

# Eliglustat tartrate: an oral therapeutic option for Gaucher disease type 1

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Gaucher disease is an inborn error of glycosphingolipid catabolism, which has been shown to be responsive to enzyme replacement therapy and substrate synthesis inhibition. Eliglustat tartrate, an analog of *D-threo*-1-phenyl-2-decanoylamino-3-morpholino-propanol, is an orally administered agent with properties of substrate synthesis inhibition and an acceptable pharmacokinetic profile. In Phase II clinical trials (both in the published pivotal and extension phase), eliglustat was shown to have a favorable, safe and efficacious profile. Three additional studies – identified by the acronyms ENCORE, ENGAGE and EDGE – are ongoing; it is anticipated these trials will provide additional information leading to regulatory approval. In addition, insights from these trials are expected to facilitate the development of therapeutic guidelines for the management of patients with Gaucher disease, incorporating eliglustat into the expanding list of therapeutic options.

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Gaucher disease (GD) type 1, an inborn error of glycosphingolipid catabolism, is characterized by anemia, thrombocytopenia, hepatosplenomegaly and bone involvement [1]. These cardinal features of GD have been shown to be responsive to enzyme replacement therapy (ERT) and substrate synthesis inhibition [2,3]. Both therapeutic approaches enhance the clearance of the accumulated substrate glucosylceramide (GL1), by either restoring enzymatic hydrolytic activity or reducing the concentration of substrate precursors to a level within the hydrolytic capacity of the mutant enzyme (glucocerebrosidase). Substrate synthesis inhibition is alternatively referred to as substrate reduction therapy. This therapeutic option entails the inhibition of glucosylceramide synthase, a Golgi complex enzyme that catalyzes the formation of glucosylceramide from ceramide and uridine diphosphate glucose.

Two classes of orally administered glucosylceramide synthase inhibitors have been described; namely, iminosugars and analogs of *D-threo*-1-phenyl-2-decanoylamino-3-morpholino-propanol (PDMP) [3,4]. *N*-butyldeoxynojirimycin, an alkylated iminosugar, was the first oral substrate synthesis inhibitor to garner regulatory approval (miglustat, Actelion Pharmaceuticals UK Ltd [London, UK]), based on clinical trials in adult patients with GD type 1, the non-neuropathic clinical variant [5]. Eliglustat tartrate, a PDMP analog, is currently in clinical trials. Therapeutic outcomes in adult GD type 1 patients (n = 26) enrolled in a Phase II clinical trial revealed eliglustat was efficacious and relatively safe [6]. Three additional ongoing studies (Table 1), identified by the acronyms ENCORE, ENGAGE and EDGE [201] are anticipated to obtain more data on safety and efficacy to fulfill regulatory requirements for approval. The introduction of eliglustat is likely to lead to a modification of current treatment paradigms, and will need delineation of suitable patient subgroups,

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Table 1. Eliglustat-related clinical trials.

Protocol	Initial protocol date	Enrolled (n)	Inclusion criteria	Efficacy end points <sup>†</sup>
Phase II GZGD00304	31 August 2005	26	Hg: 8–10 g/dl (female)/8–11 g/dl (male) PLT: 45,000–100,000 <sup>‡</sup> SV : $\geq 10 \times$ normal Age: 18–65	Inclusive of $\geq 0.5$ g/dl in Hg Inclusive of $\geq 15\%$ in PLT Reduction of $\geq 15\%$ in total SV
ENGAGE GZGD02507 (Naive to therapy, with a placebo arm for 39 weeks)	31 March 2009	40	Hg: 8–11 g/dl (Female)/8–12 g/dl (Male) PLT: 50,000–130,000 <sup>‡</sup> SV : 6–30 $\times$ MoN Age: 16 years upon randomization	Primary: ■ Percentage change in SV $\times$ MoN from baseline to 39 weeks treatment with Genz 112638 vs placebo Secondary: ■ Absolute changes in Hg level, % change from baseline in LV (MoN), and % changes from baseline in PLT count. In addition, within patient change from baseline to 39 weeks
ENCORE GZGD02607 (Switched from ERT to eliglustat) <sup>§</sup>	22 May 2009	160	No bone crises and free of symptomatic bone disease, pathological fractures Hg: $\geq 11$ g/dl (female)/ $\geq 12$ g/dl (male) PLT: $\geq 100,000/\text{mm}^3$ <sup>‡</sup> SV: $< 10 \times$ MoN	Percentage of patients who remain stable for 52 weeks (primary analysis period), for both treatment groups (ERT vs eliglustate)
EDGE GZGD03109 (randomized double blind study for q.d. vs b.i.d. dosing) <sup>†</sup>	05 November 2009	171	Screening inclusion criteria ■ Hg: $\geq 9$ g/dl ■ PLT: $\geq 70,000/\text{mm}^3$ ■ SV: $\leq 25 \times$ MoN ■ LV: $\leq 2.0 \times$ MoN ■ Age: $> 18$ years Randomization criteria ■ No more than one bone crisis, free from symptomatic bone disease, such as bone pain due to osteonecrosis and/or pathological fractures ■ Hg: $\geq 11$ g/dl (female)/ $\geq 12$ g/dl (male) ■ PLT: $\geq 100,000/\text{mm}^3$ <sup>‡</sup> ■ SV $< 10 \times$ MoN, if applicable ■ LV $< 1.5 \times$ MoN Additional randomization: ■ Dose of 50 or 100 mg b.i.d. for at least 4 months ■ Peak (2 h) Genz-99067 plasma concentration $< 50$ ng/ml	Primary: ■ Percentage of randomized patients who remain stable after treatment with Genz-112638 through week 52 (primary analysis period) assessed for both dosing regimens (b.i.d. full dose, q.d. full dose) separately along with a difference between the two dosing regimens. This end point will be used to evaluate the noninferiority of the q.d. regimen compared with the b.i.d. regimen

<sup>†</sup>A patient must meet all of the following efficacy criteria in each parameter to be considered a success; the SV assessments do not apply to patients who have had a total splenectomy.

<sup>‡</sup>Mean of two readings.

<sup>§</sup>Stable hematologic parameters include: Hg does not decrease  $> 1.5$  g/dl from baseline; PLT does not decrease  $> 25\%$  from baseline and stable organ volumes include: SV does not increase  $> 25\%$  from baseline and LV (MoN) does not increase  $> 20\%$  from baseline. A blinded independent adjudication board will review and confirm instances of failure to meet the primary end point.

<sup>†</sup>Starts with a lead in period minimum of 6 months – if stability passed – then randomized to blinded study of q.d. versus b.i.d. dosing for 69 weeks.

b.i.d.: Twice daily; ERT: Enzyme replacement therapy; Hg: Hemoglobin; LV: Liver volume; MoN: Multiples of normal; PLT: Platelets; q.d.: Once daily; SV: Spleen volume.

definition of the appropriate time to initiate therapy and therapeutic strategies using an algorithm aimed at clear therapeutic goals *vis a vis* ERT, the current standard of care. Long-term safety considerations will be critical, in view of ERTs essentially outstanding track record.

### Preclinical studies

In early studies, it was important to identify an oral drug that would promote depletion of glucosylceramide, but would restrict the accumulation of ceramide to minimize any potential toxicity as a result thereof. This objective was achieved through identification of a PDMP analog with reduced inhibitory properties on 1-*O*-acylceramide synthase [4].

Initial studies to explore proof of therapeutic principle were performed in the mouse model of Fabry disease (FD) and transformed lymphoblasts from FD patients [7]. FD is a glycosphingolipidosis, caused by deficiency of  $\alpha$ -galactosidase A and accumulation of the substrate globotriaosylceramide [8]. It should be noted that GL1, the substrate that accumulates in GD, and globotriaosylceramide (in FD) have a glycosphingolipid precursor in common. Subsequently, the PDMP-based glucosylceramide inhibitors were licensed to Genzyme (Haverhill, UK) by the University of Michigan (MI, USA) for further clinical development. Eliglustat (Genz-112638), a C8-substituted homolog, was identified as the lead candidate, based on its pharmacokinetic profile and specificity for glucosylceramide synthase, achieved at low (nanomolar) concentrations [4].

*In vitro* studies demonstrated that eliglustat reduced the levels of  $G_{M1}$ - and  $G_{M3}$ -gangliosides in cultured human erythroleukemia cells and murine melanoma cells, respectively [9].  $G_{M1}$ - and  $G_{M3}$ -gangliosides are substrates that accumulate in the gangliosidoses, additional glycosphingolipid storage disorders.

As the GD knockout mouse model suffer from a skin permeability defect and die shortly postpartum, *in vivo* studies were carried out using a knock-in mouse GD model (Asp409Val/null) that retains low basal activity of glucocerebrosidase [9]. Eliglustat given at 150 mg/kg per ore for 10 weeks to this GD mouse model, both at a presymptomatic (i.e., at age 10 weeks) and symptomatic (age 7 months) stage, was shown to lower the concentrations of GL1 in the liver, lung and spleen, and reduced the number of Gaucher cells in the liver [9]. Additional studies were conducted in 3-month old affected mice, to examine the use of eliglustat (also at 150 mg/kg per ore) when compared with short-term ERT (using imiglucerase 10 mg/kg intravenously (iv. administered) alone or in combination, and sequentially (i.e., after ERT) [10]. In these studies, eliglustat was effective in reducing GL1 storage/re-accumulation in the liver and spleen; the best response profile was

seen with combination therapy (i.e., eliglustat and imiglucerase administration) [10].

There were no observable ill effects on well-being and feeding habits in the Asp409Val/null GD mice treated with eliglustat [9,10]. In healthy dogs, a dose-dependent increase in QRS duration and P–R interval was observed on doses between 10 and 80 mg/kg, and at the higher dose there was a tendency for an increased heart rate and a decrease in the R–R interval [11]. These changes were interpreted as consistent with a potential effect on sodium channels.

### Clinical studies

Human liver microsomal enzyme assays demonstrated that eliglustat metabolism is primarily catalyzed by cytochrome P450 *CYP2D6* [11]. Eliglustat is also a P-glycoprotein substrate, which likely accounts for its poor distribution into the brain. The latter may be one reason trials in GD were initiated in type 1 patients, despite the fact that a safe and effective treatment with ERT was available to these patients, and the major unmet need was an effective treatment for primary neurodegenerative complications in patients with GD types II and III.

#### ■ Phase I clinical trials

Phase I clinical trials were undertaken in healthy volunteers, in whom plasma glucosylceramide concentrations were decreased after dosing with eliglustat. Feeding studies suggested a food effect, due to a decrease in the rate but not the degree of absorption. In the Phase Ia, single-dose, dose-escalating study, 61 subjects were identified as having drug-related adverse effects, the majority of which were deemed mild (Common Terminology Criteria grade 1) [11]. The most common complaints included dysgeusia, throat irritation and dizziness. Only one subject receiving 30 mg/kg drug reported a single Common Terminology Criteria grade III adverse event (dizziness). Doses of eliglustat tartrate >10 mg/kg produced a short-term prolongation of the QRS period and increases in  $Q-T/Q-T_c$  from 30 to 60 ms in some subjects [11].

In a multiple-dose Phase Ib study (eliglustat at 50, 200 or 350 mg twice daily over 12 days), a correlation was observed between *CYP2D6* genotype (classified as poor to ultra-rapid metabolizers) and drug exposure [11]. The higher AUC was observed in subjects with lower *CYP2D6*-associated metabolism. No changes in any cardiac parameters were observed in the multiple-dose study, probably because of the smaller dosage range used and therefore a significantly lower  $C_{max}$  than that observed in the Phase Ia study.

#### ■ Phase II clinical trial & extension study

A Phase II clinical trial in adult GD type 1 patients (n = 26) naive to therapy was initiated in July 2006 (Table 2).

Table 2. Summary of results for Phase II clinical trial in adult Gaucher disease type 1 patients.

Parameter	Baseline mean (SD); n = 26	Treatment: 52 weeks mean (95% CI); n = 22	Treatment: 2 years mean (SD); n = 20
Hemoglobin level (g/dl)	11.1 (1.7)	1.62 (+1.05–2.18)	2.1 (+20%; ± 15%)
Platelet count (n/mm <sup>3</sup> )	66,442 (20,118)	40.3% (+23.7–57.0)	Average ~50,000 (+81%; ± 56%)
Spleen volume (MoN)	20.0 (12.8)	-38.5% (-43.5–33.5%)	-52 ± 11%
Liver volume (MoN)	1.8 (0.6)	-17.0% (-21.6–12.3%)	-24 ± 13%
BMD LS (n = 19)	-1.41 (0.99)	-1.10 (0.99)	0.6 ± 0.7 (+8%; n = 16)
BMD Fr (n = 19)	-0.04 (0.75)	0.03 (0.77)	-0.1 ± 0.8 (n = 14)
Chitotriosidase (nmol/h/ml; n = 24 <sup>†</sup> )	9168 (5395)	Median level declined by 35–50% <sup>*</sup>	Median level declined by 35–50% <sup>‡</sup>

<sup>†</sup>Two patients were homozygous for the common inactivating *CHIT1* mutation.  
<sup>\*</sup>Referable to biomarkers tested: Chitotriosidase, CCL18, ACE and TRAP.  
<sup>‡</sup>Referable to biomarkers tested: Chitotriosidase and CCL18.  
BMD: Bone mineral density; Fr: Femur; LS: Lumbar spine; MoN: Multiples of normal.

Patients received either 50 or 100 mg of eliglustat for a period of 52 weeks [6]. Entry criteria required splenomegaly (>ten-times normal) with thrombocytopenia and/or anemia (Table 1). Patients on eliglustat demonstrated improvements in hemoglobin concentration and platelet counts, reduction of hepatosplenomegaly and an increase in bone density [6]. Improvements continued or were maintained in patients who participated in the extension phase. Overall, at the 2-year time point, 85% (17/20) of patients met three or more of the four therapeutic goals; individual therapeutic goal parameters were met by 90–95% of patients for spleen, liver and hemoglobin, and by 60% for platelets [12]. A subset of patients continued to receive eliglustat and will continue to do so potentially up to the regulatory approval date (anticipated in 2014). The therapeutic goals were delineated, based on the response profile observed in GD patients treated with imiglucerase [13]. It has been used as a benchmark for various therapeutic agents, including velaglucerase- $\alpha$  and miglustat [14,15]; in essence, indicating comparable short-term efficacy of these options for key features of disease. In terms of marrow infiltration, improvements were seen in a cohort of patients (n=18) treated up to 4 years; initially in 28% of these patients at the 12-month time point and in 56% by year 4 [16]. In 15 patients with data, lumbar spine bone mineral density increased from baseline to year 4 by a mean of 9.9% (95% CI: 14.2%) [16].

In the clinical trials, eliglustat was generally well tolerated. There was one case of spontaneous abortion in a female patient who got pregnant, although this was deemed unrelated to therapy [6,12]. As a precaution, contraception for both males and females was imposed for patients in the study who were of reproductive age. In subsequent trials, this proscription was rescinded for male subjects. Another patient experienced non-sustained ventricular tachycardia not associated with clinical symptoms [6,12]. As cardiac events was an area of

particular interest, given the observations in eliglustat-treated dogs and healthy volunteers, electrocardiography and Holter monitoring were part of safety evaluations for patients in the current clinical trials. As noted below, cardiac events appear isolated and in on-going trials there have been no emergent incidents or cases among study patients that raise major concerns. However, it would be prudent to remain vigilant, in the long term and also among GD patients with comorbidities or concurrent medications that may raise their risk. Patient selection for eliglustat therapy will be one of the considerations in a postregulatory environment, which will likely require certain commitments from the sponsor, such as an observational or surveillance program.

#### ■ Phase III clinical trials

There are two Phase III clinical trials, designed to evaluate the safety and efficacy of eliglustat in patients naive to therapy (ENGAGE) [101], or previously treated with ERT (ENCORE) [102]. Both trials were multicenter and enrolled only adult GD patients. The main entry criteria were splenomegaly, with either thrombocytopenia or anemia or both (Table 1).

ENGAGE was placebo-controlled, and patients on eliglustat were given 50 or 100 mg twice daily (b.i.d.) (depending on plasma levels). The trial, initiated in April 2009, enrolled 40 GD type 1 patients (mean age: 31.8 years); the primary observation period was for 9 months. At the recent 'Society of Inborn Errors of Metabolism' meeting held in Barcelona (Spain, September 2013), it was reported that after 9 months of treatment, patients on eliglustat demonstrated superior efficacy compared with placebo in the primary end point (i.e., change in spleen volume) with an absolute difference of 30% (-28 vs 2%, respectively;  $p < 0.0001$ ) [17]. All secondary end points (hemoglobin and platelet

levels; liver volume) were met and showed statistically significant improvements compared with the placebo. Platelets increased from baseline, with an absolute difference of 41% ( $p < 0.0001$ ); hemoglobin increased by 1.2 g/dl ( $p < 0.0006$ ); liver volume decreased by 7% ( $p < 0.0072$ ) [17]. A statistically significant improvement in total bone marrow burden (BMB) was also observed, and markers of bone disease were described as trending towards improvement [18]. BMB is an MRI-based semiquantitative assessment of the pattern of marrow infiltrative disease [19].

ENCORE was designed to confirm the efficacy and safety of eliglustat in patients ( $n = 160$ ) with GD type 1 who have reached therapeutic goals with ERT, by comparing outcomes with eliglustat in previously ERT-treated ( $\geq 3$  years) patients. This study was initiated in July 2009. The primary efficacy end point of stability was a composite end point of prespecified change criteria for spleen volume, hemoglobin level, platelet counts and liver volume. Patients had to remain stable in all four parameters 1 year after randomization. In total, 84% of eliglustat-treated patients, compared with 94% of imiglucerase-treated patients met the prespecified criteria; suggesting noninferiority [20]. Individual components of the composite end point showed the following: spleen volume (met by 94%), hemoglobin level (95%), platelet counts (93%) and liver volume (96%) [20]. The majority of the study patients had normal bone density scores for lumbar spine and total femur, which were maintained over the 12-month study period.

A third trial, EDGE, was opened to broaden the experience with use of eliglustat, and to some extent accommodate patients who opted to participate in a study of oral treatment during the period when access to imiglucerase was compromised by a contamination at Genzyme's manufacturing facility (Haverhill, Suffolk) [103]. EDGE, which was open-labeled, enrolled adult GD type 1 patients, naive to therapy or previously treated with ERT (imiglucerase and subsequently, velaglucerase in some cases after this formulation became available commercially). The primary objective of this study was to evaluate the efficacy and safety of once-daily versus b.i.d. dosing of eliglustat in patients with GD type 1 who have demonstrated clinical stability on b.i.d. dosing of eliglustat. Results of this study are pending.

## Discussion

Substrate reduction therapy for GD entails the inhibition of glucosylceramide synthase, which catalyzes the formation of glucosylceramide from ceramide and uridine diphosphate glucose. As glucosylceramide is the base cerebroside for more complex glycosphingolipids, a reversible synthase inhibitor might potentially be effective for

additional glycosphingolipid storage disorders, including FD,  $G_{M1}$ -gangliosidosis and Tay–Sachs disease. Interestingly, eliglustat given to obese mice led to reduced HbA1C and increased glucose tolerance, suggesting a potential role for use in a non-lysosomal disorder [21]. In this regard, insulin resistance has been described in GD [22], although the clinical significance of these findings is uncertain.

Overall, data from the Phase II and ongoing Phase III clinical trials (reported in abstract form and presented at meetings) indicate eliglustat not only stabilizes but reverses/improves clinical findings associated with GD type 1 in treatment-naïve adults patients and those previously on ERT [6,12,17,18,20]. Eliglustat-treated patients displayed an increase in red blood cell/hemoglobin level and platelet counts, and a reduction in liver and spleen volume. Increase in or stabilization of bone density and reduction of bone marrow infiltration (based on BMB score) were also noted [18]. The observed pattern of response appears comparable to that observed in patients on ERT [23,24]. Long-term follow up of eliglustat-treated GD patients should demonstrate whether these observations are durable.

In patients on ERT, a reduction in treatment dose and/or frequency of administration has been undertaken in patients who have shown initial improvement and/or appear to have stabilized, and with no active disease process [24,25]. However, interruption of therapy in a large number of patients for varying lengths of time, a situation enforced by drug (imiglucerase) shortage (which occurred prior to regulatory approval for two alternative formulations now available), indicated recrudescence or relapse; that is, the return of signs and symptoms of GD in some of the patients [26]. Eliglustat is orally administered; it is hoped it will turn out as safe as long-term ERT but perhaps made available at less expense. Its use as a bridging agent between periods of ERT treatment interruption may be a consideration, for those who travel for work or may be away for extended periods because of personal circumstances.

Preclinical trials with eliglustat revealed a dose–response relationship; an issue also currently being examined to a certain extent in the clinical trials looking not only at different doses (50–150 mg), but also alternative frequencies (once daily versus b.i.d.). Outcomes from these later studies and extended observations will inform prescribing patterns in the clinical care of GD patients. Depending on the outcome of the trials, revised monitoring studies and schedules (beyond the routine testing undertaken for GD patients on ERT) may be necessary until significant experience with the use of eliglustat has been obtained.

As an oral agent, eliglustat may be preferred by patients opposed to iv. ERT among those naive to therapy. Eventually, eliglustat may also be considered as maintenance therapy by those who started treatment with ERT and



have achieved their individualized therapeutic goals. As response to ERT is viewed by most as satisfactory, indeed robust, it is uncertain whether combination therapy (i.e., ERT and eliglustat) will be necessary for the majority of patients; although it may be an interesting consideration for those with significant bone symptomatology at baseline or persistent bone complications while on ERT, assuming that – as a small-molecular agent – eliglustat may have greater bone penetration/delivery. Interestingly, PDMP has been shown to inhibit osteoclast formation induced by m-CSF and RANK B ligand [27]. Thus, the improvements in bone density in GD patients receiving eliglustat may be mediated through other means, although this remains to be specifically demonstrated.

In addition, as an oral preparation eliglustat may be an option for patients with a more slowly progressive condition, should ascertainment of long-term risk–benefit ratio be favorable. Costs related to the use of eliglustat have not been established. Apart from high costs, access and distribution of enzyme therapy has also been an issue in certain areas; where patients live distantly from their treatment sites or in countries where the level of health-care is constrained in terms of staff/supplies. These considerations are minimized with the use of an oral drug, wherein upfront manufacturing costs, handling and administration is perhaps less complex when compared with the associated demands of ERT. Recently, Protalix (Carmiel, Israel), which has developed a plant-based recombinant enzyme formulation (taliglucerase- $\alpha$ ), has announced it is exploring an encapsulated enzyme preparation that may be administrable orally. Should oral enzyme administration be shown to be as safe and efficacious as iv. administered ERT, the convenience of an oral (chemical) drug may become moot.

Eliglustat clinical trials were conducted in adult patients, and it may be appropriate to await results of long-term safety studies prior to its use in children. As a chemical drug with uncertainty regarding its potential for adverse effects in the embryo/fetus, sexually active patients on eliglustat will need to take pregnancy precautions\contraception. Indeed, there was at least one incidence of pregnancy loss in a female study, although its causal link to the intake of eliglustat is not established. Moreover, it is probably not appropriate for women who are breastfeeding to be on eliglustat. All these concerns have not been an issue with ERT, which will be the primary mode of therapy for these patient subgroups.

The inhibition of glucosylceramide synthase by eliglustat is highly specific and there was no inhibition of sucrase or maltase observed at drug concentrations up to 10  $\mu$ M [4]. The latter reaction is the basis of osmotic diarrhea associated with the use of miglustat; gastrointestinal tolerability problems have been a factor limiting the wider use of this agent in clinical practice [28].

To address these concerns, a dietary regimen has been recommended when starting a patient on miglustat; a measure that has not been part of the regimen necessary for patients taking eliglustat [28,29]. Additional concerns with the use of miglustat include tremors and anecdotal reports of peripheral neuropathy in a small proportion of the patients on therapy [30]. Miglustat, but not eliglustat, inhibits GBA2 (nonlysosomal glucosylceramidase) [4]; recently mutations in GBA2 have been associated with an autosomal recessive form of cerebellar ataxia with spasticity [31]. Moreover, studies involving GBA1/GBA2 double knockout mice revealed GL1 levels in the spleen that were much higher than the sum of the single knockouts, implicating GBA2 in GD pathophysiology [32]. The implications of these findings are uncertain, but require further study so mechanisms of drug action or effect and their potential consequences, whether beneficial or otherwise, can be better understood. Interestingly, miglustat, which is approved in Europe but not in the USA for the treatment of Niemann-Pick type C (NPC), has been associated with a paradoxical increase in brain glucosylceramide levels in NPC mice [33]. Although the use of miglustat in NPC-treated patients, has been shown to provide some benefit, ultimate neurologic prognosis is not altered significantly [34]. Whether the increase in brain glucosylceramide levels seen in NPC mice occurs in humans, and has potential implications for GD-treated patients remains to be demonstrated. As eliglustat does not achieve sufficient concentration in the brain to effect a response, its use for other glycosphingolipidoses will be restricted. However, other P4 analogs with greater CNS retention are being examined in animal models, as a potential therapy for disease including FD [35].

Some adult patients with GD have been shown to have an increased risk for pulmonary hypertension (particularly those who have been splenectomized), multiple myeloma and Parkinson's disease [36–38]. At present, it is not certain that ERT has reduced the risks for these comorbidities; although with elimination of the need of splenectomy among symptomatic adult GD patients since ERT became available, the risk for both osteonecrosis and pulmonary hypertension appears to have diminished [36,39]. With respect to multiple myeloma and Parkinson's disease, the basis for increased incidence among GD patients is not fully understood. Moreover, with the relatively recent introduction of ERT (in the 1990s and thereafter) a significant proportion of the GD patients (in absolute terms only a small fraction of the total GD patients seen in large practices) who have developed these complications are individuals who were not treated as children. Should eliglustat be taken up by a great number of patients, and at an earlier disease stage, following a longer period of observation we may learn of its impact on these GD-associated complications, if any.

So far, there have been no reports of drug-related severe toxicity or serious adverse events associated with the use of eliglustat, and its development as a potential therapy for GD is progressing towards anticipated approval. As eliglustat tartrate is metabolized by *CYP2D6*, depending on the patients metabolic status doses and/or frequency of administration may need to be individualized to achieve optimal therapeutic levels in plasma. Preclinical studies indicated plasma eliglustat concentrations of 6–14 ng/ml (14–34 nM) would be within the therapeutic range. In clinical trials, a range in plasma concentrations of up to 100 ng/ml was set. A further consideration is potential for adverse reactions, which might be observed in patients concurrently prescribed known *CYP2D6* inhibitors. Potential for drug interactions and their implications are currently being examined in parallel trials in healthy volunteers, and this issue is also being examined closely in GD patients enrolled in the trials who have developed non-GD related medical problems for which concomitant medications were required. This will remain a practical concern with the use of eliglustat, until we gain considerable experience in a large number of patients, especially those with comorbidities and those requiring treatment for other medical conditions. As with ERT, registry/surveillance programs will likely be in place to accrue 'real-world' experience following regulatory approval of eliglustat. In the meantime, affected children, and women who are planning pregnancy and who require treatment for their GD will be precluded from taking eliglustat.

Costs related to the use of eliglustat are widely anticipated. Following the introduction of ERT for GD, cost of care was hotly debated. The recent introduction of alternative enzyme formulations (i.e., velaglucerase and taliglucerase, offered at a reduced cost in the USA when compared with imiglucerase) has been welcomed, and ultimately may influence the preferred prescription for patients requiring treatment should the efficacy–safety profile among the currently available formulations be deemed comparable.

As combination therapy (i.e., eliglustat and ERT) has not been evaluated in clinical trials, the merits of this approach remains to be demonstrated. One may argue that select populations, such as those with severe splenomegaly, thrombocytopenia and bleeding risks, and active bone disease may be appropriate targets in the short term. Over time, should the experience with the use of eliglustat remain positive, this drug might be preferred by an increasing number of patients who have been on ERT for an extended period and are stable. Meanwhile, there are ongoing preclinical evaluations of alternative analogs that lack P-glycoprotein (MDR1) recognition and have greater CNS retention and the ability to reduce GL1 in the brain, in the hope that the

benefits seen in GD type 1 patients can be extended to those with GD types II and III disease [35].

### Future perspective

Eliglustat is a small molecule that inhibits glucosylceramide synthase, thereby reducing the levels of glucosylceramide, a precursor to several downstream glycosphingolipids. Ongoing clinical trials involving the use of eliglustat in adult patients with GD type 1 indicate potential salutary effects and a relatively satisfactory safety profile. It is likely that eliglustat will be an additional therapeutic option, available to adult patients naive to any therapy and those previously treated with ERT. Putative advantages of eliglustat include its oral route of administration and being a chemical agent, absence of antibody formation and attendant side effects. On the other hand, there is extensive experience with the use of ERT and guidelines will have to be developed relating to the use of eliglustat, including a definition of most suitable patients groups and appropriate therapeutic goals. There will also need to be vigilance regarding emergent safety considerations; eliglustat is metabolized and therefore has potential for drug interaction. Optimal eliglustat dosing will also need to be identified, taking into consideration the differences in metabolic rate among patients, which may influence circulating plasma eliglustat levels. It is hoped that lessons drawn from the use of eliglustat will lead to generation of analogs that will find use in patients with neuronopathic forms of GD, and other potentially amenable glycosphingolipidosis that are currently not treatable or for which enzyme therapy does not appear to lead to full control/reversal of the disease process (e.g., FD). A major practical consideration relates to cost of care. With the increasing availability of enzyme therapy for several lysosomal storage disorders, there are advocates for cost-containment and also tying in the cost of treatment with outcome. A move towards pharmacologic agents, for which the production and distribution costs are believed to be less than for a biologic product, may ease the burden on third party payers.

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## Executive summary

- Eliglustat is a small-molecular agent that is showing a promising safety–efficacy profile in clinical trials that have enrolled adult patients with Gaucher disease (GD) type 1.
- GD is a lysosomal storage disorder caused by deficiency of the enzyme glucocerebrosidase. It is characterized predominantly by anemia, thrombocytopenia, hepatosplenomegaly and bone disease in those with the non-neuropathic form (i.e., type 1).
- Therapeutic options for GD include enzyme and/or substrate reduction therapies.
- Eliglustat is a small molecule that inhibits glucosylceramide synthase, leading to a reduction of glucosylceramide (the primary offending lipid that accumulates in tissues of patients with GD).
- Over time, it will become evident how many patients largely managed with enzyme replacement therapy will be receptive to the use of an oral agent.
- Ongoing clinical trials indicate eliglucostat can reverse the key manifestations of GD in adult patients, including those previously treated with enzyme replacement therapy.
- This event will be a paradigm shift in management and will likely be influenced by ongoing experience with the use of eliglucostat and emergent safety concerns.
- Eliglucostat appears to be relatively safe; but as a metabolized drug there is potential for drug interaction and there is also a need for ongoing monitoring of emergent safety concerns, given patients on eliglucostat will need chronic maintenance treatment.
- Optimal dose and frequency of administration and the cost of eliglucostat treatment have not been defined. Ultimately, it remains to be seen what proportion of patients considering or already on maintenance enzyme therapy will elect to go on eliglucostat therapy instead.

## References

- 1 Rosenbloom BE, Weinreb NJ. Gaucher disease: a comprehensive review. *Crit. Rev. Oncog.* 18(3), 163–75 (2013).
- 2 Deegan PB, Cox TM. Imiglucerase in the treatment of Gaucher disease: a history and perspective. *Drug Des. Devel. Ther.* 6, 81–106 (2012).
- 3 Venier RE, Igdoura SA. Miglustat as a therapeutic agent: prospects and caveats. *J. Med. Genet.* 49(9), 591–597 (2012).
- 4 Shayman JA. Eliglucostat tartrate: glucosylceramide synthase inhibitor treatment of type 1 Gaucher disease. *Drugs Future* 35(8), 613–620 (2010).
- 5 Cox T, Lachmann R, Hollak C *et al.* Novel oral treatment of Gaucher's disease with *N*-butyldeoxyinosine (OGT 918) to decrease substrate biosynthesis. *Lancet* 355(9214), 1481–1485 (2012).
- 6 Lukina E, Watman N, Arreguin EA *et al.* A Phase II study of Eliglucostat tartrate (Genz-112638), an oral substrate reduction therapy for Gaucher disease type 1. *Blood* 116(6), 893–899 (2010).
- 7 Abe A, Arend LJ, Lee L, Lingwood C, Brady RO, Shayman JA. Glycosphingolipid depletion in Fabry disease lymphoblasts with potent inhibitors of glucosylceramide synthase. *Kidney Int.* 57(2), 446–454 (2000).
- 8 Toyooka K. Fabry disease. *Curr. Opin. Neurol.* 24(5), 463–468 (2011).
- 9 McEachern KA, Fung J, Komarnitsky S *et al.* A specific and potent inhibitor of glucosylceramide synthase for substrate inhibition therapy of Gaucher disease. *Mol. Genet. Metab.* 91(3), 259–267 (2007).
- 10 Marshall J, McEachern KA, Chuang WL *et al.* Improved management of lysosomal glucosylceramide levels in a mouse model of type 1 Gaucher disease using enzyme and substrate reduction therapy. *J. Inher. Metab. Dis.* 33(3), 281–289 (2010).
- 11 Peterschmitt MJ, Burke A, Blankstein L *et al.* Safety, tolerability, and pharmacokinetics of eliglucostat tartrate (Genz-112638) after single doses, multiple doses, and food in healthy volunteers. *J. Clin. Pharmacol.* 51(5), 695–705 (2011).
- 12 Lukina E, Watman N, Arreguin EA *et al.* Improvement in hematological, visceral, and skeletal manifestations of Gaucher disease type 1 with oral eliglucostat tartrate (Genz-112638) treatment: 2-year results of a Phase II study. *Blood* 116(20), 4095–4098 (2010).
- 13 Pastores GM, Weinreb NJ, Aerts H *et al.* Therapeutic goals in the treatment of Gaucher disease. *Semin. Hematol.* 41(4 Suppl. 5), 4–14 (2004).
- 14 Elstein D, Cohn GM, Wang N, Djordjevic M, Brutaru C, Zimran A. Early achievement and maintenance of the therapeutic goals using velaglucerase alfa in type 1 Gaucher disease. *Blood Cells Mol. Dis.* 46(1), 119–123 (2011).
- 15 Pastores GM, Giraldo P, Chérin P, Mehta A. Goal-oriented therapy with miglustat in Gaucher disease. *Curr. Med. Res. Opin.* 25(1), 23–37 (2009).
- 16 Kamath RV, Lukina E, Watman N *et al.* Skeletal improvement in patients with Gaucher disease type 1: a Phase II trial of oral eliglucostat. *Skeletal. Radiol.* (2013) (In Press).
- 17 Turkia HB, Lukina E, Amato D *et al.* ENGAGE: a Phase III, randomized, double-blind, placebo-controlled, multicenter study to investigate the efficacy and safety of eliglucostat in patients with gaucher disease type 1 (gd1), 9 months result. *JIMD* 36(Suppl. 2), S268 (2013).
- 18 Dasouki M, Lukina E, Ben Dridi MF *et al.* Effects of oral eliglucostat on bone disease in Gaucher disease type 1: results from the randomized, placebo-controlled ENGAGE trial. *JIMD* 36(Suppl. 2), S268 (P-597) (2013).
- 19 Maas M, van Kuijk C, Stoker J *et al.* Quantification of bone involvement in Gaucher disease: MR imaging bone marrow burden score as an alternative to Dixon quantitative chemical shift MR imaging – initial experience. *Radiology* 229(2), 554–561 (2003).
- 20 Cox TM, Drelichman G, Cravo R *et al.* ENCORE: a multinational, randomized, controlled, open-label non-inferiority study comparing eliglucostat to imiglucerase in Gaucher disease type 1 patients on enzyme replacement therapy who have reached therapeutic goals. *JIMD* 36(Suppl. 2), S268 (2013).
- 21 Yew NS, Zhao H, Hong EG *et al.* Increased hepatic insulin action in diet-induced obese mice following inhibition of glucosylceramide synthase. *PLoS ONE* 6, e11239 (2010).



- 22 Aerts JM, Boot RG, van Eijk M *et al.* Glycosphingolipids and insulin resistance. *Adv. Exp. Med. Biol.* 721, 99–119 (2011).
- 23 Weinreb N, Taylor J, Cox T, Yee J, vom Dah S. A benchmark analysis of the achievement of therapeutic goals for type 1 Gaucher disease patients treated with imiglucerase. *Am. J. Hematol.* 83(12), 890–895 (2008).
- 24 Weinreb NJ, Goldblatt J, Villalobos J *et al.* Long-term clinical outcomes in type 1 Gaucher disease following 10 years of imiglucerase treatment. *J. Inherit. Metab. Dis.* 36(3), 543–553 (2013).
- 25 Kishnani PS, DiRocco M, Kaplan P, *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.* 96(4), 164–170 (2009).
- 26 Deroma L, Sechi A, Dardis A *et al.* Did the temporary shortage in supply of imiglucerase have clinical consequences? Retrospective observational study on 34 Italian Gaucher type I patients. *JIMD Rep.* 7, 117–122 (2013).
- 27 Iwamoto T, Fukumoto S, Kanaoka K *et al.* Lactosylceramide is essential for the osteoclastogenesis mediated by macrophage-colony-stimulating factor and receptor activator of nuclear factor- $\kappa$ B ligand. *J. Biol. Chem.* 276(49), 46031–46038 (2001).
- 28 Belmatoug N, Burlina A, Giraldo P *et al.* Gastrointestinal disturbances and their management in miglustat-treated patients. *J. Inherit. Metab. Dis.* 34(5), 991–1001 (2011).
- 29 Champion H, Ramaswami U, Imrie J *et al.* Dietary modifications in patients receiving miglustat. *J. Inherit. Metab. Dis.* 33(Suppl. 3), S379–S383 (2010).
- 30 Hollak CE, Hughes D, van Schaik IN, Schwierin B, Bembi B. Miglustat (Zavesca) in type 1 Gaucher disease: 5-year results of a post-authorisation safety surveillance programme. *Pharmacoevidenciol. Drug Saf.* 18(9), 770–777 (2009).
- 31 Hammer MB, Eleuch-Fayache G, Schottlaender LV *et al.* Mutations in GBA2 cause autosomal-recessive cerebellar ataxia with spasticity. *Am. J. Hum. Genet.* 92(2), 245–251 (2013).
- 32 Yildiz Y, Hoffmann P, vom Dahl S *et al.* Functional and genetic characterization of the non-lysosomal glucosylceramidase 2 as a modifier for Gaucher disease. *Orphanet. J. Rare Dis.* 8(1), 151 (2013).
- 33 Nietupski JB, Pacheco JJ, Chuang WL *et al.* Iminosugar-based inhibitors of glucosylceramide synthase prolong survival but paradoxically increase brain glucosylceramide levels in Niemann-Pick C mice. *Mol. Genet. Metab.* 105(4), 621–628 (2012).
- 34 Wraith JE, Vecchio D, Jacklin E *et al.* Miglustat in adult and juvenile patients with Niemann-Pick disease type C: long-term data from a clinical trial. *Mol. Genet. Metab.* 99(4), 351–357 (2010).
- 35 Larsen SD, Wilson MW, Abe A *et al.* Property-based design of a glucosylceramide synthase inhibitor that reduces glucosylceramide in the brain. *J. Lipid Res.* 53(2), 282–291 (2012).
- 36 Lo SM, Liu J, Chen F *et al.* Pulmonary vascular disease in Gaucher disease: clinical spectrum, determinants of phenotype and long-term outcomes of therapy. *J. Inherit. Metab. Dis.* 34(3), 643–650 (2011).
- 37 Ayto R, Hughes DA. Gaucher disease and myeloma. *Crit. Rev. Oncog.* 18(3), 247–268 (2013).
- 38 Bultron G, Kacena K, Pearson D *et al.* The risk of Parkinson's disease in type 1 Gaucher disease. *J. Inherit. Metab. Dis.* 33(2), 167–173 (2010).
- 39 Deegan PB, Pavlova E, Tindall J *et al.* Osseous manifestations of adult Gaucher disease in the era of enzyme replacement therapy. *Medicine (Baltimore)* 90(1), 52–60 (2011).

#### ■ Patents

- 101 Genzyme, a Sanofi Company: NCT00891202 (2009).
- 102 Genzyme, a Sanofi Company: NCT00943111 (2009).
- 103 Genzyme, a Sanofi Company: NCT01074944 (2010).

#### ■ Website

- 201 Clinical Trials database. <http://clinicaltrials.gov>