Recovered/ resolved
	Biliary colic	GZGD02607/2820	--	Not related	410	Drug interrupted	Recovered/ resolved

MedDRA System Organ Class	MedDRA Preferred Term	Study Subject /Patient ID	Dose at Time of Event (mg)	Relation to Study Drug	Days Since First Study Drug Dose	Action Taken with Study Drug	Outcome
	Cholecystitis	GZGD03109/34503	100 BID	Remote/ unlikely	69	Drug interrupted	Recovered/ resolved
<b>Infections and infestations</b>	Diverticulitis	GZGD02607/6203	50 BID	Not related	226	Dose not changed	Recovered/ resolved
	Appendicitis	GZGD02607/9202	100 BID	Not related	83	Dose not changed	Recovered/ resolved
	Hepatitis A	GZGD03109/30603	100 BID	Not related	38	Drug interrupted	Recovered/ resolved
<b>Neoplasms benign, malignant and unspecified</b>	Uterine leiomyoma	GZGD02607/5957	100 BID	Not related	191	Dose not changed	Recovered/ resolved
	Hepatic neoplasm malignant	GZGD02607/7001	50 BID	Remote/ unlikely	367	Drug withdrawn	Not recovered/ not resolved
<b>Gastrointestinal disorders</b>	Colitis ischaemic	GZGD02607/5812	100 BID	Remote/ unlikely	340	Drug interrupted	Recovered/ resolved
<b>Reproductive system and breast disorders</b>	Ovarian cyst ruptured	GZGD00304/0108	150 BID	Not related	1853	Drug interrupted	Recovered/ resolved
<b>Respiratory, thoracic and mediastinal disorders</b>	Nasal septum deviation	GZGD02607/2702	150 BID	Not related	704	Dose not changed	Recovered/ resolved
<b>Pregnancy, puerperium and perinatal conditions</b>	Abortion spontaneous	GZGD00304/0503	100 BID	Not Related	93	Drug interrupted	Recovered/ resolved

Clinical Review  
 Karyn L. Berry, MD, MPH  
 NDA 205494  
 Cerdelga (Eliglustat tartrate)

MedDRA System Organ Class	MedDRA Preferred Term	Study Subject /Patient ID	Dose at Time of Event (mg)	Relation to Study Drug	Days Since First Study Drug Dose	Action Taken with Study Drug	Outcome
<b>Surgical and medical procedures</b>	Mammoplasty	GZGD02607/7302	50 BID	Not related	--	Dose not changed	Recovered/ resolved
<b>Investigations</b>	Hepatic enzyme increased	GZGD03109/30804	50 BID	Remote/ unlikely	183	Drug interrupted	Recovered/ resolved
<b>Vascular disorders</b>	Aortic aneurysm	GZGD03109/31502	50 BID	Not related	321	Drug interrupted	Recovered/ resolved

Source: Applicant's table , ISS

**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 the 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.**

### 7.3.3 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

**Table 46: Summary of Patient Disposition by Study and Overall - Eliglustat Safety**

Category	GZGD00304 Phase 2	GZGD02507 ENGAGE (N=40)	GZGD02607 ENCORE (N=157)	GZGD03109 EDGE (N=170)	All Eliglustat (N=393)
Treated, n (%)	26 (100)	40 (100)	157 (100)	170 (100)	393 (100)
Still Active on Eliglustat Treatment, n (%)	19 (73)	38 (95)	145 (92)	158 (93)	360 (92)
Withdrawn, n (%)	7 (27)	2 (5)	12 (8)	12 (7)	33 (8)
Adverse Event	3 (12)	0	7 (4)	2 (1)	12 (3)
Wished to	1 (4)	2 (5)	2 (1)	5 (3)	10 (3)
Pregnancy <sup>a</sup>	3 (12)	0	0	2 (1)	5 (1)
Noncompliant	0	0	0	1 (1)	1 (<1)
Decline in GD	0	0	0	0	0
Lost to Follow-up	0	0	0	0	0
Other <sup>a</sup>	0	0	3 (2)	2 (1)	5 (1)

Source: Applicant's table from ISS

### 7.3.4 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.

In the HLT of Cardiac conduction disorders, a total of 6 patients (2%) experienced a TEAE. These TEAEs included Atrioventricular block second degree in 4 patients (1%; 2 of whom had a history of AV block), Atrioventricular block first degree in 1 patient with a history of AV block, and Sinoatrial block in 1 patient. Two events (in 1 patient) were SAEs. All events were mild in severity, and all but 1 patient with AV block second degree were deemed related by the investigator. No patient experienced a higher block than Mobitz type 1.

The events occurred at all doses of eliglustat, and all patients who experienced the events were extensive metabolizers (which constituted 79% of the safety set. Time from the start of dosing with eliglustat to the onset of event was 90 to 632 days. The  $C_{max}$  values prior to the event and closest in chronology to the event onset ranged from 19.4 to 60.6 ng/mL. All patients were asymptomatic at the time of the events, and for the most part the events occurred in the early morning hours on Holter. No patient discontinued treatment due to cardiac conduction disorders.

In the Ventricular arrhythmia and cardiac arrest HLT, a total of 4 patients (1%) experienced a TEAE. These TEAEs included Ventricular tachycardia (all nonsustained) in 3 patients (0.7%) and Ventricular extrasystole in 1 patient. One event of Ventricular tachycardia was an SAE. All events were considered mild in severity. Patients in whom the events occurred were taking either 50 mg or 100 mg eliglustat, and all but 1 were extensive metabolizers (the remaining patient was an intermediate metabolizer). Days from the start of eliglustat dosing to the onset of the event ranged from 1 dose to 466 days. All patients were asymptomatic at the time of the event. As a result of the events, 2 patients, both of whom experienced Ventricular tachycardia (on continuous telemetry

performed as scheduled per protocol) withdrew from the study after the first dose of 50 mg eliglustat.

Table 47: MedDRA HLGT of Cardiac Arrhythmias and HLT Terms by Study and Overall

MedDRA High Level Term MedDRA Preferred Term	GZGD00304 (Phase 2) (N=26)	GZGD02507 (ENGAGE) (N=40)	GZGD02607 (ENCORE) (N=157)	GZGD03109 (EDGE) (N=170)	All Eliglustat (N=393)
Total Patients with events n (%)	2 (8)	3 (8)	6 (4)	4 (2)	15 (4)
Cardiac conduction disorders	0	2 (5)	4 (3)	0	6 (2)
Atrioventricular block second degree	0	2 (5)	2 (1)	0	4 (1)
Atrioventricular block	0	1 (3)	0	0	1 (<1)
Atrioventricular block first degree	0	0	1 (1)	0	1 (<1)
Sinoatrial block	0	0	1 (1)	0	1 (<1)
Supraventricular arrhythmias	0	0	0	4 (2)	4 (1)
Supraventricular tachycardia	0	0	0	2 (1)	2 (1)
Arrhythmia supraventricular	0	0	0	1 (1)	1 (<1)
Atrial Tachycardia	0	0	0	1 (1)	1 (<1)
Ventricular arrhythmias and cardiac arrest	2 (8)	0	2 (1)	0	4 (1)
Ventricular tachycardia	0	0	1 (1)	0	3 (1)
Ventricular extrasystoles	0	0	1 (1)	0	1 (<1)
Rate and rhythm disorders (NEC)	0	1 (3)	0	0	1 (<1)
Tachycardia	0	1 (3)	0	0	1 (<1)

Modified Applicant's table ISS

**Medical Reviewer's comments: 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.**

#### Syncope

Syncope was identified as an AESI to analyze and characterize these events in light of the known concentration effect between eliglustat and increase in QTcF, which could

manifest as syncope (e.g., Torsades de Pointes). A total of 8/393 patients (2%) had a TEAE of Syncope: 4/157 patients (3%) in ENCORE and 4/170 patients (2%) in EDGE. One patient in ENCORE (GZGD02607/5954) had 2 Syncope events, and the remaining patients had 1 event each. All of the patients with Syncope were female, with ages ranging from 21 to 63 years. Two of the patients had a prior history of syncope, and 2 of the patients had hypertension (both were receiving metoprolol and other medications for hypertension at the time the syncope occurred).

One patient experienced Syncope 4 days before the onset of Dizziness (GZGD03109/33304). The Applicant concluded that all cases of Syncope describe vasovagal responses triggered by fasting, dehydration, blood draw, recent change in hypertensive medications, or pain except 1 case where the etiology was unclear. The eliglustat dose at the time of Syncope was 150 mg BID (3 patients), 100 mg BID (4 patients), and 50 mg QD (1 patient). The patient who had Syncope at 50 mg QD was a CYP2D6 Poor Metabolizer and the other 7 patients were Extensive Metabolizers. The time from first eliglustat dose to onset of Syncope ranged from 79 days to 461 days. The  $C_{max}$  closest to the time of the Syncope ranged from 5.0 ng/mL to 140.1 ng/mL for the 8 patients experiencing Syncope.

The Syncope events were reported as mild for 2 patients, moderate for 2 patients, and severe for 4 patients. Among the patients with severe Syncope, 3 were receiving eliglustat 150 mg BID and 1 was receiving 100 mg BID. Syncope was an SAE for 5/393 (1%) of patients; 3 of the SAEs were considered by the investigator to be related to study drug (2 possibly related, 1 definitely related). None of the other incidences of Syncope was considered related to study drug. One Syncope event led to study drug interruption and 2 led to study drug adjustment; however, none of the events of Syncope led to permanent study drug discontinuation or study withdrawal. Seven out of eight patients continued on eliglustat without further incidence of syncope. One patient (GZGD02607/5954) who had a pre-study history of syncope had a second syncopal event during the study. The patient's eliglustat dose remained the same, and treatment was not interrupted at any time.

The applicant reports that the occurrence of Syncope was not associated with cardiac conduction disorders or arrhythmias.

***Medical Reviewer's comments: The syncopal narratives were reviewed and this reviewer agrees with the Applicant's relationship to drug assessments.***

#### *Dizziness*

In the pooled Eliglustat Safety Set, 38 of 393 patients (10%) had TEAEs of Dizziness during eliglustat treatment: 1 of 26 patients (4%) in the Phase 2 study, 2 of 40 patients in ENGAGE (5%), 15 of 157 patients (10%) in ENCORE, and 20 of 170 patients (12%) in EDGE. The majority of patients had a single episode of Dizziness (a total of 42 events in 38 patients). The incidence of Dizziness was slightly higher among

female patients (26/202, 13%) compared with male patients (12/191, 6%). The age range for the patients who had Dizziness was 19 to 69 years, with 26 of patients in the > 30 to 65 year age group; 2 of the patients were > 65 years old. Patients who had Dizziness on eliglustat were receiving 50 mg BID (17 patients), 100 mg BID (16 patients) or 150 mg BID (5 patients). All incidences of Dizziness were mild or moderate (31 patients and 7 patients, respectively); there were no severe events. One episode of Dizziness was an SAE. A 19-year-old woman experienced Dizziness and fell (GZGD03109/31610).

Two patients with TEAEs of Dizziness had ECG findings of potential clinical significance. Patient GZGD03109/30903 had 1 episode of a QRS interval  $\geq$ 120 msec (122 msec, pre-dose at Week 13), which represented a 21% increase from Baseline. Patient GZGD03109/38402 had 6 episodes of QRS interval  $\geq$ 120 msec on Day 1 and at Week 2. The longest of these QRS intervals was 120 msec, which was the same as the patient's Baseline finding. This patient also had 1 episode of QTcF interval >60 msec; the QTcF was 61 msec pre-dose on Week 8. Neither of these patients had TEAEs associated with cardiac conduction or rhythm disturbances. One patient had a Mobitz Type 1 TEAE (Atrioventricular block second degree; Patient GZGD02507/4905); the onset of this TEAE occurred 2 weeks prior to the onset of Dizziness. Another patient had an episode of Mobitz Type 1 at Week 65 approximately 11 months prior to the onset of dizziness (Patient GZGD02607/5806).

### *Neuropathy*

Neuropathy TEAEs were reported as a result of nerve conduction studies or by the patient or investigator and may not have had accompanying electrophysiologic or neurophysiologic assessment. Nerve conduction studies were performed periodically per protocol in the Phase 2 study and ENCORE only.

Neuropathy-related TEAEs were Paraesthesia (9/393 patients [2%]), Neuropathy peripheral (8/393 patients [2%]), Hypoaesthesia (5/393 patients [1%]), and Nerve conduction studies abnormal (4/393 patients [1%]). The remaining TEAEs occurred in 1 patient each (Decreased vibratory sense, Polyneuropathy, Sensory loss, and Ulnar nerve injury). The TEAEs considered related to study drug by the investigators were: Paraesthesia (3/393 patients [1%]); Neuropathy peripheral (2/393 patients [1%]); Nerve conduction studies abnormal (2/393 patients [1%]); and Hypoaesthesia, Decreased vibratory sense, and Ulnar nerve injury (1/393 patients [ $<$  1%] each).

***Medical Reviewer's comments: No patient discontinued study drug or withdrew from the study due to a neuropathy event, and none of the neuropathy events was an SAE. Based on this data there does not appear to be a convincing significant safety signal observed. Because of the reported events in the clinical trials and since peripheral neuropathy and paresthesia were observed in the Zavesca clinical trials (at an increased frequency and severity than seen in***

***eliglustat trials), this reviewer recommends that the Applicant monitor peripheral neuropathy and paresthesia with routine postmarketing surveillance.***

### 7.3.5 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.

**Table 48: Analysis of exposure by duration dose**

Dose	Duration of Exposure (years)	PM (N=14)	IM (N=49)	EM (N=310)	URM (N=9)	IND (N=5)
<b>50 mg BID</b>	n	14	49	308	9	5
	Mean (SD)	1.4 (1.49)	0.6 (0.54)	0.2 (0.57)	0.1 (0.05)	0.2 (0.19)
	Median	1.1	0.5	0.1	0.1	0.1
	Min, Max	0.1, 6.0	0.0, 1.8	0.0, 5.5	0.1, 0.2	0.1, 0.5
<b>100 mg BID</b>	n	0	19	282	9	3
	Mean (SD)	--	0.9 (0.62)	0.9 (1.28)	0.4 (0.29)	0.6 (0.35)
	Median	--	0.7	0.6	0.3	0.5
	Min, Max	--	0.1, 2.7	0.0, 6.4	0.1, 0.7	0.3, 1.0
<b>150 mg BID</b>	n	0	1	88	6	1

	Mean (SD)	--	1.1 (--)	1.1 (0.66)	1.6 (1.02)	0.1 (--)
	Median	--	1.1	1.1	2.0	0.1
	Min, Max	--	1.1, 1.1	0.0, 2.8	0.2, 2.6	0.1, 0.1
<b>Overall</b>	n	14	49	310	9	5
	Mean (SD)	1.5 (1.44)	1.0 (0.51)	1.4 (1.27)	1.5 (0.86)	0.7 (0.28)
	Median	1.1	1.0	1.1	1.1	0.6
	Min, Max	0.2, 6.0	0.1, 2.8	0.0, 6.5	0.6, 2.7	0.4, 1.1

## 7.4 Supportive Safety Results

### 7.4.1 Common Adverse Events

A total of 334 eliglustat-treated patients experienced 1 or more TEAE (334/393 patients, 85%). The 3 most frequently affected SOC 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%).

**Table 49: Summary of Patients With Treatment-Emergent Adverse Events Occurring in  $\geq 2\%$  of Eliglustat-Treated Patients by MedDRA SOC and Preferred Term Overall - Eliglustat Safety Set**

	GZGD00304 Phase 2 (N=26)		GZGD02507 ENGAGE (N=40)		GZGD02607 ENCORE (N=157)		GZGD03109 EDGE (N=170)		All Eliglustat (N=393)	
System Organ Class Preferred Term	Events n (/100 py) <sup>a</sup>	Patients n (%) <sup>b</sup>	Events n (/100 py) <sup>a</sup>	Patients n (%) <sup>b</sup>	Events n (/100 py) <sup>a</sup>	Patients n (%) <sup>b</sup>	Events n (/100 py) <sup>a</sup>	Patients n (%) <sup>b</sup>	Events n (/100 py) <sup>a</sup>	Patients n (%) <sup>b</sup>
<b>Patients with Events</b>	<b>249 (215)</b>	<b>26 (100)</b>	<b>315 (548)</b>	<b>33 (83)</b>	<b>1175 (545)</b>	<b>134 (85)</b>	<b>601 (412)</b>	<b>141 (83)</b>	<b>2340 (437)</b>	<b>334 (85)</b>
<b>Infections &amp; Infestations</b>	<b>53 (46)</b>	<b>14 (54)</b>	<b>40 (70)</b>	<b>16 (40)</b>	<b>215 (100)</b>	<b>86 (55)</b>	<b>133 (91)</b>	<b>68 (40)</b>	<b>441 (82)</b>	<b>184 (47)</b>
Nasopharyngitis	5 (4)	3 (12)	8 (14)	4 (10)	35 (16)	22 (14)	36 (25)	24 (14)	84 (16)	53 (13)
Upper respiratory tract infection	7 (6)	4 (15)	6 (10)	6 (15)	37 (17)	22 (14)	15 (10)	11 (6)	65 (12)	43 (11)
Influenza	4 (3)	2 (8)	2 (3)	1 (3)	23 (11)	15 (10)	6 (4)	5 (3)	35 (7)	23 (6)
Sinusitis	4 (3)	3 (12)	4 (7)	4 (10)	22 (10)	14 (9)	2 (1)	2 (1)	32 (6)	23 (6)
Urinary tract infection	6 (5)	4 (15)	1 (2)	1 (3)	14 (6)	12 (8)	7 (5)	6 (4)	28 (5)	23 (6)
Bronchitis	3 (3)	1 (4)	3 (5)	2 (5)	9 (4)	7 (4)	3 (2)	3 (2)	18 (3)	12 (3)
Gastroenteritis	0 (0)	0 (0)	0 (0)	0 (0)	4 (2)	4 (3)	8 (5)	7 (4)	12 (2)	11 (3)
Viral infection	11 (9)	6 (23)	1 (2)	1 (3)	0 (0)	0 (0)	5 (3)	3 (2)	17 (3)	10 (3)
Gastroenteritis viral	0 (0)	0 (0)	0 (0)	0 (0)	7 (3)	7 (4)	1 (1)	1 (1)	1 (1)	8 (2)
Ear infection	0 (0)	0 (0)	0 (0)	0 (0)	6 (3)	5 (3)	2 (1)	2 (1)	8 (1)	7 (2)
Oral herpes	0 (0)	0 (0)	1 (2)	1 (3)	6 (3)	4 (3)	2 (1)	2 (1)	9 (2)	7 (2)
Pharyngitis	2 (2)	1 (4)	1 (2)	1 (3)	1 (0)	1 (1)	5 (3)	4 (2)	9 (2)	7 (2)
Pneumonia	0 (0)	0 (0)	1 (2)	1 (3)	4 (2)	4 (3)	1 (1)	1 (1)	6 (1)	6 (2)

System Organ Class Preferred Term	GZGD00304 Phase 2 (N=26)		GZGD02507 ENGAGE (N=40)		GZGD02607 ENCORE (N=157)		GZGD03109 EDGE (N=170)		All Eliglustat (N=393)	
	Events n (/100 py) <sup>a</sup>	Patients n (%) <sup>b</sup>	Events n (/100 py) <sup>a</sup>	Patients n (%) <sup>b</sup>	Events n (/100 py) <sup>a</sup>	Patients n (%) <sup>b</sup>	Events n (/100 py) <sup>a</sup>	Patients n (%) <sup>b</sup>	Events n (/100 py) <sup>a</sup>	Patients n (%) <sup>b</sup>
<b>Gastrointestinal Disorders</b>	<b>27 (23)</b>	<b>8 (31)</b>	<b>59 (103)</b>	<b>23 (58)</b>	<b>202 (94)</b>	<b>79 (50)</b>	<b>97 (66)</b>	<b>53 (31)</b>	<b>385 (72)</b>	<b>163 (41)</b>
Diarrhoea	4 (3)	4 (15)	8 (14)	5 (13)	25 (12)	19 (12)	11 (8)	11 (6)	48 (9)	39 (10)
Abdominal pain upper	1 (1)	1 (4)	2 (3)	2 (5)	25 (12)	18 (11)	13 (9)	12 (7)	41 (8)	33 (8)
Nausea	3 (3)	3 (12)	5 (9)	3 (8)	26 (12)	19 (12)	10 (7)	8 (5)	44 (8)	33 (8)
Dyspepsia	4 (3)	3 (12)	3 (5)	3 (8)	19 (9)	13 (8)	9 (6)	9 (5)	35 (7)	28 (7)
Abdominal pain	2 (2)	2 (8)	5 (9)	5 (13)	12 (6)	10 (6)	9 (6)	8 (5)	28 (5)	25 (6)
Constipation	1 (1)	1 (4)	1 (2)	1 (3)	12 (6)	11 (7)	11 (8)	10 (6)	25 (5)	23 (6)
Gastroesophageal reflux disease	0 (0)	0 (0)	5 (9)	4 (10)	15 (7)	11 (7)	5 (3)	5 (3)	25 (5)	20 (5)
Vomiting	2 (2)	1 (4)	5 (9)	3 (8)	9 (4)	6 (4)	7 (5)	7 (4)	23 (4)	17 (4)
Abdominal distension	0 (0)	0 (0)	3 (5)	2 (5)	6 (3)	4 (3)	5 (3)	5 (3)	14 (3)	11 (3)
Dysphagia	0 (0)	0 (0)	1 (2)	1 (3)	2 (1)	2 (1)	6 (4)	5 (3)	9 (2)	8 (2)
Flatulence	0 (0)	0 (0)	4 (7)	3 (8)	4 (2)	4 (3)	1 (1)	1 (1)	9 (2)	8 (2)
Toothache	2 (2)	1 (4)	3 (5)	2 (5)	5 (2)	4 (3)	1 (1)	1 (1)	11 (2)	8 (2)
Gastritis	0 (0)	0 (0)	4 (7)	3 (8)	5 (2)	3 (2)	1 (1)	1 (1)	10 (2)	7 (2)
Dry mouth	0 (0)	0 (0)	2 (3)	2 (5)	4 (2)	4 (3)	0 (0)	0 (0)	6 (1)	6 (2)
<b>Nervous System Disorders</b>	<b>17 (15)</b>	<b>8 (31)</b>	<b>56 (97)</b>	<b>16 (40)</b>	<b>125 (58)</b>	<b>55 (35)</b>	<b>91 (62)</b>	<b>47 (28)</b>	<b>289 (54)</b>	<b>126 (32)</b>
Headache	5 (4)	4 (15)	36 (63)	15 (38)	48 (22)	26 (17)	40 (27)	21 (12)	129 (24)	66 (17)
Dizziness	1 (1)	1 (4)	4 (7)	2 (5)	16 (7)	15 (10)	21 (14)	20 (12)	42 (8)	38 (10)

System Organ Class Preferred Term	GZGD00304 Phase 2 (N=26)		GZGD02507 ENGAGE (N=40)		GZGD02607 ENCORE (N=157)		GZGD03109 EDGE (N=170)		All Eliglustat (N=393)	
	Events n (/100 py) <sup>a</sup>	Patients n (%) <sup>b</sup>	Events n (/100 py) <sup>a</sup>	Patients n (%) <sup>b</sup>	Events n (/100 py) <sup>a</sup>	Patients n (%) <sup>b</sup>	Events n (/100 py) <sup>a</sup>	Patients n (%) <sup>b</sup>	Events n (/100 py) <sup>a</sup>	Patients n (%) <sup>b</sup>
Paraesthesia	1 (1)	1 (4)	4 (7)	1 (3)	6 (3)	4 (3)	3 (2)	3 (2)	14 (3)	9 (2)
Neuropathy peripheral	2 (2)	2 (8)	0 (0)	0 (0)	5 (2)	5 (3)	1 (1)	1 (1)	8 (1)	8 (2)
Syncope	0 (0)	0 (0)	0 (0)	0 (0)	5 (2)	4 (3)	4 (3)	4 (2)	9 (2)	8 (2)
Dysgeusia	0 (0)	0 (0)	0 (0)	0 (0)	4 (2)	4 (3)	3 (2)	3 (2)	7 (1)	7 (2)
Somnolence	0 (0)	0 (0)	0 (0)	0 (0)	7 (3)	4 (3)	3 (2)	3 (2)	10 (2)	7 (2)
<b>Musculoskeletal and Connective Tissue Disorders</b>	<b>43 (37)</b>	<b>13 (50)</b>	<b>49 (85)</b>	<b>14 (35)</b>	<b>157 (73)</b>	<b>58 (37)</b>	<b>56 (38)</b>	<b>40 (24)</b>	<b>305 (57)</b>	<b>125 (32)</b>
Arthralgia	5 (4)	3 (12)	24 (42)	14 (35)	41 (19)	30 (19)	13 (9)	8 (5)	83 (16)	55 (14)
Back pain	3 (3)	3 (12)	4 (7)	4 (10)	27 (13)	19 (12)	10 (7)	9 (5)	44 (8)	35 (9)
Pain in extremity	8 (7)	5 (19)	4 (7)	4 (10)	18 (8)	16 (10)	8 (5)	6 (4)	38 (7)	31 (8)
Bone pain	11 (9)	1 (4)	7 (12)	4 (10)	13 (6)	10 (6)	3 (2)	3 (2)	34 (6)	18 (5)
Myalgia	0 (0)	0 (0)	3 (5)	2 (5)	8 (4)	5 (3)	5 (3)	5 (3)	16 (3)	12 (3)
Musculoskeletal pain	5 (4)	3 (12)	2 (3)	2 (5)	4 (2)	4 (3)	2 (1)	2 (1)	13 (2)	11 (3)
<b>General Disorders and Administration Site Conditions</b>	<b>11 (9)</b>	<b>5 (19)</b>	<b>14 (24)</b>	<b>11 (28)</b>	<b>76 (35)</b>	<b>39 (25)</b>	<b>42 (29)</b>	<b>33 (19)</b>	<b>143 (27)</b>	<b>88 (22)</b>
Fatigue	2 (2)	1 (4)	3 (5)	2 (5)	24 (11)	19 (12)	7 (5)	7 (4)	36 (7)	29 (7)
Asthenia	2 (2)	1 (4)	3 (5)	3 (8)	10 (5)	9 (6)	4 (3)	3 (2)	19 (4)	16 (4)
Oedema peripheral	2 (2)	2 (8)	2 (3)	2 (5)	9 (4)	7 (4)	4 (3)	3 (2)	17 (3)	14 (4)

	GZGD00304 Phase 2 (N=26)		GZGD02507 ENGAGE (N=40)		GZGD02607 ENCORE (N=157)		GZGD03109 EDGE (N=170)		All Eliglustat (N=393)	
System Organ Class Preferred Term	Events n (/100 py) <sup>a</sup>	Patients n (%) <sup>b</sup>	Events n (/100 py) <sup>a</sup>	Patients n (%) <sup>b</sup>	Events n (/100 py) <sup>a</sup>	Patients n (%) <sup>b</sup>	Events n (/100 py) <sup>a</sup>	Patients n (%) <sup>b</sup>	Events n (/100 py) <sup>a</sup>	Patients n (%) <sup>b</sup>
Chest pain	1 (1)	1 (4)	1 (2)	1 (3)	8 (4)	6 (4)	5 (3)	4 (2)	15 (3)	12 (3)
Pyrexia	1 (1)	1 (4)	3 (5)	2 (5)	4 (2)	4 (3)	5 (3)	5 (3)	13 (2)	12 (3)
Influenza like illness	1 (1)	1 (4)	1 (2)	1 (3)	0 (0)	0 (0)	6 (4)	4 (2)	8 (1)	6 (2)
<b>Respiratory, Thoracic and Mediastinal Disorders</b>	<b>12 (10)</b>	<b>6 (23)</b>	<b>19 (33)</b>	<b>10 (25)</b>	<b>62 (29)</b>	<b>36 (23)</b>	<b>33 (23)</b>	<b>29 (17)</b>	<b>126 (24)</b>	<b>81 (21)</b>
Cough	3 (3)	2 (8)	2 (3)	2 (5)	20 (9)	11 (7)	8 (5)	8 (5)	33 (6)	23 (6)
Epistaxis	3 (3)	2 (8)	3 (5)	2 (5)	9 (4)	7 (4)	6 (4)	6 (4)	21 (4)	17 (4)
Oropharyngeal pain	3 (3)	3 (12)	2 (3)	2 (5)	7 (3)	5 (3)	8 (5)	7 (4)	20 (4)	17 (4)
Nasal congestion	3 (3)	2 (8)	3 (5)	2 (5)	2 (1)	2 (1)	2 (1)	2 (1)	10 (2)	8 (2)
Throat irritation	0 (0)	0 (0)	0 (0)	0 (0)	4 (2)	4 (3)	2 (1)	2 (1)	6 (1)	6 (2)
<b>Investigations</b>	<b>16 (14)</b>	<b>9 (35)</b>	<b>9 (16)</b>	<b>8 (20)</b>	<b>62 (29)</b>	<b>39 (25)</b>	<b>24 (16)</b>	<b>19 (11)</b>	<b>111 (21)</b>	<b>75(19)</b>
Blood creatine phosphokinase increased	0 (0)	0 (0)	3 (5)	3 (8)	12 (6)	12 (8)	3 (2)	3 (2)	18 (3)	18 (5)
Weight decreased	0 (0)	0 (0)	0 (0)	0 (0)	3 (1)	3 (2)	4 (3)	4 (2)	7 (1)	7 (2)
Alanine aminotransferase increased	0 (0)	0 (0)	1 (2)	1 (3)	4 (2)	3 (2)	2 (1)	2 (1)	7 (1)	6 (2)
<b>Skin and Subcutaneous Tissue Disorders</b>	<b>12 (10)</b>	<b>9 (35)</b>	<b>15 (26)</b>	<b>7 (18)</b>	<b>54 (25)</b>	<b>31 (20)</b>	<b>19 (13)</b>	<b>16 (9)</b>	<b>100 (19)</b>	<b>63 (16)</b>
Rash	0 (0)	0 (0)	2 (3)	2 (5)	5 (2)	5 (3)	1 (1)	1 (1)	8 (1)	8 (2)
Pruritus	1 (1)	1 (4)	1 (2)	1 (3)	2 (1)	2 (1)	3 (2)	3 (2)	7 (1)	7 (2)

Clinical Review  
 Karyn L. Berry, MD, MPH  
 NDA 205494  
 Cerdelga (Eliglustat tartrate)

System Organ Class Preferred Term	GZGD00304 Phase 2 (N=26)		GZGD02507 ENGAGE (N=40)		GZGD02607 ENCORE (N=157)		GZGD03109 EDGE (N=170)		All Eliglustat (N=393)	
	Events n (/100 py) <sup>a</sup>	Patients n (%) <sup>b</sup>	Events n (/100 py) <sup>a</sup>	Patients n (%) <sup>b</sup>	Events n (/100 py) <sup>a</sup>	Patients n (%) <sup>b</sup>	Events n (/100 py) <sup>a</sup>	Patients n (%) <sup>b</sup>	Events n (/100 py) <sup>a</sup>	Patients n (%) <sup>b</sup>
Dermatitis contact	0 (0)	0 (0)	2 (3)	1 (3)	5 (2)	5 (3)	0 (0)	0 (0)	7 (1)	6 (2)
Dry skin	0 (0)	0 (0)	0 (0)	0 (0)	6 (3)	5 (3)	1 (1)	1 (1)	7 (1)	6 (2)
<b>Injury, Poisoning and Procedural Complications</b>	<b>8 (7)</b>	<b>7 (27)</b>	<b>8 (14)</b>	<b>6 (15)</b>	<b>49 (23)</b>	<b>33 (21)</b>	<b>15 (10)</b>	<b>11 (6)</b>	<b>80 (15)</b>	<b>57 (15)</b>
Laceration	0 (0)	0 (0)	1 (2)	1 (3)	7 (3)	7 (4)	0 (0)	0 (0)	8 (1)	8 (2)
Contusion	0 (0)	0 (0)	4 (7)	2 (5)	9 (4)	5 (3)	0 (0)	0 (0)	13 (2)	7 (2)
<b>Cardiac Disorders</b>	<b>6 (5)</b>	<b>4 (15)</b>	<b>7 (12)</b>	<b>5 (13)</b>	<b>18 (8)</b>	<b>17 (11)</b>	<b>17 (12)</b>	<b>15 (9)</b>	<b>48 (9)</b>	<b>41 (10)</b>
Palpitations	1 (1)	1 (4)	3 (5)	2 (5)	8 (4)	8 (5)	11 (8)	9 (5)	23 (4)	20 (5)
<b>Reproductive System and Breast Disorders</b>	<b>13 (11)</b>	<b>7 (27)</b>	<b>11 (19)</b>	<b>3 (8)</b>	<b>25 (12)</b>	<b>16 (10)</b>	<b>7 (5)</b>	<b>6 (4)</b>	<b>56 (10)</b>	<b>32 (8)</b>
Dysmenorrhoea	0 (0)	0 (0)	4 (7)	2 (5)	4 (2)	3 (2)	4 (3)	4 (2)	12 (2)	9 (2)
Metrorrhagia	3 (3)	2 (8)	1 (2)	1 (3)	4 (2)	3 (2)	0 (0)	0 (0)	8 (1)	6 (2)
<b>Blood and Lymphatic System Disorders</b>	<b>3 (3)</b>	<b>3 (12)</b>	<b>2 (3)</b>	<b>2 (5)</b>	<b>11 (5)</b>	<b>11 (7)</b>	<b>9 (6)</b>	<b>8 (5)</b>	<b>25 (5)</b>	<b>24 (6)</b>
Splenomegaly	1 (1)	1 (4)	0 (0)	0 (0)	4 (2)	4 (3)	3 (2)	3 (2)	8 (1)	8 (2)
<b>Psychiatric Disorders</b>	<b>3 (3)</b>	<b>3 (12)</b>	<b>3 (5)</b>	<b>3 (8)</b>	<b>16 (7)</b>	<b>10 (6)</b>	<b>14 (10)</b>	<b>7 (4)</b>	<b>36 (7)</b>	<b>23 (6)</b>
Anxiety	2 (2)	2 (8)	1 (2)	1 (3)	6 (3)	4 (3)	0 (0)	0 (0)	9 (2)	7 (2)
<b>Vascular Disorders</b>	<b>3 (3)</b>	<b>3 (12)</b>	<b>2 (3)</b>	<b>1 (3)</b>	<b>9 (4)</b>	<b>7 (4)</b>	<b>12 (8)</b>	<b>9 (5)</b>	<b>26 (5)</b>	<b>20 (5)</b>
Hypertension	2 (2)	2 (8)	0 (0)	0 (0)	2 (1)	2 (1)	5 (3)	4 (2)	9 (2)	8 (2)

System Organ Class Preferred Term	GZGD00304 Phase 2 (N=26)		GZGD02507 ENGAGE (N=40)		GZGD02607 ENCORE (N=157)		GZGD03109 EDGE (N=170)		All Eliglustat (N=393)	
	Events n (/100 py) <sup>a</sup>	Patients n (%) <sup>b</sup>	Events n (/100 py) <sup>a</sup>	Patients n (%) <sup>b</sup>	Events n (/100 py) <sup>a</sup>	Patients n (%) <sup>b</sup>	Events n (/100 py) <sup>a</sup>	Patients n (%) <sup>b</sup>	Events n (/100 py) <sup>a</sup>	Patients n (%) <sup>b</sup>
Flushing	0 (0)	0 (0)	1 (2)	1 (3)	3 (1)	3 (2)	2 (1)	2 (1)	6 (1)	6 (2)
<b>Renal and Urinary Disorders</b>	<b>12 (10)</b>	<b>7 (27)</b>	<b>5 (9)</b>	<b>2 (5)</b>	<b>12 (6)</b>	<b>10 (6)</b>	<b>0 (0)</b>	<b>0 (0)</b>	<b>29 (5)</b>	<b>19 (5)</b>
Haematuria	3 (3)	3 (12)	2 (3)	1 (3)	3 (1)	3 (2)	0 (0)	0 (0)	8 (1)	7 (2)
<b>Hepatobiliary Disorders</b>	<b>2 (2)</b>	<b>2 (8)</b>	<b>0 (0)</b>	<b>0 (0)</b>	<b>11 (5)</b>	<b>8 (5)</b>	<b>6 (4)</b>	<b>5 (3)</b>	<b>19 (4)</b>	<b>15 (4)</b>
Hepatomegaly	0 (0)	0 (0)	0 (0)	0 (0)	3 (1)	3 (2)	5 (3)	4 (2)	8 (1)	7 (2)
<b>Immune System Disorders</b>	<b>0 (0)</b>	<b>0 (0)</b>	<b>3 (5)</b>	<b>3 (8)</b>	<b>8 (4)</b>	<b>7 (4)</b>	<b>2 (1)</b>	<b>2 (1)</b>	<b>13 (2)</b>	<b>12 (3)</b>
Hypersensitivity	0 (0)	0 (0)	1 (2)	1 (3)	4 (2)	3 (2)	2 (1)	2 (1)	7 (1)	6 (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 patients 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%.*

The following AEs tables are from the ENGAGE trial and the ENCORE trial. These provide comparison of AEs with placebo and Cerezyme.

**Table 50: ENGAGE - Summary of TEAEs Occurring in ≥ 10% of Patients**

MedDRA <sup>a</sup> SOC Preferred Term	Placebo (N=20)		Eliglustat (N=20)		Total (N=40)	
	Patients n (%)	Events n	Patients n (%)	Events n	Patients n (%)	Events n
<b>Patients with Any TEAE</b>	<b>14 (70)</b>	<b>95</b>	<b>18 (90)</b>	<b>137</b>	<b>32 (80)</b>	<b>232</b>
<b>Infections and infestations</b>	<b>9 (45)</b>	<b>13</b>	<b>9 (45)</b>	<b>14</b>	<b>18 (45)</b>	<b>27</b>
Upper respiratory tract infection	4 (20)	4	1 (5)	1	5 (13)	5
Nasopharyngitis	0 (0)	0	3 (15)	3	3 (8)	3
Sinusitis	1 (5)	1	2 (10)	2	3 (8)	3
Influenza	2 (10)	2	0 (0)	0	2 (5)	2
<b>Gastrointestinal disorders</b>	<b>8 (40)</b>	<b>20</b>	<b>9 (45)</b>	<b>20</b>	<b>17 (43)</b>	<b>40</b>
Diarrhea	4 (20)	5	3 (15)	6	7 (18)	11
Toothache	3 (15)	3	1 (5)	2	4 (10)	5
Abdominal pain	2 (10)	2	1 (5)	1	3 (8)	3
Flatulence	1 (5)	1	2 (10)	3	3 (8)	4
Nausea	1 (5)	1	2 (10)	2	3 (8)	3
Vomiting	2 (10)	2	1 (5)	1	3 (8)	3
<b>Nervous system disorders</b>	<b>6 (30)</b>	<b>17</b>	<b>11 (55)</b>	<b>35</b>	<b>17 (43)</b>	<b>52</b>
Headache	6 (30)	13	8 (40)	23	14 (35)	36
Dizziness	2 (10)	2	1 (5)	2	3 (8)	4

Migraine	0 (0)	0	2 (10)	2	2 (5)	2
<b>Musculoskeletal and connective tissue disorders</b>	<b>6 (30)</b>	<b>11</b>	<b>9 (45)</b>	<b>14</b>	<b>15 (38)</b>	<b>25</b>
Arthralgia	2 (10)	4	9 (45)	11	11 (28)	15
<b>General disorders and administration site conditions</b>	<b>4 (20)</b>	<b>7</b>	<b>7 (35)</b>	<b>8</b>	<b>11 (28)</b>	<b>15</b>
Fatigue	2 (10)	2	1 (5)	2	3 (8)	4
Pyrexia	0 (0)	0	2 (10)	2	2 (5)	2
<b>Respiratory, thoracic and mediastinal disorders</b>	<b>5 (25)</b>	<b>5</b>	<b>6 (30)</b>	<b>10</b>	<b>11 (28)</b>	<b>15</b>
Oropharyngeal pain	1 (5)	1	2 (10)	2	3 (8)	3
Cough	2 (10)	2	0 (0)	0	2 (5)	2
Nasal obstruction	0 (0)	0	2 (10)	3	2 (5)	3
<b>Injury, poisoning and procedural complications</b>	<b>4 (20)</b>	<b>5</b>	<b>4 (20)</b>	<b>6</b>	<b>8 (20)</b>	<b>11</b>
Contusion	3 (15)	3	2 (10)	4	5 (13)	7
<b>Skin and subcutaneous tissue disorders</b>	<b>3 (15)</b>	<b>6</b>	<b>3 (15)</b>	<b>4</b>	<b>6 (15)</b>	<b>10</b>
Pruritus	2 (10)	3	0 (0)	0	2 (5)	3

**Medical Reviewer's comments:** 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.

**Table 51: ENCORE - Summary of TEAEs Occurring in  $\geq$  5% of Patients in Either Treatment Group**

MedDRA <sup>a</sup> SOC Preferred Term	Eliglustat (N=106)		Cerezyme (N=53)		Total (N=159)	
	Patients n (%)	Events n	Patients n (%)	Events n	Patients n (%)	Events n
<b>Patients with Any TEAE</b>	<b>97 (92)</b>	<b>657</b>	<b>42 (79)</b>	<b>141</b>	<b>139 (87)</b>	<b>798</b>
<b>Infections and infestations</b>	<b>59 (56)</b>	<b>104</b>	<b>19 (36)</b>	<b>33</b>	<b>78 (49)</b>	<b>137</b>
Nasopharyngitis	11 (10)	12	5 (9)	5	16 (10)	17
Upper respiratory tract infection	11 (10)	17	3 (6)	5	14 (9)	22
Sinusitis	11 (10)	14	1 (2)	1	12 (8)	15
Urinary tract infection	5 (5)	6	5 (9)	5	10 (6)	11
Influenza	6 (6)	8	2 (4)	2	8 (5)	10
Gastroenteritis viral	5 (5)	5	1 (2)	1	6 (4)	6
<b>Gastrointestinal disorders</b>	<b>57 (54)</b>	<b>115</b>	<b>9 (17)</b>	<b>16</b>	<b>66 (42)</b>	<b>131</b>
Diarrhea	13 (12)	16	2 (4)	2	15 (9)	18
Nausea	13 (12)	18	0 (0)	0	13 (8)	18
Abdominal pain upper	11 (10)	15	0 (0)	0	11 (7)	15
Dyspepsia	7 (7)	9	1 (2)	1	8 (5)	10
Gastroesophageal reflux disease	7 (7)	7	0 (0)	0	7 (4)	7
Constipation	5 (5)	5	0 (0)	0	5 (3)	5
Toothache	2 (2)	2	3 (6)	4	5 (3)	6
<b>Musculoskeletal and connective tissue disorders</b>	<b>41 (39)</b>	<b>87</b>	<b>16 (30)</b>	<b>22</b>	<b>57 (36)</b>	<b>109</b>
Arthralgia	16 (15)	22	9 (17)	9	25 (16)	31
Back pain	13 (12)	16	3 (6)	6	16 (10)	22
Pain in extremity	12 (11)	12	1 (2)	1	13 (8)	13
Bone pain	6 (6)	7	1 (2)	1	7 (4)	8
<b>Nervous system disorders</b>	<b>37 (35)</b>	<b>75</b>	<b>5 (9)</b>	<b>8</b>	<b>42 (26)</b>	<b>83</b>
Headache	14 (13)	27	1 (2)	1	15 (9)	28
Dizziness	9 (8)	9	0 (0)	0	9 (6)	9
<b>General disorders and administration site conditions</b>	<b>29 (27)</b>	<b>50</b>	<b>4(8)</b>	<b>5</b>	<b>33 (21)</b>	<b>55</b>
Fatigue	15 (14)	20	1 (2)	1	16 (10)	21
Asthenia	9 (8)	10	0 (0)	0	9 (6)	10
<b>Investigations</b>	<b>24 (23)</b>	<b>36</b>	<b>9 (17)</b>	<b>16</b>	<b>33 (21)</b>	<b>52</b>
Blood CPK increased	7 (7)	7	1 (2)	1	8 (5)	8
<b>Injury, poisoning and procedural complications</b>	<b>21 (20)</b>	<b>32</b>	<b>6 (11)</b>	<b>6</b>	<b>27 (17)</b>	<b>38</b>
Contusion	5 (5)	8	0 (0)	0	5 (3)	8

<b>Respiratory, thoracic and mediastinal disorders</b>	<b>20 (19)</b>	<b>32</b>	<b>2 (4)</b>	<b>2</b>	<b>22 (14)</b>	<b>34</b>
Cough	7 (7)	11	2 (4)	2	9 (6)	13
Epistaxis	5 (5)	5	0 (0)	0	5 (3)	5
<b>Skin and subcutaneous tissue disorders</b>	<b>16 (15)</b>	<b>24</b>	<b>2 (4)</b>	<b>3</b>	<b>18 (11)</b>	<b>27</b>
Rash	5 (5)	5	0 (0)	0	5 (3)	5
<b>Hepatobiliary disorders</b>	<b>5 (5)</b>	<b>6</b>	<b>7 (13)</b>	<b>7</b>	<b>12 (8)</b>	<b>13</b>
Hepatomegaly	1 (1)	1	3 (6)	3	4 (3)	4
<b>Cardiac disorders</b>	<b>9 (8)</b>	<b>10</b>	<b>1 (2)</b>	<b>1</b>	<b>10 (6)</b>	<b>11</b>
Palpitations	5 (5)	5	0 (0)	0	5 (3)	5

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

#### 7.4.2 Laboratory Findings

##### Hematology

The following hematology parameters: basophils, eosinophils, mean corpuscular hemoglobin, mean corpuscular volume (MCV), and mean corpuscular hemoglobin concentration, erythrocytes, hematocrit, leukocytes, lymphocytes, monocytes, neutrophils, and reticulocytes) were assessed in the clinical trials. Results were recorded at baseline, Weeks 13, 26, 52, and 78 timepoints. Hemoglobin and platelets were assessed as efficacy endpoints and are discussed in Section 6.

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 ration. 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).

#### Chemistry

Chemistry parameters were evaluated at Week 13, 26, 52, 78, and 104 time points. Parameters assessed included: alanine aminotransferase [ALT], aspartate aminotransferase [AST], gamma-glutamyl transaminase [GGT], total bilirubin, fasting glucose, creatine kinase [CK], and cholesterol).

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.

#### Urinalysis

Urinalysis was performed in all clinical studies at protocol-specified time points and urine pH was analyzed over time at 13 week intervals for the pooled Eliglustat Safety Set.

No clinically meaningful trends were observed in urine pH shift results for the pooled Eliglustat Safety Set. Urine pH was in the normal range at Baseline and remained in the normal range for the majority of patients with urinalysis data at most assessment weeks through Week 338 (Month 78) for the pooled Eliglustat Safety Set.

#### 7.4.3 Vital Signs

Baseline vital signs and change from Baseline at Week 13 and Week 52 for the pooled Eliglustat Safety Set were assessed. Overall, there were no clinically meaningful changes in mean vital sign measurements from Baseline to any post-Baseline time point.

#### 7.4.4 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 was 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 (Patients GZGD03109/33903 and GZGD03109/35704). Six (6) patients had a QTcF change from Baseline >60 msec, all also in EDGE (Patients GZGD03109/30501, GZGD03109/31613, GZGD03109/32804, GZGD03109/32806, GZGD03109/38401 and GZGD03109/38402). All QTcF liability cases came from the EDGE study and involved in all but 1 patient (GZGD03109/30501) 1 or 2 occurrences among multiple visits and 4h 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; Patients GZGD02607/2103, GZGD02607/2703, GZGD02607/5801, GZGD02607/5957; all during the PAP, none during the extension period), and 3 patients in EDGE (2% of the study population; patients GZGD03109/31002, GZGD03109/34501, and GZGD03109/38401). Apart from ENCORE patient GZGD02607/2103, none of these patients had any episodes of 2<sup>nd</sup> Degree or higher AV Block. ENCORE patient, GZGD02607/2103, 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 (Patient GZGD02507/2401 in ENGAGE during the PAP and again during the extension period; and Patient GZGD02507/0105 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 (Patient GZGD02607/5706 during the PAP and the extension as well), and 15 patients in EDGE Lead-In Period (8.8% of the study population). For ENCORE Patient GZGD02607/5706, 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  $\geq 120$  msec represented a greater than 25% increase from Baseline in 4/18 (22%) of the patients and were observed in EDGE (Patients GZGD03109/32201, ZGD03109/32901, GZGD03109/33902, and GZGD03109/38401).

### Holter Monitor

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. These findings are summarized in Table 45.

**Table 52: Patients with Holter Findings**

Study Number/ Patient ID	Treatment Period	Study Visit (Holter Date)	Treatment Group	Sustained?	Number of Episodes	Number of Beats
Ventricular Tachycardia						
GZGD00304/0202	PAP	Day 1 (18-Sep-2006)	Eliglustat 50 mg QD	No	2	Not known
GZGD00304/0302	PAP	(b) (6)	Eliglustat 50 mg QD	No	1	3
GZGD02507/3301	PAP	Week 13 (17-Jan-2012)	Placebo	No	1	9
GZGD02507/4301	Screening	Screening (05-Apr-2011)	None	No	4	Not known
GZGD02507/4601	Screening	Screening (11-Feb-2011)	None	No	1	3
GZGD02507/6405	Screening	Screening (10-Aug-2011)	None	No	1	Not known
GZGD02607/1905	Screening	Screening (19-Jan-2010)	N/A	No	1	3
GZGD02607/1907	Screening	Screening (10-Mar-2010)	N/A	No	2	24 total

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GZGD02607/2707	Extension	Unscheduled (10-Sep-2012)	Eliglustat 150 mg BID	No	1	4
GZGD02607/2906	Extension	Week 65 (13-Feb-2012)	Eliglustat 100 mg BID	No	1	4

Study Number/ Patient ID	Treatment Period	Study Visit (Holter Date)	Treatment Group	Sustained?	Number of Episodes	Number of Beats
GZGD02607/3407	PAP	Week 13 (10-Feb-2012)	Cerezyme	No	1	<8 <sup>d</sup>
GZGD02607/5704	Screening	Screening (27-Jan-2011)	N/A	No	1	6
GZGD02607/5804	Extension	Week 65 (18-Nov-2011)	Eliglustat 100 mg BID	No	1	5
GZGD02607/8304	Screening	Screening (23-Aug-2011)	N/A	No	1	12
2 <sup>nd</sup> Degree Atrioventricular Block- Mobitz I						
GZGD00304/0105	PAP	Week 52 (10-Sep-2007)	Eliglustat 100 mg BID	N/A	2	N/A
	PAP	Week 53 (19-Sep-2007)	N/A	N/A	1	N/A
	PAP	Unscheduled (10-Oct-2007)	N/A	N/A	1	N/A
GZGD02507/0104	Extension	Week 52 (14-Dec-2010)	Eliglustat 100 mg BID	N/A	2 brief	N/A
GZGD02507/3701	Screening	Screening (07-Sep-2010)	None	N/A	16	N/A
Study Number/ Patient ID	Treatment Period	Study Visit (Holter Date)	Treatment Group	Sustained?	Number of Episodes	Number of Beats
GZGD02607/2103	PAP	Week 13 (21-Jun-2011)	Eliglustat 50 mg BID	N/A	80	N/A
GZGD02607/2816	Screening	Screening (08-Aug-2011)	N/A	N/A	1	N/A
GZGD02607/5806	Extension	Week 65 (19-Jan-2012)	Eliglustat 100 mg BID	N/A	1	N/A
2:1 Atrioventricular Block						

GZGD02507/4905	Extension	Week 52 (23-Jul-2012)	Eliglustat 150 mg BID	N/A	1	N/A
GZGD02607/2103	PAP	Week 13 (21-Jun-2011)	Eliglustat 50 mg BID	N/A	1 brief	N/A
2 <sup>nd</sup> Degree AV Block-Mobitz II						
None						
Sinus Pauses						
GZGD02507/6404	Screening	Screening (11-Aug-2011)	N/A	N/A	N/A	N/A
GZGD02507/6404	Extension	Unscheduled (31-Oct-2012)	Eliglustat 100 mg BID	N/A	N/A	N/A
GZGD02607/2707	Extension	Week 65 (14-Feb-2012)	Eliglustat 150 mg BID	N/A	N/A	N/A
GZGD02607/6904	PAP	Week 13 (10-Feb-2012)	Eliglustat 150 mg BID	N/A	N/A	N/A

**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 (GZGD00304/0302) was withdrawn from study GZGD0034 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 2<sup>nd</sup>-degree AV block that were asymptomatic and taken from unscheduled Holter monitoring.**

**Data reported from electrocardiogram monitoring during phase 2 and 3 studies showed no clinically relevant changes in QTcF. Seven subjects had PR intervals > 200 ms and increase from Baseline of ≥ 25%. One had a clinically meaningful PR prolongation. Eighteen subjects had a post-baseline QRS ≥ 120 ms, two of them had post baseline increases of 30 and 50%, which were considered clinically meaningful. While some changes were observed in ECG and Holter monitor parameters with eliglustat, most patients were asymptomatic and continued treatment. As noted in the Table 45, some cases of cardiac arrhythmias were also observed at baseline screenings and in patients who received placebo or Cerezyme.**

#### 7.4.5 Special Safety Studies/Clinical Trials

##### 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  $\Delta\Delta\text{QTcF}$  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  $\geq 480$  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  $\geq 120$  msec.

The IRT determined that even though the suprathreshold dose (800 mg) produced a geometric mean  $C_{\text{max}}$  value 14-fold higher than the geometric mean  $C_{\text{max}}$  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, P-gP inhibition, hepatic impairment, and renal impairment on the exposure to Genz-112838.

Based on the results of the TQT study and to better assess potential safety risks, the applicant agreed to additional cardiac monitoring in the trials, to include ECG's, 24 hour Holter monitor and echocardiogram (Phase 2, ENGAGE and ENCORE).

At the time of submission of the NDA, the QT-IRT conducted further analysis with datasets of the TQT study. The results show no proarrhythmia risk at the predicted steady-state  $C_{\text{max}}$  achieved (44 ng/ml) for the GD1 patients with CYP2D6 phenotype. They note that QTc, PR and QRS prolongation are expected at steady-state suprathreshold scenario  $C_{\text{max}}$  (e.g., more than 10 ms mean change in QTcF may be expected when mean  $C_{\text{max}}$  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 were "negative", eliglustat increased the QTc and PR intervals in a concentration dependent manner. Based on the concentration QT relationship, there appears to be no QTc related safety concerns for drug concentrations below 250 ng/ml. 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.***

#### 7.4.6 Immunogenicity

No immunogenicity issues were related to eliglustat.

#### 7.5 Other Safety Explorations

##### Adverse events by severity

The majority of TEAEs were mild (153/393 patients [39%]), and were mostly events in the Infections and infestations (113/393 [29%]) and Gastrointestinal disorders SOCs (105/393 [27%]). Events assessed as moderate in severity were experienced by 136/393 patients (35%), with moderate events also mostly reported in the Infections and infestations (66/393 [17%]) and Gastrointestinal SOCs (48/393 [12%]). A total of 45/393 patients (11%) experienced TEAEs which were reported as severe, with most reports in the Gastrointestinal (10/393 [3%]) and Nervous disorders [10/393 [3%] SOCs. None of the PTs reported as severe events occurred in  $\geq 2\%$  of patients.

The 3 most frequently reported TEAEs in the mild category were Headache (49/393 patients [12%]), Nasopharyngitis (44/393 [11%]), and Upper respiratory tract infection (35/393 [9%]), which were also among the most frequent TEAEs overall. Among the moderate events, the 3 most frequently reported events were Arthralgia (18/393 [5%]), Back pain (17/393 [4%]), and Headache (13/393 [3%]).

The 3 most frequently reported severe events were Arthralgia (5/393 patients [1%]), Headache (4/393 [1%]) and Syncope (4/393 [1%]). Other severe events included reports in the Gastrointestinal SOC (each PT in 1% of patients: Abdominal pain upper, Dyspepsia, and Dysphagia); and also (each PT in <1% of patients): Abdominal pain, Abdominal pain lower, Food poisoning, and Hiatus hernia). In addition to Headache

(1%), Syncope (1%), in the Nervous system disorders SOC, severe events reported included Convulsion, Migraine, and Neuralgia (each PT reported <1% of patients). In addition to Arthralgia (1%), severe events reported in the Musculoskeletal and connective tissue disorders SOC also included Back pain, Bone pain, Bursitis, Pain in extremity, and Tendon disorder (each PT reported for <1% of patients). For the General disorders and administration site conditions SOC, severe events included fatigue (1%), and Asthenia, Medical device pain, Pain, Pyrexia, and Xerosis (each PT in <1% of patients). In the Cardiac disorders SOC, the severe events included Myocardial infarction (1%), Acute myocardial infarction (<1%), and Left ventricular hypertrophy (<1%).

### 7.5.1 Dose Dependency for Adverse Events

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%]).

**Table 53: Summary of Patients with Treatment-Emergent Adverse Events by Severity, Eliglustat Dose Level at the Time of the Event, and CYP2D6 Metabolizer Status - Eliglustat Safety Set**

			All Eliglustat (N=393)		
			Mild	Moderate	Severe
Eliglustat Dose Level at the Time of the Event	n	Duration of Treatment in Years (Mean ±SD)	Patient s n (%) <sup>a</sup>	Patient s n (%) <sup>a</sup>	Patient s n (%) <sup>a</sup>
<b>50 mg BID</b>					
Poor	14	1.4 (1.49)	4 (29)	4 (29)	3 (21)
Intermediate	49	0.6 (0.54)	15 (31)	11 (22)	7 (14)
Extensive	308	0.2 (0.57)	84 (27)	35 (11)	8 (3)
Ultrarapid	9	0.1 (0.05)	2 (22)	3 (33)	0 (0)
Indeterminate	5	0.2 (0.19)	3 (60)	1 (20)	0 (0)
<b>100 mg BID</b>					
Poor	0	-	0 (0)	0 (0)	0 (0)
Intermediate	19	0.9 (0.62)	6 (32)	6 (32)	0 (0)
Extensive	282	0.9 (1.28)	114 (40)	80 (28)	13 (5)
Ultrarapid	9	0.4 (0.29)	0 (0)	5 (56)	1 (11)
Indeterminate	3	0.6 (0.35)	0 (0)	0 (0)	0 (0)

150 mg BID					
Poor	0	-	0 (0)	0 (0)	0 (0)
Intermediate	1	1.1 (--)	1 (100)	0 (0)	0 (0)
Extensive	88	1.1 (0.66)	34 (39)	22 (25)	13 (15)
Ultrarapid	6	1.6 (1.02)	0 (0)	4 (67)	1 (17)
Indeterminate	1	0.1 (--)	0 (0)	1 (100)	0 (0)

Modified Applicant's table

### 7.5.2 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, Diarrhoea, 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.

**Table 54: Summary of Patients with Treatment-Emergent Adverse Events by Time of Onset of the Event Relative to the Start of Eliglustat Treatment – Eliglustat Safety Set**

	All Eliglustat (N=393)	
	Overall TEAEs	Related TEAEs
Duration of Eliglustat Treatment (months)	Patients n (%)	Patients n (%)
0 to ≤6	298/393 (76)	121/393 (31)
>6 to ≤12	186/348 (53)	52/348 (15)
>12 to ≤18	101/204 (50)	17/204 (8)
>18 to ≤24	49/114 (43)	11/114(10)
>24 to ≤30	22/62 (35)	3/62 (5)

>30 to ≤36	8/32 (25)	0/32 (0)
>36 to ≤42	7/20 (35)	1/20 (5)
>42 to ≤48	7/19 (37)	0/19 (0)

Applicant's table

### 7.5.3 Drug-Demographic Interactions

#### *Age*

Patients were divided into three age groups, 16 to 30 years, >30 to 65 years and >65 years. The reported TEAEs were similar across age groups. Patients in the > 30 to 65 year age group had a slightly higher overall incidence of TEAEs (202/226 [89%]) compared with the other age groups (16 to 30 year group, 124/157 [79%]; >65 year group, 8/10 [80%]).

Among the TEAEs reported for patients >65 years of age in the pooled Eliglustat Safety Set, most of the reported events were in the SOCs of Infections and infestations (4 patients), Nervous system disorders (4 patients), and Gastrointestinal disorders SOC (3 patients), and the PTs reported were similar to those reported most frequently for the overall pooled Eliglustat Safety Set (nasopharyngitis, upper respiratory tract infection, UTI, diarrhoea, nausea, headache, and dizziness. All of the TEAEs in patients >65 years of age were mild with the exception of the following moderate events: dizziness, nausea, excoriation, and fall (1 incidence each); and headache (2 patients, 1 incidence each). There were no SAEs reported in patients >65 years of age.

#### *Gender*

No major difference was seen between males and females for the overall incidence of TEAEs (161/191 [84%] and 173/202 [86%], respectively). Treatment-emergent adverse events that occurred more frequently ( $\geq 5\%$  difference) in female patients than male patients were: influenza (9% versus 3%), UTI (9% versus 2%), arthralgia (18% versus 10%), abdominal pain upper (11% versus 6%), nausea (12% versus 5%), headache (20% versus 13%), dizziness (13% versus 6%), back pain (12% versus 6%), pain in extremity (11% versus 5%), fatigue (11% versus 4%), bone pain (7% versus 2%), and cough (8% versus 3%), respectively. Syncope was also reported more frequently in female (8 [4%]) than male (0 [0%]) patients. There were no TEAEs that occurred more frequently in male patients with a  $\geq 5\%$  difference as compared to female patients. No major difference was seen between males and females for the overall incidence of SAEs (14/191 [7%] and 21/202 [10%], respectively).

### 7.5.4 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.

**Table 54: Summary of Patients with Treatment-Emergent Adverse Events by Eliglustat Dose Level at the Time of the Event and by CYP2D6 Metabolizer Status Eliglustat Safety Set**

		Eliglustat Dose Level at the Time of the Event			
		50 mg BID	100 mg BID	150 mg BID	Any Dose
CYP2D6 Metabolizer Status	N	Patients n (%) <sup>a</sup>	Patients n (%) <sup>a</sup>	Patients n (%) <sup>a</sup>	Patients n (%) <sup>a</sup>
Poor	14	11 (79)	0 (0)	0 (0)	11 (79)
n		14	0	0	14
Intermediate	49	33 (67)	12 (63)	1 (100)	36 (73)
n		49	19	1	49
Extensive	310	127 (41)	207 (73)	69 (78)	272 (88)
n		308	282	88	310
Ultrarapid	9	5 (56)	6 (67)	5 (83)	9 (100)
n		9	9	6	9
Indeterminate	5	4 (80)	0 (0)	1 (100)	4 (80)
n		5	3	1	5

Source: Applicant's table ISS

### 7.5.5 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 were 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<sub>0-last</sub>) and a moderate inhibitor of CYP2D6 (2.09-fold in metoprolol AUC<sub>0-last</sub>), 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. The trials allowed for eliglustat dose adjustments based on concomitant medication use.

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 and neither patient had eliglustat exposure in the upper 10<sup>th</sup> percentile. Possible or probable related AEs reported by the Applicant for concomitant CYP2D6 medication use included: exfoliative rash, lethargy, diarrhea, dizziness, headache, nausea, thrombophlebitis and paresthesia.

***Medical Reviewer's comments: The clinical trial protocols limited the use of CYP2D6 inhibitors, especially strong inhibitors. AEs for CYP2D6 concomitant medication use was reviewed. No significant safety signals were noted with concomitant use of CYP2D6 inhibitors. During the postmarketing period, when it is expected that additional medications will be used that may interact with***

***eliglustat, routine surveillance of potential drug-drug interactions is recommended. See tables below.***

Table 55: Pooled Summary of Patients with Eliglustat Treatment-Emergent Adverse Events by MedDRA System Organ Class and Preferred Term by Medications of Interest Use – CYP2D6 Inhibitors  
 Eliglustat Safety Set

System Organ Class Preferred Term	All eliglustat patients who ever took Strong, Moderate, and/or Weak CYP2D6 inhibitors (excluding TOPICAL/OTHER routes of administration) (N=79)			Patients who never took CYP2D6 inhibitors (N=311)
	Strong (n=11) Patients n (%)	Moderate (n=4) Patients n (%)	Weak (n=64) Patients n (%)	
Patients with Events	10 ( 12.7)	3 ( 3.8)	60 ( 75.9)	258 ( 83.0)
Infections and infestations	5 ( 6.3)	2 ( 2.5)	37 ( 46.8)	138 ( 44.4)
Nasopharyngitis	1 ( 1.3)	0 ( 0.0)	8 ( 10.1)	43 ( 13.8)
Upper respiratory tract infection	3 ( 3.8)	0 ( 0.0)	7 ( 8.9)	32 ( 10.3)
Influenza	1 ( 1.3)	0 ( 0.0)	9 ( 11.4)	13 ( 4.2)
Sinusitis	1 ( 1.3)	0 ( 0.0)	7 ( 8.9)	15 ( 4.8)
Urinary tract infection	0 ( 0.0)	0 ( 0.0)	9 ( 11.4)	14 ( 4.5)
Bronchitis	2 ( 2.5)	1 ( 1.3)	2 ( 2.5)	8 ( 2.6)
Gastroenteritis	1 ( 1.3)	0 ( 0.0)	2 ( 2.5)	8 ( 2.6)
Viral infection	0 ( 0.0)	0 ( 0.0)	0 ( 0.0)	10 ( 3.2)
Gastroenteritis viral	0 ( 0.0)	0 ( 0.0)	4 ( 5.1)	4 ( 1.3)
Oral herpes	0 ( 0.0)	0 ( 0.0)	3 ( 3.8)	4 ( 1.3)
Pharyngitis	0 ( 0.0)	0 ( 0.0)	1 ( 1.3)	6 ( 1.9)
Ear infection	1 ( 1.3)	0 ( 0.0)	1 ( 1.3)	4 ( 1.3)
Pneumonia	0 ( 0.0)	0 ( 0.0)	0 ( 0.0)	6 ( 1.9)

Clinical Review  
 Karyn L. Berry, MD, MPH  
 NDA 205494  
 Cerdelga (Eliglustat tartrate)

System Organ Class Preferred Term	All eliglustat patients who ever took Strong, Moderate, and/or Weak CYP2D6 inhibitors (excluding TOPICAL/OTHER routes of administration) (N=79)			Patients who never took CYP2D6 inhibitors (N=311)
	Strong (n=11) Patients n (%)	Moderate (n=4) Patients n (%)	Weak (n=64) Patients n (%)	Patients n (%)
Infections and infestations (contd)				
Hordeolum	0 (0.0)	0 (0.0)	0 (0.0)	4 (1.3)
Otitis media	0 (0.0)	0 (0.0)	1 (1.3)	3 (1.0)
Tonsillitis	0 (0.0)	0 (0.0)	1 (1.3)	3 (1.0)
Cystitis	0 (0.0)	0 (0.0)	2 (2.5)	1 (0.3)
Fungal infection	0 (0.0)	0 (0.0)	1 (1.3)	2 (0.6)
Localised infection	1 (1.3)	0 (0.0)	1 (1.3)	1 (0.3)
Pharyngitis streptococcal	1 (1.3)	0 (0.0)	0 (0.0)	2 (0.6)
Respiratory tract infection viral	0 (0.0)	0 (0.0)	1 (1.3)	2 (0.6)
Tooth infection	0 (0.0)	0 (0.0)	2 (2.5)	1 (0.3)
Vulvovaginal candidiasis	0 (0.0)	0 (0.0)	2 (2.5)	1 (0.3)
Abscess	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.6)
Acarodermatitis	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.6)
Fungal skin infection	0 (0.0)	0 (0.0)	1 (1.3)	1 (0.3)
Herpes zoster	1 (1.3)	0 (0.0)	0 (0.0)	1 (0.3)
Infected dermal cyst	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.6)
Onychomycosis	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.6)

System Organ Class Preferred Term	All eliglustat patients who ever took Strong, Moderate, and/or Weak CYP2D6 inhibitors (excluding TOPICAL/OTHER routes of administration) (N=79)			Patients who never took CYP2D6 inhibitors (N=311)
	Strong (n=11) Patients n (%)	Moderate (n=4) Patients n (%)	Weak (n=64) Patients n (%)	Patients n (%)
Infections and infestations (contd)				
Otitis externa	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.6)
Paronychia	1 (1.3)	0 (0.0)	0 (0.0)	1 (0.3)
Respiratory tract infection	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.6)
Rhinitis	0 (0.0)	0 (0.0)	1 (1.3)	1 (0.3)
Streptococcal infection	0 (0.0)	0 (0.0)	2 (2.5)	0 (0.0)
Tinea pedis	0 (0.0)	1 (1.3)	0 (0.0)	1 (0.3)
Vaginal infection	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.6)
Acute tonsillitis	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)
Anal abscess	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)
Appendicitis	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)
Atypical pneumonia	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)
Bacteriuria	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)
Bronchopneumonia	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)
Campylobacter gastroenteritis	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)
Candidiasis	0 (0.0)	0 (0.0)	1 (1.3)	0 (0.0)
Cellulitis	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)

Clinical Review  
 Karyn L. Berry, MD, MPH  
 NDA 205494  
 Cerdelga (Eliglustat tartrate)

System Organ Class Preferred Term	All eliglustat patients who ever took Strong, Moderate, and/or Weak CYP2D6 inhibitors (excluding TOPICAL/OTHER routes of administration) (N=79)			Patients who never took CYP2D6 inhibitors (N=311)
	Strong (n=11) Patients n (%)	Moderate (n=4) Patients n (%)	Weak (n=64) Patients n (%)	Patients n (%)
Infections and infestations (contd)				
Diverticulitis	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)
Erysipelas	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)
Eye infection viral	0 (0.0)	0 (0.0)	1 (1.3)	0 (0.0)
Furuncle	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)
Gingivitis	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)
Hepatitis A	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)
Herpes simplex	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)
Hookworm infection	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)
Infection	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)
Labyrinthitis	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)
Lower respiratory tract infection	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)
Lower respiratory tract infection bacterial	0 (0.0)	0 (0.0)	1 (1.3)	0 (0.0)
Lung infection	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)
Molluscum contagiosum	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)
Mucosal infection	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)
Myringitis	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)

System Organ Class Preferred Term	All eliglustat patients who ever took Strong, Moderate, and/or Weak CYP2D6 inhibitors (excluding TOPICAL/OTHER routes of administration) (N=79)			Patients who never took CYP2D6 inhibitors (N=311)
	Strong (n=11) Patients n (%)	Moderate (n=4) Patients n (%)	Weak (n=64) Patients n (%)	Patients n (%)
Infections and infestations (contd)				
Nail bed infection	0 (0.0)	0 (0.0)	1 (1.3)	0 (0.0)
Oral candidiasis	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)
Oral fungal infection	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)
Periodontitis	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)
Pulpitis dental	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)
Pyelonephritis acute	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)
Rash pustular	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)
Sinusitis bacterial	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)
Skin infection	1 (1.3)	0 (0.0)	0 (0.0)	0 (0.0)
Tinea versicolour	0 (0.0)	0 (0.0)	1 (1.3)	0 (0.0)
Tracheobronchitis	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)
Urethritis	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)
Vaginitis bacterial	0 (0.0)	0 (0.0)	1 (1.3)	0 (0.0)
Vaginitis gardnerella	0 (0.0)	0 (0.0)	1 (1.3)	0 (0.0)
Viral upper respiratory tract infection	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)
Vulvovaginal mycotic infection	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)

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NDA 205494  
Cerdelga (Eliglustat tartrate)

System Organ Class Preferred Term	All eliglustat patients who ever took Strong, Moderate, and/or Weak CYP2D6 inhibitors (excluding TOPICAL/OTHER routes of administration) (N=79)			Patients who never took CYP2D6 inhibitors (N=311)
	Strong (n=11) Patients n (%)	Moderate (n=4) Patients n (%)	Weak (n=64) Patients n (%)	
Infections and infestations (contd)				
Wound infection	0 (0.0)	0 (0.0)	1 (1.3)	0 (0.0)
Gastrointestinal disorders	6 (7.6)	2 (2.5)	35 (44.3)	118 (37.9)
Diarrhoea	3 (3.8)	0 (0.0)	6 (7.6)	29 (9.3)
Abdominal pain upper	1 (1.3)	0 (0.0)	7 (8.9)	25 (8.0)
Nausea	4 (5.1)	0 (0.0)	9 (11.4)	20 (6.4)
Dyspepsia	0 (0.0)	0 (0.0)	8 (10.1)	19 (6.1)
Abdominal pain	0 (0.0)	0 (0.0)	6 (7.6)	19 (6.1)
Constipation	1 (1.3)	0 (0.0)	4 (5.1)	17 (5.5)
Gastroesophageal reflux disease	1 (1.3)	0 (0.0)	7 (8.9)	12 (3.9)
Vomiting	2 (2.5)	0 (0.0)	5 (6.3)	10 (3.2)
Abdominal distension	0 (0.0)	0 (0.0)	2 (2.5)	9 (2.9)
Dysphagia	0 (0.0)	0 (0.0)	3 (3.8)	5 (1.6)
Flatulence	0 (0.0)	0 (0.0)	2 (2.5)	6 (1.9)
Toothache	0 (0.0)	0 (0.0)	4 (5.1)	4 (1.3)
Gastritis	0 (0.0)	0 (0.0)	3 (3.8)	4 (1.3)
Dry mouth	0 (0.0)	0 (0.0)	0 (0.0)	6 (1.9)

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	Strong (n=11) Patients n (%)	Moderate (n=4) Patients n (%)	Weak (n=64) Patients n (%)	
Gastrointestinal disorders (contd)				
Abdominal discomfort	0 (0.0)	0 (0.0)	2 (2.5)	2 (0.6)
Food poisoning	1 (1.3)	0 (0.0)	0 (0.0)	3 (1.0)
Oesophagitis	0 (0.0)	0 (0.0)	2 (2.5)	2 (0.6)
Abdominal pain lower	0 (0.0)	0 (0.0)	0 (0.0)	3 (1.0)
Gingival bleeding	0 (0.0)	0 (0.0)	2 (2.5)	1 (0.3)
Haemorrhoids	0 (0.0)	0 (0.0)	1 (1.3)	2 (0.6)
Odynophagia	0 (0.0)	0 (0.0)	0 (0.0)	3 (1.0)
Rectal haemorrhage	0 (0.0)	0 (0.0)	2 (2.5)	1 (0.3)
Dental caries	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.6)
Hiatus hernia	0 (0.0)	0 (0.0)	1 (1.3)	1 (0.3)
Anal pruritus	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)
Bowel movement irregularity	0 (0.0)	0 (0.0)	1 (1.3)	0 (0.0)
Colitis ischaemic	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)
Diverticulum	0 (0.0)	0 (0.0)	1 (1.3)	0 (0.0)
Duodenogastric reflux	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)
Eructation	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)

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	Strong (n=11) Patients n (%)	Moderate (n=4) Patients n (%)	Weak (n=64) Patients n (%)	
Gastrointestinal disorders (contd)				
Frequent bowel movements	0 (0.0)	0 (0.0)	1 (1.3)	0 (0.0)
Gastrointestinal disorder	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)
Gingival swelling	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)
Glossodynia	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)
Haematochezia	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)
Hypertrophy of tongue papillae	0 (0.0)	1 (1.3)	0 (0.0)	0 (0.0)
Irritable bowel syndrome	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)
Lip oedema	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)
Lip swelling	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)
Oesophageal irritation	0 (0.0)	1 (1.3)	0 (0.0)	0 (0.0)
Oesophageal pain	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)
Poor dental condition	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)
Proctalgia	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)
Rectal tenesmus	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)
Reflux gastritis	0 (0.0)	0 (0.0)	1 (1.3)	0 (0.0)
Regurgitation	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)

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	Strong (n=11) Patients n (%)	Moderate (n=4) Patients n (%)	Weak (n=64) Patients n (%)	
Gastrointestinal disorders (contd)				
Tooth impacted	0 (0.0)	0 (0.0)	1 (1.3)	0 (0.0)
Musculoskeletal and connective tissue disorders				
Arthralgia	0 (0.0)	1 (1.3)	28 (35.4)	93 (29.9)
Back pain	1 (1.3)	0 (0.0)	12 (15.2)	43 (13.8)
Pain in extremity	0 (0.0)	0 (0.0)	10 (12.7)	24 (7.7)
Bone pain	0 (0.0)	0 (0.0)	9 (11.4)	21 (6.8)
Myalgia	0 (0.0)	0 (0.0)	7 (8.9)	11 (3.5)
Musculoskeletal pain	0 (0.0)	0 (0.0)	2 (2.5)	10 (3.2)
Joint stiffness	0 (0.0)	0 (0.0)	3 (3.8)	8 (2.6)
Muscular weakness	0 (0.0)	0 (0.0)	2 (2.5)	2 (0.6)
Tendonitis	0 (0.0)	0 (0.0)	2 (2.5)	2 (0.6)
Arthritis	0 (0.0)	0 (0.0)	0 (0.0)	4 (1.3)
Muscle spasms	0 (0.0)	0 (0.0)	1 (1.3)	2 (0.6)
Musculoskeletal stiffness	0 (0.0)	0 (0.0)	2 (2.5)	1 (0.3)
Osteoarthritis	0 (0.0)	0 (0.0)	0 (0.0)	3 (1.0)
Osteopenia	0 (0.0)	1 (1.3)	0 (0.0)	2 (0.6)
	0 (0.0)	0 (0.0)	0 (0.0)	3 (1.0)

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	Strong (n=11) Patients n (%)	Moderate (n=4) Patients n (%)	Weak (n=64) Patients n (%)	
Musculoskeletal and connective tissue disorders (contd)				
Osteoporosis	0 (0.0)	0 (0.0)	1 (1.3)	2 (0.6)
Bursitis	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.6)
Musculoskeletal discomfort	0 (0.0)	0 (0.0)	1 (1.3)	1 (0.3)
Neck pain	0 (0.0)	0 (0.0)	1 (1.3)	1 (0.3)
Pain in jaw	1 (1.3)	0 (0.0)	0 (0.0)	1 (0.3)
Spinal osteoarthritis	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.6)
Torticollis	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.6)
Bone infarction	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)
Flank pain	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)
Intervertebral disc disorder	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)
Intervertebral disc protrusion	0 (0.0)	0 (0.0)	1 (1.3)	0 (0.0)
Joint effusion	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)
Joint range of motion decreased	1 (1.3)	0 (0.0)	0 (0.0)	0 (0.0)
Joint swelling	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)
Medial tibial stress syndrome	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)
Muscle tightness	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)

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	Strong (n=11) Patients n (%)	Moderate (n=4) Patients n (%)	Weak (n=64) Patients n (%)	
Musculoskeletal and connective tissue disorders (contd)				
Muscle twitching	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)
Musculoskeletal chest pain	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)
Musculoskeletal disorder	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)
Myositis	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)
Osteochondrosis	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)
Osteonecrosis	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)
Sensation of heaviness	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)
Spinal deformity	0 (0.0)	0 (0.0)	1 (1.3)	0 (0.0)
Synovial cyst	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)
Temporomandibular joint syndrome	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)
Tendon disorder	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)
Upper extremity mass	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)
Nervous system disorders	5 (6.3)	2 (2.5)	24 (30.4)	92 (29.6)
Headache	2 (2.5)	0 (0.0)	13 (16.5)	48 (15.4)
Dizziness	3 (3.8)	1 (1.3)	4 (5.1)	29 (9.3)
Paraesthesia	1 (1.3)	0 (0.0)	2 (2.5)	6 (1.9)

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	Strong (n=11) Patients n (%)	Moderate (n=4) Patients n (%)	Weak (n=64) Patients n (%)	
Nervous system disorders (contd)				
Neuropathy peripheral	1 ( 1.3)	2 ( 2.5)	1 ( 1.3)	4 ( 1.3)
Dysgeusia	0 ( 0.0)	0 ( 0.0)	1 ( 1.3)	6 ( 1.9)
Somnolence	0 ( 0.0)	0 ( 0.0)	2 ( 2.5)	5 ( 1.6)
Syncope	0 ( 0.0)	0 ( 0.0)	4 ( 5.1)	3 ( 1.0)
Hypoaesthesia	1 ( 1.3)	0 ( 0.0)	1 ( 1.3)	3 ( 1.0)
Migraine	0 ( 0.0)	0 ( 0.0)	1 ( 1.3)	4 ( 1.3)
Tremor	1 ( 1.3)	0 ( 0.0)	2 ( 2.5)	2 ( 0.6)
Amnesia	0 ( 0.0)	1 ( 1.3)	2 ( 2.5)	1 ( 0.3)
Dizziness postural	1 ( 1.3)	0 ( 0.0)	0 ( 0.0)	3 ( 1.0)
Sinus headache	0 ( 0.0)	0 ( 0.0)	2 ( 2.5)	1 ( 0.3)
Balance disorder	0 ( 0.0)	0 ( 0.0)	0 ( 0.0)	2 ( 0.6)
Burning sensation	0 ( 0.0)	0 ( 0.0)	1 ( 1.3)	1 ( 0.3)
Carpal tunnel syndrome	0 ( 0.0)	0 ( 0.0)	1 ( 1.3)	1 ( 0.3)
Convulsion	0 ( 0.0)	0 ( 0.0)	0 ( 0.0)	2 ( 0.6)
Disturbance in attention	0 ( 0.0)	0 ( 0.0)	0 ( 0.0)	2 ( 0.6)
Lumbar radiculopathy	0 ( 0.0)	0 ( 0.0)	0 ( 0.0)	2 ( 0.6)

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	Strong (n=11) Patients n (%)	Moderate (n=4) Patients n (%)	Weak (n=64) Patients n (%)	
Nervous system disorders (contd)				
Neuralgia	0 ( 0.0)	0 ( 0.0)	0 ( 0.0)	2 ( 0.6)
Tension headache	0 ( 0.0)	0 ( 0.0)	1 ( 1.3)	1 ( 0.3)
Cervicobrachial syndrome	0 ( 0.0)	0 ( 0.0)	0 ( 0.0)	1 ( 0.3)
Decreased vibratory sense	0 ( 0.0)	0 ( 0.0)	0 ( 0.0)	1 ( 0.3)
Hypoglycaemic seizure	0 ( 0.0)	0 ( 0.0)	0 ( 0.0)	1 ( 0.3)
Hyposmia	0 ( 0.0)	0 ( 0.0)	0 ( 0.0)	1 ( 0.3)
Ischaemic stroke	0 ( 0.0)	0 ( 0.0)	0 ( 0.0)	1 ( 0.3)
Lethargy	1 ( 1.3)	0 ( 0.0)	0 ( 0.0)	0 ( 0.0)
Memory impairment	0 ( 0.0)	0 ( 0.0)	0 ( 0.0)	1 ( 0.3)
Narcolepsy	0 ( 0.0)	0 ( 0.0)	1 ( 1.3)	0 ( 0.0)
Olfactory nerve disorder	0 ( 0.0)	0 ( 0.0)	0 ( 0.0)	1 ( 0.3)
Parosmia	0 ( 0.0)	0 ( 0.0)	0 ( 0.0)	1 ( 0.3)
Polyneuropathy	0 ( 0.0)	0 ( 0.0)	1 ( 1.3)	0 ( 0.0)
Presyncope	0 ( 0.0)	0 ( 0.0)	1 ( 1.3)	0 ( 0.0)
Reflexes abnormal	0 ( 0.0)	0 ( 0.0)	1 ( 1.3)	0 ( 0.0)
Resting tremor	0 ( 0.0)	0 ( 0.0)	0 ( 0.0)	1 ( 0.3)

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	Strong (n=11) Patients n (%)	Moderate (n=4) Patients n (%)	Weak (n=64) Patients n (%)	Patients n (%)
Nervous system disorders (contd)				
Sciatica	0 (0.0)	0 (0.0)	1 (1.3)	0 (0.0)
Sensory loss	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)
Vllth nerve paralysis	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)
General disorders and administration site conditions				
Fatigue	2 (2.5)	1 (1.3)	8 (10.1)	17 (5.5)
Asthenia	0 (0.0)	0 (0.0)	5 (6.3)	11 (3.5)
Oedema peripheral	1 (1.3)	0 (0.0)	4 (5.1)	8 (2.6)
Chest pain	0 (0.0)	0 (0.0)	4 (5.1)	8 (2.6)
Pyrexia	1 (1.3)	0 (0.0)	1 (1.3)	10 (3.2)
Influenza like illness	0 (0.0)	0 (0.0)	1 (1.3)	5 (1.6)
Pain	0 (0.0)	2 (2.5)	1 (1.3)	2 (0.6)
Malaise	0 (0.0)	0 (0.0)	0 (0.0)	4 (1.3)
Chest discomfort	0 (0.0)	0 (0.0)	1 (1.3)	2 (0.6)
Chills	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.6)
Spinal pain	0 (0.0)	0 (0.0)	1 (1.3)	1 (0.3)

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	Strong (n=11) Patients n (%)	Moderate (n=4) Patients n (%)	Weak (n=64) Patients n (%)	Patients n (%)
General disorders and administration site conditions (contd)				
Xerosis	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.6)
Device malfunction	0 (0.0)	0 (0.0)	1 (1.3)	0 (0.0)
Early satiety	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)
Face oedema	0 (0.0)	0 (0.0)	1 (1.3)	0 (0.0)
Feeling hot	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)
Hangover	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)
Hunger	0 (0.0)	0 (0.0)	1 (1.3)	0 (0.0)
Infusion site irritation	0 (0.0)	0 (0.0)	1 (1.3)	0 (0.0)
Medical device pain	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)
Oedema	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)
Suprapubic pain	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)
Swelling	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)
Tenderness	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)
Thirst	0 (0.0)	0 (0.0)	1 (1.3)	0 (0.0)
Vessel puncture site swelling	0 (0.0)	0 (0.0)	1 (1.3)	0 (0.0)

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	Strong (n=11) Patients n (%)	Moderate (n=4) Patients n (%)	Weak (n=64) Patients n (%)	
Respiratory, thoracic and mediastinal disorders	1 (1.3)	0 (0.0)	24 (30.4)	55 (17.7)
Cough	0 (0.0)	0 (0.0)	5 (6.3)	18 (5.8)
Epistaxis	1 (1.3)	0 (0.0)	4 (5.1)	12 (3.9)
Oropharyngeal pain	1 (1.3)	0 (0.0)	1 (1.3)	15 (4.8)
Nasal congestion	0 (0.0)	0 (0.0)	4 (5.1)	4 (1.3)
Throat irritation	0 (0.0)	0 (0.0)	5 (6.3)	1 (0.3)
Rhinitis allergic	0 (0.0)	0 (0.0)	2 (2.5)	2 (0.6)
Dyspnoea	0 (0.0)	0 (0.0)	3 (3.8)	0 (0.0)
Nasal obstruction	0 (0.0)	0 (0.0)	2 (2.5)	1 (0.3)
Respiratory tract congestion	0 (0.0)	0 (0.0)	1 (1.3)	2 (0.6)
Rhinorrhoea	0 (0.0)	0 (0.0)	1 (1.3)	2 (0.6)
Sinus congestion	0 (0.0)	0 (0.0)	1 (1.3)	2 (0.6)
Dysphonia	0 (0.0)	0 (0.0)	1 (1.3)	1 (0.3)
Nasal septum deviation	0 (0.0)	0 (0.0)	1 (1.3)	1 (0.3)
Asthma	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)
Dry throat	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)
Hiccups	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)

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Respiratory, thoracic and mediastinal disorders (contd)				
Nasal dryness	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)
Nasal polyps	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)
Pulmonary hypertension	0 (0.0)	0 (0.0)	1 (1.3)	0 (0.0)
Respiratory disorder	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)
Upper respiratory tract congestion	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)
Vasomotor rhinitis	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)
Investigations	3 (3.8)	2 (2.5)	15 (19.0)	54 (17.4)
Blood creatine phosphokinase increased	0 (0.0)	0 (0.0)	6 (7.6)	11 (3.5)
Weight decreased	0 (0.0)	0 (0.0)	1 (1.3)	6 (1.9)
Alanine aminotransferase increased	0 (0.0)	0 (0.0)	1 (1.3)	5 (1.6)
Gamma-glutamyltransferase increased	0 (0.0)	0 (0.0)	0 (0.0)	5 (1.6)
Blood folate decreased	0 (0.0)	0 (0.0)	1 (1.3)	3 (1.0)
Haemoglobin decreased	1 (1.3)	0 (0.0)	3 (3.8)	0 (0.0)
Nerve conduction studies abnormal	0 (0.0)	0 (0.0)	2 (2.5)	2 (0.6)
Platelet count decreased	0 (0.0)	0 (0.0)	1 (1.3)	3 (1.0)
Blood homocysteine increased	0 (0.0)	0 (0.0)	0 (0.0)	3 (1.0)

Clinical Review  
Karyn L. Berry, MD, MPH  
NDA 205494  
Cerdelga (Eliglustat tartrate)

System Organ Class Preferred Term	All eliglustat patients who ever took Strong, Moderate, and/or Weak CYP2D6 inhibitors (excluding TOPICAL/OTHER routes of administration) (N=79)			Patients who never took CYP2D6 inhibitors (N=311)
	Strong (n=11) Patients n (%)	Moderate (n=4) Patients n (%)	Weak (n=64) Patients n (%)	
Investigations (contd)				
Blood pressure increased	0 ( 0.0)	0 ( 0.0)	0 ( 0.0)	3 ( 1.0)
Bone density decreased	0 ( 0.0)	0 ( 0.0)	1 ( 1.3)	2 ( 0.6)
C-reactive protein increased	1 ( 1.3)	0 ( 0.0)	0 ( 0.0)	2 ( 0.6)
Urine leukocyte esterase positive	0 ( 0.0)	1 ( 1.3)	0 ( 0.0)	2 ( 0.6)
Vitamin B12 decreased	0 ( 0.0)	0 ( 0.0)	1 ( 1.3)	2 ( 0.6)
Blood glucose increased	0 ( 0.0)	0 ( 0.0)	0 ( 0.0)	2 ( 0.6)
Body temperature increased	0 ( 0.0)	0 ( 0.0)	0 ( 0.0)	2 ( 0.6)
Electrocardiogram T wave inversion	0 ( 0.0)	0 ( 0.0)	0 ( 0.0)	2 ( 0.6)
Gastric pH decreased	0 ( 0.0)	0 ( 0.0)	0 ( 0.0)	2 ( 0.6)
Haematocrit decreased	0 ( 0.0)	0 ( 0.0)	1 ( 1.3)	1 ( 0.3)
White blood cell count decreased	0 ( 0.0)	0 ( 0.0)	0 ( 0.0)	2 ( 0.6)
Amino acid level increased	0 ( 0.0)	0 ( 0.0)	1 ( 1.3)	0 ( 0.0)
Angiotensin converting enzyme increased	0 ( 0.0)	0 ( 0.0)	0 ( 0.0)	1 ( 0.3)
Aspartate aminotransferase increased	0 ( 0.0)	0 ( 0.0)	0 ( 0.0)	1 ( 0.3)
Bacterial test positive	0 ( 0.0)	0 ( 0.0)	1 ( 1.3)	0 ( 0.0)
Blood acid phosphatase increased	0 ( 0.0)	0 ( 0.0)	0 ( 0.0)	1 ( 0.3)

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	Strong (n=11) Patients n (%)	Moderate (n=4) Patients n (%)	Weak (n=64) Patients n (%)	
Investigations (contd)				
Blood alkaline phosphatase decreased	0 ( 0.0)	0 ( 0.0)	0 ( 0.0)	1 ( 0.3)
Blood cholesterol increased	0 ( 0.0)	0 ( 0.0)	0 ( 0.0)	1 ( 0.3)
Blood testosterone decreased	0 ( 0.0)	1 ( 1.3)	0 ( 0.0)	0 ( 0.0)
Blood uric acid increased	0 ( 0.0)	0 ( 0.0)	0 ( 0.0)	1 ( 0.3)
Blood urine present	0 ( 0.0)	0 ( 0.0)	0 ( 0.0)	1 ( 0.3)
Electrocardiogram ST-T segment depression	0 ( 0.0)	0 ( 0.0)	0 ( 0.0)	1 ( 0.3)
Electrocardiogram abnormal	1 ( 1.3)	0 ( 0.0)	0 ( 0.0)	0 ( 0.0)
Heart rate increased	0 ( 0.0)	0 ( 0.0)	1 ( 1.3)	0 ( 0.0)
Hepatic enzyme increased	1 ( 1.3)	0 ( 0.0)	0 ( 0.0)	0 ( 0.0)
Low density lipoprotein increased	0 ( 0.0)	0 ( 0.0)	0 ( 0.0)	1 ( 0.3)
Mean cell haemoglobin increased	0 ( 0.0)	0 ( 0.0)	0 ( 0.0)	1 ( 0.3)
Mean cell volume abnormal	0 ( 0.0)	0 ( 0.0)	1 ( 1.3)	0 ( 0.0)
Neutrophil count decreased	0 ( 0.0)	0 ( 0.0)	0 ( 0.0)	1 ( 0.3)
Protein urine present	0 ( 0.0)	0 ( 0.0)	0 ( 0.0)	1 ( 0.3)
Respiratory rate decreased	0 ( 0.0)	0 ( 0.0)	1 ( 1.3)	0 ( 0.0)
Serum ferritin increased	0 ( 0.0)	0 ( 0.0)	0 ( 0.0)	1 ( 0.3)

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	Strong (n=11) Patients n (%)	Moderate (n=4) Patients n (%)	Weak (n=64) Patients n (%)	
Investigations (contd)				
Urinary sediment present	0 (0.0)	0 (0.0)	1 (1.3)	0 (0.0)
Weight increased	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)
White blood cell count increased	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)
Skin and subcutaneous tissue disorders	4 (5.1)	2 (2.5)	13 (16.5)	43 (13.8)
Pruritus	0 (0.0)	0 (0.0)	1 (1.3)	6 (1.9)
Rash	1 (1.3)	0 (0.0)	0 (0.0)	6 (1.9)
Dermatitis contact	0 (0.0)	0 (0.0)	2 (2.5)	4 (1.3)
Dry skin	1 (1.3)	0 (0.0)	1 (1.3)	4 (1.3)
Acne	1 (1.3)	0 (0.0)	3 (3.8)	1 (0.3)
Alopecia	0 (0.0)	0 (0.0)	2 (2.5)	3 (1.0)
Ecchymosis	0 (0.0)	0 (0.0)	2 (2.5)	3 (1.0)
Urticaria	0 (0.0)	0 (0.0)	0 (0.0)	4 (1.3)
Purpura	0 (0.0)	0 (0.0)	2 (2.5)	1 (0.3)
Skin lesion	0 (0.0)	0 (0.0)	0 (0.0)	3 (1.0)
Dermal cyst	0 (0.0)	0 (0.0)	1 (1.3)	1 (0.3)
Dermatitis	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.6)

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	Strong (n=11) Patients n (%)	Moderate (n=4) Patients n (%)	Weak (n=64) Patients n (%)	
Skin and subcutaneous tissue disorders (contd)				
Exfoliative rash	1 (1.3)	1 (1.3)	0 (0.0)	0 (0.0)
Increased tendency to bruise	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.6)
Petechiae	0 (0.0)	0 (0.0)	1 (1.3)	1 (0.3)
Psoriasis	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.6)
Rosacea	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.6)
Skin hyperpigmentation	1 (1.3)	0 (0.0)	1 (1.3)	0 (0.0)
Dermatitis acneiform	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)
Dermatitis allergic	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)
Dermatitis atopic	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)
Eczema	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)
Erythema	0 (0.0)	0 (0.0)	1 (1.3)	0 (0.0)
Hyperhidrosis	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)
Ingrowing nail	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)
Onychoclasia	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)
Onychogryphosis	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)
Papule	0 (0.0)	1 (1.3)	0 (0.0)	0 (0.0)

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	Strong (n=11) Patients n (%)	Moderate (n=4 ) Patients n (%)	Weak (n=64) Patients n (%)	
Skin and subcutaneous tissue disorders (contd)				
Prurigo	0 ( 0.0)	0 ( 0.0)	0 ( 0.0)	1 ( 0.3)
Rash maculo-papular	0 ( 0.0)	0 ( 0.0)	0 ( 0.0)	1 ( 0.3)
Skin exfoliation	0 ( 0.0)	0 ( 0.0)	0 ( 0.0)	1 ( 0.3)
Skin hypopigmentation	0 ( 0.0)	0 ( 0.0)	0 ( 0.0)	1 ( 0.3)
Skin striae	0 ( 0.0)	0 ( 0.0)	0 ( 0.0)	1 ( 0.3)
Sunburn	1 ( 1.3)	0 ( 0.0)	0 ( 0.0)	0 ( 0.0)
Telangiectasia	0 ( 0.0)	0 ( 0.0)	1 ( 1.3)	0 ( 0.0)
Yellow skin	0 ( 0.0)	0 ( 0.0)	0 ( 0.0)	1 ( 0.3)
Injury, poisoning and procedural complications				
Laceration	1 ( 1.3)	0 ( 0.0)	3 ( 3.8)	4 ( 1.3)
Contusion	1 ( 1.3)	0 ( 0.0)	2 ( 2.5)	4 ( 1.3)
Ligament sprain	0 ( 0.0)	0 ( 0.0)	2 ( 2.5)	3 ( 1.0)
Limb injury	0 ( 0.0)	0 ( 0.0)	3 ( 3.8)	2 ( 0.6)
Muscle strain	0 ( 0.0)	0 ( 0.0)	2 ( 2.5)	2 ( 0.6)
Procedural pain	1 ( 1.3)	0 ( 0.0)	2 ( 2.5)	1 ( 0.3)
Excoriation	0 ( 0.0)	0 ( 0.0)	0 ( 0.0)	3 ( 1.0)

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	Strong (n=11) Patients n (%)	Moderate (n=4 ) Patients n (%)	Weak (n=64) Patients n (%)	
Injury, poisoning and procedural complications (contd)				
Fall	0 ( 0.0)	0 ( 0.0)	0 ( 0.0)	3 ( 1.0)
Joint injury	0 ( 0.0)	1 ( 1.3)	0 ( 0.0)	2 ( 0.6)
Arthropod bite	0 ( 0.0)	0 ( 0.0)	0 ( 0.0)	2 ( 0.6)
Foot fracture	0 ( 0.0)	0 ( 0.0)	1 ( 1.3)	1 ( 0.3)
Hand fracture	0 ( 0.0)	0 ( 0.0)	0 ( 0.0)	2 ( 0.6)
Injury	0 ( 0.0)	0 ( 0.0)	1 ( 1.3)	1 ( 0.3)
Joint dislocation	0 ( 0.0)	0 ( 0.0)	1 ( 1.3)	1 ( 0.3)
Maternal exposure during pregnancy	0 ( 0.0)	0 ( 0.0)	0 ( 0.0)	2 ( 0.6)
Chest injury	0 ( 0.0)	0 ( 0.0)	1 ( 1.3)	0 ( 0.0)
Chillblains	0 ( 0.0)	0 ( 0.0)	1 ( 1.3)	0 ( 0.0)
Epicondylitis	0 ( 0.0)	0 ( 0.0)	0 ( 0.0)	1 ( 0.3)
Femur fracture	0 ( 0.0)	0 ( 0.0)	0 ( 0.0)	1 ( 0.3)
Foreign body	0 ( 0.0)	0 ( 0.0)	0 ( 0.0)	1 ( 0.3)
Ligament rupture	0 ( 0.0)	0 ( 0.0)	1 ( 1.3)	0 ( 0.0)
Lumbar vertebral fracture	0 ( 0.0)	0 ( 0.0)	0 ( 0.0)	1 ( 0.3)
Post-traumatic pain	1 ( 1.3)	0 ( 0.0)	0 ( 0.0)	0 ( 0.0)

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	Strong (n=11) Patients n (%)	Moderate (n=4) Patients n (%)	Weak (n=64) Patients n (%)	
Injury, poisoning and procedural complications (contd)				
Radius fracture	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)
Road traffic accident	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)
Thermal burn	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)
Traumatic haematoma	0 (0.0)	0 (0.0)	1 (1.3)	0 (0.0)
Ulnar nerve injury	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)
Cardiac disorders	1 (1.3)	0 (0.0)	7 (8.9)	33 (10.6)
Palpitations	0 (0.0)	0 (0.0)	5 (6.3)	15 (4.8)
Atrioventricular block second degree	1 (1.3)	0 (0.0)	0 (0.0)	3 (1.0)
Myocardial infarction	0 (0.0)	0 (0.0)	0 (0.0)	3 (1.0)
Ventricular tachycardia	0 (0.0)	0 (0.0)	1 (1.3)	2 (0.6)
Supraventricular tachycardia	0 (0.0)	0 (0.0)	1 (1.3)	1 (0.3)
Acute myocardial infarction	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)
Arrhythmia supraventricular	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)
Atrial tachycardia	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)
Atrioventricular block	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)
Atrioventricular block first degree	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)

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	Strong (n=11) Patients n (%)	Moderate (n=4) Patients n (%)	Weak (n=64) Patients n (%)	
Cardiac disorders (contd)				
Diastolic dysfunction	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)
Left atrial dilatation	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)
Left ventricular hypertrophy	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)
Sinoatrial block	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)
Tachycardia	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)
Ventricular extrasystoles	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)
Reproductive system and breast disorders	2 (2.5)	0 (0.0)	10 (12.7)	19 (6.1)
Dysmenorrhoea	0 (0.0)	0 (0.0)	4 (5.1)	5 (1.6)
Metrorrhagia	2 (2.5)	0 (0.0)	2 (2.5)	2 (0.6)
Erectile dysfunction	0 (0.0)	0 (0.0)	1 (1.3)	3 (1.0)
Menstruation irregular	0 (0.0)	0 (0.0)	0 (0.0)	3 (1.0)
Cervical dysplasia	1 (1.3)	0 (0.0)	1 (1.3)	0 (0.0)
Menorrhagia	0 (0.0)	0 (0.0)	1 (1.3)	1 (0.3)
Atrophic vulvovaginitis	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)
Breast cyst	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)
Breast mass	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)

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	Strong (n=11) Patients n (%)	Moderate (n=4) Patients n (%)	Weak (n=64) Patients n (%)	
<b>Reproductive system and breast disorders (contd)</b>				
Cervical polyp	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)
Dysfunctional uterine bleeding	0 (0.0)	0 (0.0)	1 (1.3)	0 (0.0)
Genital discharge	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)
Genital pain	0 (0.0)	0 (0.0)	1 (1.3)	0 (0.0)
Ovarian cyst ruptured	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)
Polycystic ovaries	0 (0.0)	0 (0.0)	1 (1.3)	0 (0.0)
Pruritus genital	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)
Uterine polyp	0 (0.0)	0 (0.0)	1 (1.3)	0 (0.0)
Vaginal haemorrhage	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)
<b>Metabolism and nutrition disorders</b>	1 (1.3)	1 (1.3)	6 (7.6)	19 (6.1)
Decreased appetite	0 (0.0)	0 (0.0)	2 (2.5)	3 (1.0)
Diabetes mellitus	0 (0.0)	0 (0.0)	0 (0.0)	4 (1.3)
Iron deficiency	1 (1.3)	0 (0.0)	2 (2.5)	1 (0.3)
Hyperglycaemia	0 (0.0)	1 (1.3)	0 (0.0)	2 (0.6)
Hyperlipidaemia	0 (0.0)	0 (0.0)	0 (0.0)	3 (1.0)
Vitamin B12 deficiency	0 (0.0)	0 (0.0)	3 (3.8)	0 (0.0)

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	Strong (n=11) Patients n (%)	Moderate (n=4) Patients n (%)	Weak (n=64) Patients n (%)	
<b>Metabolism and nutrition disorders (contd)</b>				
Hyperhomocysteinaemia	0 (0.0)	0 (0.0)	1 (1.3)	1 (0.3)
Dehydration	0 (0.0)	0 (0.0)	1 (1.3)	0 (0.0)
Dyslipidaemia	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)
Folate deficiency	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)
Hyperuricaemia	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)
Hypovitaminosis	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)
Metabolic syndrome	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)
Type 2 diabetes mellitus	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)
<b>Blood and lymphatic system disorders</b>	1 (1.3)	0 (0.0)	9 (11.4)	14 (4.5)
Splenomegaly	0 (0.0)	0 (0.0)	1 (1.3)	7 (2.3)
Lymphadenopathy	1 (1.3)	0 (0.0)	2 (2.5)	1 (0.3)
Thrombocytopenia	0 (0.0)	0 (0.0)	0 (0.0)	4 (1.3)
Anaemia	0 (0.0)	0 (0.0)	2 (2.5)	1 (0.3)
Anaemia macrocytic	0 (0.0)	0 (0.0)	1 (1.3)	0 (0.0)
Hypochromasia	0 (0.0)	0 (0.0)	1 (1.3)	0 (0.0)
Iron deficiency anaemia	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)

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	Strong (n=11) Patients n (%)	Moderate (n=4) Patients n (%)	Weak (n=64) Patients n (%)	
Blood and lymphatic system disorders (contd)				
Leukopenia	0 (0.0)	0 (0.0)	1 (1.3)	0 (0.0)
Splenic haemorrhage	0 (0.0)	0 (0.0)	1 (1.3)	0 (0.0)
Eye disorders	1 (1.3)	0 (0.0)	3 (3.8)	19 (6.1)
Cataract	0 (0.0)	0 (0.0)	0 (0.0)	3 (1.0)
Chalazion	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.6)
Abnormal sensation in eye	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)
Age-related macular degeneration	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)
Astigmatism	0 (0.0)	0 (0.0)	1 (1.3)	0 (0.0)
Blindness transient	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)
Conjunctivitis	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)
Diabetic retinopathy	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)
Dry eye	1 (1.3)	0 (0.0)	0 (0.0)	0 (0.0)
Eye haemorrhage	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)
Eye inflammation	0 (0.0)	0 (0.0)	1 (1.3)	0 (0.0)
Eye irritation	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)
Eye pain	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)

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	Strong (n=11) Patients n (%)	Moderate (n=4) Patients n (%)	Weak (n=64) Patients n (%)	
Eye disorders (contd)				
Iridocyclitis	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)
Macular hole	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)
Photophobia	0 (0.0)	0 (0.0)	1 (1.3)	0 (0.0)
Presbyopia	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)
Retinal haemorrhage	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)
Scotoma	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)
Visual acuity reduced	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)
Visual impairment	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)
Vitreous detachment	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)
Vitreous floaters	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)
Psychiatric disorders	1 (1.3)	0 (0.0)	6 (7.6)	15 (4.8)
Anxiety	0 (0.0)	0 (0.0)	4 (5.1)	3 (1.0)
Depression	0 (0.0)	0 (0.0)	1 (1.3)	4 (1.3)
Depressed mood	1 (1.3)	0 (0.0)	0 (0.0)	1 (0.3)
Insomnia	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.6)
Stress	1 (1.3)	0 (0.0)	0 (0.0)	1 (0.3)

Clinical Review  
 Karyn L. Berry, MD, MPH  
 NDA 205494  
 Cerdelga (Eliglustat tartrate)

System Organ Class Preferred Term	All eliglustat patients who ever took Strong, Moderate, and/or Weak CYP2D6 inhibitors (excluding TOPICAL/OTHER routes of administration) (N=79)			Patients who never took CYP2D6 inhibitors (N=311)
	Strong (n=11) Patients n (%)	Moderate (n=4) Patients n (%)	Weak (n=64) Patients n (%)	
Psychiatric disorders (contd)				
Anxiety disorder	0 ( 0.0)	0 ( 0.0)	1 ( 1.3)	0 ( 0.0)
Apathy	0 ( 0.0)	0 ( 0.0)	0 ( 0.0)	1 ( 0.3)
Confusional state	0 ( 0.0)	0 ( 0.0)	1 ( 1.3)	0 ( 0.0)
Initial insomnia	0 ( 0.0)	0 ( 0.0)	0 ( 0.0)	1 ( 0.3)
Libido decreased	0 ( 0.0)	0 ( 0.0)	0 ( 0.0)	1 ( 0.3)
Middle insomnia	0 ( 0.0)	0 ( 0.0)	0 ( 0.0)	1 ( 0.3)
Neurosis	0 ( 0.0)	0 ( 0.0)	0 ( 0.0)	1 ( 0.3)
Panic attack	0 ( 0.0)	0 ( 0.0)	0 ( 0.0)	1 ( 0.3)
Restlessness	0 ( 0.0)	0 ( 0.0)	0 ( 0.0)	1 ( 0.3)
Sleep disorder	0 ( 0.0)	0 ( 0.0)	0 ( 0.0)	1 ( 0.3)
Vascular disorders	2 ( 2.5)	0 ( 0.0)	3 ( 3.8)	15 ( 4.8)
Hypertension	0 ( 0.0)	0 ( 0.0)	0 ( 0.0)	8 ( 2.6)
Flushing	1 ( 1.3)	0 ( 0.0)	1 ( 1.3)	4 ( 1.3)
Haematoma	0 ( 0.0)	0 ( 0.0)	2 ( 2.5)	0 ( 0.0)
Hypotension	0 ( 0.0)	0 ( 0.0)	1 ( 1.3)	1 ( 0.3)
Aortic aneurysm	0 ( 0.0)	0 ( 0.0)	0 ( 0.0)	1 ( 0.3)

System Organ Class Preferred Term	All eliglustat patients who ever took Strong, Moderate, and/or Weak CYP2D6 inhibitors (excluding TOPICAL/OTHER routes of administration) (N=79)			Patients who never took CYP2D6 inhibitors (N=311)
	Strong (n=11) Patients n (%)	Moderate (n=4) Patients n (%)	Weak (n=64) Patients n (%)	
Vascular disorders (contd)				
Essential hypertension	0 ( 0.0)	0 ( 0.0)	0 ( 0.0)	1 ( 0.3)
Hot flush	0 ( 0.0)	0 ( 0.0)	0 ( 0.0)	1 ( 0.3)
Labile blood pressure	0 ( 0.0)	0 ( 0.0)	0 ( 0.0)	1 ( 0.3)
Peripheral coldness	0 ( 0.0)	0 ( 0.0)	0 ( 0.0)	1 ( 0.3)
Thrombophlebitis superficial	1 ( 1.3)	0 ( 0.0)	0 ( 0.0)	0 ( 0.0)
Varicose vein	0 ( 0.0)	0 ( 0.0)	0 ( 0.0)	1 ( 0.3)
Renal and urinary disorders	1 ( 1.3)	0 ( 0.0)	3 ( 3.8)	15 ( 4.8)
Haematuria	1 ( 1.3)	0 ( 0.0)	0 ( 0.0)	6 ( 1.9)
Dysuria	0 ( 0.0)	0 ( 0.0)	1 ( 1.3)	3 ( 1.0)
Proteinuria	0 ( 0.0)	0 ( 0.0)	0 ( 0.0)	3 ( 1.0)
Calculus urinary	0 ( 0.0)	0 ( 0.0)	0 ( 0.0)	2 ( 0.6)
Pollakiuria	0 ( 0.0)	0 ( 0.0)	1 ( 1.3)	1 ( 0.3)
Leukocyturia	0 ( 0.0)	0 ( 0.0)	0 ( 0.0)	1 ( 0.3)
Nephrolithiasis	0 ( 0.0)	0 ( 0.0)	0 ( 0.0)	1 ( 0.3)
Renal cyst	0 ( 0.0)	0 ( 0.0)	0 ( 0.0)	1 ( 0.3)
Renal pain	0 ( 0.0)	0 ( 0.0)	1 ( 1.3)	0 ( 0.0)

Clinical Review  
 Karyn L. Berry, MD, MPH  
 NDA 205494  
 Cerdelga (Eliglustat tartrate)

System Organ Class Preferred Term	All eliglustat patients who ever took Strong, Moderate, and/or Weak CYP2D6 inhibitors (excluding TOPICAL/OTHER routes of administration) (N=79)			Patients who never took CYP2D6 inhibitors (N=311)
	Strong (n=11) Patients n (%)	Moderate (n=4) Patients n (%)	Weak (n=64) Patients n (%)	
<b>Renal and urinary disorders (contd)</b>				
Urinary retention	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)
Urine flow decreased	0 (0.0)	0 (0.0)	1 (1.3)	0 (0.0)
<b>Hepatobiliary disorders</b>	1 (1.3)	0 (0.0)	4 (5.1)	10 (3.2)
Hepatomegaly	1 (1.3)	0 (0.0)	2 (2.5)	4 (1.3)
Cholecystitis	0 (0.0)	0 (0.0)	2 (2.5)	1 (0.3)
Cholelithiasis	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.6)
Biliary colic	0 (0.0)	0 (0.0)	1 (1.3)	0 (0.0)
Biliary dyskinesia	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)
Hepatic steatosis	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)
Jaundice	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)
<b>Ear and labyrinth disorders</b>	0 (0.0)	0 (0.0)	3 (3.8)	11 (3.5)
Tinnitus	0 (0.0)	0 (0.0)	1 (1.3)	4 (1.3)
Motion sickness	0 (0.0)	0 (0.0)	1 (1.3)	2 (0.6)
Vertigo	0 (0.0)	0 (0.0)	0 (0.0)	3 (1.0)
Hypoacusis	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.6)
Cerumen impaction	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)

System Organ Class Preferred Term	All eliglustat patients who ever took Strong, Moderate, and/or Weak CYP2D6 inhibitors (excluding TOPICAL/OTHER routes of administration) (N=79)			Patients who never took CYP2D6 inhibitors (N=311)
	Strong (n=11) Patients n (%)	Moderate (n=4) Patients n (%)	Weak (n=64) Patients n (%)	
<b>Ear and labyrinth disorders (contd)</b>				
Ear haemorrhage	0 (0.0)	0 (0.0)	1 (1.3)	0 (0.0)
Hearing impaired	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)
Middle ear effusion	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)
<b>Immune system disorders</b>	1 (1.3)	0 (0.0)	3 (3.8)	8 (2.6)
Hypersensitivity	1 (1.3)	0 (0.0)	0 (0.0)	5 (1.6)
Seasonal allergy	0 (0.0)	0 (0.0)	2 (2.5)	3 (1.0)
Drug hypersensitivity	0 (0.0)	0 (0.0)	1 (1.3)	0 (0.0)
<b>Neoplasms benign, malignant and unspecified (incl cysts and polyps)</b>	0 (0.0)	0 (0.0)	4 (5.1)	6 (1.9)
Seborrheic keratosis	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.6)
Skin papilloma	0 (0.0)	0 (0.0)	1 (1.3)	1 (0.3)
Thyroid neoplasm	0 (0.0)	0 (0.0)	1 (1.3)	1 (0.3)
Adenoma benign	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)
Chondromatosis	0 (0.0)	0 (0.0)	1 (1.3)	0 (0.0)
Hepatic neoplasm malignant	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)
Lipoma	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)

System Organ Class Preferred Term	All eliglustat patients who ever took Strong, Moderate, and/or Weak CYP2D6 inhibitors (excluding TOPICAL/OTHER routes of administration) (N=79)			Patients who never took CYP2D6 inhibitors (N=311)
	Strong (n=11) Patients n (%)	Moderate (n=4) Patients n (%)	Weak (n=64) Patients n (%)	
Neoplasms benign, malignant and unspecified (incl cysts and polyps) (contd)				
Uterine leiomyoma	0 (0.0)	0 (0.0)	1 (1.3)	0 (0.0)
Endocrine disorders	1 (1.3)	0 (0.0)	1 (1.3)	3 (1.0)
Autoimmune thyroiditis	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)
Goitre	0 (0.0)	0 (0.0)	1 (1.3)	0 (0.0)
Hyperthyroidism	1 (1.3)	0 (0.0)	0 (0.0)	0 (0.0)
Hypothyroidism	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)
Myxoedema	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)
Surgical and medical procedures	1 (1.3)	0 (0.0)	2 (2.5)	2 (0.6)
Arthrodesis	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)
Catheter removal	0 (0.0)	0 (0.0)	1 (1.3)	0 (0.0)
Mammoplasty	1 (1.3)	0 (0.0)	0 (0.0)	0 (0.0)
Tooth extraction	0 (0.0)	0 (0.0)	1 (1.3)	0 (0.0)
Wisdom teeth removal	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)

System Organ Class Preferred Term	All eliglustat patients who ever took Strong, Moderate, and/or Weak CYP2D6 inhibitors (excluding TOPICAL/OTHER routes of administration) (N=79)			Patients who never took CYP2D6 inhibitors (N=311)
	Strong (n=11) Patients n (%)	Moderate (n=4) Patients n (%)	Weak (n=64) Patients n (%)	
Pregnancy, puerperium and perinatal conditions	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)
Abortion spontaneous	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)

**Medical Reviewer's comments: Among the patients who received strong inhibitors, the TEAEs for these patients were mild and non-serious with the exception of 1 SAE in patient GZGD03109/30804 (hepatic enzyme increase).**

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).

## 7.6 Additional Safety Evaluations

Nerve conduction evaluations were performed in the Phase 2 study and the ENCORE

study only. In the Phase 2 study, nerve conduction tests were performed at screening, Weeks 52 and 104, and annually thereafter. In the ENCORE study, nerve conduction tests were performed at Baseline and Week 52, with the option to repeat any abnormal tests in 6 months. All the peripheral neuropathy findings, whether reported through nerve conduction testing or neurological examination, were reviewed by a central reader.

In the ENCORE PAP, Baseline values were similar in both the eliglustat and Cerezyme treatment groups, and mean and median values for Baseline and Week 52 assessments were within the normal range in both treatment groups. 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).

#### 7.6.1 Human Carcinogenicity

#### 7.6.2 Human Reproduction and Pregnancy Data

Women with Type 1 Gaucher disease have an increased risk of spontaneous abortion, especially if disease symptoms are not treated and controlled pre-conception and during a pregnancy. Pregnancy may exacerbate existing Type 1 Gaucher disease symptoms or result in new disease manifestations. Type 1 Gaucher disease manifestations may lead to adverse pregnancy outcomes including, hepatosplenomegaly which can interfere with the normal growth of a pregnancy and thrombocytopenia which can lead to increased bleeding and possible hemorrhage.

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.***

### 7.6.3 Pediatrics and Assessment of Effects on Growth

No patients under 16 years of age were included in the eliglustat safety database.

As an orphan designated drug, the Applicant is not required to conduct pediatric trials. Pursuant to 21 CFR314.55(d) "Exemption for orphan drugs," eliglustat is exempt from pediatric study requirements.

### 7.6.4 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 x 3) on a single occasion prior to the Week 52 blood draws. The observed C<sub>max</sub> 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.

#### 7.7 Additional Submissions / Safety Issues

## 8 Postmarket Experience

Eliglustat is not currently marketed in any country.

## 9 Appendices

### 9.1 Literature Review/References

1 Cox TM, Aerts JMFG et al., Management of non-neuronopathic Gaucher disease with special reference to pregnancy, splenectomy, bisphosphonate therapy, use of biomarkers and bone disease monitoring, *J Inherit Metab Dis* 2008; 31:319-336.

Cox TM, Aerts JMFG et al., Management of non-neuronopathic Gaucher disease with special reference to pregnancy, splenectomy, bisphosphonate therapy, use of biomarkers and bone disease monitoring, *J Inherit Metab Dis* 2008; 31:319-36.

Gaucher disease after 2 to 5 years of treatment: a report from the Gaucher Registry. *Am J Med* 2002; 113: 112–9.

Kaplan P, Baris H et al., Revised recommendations for the management of Gaucher disease in children, *Eur J Pediatr* 2013; 172(4): 447-458.

Mikosch P, Gaucher disease and bone, *Best Pract Res Clin Rheumatol* 2011; 25: 665-681.

Mistry PK, Sirrs S et al., Pulmonary hypertension in type 1 Gaucher's disease: genetic and epigenetic determinants of phenotype and response to therapy, *Mol Genet Metab* 2002; 77:91-98.

1Pastores GM, Barnett NL, Current and emerging therapies for the lysosomal storage disorders, *Expert Opin Emerging Drugs* 2005: 10(4):891-902.

Pastores GM, Weinreb NJ et al., Therapeutic goals in the treatment of Gaucher disease, *Semin Hematol* 2004; 41: 4-14.

Weinreb NJ, Charrow J et al., Effectiveness of enzyme replacement therapy in 1028 patients with type

Weinreb NJ, Deegan P et al., Life expectancy in Gaucher disease type 1, *Am J Hematol* 2008;83:896-900.

9.2 Labeling Recommendations

At the time of this review labeling was not yet negotiated with the Applicant. Labeling recommendations were obtained from the following disciplines: DCRP QT IRT, Office of Clinical Pharmacology, Maternal Health, Office of Prescription Drug Promotion, Division of Medication Error Prevention and Analysis, Division of Medical Policy Programs, CMC and Nonclinical,

9.3 Advisory Committee Meeting

No Advisory Committee meeting was convened for this application.

9.4 Financial Disclosures

Clinical Investigator Financial Disclosure Review

Clinical Investigator Financial Disclosure

Application Number: NDA 205494

Submission Date(s): September 20, 2013

Applicant: Genzyme

Product: CERDELGA

Reviewer: Karyn L. Berry, MD, MPH

Date of Review: July 23, 2014

Covered Clinical Study (Name and/or Number): GZGD02507 (ENGAGE), GZGD02607 (ENCORE), GZGD00304 (Phase 2), GZGD03109 (EDGE)

Was a list of clinical investigators provided:	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (Request list from applicant)
Total number of investigators identified: <u>718</u>		
Number of investigators who are sponsor employees (including both full-time and part-time employees): <u>0</u>		
Number of investigators with disclosable financial interests/arrangements (Form FDA		

3455): <u>13</u>		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: <u>0</u> Significant payments of other sorts: <u>13</u> Proprietary interest in the product tested held by investigator: <u>0</u> Significant equity interest held by investigator in sponsor of covered study: <u>0</u>		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (Request details from applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (Request information from applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) <u>711</u>		
Is an attachment provided with the reason:	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (Request explanation from applicant)

Discuss whether the applicant has adequately disclosed financial interests/arrangements with clinical investigators as recommended in the guidance for industry *Financial Disclosure by Clinical Investigators*.<sup>12</sup> Also discuss whether these interests/arrangements, investigators who are sponsor employees, or lack of disclosure despite due diligence raise questions about the integrity of the data:

- If not, why not (e.g., study design (randomized, blinded, objective endpoints), clinical investigator provided minimal contribution to study data)
- If yes, what steps were taken to address the financial interests/arrangements (e.g., statistical analysis excluding data from clinical investigators with such interests/arrangements)

Briefly summarize whether the disclosed financial interests/arrangements, the inclusion of investigators who are sponsor employees, or lack of disclosure despite due diligence affect the approvability of the application.

The Applicant has adequately disclosed financial interests/arrangements with clinical investigators as recommended in the guidance for industry *Financial Disclosure by Clinical Investigators*. These interests/arrangements or lack of disclosure despite due diligence do not raise questions about the integrity of the data.

<sup>12</sup> See [web address].

- All 4 clinical trials were conducted at multiple study centers both inside and outside the US. There were multiple investigators in the trials.
- Randomization was used to assign patients to treatment groups in the primary analysis periods of the ENGAGE and ENCORE trials.
- The statistical analyses were prospectively defined by the Applicant prior to access to information.

The disclosed financial interests/arrangements or lack of disclosure despite due diligence did not affect the approvability of the application.

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/s/  
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KARYN L BERRY  
08/15/2014

LARA DIMICK-SANTOS  
08/15/2014

NDA	SDN	eCTD	Consult Date	Document Type	New Submission Date	PDUFA Date
205494	33	34	11/14/2013	Efficacy Information Amendment	6/26/2014	8/20/2014

### Memorandum of Consultation Addendum

**From:** John T. Stinson, M.D., Medical Officer  
Division of Bone, Reproductive and Urologic Products (DBRUP)

**Through:** Theresa Kehoe Team Leader DBRUP  
  
Hylton Joffe, M.D., M.M.Sc., Division Director DBRUP

**To:** Karyn Berry, M.D. Medical Officer  
Division of Gastroenterology and Inborn Errors Products (DGIEP)  
  
Lara Dimick, M.D., CDTL, DGIEP  
  
Jessica Benjamin, RPM, DGIEP

**Sponsor:** Genzyme

**Drug:** Cerdelga™ (eliglustat tartrate) 84 mg capsules (Genz-99067)

**Drug class:** Substrate reduction therapy

**NDA:** 205494

**IND:** 067589

**Orphan drug designation:** 08-2654

**Proposed indication:** Long-term treatment of adults with Type I Gaucher's disease (GD1)

## Summary

The Division finds nothing in this submission that would alter our previous unfavorable conclusion regarding the [REDACTED] (b) (4)

## Introduction

This document reviews an Efficacy Information Amendment filed by the sponsor to NDA 205494 on June 26, 2014 [REDACTED] (b) (4) [REDACTED] (b) (4) for Cerdelga (eliglustat). These data were previously reviewed by DBRUP and a review was filed in DARRTS on April 24, 2014. FDA's reasoning for their [REDACTED] (b) (4) was reiterated to the sponsor at the Late Cycle Meeting on June 19, 2014.

(b) (4)

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/s/  
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JOHN T STINSON  
07/11/2014

THERESA E KEHOE  
07/14/2014

HYLTON V JOFFE  
07/14/2014

NDA	SDN	Consult Tracking Number	Consult Date	PDUFA Date
205494	000	?	11/14/2013	8/20/2014

### Memorandum of Consultation

**From:** John T. Stinson, M.D., Medical Officer  
Division of Bone, Reproductive and  
Urologic Products (DBRUP)

**Through:** Theresa Kehoe Team Leader DBRUP  
  
Hylton Joffe, M.D., M.M.Sc., Division  
Director DBRUP

**To:** Karyn Berry, M.D. Medical Officer  
Division of Gastroenterology and Inborn  
Errors Products (DGIEP)  
  
Lara Dimick, M.D., CDTL, DGIEP  
  
Jessica Benjamin, RPM, DGIEP

**Sponsor:** Genzyme

**Drug:** Cerdelga™ (eliglustat tartrate) 84 mg  
capsules (Genz-99067)

**Drug class:** Substrate reduction therapy

**NDA:** 205494

**IND:** 067589

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**Proposed indication:** Long-term treatment of adults with Type I  
Gaucher's disease

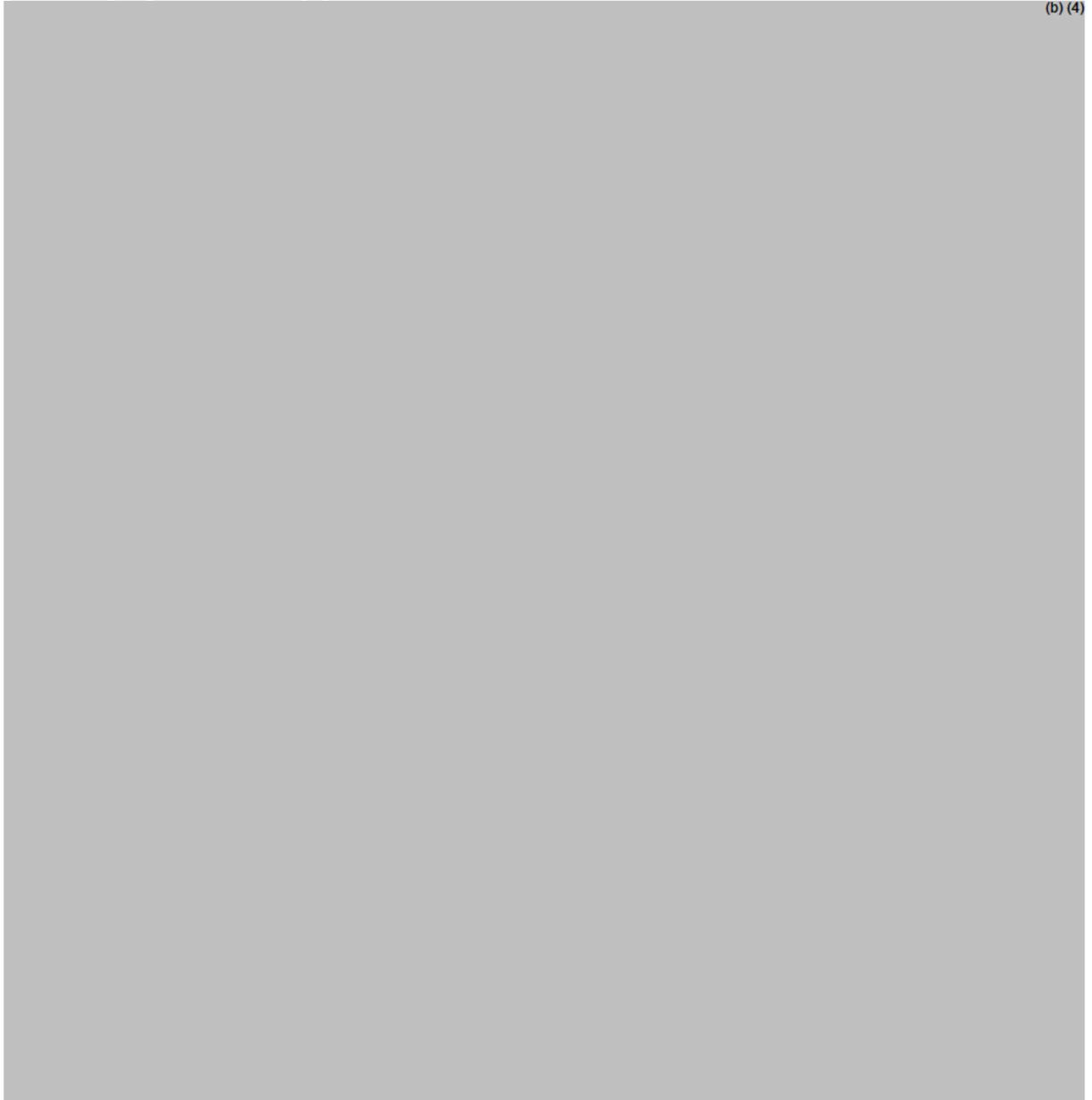
### Summary

NDA 205494 was filed on September 20, 2013 and is a “Program” NME NDA for Cerdelga, a substrate reduction therapy with a proposed indication of long-term treatment of adults with Type I Gaucher’s disease. The sponsor proposes to include (b) (4)

(b) (4) DGIEP has consulted DBRUP regarding the proposed inclusion of (b) (4) in the full prescribing information.

The sponsor’s proposed labeling germane to this consultation follows:

(b) (4)



(b) (4)

The sponsor's submission includes an integrated bone paper under section 5.3.5 "Skeletal Effects of Eliglustat in Gaucher Disease Type 1". DGIEP has consulted DBRUP to comment on:

- The sponsor's data analyses in the integrated bone paper
- The sufficiency of the trial data to support (b) (4)

The 3 studies accompanying this submission are neither powered nor designed to detect a meaningful treatment effect of Eliglustat on BMD. The clinical benefits, if any, of BMD improvement in Type I Gaucher's disease are indeterminate. (b) (4)

## Background

### Lysosomal Storage Diseases

The lysosomal storage diseases are a group of biochemically related disorders in which the enzymes required for the catabolism of glycosphingolipids are defective. Glycosphingolipids are ubiquitous components of eukaryotic cells and comprise a lipid component, ceramide, to which a glycan is covalently bound. The degradation of the carbohydrate portion of the glycolipids is mediated by lysosomal enzymes known as glycosidases. Glycosidases act in a sequential manner to remove one sugar at a time from an exposed terminal, and the action of each glycosidase is required to prepare the glycolipid for the next enzyme in the degradation pathway. A mutation in one of the glycosidases in the pathway can result in the accumulation of its glycolipid substrate in the lysosome. As the lysosome expands with undegraded glycolipid substrate, cell function becomes increasingly compromised, leading to the clinical manifestations of these disorders.

### Gaucher's Disease (GD)

GD is an autosomal recessive disorder characterized by a deficiency of the lysosomal enzyme glucocerebrosidase and is the most common lysosomal storage disorder. Glucocerebrosidase acts on the fatty acid glucosylceramide (GL1), a cell membrane constituent of red and white blood cells. The macrophages that clear these cells are unable to eliminate GL1 and turn into Gaucher cells. These appear on light microscopy to resemble crumpled paper. GL1 can collect in the spleen, liver, kidneys, lungs, brain, and bone marrow. Different mutations in glucocerebrosidase determine the remaining activity of the enzyme and to a large extent the phenotype. GD is a multi-systemic and heterogeneous disorder with persistent and irreversible morbidity that will develop over time in the majority of patients. GD has 3 common clinical subtypes, although this classification is controversial:

- Type I (non-neuropathic) is the most common form of GD, occurring in approximately 1 in 50,000 live births. Symptoms may begin early in life or in adulthood and include hepatosplenomegaly, and pancytopenia. The brain is not affected, but there may be lung and, rarely, renal dysfunction. Skeletal weakness and bone disease may be extensive. Osteoporosis, marrow infiltration, bone deformities, painful crises, pathologic fractures and osteonecrosis are common manifestations. However, many patients with Type I GD have a mild form of the disease or may be asymptomatic and live well into adulthood.
- Type II (acute infantile neuropathic GD) usually begins within 6 months of birth and has an incidence rate of approximately 1 in 100,000 live births. Symptoms include extensive and progressive brain damage, spasticity, seizures, eye movement disorders, and a poor ability to suck and swallow. Affected children usually die by age 2.
- Type III (chronic neuropathic GD) can begin at any time in childhood or even in adulthood and occurs in approximately 1 in 100,000 live births. Patients often live into their early teen years and adulthood.

#### Bone disease in Type I GD

Bone involvement in Type I GD is multidimensional and all compartments of bone are involved. Bone involvement in Type I GD appears to cause the greatest impairment in quality of life compared to the visceral and hematologic disease (Giraldo 2005). Some authors have argued that Type I GD should be viewed principally as a skeletal disorder with disabling effects on bone structure and metabolism rather than as a cytopenic disorder causing anemia, bleeding and susceptibility to infection due to marrow and spleen infiltration (Deegan 2011).

Progressive accumulation of Gaucher cells in bone marrow displaces normal adipocytes and hematopoietic elements from the marrow compartment. This process begins in the axial skeleton and, with progression, later proceeds in a predictable sequence in the appendicular skeleton, beginning in the metadiaphysis and potentially extending to the epiphysis and apophyses. The mechanistic link between bone marrow infiltration by Gaucher cells and the development of bone complications is not completely understood (Rosenthal 1986). The degree and type of bone involvement is variable, although low bone mass is common irrespective of disease severity. Reduction in BMD in Type I GD has been correlated with the severity of radiographic findings (Pastores 1996). By mechanisms not yet fully defined the presence of a Gaucher cell infiltrate in bone marrow produces secondary effects on the mineral phase of the skeleton (Rosenthal 1995). Clinically important bone manifestations of Type I GD include severe acute “bone crises” (acute avascular necrosis), medullary infarction, chronic pain, cortical and trabecular osteopenia, osteoporosis, osteolytic lesions, pathologic fractures, and growth failure. Abnormal bone remodeling is reflected in the diversity of radiographic anomalies, which also include deformity (Erlenmeyer flask femur) and joint collapse. The cause of low bone mass in Type I GD has been attributed both to increased osteoclastic bone resorption and impaired osteoblast function associated with

accumulating lipids. One clear association is that of post-splenectomy status with increased risk of bone infarct. However, there is no agreement on the nature of this association.

Much of what is known of the morbidity and mortality associated with Gaucher's disease comes from the International Collaborative Gaucher Group (ICGG) Gaucher Registry. This is the largest (> 6000 patients) and longest running (since 1991) database of patients with Gaucher's disease. Table 1 is derived from ICGG data:

**Table 1 Bone Manifestations of Type I GD at Most Recent Assessment:**

Bone manifestation	Proportion of population reporting manifestation
Symptomatic bone pain	36%
Radiologic evidence of bone disease	90%
Marrow infiltration	84%
Infarction	43%
Lytic lesions	27%
Avascular necrosis	26%
Osteopenia	65%
Fractures	14%

Source: 2009 ICGG Gaucher Registry Annual Report

Low bone mass has been identified as a predictor of fracture in Type I GD (Khan 2012). Based on the presence or absence of fractures, a risk-set matched case-control method was applied to the ICGG Registry. Excepting mean lumbar DXA Z-scores, clinical and surrogate markers of disease activity were similar in patients with and without fractures. A comparison was made between a group of 319 patients with reports of fractures and a group of 1233 patients without fractures. There were no statistical differences in gender, genotype, age, treatment status or splenectomy status between fracture cases and controls. Among patients with fractures, 49.3% had DXA Z-scores  $\leq -1$  compared to 31.0% in the control group. Patients with DXA Z-scores  $\leq -1$  had an Odds Ratio of 5.55 (95% CI, 1.81-17.02,  $p < 0.01$ ) for fracture. This difference supports the authors' recommendation that DXA Z-scores  $< -1$  should be a trigger for therapeutic intervention directed at maintaining BMD above this value.

#### Bone monitoring in Type I GD

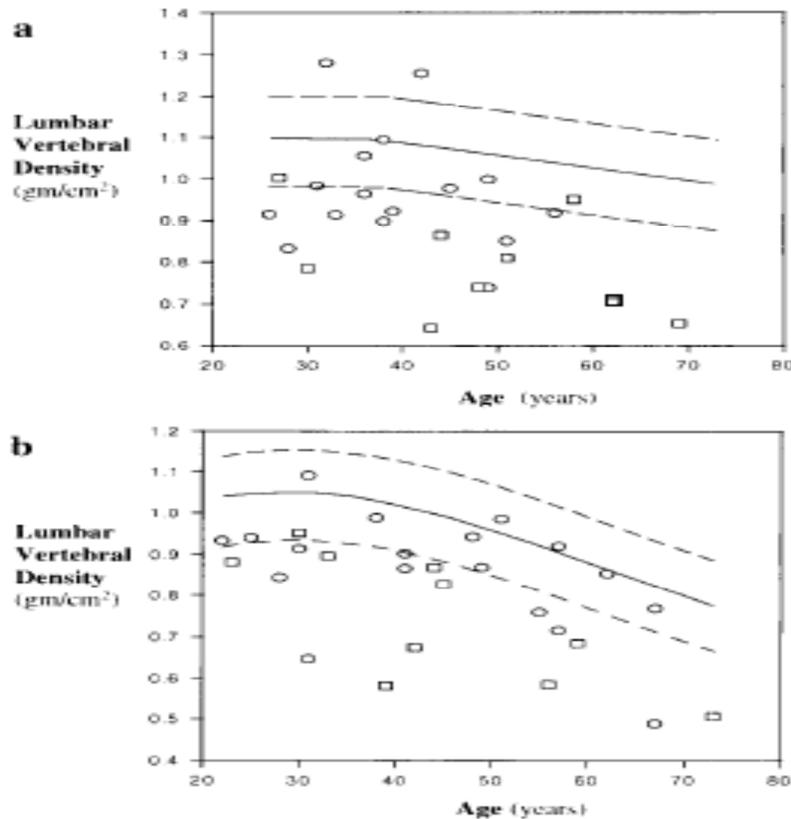
The skeletal complications of Type I GD are generally progressive and have an unpredictable course. MRI, bone densitometry (DXA), and plain radiography have been widely used to evaluate skeletal status at diagnosis and during disease progression and to monitor the response to therapy. MRI at regular intervals has been recommended for evaluation of bone marrow infiltration, as marrow involvement precedes the occurrence of irreversible bone complications such as osteonecrosis, fracture, and joint collapse. Bone marrow infiltrated by Gaucher cells is characterized by abnormally low signal intensity on conventional MRI T1- and T2-weighted spin echo sequences due to a reduction in the high-intensity normal fatty marrow. With treatment, the GL1 deposits in

Gaucher cells are reduced, permitting a reconversion to marrow fat with restoration of a normal high signal.

A variety of MRI protocols and semiquantitative scoring systems have been developed for Type I GD assessment. The scoring of imaging changes has been useful to estimate disease burden, the risk of complications, and the response to therapy. One of these, quantitative chemical shift imaging (QCSI) quantifies the fractional fat signal of bone marrow, but is not widely available. The bone marrow burden (BMB) score evaluates the lumbar spine and femur and correlates well with QCSI. BMB scoring has shown high enough sensitivity to allow detection of bone marrow response to ERT. For the BMB scoring system, a decrease of at least 2 points has been proposed as clinically significant. BMB scores appear to be higher in patients with enlarged spleens or post splenectomy.

DXA is used frequently to monitor Type I GD, as low bone mass is found in most patients and correlates significantly with other clinical indicators of disease severity, including genotype, prior splenectomy, and hepatomegaly (Pastores 1996). Figure 1 demonstrates lumbar vertebral bone densities ( $\text{g}/\text{cm}^2$ ) in a series of adult male (a) and female (b) patients with Type I GD. Circles and squares represent patients with and without spleens, respectively. Solid line represents predicted mean bone density for normals, with  $\pm$  SD shown as slash lines above and below:

**Figure 1: Lumbar bone mineral densities in Type 1 GD**



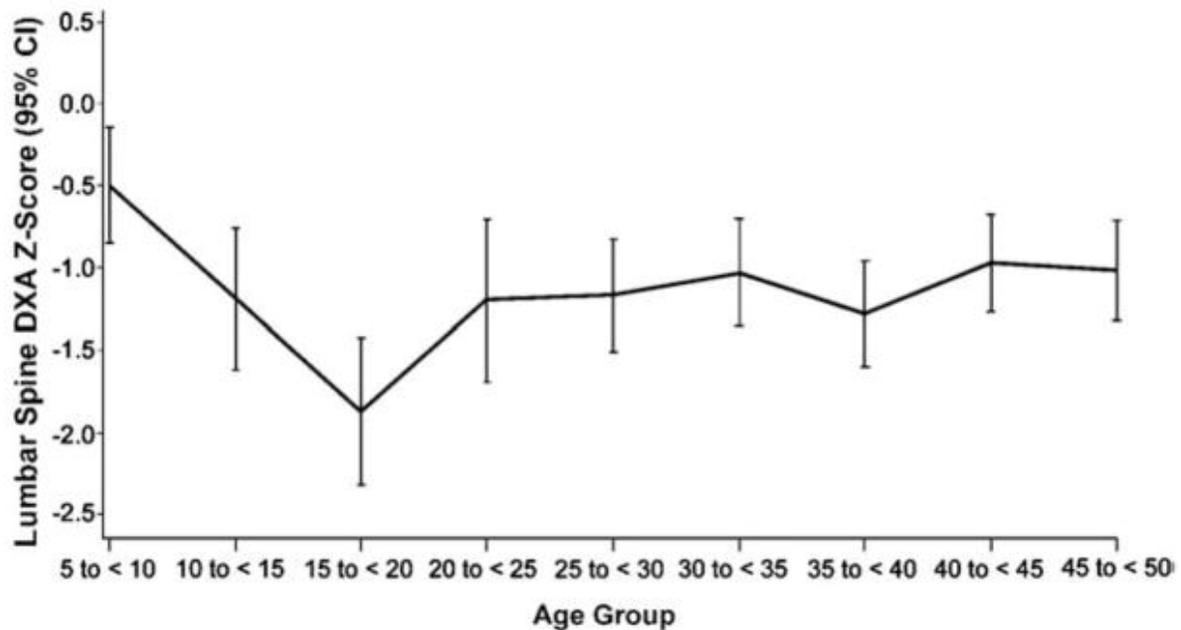
Source: Pastores 1996

Almost all of the lumbar spine bone densities were below the expected mean for age and sex. Reductions in density were similar in affected men and women, but tended to be greater in splenectomized patients.

For premenopausal women, and men below the age of 50, the International Society for Clinical Densitometry recommends the expression of bone mass by Z-score, the average score for patients of their age, sex, and ethnicity. A Z-score of  $\leq -2.0$  is defined as “below the expected range for age”, and a Z-score  $> -2.0$  is “within the expected range for age”. This corresponds to the sponsor’s definition in the submission, Z-scores  $> -2$  indicating “normal bone density” and Z-scores  $\leq -2$  indicating “below-normal bone density”. While the term “osteopenia” is frequently applied to those with lower Z-scores (e.g.  $< -1.0$ ), there is no clear distinction between “normal BMD” and “osteopenia” in this population. The relationship between Z-score and fracture risk is unclear.

DXA data are available in about 1/3 of patients in the ICGG Registry. Lumbar spine Z-scores prior to ERT were below population means for all age groups, and lowest of all in the 15-20 year old group (Figure 1). Among adolescents, 76% had Z-scores  $\leq -1$  and 42% had Z-scores  $\leq -2$ .

**Figure 2: DXA Z-scores in Type I GD Patients at the Time of their First Imiglucerase Infusion**



Source: Mistry et al. 2012

A deficiency in the ICGG Registry for purposes of DXA analysis is its limitation of data capture for potential confounders. Activity level, genetic predisposition, nutrition,

vitamin D status, alcohol use, smoking, geographic variations in sun exposure, and differences in densitometry equipment are not recorded in the Registry.

In areas of osteonecrosis or insufficiency fractures, DXA scanning may lead to falsely elevated BMD data. In some cases simultaneous X-ray or MRI may be necessary for accurate interpretation. DXA of the distal radius has been proposed as an appropriate alternative in such cases.

### Substrate Reduction Therapy (SRT)

In a metabolic or genetic pathway, enzymes catalyze a series of reactions, with each enzyme regulated or mediated by one gene through its RNA and protein products. At each phase in the pathway, enzyme activity catalyzes a reaction in which a precursor molecule, the substrate, is transformed into its next intermediate state. SRT addresses a critical failure in a metabolic pathway by reducing an accumulating substrate, to a degree where residual degradative activity is sufficient to prevent further abnormal storage.

In Type I GD disease-affected tissues such as bone marrow and cortical bone are not optimally targeted with existing treatments. The standard of care for treatment of Type I GD is enzyme replacement therapy (ERT) with recombinant acid  $\beta$ -glucosidase. Despite ERT, some patients will show persistent or worsening manifestations of bone disease regardless of dose or treatment duration. ERT reverses marrow infiltration, bone pain, and the incidence of avascular necrosis, but cannot reverse established injuries such as fractures and joint collapse that occur as a result of bone infarction or osteolysis (Mistry 2011). Improvement in BMD may require up to 8 years of ERT, even at high dosages (Wenstrup 2007).

Small molecules used in substrate reduction have different physicochemical properties and a different biodistribution than ERT. ERT is targeted primarily to macrophages. The broader distribution of SRT into the extravascular space may offer better penetration of the bone marrow and the skeleton (Pastores 2007). This may prove beneficial in light of the data from the ICGG Registry suggesting that bone disease requires a longer duration of ERT and at a higher dose compared to other Type I GD parameters.

The only approved substrate reduction therapy for Type I GD is miglustat (Zavesca® [Actelion] NDA 021346). Miglustat was approved in 2003 as a second-line treatment after ERT for Type I GD. Miglustat is a synthetic analogue of D-glucose and functions as a competitive and reversible inhibitor of the enzyme glucosylceramide synthase by mimicry of the glucose moiety of GL1. Glucosylceramide synthase is the initial enzyme in a series of reactions responsible for the generation of sphingolipids and GL1 is the first intermediate.

Miglustat was approved after efficacy was demonstrated in reducing liver and spleen volume and elevating hemoglobin concentration and platelet counts in adults with Type I GD. Miglustat is approved only for patients with mild to moderate Type 1 GD for whom enzyme replacement is not a therapeutic option. Miglustat is a second-line therapy

because of its modest efficacy and significant Adverse Event (AE) profile, including frequent diarrhea (> 80% of patients), weight loss (~65%), and tremor (~30% or more), often leading to treatment discontinuation. Development of peripheral neuropathy associated with miglustat therapy has been reported.

In treatment-naïve patients, no beneficial effects on BMD were seen after up to 24 months of treatment with miglustat. In patients who had been receiving ERT for a minimum of 2 years prior to study enrollment, there was no improvement in BMD after 12 months from switching to miglustat.

**Eliglustat** is an analogue of the ceramide moiety of GL1 and also inhibits glucosylceramide synthase. While eliglustat and miglustat share the same target enzyme, their chemical structures and pharmacologic effects are distinct. Eliglustat is approximately 1000-fold more potent and has a higher specificity for the target enzyme than miglustat (McEachern, 2007).

As with miglustat, the goal of eliglustat therapy is to promote a balance between glycolipid synthesis and degradation. By reducing the rate of GL1 synthesis, the amount of substrate is reduced to a level which allows the residual activity of the deficient enzyme glucocerebrosidase to be more effective, reducing storage and its associated pathology.

### Eliglustat clinical trials design

(b) (4)  
A total of 226 adults with confirmed Type I GD who participated in 1 of 3 eliglustat trials and had skeletal MRI, X-ray, and DXA were evaluated. The patient population included 66 treatment-naïve patients from their Phase 2 study 0304 (n=26) and one Phase 3 trial, 2507 (n=40) and 160 stabilized patients previously treated with ERT from 2607, the second Phase 3 trial.

Table 2 below summarizes designs of the clinical trials submitted in support of eliglustat approval under NDA 205494. The summarized efficacy data were collected in 2 studies in 66 treatment-naïve patients with Type I GD, and in one study in 160 patients switching from enzyme replacement therapy. Treatment-naïve patients were defined as patients who had never been treated with ERT or SRT, as well as patients who had discontinued treatment for a period of at least 6 months

**Table 2 Eliglustat Clinical Studies NDA 205494**

<b>Study</b>	<b>Phase/Blind/Control</b>	<b>(n)</b>	<b>Treatment</b>	<b>Duration</b>
<b>Treatment-Naïve</b>				
<b>GZGD02507 (2507) (ENGAGE)</b>	<b>Phase 3 double-blind, placebo-controlled</b>	<b>40 (20 eliglustat/ 20 placebo)</b>	<b>Eliglustat or placebo 50 mg bid (initial dose), up to 100 mg bid at 4 weeks and 150 mg bid at 47 weeks</b>	<b>39 weeks, long term treatment period up to 6 years on study</b>
<b>GZGD00304 (0304) (Phase 2)</b>	<b>Phase 2 open-label</b>	<b>26</b>	<b>Eliglustat or placebo 50 mg bid (initial dose), up to 100 mg bid at 4 weeks and 150 mg bid at 47 weeks</b>	<b>52 weeks (extended follow up analyzed at 48 months</b>
<b>Prior Enzyme Replacement Therapy</b>				
<b>GZGD02607 (2607) (ENCORE)</b>	<b>Phase 3, open-label, active-control</b>	<b>159 (106 eliglustat 53 cerezyme) in per protocol set 99 eliglustat 47 cerezyme</b>	<b>Eliglustat 50 mg bid (initial dose) or cerezyme eliglustat up to 100 mg bid at 4 weeks and 150 mg bid at 47 weeks</b>	<b>52 weeks long-term treatment period up to 5.5 years on study</b>

The doses of 50 mg, 100 mg or 150 mg bid were selected on the basis of safety and efficacy profiles for eliglustat in previous clinical studies, and predicted plasma exposure based on modeling of nonclinical and clinical trial data. Doses were increased if the study subject's trough levels were less than 5ng/mL after 2 weeks of dosing.

The main efficacy endpoints in these studies were chosen to confirm that reduction of the synthesis of GL1 would lead to meaningful clinical effects on organomegaly, hematologic parameters, and bone disease. Although many of the same parameters were measured in each study, the objectives and patient populations differed. Trial 2507 and the Phase 2 study 0304 were designed to assess the ability of eliglustat to improve clinical manifestations in treatment-naïve patients by reducing GL1 storage. Therefore, the primary efficacy endpoint for 2507 was % change in spleen volume and that of 0304

was pre-specified objective improvements in 2 or more of the 3 main efficacy parameters: hemoglobin increase  $\geq 0.5$  g/dL, platelet count increase  $\geq 15\%$ , and spleen volume reduction  $\geq 15\%$ .

The effects of eliglustat on the skeletal pathology associated with Type I GD were examined in these studies as secondary or tertiary endpoints. DXA was used to assess BMD. The sponsor reported DXA data results as BMD in  $\text{g/cm}^2$ , and as T- and Z-scores. As T-scores for analysis of BMD in premenopausal women and men below age 50 is not recommended, this review does not provide analysis of the sponsor's T-score data for BMD.

Key demographic and baseline characteristics for patients in the 3 eliglustat studies are shown in Table 3:

**Table 3 Key Demographic and Baseline Disease Characteristics in Eliglustat Efficacy Studies 2507, 0304, and 2607**

	Treatment-Naïve Patients			Patients Switching from ERT	
	ENGAGE		Phase 2	ENCORE	
	Eliglustat (N=20)	Placebo (N=20)	Eliglustat (N=26)	Eliglustat (N=99)	Cerezyme (N=47)
<b>Sex, n (%)</b>					
Male, n (%)	8 (40)	12 (60)	10 (38)	43 (43)	21 (45)
Female, n (%)	12 (60)	8 (40)	16 (62)	56 (57)	26 (55)
<b>Age at Day 1 (years)</b>					
Mean (SD)	31.6 (11.55)	32.1 (11.26)	34.47 (12.96)	37.2 (14.03)	38.6 (15.19)
Min, max	16.6, 62.9	16.1, 59.3	18.6, 60.3	18.1, 69.3	18.2, 66.2
<b>Age at first Gaucher symptom onset (year)<sup>a</sup></b>					
Mean (SD)	16.74 (10.526)	15.22 (12.362)	11.82 (10.95)	12.3 (11.8)	15.9 (14.2)
Min, Max	3.0, 38.0	0.0, 37.0	0.6, 40.0	1.0, 59.0	0.0, 54.0
<b>Residual Acid <math>\beta</math>-glucosidase Activity (nmol/hour/mg)</b>					
Mean (SD)	2.29 (3.380)	2.04 (3.793)	0.467 (0.773)	1.18 (1.35)	1.08 (0.97)
Min, Max	0.0, 15.7	0.0, 15.5	0.00, 3.79	0.0, 9.9	0.0, 5.8
<b>Splenomegaly severity<sup>b, c</sup>, n (%)</b>					
None/Mild	0	0	0	68 (89)	37 (95)
Moderate	12 (60)	15 (75)	14 (54)	8 (11)	2 (5)
Severe	8 (40)	5 (25)	12 (46)	0	0
<b>Hepatomegaly severity<sup>b</sup>, n (%)</b>					
None/mild	6 (30)	9 (45)	5 (19)	91 (92)	46 (98)
Moderate	14 (70)	11 (55)	20 (77)	8 (8)	1 (2)
Severe	0	0	1 (4)	0	0
<b>Anaemia severity<sup>b</sup>, n(%)</b>					
None	15 (75)	17 (85)	13 (50)	99 (100)	47 (100)
Mild	2 (10)	2 (10)	3 (12)	0	0
Moderate	2 (10)	1 (5)	6 (23)	0	0
Severe	1 (5)	0	4 (15)	0	0
<b>Thrombopenia severity<sup>b</sup>, n(%)</b>					
None	0	0	0	15 (15)	2 (4)
Mild	0	3 (15)	3 (12)	84 (85)	45 (96)
Moderate	17 (85)	13 (65)	10 (38)	0	0
Severe	3 (15)	4 (20)	13 (50)	0	0

Source: Integrated Bone Paper Section 5.3.5 in Submission

The main exclusion criteria relevant to bone for these 3 studies were symptomatic bone disease such as bone pain attributable to osteonecrosis and/or pathologic fracture, and bone crisis in the 12 months prior to randomization.

MRI was used to evaluate bone marrow infiltration and the presence of infarcts or other focal lesions. Plain X-rays were used to detect fractures, lytic lesions or other osseous complications.

### BMD Efficacy

Methods of BMD analysis applied to the three studies are described below; each study will be then discussed individually, followed by (b) (4).

DXA images of the lumbar spine and femur were obtained for measurement of BMD using Hologic or Lunar scanners. Data were excluded from the BMD analysis if:

- The presence of local abnormalities precluded BMD measurements
- Different scanner types were used on the same patient
- Bisphosphonates were used in treatment-naïve patients (Phase 2 extension study)

DXA images were obtained and interpreted by central readers. The Phase 2 bone imaging was reviewed at (b) (4).

The bone imaging from the Phase 3 trials 2507 and 2607 was reviewed by (b) (4). To ensure reproducibility, the scanning device, scanning parameters (e.g., scan speed) and side of the body scanned were specified for 2507 and 2607 but not for 0304. Central calibration was performed for 2507 and 2607 by a phantom shipped to each clinical site. No central calibration was performed for 0304, although each study site is reported to have performed the required DXA calibration and quality control procedures per manufacturer's recommendation

*Reviewer Comments: The sponsor states that a bone disease assessment using DXA may have a correction factor applied to maintain the consistency of the data. The correction factor occurs when a patient's assessment is done on a different DXA machine or the machine "has a shift" based on the individual machine quality controls. It is unclear how this reconciles with the exclusion criterion for data acquired from different machines on the same patient.*

*The sponsor's presentation of BMD data in terms of T-scores is misleading. The sponsor proposes changes in World Health Organization (WHO) BMD classification for reporting study results. The WHO classification should only be used in postmenopausal women. As noted above, the International Society for Clinical Densitometry recommends the expression of bone mass by Z-score for premenopausal women, and for men below the age of 50. T-scores compare a patient's bone density to that of a normal healthy young adult of the same sex and are used primarily in assessment of postmenopausal osteoporosis. T-scores are validated by fracture data in postmenopausal women. T- and Z-scores are derived from normative databases that may change over the duration of the trial. While Z-scores provide a useful statistical comparison to a patient's peer group, they have not been validated by any fracture data. For these reasons, percent change from baseline BMD(g/cm<sup>2</sup>) for analysis of longitudinal DXA data is the most appropriate endpoint. As change in WHO classification is not an appropriate endpoint for*

*consideration in these studies, this review does not provide analysis of the sponsor's T-score data for BMD.*

BMD efficacy will be discussed for each of the 3 studies:

### **BMD efficacy GZGD00304 (Phase 2 Study)**

Phase 2 Study GZGD00304 (0304) was an open label, single-arm investigation in 26 patients with analysis at one year and extended analysis at 4 years. This study evaluated the 1-year and the long-term (> 1 year) efficacy, safety, and pharmacokinetics of eliglustat in treatment-naïve patients. The main inclusion criteria were age 18 to 65 years, and the presence of splenomegaly with anemia and/or thrombocytopenia.

The main exclusion criteria relevant to bone for 0304 (also for 2507 and 2607) were symptomatic bone disease such as bone pain attributable to osteonecrosis and/or pathologic fracture, and bone crisis in the 12 months prior to randomization.

Of the three studies, the treatment-naïve patients in the Phase 2 study had the most severe bone loss at baseline. Twenty five patients in the Full Analysis Set for 0304 at baseline had a mean lumbar spine BMD of 0.928 g/cm<sup>2</sup>, while baseline lumbar spine BMD was higher in 2507 (1.01 g/cm<sup>2</sup>) and 2607 (1.099 g/cm<sup>2</sup>). Such patients presumably would have an increased chance of demonstrating a therapeutic effect. Also, the Phase 2 study Primary Analysis Period was 12 months. Because of the normal bone remodeling cycle, this time frame might provide a more accurate assessment of BMD efficacy than the 9 month Primary Analysis Period for 2507. For analysis of the secondary endpoint of BMD, descriptive statistics (continuous variables) are presented stratified by Baseline BMD data. Change from Baseline in DEXA T-scores and Z-scores (spine lumbar vertebrae total, femoral neck, greater trochanter, inter trochanteric area, and femur total) were calculated. No continuous variables are collected for X-ray or MRI assessments

Out of 33 screened patients, 26 patients (10 males, 16 females) with Type I GD, ranging in age at first study dose of eliglustat from 18 to 60 years, were enrolled into the study at 7 study centers in 5 countries (Russia, Argentina, the US, Israel, and Mexico). The average mean age at first diagnosis of Type I GD for all patients (n=25) was 24.04. The average mean age at first dose of eliglustat for all patients (n=26) was 34.47 (Table 3). Prior bisphosphonate therapy was exclusionary. Bone disease assessments (MRI, X-ray, and DXA) were performed at Screening 2 and at Weeks 52 and 104. In addition, MRI and DXA were performed every 12 months thereafter, and at end-of-study or patient termination.

Of the 26 patients enrolled, 22 (85%) completed 1 year of eliglustat treatment and 20 had evaluable DXA data at Baseline and at Month 12. Excluded from analysis were 2 patients scanned by different equipment at Baseline and at Month 12, 1 patient with local bone abnormalities precluding DXA measurement, and 1 patient who was reinstated on

bisphosphonate therapy. The 20 evaluable patients had an increase of 4.4% in mean lumbar spine BMD ( $\text{g}/\text{cm}^2$ ) at Month 12, or an increase in mean (standard deviation [SD]) BMD ( $\text{g}/\text{cm}^2$ ) from 0.97 (0.16) to 1.01 (0.16) for a mean increase of 0.33;  $p=0.007$  (Table 4):

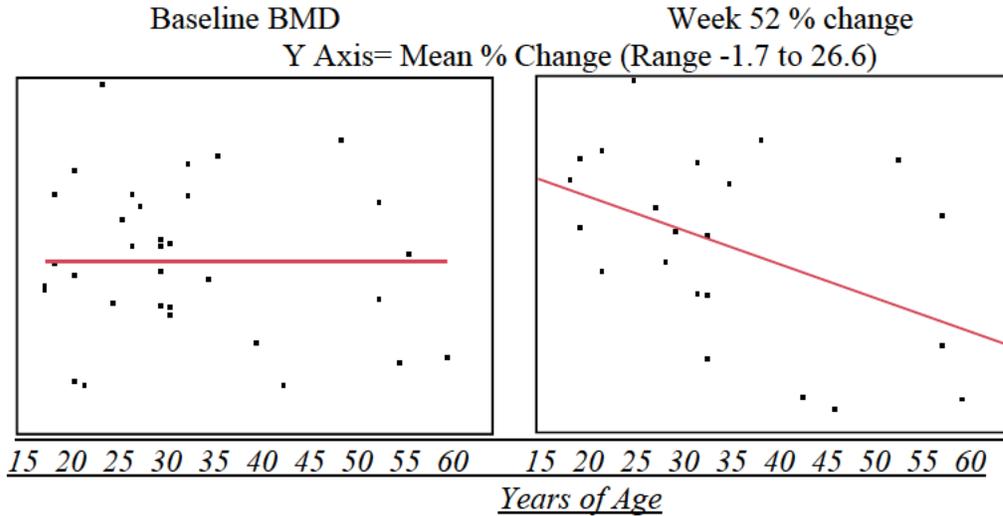
**Table 4: Lumbar BMD (DXA  $\text{g}/\text{cm}^2$ ) Assessments Baseline to Month 12 Eliglustat Phase 2 Study**

Parameter	Visit	Statistic	Baseline	Actual Value	Change from Baseline	% Change from Baseline
Lumbar BMD ( $\text{g}/\text{cm}^2$ )	Baseline	n Mean Median (SD)		25 0.95 0.95 (0.155)		
	Wk 52	n Mean Median (SD) p	20 0.97 0.95 (0.157)	20 1.01 1.04 (0.161)	20 0.04 0.02 (0.060)	20 4.4 (6.65) 2.4 0.0079

It should be noted that the data are partially driven by disproportionate percentage changes in one patient with positive change at Week 52 of 26.7%. Subject 0110 (age 18 years) was investigated in the Russian Federation. There are no changes in Genant scores suggesting vertebral compression for this subject, no change in height, nor any comments offered. Subject 0110 had commensurate percent change increases in left femoral neck BMD of 13.8% at Week 52 and of 30.7% at Month 48.

The enrolled population includes adolescent subjects who are actively growing. Therefore, an analysis of age was conducted. There does appear to be a relationship between age and BMD response (Figure 3):

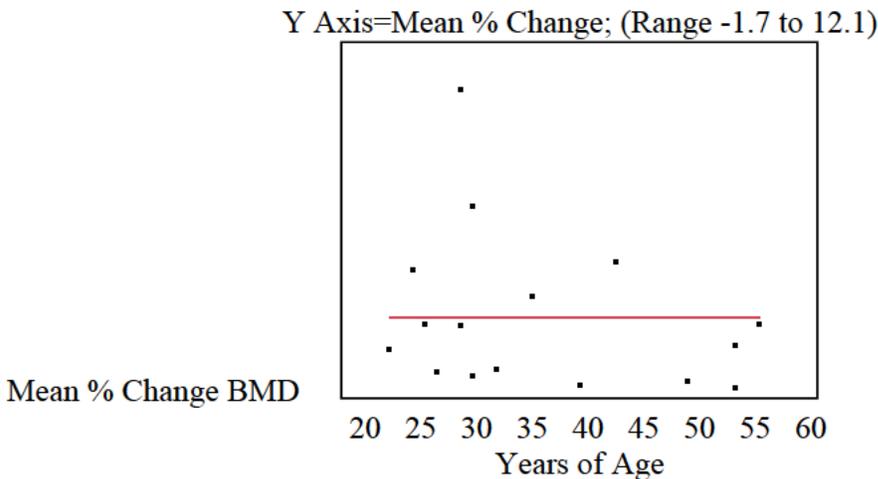
**Figure 3: BMD (g/cm<sup>2</sup>) L1-L4 by Age at Baseline and percent change at Week 52 Study 0304**



Source: Reviewer analysis of dataset ADXS, study 0304

When the subjects below 22 years of age are removed from the analysis, concordance in BMD response is seen (Figure 4). This is explained by natural bone accrual in younger individuals and subject 0110, the 18 year old outlier.

**Figure 4: Percent Change in BMD (g/cm<sup>2</sup>) Adult Subjects at Week 52**



Source: Reviewer analysis of dataset ADXS, study 0304

*Reviewer Comment: The 4.4% improvement in BMD from baseline at 12 months with eliglustat therapy is also driven in part by disproportionate increases in younger*

patients, who may be expected to undergo natural bone accrual. The reported increase of 4.4% is comparable to that achieved with bisphosphonates approved based on major fracture reductions in postmenopausal women. However, the disease process in postmenopausal osteoporosis differs markedly from that in Type I GD. Increased BMD in Type I GD has not been shown to be associated with fracture risk reduction or improvement in any other Type I GD-related bone pathology.

Mean femur Z-scores were within normal range at baseline and did not show significant change at one year of treatment. In the 52 week analysis, Z-score BMD values were defined erroneously as normal/osteopenia/osteoporosis; subsequent Z-score categories were defined correctly (normal/below normal).

A total of 19 patients completed 4 years of treatment and 15 patients had evaluable DXA data at Baseline and Month 48. Compared to the Month 12 BMD increase of 4.4% reported, the 15 patients at Month 48 had a smaller mean percentage increase (SD) in lumbar spine BMD ( $\text{g}/\text{cm}^2$ ) with a net increase from baseline to Month 48 of 7.3% (Table 5):

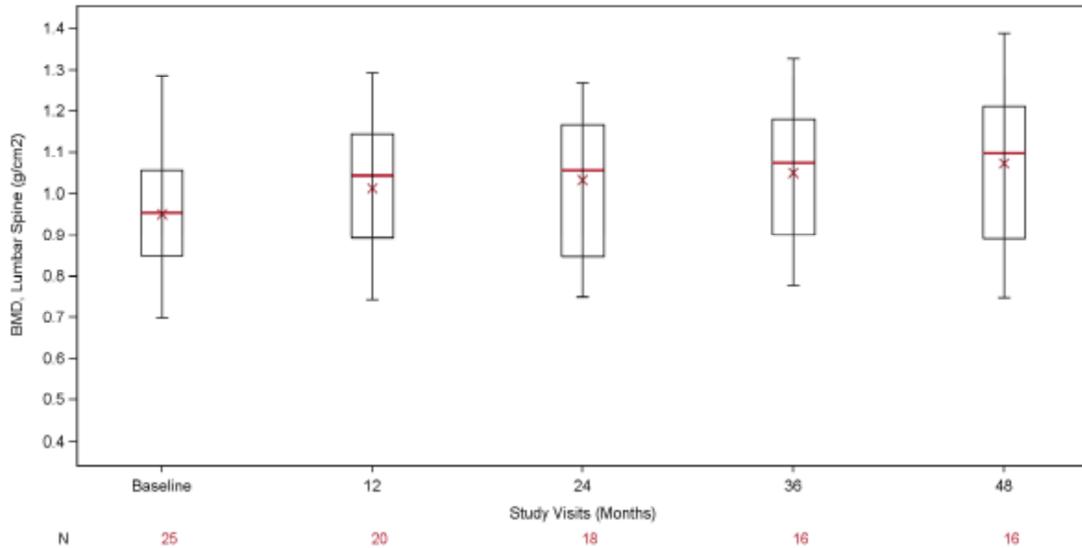
**Table 5: Lumbar Spine BMD (DXA ( $\text{g}/\text{cm}^2$ )) Assessments from Baseline to Month 48 Eliglustat Phase 2 Study 0304**

Parameter	Visit	Statistic	Baseline	Actual Value	Change from Baseline	% Change from Baseline
	Month 48	n	15	15	15	
		Mean (SD)	0.99 (0.147)	1.01 (0.161)	0.04 (0.060)	7.3 (12.81)
		Median	0.98	1.10	0.09	8.5
		95% CI				-6.9, 14.40
		p				0.0442

*Reviewer Comment: This increase is disproportionately driven by subject 0110, who is reported to have an increase of 55.9% at Month 48. Removing this subject's data from the analysis results in a mean percentage change of 6.6% for the remaining 14 subjects at Month 48.*

BMD of the lumbar spine over time is presented by the sponsor in Figure 4:

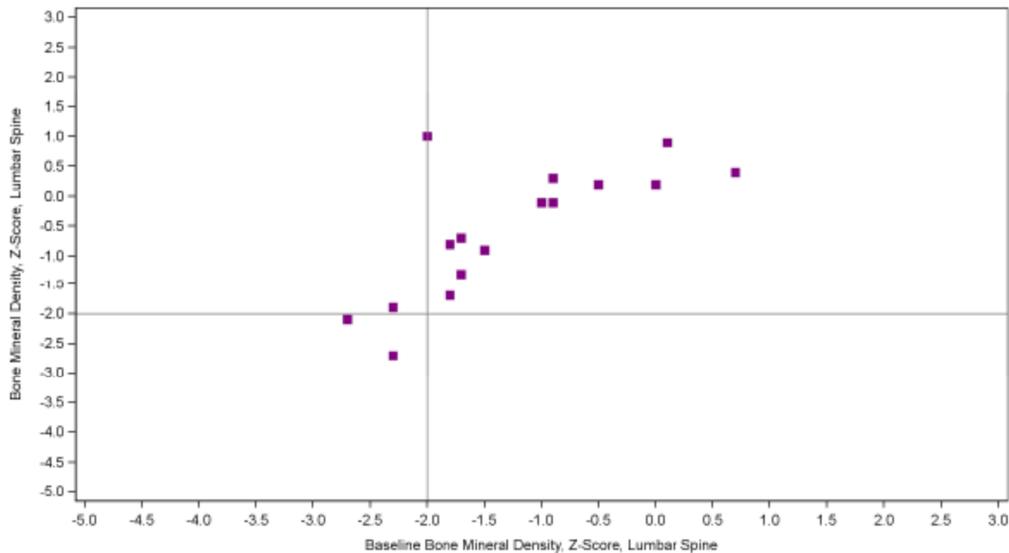
**Figure 4: Boxplot of BMD Lumbar Spine (g/cm<sup>2</sup>) over Time Eliglustat Phase 2 Study 0304**



Source: GZGD00304 Clinical Study Report

Changes from baseline to Month 48 in lumbar spine BMD are presented by the sponsor in Figure 5:

**Figure 5: Scatter Plot of Percentage Change in BMD of Lumbar Spine (DXA) from Baseline to Month 48 Eliglustat Phase 2 Study 0304**



Source: GZGD00304 Clinical Study Report

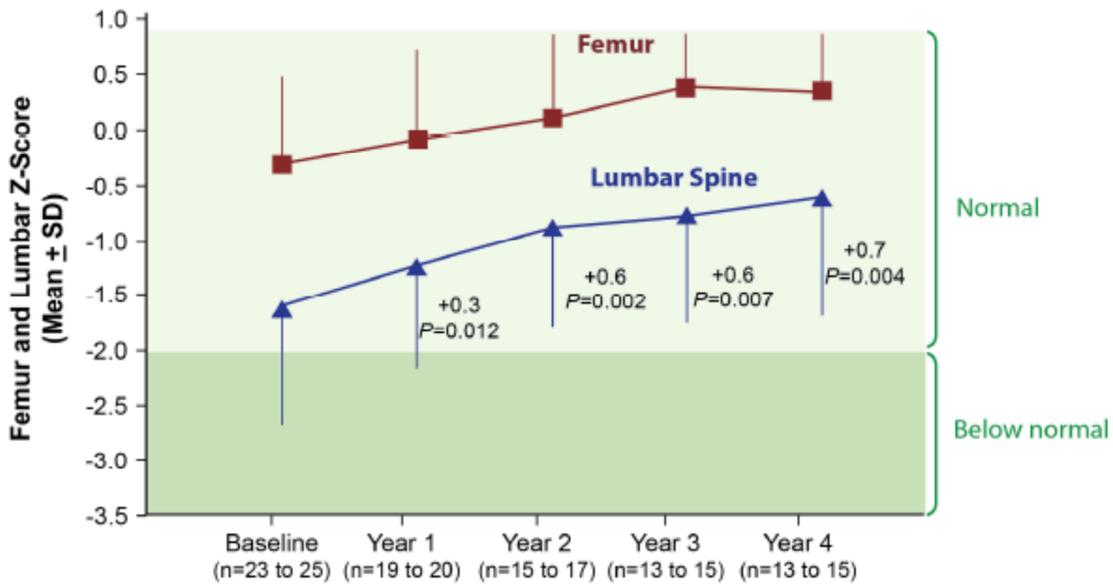
However, there appeared to be a modest beneficial shift in lumbar spine BMD Z-score categories over time in the Full Analysis Set (Table 6):

**Table 6: Summary of Shift in Spine BMD DXA Z-score Categories over Time Eliglustat Phase 2 Study 0304**

	Visit	(N)	Baseline	Eliglustat (N=26) BMD Category	
				Normal (%)	Below (%)
Spine Z-score	Wk 52	20	Normal	13(65)	2(10)
			Below	2(10)	3(15)
	Wk 104	18	Normal	12(67)	1(6)
			Below	2(11)	3(17)
	Wk 156	16	Normal	11(69)	1(6)
			Below	2(13)	2(13)
	Wk 208	16	Normal	12(75)	0
			Below	2(13)	2(13)

This increase correlated with a mean increase in lumbar spine BMD Z-score from -1.46 (SD 1.04) at Baseline to -0.48 (SD1.07; p=0.0044) at month 48. For the 15 patients with 4 year femur BMD data, the mean Z-score increased from 0.27 (0.70) to 0.48 (0.77) (Figure 7):

**Figure 7: Mean Changes in Lumbar Spine and Femur Z-scores Over Time Eliglustat Phase 2 Study 0304**



Source: GZGD00304 Clinical Study Report

Summary: Phase 2 Study 0304

This single-arm phase 2 study showed a 4.4% increase in lumbar (L1-L4) BMD (g/cm<sup>2</sup>) at 12 months with eliglustat therapy in 20 patients and an increase of 7.3% at 48 months in 15 patients over Baseline. Improvement in lumbar Z-scores observed after 52 weeks and 48 months respectively were 0.3 and 0.7. These figures are driven in part by one subject with unexplained dramatic responses in BMD efficacy and by inclusion of younger patients undergoing natural bone accrual.

*Reviewer Comment: Because 0304 does not meet the regulatory requirements for adequate and well-controlled trials as delineated in 21 CFR 314.126 (there was no control group or primary efficacy endpoint), efficacy results from the trial constitute supportive (i.e., not “substantial”) evidence of efficacy.*

Furthermore, (b) (4)  
since a relationship between BMD and bone clinical outcomes in Type I GD has not been established. While a relationship between lower BMD and increased fracture risk in Type I GD has been shown (Khan 2012), 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.

(b) (4)

### **BMD efficacy Trial GZGD02507**

Trial GZGD02507 (2507) was a 1:1 randomized double blind, placebo-controlled Phase 3 trial in 40 treatment-naïve patients, with primary analysis at 39 weeks. Patients were stratified by spleen volume (low severity spleen volume  $\leq 20$  multiples of normal or high severity spleen volume,  $> 20$  multiples of normal), then randomized in a 1:1 ratio to receive either eliglustat or placebo. After completion of the 39 week double blind

analysis, all patients entered the open-label long-term treatment period with eliglustat for up to 6 years. The main inclusion criteria were age > 16 and splenomegaly with anemia and/or thrombocytopenia. Again, symptomatic bone disease was exclusionary.

Phase 3 trial 2507 was conducted at a total of 26 sites in Latin America, the US, Canada, the Middle East, Northern Africa, India, and Europe, with 17 of these sites randomizing at least 1 eligible patient. The patient population consisted of 12 females (60%) and 8 males (40%) in the eliglustat group, and 8 females (40%) and 12 males (60%) in the placebo group. The mean (SD) age at Baseline was 32 (11) years, with ages ranging from 16 to 63 years (Table 3).

Study eligibility criteria excluded patients with symptomatic bone disease so that patients in this study had relatively little bone involvement at Baseline compared to the broader Type I GD population. Compared to Phase 2, the ENGAGE study enrolled patients with less severe bone loss at baseline due to concern about potential randomization to placebo arm. Z-scores were normal in the majority of patients in each treatment group; only 3 eliglustat and 5 placebo patients had below-normal Z-scores ( $Z\text{-score} \leq -2$ ).

Of the 39 patients who completed the 9 month Primary Analysis Period for 2507, 35 had evaluable DXA data at both baseline and Month 9. For analysis of the secondary endpoint of BMD, descriptive statistics (continuous variables) are presented stratified by trough plasma concentrations in the eliglustat treatment group, bisphosphonate use, and Baseline BMD data.

The mean BMD ( $\text{g}/\text{cm}^2$ ) and Z-scores for the lumbar spine and femur did not show clinically or statistically significant changes after 9 months of treatment in either group, or no clear relationship to the stratification variables. The sponsor reports 0.45% change from baseline in “total spine” BMD ( $\text{g}/\text{cm}^2$ ) in the eliglustat-treated group at week 39, and -0.64% change in placebo treated patients (Table 7):

**Table 7: Lumbar Spine DXA BMD ( $\text{g}/\text{cm}^2$ ) over time Trial 2507**

<b>Parameter</b>	<b>Placebo (N=20)</b>	<b>Eliglustat (N=20)</b>
Mean (SD) BMD ( $\text{g}/\text{cm}^2$ ) Baseline	1.037 (0.15)	0.991 (0.16)
Mean (SD) BMD ( $\text{g}/\text{cm}^2$ ) Week 39	1.027(0.15)	0.995 (0.16)
Mean (SD) Change from Baseline	-0.010 (0.04)	0.004(0.03)
Mean (SD) % Change from Baseline	-0.64 (3.5)	0.45 (3.16)

These figures appear comparable when BMD L1-L4 is evaluated (Table 8):

**Table 8: L1-L4 DXA BMD (g/cm<sup>2</sup>) over time Trial 2507**

Parameter	Placebo (N=20)	Eliglustat (N=20)
Mean BMD Baseline	1.047	0.975
Mean BMD Week 39	1.027	1.013
Mean Change from Baseline	-0.020	0.038
Mean % Change from Baseline	-.02	1.03

*Reviewer Comment: Throughout the submission, the terms “Total Spine”, “Total Lumbar Spine”, and “Lumbar Spine” were used interchangeably. In a response to an Information Request sent on February 21, 2014, the sponsor confirmed that these terms, although used interchangeably, are meant to refer to the same measurement of lumbar spine bone mineral density (g/cm<sup>2</sup>.) The sponsor stated that “Lumbar Spine” is the appropriate term, and that this includes assessment of bone mineral density at the L1-L4 vertebrae. For lumbar spine DXA assessment, this review assessed measurements conducted on L1-L4. The treatment difference as reported for “Total Spine” BMD over time is therefore 0.81% and that for L1-L4 is 1.05%, both inconclusively favoring eliglustat.*

At baseline, the mean lumbar spine Z-scores were in the low-normal range (Z-score > -2 to ≤ -1) for both treatment groups and very similar: -1.15 (0.94) for the eliglustat group and -1.17 (1.18) for the placebo group. There were 2 patients with abnormal Z-scores at baseline in the eliglustat group; both patients shifted into the normal category after 9 months of treatment. There were 5 patients in the placebo group with abnormal Z-scores; 2 shifted into the normal category, 2 patients had a decrease in Z-score, and one patient remained stable with no change. Table 9 summarizes shifts in spine Z-score categories after 39 weeks:

**Table 9: Summary of Shift in Spine Z-Score Categories Trial 2507**

	Placebo (N=20)				Eliglustat (N=20)			
	(n)	Week 39 Z-Score Category			(n)	Week 39 Z-Score Category		
		Baseline	Below Normal	Normal		Baseline	Below Normal	Normal
Total Spine Z-score	20	Below Normal	3 (15)	2 (10)	17	Below Normal	0	2 (12)
		Normal	1 (5)	14 (70)		Normal	0	15 (88)

While on average the trend is towards Z-score improvement in patients with abnormally low Z-scores when treated with eliglustat compared to placebo, the numbers are too small to justify any conclusion in this regard (Table 10):

**Table 10: DXA Z-Score over Time in Patients with Below-Normal Z-scores at Baseline Trial 2507**

Total Spine Z-score below normal at baseline (n=8, 5 placebo, 3 eliglustat)	Visit	Placebo (N=20)	Eliglustat (N=20)
	Baseline Mean (SD)	-2.5 (0.54) n=5	-2.67 (0.64) n=3
	Week 39 Mean (SD)	-2.4 (0.71) n=5	-2.3 (0.87) n=3
	Change from Baseline (SD)	0.06 (0.21)	0.267 (0.23)

Subjects with below-normal Z-scores at Baseline appeared to have a greater treatment effect with eliglustat compared to placebo. After 9 months of treatment mean lumbar spine Z-score was -1.08 (0.92) in the eliglustat group and -1.27 (1.15) in the placebo group, with a treatment difference of 0.2 (Least Squares Mean); p=0.057 that approached but did not reach clinical significance (Table 11):

**Table 11: Total Spine BMD Z-score changes at Month 9 Trial 2507**

	<b>eliglustat</b>	<b>placebo</b>
Baseline Mean Z-score (SD)	-1.15 (0.94)	-1.17 (1.18)
9 month Mean Z-score (SD)	-1.08 (0.92)	-1.27 (1.15)
% Change from Baseline(SD)	3.36 (23.2)	-2.47 (40.7)
Treatment difference	LS Mean 0.2; p=0.057	

Again, following 39 weeks of treatment in the Primary Analysis Period, improvements in lumbar spine Z-scores were observed more frequently in the eliglustat treatment group compared with placebo, although the numbers are too small to draw any firm conclusions. Increases in lumbar spine Z-score of  $\geq 0.1$  were reported for 9 (53%) of 17 patients in the eliglustat group compared with 6 (30%) of 20 patients in the placebo group.

Eliglustat did not have an effect on femur total BMD or Z-scores during the 39 weeks of this study. The mean Z-scores for femur were in the normal range at Baseline, and there was no statistically significant change in femur BMD after 9 months. Also, no positive trends were noted for the worst femur (i.e. the femur most affected at baseline).

*Reviewer Comment: While eliglustat did appear to effect a positive trend on spine BMD Z-score, this was statistically non-significant. An increase in Z-score  $\geq 0.1$  is of uncertain relevance to bone health. The clinical significance of BMD Z-score improvement in Type I GD is unclear, given the modest treatment effect (+0.1), the apparently small decline in placebo patients (-0.1), and the uncertain fracture prevention benefit of increased BMD in this patient population.*

Summary Trial 2507:

No conclusions can be drawn from BMD efficacy data in 2507. Trial 2507 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 Type I GD.

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 of 2507 should provide further clarity on the BMD efficacy of eliglustat in Type I GD.

(b) (4)

**BMD efficacy Phase 3 Trial GZGD02607**

Trial GZGD02607 (2607) was a 2:1 randomized, non-inferiority, active-control trial in patients switching from enzyme replacement therapy. Stabilized patients switching from ERT were defined as patients who had reached protocol-specific therapeutic goals with at least 3 years of ERT, and therefore considered to have stable disease. Patients, 18 years

of age and above, were randomized 2:1 to receive either eliglustat or Cerezyme for 12 months. 2607 assessed the ability of eliglustat to maintain pre-defined therapeutic goals by preventing reaccumulation of substrate. 2607 was designed to evaluate whether the percentage of patients who maintained stability after switching from ERT to eliglustat treatment was non-inferior to the percentage of patients who maintained stability when continued on cerezyme treatment. The amount of clinical change therefore was expected to be larger in treatment-naïve patients than in those switching from ERT.

Patients switching from ERT in 2607 were required to have already met pre-specified therapeutic goals prior to study entry. Accordingly, 2607 enrolled no patients with severe hepatosplenomegaly and few patients with moderately severe organ volume measures and mainly normal or mildly abnormal hematology values. In point of contrast, no patients in the treatment-naïve study (2507) had prior splenectomy, while 28% of those in 2607 had total splenectomy and 1% had partial splenectomy, a consequence of the differing exclusion criteria for the different studies.

Trial 2607 was conducted at a total of 39 sites in Latin America, the US, Canada, Australia, the Middle East and Europe, with 34 of these sites randomizing at least 1 eligible patient. A total of 81/99 (82%) eliglustat-treated patients and 38/47 (81%) Cerezyme-treated patients in the Per Protocol population had evaluable DXA data at both baseline and Month 12. The eliglustat group consisted of 43 males and 56 females, with a mean age (SD) of 37 (14) years and an age range of 18 to 69 years. The Cerezyme group consisted of 21 males and 26 females, with a mean age (SD) of 39 (15) and an age range of 18 to 66 years (Table 3).

The primary efficacy endpoint for 2607 was the percentage of patients who remained stable in hematological parameters (hemoglobin levels and platelet counts) and organ volumes. 2607 is a non-inferiority trial powered at 85% with a one-sided 0.025 level of significance. A non-inferiority margin of 25% was selected for this study based on considerations of a Cerezyme response rate of 95% for the defined composite primary endpoint for measuring stability and assuming a response rate of 85% for eliglustat based on Phase 2 data.

Demographic and Baseline disease characteristics were listed for all patients in the Full Analysis Set, and summarized by treatment as well as by Baseline stratification of prior ERT dose, gender, and age category. The secondary efficacy endpoints, including BMD, were analyzed using ANCOVA analysis on the full analysis set and the per-protocol set. The ANCOVA included a treatment effect (eliglustat or Cerezyme), the baseline value, and the stratification randomization indicator (equivalent ERT dose < 35 U/kg/q2w or ≥ U/kg/q2w).

*Reviewer Comment: In Trial 2607, there did not appear to be an association between age and BMD, either at Screening, or at Week 52. Exclusion of age in the ANCOVA analysis appears appropriate.*

Patients enrolled in 2607 had a longer duration of disease than those in 0304 or 2507. Unlike 0304 or 2507, patients with splenectomy were enrolled. Splenectomized patients with Type I GD are at higher risk for bone disease, possibly because of underlying disease severity or from removal of the major storage organ. At Baseline, 36 patients (25%) in the Per Protocol set were status post splenectomy: 28 (28%) in the eliglustat arm and 8 (17%) in the cerezyme arm, including one partially splenectomized patient in each group (Table 3). Patients in 2607 had been treated previously with ERT for a minimum of 3 years and therefore most patients had a normal BMD at baseline and very few had low Z-scores ( $< -2$ ): 6% in lumbar spine and 1% in femur.

Overall, the Per Protocol population showed minimal changes in BMD from baseline spine and femur Z-scores after 12 months of treatment (Table 12):

**Table 12: Baseline and Percentage Change in BMD and absolute Change in BMD ( $\text{g}/\text{cm}^3$ ) and Z-scores after 12 Months of Eliglustat or Cerezyme Treatment 2607**

	Statistic	Eliglustat (N=99)	Cerezyme (N=47)	Treatment Difference (El-Ce)
<b>Lumbar Spine (L1-L4) BMD (<math>\text{g}/\text{cm}^3</math>)</b>				
Baseline	Mean (SD)	1.09 (0.161)	1.11 (0.161)	--
Change in BMD (%) from Baseline to 12 months	LS Mean	0.49	0.55 (0.48)	-0.06 (0.58)
	95% CI	(-0.16, 1.15)	(-0.39, 1.50)	(-1.21, 1.09)
	p-value			0.9203
<b>Lumbar Spine Z-score</b>				
Baseline	Mean(SD)	-0.35 (1.260)	-0.14(1.108)	--
Absolute Change in total spine Z-score from Baseline to 12 months	LS Mean (SEM)	0.06 (0.03)	0.06 (0.04)	0.0 (0.05)
	95% CI	(0.00, 0.12)	(-0.02, 0.15)	(-0.10, 0.13)
	p-value			0.83
<b>Total Femur BMD (<math>\text{g}/\text{cm}^3</math>)</b>				
Baseline	Mean(SD)	1.01 (0.156)	0.98 (0.184)	--
% Change in total femur BMD from baseline to 12 months	LS Mean	0.18 (0.22)	0.03 (0.31)	0.19(0.38)
	95% CI	(-24, 0.61)	(-0.62, 0.62)	(-0.57, 0.94)
	p-value			0.62
<b>Total Femur Z-score</b>				
Baseline	Mean (SD)	0.09 (1.020)	-0.18(1.112)	--
Absolute change in total femur Z-score from Baseline to 12 months	LS Mean	0.03 (0.02)	0.02 (0.02)	0.02 (0.03)
	95% CI	(0.00, 0.07)	(-0.03, 0.06)	(-0.04, 0.07)
	p-value			0.58

As discussed previously, the sponsor explained in an Information Request response that varying parameters were used in calculating BMD and Z-scores for Lumbar Spine. Lumbar spine (L1-L4) BMD figures are comparable (Table 13):

**Table 13: L1-L4 DXA BMD (g/cm<sup>2</sup>) over time Trial 2607**

Parameter	Eliglustat (N=99)	Cerezyme (N=47)
Mean BMD Baseline	1.088	1.118
Mean BMD Week 52	1.096	1.131
Mean Change from Baseline	0.008	0.013
Mean % Change from Baseline	0.52	0.75

Both treatment groups had similar proportions of patients with similar magnitudes of Z-score changes. In the eliglustat treatment arm, 47% (44/94) showed lumbar spine Z-score increases of 0.1 to 1.2, 39% (37/94) showed decreases of -0.1 to -0.5, and 14% (13/94) showed no change. In the Cerezyme arm, 44% (20/45) showed lumbar spine Z-score increases of 0.1 to 0.9, 40% (18/45) showed decreases of -0.1 to -0.6, and 16% (7/45) showed no change in Z-score (Table 14):

**Table 14: Shift in BMD Z-scores after 12 months of treatment 2607**

Treatment Group	Parameter	Total n	Baseline BMD Category	Month 12 BMD Category	
				Below Normal	Normal
Eliglustat (N=99)	Spine Z-score	94	Below Normal	6 (6)	1 (1)
			Normal	2 (2)	85 (90)
	Femur Z-score	93	Below Normal	0	0
			Normal	0	93 (100)
Cerezyme (N=47)	Spine Z-score	45	Below Normal	2 (4)	0
			Normal	0	43 (96)
	Femur Z-score	44	Below Normal	2 (5)	0
			Normal	0	42 (95)

Summary Trial GZGD02607:

BMD values 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. At Week 52, subjects in the eliglustat arm had a mean percent change at L1-L4 DXA (g/cm<sup>2</sup>) of 0.52; those in the cerezyme arm had a value of 0.76. There were insignificant differences in BMD (g/cm<sup>2</sup> and Z-scores) between both groups at Baseline and at Week 52, and minimal changes in both groups for these parameters at Week 52. BMD data

showed no relationship to the stratification randomization indicator (equivalent ERT dose < 35 U/kg/q2w or  $\geq$  U/kg/q2w), or to subject age.

(b) (4)

### Discussion

The sponsor's position is that eliglustat, as a unique class of glucosylceramide synthase inhibitor, would meet an unmet medical need for an oral therapy that addresses the broad Type I GD population, offering the convenience of an oral therapy.

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(b) (4)

The single-arm phase 2 study 0304 showed a 4.4 % increase in lumbar L1-L4 BMD ( $\text{g}/\text{cm}^2$ ) 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 ( $\text{g}/\text{cm}^2$  and Z-scores) between both groups at Baseline and at Week 52, and minimal changes in both groups for these parameters at Week 52.

While positive trends for BMD increase were noted in 0304 and 2507 and no significant BMD difference between eliglustat and Cerezyme were found in 2607, there is

uncertainty regarding

(b) (4)

. BMD is well-validated as a marker for antiresorptive and anabolic drugs effective in the treatment of postmenopausal osteoporosis. However, other drugs have increased BMD in patients with postmenopausal osteoporosis with no fracture benefit realized.

In contrast to the diffuse process of postmenopausal osteoporosis, bone pathology in Type I GD is more localized, and associated with pathologic fracture. The relationship between low BMD and fracture in Type I GD is unclear.

### Conclusions

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

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

### References:

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Giraldo P, Solano V, Perez-Calvo JI, Giralt M, Rubio-Felix D. Quality of life related to type 1 Gaucher disease: Spanish experience. *Qual Life Res.* 2005 Mar; 14(2):453–62.

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/s/  
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JOHN T STINSON  
04/18/2014

THERESA E KEHOE  
04/18/2014

HYLTON V JOFFE  
04/24/2014



## CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	adult pts with type 1 Gaucher's  Pivotal Study #2- ENCORE  Indication: Treatment of adult pts with type 1 Gaucher's				
15.	Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?	X			
16.	Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.	X			
17.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?	X			
<b>SAFETY</b>					
18.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?	X			
19.	Has the applicant submitted adequate information to assess the arrhythmogenic potential of the product (e.g., QT interval studies, if needed)?	X			
20.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?	X			
21.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure <sup>1</sup> ) been exposed at the dose (or dose range) believed to be efficacious?	X			
22.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?			X	
23.	Has the applicant submitted the coding dictionary <sup>2</sup> used for mapping investigator verbatim terms to preferred terms?	X			
24.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?	X			

<sup>1</sup> For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

<sup>2</sup> The "coding dictionary" consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

File name: 5\_Clinical Filing Checklist for NDA\_BLA or Supplement 010908

## CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
25.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?	X			
<b>OTHER STUDIES</b>					
26.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?	X			
27.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included ( <i>e.g.</i> , label comprehension, self selection and/or actual use)?			X	
<b>PEDIATRIC USE</b>					
28.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?			X	orphan designation
<b>ABUSE LIABILITY</b>					
29.	If relevant, has the applicant submitted information to assess the abuse liability of the product?			X	
<b>FOREIGN STUDIES</b>					
30.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?	X			
<b>DATASETS</b>					
31.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?	X			
32.	Has the applicant submitted datasets in the format agreed to previously by the Division?	X			
33.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?	X			
34.	Are all datasets to support the critical safety analyses available and complete?	X			
35.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?	X			
<b>CASE REPORT FORMS</b>					
36.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?	X			
37.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?			X	
<b>FINANCIAL DISCLOSURE</b>					
38.	Has the applicant submitted the required Financial Disclosure information?	X			
<b>GOOD CLINICAL PRACTICE</b>					
39.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?	X			

**IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? Yes \_\_\_\_\_**

If the Application is not fileable from the clinical perspective, state the reasons and provide comments to be sent to the Applicant.

File name: 5\_Clinical Filing Checklist for NDA\_BLA or Supplement 010908

# CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

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Reviewing Medical Officer

Date

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Clinical Team Leader

Date

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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KARYN L BERRY  
10/25/2013

JESSICA J LEE  
10/25/2013