CADTH

CADTH COMMON DRUG REVIEW

Clinical Review Report

ELIGLUSTAT (Cerdelga)

(Sanofi Genzyme)

Indication: Gaucher Disease Type 1

Service Line:	CADTH Common Drug Review
Version:	1.0
Publication Date:	August 2017
Report Length:	93 Pages

CADTH

About CADTH: CADTH is an independent, not-for-profit organization responsible for providing Canada's health care decision-makers with objective evidence to help make informed decisions about the optimal use of drugs, medical devices, diagnostics, and procedures in our health care system.

Funding: CADTH receives funding from Canada's federal, provincial, and territorial governments, with the exception of Quebec.

CADTH

Table of Contents

Abbreviations

BMD	bone mineral density
BPI	Brief Pain Inventory
CDR	CADTH Common Drug Review
CCL18	chemokine C-C motif ligand 18
CGI-S	Clinical Global Impression–Severity of Illness
CI	confidence interval
CYP2D6	cytochrome P450 2D6
CYP3A	cytochrome P450 3A
DS3	Gaucher disease severity scoring system
ECG	electrocardiogram
ERT	enzyme replacement therapy
FAS	full analysis set
FSS	Fatigue Severity Scale
GD1	Gaucher disease type 1
IV	intravenous
LTTP	long-term treatment period
LS	least square
MCID	minimal clinically important difference
MN	multiples of normal
MRI	magnetic resonance imaging
PAP	primary analysis period
PPS	per-protocol set
SD	standard deviation
SE	standard error
SF-36	Short Form (36) Health Survey
SRT	substrate reduction therapy

Drug	Eliglustat (Cerdelga)
Indication	For the long-term treatment of adult patients with Gaucher disease type 1 who are CYP2D6 poor metabolizers, intermediate metabolizers or extensive metabolizers, as determined by CYP2D6 genotype testing.
Listing Request	As per indication
Manufacturer	Sanofi Genzyme

Executive Summary

Introduction

Gaucher disease is an autosomal, recessive lysosomal storage disease that results from deficiency of the lysosomal enzyme glucocerebrosidase.[1] Consequently, the enzyme's substrate, glucocerebroside, accumulates in macrophages of the reticuloendothelial system, particularly those in the spleen, liver, bone marrow, skeleton, and lung. This leads to multiple manifestations, including anemia, thrombocytopenia, hepatosplenomegaly, growth retardation in children, skeletal disease, and increased rates of malignancies. The prevalence of Gaucher disease is approximately one in 50,000 to 100,000 people globally.[2,3] Gaucher disease type 1 (GD1), the non-neuronopathic variant, is the most prevalent form of the disease, accounting for 95% of cases.[1,4]

Two pharmacotherapeutic modalities have been used to treat Gaucher disease: enzyme replacement therapy (ERT), which replaces the missing or defective lysosomal enzyme, and substrate reduction therapy, which aims to decrease the production of glucocerebroside rather than accelerating its elimination.[1] Eliglustat is a new substrate reduction therapy that inhibits glucosylceramide synthase, thereby reducing the synthesis of glucocerebroside.[5]

The indication for eliglustat is for the long-term treatment of adult patients with GD1 who are cytochrome P450 2D6 (CYP2D6) poor metabolizers, intermediate metabolizers, or extensive metabolizers, as determined by CYP2D6 genotype testing. The recommended dosage is 84 mg once daily, orally, in CYP2D6 poor metabolizers and 84 mg twice daily in intermediate and extensive metabolizers.[5] Eliglustat 84 mg is equivalent to eliglustat tartrate 100 mg.[5]

The objective of this report was to perform a systematic review of the beneficial and harmful effects of eliglustat 84 mg capsules for the long-term treatment of adults with GD1 who are CYP2D6 poor metabolizers, intermediate metabolizers, or extensive metabolizers.

Results and Interpretation

Included Studies

Two pivotal phase III trials met the inclusion criteria. The ENGAGE study was a randomized double-blind study evaluating the efficacy and safety of eliglustat versus placebo in patients with GD1 who were treatment-naive (N = 40). Patients were randomized 1:1 to 39 weeks of eliglustat tartrate (50 mg to 100 mg twice daily) or placebo treatment. The primary outcome was the percentage change in spleen volume from baseline to week 39. The patients enrolled had a mean age of 31.8 years, were predominantly white (98%), and had moderate to severe thrombocytopenia ([redacted]) and hepatosplenomegaly.

The ENCORE study was a randomized open-label study designed to assess if eliglustat was noninferior to imiglucerase in patients with GD1 who had been treated with ERT for at least three years and had reached therapeutic goals (N = 160). Patients were

randomized 2:1 to eliglustat tartrate (50 mg to 150 mg twice daily) or imiglucerase ([redacted]). The primary outcome was the proportion of patients who remained stable at 52 weeks, defined as the change from baseline in the following measures: hemoglobin level did not decrease > 15 g/L, platelet count did not decrease > 25%, spleen volume (in multiples of normal) did not increase > 25%, and liver volume (in multiples of normal) did not increase > 20%. Eliglustat was noninferior to imiglucerase if the lower bound of the 95% confidence interval (CI) for the difference in the percentage stable was within the 25% noninferiority margin based on the per-protocol set. Those enrolled had a mean age of 37.5 years and were white (92%), and 59% had previously been treated with ERT at a dose ≥ 35 U/kg every two weeks.

Efficacy

In treatment-naive patients in the ENGAGE study, eliglustat showed statistically significant reductions in spleen volume after 39 weeks of treatment compared with placebo (treatment difference in percentage change from baseline: −30%; 95% CI, −37% to −23%; *P* < 0.0001). Statistically significant differences between eliglustat and placebo were also detected in the percentage change from baseline in liver volume (−6.6%; 95% CI, −11.4% to −1.9%; *P* = 0.007) and platelet counts (41%; 95% CI, 24% to 58%; *P* < 0.0001), and in the absolute change from baseline in hemoglobin levels (12 g/L; 95% CI, 6 to 19; *P* = 0.0006) (Table 1).

Among treatment-experienced patients with well-controlled Gaucher disease, 85% of those who received eliglustat remained stable for 52 weeks compared with 94% of patients treated with imiglucerase, based on the per-protocol set of the ENCORE trial (absolute difference −8.8%; 95% CI, −17.6% to 4.2%). Eliglustat met the noninferiority criteria set by the manufacturer, as the lower limit of the 95% CI was within the predefined 25% noninferiority margin. This noninferiority threshold, however, was not supported by the literature, and was based on a theoretical difference between ERT and placebo.[6,7]

Eliglustat met the noninferiority criteria versus imiglucerase based on the percentage change in spleen volume (−2.8%; 95% CI, −8.1 to 2.5%, per-protocol set), as the upper limit of the 95% CI was less than the 15% noninferiority margin in ENCORE. No statistically significant differences were detected between eliglustat and imiglucerase in the percentage change in liver volume (−0.3%; 95% CI, −3.3% to 2.8%) or platelet count (2.8%; 95% CI, −3.0% to 8.5%) and no clinically important difference was observed in the absolute change from baseline in hemoglobin levels (−3 g/L; 95% CI, -6, -0.3). These outcomes in the ENCORE trial were considered exploratory by CADTH Common Drug Review (CDR) reviewers, as there was no attempt to control for family-wise type I error across the multiple outcomes tested.

Both the ENGAGE and ENCORE trials examined a number of surrogate and exploratory outcomes. Chitotriosidase levels were reduced by 44% in the eliglustat group relative to placebo in the ENGAGE study, and were similar at baseline and week 52 in both the eliglustat and imiglucerase groups in the ENCORE trial (descriptive data only). No data on CCL18 (chemokine C-C motif ligand 18) levels were reported due to quality control issues in the laboratory that performed the analyses for both trials.

Neither trial was designed and powered to detect differences in bone disease, which patient groups report as important to patients. No differences in bone mineral density were detected in either study based on T-scores or Z-scores of the spine or femur. However, the clinical expert consulted by CDR stated that the duration of the trials was insufficient to detect clinically important differences in bone disease. A reduction in the bone marrow burden score was observed for eliglustat versus placebo (least square mean difference −1.1; 95% CI, −1.7 to −0.4); however, the clinical importance of this difference is unclear. One patient in the placebo group and one in the imiglucerase group experienced a bone crisis during the 39-week ENGAGE study and the 52-week ENCORE study, respectively; no patients who received eliglustat reported a bone crisis. Both trials had an open-label extension period, where patients were treated with eliglustat for a median of 11 months (ENGAGE) and 41 months (ENCORE). In the ENCORE extension, two patients experienced a bone crisis.

The Gaucher disease severity scoring system, a measure of disease burden, was presented in both studies. No clinically important difference between eliglustat and placebo was observed after 39 weeks of treatment in the ENGAGE study, as the least square mean difference between groups (−0.3 points) did not exceed the minimal clinically important difference of 3.17 that has been reported in the literature. The Gaucher disease severity scoring system scores were reported for the ENCORE trial, but these data were missing values for [redacted] of patients and no between-group comparisons were estimated.

Quality of life was assessed using the Short Form (36) Health Survey (SF-36) as an exploratory outcome in both trials. In the ENGAGE study, no statistically significant differences were detected between eliglustat and placebo in the individual domain or

component scores, except for the physical functioning domain. Although the ENCORE study also reported data on SF-36, there were no between-group comparisons; thus, no conclusions can be made on the relative treatment effects. The Fatigue Severity Scale (FSS) was higher by 0.7 points for eliglustat versus placebo in the ENGAGE study, although the clinical importance of this difference is unclear. No statistically significant differences between groups were detected in any domain of the Brief Pain Inventory (BPI). In the ENCORE study, the FSS and BPI scores were similar within groups at baseline and week 52. No between-group comparisons were calculated. Neither trial was designed or powered to detect differences in SF-36, FSS, or BPI.

The key limitations of the ENGAGE trial were its small sample size (N = 40) and relatively short duration (nine months). No studies were found that compared eliglustat to imiglucerase in treatment-naive patients or that compared eliglustat to other drugs to treat Gaucher disease besides imiglucerase. These data would be of interest to clinicians and policy-makers to help define eliglustat's place in therapy. Although the key outcomes evaluated in ENCORE and ENGAGE (hemoglobin, platelets, and liver and spleen volume) are important intermediate outcomes and are part of the treatment goals for patients with Gaucher disease,[1] the studies did not address other important outcomes such as serious skeletal complications, risk of bleeding, and patient's functional status. In ENCORE, patients were switched from ERT to eliglustat; thus, some of the treatment effects observed in the eliglustat group may be attributable to potential carry-over effects of ERT.

In both studies, the dose of eliglustat was titrated based on the patients' trough serum levels in the first four weeks to eight weeks of treatment. The drug, however, was approved using a simplified dosage regimen based on CYP2D6 metabolizer status.[7] Of note, 15% of patients in the ENGAGE study and 68% of patients in the ENCORE trial did not receive an approved dosage regimen. Of these, 48% of patients in the ENCORE trial received a dose that was 50% higher than the Health Canada–recommended maximum daily dose.

Harms

Overall, 90% and 92% of patients who received eliglustat reported one or more adverse events in the ENGAGE and ENCORE trials, respectively, compared with 70% of patients who received placebo and 79% who received imiglucerase. In the ENGAGE trial, the most frequently reported adverse events in the eliglustat group were arthralgia (45%), headache (40%), nasopharyngitis (15%), and diarrhea (15%). In the eliglustat group of the ENCORE trial, arthralgia (15%), fatigue (14%), headache (13%), nausea (12%), diarrhea (12%), and back pain (12%) were most common.

In the ENCORE study, 11 patients (10%) in the eliglustat group and no patients in the imiglucerase group had a serious adverse event. Except for syncope, which occurred in two patients, all other specific events were reported in one patient with no clustering in a particular system organ class. Two eliglustat patients and one imiglucerase patient stopped treatment due to adverse events (2% per group). No serious adverse events were reported and no patients stopped treatment due to adverse events in the ENGAGE study. There were no deaths in either study.

[redacted] neoplasms were reported in the eliglustat group ([redacted]) in the ENCORE study. They included [redacted] neoplasms were reported in the imiglucerase group in the ENCORE study or in either group in the ENGAGE study.

Cardiac arrhythmias or syncope were observed in [redacted] eliglustat patients ([redacted]) and [redacted] imiglucerase patients in the ENCORE study, and [redacted] ([redacted]) in the placebo group and [redacted] in the eliglustat group in the ENGAGE study. Treatment-emergent peripheral neuropathy was reported in [redacted] patients ([redacted]) in the eliglustat group, compared with [redacted] in the imiglucerase group in ENCORE.

No new safety signals were identified in the ENGAGE and ENCORE extension studies (median treatment duration 11 months in ENGAGE and 41 months in ENCORE) or in two other supporting trials (i.e. the phase II Study 304 and phase III EDGE randomized controlled trials, which did not meet the inclusion criteria for this systematic review).

As eliglustat has the potential to prolong the PR, QTc, or QRS cardiac interval, which could result in cardiac arrhythmias, the product monograph includes warnings and contraindications regarding its concurrent use with drugs that could potentially interact with eliglustat, and in patients with pre-existing cardiovascular conditions.[5] Additional electrocardiogram (ECG) monitoring is recommended for specific patient populations at increased risk of having ECG abnormalities.[5]

Place in Therapy

This information is based on information provided in draft form by the clinical expert consulted by CDR reviewers for the purpose of this review.

ERT for Gaucher disease is effective at controlling common manifestations of the disease such as cytopenias, organomegaly, and progressive bone infiltration. ERT for Gaucher disease remains the most successful treatment for a lysosomal storage disorder currently available, but there are still some challenges in treating patients with Gaucher disease. ERT requires regular biweekly intravenous (IV) infusions. While the manufacturers of ERT support patients to receive these infusions in their home, this still remains an inconvenient and minimally invasive form of therapy. Severe allergic reactions to ERT for Gaucher disease are uncommon; however, there are a small number of patients with severe allergic reactions who either have to stop ERT or who have to take premedications such as hydrocortisone, which have their own adverse effects. While most patients receive their infusions through a peripheral IV line, some patients over time lose peripheral IV access and will require insertion of a central venous catheter with its attendant risks. Miglustat, the other oral substrate inhibitor for Gaucher disease, has an undesirable side-effect profile, which limits its use in many patients. An oral medication such as eliglustat may provide treatment that is more convenient for patients who tolerate ERT, would remove the need to insert a central venous catheter in the small number of adult patients who require this, and could potentially offer an alternative for patients who are unable to tolerate ERT or in whom premedications are required to prevent allergic reactions. Due to the psychological impact of regular venepuncture on children with Gaucher disease, it is more common to insert a central venous catheter for ERT infusions; therefore, effective and well-tolerated oral therapy would be even more of an advantage in children than in adults. There is a certain probability that eliglustat, because of its oral route of administration, could be considered for use in children with Gaucher disease; however, it is not indicated for patients under the age of 18.

ERT is not 100% effective and there are still some patients who continue to have disease progression despite treatment. There are some patients with rare and life-threatening manifestations of Gaucher disease (such as pulmonary hypertension) on whom the impact of ERT is unclear, due to limited data. There are some longer term complications of Gaucher disease for which the mechanisms have not been fully defined (such as the risk of developing malignancy or features of Parkinson disease). Finally, some patients with Gaucher disease present late with irreversible disease manifestations such as bone infarction for which ERT is of no benefit. There are no data available on the effects of eliglustat in any of these situations, which will therefore remain as unmet needs until more data are available for ERT, eliglustat, or both. Also, as ERT has been available for decades, there is information on its effects and limitations in patients with very severe Gaucher disease (both patients with GD1 and the other subtypes). Eliglustat is indicated only for GD1 and, as the pivotal study on eliglustat has been designed as a noninferiority trial in patients with mild to moderate Gaucher disease, the impact of eliglustat on patients with very severe GD1 manifestations is not well defined.

ERT for Gaucher disease is a therapy for which flexible dosages are possible and close patient monitoring allows the dose to be adjusted to minimum effective doses. As ERT for Gaucher disease has been available for decades, data on the efficacy of this dosage flexibility are widely available, and dose tapering can result in considerable cost savings while maintaining excellent patient outcomes. It is standard practice in the care of patients with Gaucher disease to use flexible dosage regimens. It is important, therefore, that any treatment alternatives, including eliglustat, show cost-effectiveness comparable to the flexible dosage practices of ERT.

ERT for Gaucher disease is currently prescribed for patients who have established manifestations of the disease and is not currently recommended for patients who do not have evidence of disease involvement. Guidelines from Ontario for the use of ERT are in the public domain[8] and most other provinces follow very similar guidelines. These guidelines include the currently available oral therapy, miglustat. The clinical trials of eliglustat involved two patient groups: patients who required treatment but were naive to ERT, and patients who had been stabilized on ERT and were then switched to eliglustat. In both cases, though, treatment for Gaucher disease was thought to be indicated by the referring physician. Therefore, it is not expected that the indications for treatment (or the number of patients eligible for treatment) will be altered by the emergence of a well-tolerated oral therapy but, rather, that eliglustat will be added to the list of products available to choose from. Patients being considered for therapy have to have a series of assessments that would be similar for patients being considered for ERT or either oral therapy. However, patients being considered for eliglustat would have to have some investigations that would not be required for ERT patients, including CYP2D6 genotype testing, assessment of concurrent medications for drug-drug interactions (i.e., moderate to strong CYP2D6 or CYP3A inhibitors), and baseline ECG assessment (with ECG monitoring during treatment as clinically indicated).

Other Considerations

CYP2D6 genotype testing is required in order to determine a patient's eligibility for treatment with eliglustat and to determine dosages.[5] In correspondence with CDR, the manufacturer has stated that they are [redacted].[9] The manufacturer expects the proportions of Canadian patients who are poor, intermediate, or extensive CYP2D6 metabolizers to be similar to those observed in the ENCORE trial (4%, 13%, and 77%, respectively). Based on ENCORE, approximately 6% of patients would be ultra-rapid or indeterminate metabolizers and therefore not suitable for treatment with eliglustat.

Although eliglustat is currently not approved for use in children, or in combination with ERT, there may be interest in expanding its use to include these populations. At present, there is no evidence available on the efficacy and safety of eliglustat in combination with ERT. In the pivotal ENGAGE and ENCORE trials, only two patients enrolled were less than 18 years of age.

Conclusions

In treatment-naive patients with GD1, eliglustat was associated with statistically significant decreases in liver and spleen volume, and increased hemoglobin and platelet levels compared with placebo.

In adults whose GD1 was well controlled with ERT, fewer patients who switched to eliglustat treatment met hematologic and organ volume disease stability criteria than those who remained on imiglucerase, though eliglustat met the noninferiority criteria versus imiglucerase. There is, however, some uncertainty in the noninferiority margin used in the analysis, and the possibility of carry-over effects among patients switched from ERT to eliglustat.

Efficacy data are lacking in patients with symptomatic bone disease, as these patients were excluded from the clinical trials. There is insufficient evidence from the pivotal ENGAGE and ENCORE randomized controlled trials to draw any conclusions regarding the impact of eliglustat on bone disease, due to lack of statistical power and insufficient follow-up time in the available trials. Neither trial was designed to detect differences in quality of life or symptoms of Gaucher disease.

Few patients stopped eliglustat treatment due to adverse events. Additional data are required to determine the safety of eliglustat in patients with cardiovascular disease, and to determine the risk of long-term adverse events.

Table 1: Summary of Efficacy Outcomes

Study / Treatment	N	Patients Stable for 52 Weeks, n (%)[a]		Absolute Difference in Percentage Stable (95% CI) for Eliglustat vs. Imiglucerase		*P* Value
ENCORE (PPS)						
Eliglustat	99	84 (85)		−8.8 % (-17.6% to 4.2%)		NR
Imiglucerase	47	44 (94)				
Study / Treatment	**N**	**Baseline Mean (SD)**	**End of Treatment, Mean (SD)**	**LS Mean % Change From Baseline to End of Treatment (SE)**	**Treatment Difference (%) (95% CI)[a]**	***P* Value**
Spleen volume (MN)						
ENGAGE			**Week 39**			
Eliglustat[b]	20	13.9 (5.9)	10.2 (5.1)	−27.8 (2.4)	−30.0 (−36.8 to −23.2)	< 0.0001
Placebo	20	12.5 (6.0)	12.8 (6.4)	2.3 (2.4)		
ENCORE (PPS)[c]			**Week 52**			
Eliglustat	70	3.2 (1.4)	3.1 (1.4)	−6.1 (1.6)	−2.8 (−8.1 to 2.5)	0.29[d]
Imiglucerase	39	2.6 (1.1)	2.5 (1.0)	−3.2 (2.1)		
Liver Volume (MN)						
ENGAGE			**Week 39**			
Eliglustat[b]	20	1.44 (0.35)	1.35 (0.28)	−5.2 (1.6)	−6.6 (−11.4 to −1.9)	0.007
Placebo	20	1.36 (0.28)	1.39 (0.31)	1.4 (1.6)		
ENCORE (FAS)[e,]			**Week 52**			
Eliglustat	106	0.94 (0.19)	0.96 (0.18)	2.3 (0.9)	−0.3 (−3.3 to 2.8)	0.86[d]
Imiglucerase	53	0.92 (0.16)	0.95 (0.16)	2.6 (1.3)		
Platelet Count (10^9/L)						
ENGAGE			**Week 39**			
Eliglustat[b]	20	75.1 (14.1)	99.0 (28.4)	32.0 (6.0)	41.1 (24.0 to 58.2)	< 0.0001
Placebo	20	78.5 (22.6)	71.5 (25.2)	−9.1 (6.0)		
ENCORE (FAS)[c]			**Week 52**			
Eliglustat	106	203.3 (79.3)	214.5 (83.3)	4.2 (1.7)	2.7 (−3.1 to 8.5)	0.36[d]
Imiglucerase	53	187.5 (56.8)	192.0 (61.9)	1.5 (2.4)		
Hgb (g/L)				**LS Mean Change From Baseline to End of Treatment (SE)**	**Treatment Difference (g/L) (95% CI)**	***P* Value**
ENGAGE			**Week 39**			
Eliglustat[b]	20	121 (18)	128 (16)	7 (2)	12 (6 to 19) [a]	0.0006
Placebo	20	128 (16)	122 (20)	−5 (2)		
ENCORE (FAS)			**Week 52**			
Eliglustat [c]	106	136 (13)	134 (13)	−2 (0.8)	−3.3 (−5.9 to −0.7)	0.013[d]
Imiglucerase	53	139 (13)	140 (14)	1 (1.1)		

CI = confidence interval; FAS = full analysis set; Hgb = hemoglobin; LOCF = last observation carried forward; LS = least square; MN = multiples of normal; NR = not reported; PPS = per-protocol set; SD = standard deviation; SE = standard error; vs. = versus.

[a] The analysis of covariance model includes treatment group, baseline value, and stratification factors (LOCF).

[b] LOCF was used for one patient who was missing data for week 39.

[c] One eliglustat patient who switched to imiglucerase, and all patients with total splenectomy, were excluded from the analysis.

[d] Outside the closed statistical testing procedure and at risk of inflated family-wise type I error.

Source: Clinical Study Report.[10,11]

Table 2: Summary of Harms

	ENGAGE (39 Weeks)		ENCORE (52 Weeks)	
	Eliglustat N = 20	**Placebo N = 20**	**Eliglustat N = 106**	**Imiglucerase N = 53**
Patients with ≥1 adverse events, n (%)	18 (90)	14 (70)	97 (92)	42 (79)
SAEs, n (%)	0	0	11 (10)	0
Deaths, n (%)	0	0	0	0
Discontinued treatment due to adverse events, n (%)	0	0	2 (2)	1 (2)
Notable adverse events, n (%)				
Clinically significant cardiac arrhythmia or syncope	[redacted]	[redacted]	[redacted]	[redacted]
Peripheral neuropathy	[redacted]	[redacted]	[redacted]	[redacted]
Abnormal nerve conduction study	[redacted]	[redacted]	[redacted]	[redacted]
Neoplasm	[redacted]	[redacted]	[redacted]	[redacted]

NR = not reported; SAE = serious adverse event.

Source: Clinical Study Report: CSR.[10,11]

Introduction

Disease Prevalence and Incidence

Gaucher disease is an autosomal, recessive lysosomal storage disease that results from deficiency of the lysosomal enzyme glucocerebrosidase.[1] Consequently, the enzyme's substrate, glucocerebroside, accumulates in macrophages of the reticuloendothelial system, particularly those in the spleen, liver, bone marrow, skeleton, and lung. This leads to multiple manifestations, including anemia, thrombocytopenia, hepatosplenomegaly, growth retardation in children, skeletal disease, and increased rate of malignancies.

Gaucher disease is classified into three subtypes based on the presence and nature of central nervous system involvement.[1] The most prevalent form, accounting for 95% of cases, is the non-neuronopathic (type 1) variant, which lacks primary involvement of the central nervous system characteristic of the type 2 (acute neuronopathic) and type 3 (chronic neuronopathic) variants.[1,4] However, Gaucher disease type 1 (GD1) patients may present with peripheral neuropathy. Clinical manifestations and time of onset are very heterogeneous among patients as some patients may be asymptomatic or show very mild symptoms.[1] An onset of symptoms during childhood suggests a more rapidly progressing disease.[4] Skeletal manifestations of Gaucher disease have a greater impact on quality of life than hematological and visceral abnormalities. Accumulation of glucocerebroside in bone marrow is associated with osteopenia, lytic lesions, pathological fractures, chronic bone pain, acute episodes of bone crisis (i.e., severe pain), bone infarcts, osteonecrosis, skeletal deformities, and delayed growth in childhood and adolescence.[1]

The prevalence of Gaucher disease is approximately one in 50,000 to 100,000 people globally.[2,3] Of the 3,337 patients entered in the International Collaboration Gaucher Group (ICGG) Gaucher Registry by the end of 2003, 4% were Canadians.[12] The frequency of GD1 ranges from one in 20,000 to one in 200,000 in the general population, reaching one in 400 to one in 600 among Ashkenazi Jews.[4,13]

Gaucher disease is diagnosed with reduced glucocerebrosidase activity in peripheral leukocytes and targeted genetic analysis. The variables providing the best indication of the severity of disease are the age of onset, platelet count, hemoglobin concentration, the size of the spleen and/or liver relative to total body mass, and the amount of bone marrow replacement by storage cells.[8] According to the clinical expert consulted for this review, bone crises and pulmonary involvement are also an indicator of a severe disease.

Standards of Therapy

The general treatment goal in Gaucher disease patients with moderate to severe clinical symptoms of the disease is to achieve a state of equilibrium such that degradatory activity within the endosomal and lysosomal system can maintain homeostasis and prevent the accumulation of glucocerebroside.[14] Two pharmacotherapeutic modalities have been used to achieve this target in Gaucher disease: enzyme replacement therapy (ERT), which replaces the missing or defective lysosomal enzyme, and substrate reduction therapy (SRT), which aims to decrease the production of glucocerebroside rather than accelerate its elimination (Table 3).[1] Because the systemic manifestations of GD1 respond well to ERT with human beta-glucocerebrosidase, this type of therapy has been used as a first-line treatment for more than two decades.[15] Three ERTs are available in Canada: imiglucerase (Cerezyme), velaglucerase alfa (VPRIV) and taliglucerase alfa (Elelyso).[16-18]

ERT is administered by intravenous (IV) infusion. The indicated initial treatment regimen with ERT varies from 2.5 U/kg three times a week to 60 U/kg biweekly,[16-18] which aligns with the Ontario guidelines.[8] Dosages may be individualized to each patient based on the severity of the disease.[8] According to the clinical expert involved in this review, doses below the product monograph dose of 60 U/kg biweekly are commonly used in Canada. For example, in one jurisdiction, the average dosage for imiglucerase and velaglucerase was 30 U/kg every two weeks with a range of 20 U/kg to 40 U/kg for velaglucerase and a range of 19 U/kg to 43 U/kg for imiglucerase (BC Ministry of Health, Medical Beneficiary and Pharmaceutical Services Division, New Westminster, BC: personal communication, 2017 May).

Because of the wide clinical variability in the severity of symptoms and the course of the disease, the magnitude and time course of responses to ERT are variable.[1,19] Hemoglobin levels respond most rapidly (50% improvement in four months to six months), followed by platelet count (five months to 18 months), decrease in spleen size (27 months to 54 months) and decrease in liver size (24 months to 90 months).[20] Gaucher disease patients identified bone pain and bone crises as their major concerns. While the severity, frequency, and duration of painful bone crises may be reduced within the first year of ERT, long-term treatment over three years to four years is required to improve marrow composition and bone mass.[1, 21-23]

Besides eliglustat, one other SRT is available in Canada. Miglustat (Zavesca) is an oral competitive reversible inhibitor of glucosylceramide synthase.[24] It is indicated for the treatment of adults with mild to moderate GD1 for whom ERT is not a therapeutic option (e.g., due to allergy, hypersensitivity, or poor venous access)[24] or can be used by patient choice.[8] Use of miglustat is limited by the frequency of adverse events, particularly gastrointestinal adverse effects, which are thought to be due to inhibition of intestinal disaccharidases in the gastrointestinal tract leading to reduced absorption of dietary disaccharides in the small intestine.[24] Miglustat is reserved for second-line therapy for Gaucher disease.[8]

ERT or SRT may be supplemented by treatment with analgesics, anti-inflammatory drugs, bisphosphonates, or other medications for specific complications of the disease.[8]

Drug

Eliglustat is an inhibitor of glucosylceramide synthase, which reduces the synthesis of glucocerebroside.[5] The goal of SRT is to reduce the rate of synthesis of glucocerebroside to match its impaired rate of catabolism in patients with Gaucher disease, thereby reducing substrate accumulation.

The indication for eliglustat is for the long-term treatment of adult patients with GD1 who are cytochrome P450 2D6 (CYP2D6) poor metabolizers, intermediate metabolizers, or extensive metabolizers, as determined by CYP2D6 genotype testing. The recommended dosage is 84 mg once daily, orally, in CYP2D6 poor metabolizers and 84 mg twice daily in intermediate and extensive metabolizers.[5]

Table 3: Key Characteristics of Drugs for Gaucher Disease Type 1

	SRT		ERT		
	Eliglustat	**Miglustat**	**Imiglucerase**	**Velaglucerase Alfa**	**Taliglucerase Alfa**
Mechanism of Action	Glucosylceramide synthase inhibitor	Glucosylceramide synthase inhibitor	Replacement of beta-glucocerebrosidase in monocyte/macrophages-derived cells		
Indication[a]	Long-term treatment of adult patients with GD1 who are CYP2D6 poor metabolizers, intermediate metabolizers, or extensive metabolizers[b]	Treatment of adult patients with mild to moderate GD1for whom ERT is not a therapeutic option (e.g., due to constraints such as allergy, hypersensitivity, or poor venous access)	Long-term ERT in patients with a confirmed diagnosis of non-neuropathic (type 1) or chronic neuropathic (type 3) GD who exhibit non-neurological manifestations of the disease	Long-term ERT for pediatric and adult patients with GD1	Long-term ERT for adults and children (2 years to 17 years old) with a confirmed diagnosis of GD1 and for hematological manifestations in pediatric patients with a confirmed diagnosis of type 3 GD
Route of Administration	oral		IV infusion		
Recommended Dose	84 mg once daily in poor metabolizers; 84 mg twice daily in intermediate	100 mg three times daily	From 2.5 U/kg three times a week up to 60 U/kg every two weeks as initial	60 U/kg administered every other week (dosage adjustments can	From 30 U/kg to 60 U/kg every two weeks as an initial dosage

	SRT		ERT		
	Eliglustat	Miglustat	Imiglucerase	Velaglucerase Alfa	Taliglucerase Alfa
	and extensive metabolizers		dosage	be made)	
Serious Side Effects / Safety Issues	Caution in patients with pre-existing cardiac conditions due to risk of ECG changes; numerous drug interactions (see Appendix 8)	Gastrointestinal adverse effects common (85%), weight loss, neurologic adverse events (e.g., tremor, paresthesia)	Infusion-related reaction, hypersensitivity (including anaphylaxis), development of anti-drug antibodies	Infusion-related reaction, hypersensitivity (including anaphylaxis), development of anti-drug antibodies	Infusion-related reaction, hypersensitivity (including anaphylaxis), development of anti-drug antibodies

CDR = CADTH Common Drug Review; CYP2D6 = cytochrome P450 2D6; ECG = electrocardiogram; ERT = enzyme replacement therapy; GD = Gaucher disease; GD1 = Gaucher disease type 1; IV = intravenous; SRT = substrate reduction therapy.

[a] Health Canada indication.

[b] The manufacturer responded to questions from CDR that it has committed to making CYP2D6 genotype testing available and funding these costs for patients with Gaucher disease in Canada.[9]

Source: Product monographs.[5,16-18,24]

Objectives and Methods

Objectives

To perform a systematic review of the beneficial and harmful effects of eliglustat 84 mg capsules for the long-term treatment of adults with GD1 who are CYP2D6 poor metabolizers, intermediate metabolizers, or extensive metabolizers.

Methods

All manufacturer-provided trials considered pivotal by Health Canada were included in the systematic review. Phase III studies were selected for inclusion based on the selection criteria presented in Table 4.

Table 4: Inclusion Criteria for the Systematic Review

Patient Population	Adults with GD1 who are CYP2D6 poor metabolizers, intermediate metabolizers, or extensive metabolizers Subgroup: • Prior therapy for Gaucher disease
Intervention	Eliglustat 84 mg once or twice daily
Comparators	• ERT (taliglucerase alfa, velaglucerase alfa, imiglucerase) • Substrate inhibition therapy (miglustat) • Placebo Alone or in combination with supportive care
Outcomes	**Key efficacy outcomes:** • Days of work (or school) missed[a] • Number of hospitalizations • Need for surgical intervention • Improvement of hematological parameters (hemoglobin concentration, platelet count) • Reduction in liver and spleen size[a] • Incidence of bone crises[a] **Other efficacy outcomes:** • Health-related quality of life[a] • Symptoms (e.g., bone pain, fatigue)[a] • Disease severity (e.g., DS3) • Bone disease markers (e.g., BMD, bone marrow burden score) • Biomarkers (e.g., CCL18, chitotriosidase) **Harms outcomes:** • AEs • SAEs • WDAEs • Mortality Notable harms: arrhythmia, syncope, peripheral neuropathy, malignancy
Study Design	Published and unpublished phase III RCTs

AE = adverse event; BMD = bone mineral density; CCL18 = chemokine C-C motif ligand 18; CDR = CADTH Common Drug Review; CYP2D6 = cytochrome P450 2D6; DS3 = Gaucher disease severity scoring system; ERT = enzyme replacement therapy; GD1 = Gaucher disease type 1; RCT = randomized controlled trial; SAE = serious adverse event; WDAE = withdrawal due to adverse event.

[a] These outcomes were identified as being of particular importance to patients in the input received by CDR from patient groups.

The literature search was performed by an information specialist using a peer-reviewed search strategy.

Published literature was identified by searching the following bibliographic databases: MEDLINE (1946–), with in-process records and daily updates via Ovid; Embase (1974–) via Ovid; and PubMed. The search strategy consisted of both controlled vocabulary,

such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concept was Cerdelga (eliglustat).

No methodological filters were applied to limit retrieval. Where possible, retrieval was limited to the human population. Retrieval was not limited by publication year or by language. Conference abstracts were excluded from the search results. See Appendix 2 for the detailed search strategies.

The initial search was completed on February 17, 2017. Regular alerts were established to update the search until the meeting of the CADTH Canadian Drug Expert Committee on June 21, 2017. Regular search updates were performed on databases that do not provide alert services.

Grey literature (literature that is not commercially published) was identified by searching relevant websites from the following sections of the *Grey Matters* checklist (https://www.cadth.ca/grey-matters):

- Health Technology Assessment Agencies
- Health Economics
- Clinical Practice Guidelines
- Drug and Device Regulatory Approvals
- Advisories and Warnings
- Drug Class Reviews
- Databases (free)
- Internet Search

Google and other Internet search engines were used to search for additional Web-based materials. These searches were supplemented by reviewing the bibliographies of key papers and through contacts with appropriate experts. In addition, the manufacturer of the drug was contacted for information regarding unpublished studies.

Two CADTH Common Drug Review (CDR) clinical reviewers independently selected studies for inclusion in the review based on titles and abstracts, according to the predetermined protocol. Full-text articles of all citations considered potentially relevant by at least one reviewer were acquired. Reviewers independently made the final selection of studies to be included in the review, and differences were resolved through discussion. Included studies are presented in Table 5; excluded studies (with reasons) are presented in Appendix 3.

Results

Findings From the Literature

A total of 68 studies were identified from the literature for inclusion in the systematic review (Figure 1). The included studies are summarized in Table 5 and described in the “Included Studies” section of this report. A list of excluded studies is presented in Appendix 3.

Figure 1: Flow Diagram for Inclusion and Exclusion of Studies

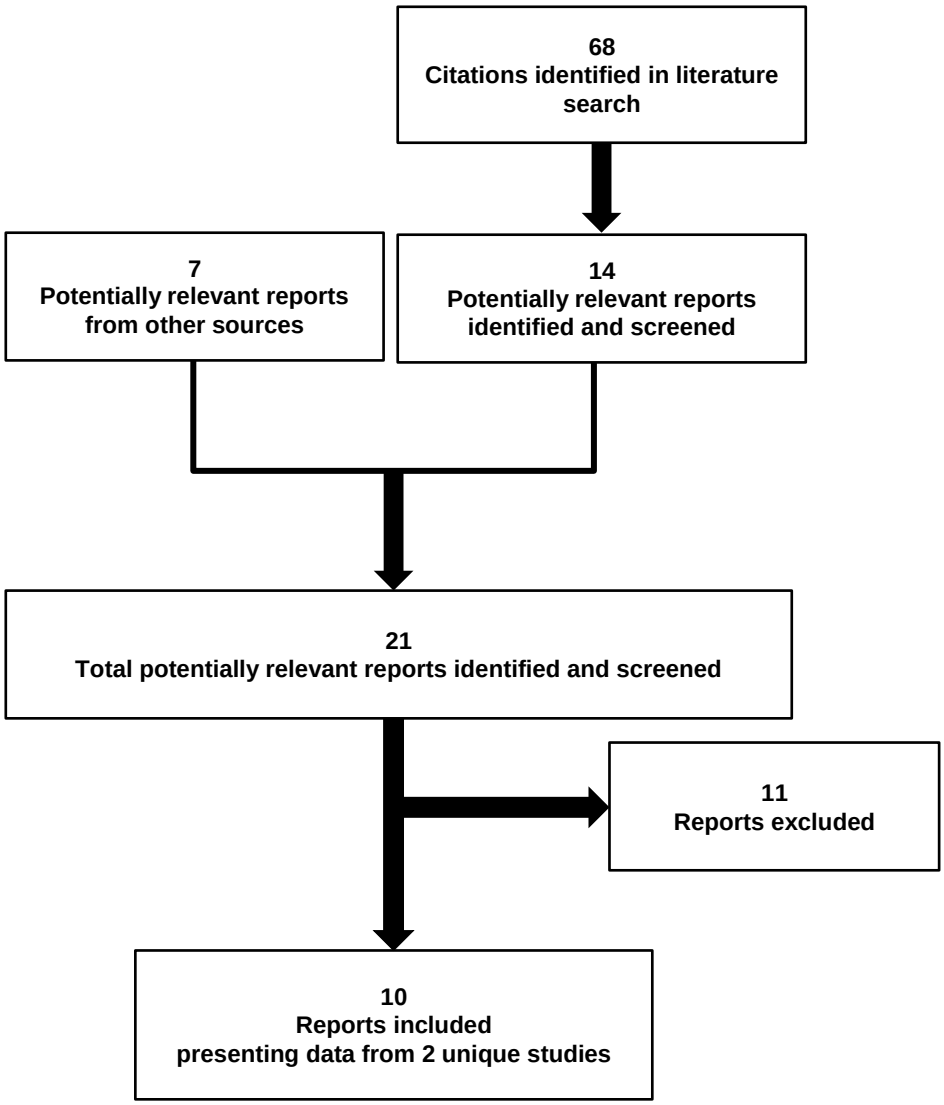


Table 5: Details of Included Studies

		ENGAGE	ENCORE
	Study Design	DB RCT	OL RCT, noninferiority study
	Locations	US, Canada, Latin America, Middle East and Northern Africa, India, Europe	Latin America, US, Canada, Australia, Middle East, Europe, Russia
	Randomized (N)	40	160

	Inclusion Criteria	• Age ≥ 16 years with confirmed GD1
		• Symptoms of Gaucher disease during screening including:
		  ○ Hgb 80 g/L to 110 g/L (females) or 80 g/L to 120 g/L (males), and/or platelet count of 50,000/mm^3 to 130,000/mm^3 (mean of 2 measures)
		  ○ splenomegaly (6 MN to 30 MN)
		  ○ if hepatomegaly present, liver volume < 2.5 MN
		• No treatment with SRT within 6 months or ERT within 9 months
		• Tanner Stage ≥ 4
			• Age ≥ 18 years with confirmed GD1
			• Received ERT for 3 years or more (total monthly dose of 30 U/kg to 130 U/kg for 6 months of the last 9 months)
			• Reached Gaucher disease therapeutic goals prior to randomization defined as:
			  ○ no bone crisis and free of symptomatic bone disease such as bone pain or fractures in the last year
			  ○ mean Hgb ≥ 110 g/L (females) or 120 g/L (males)
			  ○ mean platelet count of ≥ 100,000/mm$^{3.}$
			• Spleen volume < 10 MN
			• Liver volume < 1.5 MN
			• Tanner Stage ≥ 4

	Exclusion Criteria	• History of splenectomy, neurologic involvement, or pulmonary involvement related to Gaucher disease • Current symptomatic bone disease or bone crises within the past 12 months • Transfusion-dependent • Anemia from another cause that was not treated or stabilized within past 3 months • Prior esophageal varices or liver infarction • Elevated liver enzymes (> 2 ULN) unless patient had Gilbert syndrome • Treated within past 30 days with drugs that alter the metabolism of eliglustat, or prolong QT interval	• Received SRT in past 6 months • Partial or total splenectomy in past 3 years • History of clinically significant coronary artery disease including MI, ongoing coronary ischemia or heart failure, arrhythmia or conduction defect (second or third degree AV block, complete bundle branch block, prolonged QTc interval or sustained ventricular tachycardia) • Evidence of neurologic or pulmonary involvement related to Gaucher disease • Transfusion-dependent • Prior esophageal varices or liver infarction • Elevated liver enzymes (> 2 ULN) unless patient had Gilbert syndrome • Treated within past 30 days with drugs that alter the metabolism of eliglustat, or prolong QT interval • Any other clinically significant disease
DRUGS	**Intervention**	Eliglustat 50 mg or 100 mg twice daily (individualized dose based on plasma levels)	Eliglustat 50 mg to 150 mg twice daily (individualized dose based on plasma levels)
DRUGS	**Comparator(s)**	Placebo	Imiglucerase IV twice weekly at patients' pre-trial dose
DURATION	**Phase**	III	III
DURATION	Randomized period (DB or OL)	39 weeks	52 weeks
DURATION	Extension	Up to 6 years	Up to 5.5 years
DURATION	Follow-up	30 days to 37 days	30 days to 37 days
OUT	**Primary End Point**	Change from baseline to 39 weeks in spleen volume	Percentage of patients with stable hematological variables and organ volumes after 52 weeks

		ENGAGE	ENCORE
	Other End Points	• Hemoglobin level • Liver volume • Platelet count • BMD • Bone marrow burden score • Mobility, bone crises, bone pain • SF-36 • BPI • FSS • DS3 • Biomarkers • % reaching therapeutic goals • Harms	• Hemoglobin level • Platelet count • Spleen and liver volume • BMD • Bone marrow burden score • Mobility, bone crises, bone pain • SF-36 • BPI • FSS • DS3 • Treatment preference (oral vs. IV) • Biomarkers • Harms
NOTES	**Publications**	Mistry 2015[25]	Cox 2015,[26] Pleat 2016[27]

AV = atrioventricular; BMD = bone mineral density; BPI = Brief Pain Inventory; CSR = Clinical Study Report; DB = double blind; DS3 = Gaucher disease severity scoring system; ERT = enzyme replacement therapy; FSS = Fatigue Severity Scale; GD1 = Gaucher disease type 1; IV = intravenous; MI = myocardial infarction; MN = multiples of normal; OL = open label; RCT = randomized controlled trial; SF-36 = Short Form (36) Health Survey; SRT = substrate reduction therapy; ULN = upper limit of normal; vs. = versus.

Note: Five additional reports were included (FDA,[6,28] manufacturer's submission,[29] supplementary CSRs[30,31]).

Source: CSR.[10,11]

Included Studies

Description of Studies

The ENGAGE study was a randomized double-blind study evaluating the efficacy and safety of eliglustat versus placebo in patients with GD1 who were treatment-naive. Patients were randomized 1:1 to eliglustat (50 mg to 100 mg twice daily) or placebo, stratified by baseline spleen volume (≤ 20 multiples of normal [MN] or > 20 MN). Patients were allocated to treatment using an interactive voice-response or Web-response system. The trial used an identical placebo and double-dummy design to conceal the treatments and dosages received. The primary outcome was the percentage change from baseline in spleen volume to week 39.

The ENCORE study was a randomized open-label study designed to assess if eliglustat was noninferior to imiglucerase in patients with GD1 who had been treated with ERT for at least three years and had reached therapeutic goals. Patients were randomized 2:1 to eliglustat (50 mg to 150 mg twice daily) or imiglucerase (same as previous dose), stratified by ERT dose (< 35 U/kg or ≥ 35 U/kg IV every two weeks). The allocation sequence was generated centrally by the manufacturer (block size of six) and patients were assigned to treatment by the central clinical research pharmacy after receiving a request for randomization from the site physician.[26, 32] The primary outcome was the proportion of patients that remained stable in terms of a composite outcome including hemoglobin and platelet levels, and spleen and liver volumes, at 52 weeks.

After completion of the 39-week double-blind period in the ENGAGE study and the 52-week primary analysis period in the ENCORE study, all patients were eligible to enter the long-term treatment period and receive open-label eliglustat for up to six years.

Populations

Inclusion and Exclusion Criteria

The ENGAGE trial enrolled patients with GD1 who had hematologic and visceral symptoms of Gaucher disease and who were treatment-naive (defined as no treatment with SRT within six months, or ERT within nine months) (Table 5). In the ENCORE study, patients with GD1 were enrolled if they had received ERT for three years or more (total monthly dose of 30 U/kg to 130 U/kg for six months of the last nine months) and had reached therapeutic goals. In both trials, Gaucher disease was confirmed by documented deficiency of acid beta-glucosidase activity by enzyme assay.

Both trials excluded patients with symptomatic bone disease, or bone crises in the past year, and any neurologic or pulmonary involvement related to Gaucher disease. The ENGAGE trial excluded all patients with a splenectomy, whereas the ENCORE trial excluded those who underwent a total or partial splenectomy in the past three years. The ENCORE trial also excluded patients with clinically significant coronary artery disease, including prior myocardial infarction, ongoing coronary ischemia or heart failure, arrhythmia, or conduction defect (second-degree or third-degree atrioventricular block, complete bundle branch block, prolonged QTc interval, or sustained ventricular tachycardia). In addition, restrictions and exclusions were applied for patients receiving treatment with drugs that may interact with eliglustat. These drugs are discussed in the "Intervention" section of this report and in Appendix 8.

Baseline Characteristics

The patients enrolled in the ENGAGE trial were younger at the start of the trial (mean age 31.8 years) and had Gaucher disease symptom onset at an older age (mean 16.0 years) compared with the ENCORE trial (mean study age 37.6 years; symptom onset age 13.5 years) (Table 6). Patients in the ENGAGE trial also showed higher liver and spleen volumes at baseline, and had lower hemoglobin and platelet counts compared with those in the ENCORE trial, which was to be expected given the inclusion criteria of the two studies. In both trials, the patients enrolled were predominantly white (ranging from 91% to 100% across treatment groups) and were extensive CYP2D6 metabolizers (72% to 90%).

The patients' baseline characteristics were generally balanced between groups in the ENCORE trial, although there were more patients in the eliglustat group who had undergone a splenectomy than in the imiglucerase group (28% versus 17%). A number of imbalances were noted between groups in the ENGAGE study, including the percentage of males (eliglustat 40%, placebo 60%). More patients in the eliglustat group had severe splenomegaly (> 15 MN) (40% versus 25%) and moderate hepatomegaly (> 1.25 to ≤ 2.5 MN) (70% versus 55%) compared with the placebo group. Moderate or severe anemia at baseline was present in three eliglustat patients (15%) and one placebo patient (10%). Three patients in the eliglustat group and one patient in the placebo group were judged by the investigator as having moderate or severe bone disease. No further details were provided on the investigator's classification of bone disease, even though patients with current symptomatic bone disease were excluded from the study. Considering the limited sample size in the ENGAGE study (20 patients per group), some baseline imbalances between groups was not unexpected.

Table 6: Summary of Baseline Characteristics

	ENGAGE		ENCORE (FAS)		ENCORE (PPS)	
	Eliglustat N = 20	Placebo N = 20	Eliglustat N = 106	Imiglucerase N = 53	Eliglustat N = 99	Imiglucerase N = 47
Age, years, mean (SD)	31.6 (11.6)[a]	32.1 (11.3)[a]	37.6 (14.2)	37.5 (14.9)	37.2 (14.0)	38.6 (15.2)
Male, n (%)	8 (40)	12 (60)	47 (44)	25 (47)	43 (43)	21 (45)
Caucasian, n (%)	19 (95)	20 (100)	98 (92)	48 (91)	91 (92)	45 (96)
Jewish descent, n (%)	3 (15)	8 (40)	29 (27)	14 (26)	25 (25)	13 (28)
Body weight (kg)						
Mean (SD)	64.8 (11.7)	68.6 (17.2)	70.8 (16.8)	67.8 (14.4)	70.8 (17.3)	67.5 (15.0)
Median (range)	67.4 (40.0 to 81.7)	64.8 (46.0 to 102.2)	69.0 (43.1 to 136.0)	65.4 (40.6 to 101.1)	68.9 (43.1 to 136.0)	65.0 (40.6 to 101.1)
Spleen volume (MN), mean (SD)	13.9 (5.9)	12.5 (6.0)	3.2 (1.3)	2.7 (1.2)	3.2 (1.4)	2.6 (1.1)

	ENGAGE		ENCORE (FAS)		ENCORE (PPS)	
	Eliglustat N = 20	Placebo N = 20	Eliglustat N = 106	Imiglucerase N = 53	Eliglustat N = 99	Imiglucerase N = 47
Liver volume (MN), mean (SD)	1.4 (0.4)	1.4 (0.3)	0.9 (0.2)	0.9 (0.2)	0.9 (0.2)	0.9 (0.2)
Hemoglobin (g/L), mean (SD)	121 (18)	128 (16)	136 (13)	139 (13)	136 (12)	138 (12)
Platelet count (10^9/L), mean (SD)	75.1 (14.1)	78.5 (22.6)	203.3 (79.3)	187.5 (56.8)	206.8 (80.7)	192.3 (57.3)
Splenectomy performed, n (%)						
No	20 (100)[b]	20 (100)[b]	76 (72)	44 (83)	70 (71)	38 (81)
Partial	0	0	1 (1)	1 (2)	1 (1)	1 (2)
Total	0	0	29 (27)	8 (15)	28 (28)	8 (17)
Age at Gaucher symptom onset, years, mean (SD)	16.7 (10.5)	15.2 (12.4)	12.7 (12.0)	15.7 (14.2)	12.3 (11.8)	15.9 (14.2)
Age at Gaucher diagnosis, years, mean (SD)	22.3 (9.6)	20.1 (13.2)	17.8 (13.6)	20.3 (14.3)	17.1 (13.1)	20.8 (14.5)
CYP2D6 status, n (%)						
Poor	0	0	4 (4)	2 (4)	4 (4)	2 (4)
Intermediate	1 (5)	2 (10)	12 (11)	9 (17)	10 (10)	8 (17)
Extensive	18 (90)	18 (90)	84 (79)	38 (72)	79 (80)	33 (70)
Ultra-rapid	1 (5)	0	4 (4)	1 (2)	4 (4)	1 (2)
Indeterminate	0	0	0	2 (4)	0	2 (4)
Randomization stratification groups						
ERT < 35 U/kg every 2 weeks	NA	NA	43 (41)	22 (42)	38 (38)	18 (38)
ERT ≥ 35 U/kg every 2 weeks	NA	NA	63 (59)	31 (58)	61 (62)	29 (62)
Low spleen severity (≤ 20 MN)	16 (80)	17 (85)	NA	NA	NA	NA
High spleen severity (> 20 MN)	4 (20)	3 (15)	NA	NA	NA	NA

CYP2D6 = cytochrome P450 2D6; ERT = enzyme replacement therapy; FAS = full analysis set; MN = multiples of normal; NA = not applicable; PPS = per-protocol set; SD = standard deviation.

[a] One patient in each group was < 18 years of age.

[b] Patients with a total or partial splenectomy were excluded from the ENGAGE study.

Source: Clinical Study Report.[10,11]

In the ENGAGE trial, two eliglustat patients and three placebo patients had received prior ERT therapy, and four of these five patients had received prior miglustat. As per the inclusion criteria, all patients had discontinued ERT for at least nine months and stopped SRT at least six months prior to enrolment.

In the ENCORE study, all patients were treated with ERT for an average of 10 years (Table 7). In the full analysis set (FAS), 21% and 15% in the eliglustat and imiglucerase groups, respectively, were treated with velaglucerase: all others were on imiglucerase. At baseline, the median ERT dose was [redacted] in the eliglustat group and [redacted] in the imiglucerase group. [redacted]. The manufacturer stated that patients randomized to imiglucerase received the ERT dose they were on prior to any unanticipated changes related to the shortage.[33]

Table 7: Summary of Prior ERT

	ENCORE (FAS)		ENCORE (PPS)	
	Eliglustat N = 106	**Imiglucerase N = 53**	**Eliglustat N = 99**	**Imiglucerase N = 47**
Years on imiglucerase, median (range)	9.8 (4.0) N = 73	10.0 (3.6) N = 34	10.8 (3.1 to 18.2) N = 67	10.8 (3.2 to 17.1) N = 28
ERT prior to enrolment, n (%)				
Imiglucerase	80 (75)	44 (83)	76 (77)	38 (81)
Velaglucerase	22 (21)	8 (15)	20 (20)	8 (17)
ERT dose (U/kg/month) prior to enrolment[a]				
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Median (range)	[redacted]	[redacted]	[redacted]	[redacted]
Unanticipated treatment interruption, dose reduction, or regimen change of ERT (starting June 2009), n (%)	[redacted]	[redacted]	[redacted]	[redacted]

ERT = enzyme replacement therapy; FAS = full analysis set; PPS = per-protocol set; SD = standard deviation.

[a] Dosage data missing for 5 and 1 patients in the FAS and 4 and 1 in the PPS, for eliglustat and imiglucerase, respectively.

Source: Clinical Study Report.[10]

Interventions

In the ENGAGE and ENCORE studies, patients randomized to eliglustat had their dose titrated based on their trough serum levels over the first four weeks to eight weeks. In the ENGAGE study, the dose of eliglustat was 50 mg once daily on day 1, then 50 mg twice daily from day 2 to week 4. For week 5 to 39, the dosage was increased to 100 mg twice daily in patients with a trough serum level < 5 ng/mL: otherwise, patients remained on the 50 mg twice-daily dosage. Eliglustat was administered as 50 mg or 100 mg capsules of eliglustat tartrate, with 100 mg equivalent to 84 mg of eliglustat base. A double-dummy placebo control was used to maintain blinding to the treatment and dosage received.

In the ENCORE trial, the initial dosage of eliglustat was 50 mg twice daily, and it was increased to 100 mg twice daily at week 4, or 150 mg twice daily at week 8 if the patient's trough eliglustat serum levels were < 5 ng/mL. Patients with trough levels ≥ 5 ng/mL remained on the same dose. Patients randomized to imiglucerase continued with their previous ERT dose-administered IV every two weeks for 52 weeks[redacted].[34] Patients on velaglucerase prior to randomization were switched to equivalent imiglucerase doses. Patients in the eliglustat group who showed a decline in Gaucher disease could be switched to ERT. The criteria for switching to ERT were as follows:

- hemoglobin level < 80 g/L, confirmed with repeated testing within two weeks
- platelet count < 45,000/mm^3 (confirmed with repeated testing within two weeks) or clinically significant bleeding episode that was 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.

Patients who switched from eliglustat to ERT continued to be followed in the study until their disease returned to baseline values (e.g., platelet count, spleen volume) or there was no additional occurrence or further worsening of measures causing the decline. Patients were then discontinued from the study, based on the decision of the sponsor and in consultation with the investigator.

The ENGAGE and ENCORE studies excluded patients who were taking medications within the past 30 days that could interact with eliglustat (i.e., inducers or strong inhibitors of CYP3A4, and strong inhibitors of CYP2D6) or drugs that may cause QTc interval prolongation. An exception was made to allow enrolment of pre-existing chronic users of strong inhibitors of either CYP3A4 or CYP2D6 (not both), if the patient was not a CYP2D6 poor or indeterminate metabolizer. Chronic users of these interacting medications continued with the same dosage regimen during the study. Short-term use of interacting medications was allowed during the trial if the patient interrupted the study drug while taking the other medication. In the ENCORE trial, an exception was

made to allow administration of medications that may alter CYP2D6 or CYP3A4 metabolism if they were used as premedications prior to ERT infusions.

In the ENCORE trial, 7% and 8% in the eliglustat and imiglucerase groups, respectively, were taking bisphosphonates. One patient in the ENGAGE study (placebo group) had taken bisphosphonates but had discontinued therapy prior to enrolment. Other medications used concomitantly by patients in the ENGAGE and ENCORE studies included aniline analgesics, nonsteroidal anti-inflammatory agents, corticosteroids, and nutritional supplements.

Outcomes

In the ENGAGE study, the primary outcome was the percentage change in spleen volume in MN from baseline to week 39. Secondary outcomes were the absolute change in hemoglobin level (g/L), percentage change in liver volume (in MN), and percentage change in platelet count (in mm^3) (baseline to week 39). Exploratory outcomes included the change from baseline in health-related quality of life (Short Form [36] Health Survey, known as SF-36) and symptom score (Brief Pain Inventory [BPI] and Fatigue Severity Scale [FFS]), bone mineral density (BMD), bone marrow burden, and bone crises.

Hemoglobin and platelet counts were evaluated at baseline, week 4, week 13, week 26, and week 39 of the double-blind period. Samples were analyzed by the local laboratory, and baseline and week 39 results were the average of two samples taken 24 hours apart. Liver and spleen volumes were assessed using magnetic resonance imaging (MRI) at baseline, week 26 and 39 (week 26 and week 39 scans were read by two readers and the results averaged). The following calculations were used to determine the organ MN: spleen MN = volume in cc/(weight in kg x 2); liver MN = volume in cc/(weight in kg x 25). Patients whose liver or spleen volume increased by > 30% had their MRI repeated within four weeks. All imaging data were read by central readers who were blinded to patient, treatment, and time point. Bone markers were evaluated at baseline and week 39 (X-ray, MRI, and dual energy X-ray absorptiometry of the femur and spine). SF-36, FSS, and BPI were completed at baseline, week 26, and week 39.

In the ENCORE study, the primary outcome was the proportion of patients who remained stable for 52 weeks, according to the following criteria:

- hemoglobin level did not decrease > 15 g/L from baseline
- platelet count did not decrease > 25% from baseline
- spleen volume (in MN) did not increase > 25% from baseline (if applicable)
- liver volume (in MN) did not increase > 20% from baseline.

An independent blinded review committee adjudicated all treatment failures. The committee confirmed that failure to meet the primary outcome was attributable to a decline in Gaucher disease.

The sponsor also defined a secondary objective that the majority of patients on eliglustat would remain stable after 52 weeks. The primary efficacy outcome used for FDA approval was the percentage change in spleen volume (in MN) from baseline to week 52. Other outcomes included the absolute change from baseline BMD (T-scores and Z-scores for femur and lumbar spine), absolute change in hemoglobin level (g/L), percentage change from baseline in platelet count (in mm^3), and percentage change from baseline in liver volume (in MN). Exploratory outcomes included the change from baseline in health-related quality of life (SF-36, BPI, and FFS), bone marrow burden, and bone crises.

In the ENCORE study, hemoglobin and platelet counts were evaluated at baseline, week 13, week 26, week 39, and week 52 by the local laboratory (baseline and 52-week data were based on the average of two samples taken at least 24 hours apart). Liver and spleen volumes were assessed using MRI at baseline, week 26, and week 52 (week 26 and week 52 scans were read by two readers and the results averaged). Patients whose liver volume increased by > 20% or spleen volume increased by > 25% (MN) had their MRI repeated within four weeks and the value from the second test was used in the analysis. All imaging data were read by central readers who were blinded to patient, treatment, and time point. Bone markers were evaluated at baseline and week 52 (X-ray, MRI, and dual energy X-ray absorptiometry of the femur and spine). SF-36, FSS, and BPI were completed at baseline, week 26, and week 52.

In both trials, a bone crisis was defined as bone pain with acute onset requiring immobilization of the affected area and narcotics for pain relief and possibly accompanied by periosteal elevation, an elevated white blood cell count, fever, or debilitation of more than three days.

BMD for the lumbar spine and femur was measured using dual energy X-ray absorptiometry. T-scores were calculated by comparing dual energy X-ray absorptiometry test results to the ideal or peak BMD of a healthy 30-year-old adult, with differences reported in terms of the number of standard deviations (SDs). Based on the World Health Organization's definition, a T-score of 0 means that BMD is equal to the norm for a healthy young adult.[35] A T-score between +1 and −1 is considered normal or healthy in adults. A T-score between −1 and −2.5 indicates low bone mass, and a T-score of −2.5 or lower indicates osteoporosis. Z-score is calculated by comparing the dual energy X-ray absorptiometry results with an age-matached and sex-matched group, with scores > −2 considered normal and ≤ −2 SD below normal.[10]

The degree of bone marrow infiltration by Gaucher cells was measured based on the total bone marrow burden score. The total bone marrow burden score was calculated by summing six MRI-based scores of the lumbar spine and femur, with scores ranging from 0 to 16. Two central readers scored each patient and the average bone marrow burden score was calculated for patients who had non-missing values for all six scores. Infiltration was classified as mild (score 0 to 4), moderate (score 5 to 8), or marked to severe (score 9 to 16).[10]

SF-36 is a generic health assessment questionnaire that has been used in clinical trials to study the impact of chronic disease on health-related quality of life. SF-36 consists of eight domains: physical functioning, role physical, bodily pain, general health, vitality, social functioning, role emotional, and mental health. SF-36 also provides two component summaries: the physical component summary and the mental component summary, which are created by aggregating the eight domains. The SF-36 component scores and eight domains are each measured on a scale of 0 to 100, with an increase in score indicating improvement in health status. In general use of the SF-36, a change of 2 to 4 points in each domain or 2 to 3 points in each component summary indicates a clinically meaningful improvement as determined by the patient. [36] No minimal clinically important difference (MCID) in patients with Gaucher disease was found in the literature.

BPI is a patient-reported pain questionnaire used to assess the intensity of pain experienced, as well as the degree to which this pain interferes with function, using a 24-hour recall period.[37] It consists of a diagram of a human body onto which the location of pain is recorded. There is a section for reporting use of analgesics and the relief these provide. Pain measurement is divided into two categories: severity (consisting of four items: pain now, average pain, worst pain, and least pain), and interference with function (subdivided into seven items: general activity, mood, walking ability, normal work, relations with other persons, sleep, and enjoyment of life). Each item is scored on an 11-point scale from 0 to 10, where 0 is no pain/no interference and 10 is the worst pain/complete interference. Scores for items in the sensory dimension are reported separately, whereas a mean score is reported for all seven items in the reactive dimension. BPI may be used to assess pain in a multitude of diseases and conditions.[38] No MCID has been estimated.

FSS is a generic, unidimensional, psychometric instrument designed to assess the impact of fatigue over the past week. FSS consists of a self-administered questionnaire comprising nine items, each using a seven-point Likert scale that attempts to explore a patient's severity of fatigue symptoms as they relate to daily activities such as physical functioning, exercise, and work, family, or social life.[39,40] Scores should be reported as a total (range 9 to 63 points), but are also reported as a mean (range 1 to 7 points). Lower scores indicate less fatigue in daily life. The FSS has been tested for validity and reliability in a number of diseases and conditions;[40-46] however, no MCID has been established. In the ENGAGE and ENCORE trials, a two-week recall period was used and the studies reported the averaged total FSS score.

The Gaucher disease severity scoring system (DS3) is a physician-reported measure of disease burden for adults with GD1.[47] It includes three domains (bone involvement and pain, hematologic involvement, and visceral involvement), which are based on data from routine assessments, such as medical history, blood chemistry, liver and spleen volume measurements, and bone evaluations. An average score for each domain is calculated by dividing the sum of the individual assessment scores within the domain by the number of completed domain assessments. The three domain scores are summed to obtain a total DS3 score, which has a maximum score of 19. Disease severity categories have been defined as follows: borderline to mild disease (score 0 to 3), moderate disease (3 to 6), marked disease (6 to 9), and severe disease (9 to 19). An MCID of −3.17 for improvement and 3.86 for worsening

were reported based on physicians' assessment of the Clinical Global Impression of a retrospective sample of 20 patients.[47] The DS3 is susceptible to error when comorbidities are present. Additional assessment of the validity of this measure is warranted (Appendix 5).

The biomarkers chitotriosidase and chemokine C-C motif ligand 18 (CCL18) are surrogate measures used for monitoring disease activity in GD1.[48] Progressive storage of glucosylceramide in mononuclear cells and macrophages results in elevated levels of chitotriosidase and CCL18, which have been correlated with disease severity in individual patients monitored serially over many years.[49] As patients with a certain genetic mutation do not produce chitotriosidase, the biomarker data in both trials were reported as normalized values. Patients homozygous for the mutant allele had their chitotriosidase level set to missing (these patients are not expected to produce any chitotriosidase). Those heterozygous for the mutation had their chitotriosidase levels multiplied by two.[10,11]

In both studies, all adverse events from randomization to the end of follow-up (30 days to 37 days after the last dose of study drug) were included in the analysis. The safety evaluation included electrocardiogram (ECG) and Holter monitor data, and complete neurologic assessments. Adverse events of special interest in both trials were defined as clinically significant cardiac arrhythmias detected by ECG or Holter monitoring that did not meet the criteria for a serious adverse event, as well as syncope from any cause.

Statistical Analysis

In the ENGAGE trial, the primary outcome (percentage change from baseline to week 39 in the spleen volume [in MN]) was analyzed using an analysis of covariance model that included treatment and baseline spleen severity group (≤ 20 MN or > 20 MN) as variables. Secondary outcomes (change from baseline to week 39 in hemoglobin, liver volume, and platelet levels) were analyzed using an analysis of covariance model with treatment, baseline spleen severity group, and baseline outcome values as variables. A closed testing procedure was used with the primary and secondary outcomes analyzed sequentially, dependent upon the previous outcome showing statistically significant results. The last observation carried forward was used if data were missing for week 39.

For the ENGAGE study, a sample size of 36 patients was estimated to provide 92% power to detect a 20% difference between eliglustat and placebo in the percentage change in spleen volume over 39 weeks, based on a 5% significance level and two-sided two-sample t-test and assuming a 20% dropout rate and an SD of 15% for the change in spleen volume.

In the ENGAGE study, a number of exploratory outcomes were analyzed, including using analysis of covariance models. These outcomes included the change from baseline to week 39 in BMD, bone marrow burden score, SF-36, BPI, and FSS. There was no control of multiplicity for these outcomes. No subgroup analyses were conducted.

The primary composite outcome in the ENCORE trial was the percentage of patients remaining stable at 52 weeks. The percentage stable for the two randomization stratification groups in each treatment group were calculated, and the difference between eliglustat and imiglucerase was estimated as the weighted combined difference within the two randomization stratification groups. The analyses used Agresti and Caffo's adjusted Wald CI method that adds "one success and one failure" to each group. If the lower bound of the 95% CI for the difference was within the 25% noninferiority margin, then eliglustat was declared noninferior to imiglucerase, based on the per-protocol set (PPS). The analysis was repeated with the FAS, with patients who did not complete 52 weeks of treatment or who switched to imiglucerase counted as failures. The secondary objective (majority of eliglustat patients remain stable at 52 weeks) was said to be met if the lower bound of the 95% CI for the eliglustat group was > 50%.

The 25% noninferiority margin for the primary composite outcome in the ENCORE study was based on half the expected difference from the estimated stability rate in the imiglucerase group (95%) and the observed 51% stability rate from a matched group of patients from the International Collaborative Gaucher Group (ICGG) Gaucher Registry who had reached therapeutic goals while on imiglucerase but had discontinued treatment for one year. The sponsor assumed that 95% of patients in the imiglucerase group and 85% of patients in the eliglustat group would remain stable at one year in the ENCORE trial. With a proposed sample size of 132 patients and 20% dropout rate, the trial had 85% to determine noninferiority for the primary stability outcome with a one-sided significance level of 0.025. The stability criteria for each component of the composite outcome were based on the 95% CI of values observed for these parameters in GD1 patients treated with maintenance doses of imiglucerase in the trial by Kishnani et al., 2009.[50]

In the ENCORE trial, the percentage change from baseline to week 52 in spleen volume (in MN) was analyzed using an analysis of covariance model that included treatment, baseline spleen volume, and stratification variables (ERT dose < 35 U/kg or ≥ 35 U/kg IV every two weeks). The difference between eliglustat versus imiglucerase in the percentage change spleen volume was estimated (with two-sided 95% CI) and eliglustat was considered noninferior if the upper bound of the 95% CI was within the 15% noninferiority margin (in the PPS). Based on 132 patients enrolled, the trial had > 95% power to test the noninferiority of eliglustat versus imiglucerase for the per cent change in spleen volume. No data were provided to support the 15% noninferiority margin selected.

Secondary outcomes in ENCORE included BMD (absolute change in total T-scores and Z-scores) for femur and lumbar spine, absolute change in hemoglobin levels, and percentage change in platelet count, spleen, and liver volumes from baseline to week 52. These were analyzed using the same analysis of covariance model as mentioned previously (FAS and PPS, 5% significance level, last observation carried forward). There was no control of alpha error for the multiple secondary outcomes tested. SF-36, BPI, FSS, DS3, bone marrow burden score, and biomarker data were reported descriptively, using the last observation carried forward for patients with missing data at week 52.

Analysis Populations

In the ENGAGE and ENCORE trials, the FAS and safety set included all patients who signed informed consent and received at least one dose of study drug. The PPS included patients in the FAS with at least 80% compliance with treatment and no major protocol deviations, and who did not exhibit hematological decline due to causes other than Gaucher disease. In ENCORE, patients in the eliglustat group who switched to ERT due to a decline in Gaucher disease were included in the PPS and were recorded as treatment failures at week 52.

Patient Disposition

Of the patients screened, 56% (N = 40) and 77% (N = 160) of patients were randomized in the ENGAGE and ENCORE trials, respectively (Table 8). Most patients completed the trials, with one patient (5%) in the eliglustat group and none in the placebo group withdrawing from the ENGAGE study, and 2% per group discontinuing in the ENCORE study. In the PPS of the ENCORE trial, 7% were excluded from the eliglustat group compared with 13% in the imiglucerase group. One patient switched from eliglustat to imiglucerase due to a decline in Gaucher disease and completed the 52-week treatment period.

Table 8: Patient Disposition

	ENGAGE		ENCORE	
	Eliglustat	**Placebo**	**Eliglustat**	**Imiglucerase**
Screened, N	72		209	
Randomized, N (%)	40 (56)[a]		160 (77)[b]	
	20	20	106	54
Treated, N (%)	20	20	106 (100)	53 (98)
Discontinued (ITT), N (%)	1 (5)	0	2 (2)	1 (2)
Adverse event	0	0	2 (2)	1 (2)
Withdrew consent	1 (5)	0	0	0
Discontinued (PPS), N (%)	NR	NR	7 (7)	7 (13)
Did not reach week 52			2 (2)	1 (2)
Dosage compliance < 80%			2 (2)	3 (6)
Mismatch between randomized dose stratum and actual pre-study ERT dose			2 (2)	2 (4)
Missing baseline or week 52 platelet or Hgb level			1 (1)	0
Randomized but not dosed			0	1 (2)
FAS (mITT), N	20 (100)	20 (100)	106 (100)	53 (98)
PPS, N	18 (90)	20 (100)	99 (93)	47 (87)
Safety, N	20 (100)	20 (100)	106 (100)	53 (98)

ERT = enzyme replacement therapy; FAS = full analysis set; Hgb = hemoglobin; ITT = intention-to-treat; mITT = modified intention-to-treat; NR = not reported; PPS = per-protocol set.
[a] Reason for screening failure: did not complete screening procedure, did not meet eligibility criteria, or patient withdrew (number of patients not reported).
[b] Reason for screening failure and number of patients not reported.
Source: Clinical Study Report.[10,11]

Exposure to Study Treatments

The median treatment duration was 277.5 and 273 days for eliglustat and placebo groups, respectively, in the ENGAGE study, and 364 days and 353 days for eliglustat and imiglucerase groups, respectively, in the ENCORE study (Table 9). Most patients in ENGAGE received eliglustat 100 mg twice daily (85%), whereas in ENCORE, the most common dosage was 150 mg twice daily (48%) followed by 100 mg twice daily (32%). The mean number of imiglucerase infusions per patient was [redacted] in ENCORE. At baseline, patients in the imiglucerase group were receiving on average [redacted] of ERT.

Table 9: Treatment Exposure

	ENGAGE		ENCORE	
	Eliglustat N = 20	**Placebo N = 20**	**Eliglustat N = 106**	**Imiglucerase N = 53**
Duration of study participation, days, median (range)	NR	NR	420.5 (261, 534)	408 (288, 483)
Total time on treatment, days, median (range)	277.5 (166, 296)	273 (263, 301)	[redacted]	[redacted]
Eliglustat dose (mg twice daily), n (%)[a]				
50 mg	3 (15)	NA	21 (20)	NA
100 mg	17 (85)	NA	34 (32)	NA
150 mg	NA	NA	51 (48)	NA

NA = not applicable; NR = not reported.

[a] At end of titration period.

Source: Clinical Study Report.[10,11]

Critical Appraisal

Internal Validity

ENGAGE

The ENGAGE study randomized patients to eliglustat or placebo using an interactive voice-response or Web-response system and used a double-dummy design to maintain blinding to the treatment and dosage administered. There were some imbalances between groups at baseline, with the eliglustat group having more females and more patients with moderate or severe organomegaly, and lower hemoglobin and platelet counts compared with placebo. This is not unexpected considering the limited sample size (20 patients per group). Since the key outcomes were measured as a change from baseline, these differences were not expected to bias the findings. One patient in the eliglustat group (5%) stopped the study early; all 20 patients in the placebo group completed 39 weeks.

The primary outcome was the percentage change from baseline to week 39 in spleen volume; secondary outcomes included the change from baseline in hemoglobin, liver volume, and platelet count, all of which were part of a closed statistical testing procedure to control for family-wise type I error. The clinical expert commented that 39 weeks may be sufficient to see changes in organ volumes and hematologic parameters; however, the maximal response to treatment for some of these measures would not be expected to occur for years.

The ENGAGE study tested a number of other outcomes (SF-36, BPI, FSS, bone marrow burden, BMD) but due to the lack of control for type I error across these outcomes, any statistically significant differences should be interpreted with caution. Outcomes were analyzed with analysis of covariance models, using the last observation carried forward for missing data, and were based on the intention-to-treat population. One patient had missing data at week 39 for the primary and key secondary outcomes. The study was powered for the change in spleen volume and was not designed to test for differences between treatments in outcomes, such as quality of life, bone pain, or bone crises, that are important to patients. The expert stated that nine months of treatment was insufficient to detect clinically important changes in bone disease.

ENCORE

Details on the methods used to generate the randomization sequence and to allocate patients to treatments were not listed in the Clinical Study Report; however, the published report indicates a computer-generated randomization schedule was created by the sponsor, using a block size of six, and stratified by ERT dose.[26,32] The FDA statistical report[6] indicates that an interactive voice-response or Web-response system was used to allocate patients to treatment, which is an accepted method to maintain allocation concealment. As ENCORE was an open-label study, patients and investigators were aware of which treatment they were randomized to receive; however, the assessors of organ volume, bone marrow burden score, and BMD data were blinded to patient, treatment, and timing. An independent blinded review committee adjudicated all patients who failed to meet the primary outcome. Hemoglobin and platelet counts at baseline and the end of treatment were analyzed in duplicate and the average of the two results used in the statistical analysis. Thus, it is unlikely that the primary and the organ or hematologic outcomes were biased by the lack of blinding. Subjective outcomes, such as health-related quality of life or symptom scores, and adverse event reporting may be affected by the knowledge of the treatment received.

The patient characteristics appear to be balanced between treatment groups at baseline, except for the proportion of patients who had a splenectomy, which was higher in the eliglustat group than the imiglucerase group (28% versus 17%). This could potentially bias against eliglustat as those with splenectomy tend to have worse visceral and skeletal manifestations of Gaucher disease. Overall, most patients completed the 52-week trial with only 2% of patients per group discontinuing. One patient in the eliglustat group switched to imiglucerase due to a significant decline in Gaucher disease and was analyzed as a treatment failure for the primary outcome. The median dose of imiglucerase for patients randomized to eliglustat was [redacted] every two weeks [redacted].[34] The clinical expert stated that in Canada, maintenance doses of ERT have declined over time, and that many patients can be controlled on doses below the product monograph recommended dosage of 60 U/kg every two weeks. Limited data were available regarding the doses of ERT used in Canada; however, the clinical expert consulted for this review considered the doses used in the ENCORE trial to be consistent with current practice.

The objective of the ENCORE study was to determine if eliglustat was noninferior to imiglucerase in terms of the proportion who remained stable after 52 weeks, and based on a 25% noninferiority margin. The PPS was used for the primary analysis, which is generally the more conservative estimate in a noninferiority study. Gaucher disease stability was defined as maintaining hemoglobin, platelets, and liver and spleen volumes within a set percentage or absolute change from baseline. The clinical expert consulted stated that these change thresholds may be considered overly broad, depending on the patient's hematologic or organ volumes at baseline. The FDA and European Medicines Agency both stated that the 25% noninferiority margin was not acceptable.[6,7] The 25% value was selected based on a hypothetical difference between imiglucerase and placebo, and was not supported by the literature as no studies comparing imiglucerase to placebo have been conducted.[6] The European Medicines Agency accepted a 20% noninferiority margin for the stability outcome, although no justification for this margin was presented in the European public assessment report.[7] Additionally, the FDA statistical review did not support the 15% noninferiority margin that was used for the percentage change in spleen volume outcome.[6]

The ENCORE trial tested numerous secondary outcomes; however, there was no control for multiple testing and therefore the risk of family-wise type I error is increased. Continuous outcomes were analyzed with analysis of covariance models, using the last observation carried forward for missing data. For the hematologic and organ volume outcomes, it appears that few patients had missing data; however, for some outcomes, the extent of missing data was higher ([redacted]). The reasons for missing data were unclear.

The duration of the primary analysis period was 52 weeks, which the expert stated was sufficient to see changes in hematologic parameters, but organ volumes may be slower to change with the switch in treatments. It is possible that some of the effects attributed to eliglustat are carry-over effects from the patients' prior ERT. The duration of the trial was insufficient to detect changes in bone disease outcomes, nor was the trial designed or powered for these clinically important outcomes.

Also of note, the dosage of eliglustat in the ENGAGE and ENCORE studies was titrated based on serum levels; however, the dosage regimen in the Canadian product monograph is based on CYP2D6 metabolizer status (either eliglustat tartrate 100 mg daily or 100 mg twice daily). In ENCORE, 48% of patients received eliglustat 150 mg twice daily, which is 50% higher than the Health Canada–recommended maximum dose. Another 20% received eliglustat 50 mg twice daily. A post hoc subgroup analysis did not

suggest a difference in treatment effect among those who received the eliglustat 100 mg or 150 mg twice daily; however, the study was not designed to test for dosage effects.

External Validity

The clinical expert indicated that the patients enrolled in the ENCORE and ENGAGE trials would be generalizable to Canadian patients with mild to moderate GD1. Most patients enrolled in the trials would be consistent with the Health Canada–approved population, which was limited to adults and excluded those who were CYP2D6 ultra-rapid or indeterminate metabolizers. Based on age and metabolizer status, two patients (5%) in the ENGAGE study and seven patients (4%) in the ENCORE trial would not be eligible for treatment, according to the product monograph. Patients with a recent bone crisis were excluded from both trials. Thus, the findings of these trials may not be generalizable to patients with severe symptomatic bone disease. In addition, patients with pre-existing cardiac conditions were excluded from the ENCORE trial; therefore, data are lacking on the safety of eliglustat in these patients.

As mentioned previously, most of the patients randomized to eliglustat in the ENCORE study were treated with a dosage that is different than those recommended in the Canadian product monograph. The clinical implications of these dosage differences are unclear. Data are lacking that compare eliglustat to imiglucerase in Gaucher disease patients who are treatment-naive.

Efficacy

Only those efficacy outcomes identified in the review protocol are reported here (Table 4). See Appendix 4 for additional efficacy data.

No data were available for some outcomes listed in the review protocol — specifically, days of work (or school) missed, number of hospitalizations, or need for surgical intervention.

Graphs showing the change from baseline in hematologic parameters and organ volumes for the ENGAGE and ENCORE trials are included in Appendix 4, Figure 3 to Figure 10.

Disease Stability

In the PPS of the ENCORE study, 85% of eliglustat and 94% of imiglucerase patients met the stability criteria at week 52, for a treatment difference of −8.8% (95% CI, −17.6% to 4.2%). The lower bound of the 95% CI was within the −25% noninferiority margin; thus, eliglustat met the noninferiority criteria versus imiglucerase. Similar results were reported based on the FAS (Table 10).

In total, 18 patients did not meet the composite stability criteria at week 52 in the PPS (15 eliglustat, three imiglucerase). One eliglustat patient failed to meet two of the components of the stability criteria, and 13 eliglustat patients and three imiglucerase patients failed to meet one of the clinical components for stability. [redacted]. Data for the individual components of the composite stability criteria are presented in Figure 2 and in Appendix 4, Table 20.

A post hoc subgroup analysis was reported for patients who were treated with velaglucerase prior to entering the ENCORE study (Appendix 4, Table 21). For this subgroup, 90% of patients (18 of 20 patients) randomized to eliglustat and 88% (seven of eight patients) randomized to imiglucerase remained stable (PPS). In the FAS, 86% and 88% of eliglustat and imiglucerase patients, respectively, remained stable at 52 weeks. No between-group comparisons were calculated and the interaction between prior ERT and study treatment was not tested. The manufacturer provided data on the percentage of patients who remained stable according to eliglustat dose (Appendix 4, Table 21).[33] In the FAS, 71%, 82%, and 86% of patients who received eliglustat 50 mg, 100 mg, and 150 mg twice daily, respectively, met the stability criteria at 52 weeks.

Table 10: Disease Stability – Composite Outcome

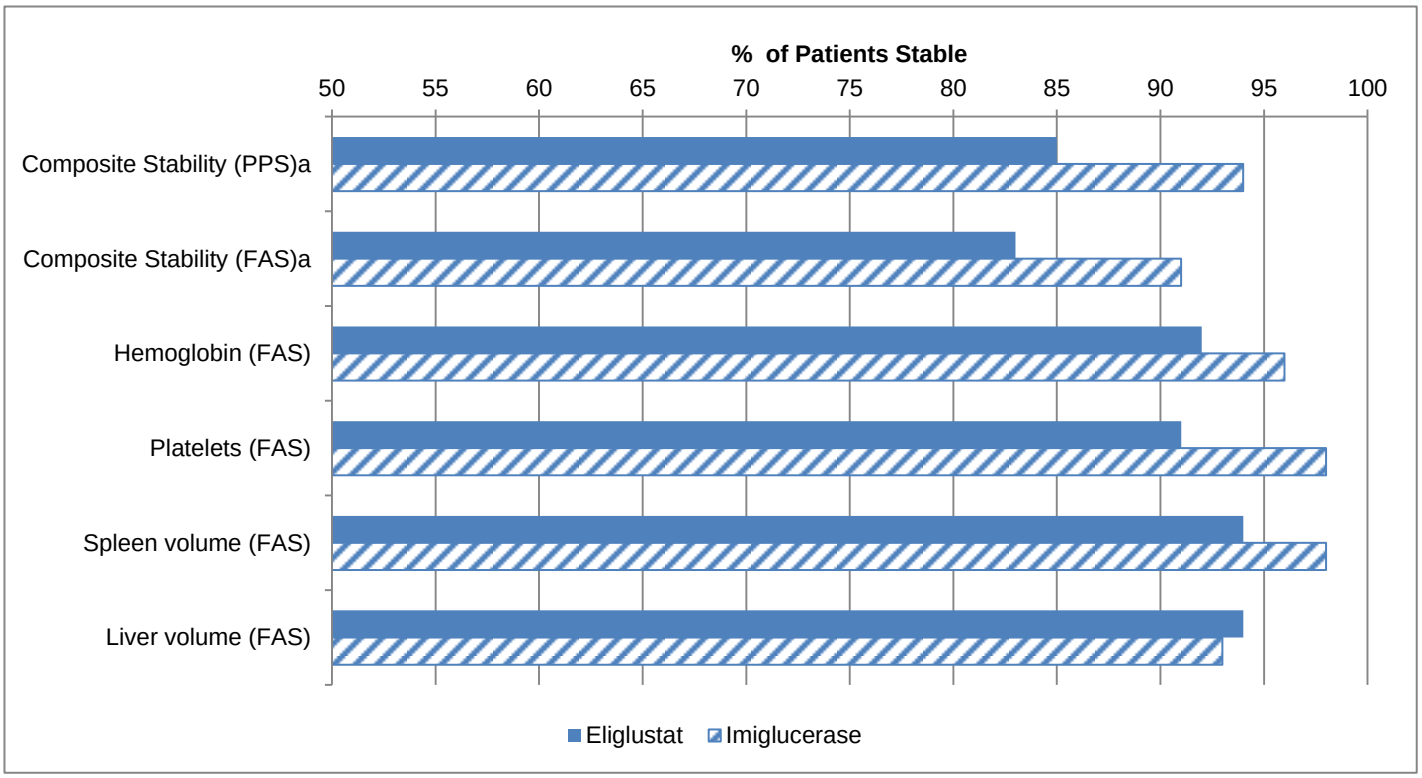
Study /Treatment	N	Patients Stable for 52 Weeks, n (%)[a]	Absolute Difference (95% CI) Eliglustat vs. Imiglucerase	*P* Value
ENCORE (PPS)				
Eliglustat	99	84 (85)	−8.8 % (−17.6 to 4.2%)	NR
Imiglucerase	47	44 (94)		
ENCORE (FAS)				
Eliglustat	106	88 (83)	−7.5% (−17.1 to 5.1%)	NR
Imiglucerase	53	48 (91)		

CI = confidence interval; FAS = full analysis set; MN = multiples of normal; NR = not reported; PPS = per-protocol set; vs. = versus.

[a] Stability criteria: Hemoglobin level did not decrease > 15 g/L from baseline, platelet count did not decrease > 25% from baseline, spleen volume (in MN) did not increase > 25% from baseline (if applicable), and liver volume (in MN) did not increase > 25% from baseline.

Source: Clinical Study Report.[10]

Figure 2: Percentage of Patients Stable – ENCORE Study



FAS = full analysis set; MN = multiples of normal; PPS = per-protocol set.

[a] Stability criteria: Hemoglobin level did not decrease > 15 g/L from baseline, platelet count did not decrease > 25% from baseline, spleen volume (in MN) did not increase > 25% from baseline (if applicable), and liver volume (in MN) did not increase > 25% from baseline.

Source: Clinical Study Report.[10]

Spleen Volume

In the ENGAGE study, the mean baseline spleen volumes were 13.9 MN and 12.5 MN; at week 39, they were 10.2 MN and 12.8 MN in the eliglustat and placebo groups, respectively (Table 11). The difference between eliglustat and placebo for the percentage change from baseline in spleen volume was −30% (95% CI, −37% to −23%), which was statistically significant (*P* < 0.001).

In the ENCORE trial, the baseline mean spleen volume was 3.2 MN and 2.6 MN in the eliglustat and imiglucerase PPS groups, respectively (Table 11). At 52 weeks, the mean values were 3.1 MN and 2.5 MN for eliglustat and imiglucerase, respectively. The percentage change from baseline was −2.8% (95% CI, −8.1% to 2.5%) for eliglustat versus imiglucerase. The upper bound of the 95% CI was less than the noninferiority margin of 15%; thus, eliglustat met the criteria for noninferiority versus imiglucerase. The results in the FAS were similar (treatment difference −1.8%; 95% CI, −6.8% to 3.1%). These analyses were outside the closed statistical testing procedure and should be considered exploratory.

Table 11: Spleen Volume

	Baseline		End of Treatment			Treatment Difference (%) Eliglustat vs. Placebo (95% CI)[a]	*P* Value
Study/Treatment	**N**	**Baseline Spleen Volume (MN), Mean (SD)**	**N**	**Week 39 Spleen Volume (MN), Mean (SD)**	**LS Mean % Change From Baseline to Week 39 (SE)**		
ENGAGE							
Eliglustat[b]	20	13.9 (5.9)	20	10.2 (5.1)	−27.8 (2.4)	−30.0 (−36.8 to −23.2)	< 0.0001
Placebo	20	12.5 (6.0)	20	12.8 (6.4)	2.3 (2.4)		
	N	**Baseline Spleen Volume (MN), Mean (SD)**	**N**	**Week 52 Spleen Volume (MN), Mean (SD)**	**LS Mean % Change From Baseline to Week 52 (SE)**	**Treatment Difference (%) Eliglustat vs. Imiglucerase (95% CI)[a]**	***P* Value**
ENCORE (PPS)[c]							
Eliglustat	70	3.2 (1.4)	70	3.1 (1.4)	−6.1 (1.6)	−2.8 (−8.1 to 2.5)	0.29[d]
Imiglucerase	39	2.6 (1.1)	39	2.5 (1.0)	−3.2 (2.1)		
ENCORE (FAS)[e]							
Eliglustat	77	3.2 (1.3)	77	3.0 (1.4)	−5.1 (1.5)	−1.8 (−6.8 to 3.1)	0.47[d]
Imiglucerase	45	2.7 (1.2)	45	2.6 (1.1)	−3.3 (2.0)		

CI = confidence interval; LOCF = last observation carried forward; LS = least square; FAS = full analysis set; MN = multiples of normal; PPS = per-protocol set; SD = standard deviation; SE = standard error; vs. = versus.

[a] The analysis of covariance model includes treatment group, baseline value, and stratification factors (LOCF).

[b] LOCF was used for one patient who was missing data for week 39 (baseline spleen volume [21.9 MN] was carried forward).

[c] One eliglustat patient who switched to imiglucerase and all patients with total splenectomy were excluded from the analysis.

[d] Outside the closed statistical testing procedure and at risk of inflated family-wise type I error.

Source: Clinical Study Report.[10,11]

Liver Volume

In the ENGAGE study, the mean liver volume at baseline and week 39 was 1.44 MN and 1.35 MN, respectively, in the eliglustat group, and 1.36 MN and 1.39 MN in the placebo group (Table 12). The difference between groups in the percentage change from baseline was statistically significant, favouring eliglustat (−6.6%; 95% CI, −11.4% to −1.9%; *P* = 0.007).

In the ENCORE study, the mean baseline liver volume was 0.94 MN and 0.92 MN, and increased at week 52 to 0.96 MN and 0.95 MN in the eliglustat and imiglucerase FAS groups, respectively. The difference between groups in the percentage change from baseline was not statistically significant for the PPS or the FAS. These analyses, however, were outside the statistical testing hierarchy.

Table 12: Liver Volume

Study/ Treatment	Baseline N	Baseline Liver Volume (MN), Mean (SD)	End of Treatment N	Week 39 Liver Volume (MN), Mean (SD)	LS Mean % Change From Baseline to Week 39 (SE)	Treatment Difference (%) Eliglustat vs. Control (95% CI)[a]	*P* Value
ENGAGE							
Eliglustat[b]	20	1.44 (0.35)	20	1.35 (0.28)	−5.2 (1.6)	−6.6 (−11.4 to −1.9)	0.007
Placebo	20	1.36 (0.28)	20	1.39 (0.31)	1.4 (1.6)		
Study / Treatment	**N**	**Baseline Liver Volume (MN), Mean (SD)**	**N**	**Week 52 Liver Volume (MN), Mean (SD)**	**LS Mean % Change From Baseline to Week 52 (SE)**	**Treatment Difference (%) Eliglustat vs. Control (95% CI)[a]**	***P* Value**
ENCORE (FAS)[c,d]							
Eliglustat	106	0.94 (0.19)	106	0.96 (0.18)	2.3 (0.9)	−0.3 (−3.3 to 2.8)	0.86[e]
Imiglucerase	53	0.92 (0.16)	53	0.95 (0.16)	2.6 (1.3)		

CI = confidence interval; FAS = full analysis set; LOCF = last observation carried forward; LS = least square; MN = multiples of normal; SD = standard deviation; SE = standard error; vs. = versus.

[a] The analysis of covariance model includes treatment group, baseline value, and stratification factors (LOCF).

[b] LOCF was used for one patient who was missing data for week 39 (baseline liver volume [1.22 MN] was carried forward).

[c] Eliglustat patients who switched to imiglucerase were censored after the switch.

[d] Per-protocol set treatment difference in % change from baseline: −1.1%; 95% CI, −4.4 to 2.2%; *P* = 0.49.

[e] Outside the closed statistical testing procedure and at risk of inflated family-wise type I error.

Source: Clinical Study Report.[10,11]

Hemoglobin Level

In the ENGAGE study the mean hemoglobin level was 121 g/L in the eliglustat group, and 128 g/L in the placebo group at baseline, and 128 g/L and 122 g/L at week 39, respectively (Table 13). The absolute difference in the change from baseline in hemoglobin was statistically significant, favouring eliglustat (12 g/L; 95% CI, 6 to 19; *P* = 0.0006).

In the ENCORE study, mean hemoglobin values were 136 g/L and 139 g/L at baseline and 134 g/L and 140 g/L at week 52 in the eliglustat and imiglucerase groups, respectively. The absolute difference in the change from baseline in hemoglobin was −2.9 g/IL (95% CI, −5.6 to −0.3). The results for the PPS were similar (LS mean difference −2.8 g/dL; 95% CI, −5.2 to −0.3; *P* = 0.025).This outcome was outside the closed statistical testing procedure and should be considered exploratory.

Table 13: Hemoglobin Level

Study/ Treatment	Baseline N	Baseline Hgb (g/L), Mean (SD)	End of Follow-Up N	Week 39 Hgb (g/L), Mean (SD)	LS Mean Change From Baseline to Week 39 (SE)	Treatment Difference (g/L) Eliglustat vs. Placebo (95% CI)[a]	*P* Value
ENGAGE							
Eliglustat[b]	20	121 (18)	20	128 (16)	7 (2)	12 (6 to 19)[b]	0.0006
Placebo	20	128 (16)	20	122 (20)	−5 (2)		
Study/ Treatment	**N**	**Baseline Hgb (g/L), Mean (SD)**	**N**	**Week 52 Hgb (g/L), Mean (SD)**	**LS Mean Change From Baseline to Week 52 (SE)**	**Treatment Difference (g/L) Eliglustat vs. Imiglucerase (95% CI)[a]**	***P* Value**
ENCORE (FAS)							
Eliglustat[c]	106	136 (13)	105	134 (13)	−2 (0.8)	−3.3 (−5.9 to −0.7)	0.013[d]
Imiglucerase	53	139 (13)	53	140 (14)	1 (1.1)		

CI = confidence interval; FAS = full analysis set; Hgb = hemoglobin; LOCF = last observation carried forward; LS = least square; SD = standard deviation; SE = standard error; vs. = versus.

[a] The analysis of covariance model includes treatment group, baseline value, and stratification factors (LOCF).

[b] LOCF was used for one patient who was missing data for week 39.

[c] One eliglustat patient who switched to imiglucerase was censored after the switch.

[d] Outside the closed statistical testing procedure and at risk of inflated family-wise type I error.

Source: Clinical Study Report.[10,11]

Platelet Count

In the ENGAGE study, the baseline mean platelet count was 75.1 and 78.5 × 10^9/L in the eliglustat and placebo groups, respectively, and at 39 weeks, the counts were 99.0 and 71.5 × 10^9/L (Table 14). The difference between groups in the percentage change from baseline was statistically significant, favouring eliglustat over placebo (41.1%; 95% CI, 24.0 to 58.2; $P < 0.0001$).

The baseline mean platelet counts in the ENCORE trial were 203.3 and 187.5 × 10^9/L and at week 52 were 214.5 and 192.0 × 10^9/L in the eliglustat and imiglucerase groups, respectively. There was no statistically significant difference between treatments in the FAS or PPS for this exploratory outcome.

Table 14: Platelet Count

Study / Treatment	Baseline N	Baseline Platelet Count (10^9/L), Mean (SD)	End of Treatment N	Week 39 Platelet Count (10^9/L), Mean (SD)	LS Mean % Change From Baseline to Week 39 (SE)	Treatment Difference (%), Eliglustat vs. Placebo (95% CI)[a]	*P* Value
ENGAGE							
Eliglustat[b]	20	75.1 (14.1)	20	99.0 (28.4)	32.0 (6.0)	41.1 (24.0 to 58.2)	< 0.0001
Placebo	20	78.5 (22.6)	20	71.5 (25.2)	−9.1 (6.0)		
Study/ Treatment	**N**	**Baseline Platelet Count (10^9/L), Mean (SD)**	**N**	**Week 52 Platelet Count (10^9/L), Mean (SD)**	**LS Mean % Change From Baseline to Week 52 (SE)**	**Treatment Difference (%), Eliglustat vs. Imiglucerase (95% CI)[a]**	***P* Value**
ENCORE (FAS)[c]							
Eliglustat	106	203.3 (79.3)	105	214.5 (83.3)	4.2 (1.7)	2.7 (−3.1 to 8.5)	0.36[d]
Imiglucerase	53	187.5 (56.8)	53	192.0 (61.9)	1.5 (2.4)		

CI = confidence interval; LOCF = last observation carried forward; LS = least square; SD = standard deviation; SE = standard error; vs. = versus.

[a] The analysis of covariance model includes treatment group, baseline value, and stratification factors (LOCF).

[b] LOCF was used for one patient who was missing data for week 39.

[c] Eliglustat patients who switched to imiglucerase were censored after the switch.

[d] Outside the closed statistical testing procedure and at risk of inflated family-wise type I error.

Source: Clinical Study Report.[10,11]

Health-Related Quality of Life

Data for the SF-36 from the ENGAGE study is presented in Table 15. At baseline, the mean domain scores ranged from 50.9 (vitality) to 80.6 (social functioning) in the eliglustat group, and from 63.4 (vitality) to 88.3 (physical functioning) in the placebo group. The differences between groups in the change from baseline in domain scores or component scores ranged from −8.9 (social functioning) to 13.2 (physical functioning) and were not statistically significantly different, except for physical functioning. However, there was no control of multiplicity for these analyses, and thus statistically significant results (i.e., physical functioning) should be interpreted with caution.

Table 15: SF-36 – ENGAGE Trial

Domain[a] / Treatment	N	Baseline, Mean (SD)	LS Mean Change From Baseline to Week 39 (SE)	Treatment Difference, Eliglustat vs. Placebo (95% CI)[b]	*P* Value
Physical Component Score					
Eliglustat	20	46.1 (9.3)	0.8 (1.4)	3.3 (−0.7 to 7.3)	0.12[c]
Placebo	20	51.9 (7.2)	−2.5 (1.3)		
Mental Component Score					
Eliglustat	20	45.2 (14.0)	1.6 (1.7)	−2.2 (−7.0 to 2.6)	0.36[c]
Placebo	20	49.3 (11.9)	3.8 (1.6)		
Physical Functioning					
Eliglustat	20	75.3 (21.1)	3.2 (4.3)	13.2 (0.5 to 26.0)	0.01[c]
Placebo	20	88.3 (13.4)	−10.0 (4.3)		
Role Physical					
Eliglustat	20	68.8 (28.2)	3.3 (4.1)	4.5 (−7.5 to 16.4)	0.42[c]
Placebo	20	83.4 (15.9)	−1.1 (4.1)		
Bodily Pain					
Eliglustat	20	62.8 (27.7)	6.8 (4.1)	3.6 (−8.4 to 15.5)	0.77[c]
Placebo	20	78.8 (22.2)	3.2 (4.0)		

Domain[a] / Treatment	N	Baseline, Mean (SD)	LS Mean Change From Baseline to Week 39 (SE)	Treatment Difference, Eliglustat vs. Placebo (95% CI)[b]	*P* Value
General Health					
Eliglustat	20	55.8 (27.7)	−1.7 (2.6)	−2.4 (−9.8 to 4.9)	0.51[c]
Placebo	20	66.7 (24.7)	0.7 (2.6)		
Vitality					
Eliglustat	20	50.9 (23.2)	1.1 (3.3)	−3.4 (−13.0 to 6.2)	0.47[c]
Placebo	20	63.4 (22.7)	4.5 (3.3)		
Social Functioning					
Eliglustat	20	80.6 (24.8)	−6.6 (4.2)	−8.9 (−21.1 to 3.3)	0.08[c]
Placebo	20	86.3 (21.4)	2.3 (4.2)		
Role Emotional					
Eliglustat	20	72.5 (28.6)	9.2 (3.7)	5.6 (−5.2 to 16.4)	0.30[c]
Placebo	20	85.0 (22.2)	3.7 (3.7)		
Mental Health					
Eliglustat	20	66.3 (26.3)	3.1 (3.0)	−2.0 (−10.7 to 6.8)	0.65[c]
Placebo	20	74.3 (20.2)	5.1 (3.0)		

CI = confidence interval; LS = least square; SD = standard deviation; SE = standard error; SF-36 = Short Form (36) Health Survey; vs. = versus.

[a] SF-36 domain and component scores range from 0 to 100 with higher scores indicating better quality of life. In general use of SF-36, a change of 2 to 4 points in each domain or 2 to 3 points in each component summary indicates a clinically meaningful improvement as determined by the patient. [36]

[b] Based on the analysis of covariance model that includes treatment group, stratification variable, and baseline value. Last observation carried forward was used for patients who were missing data for week 39.

[c] Outside the closed statistical testing procedure and at risk of inflated family-wise type I error.

Source: Clinical Study Report.[11]

In the ENCORE study, data for SF-36 were reported descriptively and no between-group differences were calculated (Table 16). At baseline, the mean scores of the individual domains were lowest for vitality (eliglustat, 64.1; imiglucerase, 63.7) and were highest for social functioning (eliglustat, 84.4; imiglucerase, 92.1). The mean change from baseline to week 52 ranged from −2.5 (mental health) to 3.4 (physical functioning) in the eliglustat group, and from −2.2 (social functioning) to 3.3 (general health) in the imiglucerase group. Data were missing for 1% to 7% of patients.

Table 16: SF-36 – ENCORE Trial

Domain[a]/Treatment	Baseline		Week 52	
	N	Mean (SD)	N	Change From Baseline to Week 52, Mean (SD)
Physical Component Score				
Eliglustat	102	49.5 (9.2)	99	1.6 (5.9)
Imiglucerase	52	53.6 (7.1)	52	1.4 (6.0)
Mental Component Score				
Eliglustat	102	51.7 (10.0)	99	−1.0 (9.2)
Imiglucerase	52	52.0 (8.8)	52	−0.5 (7.2)
Physical Functioning				
Eliglustat	105	81.2 (22.0)	102	3.4 (15.0)
Imiglucerase	52	90.1 (15.7)	52	2.8 (11.3)
Role Physical				
Eliglustat	105	80.8 (23.9)	102	2.5 (17.4)
Imiglucerase	52	90.4 (15.1)	52	0.2 (14.6)
Bodily Pain				
Eliglustat	104	75.1 (23.1)	101	−0.2 (21.5)
Imiglucerase	52	82.7 (18.7)	52	3.2 (14.7)
General Health				
Eliglustat	104	70.3 (19.4)	101	0.4 (14.6)

Domain[a]/Treatment	Baseline		Week 52	
	N	Mean (SD)	N	Change From Baseline to Week 52, Mean (SD)
Imiglucerase	52	76.0 (18.5)	52	3.3 (13.5)
Vitality				
Eliglustat	103	64.1 (20.2)	100	2.3 (15.8)
Imiglucerase	52	63.7 (21.3)	52	1.8 (16.9)
Social Functioning				
Eliglustat	104	84.4 (22.2)	101	1.5 (20.6)
Imiglucerase	52	92.1 (15.7)	52	−2.2 (11.8)
Role Emotional				
Eliglustat	105	87.9 (20.2)	102	−1.4 (18.5)
Imiglucerase	52	91.7 (17.3)	52	−1.3 (11.5)
Mental Health				
Eliglustat	103	77.9 (17.0)	100	−2.5 (15.4)
Imiglucerase	52	79.2 (13.2)	52	0.9 (13.1)

SD = standard deviation; SF-36 = Short Form (36) Health Survey.

a SF-36 domain and component scores range from 0 to 100 with higher scores indicating better quality of life. In general use of SF-36, a change of 2 to 4 points in each domain or 2 to 3 points in each component summary indicates a clinically meaningful improvement as determined by the patient.36

Source: Clinical Study Report.10

Bone Disease

In the ENGAGE and ENCORE trials, no patients had a bone crisis in the year prior to enrolment (as per the study eligibility criteria). During the ENGAGE study, one patient in the placebo group experienced a bone crisis that was reported as an adverse event of intermittent bone pain in the left leg (onset day 226, duration 25 days). In the ENCORE trial, one patient in the imiglucerase group experienced a bone crisis on day 239, which was reported as an adverse event of severe bone pain in the left hip (duration 87 days). No patients in the eliglustat groups reported a bone crisis in the ENCORE or ENGAGE studies.

At baseline in the ENGAGE study, the mean T-score or Z-score of the spine or worst femur ranged from −1.1 to −0.1 in the eliglustat group and from −1.4 to −0.4 in the placebo group (Table 17). The least square (LS) mean change from baseline to week 39 ranged from −0.1 to 0.1 across treatment groups and BMD measures, with no statistically significant differences detected between groups. Data were missing for 0% to 15% of patients. BMD outcomes were outside the closed statistical testing procedure and thus should be considered exploratory.

In the ENCORE study, the baseline mean BMD was in the normal range for both groups based on T-scores and Z-scores for the total lumbar spine and total femur (Table 17). No substantial change from baseline was observed after 52 weeks and no statistically significant differences were detected between groups. Of note, T-scores were reported for 79% to 84% of patients, and Z-scores for 94% to 96% of patients: the reason for missing data was unclear.

At baseline in the ENGAGE study, the mean bone marrow burden scores were 10.9 and 9.8 in the eliglustat and placebo groups, respectively, and 9.8 in both groups at week 39 (Table 18). The LS mean change from baseline to week 39 was −1.1 points (95% CI, −1.7 to −0.4) for eliglustat versus placebo for this exploratory outcome.

In the ENCORE trial, the mean total bone marrow burden score was 8.2 (SD 2.7) and 8.1 (SD 2.6) at baseline in the eliglustat and imiglucerase groups, respectively (FAS). At week 52, the results were similar with a mean change of −0.13 points for eliglustat and −0.19 points for imiglucerase. No between-group comparisons were conducted.

Table 17: BMD

ENGAGE Study	Treatment	Baseline		End of Treatment		Treatment Difference Eliglustat vs. Placebo (95% CI)[a]	*P* Value
		N	Mean (SD)	N	LS Mean Change From Baseline to Week 39 (SE)		
Total Spine T-Score							
	Eliglustat	17	−1.1 (0.8)	17	0.0 (0.07)	0.1 (−0.05 to 0.33)	0.14[b]
	Placebo	18	−1.1 (1.2)	18	−0.1 (0.06)		
Total Spine Z-Score							
	Eliglustat	19	−1.1 (0.9)	19	0.1 (0.06)	0.2 (−0.01 to 0.36)	0.06[b]
	Placebo	20	−1.2 (1.2)	20	−0.1 (0.06)		
Worst Total Femur T-Score							
	Eliglustat	17	−0.3 (0.8)	17	−0.1 (0.05)	−0.1 (−0.25, 0.04)	0.15[b]
	Placebo	18	−0.5 (1.2)	18	0.0 (0.05)		
Worst Total Femur Z-Score							
	Eliglustat	18	−0.1 (0.7)	18	0.0 (0.05)	0.0 (−0.18, 0.10)	0.57[b]
	Placebo	20	−0.4 (1.2)	20	0.0 (0.05)		
ENCORE Study (FAS)	**Treatment**	**N**	**Mean (SD)**	**N**	**LS Mean Change From Baseline to Week 52 (SE)**	**Treatment Difference, Eliglustat vs. Imiglucerase (95% CI)[a]**	***P* Value**
Total Spine T-Score							
	Eliglustat	89	0.5 (1.4),	88	0.03 (0.03)	0.0 (−0.11 to 0.10)	0.96[b]
	Imiglucerase	43	−0.3 (1.2)	43	0.04 (0.04)		
Total Spine Z-Score							
	Eliglustat	102	−0.3 (1.3)	101	0.06 (0.03)	−0.02 (−0.12 to 0.08)	0.71[b]
	Imiglucerase	51	−0.2 (1.1)	51	0.08 (0.04)		
Worst Total Femur T-Score							
	Eliglustat	88	−0.2 (1.1)	87	0.0 (0.02)	0.02 (−0.04 to 0.08)	0.45[b]
	Imiglucerase	42	−0.4 (1.3)	42	−0.02 (0.02)		
Worst Total Femur Z-Score							
	Eliglustat	101	0.07 (1.0)	100	0.04 (0.02)	0.02 (−0.03 to 0.07)	0.46[b]
	Imiglucerase	50	−0.1 (1.1)	50	0.02 (0.02)		

BMD = bone mineral density; CI = confidence interval; FAS = full analysis set; LS = least square; SD = standard deviation; SE = standard error; vs. = versus.

a The analysis of covariance model includes treatment group, baseline value, and stratification variables. Last observation carried forward was used for patients with missing end point data.

b Outside the closed statistical testing procedure and at risk of inflated family-wise type I error.

Source: Clinical Study Report.[10,11]

Disease Severity Score

The mean baseline DS3 scores for patients in the ENGAGE study were 4.7 and 4.4, and decreased 0.4 and 0.1 points after 39 weeks in the eliglustat and placebo groups, respectively (Table 18). The LS mean difference between treatments was −0.3 points (95% CI, −0.67 to −0.01). The clinical importance of these differences was limited given that an MCID of 3.17 has been reported in the literature, and this outcome was exploratory.

In the ENCORE trial, the mean total DS3 score was 2.4 points (SD 0.9) and 2.1 points (SD 0.9) at baseline in the eliglustat and imiglucerase groups, respectively (FAS). DS3 scores were largely unchanged at week 52 (mean difference of 0.03 for eliglustat and −0.01 for imiglucerase). Of note, DS3 scores were reported for patients who had both baseline and week 52 data available (71% of eliglustat and 83% of imiglucerase patients [FAS]). Most of the missing data for this exploratory outcome were due to missing visceral domain results.

Symptoms

In the ENGAGE study, the mean baseline FSS score was 3.8 and 3.5 points in the eliglustat and placebo groups, respectively, and at week 39 was 3.9 and 3.0 in these respective groups, with the LS mean difference of 0.7 points (95% CI, 0.02 to 1.3 points) (Table 18). The clinical importance of the differences is unclear for this exploratory outcome as there is no known MCID. No statistically significant differences were detected between eliglustat and placebo for any of the domains of the BPI after 39 weeks of treatment (Table 18).

In the ENCORE study, the mean baseline FSS was 3.1 points (SD 1.5) and 2.9 points (SD 1.6) in the eliglustat and imiglucerase groups, respectively. At week 52, the scores were similar (eliglustat 3.2; imiglucerase 2.8), with no substantive changes within groups. No between-group differences were reported. The mean scores for the domains of the BPI were generally low at baseline and were reported as follows for the eliglustat and imiglucerase groups, respectively: worst pain in past 24 hours (1.8 and 1.6 points); least pain in past 24 hours (0.9 and 0.4); average pain (1.7 and 1.3); pain right now (1.0 and 0.4); and average pain interference (1.0 and 0.8). The mean scores were similar at 52 weeks, with the change from baseline ranging from −0.14 to 0.08 points in the eliglustat group, and from −0.5 to −0.02 in the imiglucerase group (FAS). No between-group comparisons were reported in the ENCORE study.

Table 18: Exploratory Outcomes – ENGAGE Study

	Baseline		End of Treatment (Week 39)			Treatment Difference, Eliglustat vs. Placebo	
Outcome/Treatment	**N**	**Mean (SD)**	**N**	**Mean (SD)**	**LS Mean Change From Baseline to Week 39 (SE)**	**LS Mean Difference in Change From Baseline (95% CI)**	***P* Value**
Total BMB Score[a]							
Eliglustat	20[a]	10.9 (2.6)	20	9.8 (2.6)	−1.1 (0.2)	−1.1 (−1.7 to −0.4)	0.0021[b]
Placebo	20	9.8 (2.8)	20	9.8 (2.8)	0.0 (0.2)		
Total DS3 Score[c]							
Eliglustat	20	4.7 (1.0)	20	4.2 (0.8)	−0.4 (0.1)	−0.3 (−0.67 to −0.01)	0.045[b]
Placebo	20	4.4 (1.2)	20	4.4 (1.0)	−0.1 (0.1)		
FSS Score[d]							
Eliglustat	20	3.8 (1.7)	20	3.9 (1.5)	0.1 (0.2)	0.7 (0.02 to 1.3)	0.043[b]
Placebo	20	3.5 (1.6)	20	3.0 (1.6)	−0.6 (0.2)		
BPI Domains[e]							
Worst pain in past 24 hours							
Eliglustat	19	2.2 (2.5)	19	1.4 (2.3)	−0.8 (0.3)	−0.2 (−1.1 to 0.7)	0.65[b]
Placebo	20	2.3 (3.2)	20	1.7 (2.4)	−0.6 (0.3)		
Least pain in past 24 hours							
Eliglustat	19	1.1 (2.1)	19	0.8 (1.9)	−0.2 (0.1)	0.0 (−0.4 to 0.3)	0.90[b]
Placebo	20	0.7 (1.5)	20	0.5 (1.4)	−0.2 (0.1)		
Average pain							
Eliglustat	19	1.7 (2.5)	19	1.2 (2.3)	−0.4 (0.2)	−0.2 (−0.8 to 0.4)	0.52[b]
Placebo	20	1.1 (2.0)	20	0.9 (1.5)	−0.2 (0.2)		
Pain right now							
Eliglustat	19	1.4 (2.4)	19	0.7 (1.8)	−0.6 (0.3)	−0.1 (−0.8 to 0.6)	0.59[b]
Placebo	20	1.0 (1.9)	20	0.6 (1.4)	−0.5 (0.3)		
Average pain interference							
Eliglustat	19	1.7 (2.4)	19	1.1 (1.9)	−0.6 (0.2)	0.0 (−0.5 to 0.5)	0.95[b]
Placebo	20	1.2 (2.0)	20	0.7 (1.5)	−0.6 (0.2)		
Normalized Chitotriosidase (nmoL/hr/mg)[f]	**N**	**Median (Range)**	**N**	**Median (Range)**	**Median % Change From Baseline to Week 39 (Range)**	**LS Mean Difference in % Change From Baseline (SE)**	***P* Value**
Eliglustat	19	14,229 (2,298 to 35,106)	19	7,572 (587 to 22,766)	−39 (−78 to −1)	−44 (10)	< 0.0001[b]

	Baseline		End of Treatment (Week 39)			Treatment Difference, Eliglustat vs. Placebo	
Outcome/Treatment	N	Mean (SD)	N	Mean (SD)	LS Mean Change From Baseline to Week 39 (SE)	LS Mean Difference in Change From Baseline (95% CI)	*P* Value
Placebo	20	11,030.5 (724 to 35,960)	20	10,197 (435 to 32,435)	−5 (−40 to 86)		

BMB = bone marrow burden; BPI = Brief Pain Inventory; CI = confidence interval; DS3 = Gaucher disease severity scoring system; FSS = Fatigue Severity Scale; LS = lease square; MCID = minimal clinically important difference; SD = standard deviation; SE = standard error; vs. = versus.

[a] BMB score ranges from 0 to 19 with higher numbers suggesting worse bone marrow infiltration.

[b] Outside the closed statistical testing procedure and at risk of inflated family-wise type I error.

[c] DS3 score ranges from 0 to 16 with higher numbers indicating more severe disease burden. An MCID of 3.17 points for improvement has been reported in the literature.

[d] FSS score ranged from 1 to 7 with higher scores indicating more severe fatigue.

[e] BPI domains are scored from 0 to 10 with higher values indicating more severe pain.

[f] Median values were reported because data were not normally distributed.

Source: Clinical Study Report.[11]

Biomarkers

Data for the chitotriosidase levels were reported in both studies. In the ENGAGE trial, the median chitotriosidase level in the eliglustat group was 14,229 nmol/hr/mg at baseline, and decreased to 7,572 nmol/hr/mg at week 39 (Table 18). In the placebo group the median levels were 11,031 and 10,197 nmol/hr/mg at baseline and week 39. The LS mean difference in the median percentage change from baseline to week 39 was −44% (SE 10%). Although the difference was statistically significant, there was no control for multiplicity across the numerous exploratory outcomes in the ENGAGE study and, thus, there is the possibility of an inflated risk of type I error across these outcomes.

In the ENCORE trial, the median baseline normalized chitotriosidase levels were 710 nmol/hr/mL and 758.5 nmol/hr/mL in the eliglustat and imiglucerase groups, respectively, and these decreased to 644 nmol/hr/mL and 569 nmol/hr/mL at week 52. The sponsor stated that there was substantial between-patient variability in chitotriosidase levels and data were not normally distributed; thus, median values were reported. This outcome was exploratory and no between-group estimates were calculated. Data were missing for 10% of eliglustat patients and 4% of imiglucerase patients, with no explanation for missing data.

There were data quality issues with the CCL18 data and no results for this biomarker were reported for ENCORE and ENGAGE studies. The sponsor stated that there were methodological inconsistencies and lack of reproducibility in the plasma CCL18 assay from the central laboratory, and the data were unreliable.

Harms

Only those harms identified in the review protocol are reported here (Table 4).

Adverse Events

Overall, 90% and 97% of patients who received eliglustat reported one or more adverse events in the ENGAGE and ENCORE trials, compared with 70% of patients who received placebo and 79% who received imiglucerase (Table 19). In the ENGAGE trial, the most frequently reported adverse events in the eliglustat group were arthralgia (45%), headache (40%), nasopharyngitis (15%), and diarrhea (15%). In the eliglustat group of the ENCORE trial, arthralgia (15%), fatigue (14%), headache (13%), nausea (12%), diarrhea (12%), and back pain (12%) were most common.

[redacted].

Serious Adverse Events

In the ENCORE study, 11 patients in the eliglustat group and no patients in the imiglucerase group had a serious adverse event. Except for syncope, which occurred in two patients, all other specific events were reported in one patient with no clustering in a particular system organ class. One patient discontinued the study after experiencing a myocardial infarction. No other patient stopped treatment due to serious adverse events. Other serious adverse events reported in one patient included the following: appendicitis, diverticulitis, hepatic neoplasm, uterine leiomyoma, ischemic colitis, cholecystitis, joint dislocation, and mammoplasty. No serious adverse events were reported in the ENGAGE trial (Table 19).

Withdrawals Due to Adverse Events

Two eliglustat and one imiglucerase patient stopped treatment due to adverse events in the ENCORE study (2% per group). Adverse events that led to discontinuation were palpitations and myocardial infarction in the eliglustat group, and psychotic disorder in the imiglucerase group. No patients stopped treatment due to adverse events in the ENGAGE study (Table 19).

Mortality

No deaths were reported in the ENCORE or ENGAGE clinical trials.

Notable Harms

In ENCORE, [redacted] patients in the eliglustat group had a neoplasm, [redacted] (Table 19). The sponsor stated that [redacted] of hepatocellular carcinoma was malignant and this was found, retrospectively, on the patient's baseline MRI. [redacted] neoplasms were reported in the imiglucerase group in the ENCORE study, or in either group in the ENGAGE study.

In the ENGAGE study, neurological examinations were performed at baseline and week 39. The authors reported that although some patients had abnormal findings at week 39, [redacted] in either treatment group had clinically significant worsening on any test. In ENCORE, [redacted] in the eliglustat group had treatment-emergent peripheral neuropathy, compared with [redacted] in the imiglucerase group. Nerve conduction studies were abnormal [redacted] (Table 19).

In ENCORE, cardiac arrhythmias or syncope were observed in [redacted] eliglustat patients and [redacted] imiglucerase patients. These included [redacted] events of syncope in [redacted] patients; [redacted] were classified as serious adverse events. All syncope events were vasovagal in nature with pre-disposing factors (e.g., blood draw, fasting). Four events of cardiac arrhythmia in three patients were also reported. These events were detected during scheduled Holter or ECG monitoring and were asymptomatic. In the ENGAGE study, [redacted] patient in the placebo group and no patients in the eliglustat group reported clinically significant cardiac arrhythmias or syncope.

Table 19: Harms

	ENGAGE (39 weeks)		ENCORE (52 weeks)	
	Eliglustat N = 20	Placebo N = 20	Eliglustat N = 106	Imiglucerase N = 53
Patients With ≥ 1 Adverse Events[a], n (%)	18 (90)	14 (70)	97 (92)	42 (79)
Headache	8 (40)	6 (30)	14 (13)	1 (2)
Migraine	2 (10)	0	0	1 (2)
Dizziness	1 (5)	2 (10)	9 (8)	0
Arthralgia	9 (45)	2 (10)	6 (15)	9 (17)
Back pain	0	1 (5)	13 (12)	3 (6)
Pain in extremity	0	1 (5)	12 (11)	1 (2)
Upper respiratory infection	1 (5)	4 (20)	11 (10)	3 (6)
Nasopharyngitis	3 (15)	0	11 (10)	5 (9)

	ENGAGE (39 weeks)		ENCORE (52 weeks)	
	Eliglustat N = 20	Placebo N = 20	Eliglustat N = 106	Imiglucerase N = 53
Sinusitis	2 (10)	1 (5)	11 (10)	1 (2)
Pyrexia	2 (10)	0	2 (2)	1 (2)
Oropharyngeal pain	2 (10)	1 (5)	4 (4)	0
Nasal obstruction	2 (10)	0	NR	NR
Diarrhea	3 (15)	4 (20)	13 (12)	2 (4)
Nausea	1 (5)	2 (10)	13 (12)	0
Abdominal pain, upper	0	1 (5)	11 (10)	0
Flatulence	2 (10)	1 (5)	3 (3)	0
Contusion	2 (10)	3 (15)	5 (5)	0
Fatigue	1 (5)	2 (10)	15 (14)	1 (2)
SAE, n (%)	0	0	11 (10)	0
Deaths, n (%)	0	0	0	0
Discontinued Treatment due to Adverse Events, n (%)	0	0	2 (2)	1 (2)
Notable Adverse Events, n (%)				
Clinically significant cardiac arrhythmia or syncope	[redacted]	[redacted]	[redacted]	[redacted]
Peripheral neuropathy	[redacted]	[redacted]	[redacted]	[redacted]
Abnormal nerve conduction study	[redacted]	[redacted]	[redacted]	[redacted]
Neoplasm	[redacted]	[redacted]	[redacted]	[redacted]

NR = not reported; SAE = serious adverse event.

[a] Frequency ≥ 10% in eliglustat treatment arm.

Source: Clinical Study Report.[10,11]

Discussion

Summary of Available Evidence

Two pivotal randomized controlled trials evaluated the safety and efficacy of eliglustat tartrate (50 mg to 150 mg twice daily) compared with placebo (ENGAGE) or imiglucerase (ENCORE). The double-blind ENGAGE study enrolled patients with GD1 who were treatment-naive and had hematologic and visceral symptoms related to the disease, whereas the open-label ENCORE trial included treatment-experienced patients who had received ERT for at least three years and had met treatment goals. The primary objective of the ENGAGE study was to determine if eliglustat was superior to placebo in terms of the percentage change in spleen volume from baseline to week 39. The ENCORE study was designed to assess if eliglustat was noninferior to imiglucerase in the proportion of patients who maintained stability over 52 weeks based on a composite outcome that included hematologic and organ volume variables. Key limitations included the small sample size of the ENGAGE study and, for the ENCORE study, carry-over effects of ERT, the lack of blinding for subjective outcomes, and a noninferiority margin that was not supported by the literature. Both trials focused on intermediate outcomes for Gaucher disease and were not designed to assess longer-term outcomes, such as bone disease, that are of concern to patients.

Interpretation of Results

Efficacy

In treatment-naive patients, eliglustat showed statistically significant reductions in spleen volume after 39 weeks of treatment compared with placebo (treatment difference in percentage change from baseline: −30%; 95% CI, −37% to −23%; $P < 0.0001$). Statistically significant differences between eliglustat and placebo were also detected in the percentage change from baseline in liver volume (−6.6%; 95% CI, −11.4% to −1.9%; $P = 0.007$) and platelet counts (41%; 95% CI, 24% to 58%; $P < 0.0001$), and in the absolute change from baseline in hemoglobin levels (12 g/L; 95% CI, 6 to 19; $P = 0.0006$).

Among treatment-experienced patients with well-controlled Gaucher disease, 85% of those who received eliglustat remained stable for 52 weeks compared with 94% of patients who remained on imiglucerase, based on the PPS of the ENCORE trial (absolute difference −8.8%; 95% CI, −17.6% to 4.2%). Eliglustat met the noninferiority criteria set by the manufacturer, as the lower limit of the 95% CI was within the predefined 25% noninferiority margin. This noninferiority threshold, however, was not supported by the literature, and both the FDA and European Medicines Agency expressed concerns with this margin.[6,7] The European Medicines Agency selected a −20% noninferiority margin and reanalyzed the proportion of patients stable (and 95% CI) using other standard statistical methods. The lower bound of the 95% CI did not exclude −20% for all analyses and the European Medicines Agency stated that noninferiority was not comprehensively demonstrated.[7] Despite these concerns regarding the noninferiority threshold, the drug was approved by the FDA and European Medicines Agency for long-term treatment of adult patients with GD1. Health Canada accepted the 25% noninferiority margin for the primary outcome in ENCORE.[51]

Eliglustat met the noninferiority criteria versus imiglucerase, based on the percentage change in spleen volume (−2.8%; 95% CI, −8.1 to 2.5%) (PPS), as the upper limit of the 95% CI was less than the 15% noninferiority margin. No statistically significant differences were detected between eliglustat and imiglucerase in the percentage change in liver volume (−0.3%; 95% CI, −3.3% to 2.8%) or platelet count (2.8%; 95% CI, −3.0% to 8.5%), and no clinically important differences were observed in the absolute change from baseline in hemoglobin levels (−3 g/L; 95% CI, −6 to −0.3). These outcomes in the ENCORE trial were considered exploratory, as there was no attempt to control for family-wise type I error.

Although both trials tested several bone-related outcomes, neither trial was designed or powered to detect differences in bone disease, which patient groups report as important to patients. No differences in BMD were detected in either study based on T-scores or Z-scores of the spine or femur; however, the clinical expert stated that the duration of the trials was insufficient to detect clinically important differences in bone disease. A reduction in the bone marrow burden score was observed for eliglustat versus placebo (LS mean difference −1.1; 95% CI, −1.7 to −0.4); however, the clinical importance of this difference is unclear. One patient in the placebo group of the 39-week ENGAGE study and one patient in the imiglucerase group of 52-week ENCORE study

experienced a bone crisis. No patients who received eliglustat reported a bone crisis in either trial. Both trials had an open-label extension period, where patients were treated with eliglustat for a median of [redacted] (ENGAGE) and [redacted] (ENCORE). In the ENCORE extension, two patients experienced a bone crisis: one event reported at [redacted] and two events (in one patient) reported at [redacted]. One other patient reported a bone crisis prior to starting eliglustat treatment in the extension study, and no repeat events were reported after [redacted] of eliglustat. Additional data were available from the EDGE trial that compared once-daily versus twice-daily eliglustat regimens (Appendix 7). In this study, three patients (2.3%) experienced a bone crisis during the one-year randomized period.[52]

Both the ENGAGE and ENCORE trials examined a number of surrogate and exploratory outcomes. Chitotriosidase levels were reduced by 44% in the eliglustat group relative to placebo in the ENGAGE study, and were similar at baseline and week 52 in both the eliglustat and imiglucerase groups in the ENCORE trial (descriptive data only). No data on CCL18 levels were reported due to quality control issues in the laboratory that performed the analyses for both trials.

The DS3, a measure of disease burden, was presented in both studies. No clinically important difference between eliglustat and placebo was observed after 39 weeks of treatment in the ENGAGE study, as the LS mean difference between groups (−0.3 points) did not exceed the MCID of 3.17 that has been reported in the literature. DS3 scores were reported for the ENCORE trial but these data were missing values for 19% to 29% of patients and no between-group comparisons were estimated.

Quality of life was assessed using the generic SF-36 instrument as an exploratory outcome in both trials. In the ENGAGE study, no statistically significant differences were detected between eliglustat and placebo in the individual domains or component scores, except for the physical functioning domain. Although the ENCORE study also reported data on SF-36, there were no between-group comparisons; thus, no conclusions can be made on the relative treatment effects. The FSS increased by 0.7 points for eliglustat versus placebo in the ENGAGE study, which suggests more severe fatigue in the eliglustat group; however, it is unclear if this difference is clinically important as there is no known MCID for the FSS. No statistically significant differences between eliglustat and placebo were detected in any domain of the BPI. In the ENCORE study, scores for the FSS and the BPI were similar at baseline and week 52 within groups. No between-group comparisons were calculated. Neither trial was designed or powered to detect differences in SF-36, FSS or BPI, and in the ENCORE trial these subjective outcomes may be prone to reporting bias due to the open-label design.

The key limitations of the ENGAGE trial were its small sample size (N = 40) and relatively short duration (nine months). No studies were found that compared eliglustat to imiglucerase in treatment-naive patients, or that compared eliglustat to other drugs to treat Gaucher disease besides imiglucerase. These data would be of interest to clinicians and policy-makers to help define eliglustat's place in therapy. Although the key outcomes evaluated in ENCORE and ENGAGE (hemoglobin, platelets, liver volume, and spleen volume) are important intermediate outcomes and are part of the treatment goals for patients with Gaucher disease,[1] the studies did not address other important outcomes such as serious skeletal complications, risk of bleeding, and patient's functional status. In ENCORE, patients were switched from ERT to eliglustat; thus, some of the treatment effects observed in the eliglustat group may be attributable to potential carry-over effects of ERT.

In both studies, the dose of eliglustat was titrated based on the patients' trough serum levels in the first four to eight weeks of treatment. The drug, however, was approved using a simplified dosage regimen based on CYP2D6 metabolizer status.[7] This dosage regimen was based on a population pharmacokinetic model, using data from healthy subjects and patients with Gaucher disease which found that CYP2D6 status was the most significant determinant of exposure to eliglustat.[7] Of note, 15% of patients in the ENGAGE study and 68% of patients in the ENCORE trial did not receive an approved dosage regimen. Of these, 48% of patients in the ENCORE trial received a dose that was 50% higher than the Health Canada–recommended maximum daily dose. The manufacturer's pharmacokinetic model predicted that any differences in efficacy with the CYP2D6 dosage regimen would be clinically negligible.[7]

Harms

Overall, most patients in the ENGAGE and ENCORE trials reported one or more adverse events, including 90% and 97% of those who received eliglustat, respectively, 70% who received placebo, and 79% who received imiglucerase. The most common adverse events in the eliglustat group included arthralgia, headache, nasopharyngitis, diarrhea, nausea, fatigue, and back pain.

In the ENCORE study, 11 patients (10%) in the eliglustat group and no patients in the imiglucerase group had a serious adverse event. Except for syncope, which occurred in two patients, all other specific events were reported in one patient with no clustering in a particular system organ class. Two eliglustat and one imiglucerase patient stopped treatment due to adverse events (2% per group). No serious adverse events were reported and no patients stopped treatment due to adverse events in the ENGAGE study. There were no deaths in either study.

Of the notable harms listed in the protocol, neoplasms were reported [redacted] of patients in the eliglustat group in the ENCORE study. This included [redacted] case each of [redacted]. No neoplasms were reported in the imiglucerase group in the ENCORE study, or in either group in the ENGAGE study. Cardiac arrhythmias or syncope were observed in [redacted] eliglustat patients ([redacted]) and [redacted] imiglucerase patients in the ENCORE study, and [redacted] patient ([redacted]) in the placebo group and [redacted] patients in the eliglustat group in the ENGAGE study. Treatment-emergent peripheral neuropathy was reported in [redacted] patients in the eliglustat group, compared with [redacted] patients in the imiglucerase group in ENCORE.

Of note, the included studies were not powered to detect infrequent adverse events as the sample size was limited (40 patients to 159 patients). Furthermore, the duration of treatment of the randomized portion of these studies was 39 weeks to 52 weeks – time frames that may be insufficient to identify adverse events such as malignancy, which require a longer duration of study to observe. Although the frequency of adverse events was higher in the eliglustat group than the imiglucerase group in the ENCORE trial, this is not unexpected as all patients had received ERT for at least three years prior to randomization. Most adverse events related to imiglucerase would be expected to occur in the first few months of treatment. In addition, this trial was open label, and knowledge of the treatment received may have influenced the reporting of adverse events.

Additional safety data were available from the open-label, extension period of the ENGAGE and ENCORE studies (Appendix 6), a phase II trial (Study 304) and an eliglustat once-daily versus twice-daily dosage response study (EDGE) (Appendix 7). This included data for 40 patients with median treatment duration [redacted] (ENGAGE) and 157 patients treated for [redacted] (ENCORE). In the uncontrolled phase II trial (N = 26), the median eliglustat treatment duration was 47.8 months for the primary study period and the extension study and 42 months in the EDGE randomized controlled trial and its extension (N = 170). No new safety signals were identified in these trials. [redacted].

Eliglustat can potentially interact with a number of other medications that affect the CYP2D6 and CYP3A metabolic enzymes, and with drugs that prolong the QTc interval. The drug has the potential to prolong the PR, QTc, or QRS cardiac interval, which could result in cardiac arrhythmias.[5] Restrictions and exclusions were applied during the ENGAGE and ENCORE studies to minimize the risk of an interaction. The product monograph also has recommended eliglustat dosage modifications or has placed warnings or contraindications on the concurrent use of these medications (Appendix 8). Moreover, patients with pre-existing cardiac conditions were excluded from the ENCORE trial; therefore, data are lacking on the safety of eliglustat in these patients. The product monograph includes a warning on the use of eliglustat in patients with pre-existing cardiovascular disease, electrolyte disturbances, or conditions that can lead to electrolyte disturbances, and in combination with Class IA and Class II antiarrhythmic drugs.[5] Moreover, caution is advised in patients with a history of syncope or family history of sudden cardiac death at less than 50 years of age.[5] ECG monitoring is recommended in patients with baseline ECG abnormalities, or those receiving QTc-interval, QRS-interval, or PR-interval prolonging drugs.[5] Use in patients with any hepatic impairment or moderate to severe renal impairment is also not recommended, as the drug has not been studied in these patient populations.[5]

Potential Place in Therapy[1]

ERT for Gaucher disease is effective at controlling common manifestations of the disease such as cytopenias, organomegaly, and progressive bone infiltration. ERT for Gaucher disease remains the most successful treatment for a lysosomal storage disorder

1 This information is based on information provided in draft form by the clinical expert consulted by CDR reviewers for the purpose of this review.

currently available, but there are still some challenges in treating patients with Gaucher disease. ERT requires regular biweekly IV infusions. While the manufacturers of ERT support patients to receive these infusions in their home, this still remains an inconvenient and minimally invasive form of therapy. Severe allergic reactions to ERT for Gaucher disease are uncommon; however, there are a small number of patients with severe allergic reactions who either have to stop ERT or who have to take premedications such as hydrocortisone, which have their own adverse effects. While most patients receive their infusions through a peripheral IV line, some patients over time lose peripheral IV access and will require insertion of a central venous catheter with its attendant risks. Miglustat, the other oral substrate inhibitor for Gaucher disease, has an undesirable side-effect profile, which limits its use in many patients. An oral medication such as eliglustat may provide treatment that is more convenient for patients who tolerate ERT, would remove the need to insert a central venous catheter in the small number of adult patients who require this, and could potentially offer an alternative for patients who are unable to tolerate ERT or in whom premedications are required to prevent allergic reactions. Due to the psychological impact of regular venepuncture on children with Gaucher disease, it is more common to insert a central venous catheter for ERT infusions; therefore, effective and well-tolerated oral therapy would be even more of an advantage in children than in adults. There is a certain probability that eliglustat, because of its oral route of administration, could be considered for use in children with Gaucher disease; however, it is not indicated for patients under the age of 18.

ERT is not 100% effective and there are still some patients who continue to have disease progression despite treatment. There are some patients with rare and life-threatening manifestations of Gaucher disease (such as pulmonary hypertension) on whom the impact of ERT is unclear due to limited data. There are some longer-term complications of Gaucher disease for which the mechanisms have not been fully defined (such as the risk of developing malignancy or features of Parkinson disease). Finally, some patients with Gaucher disease present late with irreversible disease manifestations such as bone infarction for which ERT is of no benefit. There are no data available on the effects of eliglustat in any of these situations, which will therefore remain as unmet needs until more data are available for ERT, eliglustat, or both. Also, as ERT has been available for decades, there is information on its effects and limitations in patients with very severe Gaucher disease (both patients with GD1 and the other subtypes). Eliglustat is only indicated for GD1 and, as the pivotal study on eliglustat has been designed as a noninferiority trial in patients with mild to moderate Gaucher disease, the impact of eliglustat on patients with very severe GD1 manifestations is not well defined.

ERT for Gaucher disease is a therapy for which flexible dosage regimens are possible and close patient monitoring allows the dose to be adjusted to minimum effective doses. As ERT for Gaucher disease has been available for decades, data on the efficacy of this dosage flexibility are widely available and dose tapering can result in considerable cost savings while maintaining excellent patient outcomes. It is standard practice in the care of patients with Gaucher disease to use flexible dosage regimens. It is important, therefore, that any treatment alternatives, including eliglustat, show cost-effectiveness comparable to the flexible dosage practices of ERT.

ERT for Gaucher disease is currently prescribed for patients who have established manifestations of the disease and is not currently recommended for patients who do not have evidence of disease involvement. Guidelines from Ontario for the use of ERT are in the public domain[8] and most other provinces follow very similar guidelines. These guidelines include the currently available oral therapy, miglustat. The clinical trials of eliglustat involved two patient groups: patients who required treatment but were naive to ERT, and patients who had been stabilized on ERT and were then switched to eliglustat. In both cases, though, treatment for Gaucher disease was thought to be indicated by the referring physician. Therefore, it is not expected that the indications for treatment (or the number of patients eligible for treatment) will be altered by the emergence of a well-tolerated oral therapy but, rather, that eliglustat will be added to the list of products available to choose from. Patients being considered for therapy have to have a series of assessments that would be similar for patients being considered for ERT or either oral therapy. However, patients being considered for eliglustat would have to have some investigations that would not be required for ERT patients, including CYP2D6 genotype testing, assessment of concurrent medications for drug-drug interactions (i.e., moderate to strong CYP2D6 or CYP3A inhibitors), and baseline ECG assessment (with ECG monitoring during treatment in patient populations at an increased risk of having ECG abnormalities).

Other Considerations

CYP2D6 genotype testing is required in order to determine a patient's eligibility for treatment with eliglustat and to determine dosages.[5] In correspondence with CDR, the manufacturer has stated that they are committed to making CYP2D6 genotype testing available and funding these costs for patients with Gaucher disease in Canada.[9] The manufacturer expects the proportion of

Canadian patients who are poor, intermediate, or extensive CYP2D6 metabolizers to be similar to that observed in the ENCORE trial (4%, 13%, and 77%, respectively). Based on ENCORE, approximately 6% of patients would be ultra-rapid or indeterminate metabolizers and therefore not suitable for treatment with eliglustat.

Although eliglustat is currently not approved for use in children, or in combination with ERT, there may be interest in expanding its use to include these populations. At present, there is no evidence available on the efficacy and safety of eliglustat in combination with ERT. In the pivotal ENGAGE and ENCORE trials, only two patients enrolled were less than 18 years of age.

Conclusions

In treatment-naive patients with GD1, eliglustat was associated with statistically significant decreases in liver and spleen volume, and increased hemoglobin and platelet levels compared with placebo.

In adults whose GD1 was well controlled with ERT, fewer patients who switched to eliglustat treatment met hematologic and organ volume disease stability criteria than those who remained on imiglucerase, though eliglustat met the noninferiority criteria versus imiglucerase. There is, however, some uncertainty in the noninferiority margin used in the analysis, and the possibility of carry-over effects among patients switched from ERT to eliglustat.

Efficacy data are lacking in patients with symptomatic bone disease, as these patients were excluded from the clinical trials. There is insufficient evidence from the pivotal ENGAGE and ENCORE randomized controlled trials to draw any conclusions regarding the impact of eliglustat on bone disease, due to lack of statistical power and insufficient follow-up time in the available trials. Neither trial was designed to detect differences in quality of life or symptoms of Gaucher disease.

Few patients stopped eliglustat treatment due to adverse events. Additional data are required to determine the safety of eliglustat in patients with cardiovascular disease, and to determine the risk of long-term adverse events.

Appendix 1: Patient Input Summary

This section was prepared by CADTH staff based on the input provided by patient groups.

1. Brief Description of Patient Group Supplying Input

One patient group contributed information for this summary: the National Gaucher Foundation of Canada. The Foundation is a voluntary group of individuals, families, health professionals, and affiliated organizations with the purpose of providing support and information to those afflicted with Gaucher disease, their families, and their caregivers. With respect to a conflict of interest of sponsorship or funding arrangement, in 2015 and 2016, the National Gaucher Foundation of Canada received unrestricted educational grants to help fund patient support efforts from Shire Canada, Actelion Pharmaceuticals Ltd., Sanofi Genzyme Canada, and Pfizer Canada. A declaration of no conflict of interest was made in respect to those compiling the patient input submission.

2. Condition-Related Information

The information compiled herein is a summary of (1) an online survey posed to patients and caregivers of Gaucher disease in February and March 2016, (2) the views of two treating clinicians with respect to existing therapies and current unmet needs in the treatment of Gaucher disease, and (3) background information about Gaucher disease from the National Gaucher Foundation of Canada website: www.gauchercanada.ca. Of the 37 survey respondents, 33 were patients with Gaucher disease type 1 and 31 were reported as Canadian. Experience with eliglustat was reported by seven participants (six patients and one caregiver).

For patients and caregivers, there is often a feeling of uncertainty about the future due to the variable and unpredictable nature of the disease. In fact, nearly half of survey respondents reported psychological distress related to Gaucher disease. Body image can be a difficult challenge among those with pronounced spleen or liver enlargement. The “long diagnostic odyssey” and the ensuing treatments take a physical and emotional toll on patients and caregivers alike.

The survey respondents reported experiencing several symptoms of Gaucher disease, including low red blood cell and platelet counts (86%), bone pain and bone fractures (67%), easy bruising (67%), fatigue (extreme for some) (67%), and aching joints and enlarged belly (due to liver and spleen enlargement) (~55%). Symptoms less frequently reported reported consisted of nose bleeds, delayed growth, and reduced appetite (11% to 47%).

An ongoing concern, even throughout treatment, is that Gaucher disease patients frequently suffer from residual bone disease, which can limit normal activities, make slight movements painful, make sleeping difficult, and may require hospitalization. A range of experiences was reported in the survey, but a common thread is that fatigue and pain can seriously impact quality of life. One patient wrote, “The most difficult aspect of this disease is its effect on my bones. I live with chronic bone pain. I have little stamina for either physical or social activities... The acute episodes of bone pain I experience are extremely difficult. I become lethargic and have little strength for basic daily activities.” On the other side of the spectrum, another patient commented that Gaucher disease had “no real impact on my life.”

3. Current Therapy-Related Information

Information for this section was compiled from the online survey of patients and caregivers, the input of treating clinicians, and the National Gaucher Foundation of Canada’s website.

Gaucher disease-specific treatments have the goal of reducing the buildup of glucocerebroside in cells. This accumulation can be mediated by treating the deficiency of glucocerebrosidase through enzyme replacement therapy (ERT), or by reducing the production of glucocerebroside through substrate reduction therapy. Canadian patients currently undergoing front-line treatment for Gaucher disease receive one of two ERT drugs: imiglucerase or velaglucerase. Both options require biweekly intravenous infusions. There is one second-line treatment currently used in Canada: miglustat, an oral SRT. The use of miglustat is limited in Canada, as the Canadian Expert Drug Advisory Committee made a do-not-reimburse recommendation in 2004.

Two major unmet needs experienced by Gaucher disease patients and their caregivers stand out in this patient input submission. Firstly, patients are seeking a more effective treatment for their disease. Despite receiving ERT, 50% of survey respondents

reported residual bone disease or skeletal complications, including bone pain (chronic and acute), osteopenia, osteoporosis, osteonecrosis, or joint collapse. Almost all ERT patients felt that access to a drug that could improve bone manifestations would be of value. Secondly, the current standard of therapy, biweekly intravenous infusions, is an inconvenient, disruptive, and sometimes costly burden. Many ERT patients (and often their caregivers) must travel twice a month to a clinical setting to receive the infusion, a process that requires several hours and can incur out-of-pocket expenses. This therapy can interfere significantly with school, careers, and recreational and domestic activities. Nonetheless, patients receiving ERT appreciate that while the current therapies can be onerous, they are generally beneficial and worthwhile. One patient remarked, “On treatment, my symptoms associated with Gaucher disease have no impact on my day-to-day life. Without treatment I would be unable to continue in my current employment due to pain and fatigue.”

It should be noted that a small number of patients cannot receive ERT due to adverse reactions.

4. Expectations About the Drug Being Reviewed

Six patients and one caregiver surveyed had experience with eliglustat. Of this sampling, one patient reported diarrhea, while five reported “no noticeable side effects.” Four of six patients felt there had been a “significant improvement” in the management of their Gaucher disease while on eliglustat. The survey also revealed that the overriding motivator behind switching from ERT to eliglustat had been the cessation of inconvenient infusions: “Freedom!!! Not living life in two-week intervals...” A secondary benefit seemed to be reduced fatigue and bone pain, although one patient commented: “It greatly helped with my fatigue and bone pain, but gradually my spleen and liver volumes increased and my platelet counts decreased.”

Because eliglustat is an oral therapy, patients appreciate that despite improvement in quality of life upon switching from biweekly infusions to oral therapy, compliance might be an issue for some. However, most feel that oral therapy affords a greater freedom from the burden of infusion therapy and that eliglustat likely has a beneficial effect on fatigue and on the bone manifestations of Gaucher disease.

Appendix 2: Literature Search Strategy

OVERVIEW	
Interface:	Ovid
Databases:	Embase 1974 to present Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present Note: Subject headings have been customized for each database. Duplicates between databases were removed in Ovid.
Date of Search:	February 17, 2017
Alerts:	Weekly search updates until June 21, 2017
Limits:	No date or language limits were used Conference abstracts were excluded

SYNTAX GUIDE	
/	At the end of a phrase, searches the phrase as a subject heading
.sh	At the end of a phrase, searches the phrase as a subject heading
MeSH	Medical Subject Heading
exp	Explode a subject heading
*	Before a word, indicates that the marked subject heading is a primary topic; or, after a word, a truncation symbol (wildcard) to retrieve plurals or varying endings
adj#	Adjacency within # number of words (in any order)
.ti	Title
.ab	Abstract
.ot	Original title
.hw	Heading word; usually includes subject headings and controlled vocabulary
.kf	Author keyword heading word (MEDLINE)
.kw	Author keyword (Embase)
.rn	CAS registry number
.nm	Name of substance word
ppez	Ovid database code; Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present
oemezd	Ovid database code; Embase 1974 to present, updated daily

MULTI-DATABASE STRATEGY

#	Searches	Results
1	(cerdelga* or eliglustat* or genz99067 or genz-99067 or genz112638 or genz-112638 or DR40J4WA67 or N0493335P3).ti,ab,kf,ot,hw,rn,nm.	274
2	(491833-29-5 or 928659-70-5).rn,nm.	116
3	1 or 2	274
4	3 use ppez	56
5	*cerdelga/	67
6	(cerdelga* or eliglustat* or genz99067 or genz-99067 or genz112638 or genz-112638 or DR40J4WA67 or N0493335P3).ti,ab,ot,kw.	183
7	5 or 6	184
8	7 use oemezd	133
9	4 or 8	189

MULTI-DATABASE STRATEGY	
10 remove duplicates from 9	138
11 conference abstract.pt.	2472434
12 10 not 11	74

OTHER DATABASES	
PubMed	A limited PubMed search was performed to capture records not found in MEDLINE. Same MeSH, keywords, limits, and study types used as per MEDLINE search, with appropriate syntax used.
Trial registries (Clinicaltrials.gov and others)	Same keywords, limits used as per MEDLINE search.

Grey Literature

Dates for Search:	February 2017
Keywords:	Cerdelga (eliglustat)
Limits:	Conference abstracts removed

Relevant websites from the following sections of the CADTH grey literature checklist *Grey Matters: a practical tool for searching health-related grey literature* (https://www.cadth.ca/grey-matters) were searched:

- Health Technology Assessment Agencies
- Health Economics
- Clinical Practice Guidelines
- Drug and Device Regulatory Approvals
- Advisories and Warnings
- Drug Class Reviews
- Databases (free)
- Internet Search

Appendix 3: Excluded Studies

Reference		Reason for Exclusion
1.	Kamath RS, Lukina E, Watman N, Dragosky M, Pastores GM, Arreguin EA, et al. Skeletal improvement in patients with Gaucher disease type 1: a phase 2 trial of oral eliglustat. Skeletal Radiol [Internet]. 2014 Oct [cited 2017 Feb 21];43(10):1353-60. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4141971/pdf/256_2014_Article_1891.pdf	Phase II trial
2.	Lukina E. Latest data on Genz-112638, an investigational oral therapy for type 1 Gaucher disease: Phase II clinical trial results after 1 year of treatment. Clin Ther. 2009;31(Suppl 3):S194-S195.	
3.	Lukina E, Watman N, Dragosky M, Pastores GM, Arreguin EA, Rosenbaum H, et al. Eliglustat, an investigational oral therapy for Gaucher disease type 1: Phase 2 trial results after 4 years of treatment. Blood Cells Mol Dis. 2014 Dec;53(4):274-6.	
4.	Lukina E, Watman N, Arreguin EA, Dragosky M, Iastrebner M, Rosenbaum H, et al. Improvement in hematological, visceral, and skeletal manifestations of Gaucher disease type 1 with oral eliglustat tartrate (Genz-112638) treatment: 2-year results of a phase 2 study. Blood. 2010 Nov 18;116(20):4095-8. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2993616	
5.	Lukina E, Watman N, Arreguin EA, Banikazemi M, Dragosky M, Iastrebner M, et al. A phase 2 study of eliglustat tartrate (Genz-112638), an oral substrate reduction therapy for Gaucher disease type 1. Blood. 2010 Aug 12;116(6):893-9. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2924227	
6.	Clinical Study Report: GZGD00304. A phase 2, open-label, multi-center study evaluating the efficacy, safety, and pharmacokinetics of Genz-112638 in Gaucher Type 1 patients [CONFIDENTIAL internal manufacturer's report]. Cambridge (MA): Genzyme Corporation, a Sanofi Company; 2012 Sep 28.	
7.	Cox TM, Drelichman G, Cravo R. Eliglustat compared with imiglucerase in patients with Gaucher's disease type 1 stabilised on enzyme replacement therapy: a phase 3, randomised, open-label, non-inferiority trial. Lancet. 2015 Jun 13;385(9985):2354. Erratum for: Lancet 2015; 385:2355-62.	Wrong study design/erratum
8.	Cox TM, Drelichman G, Cravo R. Eliglustat compared with imiglucerase in patients with Gaucher's disease type 1 stabilised on enzyme replacement therapy: a phase 3, randomised, open-label, non-inferiority trial. Lancet. 2015 Nov 17;386:e45. Erratum for: Lancet 2015;385:2355-62.	
9.	Cox TM, Drelichman G, Cravo R, Balwani M, Burrow TA, Martins AM, et al. Eliglustat maintains long-term clinical stability in patients with Gaucher disease type 1 stabilized on enzyme therapy. Blood [Internet]. 2017 Feb 6 [cited 2017 Feb 17]. Available from: http://www.bloodjournal.org/content/bloodjournal/early/2017/02/06/blood-2016-12-758409.full.pdf	
10.	Ibrahim J, Underhill LH, Taylor JS, Angell J, Peterschmitt MJ. Clinical response to eliglustat in treatment-naive patients with Gaucher disease type 1: Post-hoc comparison to imiglucerase-treated patients enrolled in the International Collaborative Gaucher Group Gaucher Registry. Mol Genet Metab Rep [Internet]. 2016 Sep [cited 2017 Feb 21];8:17-9. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4927653/pdf/main.pdf	
11.	Clinical Study Report: GZGD03109. A phase 3, randomized, multi-center, multi-national, double-blind study to evaluate the efficacy, safety, and pharmacokinetics of once daily versus twice daily dosing of eliglustat in patients with Gaucher disease Type 1 who have demonstrated clinical stability on a twice daily dose of Genz-112638 (EDGE)[**CONFIDENTIAL** internal manufacturer's report]. Mississauga (ON): Sanofi Genzyme; 2016 Sep 30.	Wrong comparator

Appendix 4: Detailed Outcome Data

Table 20: Disease Stability – Individual Components

Outcome / Treatment	ENCORE (PPS)		ENCORE (FAS)	
Stability Criteria Met[a]	N	Patients Stable for 52 Weeks, n (%)	N	Patients Stable for 52 Weeks, n (%)
Hemoglobin				
Eliglustat	99	94 (95)	106	98 (92)
Imiglucerase	47	47 (100)	53	51 (96)
Platelets				
Eliglustat	99	92 (93)	106	96 (91)
Imiglucerase	47	47 (100)	53	52 (98)
Spleen Volume[b]				
Eliglustat	71	68 (96)	77	72 (94)
Imiglucerase	39	39 (100)	45	44 (98)
Liver Volume				
Eliglustat	99	95 (96)	106	100 (94)
Imiglucerase	47	44 (94)	53	49 (93)

FAS = full analysis set; MN = multiples of normal; PPS = per-protocol set.

[a] Stability criteria: Hemoglobin level did not decrease > 15 g/L from baseline; platelet count did not decrease > 25% from baseline; spleen volume (in MN) did not increase > 25% from baseline (if applicable); liver volume (in MN) did not increase > 25% from baseline.

[b] Patients who had undergone a splenectomy were excluded.

Source: Clinical Study Report.[10]

Table 21: Disease Stability – Post Hoc Subgroup Data for Composite Outcome

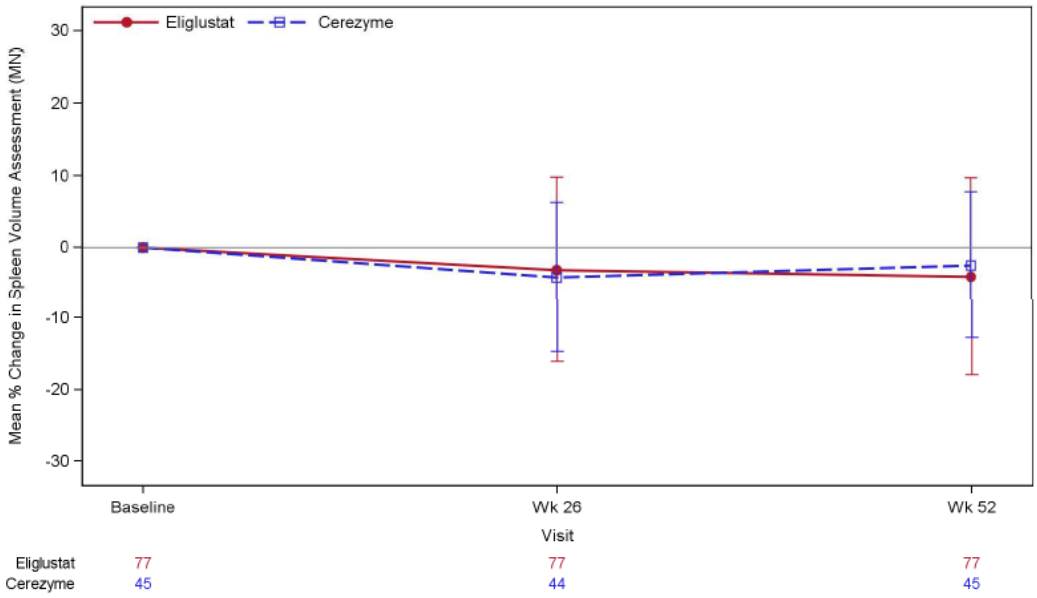
Subgroup / Treatment	ENCORE (PPS)	ENCORE (FAS)
	Patients Stable for 52 Weeks, n/N (%)	Patients Stable for 52 Weeks, n/N (%)
Prior ERT		
Velaglucerase use		
Eliglustat	18/20 (90)	19/22 (86)
Imiglucerase	7/8 (88)	7/8 (88)
Imiglucerase use[a]		
Eiglustat	[redacted]	[redacted]
Imiglucerase	[redacted]	[redacted]
Dosage of Eliglustat		
50 mg	[redacted]	[redacted]
100 mg	[redacted]	[redacted]
150 mg	[redacted]	[redacted]

ERT = enzyme replacement therapy; FAS = full analysis set; PPS = per-protocol set.

[a] Number and percentage of patients stable calculated by CADTH Common Drug Review.

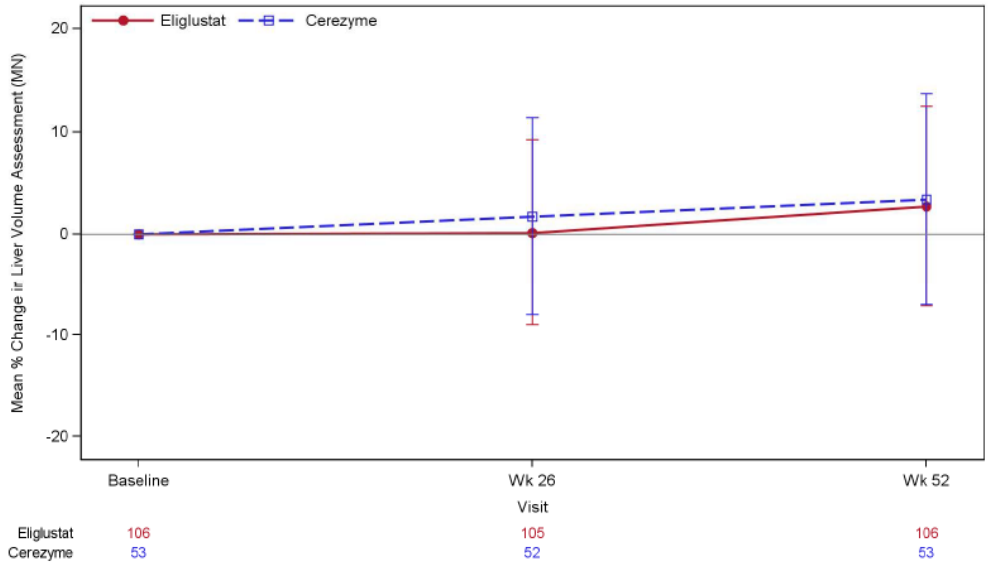
Source: Pleat 2016;[27] additional data provided by manufacturer.[33]

Figure 3: Mean Percentage Change From Baseline in Spleen Volume – ENCORE (FAS)



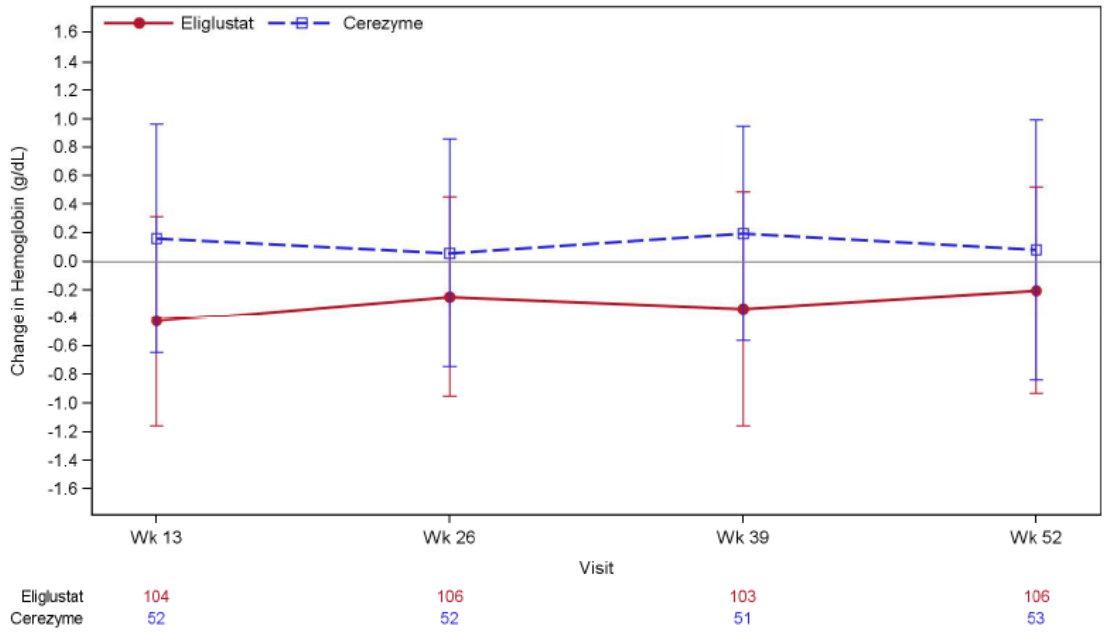
FAS = full analysis set; MN = multiples of normal; Wk = week.
Source: Clinical Study Report.[10]

Figure 4: Mean Percentage Change From Baseline in Liver Volume – ENCORE (FAS)



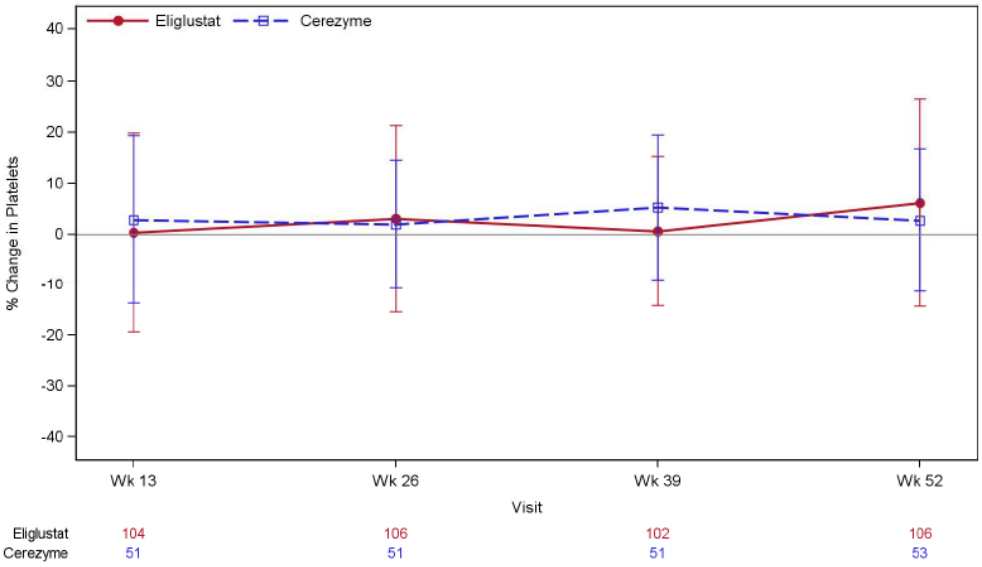
FAS = full analysis set; MN = multiples of normal; Wk = week.
Source: Clinical Study Report: CSR.[10]

Figure 5: Mean Change From Baseline in Hemoglobin (g/dL) – ENCORE (FAS)



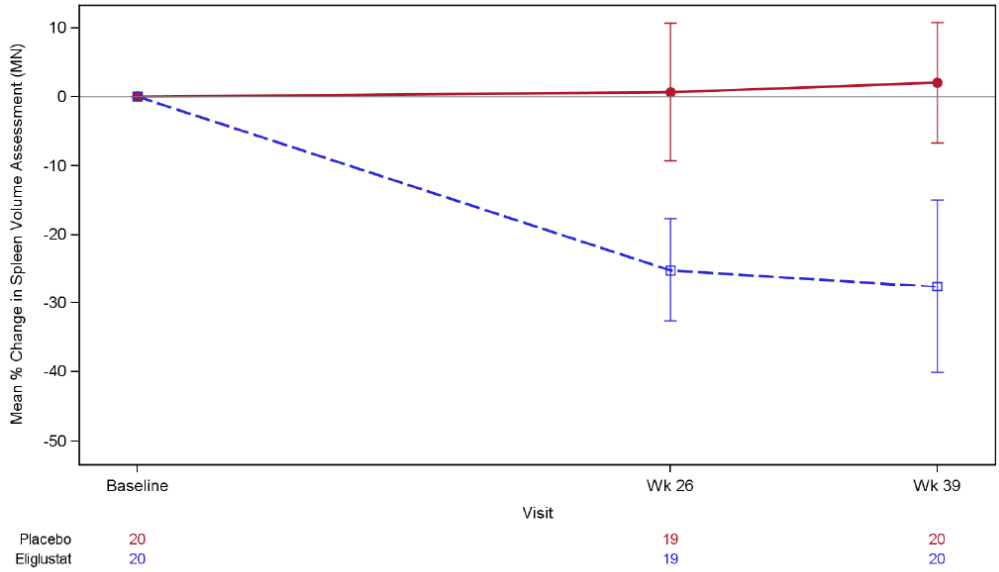
FAS = full analysis set; Wk = week.
Source: Clinical Study Report.[10]

Figure 6: Mean Percentage Change From Baseline for Platelet Count – ENCORE (FAS)



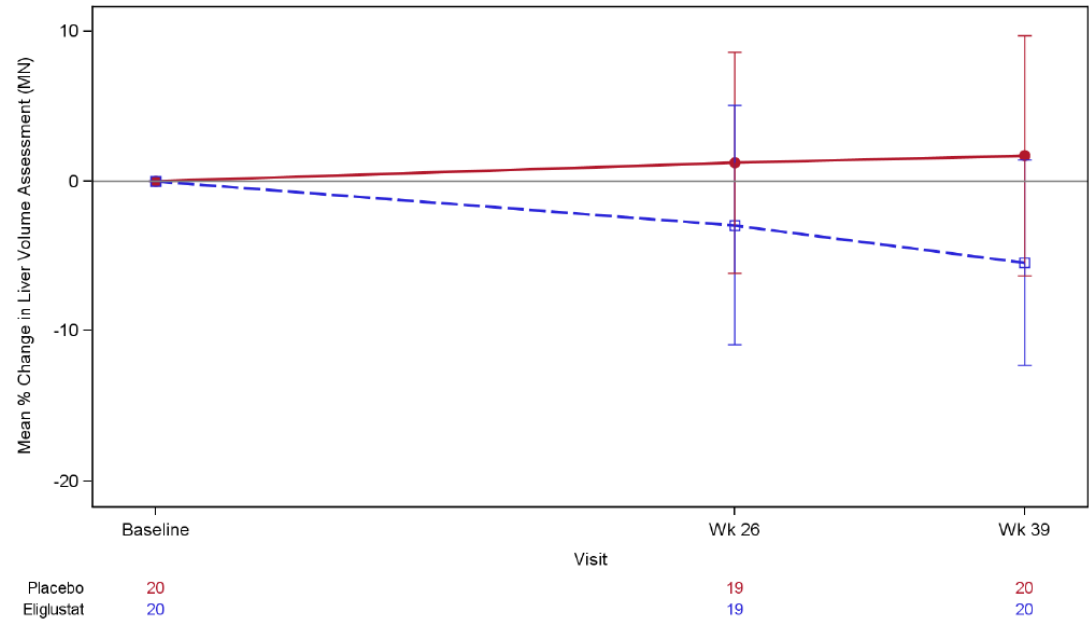
FAS = full analysis set; Wk = week.
Source: Clinical Study Report.[10]

Figure 7: Mean Percentage Change in Spleen Volume – ENGAGE (FAS)



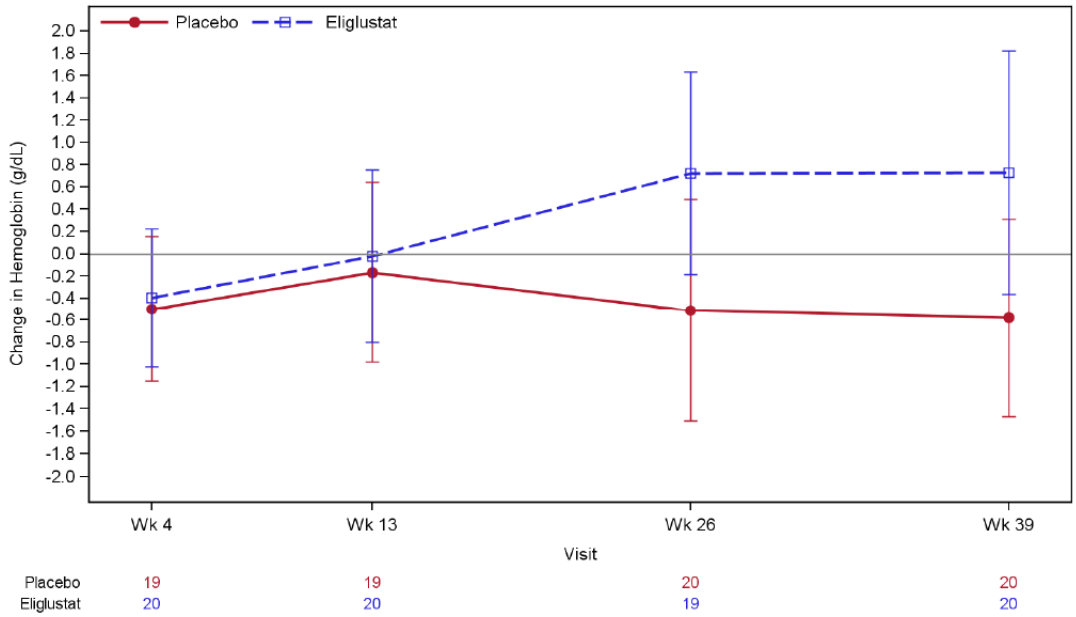
FAS = full analysis set; MN = multiples of normal; Wk = week.
Source: Clinical Study Report: CSR.[11]

Figure 8: Mean Percentage Change in Liver Volume – ENGAGE (FAS)



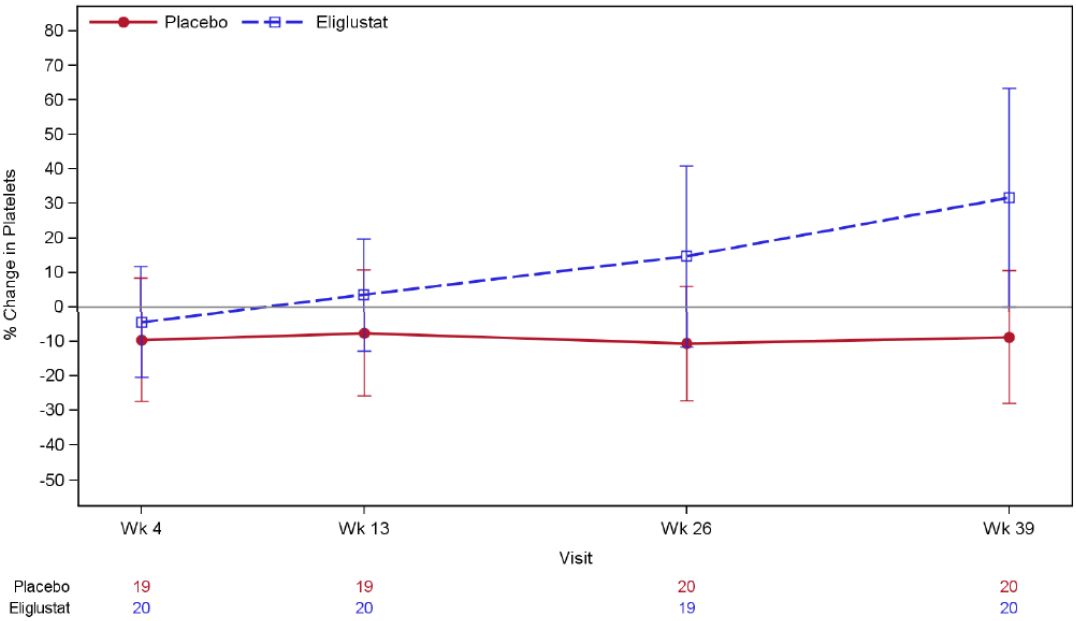
Source: Clinical Study Report.[11]

Figure 9: Mean Change From Baseline in Hemoglobin (g/dL) – ENCORE (FAS)



FAS = full analysis set; Wk = week.
Source: Clinical Study Report.[11]

Figure 10: Mean Percentage Change in Platelet Count – ENGAGE (FAS)



FAS = full analysis set; Wk = week.
Source: Clinical Study Report.[11]

Appendix 5: Validity of Outcome Measures

Aim

To summarize the measurement properties (e.g., reliability, validity, minimal clinically important difference [MCID]) of the following outcome measures:

- Brief Pain Inventory (BPI)
- Fatigue Severity Scale (FSS)
- Short Form (36) Health Survey (SF-36)
- Gaucher disease type 1 (GD1) disease severity scoring system (DS3)

Findings

Outcome measures, discussed in detail here, are summarized in Table 22.

Table 22: Summary of Validity of Outcome Measures

Instrument	Type	Evidence of Validity	MCID	References
BPI	Patient-reported generic psychometric questionnaire for pain intensity and impact (11-point numerical scale)	Yes	Unknown	37,38,53,54
FSS	Patient-reported generic questionnaire measuring impact of fatigue (seven-point Likert scale)	Yes	Unknown	39,40
SF-36	Patient-reported generic quality of life instrument	Yes	PCS 2 to 4.1[a] MCS 3 to 3.9[a]	36
GD1-DS3	Clinically based, physician-reported instrument assessing the severity of GD1	Yes	−3.17 (improvement) 3.86 (worsening)	47

BPI = Brief Pain Inventory; FSS = Fatigue Severity Scale; GD1 = Gaucher disease type 1; DS3 = Gaucher disease severity scoring system; MCID = minimal clinically important difference; MCS = mental component score; PCS = physical component score; SF-36 = Short Form (36) Health Survey.

[a] A general range in the MCID has been established for the SF-36, but there is no validated MCID for Gaucher disease.

Brief Pain Inventory

The BPI is a patient-reported pain questionnaire used to assess the intensity of pain experienced, as well as the degree to which this pain interferes with function.[37] Initially developed as the Wisconsin Brief Pain Questionnaire, the later iteration was renamed the BPI.[37,53] It is one of the most widely used clinical tools for measuring pain,[38] has been assessed in multiple languages, and employs a numerical reporting scale permitting its use across multiple countries and education levels.[37] The BPI is available as a long and short version, the latter preponderating. The short form has a 24-hour recall period. It consists of a diagram of a human body onto which the location of pain is recorded. There is a section for reporting use of analgesics and the relief these provide. Pain measurement is divided into two categories: severity and interference with function. The severity category consists of four items: pain now, average pain, worst pain, and least pain. The interference with function category is divided into seven items: general activity, mood, walking ability, normal work, relations with other persons, sleep, and enjoyment of life. Each item is scored on an 11-point scale from 0 to 10, where 0 is no pain/no interference and 10 is the worst pain/complete interference. It should be noted that many studies report the mean of only two items of the BPI pain severity category, but this is not recommended as the models for validation used all four items. With respect to the pain interference category, a mean can be reported if a minimum of four of the seven items are assessed.[38]

The BPI was originally designed and validated to assess cancer pain,[38,53] but it has since been validated as a generic measurement tool for non-cancer pain.[38,54] Reliability and validity were specifically assessed for arthritis and lower back pain, two common pain conditions with well-developed, condition-specific pain measurement tools. Reliability alpha coefficients for BPI severity and BPI interference categories ranged from 0.82 to 0.95, comparable to accepted measurement tools for these conditions. Construct validity was assessed for factor structure and relationship by determining correlation with other pain scales (r values ranging from 0.58 to 0.81). Overall BPI scores, as well as BPI severity scores and BPI interference scores, were able to distinguish patients according to their chronic pain classification in both lower back pain and arthritis patients. It was also shown that the BPI scale could detect decline or improvement in both groups of patients, when BPI reporting was compared with accepted condition-specific measures, but no MCID was established for the BPI.[54] The BPI has since been assessed under different conditions, over different time frames, and using different patient populations and diseases. The measure is currently used to assess pain in a multitude of diseases and conditions.[38] However, our search for the validation of the BPI in Gaucher disease did not yield any results and no MCID has been estimated.

Fatigue Severity Scale

The FSS is a generic, unidimensional, psychometric instrument designed to assess the impact of fatigue over the past week. The FSS consists of a self-administered questionnaire comprising nine items, each using a seven-point Likert scale. Responses can vary from strongly disagree (1) to strongly agree (7).[39,40] Scores should be reported as a total (minimum and maximum scores = 9 and 63, respectively), but are also reported as a mean (minimum and maximum means = 1 or 7, respectively). Lower scores indicate less fatigue in daily life. One group found that, if reporting the FSS mean, removing the first two items from the nine-item FSS before calculating the mean provided better validity and reliability, and has possibly better sensitivity in detecting changes in fatigue.[41]

Originally designed and initially validated to measure fatigue in multiple sclerosis and systemic lupus erythematosus,[39] the FSS has been tested for validity and reliability in a number of diseases and conditions including, but not limited to, Parkinson's disease, multiple sclerosis, hepatitis C, stroke, and obesity.[40-46] No general MCID has been established for the FSS. According to our search, the FSS has not been validated for Gaucher disease and no estimate of a Gaucher disease-specific MCID has been made.

Short Form (36) Health Survey

The SF-36 is a generic health assessment questionnaire that has been used in clinical trials to study the impact of chronic disease on health-related quality of life. SF-36 consists of eight domains: physical functioning, role physical, bodily pain, general health, vitality, social functioning, role emotional, and mental health. SF-36 also provides two component summaries: the physical component summary (SF-36 PCS) and the mental component summary (SF-36 MCS), which are created by aggregating the eight domains. The SF-36 PCS, SF-36-MCS, and eight domains are each measured on a scale of 0 to 100, with an increase in score indicating improvement in health status. In general use of SF-36, a change of 2 to 4 points in each domain or 2 to 3 points in each component summary indicates a clinically meaningful improvement as determined by the patient. [36]

Our search for a validated outcome measure for SF-36 in Gaucher disease did not yield any results. While the use of SF-36 in the treatment of Gaucher disease is recommended,[55] there is no literature to support the validity, reliability, or MCID of this particular tool in the treatment and study of Gaucher disease progression.

GD1-DS3

Findings

Instrument Development

The GDI-DS3 was developed to create a reliable and valid measurement tool for the assessment and progression of GD1 in adults as well as a means of comparing patient groups in adult clinical trials.[47]

A working group of nine GD1 expert physicians and 74 non-working group Gaucher disease physicians were invited to participate. An experienced methodologist-biostatistician was employed to help develop and validate the instrument. A group of 12 international Gaucher disease experts (without prior exposure) were assembled to evaluate the GD1-DS3. A further 23 physicians attending a

Gaucher disease workshop participated in testing the feasibility and content validity using a single patient profile and the preliminary GD1-DS3.

The GD1-DS3 instrument was developed using a survey, followed by refinement. The working group identified putative GD1-DS3 domains via the nominal group technique of consensus formation and compiled these in a survey. The surveys were posed to the non-working group, of which 36 physicians responded. The completed surveys ranked six domains in order of relative importance (from most important to least): bone disease/skeletal (to reduce redundancy in reporting, this domain includes pain), hematological, visceral, patient-reported, growth/metabolism, and physician-reported. The working group further refined the domains as follows. The bottom three domains were dropped to reduce redundancy in reporting (patient-reported) because the domain applied mostly to children (growth/metabolism) or because it was thought that due to the rarity of Gaucher disease, the domain was not reliable (physician-reporting). In the hematological domain, the following three items were estimated to be non-redundant: thrombocytopenia, anemia, and bleeding. The nominal group technique of consensus determined the methods of assessment for each item, as well as preliminary weighting, based on the degree to which each item and domain impacts GD1-related morbidity and mortality.

Two conferences were held for the12 international Gaucher disease experts not previously exposed to the preliminary GD1-DS3. Twenty patient profiles from the International Collaborative Gaucher Group Gaucher Registry were selected by the working group. Profiles contained complete clinical and diagnostic information from two sequential visits (initial and follow-up); thus, no imputing was required. All patients were untreated at the time of initial assessment. At both conferences, physicians scored each patient profile visit using the Clinical Global Impression (CGI) scores, and then a consensus was reached for the Clinical Global Impression–Severity of Illness (CGI-S) score, and therapy and prognosis change between visits. Each physician then used the DS3 to independently score the patient profile for each visit. Test-retest results for the CGI-S score and the preliminary GD1-DS3 were not statistically different, and so were combined for analyses.

Further refinement of the preliminary GD1-DS3 removed items based on statistical tests for reliability and stability. Scaling and maximum scores for DS3 items and domains were optimized to maximize correlation with consensus CGI-S scores in the presence or absence of bone density and infiltration data (most likely to be missing from a patient's records).[47]

The Scoring System of GD1-DS3

The system encompasses three disease domains relevant to adult GD1 — bone, hematologic, and visceral — weighted respectively at 42.1%, 31.6%, and 26.3%. The maximum possible score for disease severity is 19.0. Each domain is broken into items relevant to disease severity determined to have minimal overlap. The bone domain encompasses the pain component of the disease. The ranges of scores, out of a possible 19, are as follows: mild disease has a score < 3; moderate disease, between 3 and 6; marked disease, 6 to 9; and severe disease, > 9.[47]

Validity Results

The Content Validity Index (as evaluated by 35 physicians) was found to be 0.96, signifying that 96% of participants rated the content validity of the GD1-DS3 as 3 (relevant, but needs minor modifications) or 4 (very relevant).

Construct validity was shown using the Pearson correlation R2 for GD1-DS3 and CGI-S scores. Generally, a CGI-S score of mild disease was correlated with a GD1-DS3 score of < 3; moderate disease correlated with DS3 scores of 3 to 6; marked disease with DS3 scores of 6 to 9; and severe disease with DS3 scores > 9. When bone data were available, DS3 correlation with CGI-S had an R2 of 0.89; in the absence of bone data, R2 was 0.77.[47]

Reliability

Interrater reliability between any two physicians in scoring 10 patients was 0.97 (Cohen's kappa). Intrarater reliability was not assessed.[47]

Minimal Clinically Important Difference

Using the CGI, the physicians assessed whether prognosis of a patient profile was improved, unchanged, or worsened from initial visit to follow-up using the change in the two DS3 scores. This was repeated for all 20 profiles. The MCID for the GD1-DS3 was

found to be −3.17 (improvement) and 3.86 (worsening). All profiles with changes in GD1-DS3 scores that fell between these MCID values scored a “no change in prognosis” by at least 75% of the physicians.[47]

Discussion of GD1-DS3

GD1 is a rare, heterogeneous disease with irregular manifestations. Particularly in clinical trials, outcome measurements can be difficult to assess. A scoring system that can capture the overall impression of disease severity is lacking. The authors and Gaucher disease expert physicians found the GD1-DS3 to offer a global assessment tool for monitoring disease stability and progression in adult patients.

The refinement of the GD1-DS3 is not complete and requires further validation. A total of 20 patient profiles (two visits each) were used to develop this tool. All the studies were retrospective from the International Collaborative Gaucher Group (ICGG) Gaucher Registry and have yet to be tested for validity in a clinical prospective setting. Construct validity has been assessed for convergence, but not for divergence. Additional testing should also be performed for sensitivity, specificity, and area under the curve.

The GD1-DS3 is not suitable for patients < 18 years (whose manifestations of GD1 are different from adults) and neuronopathic Gaucher disease patients. The test is also susceptible to error when comorbidities are present. The scoring system correlates well with overall clinical impressions of disease when bone data are available (R2 = 0.89), but performs less well when bone data from patients are absent (R2 = 0.77), which is frequently the case in current clinical settings.[47]

Conclusion

The BPI, FSS, and SF-36 are generic, psychometric instruments designed to assess pain, fatigue, and quality of life, respectively. None has been validated for GD1, specifically, but each is a well-established tool frequently used in clinical settings and clinical trials. The DS3-GD1 is an instrument specifically designed to monitor adult GD1 stability and progression in a clinical setting and in clinical trials. The final score is based on a weighting system incorporating three major clinical manifestations of GD1: bone involvement and pain, hematologic involvement, and hepatosplenomegaly. Validation of this tool is ongoing and it is not meant to be used in isolation.

Appendix 6: Summary of Extension Studies

Aim

To summarize the details and findings of two phase III randomized controlled trial extension studies:

- extension of ENGAGE (EFC12813)[30]
- extension of ENCORE (EFC12812).[31]

Findings

Study Design

Both extension studies were designed as uncontrolled (single-arm), switch-over, open-label continuations of the ENGAGE[11] and ENCORE[10] randomized controlled trials. The objectives of both extension studies were to examine the long-term efficacy, tolerability, safety, and pharmacokinetics of eliglustat. The study design, populations, treatments, and outcomes are summarized in Table 23.

Patients who completed the 39-week and 52-week primary analysis periods (PAP) of the ENGAGE and ENCORE trials, respectively, were eligible to enter the extension periods, referred to as the long-term treatment periods (LTTPs) of these studies.

Population Demographics and Baseline Disease Characteristics

Demographic and baseline disease characteristics for eliglustat-treated patients who participated in the extension studies are described in Table 24. The mean age at start of treatment was 31.8 years (ENGAGE) and 38 years (ENCORE). Both sexes participated in the studies in roughly equal numbers. The ENGAGE study was for adult Gaucher disease type 1 patients previously naive to enzyme replacement therapy (ERT) or substrate reduction therapy. The ENGAGE study stratified patients based on baseline spleen severity, with the requirement that the spleen be intact. The ENCORE study was for adult Gaucher disease type 1 patients previously stabilized with ERT. In the ENCORE study, 25% of patients had undergone partial or full splenectomy. In both studies, the predominant cytochrome P450 2D6 metabolizer status was extensive — 90% (ENGAGE) and 77.7% (ENCORE) — followed by intermediate — 8% (ENGAGE) and 13.4% (ENCORE). Only six patients in ENCORE were poor metabolizers (none in ENGAGE). Ultra-rapid and indeterminate metabolizer numbers were also low. These characteristics are similar to those reported in PAP of the studies.

Intervention

Patients who entered the LTTP of the ENCORE and ENGAGE studies received open-label oral eliglustat at dosages of 50 mg, 100 mg, or 150 mg twice daily. Both extension studies aimed to maintain a plasma eliglustat trough concentration ≥ 5 ng/mL and a peak concentration < 150 ng/mL. Patients began dosages at 50 mg twice daily with the potential to increase to 100 mg twice daily (first dose adjustment) or to 150 mg twice daily (second dose adjustment) if a plasma trough concentration of ≥ 5 ng/mL could not be achieved at a lower dose. Dose adjustments were also made over the course of the study if plasma concentrations exceeded 150 ng/mL. The lowest allowable dose in these studies was 50 mg once daily based on plasma peak concentrations of higher doses of eliglustat or in combination with adverse events. Eliglustat could be stopped temporarily for patient assessment in certain circumstances, without withdrawal from the study.[30,31]

In ENCORE, dose adjustments were made at week 3 and week 5 after the start of eliglustat exposure. For patients originally randomized to the eliglustat arm, this adjustment occurred at the beginning of the PAP; for patients randomized to imiglucerase, this adjustment was made at the beginning of the LTTP, following switch-over to eliglustat.

In ENGAGE, all patients, regardless of their randomization arm, received eliglustat 50 mg twice daily on week 39 plus one day through week 42, with a possible increase in dosage to 100 mg twice daily in week 43, and another possible dosage adjustment to 150 mg twice daily at week 47.

Outcomes

The primary efficacy outcomes measured in the extension periods were improvement of spleen volume (ENGAGE) and the percentage of patients with maintained disease stability based on a composite of multiple parameters (ENCORE). These outcomes were reported on an annual basis following the PAP. Other outcomes reported in each study were hematological, organ volumes, bone disease, biomarkers, and patient-reported.[30,31] Hematological and organ volume outcomes are reported in this appendix.

For the ENCORE extension study main efficacy outcome, the composite end point was measured as described in the PAP, following the trial parameters of change from baseline values. The extension analyses also presented a second composite end point based on pre-established Gaucher disease absolute threshold values for each of the individual parameters constituting the composite. Stability was defined as meeting each of the following four therapeutic goals: (1) hemoglobin ≥ 110 g/L for women and ≥ 120 g/L for men, (2) platelet count ≥ 100 × 10^9/L, (3) spleen volume ≤8 multiples of normal (MN), when applicable, and (4) liver volume ≤ 1.5 MN.[1,56] Success on individual hematologic parameters and organ volumes was defined based on the same criteria used for the PAP, or using the predefined therapeutic threshold values for Gaucher disease described previously. The analyses presented for the composite end points are the complete data, representing only patients for whom all parameters of the composite were available at a given time point.[31]

Patient Disposition and Exposure

The ENGAGE PAP randomized 40 patients, of whom 40 progressed to the extension study and completed both dose adjustment periods. Measurements of outcomes were taken after 39 weeks of eliglustat exposure, and afterward on an annual basis. ENCORE randomized 160 patients, with 152 entering the LTTP. Measurements of outcomes were analyzed annually. The median exposure time for dose-adjusted patients was 45.4 weeks (ENGAGE) and 41.3 months (ENCORE). Patient exposure in both studies is summarized in Table 26.

Adherence in both studies was defined as taking ≥ 80% of study dosages. ENGAGE recorded adherence in 93% of patients[30] while ENCORE recorded 95% adherence, with 89% of patients taking ≥ 90% eliglustat dosages.[31]

The disposition of patients in both studies is summarized in Table 25. [redacted]. Analyses were cut off at the 234-week mark (ENGAGE) and the four-year mark (ENCORE), prior to the last patients officially exiting the extension studies (patients could remain in the studies for up to six or 5.5 years, respectively). Withdrawals due to adverse events in ENCORE represented [redacted] of patients, with another [redacted] leaving the study for other reasons or due to nonadherence. ENGAGE reported [redacted] withdrawal for reasons other than adverse events or nonadherence, which did not occur in this study.

Recruitment for both extension studies required close to two years. Patients recruited early in the studies had the potential to receive eliglustat for a longer period prior to study end date than patients recruited later in the process. As a result, some patients timed out of the ENCORE study prior to reaching the longer-term eliglustat exposure time points of three years, four years, five years, and 5.5 years. Furthermore, commercial eliglustat became available in the US in 2014, resulting in multiple departures from both extension studies before the predefined end date or termination by the sponsor.[30,31,56]

Table 23: Details of Extension Studies – ENGAGE and ENCORE

		ENGAGE	ENCORE
Designs and Populations	**Study Design**	Phase III, multi-centre, multi-national, open-label, switch-over, extension	
	Locations	26 sites in Latin America, US, Canada, Middle East and Northern Africa, India, and Europe	39 sites in Latin America, US, Canada, Australia, Middle East, and Europe
	Number of Participants (N)	40	152 enrolled in LTTP[a] 157 analyzed[a]
	Inclusion Criteria	Must have qualified for, and completed, the PAP As described for patients previously participating in the ENGAGE PAP[11]	Must have qualified for, and completed, the PAP As described for patients previously participating in the ENCORE PAP[10]
	Exclusion Criteria	As described for patients previously participating in the ENGAGE PAP	As described for patients previously participating in the ENCORE PAP
	Objective	To evaluate the long-term (after 39-week PAP) efficacy, safety, and PK of eliglustat as a first-line therapy for GD1	To annually evaluate the long-term efficacy, safety, and PK of eliglustat in patients with GD1 who had reached therapeutic goals with ERT
Exposure	**Intervention**	Oral eliglustat tartrate at 50 mg, 100 mg, or 150 mg b.i.d.	Oral eliglustat tartrate at 50 mg, 100 mg, or 150 mg b.i.d
	Phase		
	Extension period[b]	Week 39 + 1 day through (up to) 6 years	Week 53 through (up to) 5.5 years
	Follow-up	30 days to 37 days after study completion	30 days to 37 days after study completion
Outcomes	**Main End Point(s)**	Change in spleen volume after initiation of eliglustat treatment	Percentage of patients who remained clinically stable after initiation of eliglustat treatment
	Other End Points	Hemoglobin level, platelet count, and spleen and liver volumes Harms	Hemoglobin level, platelet count, and spleen and liver volumes Harms
Notes	**Publications**	Clinical Study Report (ENGAGE)[11] Clinical Study Report (ENGAGE extension)[30]	Clinical Study Report (ENCORE)[10] Clinical Study Report (ENCORE extension)[31] Cox et al.[56]

b.i.d. = twice daily; ERT = enzyme replacement therapy; GD1 = Gaucher disease type 1; ITT = intention-to-treat; LTTP = long-term treatment plan; PAP = primary analysis period; PK = pharmacokinetics.

[a] Efficacy and safety analyses in the extension period used the ITT population, defined as any patient who received at least one dose of eliglustat throughout ENCORE (i.e., PAP plus LTTP phases). Thus, eliglustat-treated patients who did not qualify for the LTTP because they did not complete the PAP were nonetheless included in the extension data analysis, bringing the ITT and safety populations to N = 157.

[b] The extension studies began after the final week of the PAP of the randomized control trials, ENGAGE and ENCORE.

Source: ENGAGE clinical study reports,[11,30] ENCORE clinical study reports,[10,31] Cox et al.[56]

Table 24: Patient Demographics and Baseline Characteristics – ENGAGE and ENCORE Extensions

	ENGAGE	ENCORE	
	ITT	**ITT: All Eliglustat-Treated Patients**	**Extension Patients with 4-Year Data**
Number of Patients, N	**40**	**157**	**46**
Male, n (%)	20 (50)	72 (46)	20 (44)
Disease/Treatment			
Age at first symptom (y), mean (SD), n = 38	16.0 (11.4)	13.9 (12.8)	10.1 (8.6)
Age at diagnosis (y), mean (SD), n = 39	21.1 (11.5)	18.8 (13.9)	14.8 (11.9)
Ys on ERT prior to eliglustat, mean (SD)	NA	10.5 (4.1)	9.4 (4.5)
Age at start of eliglustat[a] (y), mean (SD)	31.8 (11.3)	38.0 (14.0)	34.0 (14.4)

	ENGAGE	ENCORE	
	ITT	ITT: All Eliglustat-Treated Patients	Extension Patients with 4-Year Data
Baseline Spleen Severity Group, n (%)			
Low (≤ 20 MN)	33 (83)	NA	NA
High (> 20 MN)	7 (18)	NA	NA
Splenectomy Performed, n (%)			
Partial	NA	2 (1)	2 (4)
Total	NA	37 (24)	13 (28)
CYP2D6 Metabolizer Status, n (%)			
Poor	0	6 (3.8)	3 (6.5)
Intermediate	3 (8)	21 (13.4)	3 (6.5)
Extensive	36 (90)	122 (77.7)	37 (80.4)
Ultra-rapid	1 (3)	5 (3.2)	3 (6.5)
Indeterminate	0	3 (1.9)	0

CYP2D6 = cytochrome P450 2D6; ERT = enzyme replacement therapy; ITT = intention-to-treat; MN = multiples of normal; NA = not applicable; SD = standard deviation; y = year.

[a] Age on day 1 of first dose of eliglustat.

Source: ENGAGE Clinical Study Report,[30] ENCORE Clinical Study Report,[31] Cox et al.[56]

Table 25: Patient Disposition – ENGAGE and ENCORE Extensions

	ENGAGE	ENCORE
Enrolled in LTTP	**40**	**152**
Received at Least 1 Dose Eliglustat in PAP and/or in LTTP, N[a]	**40**	**157**
Completed 1 year, N (%)	NA	148 (94.3)
Completed 2 years, N (%)	NA	139 (88.5)
Completed 3 years, N (%)	NA	115 (73.2)
Completed LTTP,[a] N (%)	27 [redacted]	46 [redacted]
Discontinued Before End[a] of LTTP, N (%)	13 [redacted]	111 [redacted]
Participants switched to commercial eliglustat when it became available in fall 2014	7 [redacted]	36 [redacted]
Timed out of study	0	48 [redacted]
AE	0	12 [redacted]
Reasons unrelated to AE/ wished to withdraw	5 [redacted]	9 [redacted]
Pregnancy	1 [redacted]	3 [redacted]
Nonadherence	0	2 [redacted]
ITT, N	40	157
Safety, N	40	157

AE = adverse event; ITT = intention-to-treat; LTTP = long-term treatment period; NA = not applicable; PAP = primary analysis period.

[a] Completion of extension study analyses was reported at the 4-year time point for ENCORE and between week 182 and week 234 for ENGAGE; however, individual patients could remain in studies for up to 5.5 and 6 years, respectively.

Source: ENGAGE Clinical Study Report,[30] ENCORE Clinical Study Report,[31] Cox et al.[56]

Table 26: Treatment Exposure – ENGAGE and ENCORE Extensions

	ENGAGE	ENCORE
Number of Patients Receiving ≥ 1 Dose Eliglustat	**N = 40**	**N = 157**
Number of patients on eliglustat after dose adjustments, n (%)	40 (100%)	152 (95%)
Eliglustat exposure (weeks) of dose-adjusted patients, median (minimum, maximum)	46.4 (6, 72)	
Eliglustat exposure (months) of dosed-adjusted patients, median (minimum, maximum)		41.3 (2.5, 63.2)
Long-term dosages[a] – patient number, n (%)		
50 mg b.i.d.	[redacted]	[redacted]
100 mg b.i.d.	[redacted]	[redacted]
150 mg b.i.d.	[redacted]	[redacted]

b.i.d. = twice daily.

[a] Long-term dosages refers to the stable dosage that the patient received throughout the study, following the two dose-adjustment periods.

Source: ENGAGE Clinical Study Report,[30] Cox et al.,[56] additional information from the manufacturer.[33]

Efficacy

ENGAGE

Long-term efficacy was summarized for each parameter based on patients who remained in the study during the open-label period and who had data at the reported collection time points. While 27 patients (68%) completed the LTTP, complete data (spleen and liver volumes, hemoglobin levels, and platelet counts) are only available for a subset of patients. Therefore, each outcome for which a measurement was available, is reported individually, as shown in Table 27. Patients were stratified by spleen volume at baseline (≤ 20 MN = low spleen group; > 20 MN = high spleen group). Overall, improvement in spleen volume, the primary efficacy outcome, continued throughout the study's LTTP. Mean spleen volumes decreased from baseline in both groups at week 39 relative to the eliglustat start date: a 31% decrease in the low spleen group and a 29% decrease in the high spleen group. The week-234 percentage decreases of means from baseline were 66% for both spleen groups. The other efficacy outcomes also improved throughout the LTTP and are summarized in Table 27.

Table 27: ENGAGE Extension Main Efficacy Outcome (Spleen Volume) and Other Individual Parameters

ENGAGE						
	Low Spleen Group (N = 33)			High Spleen Group (N = 7)		
Time Points After Start of Eliglustat Treatment	**n**	**Spleen Volume (MN), Mean (SD)**	**% Change Relative to Baseline, Mean (SD)**	**n**	**Spleen Volume (MN), Mean (SD)**	**% Change Relative to Baseline, Mean (SD)**
Baseline[a] (N = [redacted])	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 39[b] (N = [redacted])	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 78 (N = [redacted])	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 130 (N = [redacted])	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 182 (N = [redacted])	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 234 (N = [redacted])	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	n	**Hemoglobin (g/L)**	**% Change Relative to Baseline, Mean (SD)**	**n**	**Hemoglobin (g/L)**	**% Change Relative to Baseline, Mean (SD)**
Baseline[a] (N = [redacted])	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 39[b] (N = [redacted])	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 78 (N = [redacted])	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 130 (N = [redacted])	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 182 (N = [redacted])	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

ENGAGE						
Week 234 (N = [redacted])	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	n	**Platelet Count (10^9/L)**	**% Change Relative to Baseline, Mean (SD)**	**n**	**Platelet Count (10^9/L)**	**% Change Relative to Baseline, Mean (SD)**
Baseline[a] (N = [redacted])	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 39[b] (N = [redacted])	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 78 (N = [redacted])	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 130 (N = [redacted])	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 182 (N = [redacted])	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 234 (N = [redacted])	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	n	**Liver Volume (MN)**	**% Change Relative to Baseline, Mean (SD)**	**n**	**Liver Volume (MN)**	**% Change Relative to Baseline, Mean (SD)**
Baseline[a] (N = [redacted])	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 39[b] (N = [redacted])	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 78 (N = [redacted])	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 130 (N = [redacted])	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 182 (N = [redacted])	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 234 (N = [redacted])	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

MN = multiples of normal; SD = standard deviation.

[a] Baseline refers to measurements or means taken immediately prior to eliglustat exposure. All time points refer to time after initiation of eliglustat treatment, regardless of whether first exposure occurred in the randomized control phase of the trial, or the extension period.

[b] Week 39 relative to first dose of eliglustat. Week 39 is the end of the primary analysis period for ENGAGE patients originally randomized to eliglustat, or week 39 of the long-term treatment period for ENGAGE patients originally randomized to the placebo.

Source: ENGAGE Clinical Study Report.[30]

ENCORE

For patients who remained in the study and who had measurements for all parameters of the composite outcome, annual disease stability was reported to range from 84.4% to 91.1%, based on the trial definitions of stability. When Gaucher disease therapeutic threshold values were used to define stability, percentages of stable patients ranged from 91.7% to 95.6% over the course of four years. These data are summarized in Table 28. Analyses did not identify common clinical characteristics among patients who failed to meet the composite end point.[56] It is unclear whether these analyses were pre-specified or post hoc. The individual end point parameters that constitute the composite are also summarized for ENCORE in Table 29.

Table 28: ENCORE Extension Main Efficacy Outcome (Composite of Disease Stability)

ENCORE				
	Patients Stable on Composite End Point According to Trial Parameters[a] N = 157		Patients Stable on Composite End Point According to Predefined Absolute Therapeutic Goal Thresholds[b] N = 157	
Time Point	n/N	% Stable (95% CI)[c]	n/N	% Stable (95% CI)[c]
Baseline[d]	157/157	–	156/157	99.4 (1.0 to 1.0)
Year 1	128/151	84.8 (0.8 to 0.9)	139/151	92.1 (0.9 to 1.0)
Year 2	115/136	84.6 (0.8 to 0.9)	126/136	92.6 (0.9 to 1.0)
Year 3	92/109	84.4 (0.8 to 0.9)	100/109	91.7 (0.8 to 1.0)
Year 4	41/45	91.1 (0.8 to 1.0)	43/45	95.6 (0.8 to 1.0)

CI = confidence interval; MN = multiples of normal.

[a] Composite end-point trial parameters: For a patient to remain stable, the following four conditions must be met: (1) hemoglobin concentration does not decrease > 15 g/L from baseline, (2) platelet count does not decrease > 25% from baseline, (3) spleen volume (MN) does not increase > 25% from baseline, (4) liver volume (MN) does not increase > 20% from baseline.

[b] The composite end point of pre-specified absolute values was established by trial criteria and by therapeutic goals for Gaucher disease. For a patient to remain stable on this composite end point, the following four conditions must be met: (1) hemoglobin ≥ 110 g/L for women and ≥ 120 g/L for men, (2) platelet count ≥ 100 × 10^9/L, (3) spleen volume ≤ 8 MN, (4) liver volume ≤ 1.5 MN.

[c] Percentages of patients reaching goals and binomial exact 95% CI were calculated based on number of patients with a measurement for the parameter of interest at each visit, for each goal, and for all four goals collectively.[56]

[d] Baseline refers to measurements or means taken immediately prior to eliglustat exposure. All time points refer to time after initiation of eliglustat treatment, regardless of whether first exposure occurred in the randomized control phase of the trial, or the extension period.

Source: Cox et al.,[56] additional information from manufacturer. [33]

Table 29: ENCORE Extension Efficacy Outcomes – Individual Parameters

	ENCORE			
	N = 157			
Parameter	n[a]	LS Mean (95% CI)	LS Mean Change From Baseline (95% CI)	*P* Value
Hemoglobin (g/L)				
Baseline[b]	157	137	—	—
Year 1	151	136 (134 to 137)	−1 (−3 to 1)	0.2
Year 2	139	136 (134 to 137)	−1 (−3 to 1)	0.3
Year 3	110	136 (135 to 138)	−0.4 (−2 to 2)	0.7
Year 4	45	139 (137 to 141)	0.3 (−0.1 to 5)	0.06
Test for linear trend (B,1,2,3,4)		—	—	0.05
Platelet Count (× 10^9/L)				
Baseline[b]	157	200.3 (194.4 to 206.1)	—	—
Year 1	151	206.7 (200.7 to 212.7)	6.4 (−1.4 to 14.3)	0.1
Year 2	139	202.4 (196.2 to 208.6)	2.1 (−6.4 to 10.6)	0.6
Year 3	110	210.7 (203.8 to 217.6)	10.4 (1.4 to 19.5)	0.02
Year 4	45	209.9 (199.2 to 220.7)	9.6 (−2.6 to 21.9)	0.1
Test for linear trend (B,1,2,3,4)		—	—	0.09
Spleen Volume (MN)				
Baseline[b]	120	3.1 (3.0 to 3.2)	—	—
Year 1	115	2.9 (2.9 to 3.0)	−0.1 (−0.2 to −0.1)	0.002
Year 2	105	2.9 (2.8 to 3.0)	−0.2 (−0.3 to −0.1)	0.0003
Year 3	80	2.9 (2.8 to 3.0)	−0.2 (−0.4 to −0.1)	0.0004
Year 4	33	2.7 (2.5 to 2.8)	−0.4 (−0.6 to −0.2)	< 0.0001
Test for linear trend (B,1,2,3,4)		—	—	< 0.0001
Liver Volume (MN)				
Baseline[b]	157	0.9 (0.9 to 1.0)	—	—
Year 1	151	1.0 (0.9 to 1.0)	0.01 (−0.01 to 0.03)	0.17
Year 2	139	1.0 (0.9 to 1.0)	0.01 (−0.01 to 0.03)	0.29

	ENCORE			
	N = 157			
Parameter	**n[a]**	**LS Mean (95% CI)**	**LS Mean Change From Baseline (95% CI)**	***P* Value**
Year 3	110	1.0 (0.9 to 1.0)	0.01 (−0.01 to 0.03)	0.46
Year 4	46	0.9 (0.9 to 0.9)	-0.03 (−0.1 to −0.004)	0.03
Test for linear trend (B,1,2,3,4)		—	—	0.04

CI = confidence interval; LS = least square; MN = multiples of normal.

[a] For which complete long-term data are available.

[b] Baseline refers to measurements or means taken immediately prior to eliglustat exposure. All time points refer to time after initiation of eliglustat treatment, regardless of whether first exposure occurred in the randomized control phase of the trial, or the extension period.

Source: Permission to reproduce obtained from the American Society of Hematology for Cox TM, et al. Eliglustat maintains long-term clinical stability in patients with Gaucher disease type 1 stabilized on enzyme therapy. Blood, 2017 February 6.[56]

Harms

Of the 40 patients participating in the ENGAGE extension, 36 (90%) experienced a treatment-emergent adverse event. The most commonly reported adverse events included headaches (42.5%); arthralgia (37.5%); pain in extremity (20%); back pain, upper respiratory tract infection, and nasopharyngitis (17.5% each); abdominal pain, diarrhea or dyspepsia (15% each); and upper abdominal pain, gastritis, gastroesophageal reflux disease, and sinusitis (12.5% each). One patient (2.5%) reported peripheral neuropathy, one reported polyneuropathy, and one reported a neoplasm (skin papilloma). Seven serious adverse events were reported by five patients; two of these events (atrioventricular block and second-degree atrioventricular block) were considered by the investigational team to have a probable relationship to eliglustat. Upon reviewing a draft of the CADTH Common Drug Review (CDR) Clinical Review Report for Cerdelga, the manufacturer informed CDR that both patients were asymptomatic and recovered without treatment, and the adverse events did not lead to study discontinuation. No patient reported severe or extreme bone pain and no bone crises occurred in patients treated with eliglustat over the course of the study. No treatment-emergent adverse event or serious adverse event resulted in withdrawal, and no deaths occurred over the course of the ENGAGE extension study.[30]

Overall, 147 patients (94%) in the ENCORE extension analyses experienced treatment-emergent adverse event; 53% of patients were indicated in the Clinical Study Report to have had an eliglustat-related treatment-emergent adverse event. The most commonly reported adverse events for patients who completed both dose adjustment periods (n = 152) included arthralgia (33.6%), nasopharyngitis (25%), headache (23%), abdominal upper pain and back pain (19.1%), fatigue (17.8%), pain in extremity (17.1%), nausea (16.4%), dizziness and diarrhea (14.5% each), abdominal pain (13.2%), and dyspepsia and increased blood creatine phosphokinase (12.5% each). Neoplasms (benign, malignant, and unspecified, including cysts and polyps) were reported in [redacted] patients ([redacted]) and abnormal nerve conduction studies were reported in [redacted] patients ([redacted]).[31] Adverse events of special interest in the ENCORE study were defined as syncope and cardiac arrhythmia. Twelve patients reported at least [redacted] of these events ([redacted] patients reported arrhythmia; [redacted] reported syncope). Twenty-seven patients reported at least one serious event: [redacted] reported syncope, three reported gastrointestinal treatment-emergent adverse events, four reported nervous system disorders, and [redacted] reported neoplasms.[31,56] The investigational team considered two of these serious adverse events to be eliglustat-related: peripheral neuropathy and intestinal obstruction (neither resulted in withdrawal from the study). Three patients (2%) experienced bone crises over the course of the study. One patient originally randomized to imiglucerase had a bone crisis at baseline, but completed the 130-week time point. Two patients originally randomized to the eliglustat arm experienced bone crises. The first patient had one bone crisis and moderate pain documented at week 78; the second patient experienced worsening bone pain over the course of the study, and had two bone crises documented at the 130-week time point. These patients completed the week-208 and week-182 time points, respectively.[31,56] A total of 12 patients withdrew from study treatment due to adverse events. No deaths occurred over the course of the ENCORE extension study.[56]

Table 30: Harms – ENGAGE and ENCORE Extensions

	ENGAGE	ENCORE
	N = 40	N = 157
Subjects With > 0 AEs, N (%)	36 (90)	147 (94)
Subjects with > 0 SAEs, N (%)	5 (12.5)	27 (17)
WDAEs, N (%)	0	12 (8)
Number of deaths, N (%)	0	0

AE = adverse event; SAE = serious adverse event; WDAE = withdrawal due to adverse event.
Source: ENGAGE Clinical Study Report,[30] Cox et al.[56]

Limitations

The uncontrolled nature of the extension studies and the bias of high attrition rates for later time points are key limitations when assessing the safety and efficacy of eliglustat in the long term. Analyses for clinically and statistically meaningful differences were not possible for these extension studies. Both were switch-over studies, in which all patients were treated with eliglustat, and the outcomes presented are only for patients who had measurements taken at the reported time points. As a result, the efficacy measurements lack data due to patient attrition or the absence of time point measurements. The population lost to a long-term extension study may enrich the apparent success of the study as those who remain are more likely those achieving study goals and tolerating treatment, as compared with those who discontinue the treatment and/or the study altogether. The investigators report that the two major contributing factors to explain this attrition were unrelated to failure. Firstly, commercial eliglustat became available in the US in 2014. As a result, 36 patients (23%) left the ENCORE study prior to the three-year and four-year annual assessments and were transitioned to commercial eliglustat. Secondly, another 48 patients (31%) did not reach these annual time points as they timed out of the study and were lost to analysis.[31,56] Similarly, the ENGAGE extension lost seven patients (18%) to the commercialization of eliglustat.[30]

Both extension studies were unblinded, which can introduce bias in the reporting of outcomes and adverse events and in the analysis of data. Some precautions were taken to reduce this bias. During the LTTP of ENGAGE, liver and spleen volume imaging data were analyzed by central readers who were blinded to patient, treatment, and time point.[30] During the ENCORE LTTP, some evaluations were blinded, including organ volume and bone imaging data, electrocardiogram (ECG) and Holter monitor data, and nerve conduction data. A blinded independent adjudication board reviewed and confirmed instances of failure to meet the primary end point.[31]

ENCORE's 52-week PAP randomized 160 patients, of whom 152 progressed into the extension study. However, efficacy and safety analyses in the LTTP used the intention-to-treat population, defined as any patient who received at least one dose of eliglustat throughout ENCORE (i.e., PAP plus LTTP phases). Thus, eliglustat-treated patients who did not complete the PAP were nonetheless included in the extension data, bringing the intention-to-treat and safety populations to 157. Because patients who received eliglustat in PAP are also included in the long-term analyses, there is some overlap in reporting between these two periods of the study.[31]

The ENCORE extension data include an additional composite end point, not reported in the PAP, which used Gaucher disease therapeutic threshold values to define disease stability. When these therapeutic goals were used rather than predefined study parameters, there was an increase in the percentage of patients with stable disease. Because ENCORE patients were predominantly mild cases with stable disease, the therapeutic goal definition of Gaucher disease stability, in fact, relaxes the stringency of the outcome measure. For example, the average ENCORE patient at baseline had a mean spleen volume of 3.1 MN. The trial requirement for spleen stability was defined as a volume increase of no greater than 25%, whereas the therapeutic threshold for spleen volume is ≤ 8 MN, which would represent a > 250% increase from baseline. Thus, relative to mean baseline disease, the trial parameters were more stringent and more likely to show a change in disease stability than the additional composite end point reported.

Finally, in both extension studies, [redacted] of patients (ENGAGE and ENCORE, respectively) received the 150 mg twice-daily dosage to maintain predicted plasma exposure based on modelling of nonclinical and clinical trial data. This dose adjustment was established in the phase II study, which showed pharmacokinetic correlations with spleen volume reductions.[10,11,30,31,57,58] The

150 mg twice-daily dosage is not indicated in the product monograph.[5] Whether these patients would have maintained disease stability at the lower indicated dosage of 100 mg twice daily is unknown.

Summary

Over the course of the ENGAGE LTTP, for patients who remained in the study, means of individual parameters generally appeared to continue to improve from baseline, including the primary outcome and mean spleen volume, which was reduced by approximately 66% in both low and high spleen groups. For patients remaining in the ENCORE LTTP, the mean hematologic and organ volume values appeared to be maintained with long-term treatment, and overall patient stability was assessed between 84.4% and 95.6% throughout the extension. No withdrawals due to adverse events were reported for ENGAGE, while in ENCORE, 12 withdrawals due to adverse events occurred. No deaths occurred during either study. [redacted] As both studies were open-label and uncontrolled, with high attrition rates in the long term, interpretability of the results is limited.

Appendix 7: Summary of Non-Pivotal Studies

Aim

To summarize the details and findings of two non-pivotal trials that did not meet the inclusion criteria of the systematic review:

- phase II study (GZGD00304)[57]
- phase III randomized control trial EDGE (EFC12818).[52]

Findings

Study Design

Phase II

The phase II study was as a single-arm, open-label trial designed to evaluate the efficacy, safety, and pharmacokinetics of oral eliglustat in patients with GD1, untreated within 12 months of beginning the trial. The study followed improvements on a composite hematologic and spleen volume end point over a 52-week primary analysis period (PAP). The trial also included a long-term treatment period (LTTP), after the 12-month PAP, for up to 48 months after the first eliglustat dose. The LTTP evaluated longer-term outcomes, including the change from baseline in hemoglobin, platelet count, spleen and liver volume, biomarkers, patient self-reported quality of life, Gaucher disease assessments (mobility, bone crisis, and bone pain), and bone disease assessments. After month-48 assessments, patients could remain on eliglustat until certain conditions were met, including end-of-study, commercial availability, regulatory requirements, and patient withdrawal. No element, patient, or investigator in this trial was blinded.[57]

EDGE

The phase III EDGE study was a randomized, blinded controlled trial designed to test noninferiority of a once-daily administration regimen for oral eliglustat, compared with the twice-daily regimen, in patients with GD1. The twice-daily regimen was previously established in the phase II[57] and the phase III pivotal trials, ENGAGE and ENCORE.[10,11] EDGE consisted of four distinct treatment periods: lead-in period, PAP, LTTP, and extended treatment period. Patients could be treatment-naive or treatment-experienced and could be receiving enzyme replacement therapy up to one day before the first dose of eliglustat.[52]

All patients participating in EDGE were first treated in the lead-in period. Patients were titrated onto eliglustat at a starting dose of 50 mg twice daily. Dosage adjustments were made according to the following criteria:

[redacted]

Patients were treated with eliglustat in the lead-in period for a minimum of six months to a maximum of 18 months, until they achieved disease stability on all five of the following therapeutic goals concurrently:

1. no more than one bone crisis and free of other clinical symptomatic bone disease (such as bone pain attributable to osteonecrosis and/or pathological fractures) during the previous six months of the lead-in period
2. mean hemoglobin level of ≥ 110 g/L if female and ≥ 120 g/L if male
3. mean platelet count ≥ 100,000/mm^3
4. liver volume ≤ 1.5 multiples of normal
5. spleen volume ≤ 10 multiples of normal (if applicable).

Patients achieving these five therapeutic goals were eligible for randomization if they met two additional criteria: (1) they had been on a dosage of 50 mg twice daily or 100 mg twice daily for at least four months before randomization, and (2) they had a peak eliglustat plasma concentration < 50 ng/mL. All randomized patients entered the PAP, during which they received a total daily dose of eliglustat. This total daily dose was determined by eliglustat plasma levels in each patient, with the same goals applied to all patients (trough concentration ≥ 5 ng/mL and peak concentration < 50 ng/mL). Patients were stratified according to their total daily dose of 100 mg or 200 mg. [redacted][52].

The primary objective from the PAP was to test whether administration of total daily dose on a once-daily basis was noninferior to dividing the total daily dose over a twice-daily administration regimen for the composite end point of disease stability.

The EDGE trial consisted of two long-term non-randomized periods. The first long-term period was the open-label, switch-over LTTP, post week 52 of the PAP, which continued for up to 42 months after the lead-in period. During the LTTP, patients who completed the PAP and maintained disease stability on either dosage regimen were switched to a once-daily eliglustat regimen according to their total daily dose, while those who did not maintain disease stability during the PAP received their lead-in twice-daily dosage until the end of the LTTP. The second long-term period was the extended treatment period, which continued for 42 months after the lead-in period for non-randomized patients. If patients failed to meet any of the randomization criteria for the PAP, they were eligible to remain in the EDGE study under the extended treatment period [redacted]. The results of the extended treatment period are not presented in this appendix.

Table 31: Summary of the Design of the Phase II and Phase III EDGE Trials

		PHASE II	EDGE
DESIGNS AND POPULATIONS	**Study Design**	Phase II, international multi-centre, uncontrolled, OL	Phase III, DB RCT, international multi-centre, multi-regimen noninferiority trial • LTTP: OL, uncontrolled
	Locations	Russia, Argentina, US, Israel, and Mexico	17 countries (Australia, Brazil, Canada, China, Europe, India, Japan, Russian Federation, and US)
	Number of Participants (N)	26	• 170 (total) • 131 (randomized)
	Main Inclusion Criteria	• Confirmed diagnosis of GD1 • The following signs or symptoms of GD1: ○ mean hemoglobin between 80 g/L and 100 g/L (female), or between 80 g/L and 110 g/L (male) ○ mean platelet count between 45,000 and 100,000/mm^3 ○ spleen volume ≥ 10 MN	• ≥ 18 years of age • Confirmed diagnosis of GD1 [redacted] • [redacted] • Genotyping for GD and CYP2D6 • Meet all of the following criteria at the time of screening: ○ hemoglobin level ≥ 90 g/L (mean of 2 measurements) ○ platelet count ≥ 70,000/mm^3 (mean of 2 measurements) ○ spleen volume ≤ 25 MN ○ liver volume ≤ 2.0 MN

		PHASE II	EDGE
	Main Exclusion Criteria	• Partial or total splenectomy; evidence of any neurologic or pulmonary involvement • Current pathological bone involvement or bone crisis in the 12 months prior to enrolment • Mean hemoglobin level < 80 g/L or mean platelet level < 45,000/mm^3 • Receiving ERT, SRT, or corticosteroids for GD1 within 12 months, or bisphosphonates within 3 months prior to enrolment • Other serious comorbidities • Patients with cardiac functional and/or anatomical abnormalities • Received any medication within 30 days prior to enrolment that alters the metabolism of eliglustat, or prolongs QT interval	• Eligible for enrolment in ENGAGE or ENCORE studies • Received miglustat within 6 months, or another investigational drug within 30 days • Partial or total splenectomy within 3 years • Neurologic or pulmonary involvement related to GD • Prior esophageal varices or clinically significant liver infarction, liver enzymes, or total bilirubin > 2 times upper limit of normal, unless patient had Gilbert syndrome • Pregnant or lactating • Treatment with drugs within past 30 days that alter metabolism of eliglustat or may cause QT interval prolongation • Any other clinically significant diseases
	Objective	• Primary: efficacy, safety, and PK of oral eliglustat for 52 weeks • Secondary: long-term efficacy, safety, and PK effects of eliglustat, at dosages of 50 mg, 100 mg, or 150 mg b.i.d., up to 48 months	• Primary: percentage of patients stable after 52 weeks on different dosage regimens. Efficacy and safety of q.d. vs. b.i.d. oral dosage of eliglustat in patients with demonstrated clinical stability on b.i.d. dosages. • Secondary: PK of oral eliglustat administered q.d. and b.i.d., and long-term efficacy, safety, and PK of q.d. regimen of oral eliglustat
DRUGS	**Intervention**	• PAP: oral eliglustat 50 mg or 100 mg, b.i.d. • LTTP: oral eliglustat 50 mg, 100 mg, or 150 mg b.i.d.	• TDD of 100 mg or 200 mg oral eliglustat; administered in q.d. or b.i.d regimens
DRUGS	**Comparator**	None	None (comparison is between dosage regimens of eliglustat)
DURATION	**Phase**		
DURATION	Lead-in period or dose adjustment	Days 1 to 30	OL: 6 to 18 months; titrated dosage
DURATION	PAP	Post day 30, week 52	DB: R-day 1 through R-week 52
DURATION	LTTP	Week 54 to 48 months, or study termination	OL: R-week 53 up to 42 months
DURATION	Extended period	NA	OL: 42 months (post lead-in)
DURATION	Follow-up	30 days to 37 days after study completion	[redacted]
OUTCOMES	**Main End Point(s)**	Percentage of patients with a clinical response after 52 weeks	Percentage of randomized patients who remain clinically stable after completing 52 weeks
OUTCOMES	**Other End Points**	Changes in hemoglobin, platelets, spleen volume, and liver volume	Changes in hemoglobin, platelets, spleen volume, and liver volume
NOTES	**Publications**	Clinical Study Report[57] Lukina et al. [59-61]	Clinical Study Report (EDGE)[52]

b.i.d.= twice daily; CYP2D6 = cytochrome P450 2D6; DB = double blind; ERT = enzyme replacement therapy; GD = Gaucher disease; GD1 = Gaucher disease type 1; LTTP = long-term treatment period; MN = multiples of normal; NA = not applicable; OL = open label; PAP = primary analysis period; PK = pharmacokinetics; q.d. = once daily; RCT = randomized controlled trial; R = post-randomization; SRT = substrate reduction therapy; TDD = total daily dose; vs. = versus.

Source: Clinical study reports.[52,57]

Population Demographics and Baseline Disease Characteristics

The population characteristics of both studies are summarized in Table 32.

Phase II

The phase II study recruited 26 patients ranging in age at first study dosage of eliglustat from 18 years to 60 years, with a mean age of 34.5 years. Ethnicity was reported as non-Jewish Caucasian (62%) and Ashkenazi Jewish (27%). No patients had undergone splenectomy. The phase II patients were almost exclusively (96%) cytochrome P450 2D6 extensive metabolizers.[57]

EDGE

[redacted] Patients ranged from [redacted] years with a mean age of 37.7 years. [redacted].[52]

Table 32: Summary of Demographics and Baseline Disease Characteristics of Phase II and EDGE ITT Populations

	Phase II	EDGE		
		Randomized		Non-Randomized
	Received At Least 1 Dose N = 26	Once-Daily Regimen N = 65	Twice-Daily Regimen N = 66	N = 39
Age in years, mean (SD)	34.5 (13.0)	[redacted]	[redacted]	[redacted]
Male, n (%)	10 (38)	[redacted]	[redacted]	[redacted]
Non-Jewish Caucasian, n (%)	16 (62)	[redacted]	[redacted]	[redacted]
Ashkenazi Jewish, n (%)	7 (27)	[redacted]	[redacted]	[redacted]
Hispanic	NR	[redacted]	[redacted]	[redacted]
Non-Hispanic	NR	[redacted]	[redacted]	[redacted]
Jewish		[redacted]	[redacted]	[redacted]
Japanese		[redacted]	[redacted]	[redacted]
Chinese		[redacted]	[redacted]	[redacted]
Splenectomy performed, n (%)				
No	26 (100)	[redacted]	[redacted]	[redacted]
Partial	NA	[redacted]	[redacted]	[redacted]
Total	NA	[redacted]	[redacted]	[redacted]
Age at Gaucher symptom onset, years, mean (SD)	11.8 (10.9) n = 21	[redacted]	[redacted]	[redacted]
Age at Gaucher diagnosis, years, mean (SD)	24.0 (14.8) n = 25	[redacted]	[redacted]	[redacted]
Age at first dosage, years, mean (SD)	34.5 (13.0)	[redacted]	[redacted]	[redacted]
Spleen volume (MN), mean (SD)	20.0 (12.8)	[redacted]	[redacted]	[redacted]
Splenomegaly severity at study entry[a]	NR			
Mild		[redacted]	[redacted]	[redacted]
Moderate		[redacted]	[redacted]	[redacted]
Severe		[redacted]	[redacted]	[redacted]
Missing or unknown		[redacted]	[redacted]	[redacted]

	Phase II	EDGE		
		Randomized		Non-Randomized
	Received At Least 1 Dose N = 26	Once-Daily Regimen N = 65	Twice-Daily Regimen N = 66	N = 39
Liver volume (MN), mean (SD)	1.8 (0.6)	[redacted]	[redacted]	[redacted]
Hepatomegaly severity at study entry[a]	NR			
Mild		[redacted]	[redacted]	[redacted]
Moderate		[redacted]	[redacted]	[redacted]
Severe		[redacted]	[redacted]	[redacted]
Missing or unknown		[redacted]	[redacted]	[redacted]
Hemoglobin (g/L), mean (SD)	111 (17)	[redacted]	[redacted]	[redacted]
Anemia severity at study entry[a]	NR			
Mild		[redacted]	[redacted]	[redacted]
Moderate		[redacted]	[redacted]	[redacted]
Severe		[redacted]	[redacted]	[redacted]
Missing or unknown		[redacted]	[redacted]	[redacted]
Platelet count (10^9/L), mean (SD)	66.4 (20.1)	[redacted]	[redacted]	[redacted]
Thrombocytopenia severity at study entry[a]	NR			
Mild		[redacted]	[redacted]	[redacted]
Moderate		[redacted]	[redacted]	[redacted]
Severe		[redacted]	[redacted]	[redacted]
Missing or unknown		[redacted]	[redacted]	[redacted]
Bone disease severity at study entry[a]	NR			
Mild		[redacted]	[redacted]	[redacted]
Moderate		[redacted]	[redacted]	[redacted]
Severe		[redacted]	[redacted]	[redacted]
Missing or unknown		[redacted]	[redacted]	[redacted]
CYP2D6 status, n (%)				
Poor	1 (4)	[redacted]	[redacted]	[redacted]
Intermediate	0	[redacted]	[redacted]	[redacted]
Extensive	25 (96)	[redacted]	[redacted]	[redacted]
Ultra-rapid	0	[redacted]	[redacted]	[redacted]
Indeterminate	NA	[redacted]	[redacted]	[redacted]

CYP2D6 = cytochrome P450 2D6; ITT = intention-to-treat; MN = multiples of normal; NA = not applicable; NR = not reported; SD = standard deviation.

[a] Definitions of severity:

- splenomegaly: mild, < 5 MN spleen volume; moderate, > 5 MN to 15 MN; severe, > 15 MN
- hepatomegaly: mild, < 1.25 MN liver volume; moderate, 1.25 MN to 2.50 MN; severe, > 2.50 MN
- anemia: none, hemoglobin 120 g/L (males), 110 g/L (females); mild, hemoglobin 110 g/L to < 120 g/L (males), 100 g/L to < 110 g/L (females); moderate, hemoglobin 90 g/L to < 110 g/L (males), 90 g/L to < 100 g/L (females); severe, < 90 g/L
- thrombocytopenia; none, platelets 130,000/mm^3 to 400,000/mm^3; mild, 100,000/mm^3 to < 130,000 /mm^3; moderate, 60,000/mm^3 to < 100,000 /mm^3; severe, < 60,000 /mm^3
- bone disease severity: as reported by investigator

Source: Clinical study reports.[52,57]

Intervention

Phase II

During the 52-week PAP, patients received an initial dose of 50 mg oral eliglustat on day 1, after which adverse events and pharmacokinetics were monitored. During days 2 through 20, patients received the eliglustat starting dosage of 50 mg twice daily. Pharmacokinetic data from day 10 informed whether a dose adjustment was necessary on day 20, according to the following criteria:

- If the patient's eliglustat plasma trough concentration was ≥ 5 ng/mL, the patient's dose remained at 50 mg twice daily.
- If the patient's eliglustat plasma trough concentration was < 5 ng/mL, the patient's eliglustat dose increased to 100 mg twice daily.

Dosage regimens were based in part on pharmacokinetic data from healthy participants in phase I trials and on nonclinical data for glucosylceramide synthase inhibition by eliglustat.[57,58,62] Following the 52-week PAP and a one-week to two-week treatment interruption, patients could begin the LTTP in which dosages were based on results from the first 52 weeks of this phase II trial. Dosages could be increased to 150 mg twice daily if the patient had been on treatment for at least 24 months, if the patient had not reached therapeutic goals established for patients receiving imiglucase (enzyme replacement therapy), and if all other causes for lack of treatment effect had been ruled out. As of the study report date, no patients were being treated with 150 mg twice daily.[57]

EDGE

In the EDGE trial, patients were first treated in a lead-in period with oral eliglustat twice-daily dosages, according to their plasma trough and peak concentrations of eliglustat, for a minimum of six months and a maximum of 18 months, to reach therapeutic goals. Patients who met the randomization criteria after lead-in dosages were eligible to enter the PAP and to be randomized to either a twice-daily regimen or a once-daily regimen. Both regimens were stratified according to patient's total daily dose (100 mg or 200 mg). The patient's total daily dose was based on maintaining plasma trough and peak concentrations of eliglustat such that the overall regimens (dosing stratification collapsed) could be compared. The total daily dose was divided either over one administration or over two administrations per day. The same total daily dose established in the lead-in period was administered throughout the PAP and the LTTP.[52]

[redacted]

[redacted]. [52]

Outcomes

Phase II

The main efficacy outcome for the phase II study was a composite end point of improvement from baseline to week 52 in hemoglobin levels, in platelet counts, and in spleen volume. A clinically meaningful response was defined as a response in at least two of the following three parameters: (1) an increase of ≥ 5 g/L in hemoglobin (if abnormal at baseline), (2) an increase of ≥ 15% in platelets (if abnormal at baseline), and (3) a reduction of ≥ 15% in total spleen volume (based on magnetic resonance imaging or spiral computed tomography). A change in liver volume from baseline to week 52 was identified as an additional efficacy end point. Long-term outcomes included changes from baseline in hemoglobin, platelet count, spleen and liver volume, biomarkers, patient self-reported quality of life, Gaucher disease assessments (mobility, bone crisis, and bone pain), bone disease assessments, pharmacokinetic data, and safety.[57]

EDGE

The primary efficacy end point of EDGE was maintained disease stability, defined as a composite of the following criteria:

1. bone criterion: no more than two bone crises during the PAP (with no more than one bone crisis during either the first six months or the latter six months of the period) and is free of other clinically symptomatic bone disease (such as bone pain attributable to osteonecrosis or pathological fractures) during the entire 52-week PAP
2. hemoglobin criterion: level does not decrease > 15 g/L below baseline for PAP
3. platelet criterion: counts do not decrease > 25% below baseline for PAP
4. liver criterion: volume does not increase > 20% above baseline for PAP
5. spleen criterion: volume does not increase > 25% above baseline for PAP (if applicable).

[redacted]. Other outcomes measured in the PAP and the LTTP included hemoglobin level, platelet count, spleen and liver volumes (multiples of normal), biomarkers, bone disease assessments, Gaucher assessments (mobility, bone crisis, and bone pain), and pharmacokinetic data and safety.[52]

Statistical Analysis

Phase II

The phase II primary efficacy outcome analyses at the week-52 time point used the per-protocol population, which consisted of all intention-to-treat patients without major protocol deviations. The intention-to-treat population and safety populations were the same and included all consenting patients who received at least one dose of eliglustat. The proportion of patients who met the primary efficacy success criteria for a meaningful clinical response from baseline to week 52 was calculated, along with a 95% confidence interval (CI). Statistical inference (*P*-value calculation) was performed, testing whether the proportion of patients who met the definition of improvement was significantly different from zero, as well as testing the significance of improvement of individual efficacy parameters (hemoglobin and platelet values and spleen and liver volumes).[57]

EDGE

The EDGE trial enrolled 170 patients to [redacted] noninferiority margin of 15%, [redacted] Efficacy analyses were performed on both the intention-to-treat population (received at least one dose of eliglustat) and the per-protocol population (subset of intention-to-treat population with ≥ 80% adherence during the PAP, no major protocol deviations, and completion of all assessments at baseline and week 52). [redacted] 95% CI on the difference between the percentage of randomized patients stable on once-daily regimen versus twice-daily regimen at week 52 post-randomization. Noninferiority would be declared if the lower bound of the CI fell within the 15% noninferiority margin.[52]

[redacted].[52]

[redacted].[52]

[redacted][52].

Patient Disposition and Treatment Exposure

Phase II

Patient disposition is summarized in Table 33. In total, 26 patients were enrolled. Two patients withdrew from study after a single dosage, due to treatment-emergent adverse events. A total of 24 patients (92%) received twice-daily dosage in the PAP. Two other patients did not complete PAP due to pregnancy. Patients who completed the PAP underwent a one-week to two-week treatment interruption for safety and pharmacokinetic sampling, then returned to their PAP eliglustat dosages for the LTTP. Over the full length of the trial described in the Clinical Study Report (up to and including month 48), 19 of 26 patients completed the trial, three patients discontinued due to treatment-emergent adverse events, three discontinued due to pregnancy, and one withdrew to resume treatment with imiglucerase due to a protocol amendment. Mean treatment exposure for patients in the safety set was 37.3 months (ranging from 0 months to 48.6 months); median exposure was 47.8 months. Adherence was ≥ 90% for all patients throughout this trial. Some patients continued on treatment beyond 48 months, but data analyses were cut off after this time point.[57]

EDGE

The EDGE trial enrolled 170 patients and included multiple treatment periods. During the lead-in period, in which all patients received twice-daily dosages based on individual's eliglustat pharmacokinetics, 13 patients withdrew (two due to adverse events). Of the 157 patients who completed the lead-in period, 131 patients met the PAP requirements and were randomized into either the once-daily or the twice-daily administration regimen. Seventeen randomized patients did not complete the PAP. [redacted]. Those who completed the PAP and maintained therapeutic goals were switched to the once-daily dosage regimen in the LTTP. Patients who failed to maintain therapeutic goals on once-daily dosages at any time in the PAP or LTTP were returned to the twice-daily dosage of their lead-in period and remained in the study's ITT population.[52]

[redacted][52].

Table 33: Patient Disposition in Phase II Trial

	Phase II
Screened and Received Day 1 Dose of Eliglustat, N (%)	**26**
Discontinued before day 2 b.i.d. dosage, n (%)	2 (8)
Adverse event	2 (8)
Participated in b.i.d. dosage	**24 (92)**
Completed week 52, n (%)	**22 (85)**
Discontinued before end of week 52, N (%)[a]	2 (8)
Pregnancy	2 (8)
Completed month 48, n (%)	**19 (73)**
Discontinued after week 52, before end of month 48, N (%)[b]	3 (12)
Pregnancy	1 (4)
Adverse event	1 (4)
Other	1 (4)

b.i.d. = twice daily.

[a] Reported number only includes discontinuations after patients received twice-daily dosages until week 52 (end of the primary analysis period).

[b] Reported number includes discontinuations only during the long-term treatment period.

Source: Clinical Study Report.[57]

Table 34: Patient Disposition in EDGE Trial

	EDGE		
Number of Patients, n (%)	**Randomized (N = 131)**		**All Treated Patients (N = 170)**
Regimen	**Once Daily**	**Twice Daily**	
Lead-In Period, n = 170			
Treated	65	66	170 (100.0)
Completed	65	66	157 (92.4)
Withdrew from study	NA	NA	13 (7.6)
Reason for withdrawal			
Wished to withdraw			6 (3.5)
Pregnancy			4 (2.4)
Adverse events			2 (1.2)
Non-compliant			1 (0.6)
PAP, [redacted]	**N = 65**	**N = 66**	
Treated	65 (100)	66 (100)	[redacted]
Completed	54 (83)	60 (91)	[redacted]
Did not complete PAP	11 (16.9)	6 (9)	[redacted]
Returned to lead-in dosage	[redacted]	[redacted]	[redacted]
Withdrew from study	5 (8)	5 (8)	[redacted]
Wished to withdraw	1 (2)	1 (2)	[redacted]
Pregnancy	1 (2)	0	[redacted]
Adverse events	2 (3)	3 (5)	[redacted]
Non-compliant	1 (2)	1 (2)	[redacted]
LTTP, n = 121	**N = 131**		
Treated	120 (91.6)		[redacted]
Completed	95 (72.5)		[redacted]
Withdrew from study	26 (19.8)		[redacted]

Number of Patients, n (%)	EDGE	
	Randomized (N = 131)	All Treated Patients (N = 170)
Wished to withdraw	2 (1.5)	[redacted]
Adverse events	3 (2.3)	[redacted]
Switched to commercial product	18 (13.7)	[redacted]
Lost to follow-up	2 (1.5)	[redacted]
Prohibited concomitant medication	1 (0.8)	[redacted]

LTTP = long-term treatment period; NA = not applicable; PAP = primary analysis period.

[redacted]

Source: Clinical Study Report.[52]

Table 35: Treatment Exposure in EDGE Trial

Number of Patients Receiving ≥ 1 Dose Eliglustat, n (%)	EDGE	
	Randomized N = 131	All Treated N = 170
Overall Eliglustat Exposure During Trial		
Exposure in years, median (minimum, maximum)	[redacted]	[redacted]
Lead-In Period, n = 170		
Eliglustat exposure in years, mean (SD), (minimum, maximum)	[redacted]	[redacted]
PAP, n = 131		
Eliglustat exposure in years, mean (SD), minimum, maximum	[redacted]	[redacted]
Patients receiving eliglustat, n (%)		
q.d.: 100 mg (TDD = 100 mg)	[redacted]	[redacted]
q.d.: 200 mg (TDD = 200 mg)	[redacted]	[redacted]
b.i.d.: 50 mg (TDD = 100 mg)	[redacted]	[redacted]
b.i.d.: 100 mg (TDD = 200 mg)	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
LTTP, n = 121		
Eliglustat exposure in years, mean (SD), minimum, maximum	[redacted]	[redacted]
Patients receiving eliglustat, n (%)		
q.d.: 100 mg (TDD = 100 mg)	[redacted]	[redacted]
q.d.: 200 mg (TDD = 200 mg)	[redacted]	[redacted]
b.i.d.: 50 mg (TDD = 100 mg)	[redacted]	[redacted]
b.i.d.: 100 mg (TDD = 200 mg)	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

b.i.d. = twice daily; NA = not applicable; LTTP = long-term treatment period; q.d. = once daily; PAP = primary analysis period; SD = standard deviation; TDD = total daily dose.

[redacted]

Source: Clinical Study Report.[52]

Efficacy

Phase II

Using the full analysis set, the primary composite end point was met by 77% (95% CI: 0.5795, 0.8944), or 20 of 26 patients, which was statistically significant (< 0.0001) in the phase II study. In the per-protocol population, success rates were higher (see Table 36). Long-term treatment efficacy outcomes, including hematologic and organ volumes, are presented in Table 37. Overall, 19 of 26 patients completed 48 months of eliglustat treatment, showing a statistically significant improvement in the means of four Gaucher disease parameters, from baseline through month 48.[57]

Table 36: Primary Composite End Point and Associated Individual Parameters in Phase II Trial

	Phase II	
	FAS	PPS
Parameter	**N = 26**	**N = 17**
Composite End Point for Success		
Number of patients with 2/3 abnormal baseline parameters, n (%)	26	17
Success	20 (77)	16 (94)
Failure	2 (8)	1 (6)
No week-52 data (failure)	4 (15)	n/a
Hemoglobin Criterion		
Number of patients with abnormal baseline hemoglobin, n (%)	10	7
Success	9 (90)	7 (100)
Failure	0	0
No week-52 data (failure)	1 (10)	n/a
Platelet Criterion		
Number of patients with abnormal baseline platelets, n (%)	25	16
Success	17 (68)	14 (87.5)
Failure	4 (16)	2 (12.5)
No week-52 data (failure)	4 (16)	NA
Spleen Criterion		
Number of patients with abnormal baseline spleen volume, n (%)	26	17
Success	22 (85)	17 (100)
Failure	0	0
No week-52 data (failure)	4 (15)	n/a

FAS = full analysis set; NA = not applicable; PPS = per-protocol set.
Source: Clinical Study Report.[57]

Table 37: PAP and LTTP Individual Efficacy Outcomes (FAS) in Phase II Trial

		Phase II		
Parameter	**N**	**Mean (SD)**	**Change from Baseline Mean or Median (95% CI)**	***P* Value**
Hemoglobin[a] (g/L)				
Baseline	26	111 (17)	-	-
Week 52	22	127 (16)	17 (11 to 23)	< 0.0001
Week 104 (month 24)	20	133 (15)	21 (14 to 28)	< 0.0001
Week 156 (month 36)	18	137 (14)	25 (18 to 32)	< 0.0001
Week 208 (month 48)	19	136 (12)	23 (16 to 30)	< 0.0001
Platelet Count[b] ($x10^9$/L)				
Baseline	26	66.4 (20.1)	-	-
Week 52	22	93.9 (32.3)	26.5 (16.4 to 36.5)	< 0.0001
Week 104 (month 24)	20	119.2 (42.4)	51.3 (34.7 to 67.9)	< 0.0001
Week 156 (month 36)	18	124.7 (40.3)	54.8 (35.9 to 73.7)	< 0.0001
Week 208 (month 48)	19	125.4 (51.1)	56.7 (32.1 to 81.3)	< 0.0001
Spleen Volume[c] (MN)				
Baseline	26	20.0 (12.8)	-	-
Week 52	22	12.7 (10.5)	−6.0 (−8.6 to −4.2)	< 0.0001
Week 104 (month 24)	20	8.1 (4.6)	−6.8 (−11.1 to −6.0)	< 0.0001
Week 156 (month 36)	19	6.4 (3.5)	−7.3 (−10.2 to −6.0)	< 0.0001
Week 208 (month 48)	18	6.1 (3.4)	−8.5 (−13.0 to −6.3)	< 0.0001
Liver Volume[d] (MN)				
Baseline	26	1.8 (0.6)	-	-
Week 52	22	1.4 (0.3)	−0.3 (−0.4 to −0.1)	< 0.0001
Week 104 (month 24)	20	1.2 (0.3)	−0.4 (−0.7 to −0.3)	< 0.0001
Week 156 (month 36)	19	1.2 (0.3)	−0.5 (−0.6 to −0.2)	< 0.0001
Week 208 (month 48)	18	1.19 (0.279)	−0.5 (−0.7 to −0.2)	< 0.0001

CI = confidence interval; FAS = full analysis set; LTTP = long-term treatment period; MN = multiples of normal; PAP = primary analysis period; SD = standard deviation.

[a] Hemoglobin: 95% CI on mean change from baseline. *P* value is from a paired t-test for change from baseline.

[b] Platelets: 95% CI on mean change from baseline. *P* value is from a paired t-test.

[c] Spleen: Median change from baseline is reported instead of mean change. 95% CI on median change from baseline. *P* value is from Wilcoxon signed rank test for change from baseline.

[d] Liver: Median change from baseline is reported instead of mean change. 95% CI on median change from baseline; *P* value is from Wilcoxon signed rank test for change from baseline.

Source: Clinical Study Report.[57]

EDGE

For the primary outcome, the proportion of patients who met the stability criteria at week 52 in the once-daily eliglustat regimen was lower than that in the twice-daily regimen (80.4% versus 83.1%, respectively) in the per-protocol population; [redacted].[52] The observed difference between patients stable on the once-daily regimen compared with the twice-daily regimen was −2.7% (95% CI, −17.7% to 11.9%). Based on the noninferiority margin of −15.0%, the once-daily regimen could not be declared noninferior to the twice-daily regimen in tolerability and efficacy, summarized in Table 38. [redacted].[52] The proportions of patients stable on individual components of the composite end point are also presented in Table 38.

Table 39 summarizes the efficacy data for patients who continued receiving eliglustat in the LTTP. [redacted].

Table 38: Primary Composite End Point and Associated Individual Parameters (Per-Protocol Set) in EDGE Trial

	EDGE	
Randomization Regimen	**Once-Daily Regimen**	**Twice-Daily Regimen**
Parameter	**N = 56**	**N = 59**
Composite end point: Patients stable for 52 weeks, n (%)	[redacted] (80.4)	[redacted] (83.1)
[redacted]95% CI on proportion stable[redacted]	(67.6 to 89.8)	(71.0 to 91.6)
Difference in proportion stable (q.d. minus b.i.d.) %	−2.7	
[redacted] 95% CI on difference in proportion stable[b]	(−17.7, 11.9)	
Individual Parameters		
Bone criteria met		
Number of patients, n (%)	[redacted]	[redacted]
[redacted] 95% CI (%)[redacted]	[redacted]	[redacted]
Stable hemoglobin criteria		
Number of patients, n (%)	[redacted]	[redacted]
[redacted] 95% CI (%)[redacted]	[redacted]	[redacted]
Stable platelet criteria		
Number of patients, n (%)	[redacted]	[redacted]
[redacted] 95% CI (%)[redacted]	[redacted]	[redacted]
Stable liver criteria		
Number of patients, n (%)	[redacted]	[redacted]
[redacted] 95% CI (%)[redacted]	[redacted]	[redacted]
Stable spleen criteria[c]		
N	[redacted]	[redacted]
Number of patients, n (%)	[redacted]	[redacted]
[redacted] 95% CI (%)[redacted]	[redacted]	[redacted]

b.i.d. = twice daily; CI = confidence interval; q.d. = once daily.

[redacted]

[b] [redacted] 95% CI: If the lower bound of the 95% CI for the difference in the overall column is within the noninferiority margin of −0.15 (or −15%), then the q.d. treatment will be declared noninferior to b.i.d treatment.

[c] Among patients who did not have splenectomy in per-protocol population.

Source: Clinical Study Report.[52]

Table 39: Long-Term Efficacy Outcomes (ITT) in EDGE Trial

Parameter	EDGE				
	Individual Parameters of Primary Outcome, in ITT Population				
	Bone Criteria	Hemoglobin Criteria	Platelet Criteria	Liver Criteria	Spleen Criteria
Proportion of patients stable after 1 year, [b] n/N (%) [redacted] 95% CI on proportion stable	[redacted] (92.3) (85.4, 96.6)	[redacted] (92.3) (85.4, 96.6)	[redacted] (93.3) (86.6, 97.3)	[redacted] (93.2) (86.5, 97.2)	[redacted] (95.8) (88.3, 99.1)
Proportion of patients stable after 2 years,[b] n/N (%) [redacted] 95% CI on proportion stable	[redacted] (84.4) (67.2, 94.7)	[redacted] (81.3) (63.6, 92.8)	[redacted] (84.4) (67.2, 94.7)	[redacted] (83.9) (66.3, 94.5)	[redacted] (95) (75.1, 99.9)

CI = confidence interval; ITT = intention-to-treat.

[redacted]

[b] Time points refer to long-term treatment period only and do not include treatment exposure times in the lead-in period or in the primary analysis period.

[redacted]

Source: Clinical Study Report.[52]

Safety and Harms

Phase II

The harms reported for the phase II study are briefly summarized in Table 40. Two patients (8%) were discontinued after a single dose of eliglustat due to asymptomatic non-sustained ventricular tachycardia. One other patient withdrew from the LTTP due to a serious adverse event (avascular necrosis of right femoral head). No patients experienced syncope; one patient reported peripheral neuropathy at month 48. Overall, 23 of 26 patients (88%) reported treatment-emergent adverse events, the most common of which were viral infection (in 23% of patients); upper respiratory tract and urinary tract infections (each in 15% of patients); and nasopharyngitis, sinusitis, arthralgia, pain in extremity, an increase in blood pressure, abnormal nerve conduction studies, diarrhea, and headache (each in 12% of patients). No neoplasms and no bone crises were reported, but new bone infarcts were reported in two patients, one of which was under review at the time of the Clinical Study Report. No deaths occurred during this study.[57]

EDGE

Harms data were provided for all 170 study patients of the EDGE trial. Table 40 summarizes the harms for the PAP and LTTP. [redacted]

[redacted].[52]

Table 40: Harms in Phase II and EDGE Safety Populations

	Phase II	EDGE (PAP)		EDGE (LTTP)
Regimen	**All Treated Patients**	**Once-Daily Regimen**	**Twice-Daily Regimen**	**All Treated Patients**
Safety Population	**N = 26**	[redacted]	[redacted]	[redacted]
Parameter				
Patients with > 0 AEs, N (%)	23 (88)	[redacted]	[redacted]	[redacted]
Patients with > 0 SAEs, N (%)	3 (12)	[redacted]	[redacted]	[redacted]
WDAEs, N (%)	3 (12)	[redacted]	[redacted]	[redacted]
Number of deaths, N (%)	0	[redacted]	[redacted]	[redacted]

AE = adverse event; LTTP = long-term treatment period; PAP = primary analysis period; SAE = serious adverse event; WDAE = withdrawal due to adverse event.
[redacted]

Source: clinical study reports.[52,57]

Limitations and Other Considerations

Phase II

The phase II trial was designed to assess the efficacy, safety, and pharmacokinetics of oral eliglustat at doses of 50 mg or 100 mg twice daily over the course of 52 weeks in adult male and female patients of GD1. The phase II trial was also designed to capture long-term data for 48 months. Pharmacokinetic data from this trial were used to inform dosages in the ENGAGE, ENCORE, and EDGE phase III trials. The nature of the phase II trial presents many limitations: no blinding was implemented at any stage of this study; no comparisons were made with a placebo, or an active comparator; and a small number of GD1 patients were recruited.

EDGE

The double-blind PAP of the phase III clinical trial, EDGE, sought to test noninferiority of a once-daily dosage regimen (all previous studies of oral eliglustat assessed twice-daily dosages) and to follow long-term, open-label outcomes for efficacy, safety, and pharmacokinetics of the once-daily regimen of oral eliglustat. The limitations of the PAP include [redacted]; a lack of active comparator (this study compared different regimens of the same drug), small patient numbers with different dosage stratifications, [redacted]. This trial was not able to prove noninferiority. EDGE's LTTP was an open-label, switch-over extension trial following patients for up to 42 months on the once-daily oral eliglustat regimen. Limitations of this period of the trial include its open-label, single-arm nature; [redacted] and mixed dosage regimens within the cohort.

[redacted]. Uncontrolled trials cannot objectively assess the safety and efficacy profiles of a treatment, as it is not possible to definitively link outcomes to treatment. In an uncontrolled trial, assessment of the relationship between harms and treatment is subject to investigator or reporter bias, so it is difficult to ascertain true safety outcomes. Open-label trial designs, in which both the investigators and the patients are unblinded to treatment allocation, can

influence the reporting of adverse events by patients and can impact on subjective outcomes and assessments. Long-term extension trials can overestimate efficacy and underestimate safety, as these report on a subset of the population that tolerates, and is more likely to be responding to, the treatment. Patients who fail to respond to treatment withdraw earlier in the trial and, as such, may be excluded from long-term analyses. Finally, smaller sample sizes make statistical calculations difficult and limit the interpretability of results.

Summary

Results from the phase II international, multi-centre, open-label, uncontrolled, short-term and long-term efficacy, safety, and pharmacokinetic trial suggest that oral eliglustat can show efficacy on a primary composite outcome (77% of patients over 52 weeks) and can improve disease parameters from baseline in patients with GD1 over the course of a long-term 48-month treatment period.

The primary analysis period of the phase III EDGE, international, multi-centre, randomized, double-blind, multi-regimen trial failed to show noninferiority of a once-daily regimen compared with a twice-daily regimen for oral eliglustat in patients with GD1 achieved or maintained stable disease on an oral eliglustat twice-daily regimen. The long-term, open-label, uncontrolled phase of the trial reported efficacy and safety of the once-daily regimen for two years. Disease stability was assessed for five parameters (hemoglobin and platelet levels, spleen and liver volume, and bone disease), but the single cohort was composed of patients following either the once-daily or twice-daily regimens, [redacted], complicating interpretation of the outcomes.

In both trials [redacted] experienced adverse events: 88% in phase II, and ranging from [redacted] in the EDGE primary and LTTPs. Commonly reported adverse events occurring in both trials included [redacted]. Two patients withdrew from the phase II study after the first dosage of eliglustat due to asymptomatic non-sustained ventricular tachycardia. [redacted]. No deaths occurred in the phase II trial. [redacted].

Both trials lacked an active comparator and the long-term outcomes offer limited interpretability due to the uncontrolled, unblinded nature of the studies.

Appendix 8: Summary of Drug Interactions

Eliglustat is metabolized in the liver by the cytochrome P450 2D6 (CYP2D6) and cytochrome P450 3A (CYP3A) metabolism pathways. Thus, any drugs, foods, or natural products that inhibit these systems could increase exposure to eliglustat and may result in prolongation of PR, QTc, or QRS cardiac intervals, which can produce arrhythmias.[5] The product monograph outlines key drug interactions that may increase or decrease eliglustat levels based on data from clinical trials and predicted interaction effects (Table 41 and Table 42).[5] In addition to these agents, consumption of grapefruit and its juice should be avoided in patients treated with eliglustat as grapefruit contains components that inhibit CYP3A.

Eliglustat may alter the elimination of other drugs including *P*-glycoprotein substrates (e.g., digoxin, colchicine, dabigatran, phenytoin, pravastatin) and CYP2D6 substrates (e.g., tricyclic antidepressants, phenothiazines, dextromethorphan, and atomoxetine).[5]

Table 41: Key Drug Interactions with Eliglustat for Extensive and Intermediate CYP2D6 Metabolizers

Concomitant Drug	Effect	Clinical Comment and Alteration of Dosages	
		Extensive Metabolizers	Intermediate Metabolizers
Strong or moderate CYP2D6 inhibitors used concomitantly with strong or moderate CYP3A inhibitors[a] (e.g., paroxetine + ketoconazole, terbinafine + fluconazole)	Increase in eliglustat exposure and maximal concentration	Contraindicated	Contraindicated
Strong CYP2D6 inhibitors[a,b] (e.g., paroxetine, fluoxetine, quinidine, bupropion)	Increase in eliglustat exposure and maximal concentration	Not recommended	Not recommended
Moderate CYP2D6 inhibitors[a] (e.g., duloxetine, terbinafine, moclobemide, mirabegron, cinacalcet, dronedarone)	Increase in eliglustat exposure and maximal concentration	Reduce dose to 84 mg once daily	Reduce dose to 84 mg once daily
Strong CYP3A inhibitors[a,b] (e.g., ketoconazole, clarithromycin, itraconazole, cobicistat, indinavir, lopinavir, ritonavir, saquinavir, telaprevir, tipranavir, posaconazole, voriconazole, conivaptan, boceprevir)	Increase in eliglustat exposure and maximal concentration	Reduce dose to 84 mg once daily	Contraindicated
Moderate CYP3A inhibitors[a] (e.g., fluconazole, erythromycin, ciprofloxacin, diltiazem, verapamil, aprepitant, atazanavir, darunavir, fosamprenavir, imatinib, cimetidine)	Increase in eliglustat exposure and maximal concentration	Reduce dose to 84 mg once daily	Reduce dose to 84 mg once daily
Strong CYP3A inducers[b] (e.g., rifampin, carbamazepine, phenobarbital, phenytoin, rifabutin)	Decrease in eliglustat exposure and maximal concentration	Not recommended	Not recommended

CYP2D6 = cytochrome P450 2D6; CYP31 = cytochrome P450 3A.

[a] Interaction effects predicted.

[b] Interaction based on clinical trial data.

Source: Product monograph.[5]

Table 42: Key Drug Interactions with Eliglustat for CYP2D6 Poor Metabolizers

Concomitant Drug	Effect	Clinical Comment and Alteration of Dosages
		Poor Metabolizers
Strong CYP3A inhibitors[a] (e.g., ketoconazole, clarithromycin, itraconazole, cobicistat, indinavir, lopinavir, ritonavir, saquinavir, telaprevir, tipranavir, posaconazole, voriconazole, conivaptan, boceprevir)	Increase in eliglustat exposure and maximal concentration	Contraindicated
Moderate CYP3A inhibitors[a] (e.g., fluconazole, erythromycin, ciprofloxacin, diltiazem, verapamil, aprepitant, atazanavir, darunavir, fosamprenavir, imatinib, cimetidine)	Increase in eliglustat exposure and maximal concentration	Not recommended
Weak CYP3A inhibitors[a] (e.g., ranitidine, amlodipine, fluvoxamine, goldenseal, isoniazid)	Increase in eliglustat exposure and maximal concentration	Not recommended
Strong CYP3A inducers[b] (e.g., rifampin, carbamazepine, phenobarbital, phenytoin, rifabutin)	Decrease in eliglustat exposure and maximal concentration	Not recommended

CYP2D6 = cytochrome P450 2D6; CYP3A = cytochrome P450 3A.

[a] Interaction effects predicted.

[b] Interaction based on clinical trial data.

Source: Product monograph.[5]

Appendix 9: Summary of Other Studies

Aim

To critically appraise an observational trial that investigated the Gaucher disease scoring system (DS3) (known as the DS3 study)[63] for the initial assessment and long-term follow-up of patients with GD1. This review was undertaken at the request of the CADTH Common Drug Review pharmacoeconomic team, as data from this study were used to determine long-term transition matrices in the pharmacoeconomic model.

Summary

The DS3 study was a retrospective cohort study of GD1 patients (18 years and older) in the International Collaborative Gaucher Group (ICGG) Gaucher Registry from four US clinical centres and one Canadian clinical centre. All patients had received enzyme replacement therapy (ERT) or substrate reduction therapy; treatment-naive patients were excluded. DS3 scores were calculated at baseline (at or before initiation of ERT) and annually based on data available from the registry. The study examined baseline DS3 scores, their change over time, and association with disease-related factors.

Of the 173 patients recruited, 166 patients had sufficient data and 133 patients had received treatment and were analyzed (prior therapy: miglustat, N = 1; ERT, N = 132). Overall, 61% of patients were female, with a mean age of 57.8 years at baseline. The median age at diagnosis was 28 years (range 0 to 85), and 29% had had a total splenectomy prior to starting ERT. The median baseline DS3 score was 5.5 points (interquartile range 3.7 to 7.5). Due to the limited number of patients with DS3 scores ≥ 9 (N = 15), the severe (DS3 score 9 to 12) and marked (DS3 score 6 to 8.99) classifications were analyzed as one group. The median starting dose of ERT was 60 U/kg every two weeks (range 8 to 60) and at last follow-up was 45 U/kg (range 10 to 120).

Baseline DS3 scores were found to vary by the patient's genotype, history of splenectomy, history of severe bone events, age at diagnosis (< 18 or older), and year of diagnosis (prior to 1991 or later). At baseline, 17%, 40%, and 44% of patients were classified as having mild, moderate, or marked Gaucher disease, respectively, based on their DS3 score. Among those with marked disease at baseline, 45%, 46%, and 69% had transitioned to a moderate or mild disease classification at year 1, year 2, and year 5, respectively. For those with moderate disease, 41%, 49%, and 49% had transitioned to mild disease at year 1, year 2, and year 5, respectively. Among those with mild disease at baseline, 82%, 64%, and 64% remained in the mild category at year 1, year 2, and year 5, respectively; 9% had transitioned to moderate disease at year 2 and year 5; and the remainder had data missing.

A number of limitations were identified with this cohort study, including uncertainty in the DS3 scores, patient attrition, lack of adjustment for confounders, and potential issues with external validity. With regards to the DS3 scores, data availability or other issues could impact the confidence in these estimates. The authors noted that registry data on bone pain may not distinguish between pain related to Gaucher disease and that from other causes. Also, it was not possible to correlate the timing of bone events, such as fractures or avascular necrosis, with acute symptoms and pain based on the retrospective data available. The extent of missing data was substantial for some measures used to estimate the DS3 score. Imputation was used for bone mineral density and bone marrow burden, assuming no change if the previous year and subsequent year data were similar. It was not clear if the same imputation strategy was used for missing data for other parameters. Data were imputed for 33% of bone marrow burden scores, 30% for bone mineral density, 27% of spleen volume, 43% of liver volume measurements, 6% of major bone lesions, and < 2.6% of other measures. When imputation was not possible, DS3 scores were calculated without that parameter. Missing data that could not be imputed were < 1% for most measures except bone mineral density (31%) and bone marrow burden (4.4%). Also of note, data availability varied over time, with more bone mineral density data missing in earlier time periods. The authors stated that the calculation of DS3 scores is sensitive to missing data; thus, given the extent of missing parameters, some caution is warranted with interpreting these data.

Patient attrition was also an issue in this retrospective cohort study. The authors stated that patient attrition after 10 years was considerable; however, even in the first few years of follow-up, missing data were noteworthy. Among the patient groups with mild, moderate, or marked disease at baseline, data were unavailable to estimate DS3 scores for 18% to 22% of patients at year 1, 26%

to 31% of patients at year 2, and 17% to 27% of patients at year 5. Moreover, the initial sample sizes in these groups were small (mild, N = 22; moderate, N = 53; marked, N = 58). Both the initial sample size and the extent of missing data could potentially affect the reliability of the transition probabilities estimates.

The authors used t-tests and simple linear regression to explore correlations between variables, with no adjustment for confounders. For example, 59% of patients were diagnosed before 1991 (when ERT became available) and these patients were more likely to have a splenectomy, to have higher DS3 scores at baseline, and to have more bone events. Data from patients diagnosed before ERT may be less generalizable to those diagnosed and treated now. Given the small sample size, it would not have been possible to adjust for many variables in the analysis; however, there were some important confounders present. As there was no attempt to explore these potential confounders, it is difficult to interpret the results. Another issue with external validity relates to the selection of study sites. It is unclear how these sites were chosen and if the patients included in the DS3 study were similar to other treated patients in the International Collaborative Gaucher Group (ICGG)Gaucher Registry.

References

1. Pastores GM, Weinreb NJ, Aerts H, Andria G, Cox TM, Giralt M, et al. Therapeutic goals in the treatment of Gaucher disease. Semin Hematol. 2004 Oct;41(4 Suppl 5):4-14.
2. Vom Dahl S, Poll L, Di Rocco M, Ciana G, Denes C, Mariani G, et al. Evidence-based recommendations for monitoring bone disease and the response to enzyme replacement therapy in Gaucher patients. Curr Med Res Opin. 2006 Jun;22(6):1045-64.
3. Prevalence and incidence of rare diseases: bibliographic data. Prevalence, incidence or number of published cases listed by diseases (in alphabetical order) [Internet]. [place unknown]: Orphanet; 2016. [cited 2017 Mar 27]. (Orphanet report series; no.1). Available from: http://www.orpha.net/orphacom/cahiers/docs/GB/Prevalence_of_rare_diseases_by_alphabetical_list.pdf
4. Bennett LL, Mohan D. Gaucher disease and its treatment options. Ann Pharmacother. 2013 Sep;47(9):1182-93.
5. Cerdelga (eliglustat): 84 mg eliglustat capsules (as eliglustat tartrate) [product monograph]. Mississauga (ON): Genzyme Canada, a division of sanofi-aventis Canada Inc.; 2017 Apr 21.
6. Center for Drug Evaluation and Research, U.S. Food and Drug Administration. Statistical review(s). In: Cerdelga (eliglustat). Company:Genzyme Corporation. Application no.: 205494. Approval date: 19/08/2014 [Internet]. Rockville (MD): FDA; 2014 Aug 19 [cited 2017 Feb 7]. (FDA drug approval package). Available from: http://www.accessdata.fda.gov/drugsatfda_docs/nda/2014/205494Orig1s000TOC.cfm
7. European Public Assessment Report (EPAR). Assessment report for Cerdelga [Internet]. London: European Medicines Agency; 2014 Nov 20. [cited 2017 May 2]. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/003724/WC500182389.pdf
8. Ontario guidelines for treatment of Gaucher disease by enzyme replacement with imiglucerase or velaglucerase, or substrate reduction therapy with miglustat [Internet]. Version 9. Ottawa (ON): The Garrod Association; 2011 Aug. [cited 2017 Mar 9]. Available from: http://www.garrod.ca/wp-content/uploads/ONTARIO-GUIDELINES-FOR-TREATMENT-OF-GAUCHER-August-2011-2.pdf
9. Sanofi Genzyme response to April 20 2017 CDR request for additional information regarding the Cerdelga CDR review: [CYP2D6 genotype][**CONFIDENTIAL** additional manufacturer's information]. Mississauga (ON): Sanofi Genzyme; 2017 Apr 24.
10. Clinical Study Report: GZGD02607. A phase 3, randomized, multi-center, multi-national, open-label, active comparator study to evaluate the efficacy, and safety of Genz-112638 in patients with Gaucher disease Type 1 who have reached therapeutic goals with enzyme replacement therapy (ENCORE) [**CONFIDENTIAL** internal manufacturer's report]. Cambridge (MA): Genzyme Corporation, a Sanofi Company; 2014 Apr 18.
11. Clinical Study Report: GZGD02507. A phase 3, randomized, double-blind, placebo-controlled, multi-center study confirming the efficacy and safety of Genz-112638 in patients with Gaucher disease Type 1 (ENGAGE) [**CONFIDENTIAL** internal manufacturer's report]. Cambridge (MA): Genzyme Corporation, a Sanofi Company; 2013 Mar 28.
12. Weinreb NJ. Introduction. Advances in Gaucher disease: therapeutic goals and evaluation and monitoring guidelines. Semin Hematol. 2004 Oct;41(4 Suppl 5):1-3.
13. Martins AM, Valadares ER, Porta G, Coelho J, Semionato FJ, Pianovski MA, et al. Recommendations on diagnosis, treatment, and monitoring for Gaucher disease. J Pediatr. 2009 Oct;155(4 Suppl):S10-S18.
14. Sobera LA, Sundaravinayagam D, Dulsat C, Rosa E. Therapeutic targets for Gaucher's disease. Drugs Future. 2009 Dec;34(12):1001-4.
15. Zimran A, Elstein D. Management of Gaucher disease: Enzyme replacement therapy. Pediatr Endocrinol Rev. 2014 Sep;12 Suppl 1:82-7.
16. Cerezyme (imiglucerase for injection): lyophilized powder 400 units / vial [product monograph]. Mississauga (ON): Sanofi Genzyme; 2016 Nov 30.
17. VPRIV (velaglucerase alfa): 400 U / vial powder for solution for injection [product monograph]. Lexington (MA): Shire Human Genetics Therapies, Inc.; 2015 May 7.
18. Elelyso (taligulcerase alfa for injection): lyophilized powder 200 units / vial [product monograph]. Kirkland (QB): Pfizer Canada Inc.; 2017 Mar 16.
19. Weinreb NJ, Charrow J, Andersson HC, Kaplan P, Kolodny EH, Mistry P, 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 Aug 1;113(2):112-9.
20. Grabowski GA, Kacena K, Cole JA, Hollak CE, Zhang L, Yee J, et al. Dose-response relationships for enzyme replacement therapy with imiglucerase/alglucerase in patients with Gaucher disease type 1. Genet Med [Internet]. 2009 Feb [cited 2017 Mar 27];11(2):92-100. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3793250
21. Beutler E, Demina A, Laubscher K, Garver P, Gelbart T, Balicki D, et al. The clinical course of treated and untreated Gaucher disease. A study of 45 patients. Blood Cells Mol Dis. 1995;21(2):86-108.
22. Pastores GM, Sibille AR, Grabowski GA. Enzyme therapy in Gaucher disease type 1: dosage efficacy and adverse effects in 33 patients treated for 6 to 24 months. Blood. 1993 Jul 15;82(2):408-16.
23. Rosenthal DI, Doppelt SH, Mankin HJ, Dambrosia JM, Xavier RJ, McKusick KA, et al. Enzyme replacement therapy for Gaucher disease: skeletal responses to macrophage-targeted glucocerebrosidase. Pediatrics. 1995 Oct;96(4 Pt 1):629-37.
24. Zavesca (miglustat): 100 mg capsule [product monograph]. Allschwil (CH): Actelion Pharmaceuticals Canada Inc.; 2012 Jul 31.
25. Mistry PK, Lukina E, Ben TH, Amato D, Baris H, Dasouki M, et al. Effect of oral eliglustat on splenomegaly in patients with Gaucher disease type 1: the ENGAGE randomized clinical trial. JAMA. 2015 Feb 17 [cited 2017 May 2];313(7):695-706. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4962880

26. Cox TM, Drelichman G, Cravo R, Balwani M, Burrow TA, Martins AM, et al. Eliglustat compared with imiglucerase in patients with Gaucher's disease type 1 stabilised on enzyme replacement therapy: a phase 3, randomised, open-label, non-inferiority trial [supplementary appendix]. Lancet. 2015 Jun 13;385(9985):2355-62.

27. Pleat R, Cox TM, Burrow TA, Giraldo P, Goker-Alpan O, Rosenbloom BE, et al. Stability is maintained in adults with Gaucher disease type 1 switched from velaglucerase alfa to eliglustat or imiglucerase: A sub-analysis of the eliglustat ENCORE trial. Mol Genet Metab Rep [Internet]. 2016 Dec [cited 2017 Feb 17];9:25-8. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5050260/pdf/main.pdf

28. Center for Drug Evaluation and Research, U.S. Food and Drug Administration. Medical review(s). In: Cerdelga (eliglustat). Company:Genzyme Corporation. Application no.: 205494. Approval date: 19/08/2014 [Internet]. Rockville (MD): FDA; 2014 Aug 19 [cited 2017 Feb 7]. (FDA drug approval package). Available from: http://www.accessdata.fda.gov/drugsatfda_docs/nda/2014/205494Orig1s000TOC.cfm

29. CDR submission: Cerdelga (eliglustat), 84 mg capsule. Company: Sanofi Genzyme [**CONFIDENTIAL** manufacturer's submission]. Mississauga (ON): Sanofi Genzyme; 2017 Jan 15.

30. Clinical Study Report: GZGD02507 [Extension data]. A phase 3, randomized, double-blind, placebo controlled, multi center study confirming the efficacy and safety of Genz 112638 in patients with Gaucher disease Type 1 (ENGAGE) [**CONFIDENTIAL** internal manufacturer's report]. Mississauga (ON): Sanofi Genzyme; 2016 Oct 25.

31. Clinical Study Report: GZGD02607 [Extension data]. A phase 3, randomized, multi-center, multi-national, open-label, active comparator study to evaluate the efficacy, and safety of Genz-112638 (eliglustat) in patients with Gaucher disease Type 1 who have reached therapeutic goals with enzyme replacement therapy (ENCORE) [**CONFIDENTIAL** internal manufacturer's report]. Mississauga (ON): Sanofi Genzyme; 2016 May 15.

32. Cox TM, Drelichman G, Cravo R. Eliglustat compared with imiglucerase in patients with Gaucher's disease type 1 stabilised on enzyme replacement therapy: a phase 3, randomised,
open-label, non-inferiority trial. Lancet. 2015 Nov 17;386:e45. Erratum for: Lancet 2015;385:2355-62.

33. Sanofi Genzyme response to March 16 2017 CDR request for additional information regarding the Cerdelga CDR review:[**CONFIDENTIAL** additional manufacturer's information]. Mississauga (ON): Sanofi Genzyme; 2107 Mar 23.

34. Sanofi Genzyme response to March 24 2017 CDR request for additional information regarding the Cerdelga CDR review:[**CONFIDENTIAL** additional manufacturer's information]. Mississauga (ON): Sanofi Genzyme; 2017 Mar 28.

35. Assessment of fracture risk and its application to screening for postmenopausal osteoporosis. Geneva: World Health Organization (WHO); 1994.

36. User's manual for the SF-36v2 health survey. 3rd ed. Lincoln (RI): Quality Metric Incorporated; 2011.

37. Cleeland CS, Ryan KM. Pain assessment: global use of the Brief Pain Inventory. Ann Acad Med Singapore. 1994 Mar;23(2):129-38.

38. Cleeland CS. The brief pain inventory: user guide. Houston (TX): The University of Texas M. D. Anderson Cancer Center; 2009.

39. Krupp LB, LaRocca NG, Muir-Nash J, Steinberg AD. The fatigue severity scale. Application to patients with multiple sclerosis and systemic lupus erythematosus. Arch Neurol. 1989 Oct;46(10):1121-3.

40. Whitehead L. The measurement of fatigue in chronic illness: a systematic review of unidimensional and multidimensional fatigue measures. J Pain Symptom Manage. 2009 Jan;37(1):107-28.

41. Lerdal A, Kottorp A. Psychometric properties of the Fatigue Severity Scale-Rasch analyses of individual responses in a Norwegian stroke cohort. Int J Nurs Stud. 2011 Oct;48(10):1258-65.

42. Rosa K, Fu M, Gilles L, Cerri K, Peeters M, Bubb J, et al. Validation of the Fatigue Severity Scale in chronic hepatitis C. Health Qual Life Outcomes. 2014 Jun 11 [cited 2017 Mar 14];12:90. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4094687

43. Grace J, Mendelsohn A, Friedman JH. A comparison of fatigue measures in Parkinson's disease. Parkinsonism Relat Disord. 2007 Oct;13(7):443-5.

44. Hagell P, Hoglund A, Reimer J, Eriksson B, Knutsson I, Widner H, et al. Measuring fatigue in Parkinson's disease: a psychometric study of two brief generic fatigue questionnaires. J Pain Symptom Manage. 2006 Nov;32(5):420-32.

45. Impellizzeri FM, Agosti F, De CA, Sartorio A. Psychometric properties of the Fatigue Severity Scale in obese patients. Health Qual Life Outcomes. 2013 Mar 6 [cited 2017 Mar 14];11:32. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3599447

46. Learmonth YC, Dlugonski D, Pilutti LA, Sandroff BM, Klaren R, Motl RW. Psychometric properties of the Fatigue Severity Scale and the Modified Fatigue Impact Scale. J Neurol Sci. 2013 Aug 15;331(1-2):102-7.

47. Weinreb NJ, Cappellini MD, Cox TM, Giannini EH, Grabowski GA, Hwu WL, et al. A validated disease severity scoring system for adults with type 1 Gaucher disease. Genet Med. 2010 Jan;12(1):44-51.

48. Stein P, Yang R, Liu J, Pastores GM, Mistry PK. Evaluation of high density lipoprotein as a circulating biomarker of Gaucher disease activity. J Inherit Metab Dis [Internet]. 2011 Apr [cited 2017 Mar 27];34(2):429-37. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3186206

49. Bodamer OA, Hung C. Laboratory and genetic evaluation of Gaucher disease. Wien Med Wochenschr. 2010 Dec;160(23-24):600-4.

50. Kishnani PS, DiRocco M, Kaplan P, Mehta A, Pastores GM, Smith SE, et al. A randomized trial comparing the efficacy and safety of imiglucerase (Cerezyme) infusions every 4 weeks versus every 2 weeks in the maintenance therapy of adult patients with Gaucher disease type 1. Mol Genet Metab. 2009 Apr;96(4):164-70.

51. Health Canada reviewer's report: Cerdelga (eliglustat as tartate) [**CONFIDENTIAL** internal report]. Ottawa: Therapeutics Products Directorate, Health Canada; 2017 Apr 20.

52. Clinical Study Report: GZGD03109. A phase 3, randomized, multi-center, multi-national, double-blind study to evaluate the efficacy, safety, and pharmacokinetics of once daily versus twice daily dosing of eliglustat in patients with Gaucher disease Type 1 who have demonstrated clinical stability on a twice daily dose of Genz-112638 (EDGE)[**CONFIDENTIAL** internal manufacturer's report]. Mississauga (ON): Sanofi Genzyme; 2016 Sep 30.

53. Daut RL, Cleeland CS, Flanery RC. Development of the Wisconsin brief pain questionnaire to assess pain in cancer and other diseases. Pain. 1983 Oct;17(2):197-210.

54. Keller S, Bann CM, Dodd SL, Schein J, Mendoza TR, Cleeland CS. Validity of the brief pain inventory for use in documenting the outcomes of patients with noncancer pain. Clin J Pain. 2004 Sep;20(5):309-18.

55. Weinreb NJ, Aggio MC, Andersson HC, Andria G, Charrow J, Clarke JT, et al. Gaucher disease type 1: revised recommendations on evaluations and monitoring for adult patients. Semin Hematol. 2004 Oct;41(4 Suppl 5):15-22.

56. Cox TM, Drelichman G, Cravo R, Balwani M, Burrow TA, Martins AM, et al. Eliglustat maintains long-term clinical stability in patients with Gaucher disease type 1 stabilized on enzyme therapy. Blood [Internet]. 2017 Feb 6 [cited 2017 Feb 17]. Available from: http://www.bloodjournal.org/content/bloodjournal/early/2017/02/06/blood-2016-12-758409.full.pdf

57. Clinical Study Report: GZGD00304. A phase 2, open-label, multi-center study evaluating the efficacy, safety, and pharmacokinetics of Genz-112638 in Gaucher Type 1 patients [**CONFIDENTIAL** internal manufacturer's report]. Cambridge (MA): Genzyme Corporation, a Sanofi Company; 2012 Sep 28.

58. Peterschmitt MJ, Burke A, Blankstein L, Smith SE, Puga AC, Kramer WG, et al. Safety, tolerability, and pharmacokinetics of eliglustat tartrate (Genz-112638) after single doses, multiple doses, and food in healthy volunteers. J Clin Pharmacol. 2011 May;51(5):695-705.

59. Lukina E, Watman N, Arreguin EA, Banikazemi M, Dragosky M, Iastrebner M, et al. A phase 2 study of eliglustat tartrate (Genz-112638), an oral substrate reduction therapy for Gaucher disease type 1. Blood. 2010 Aug 12 [cited 2017 May 2];116(6):893-9. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2924227

60. Lukina E, Watman N, Arreguin EA, Dragosky M, Iastrebner M, Rosenbaum H, et al. Improvement in hematological, visceral, and skeletal manifestations of Gaucher disease type 1 with oral eliglustat tartrate (Genz-112638) treatment: 2-year results of a phase 2 study. Blood. 2010 Nov 18 [cited 2017 May 2];116(20):4095-8. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2993616

61. Lukina E, Watman N, Dragosky M, Pastores GM, Arreguin EA, Rosenbaum H, et al. Eliglustat, an investigational oral therapy for Gaucher disease type 1: Phase 2 trial results after 4 years of treatment. Blood Cells Mol Dis. 2014 Dec;53(4):274-6.

62. Shayman JA. Eliglustat tartrate: Glucosylceramide synthase inhibitor treatment of type 1 Gaucher disease. Drugs Future. 2010 Aug 1 [cited 2017 May 2];35(8):613-20. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3340614

63. Weinreb NJ, Finegold DN, Feingold E, Zeng Z, Rosenbloom BE, Shankar SP, et al. Evaluation of disease burden and response to treatment in adults with type 1 Gaucher disease using a validated disease severity scoring system (DS3). Orphanet J Rare Dis [Internet]. 2015 May 22 [cited 2017 Mar 9];10:64. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4471923