Drugs of the Future 2010, 35(8): 613-620

CCC: 0377-8282/2010
DOI: 10.1358/dof.2010.35.8.1505566

MONOGRAPH

ELIGLUSTAT TARTRATE

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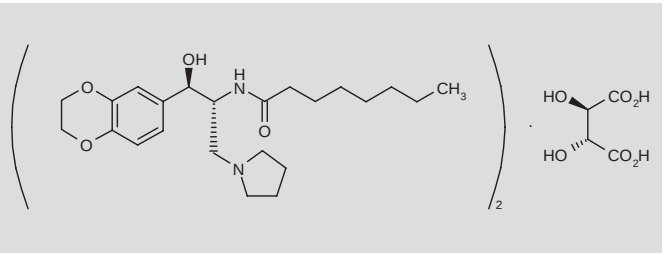
Glucosylceramide Synthase Inhibitor
Treatment of Type 1 Gaucher Disease

Genz-112638

N-[2-(2,3-Dihydro-1,4-benzodioxin-6-yl)-2(*R*)-hydroxy-1(*R*)-(pyrrolidin-1-ylmethyl)ethyl]octanamide L-tartrate

InChI: 1S/C23H36N2O4.C4H6O6/c1-2-3-4-5-6-9-22(26)24-19(17-25-12-7-8-13-25)23(27)18-10-11-20-21(16-18)29-15-14-28-20;5-1(3(7)8)2(6)4(9)10/h10-11,16,19,23,27H,2-9,12-15,17H2,1H3,(H,24,26);1-2,5-6H,(H,7,8)(H,9,10)/t19-,23-;1-,2-/m11/s1



$C_{27}H_{42}N_2O_{10}$
Mol wt: 554.6298
CAS: 928659-70-5
EN: 367485

SUMMARY

Eliglustat tartrate (Genz-112638) is a novel, orally administered agent currently in development for the treatment of lysosomal storage disorders, including type 1 Gaucher disease and Fabry disease. This glucosylceramide analogue acts as an inhibitor of glucosylceramide synthase, a Golgi complex enzyme that catalyzes the formation of glucosylceramide from ceramide and UDP-glucose and is the first step in the formation of glucocerebroside-based glycosphingolipids. Preclinical pharmacological studies demonstrate that the agent has a high therapeutic index, excellent oral bioavailability and limited toxicity. Phase I studies in healthy volunteers revealed limited toxicity with an excellent pharmacodynamic response, as measured by decreased plasma glucosylceramide concentrations. Phase II studies in patients with type 1 Gaucher disease have demonstrated promising clinical responses, as measured by decreases in spleen size, improvement in hemoglobin concentrations and increased platelet counts. Two randomized phase III trials testing the efficacy and safety of eliglustat tartrate are currently in progress.

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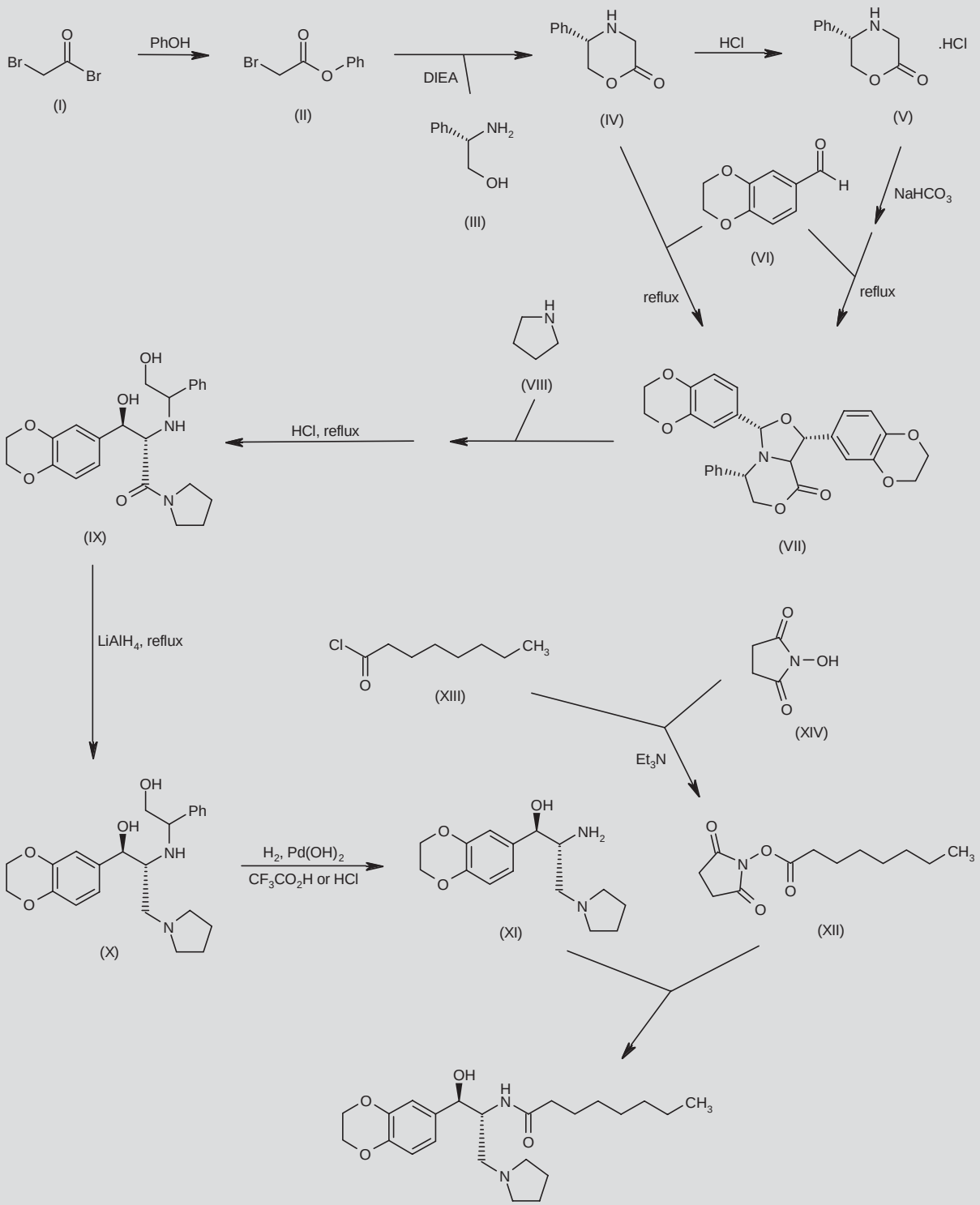
SYNTHESIS*

Reaction of bromoacetyl bromide (I) with phenol at 80 °C gives the phenyl ester (II) (1), which by cyclization with (*S*)-(+)-phenylglycinol (III), previously treated with DIEA, in acetonitrile provides 5(*S*)-phenylmorpholin-2-one (IV) (1, 2). Treatment of compound (IV) with HCl affords the corresponding HCl salt (V), which is reacted with $NaHCO_3$ followed by coupling with benzodioxane-6-carboxaldehyde (VI) in refluxing EtOAc/toluene to yield the oxazine adduct (VII). Oxazine derivative (VII) can also be obtained by direct coupling of 5(*S*)-phenylmorpholin-2-one (IV) with aldehyde (VI) in refluxing toluene. Opening of adduct (VII) with pyrrolidine (VIII) in CH_2Cl_2, $CHCl_3$ or refluxing THF followed by addition of HCl in refluxing MeOH leads to 3-(1,4-benzodioxan-6-yl)-3(*R*)-hydroxy-2(*R*)-(2-hydroxy-1-phenylethylamino)-1-(pyrrolidin-1-yl)propanone (IX), which is reduced with $LiAlH_4$ in refluxing THF to give diol (X). Cleavage of diol (X) by means of H_2 and $Pd(OH)_2$ in the presence of either CF_3COOH or HCl in MeOH or $EtOH/H_2O$ provides amine (XI), which is finally coupled with octanoic acid *N*-hydroxysuccinimide ester (XII) in CH_2Cl_2 (2). Ester (XII) is prepared by condensation of octanoyl chloride (XIII) with *N*-hydroxysuccinimide (XIV) by means of Et_3N in CH_2Cl_2 (2). Scheme 1.

BACKGROUND

Gaucher disease is an autosomal recessive inherited deficiency of β-glucocerebrosidase (3). A deficiency or loss of activity of this glucosidase results in the accumulation of glucosylceramide within the lysosomes of cells. Gaucher disease is the most common lysosomal storage disease, occurring in approximately 1 in 75,000 live births (4, 5). While most common in the Ashkenazi Jewish population, the disorder is present worldwide, with affected individuals represented among every geographic and ethnic group. There are three clinical variants of Gaucher disease. All three variants are associated with visceral organ involvement, most notably spleen and liver, and bone (3, 6). The type 2 and 3 variants are less common than type 1 disease, and are characterized by central nervous system (CNS) involvement (7, 8). Type 1 Gaucher disease is by far the most common clinical variant, seen in approximately 90% of cases. Patients with type 1 disease typically retain some basal, albeit low, activity of β-glucocerebrosidase. Histologically, glucosylceramide accumulation is most commonly seen within macrophages. These cells acquire a foam cell phenotype and are termed Gaucher cells.

Scheme 1. Synthesis of Eliglustat



The clinical presentation and manifestations of type 1 Gaucher disease are variable in terms of age of onset and severity. Patients may present within the first 2 years of age or may remain asymptomatic until late in life. Hepatomegaly and splenomegaly are observed in all cases (6). The median growth of the spleen is 15 times normal size and may be as high as 75 times normal size (3). The livers typically grow to two or three times normal size. Bone marrow involvement results in anemia and thrombocytopenia. Bone disease is particularly debilitating and manifests as bone pain, osteonecrosis, lytic lesions and osteopenia (9, 10). These often result in pathological fractures and vertebral compression. Interstitial lung disease is a less common clinical manifestation of Gaucher disease.

The most common laboratory abnormalities observed in type 1 Gaucher disease are anemia and thrombocytopenia. Less commonly, there may be elevation of liver transaminases and alkaline phosphatase. Several biomarkers are elevated in Gaucher disease, including chitotriosidase, C-C motif chemokine 18 (CCL18), angiotensin-converting enzyme (ACE) and TRAP. The most common biomarker followed in clinical research studies is chitotriosidase (11). The activity of this enzyme, likely from macrophages, is > 100 times higher in affected Gaucher patients and decreases with enzyme replacement therapy. Thus, chitotriosidase is a robust marker of disease activity and response to therapy.

The current first-line treatment for the non-neuronopathic complications of Gaucher disease is enzyme replacement therapy (12, 13). The operative principle underlying this therapy is the use of mannose-terminated recombinant glucocerebrosidase, or imiglucerase, based on the observation that macrophages bind enzyme through mannose receptors and traffic it to lysosomes. Clinical improvement, as manifested by reduction in spleen and liver size, increased hemoglobin and platelet counts, and reduction in fatigue, is typically observed within 6 months of the initiation of therapy. The skeletal manifestations are slower to respond, with stabilization in bone mineral density (BMD) and reduction in pain crises at 2-3 years into therapy. Adverse effects of enzyme replacement therapy include the development of immune hypersensitivity and pulmonary hypertension. Over the long term, patients may develop antibodies to the enzyme, limiting its effectiveness. Major limitations of enzyme replacement therapy include the need for i.v. administration and its cost. The cost of treatment for a 70-kg patient receiving 60 U/kg every 2 weeks may be as high as USD 400,000 per year.

More recently, *N*-butyldeoxynojirimycin (miglustat) has been approved for the treatment of type I Gaucher disease in patients for whom enzyme replacement is unsuitable. Miglustat was originally developed as an α-glucosidase inhibitor for the potential treatment of HIV. The compound was later discovered to inhibit glucosylceramide synthase, albeit in the mid-micromolar range. The therapeutic use of miglustat has been limited by a high occurrence of untoward side effects that include diarrhea, weight loss, abdominal distension and tremor. Major clinical outcomes, including a reduction in spleen size and increase in hemoglobin and platelet counts, are less pronounced and occur over longer treatment periods compared to imiglucerase. The reader is referred to a recent review of the clinical experience with miglustat (14).

The therapeutic strategy of "substrate reduction therapy" as applied to lysosomal storage disorders was first proposed by Radin in 1972 (15, 16). This concept stated that inhibition of sphingolipid synthesis would be clinically effective as an alternative to enzyme replacement, particularly if the defective hydrolase retained some basal activity. Specifically, in the case of type 1 Gaucher disease, the accumulation of glucosylceramide results from a disequilibrium between normal glucosylceramide synthase activity and impaired β-glucocerebrosidase activity (Fig. 1). Because glucosylceramide is the base cerebroside for more complex glycosphingolipids, a reversible synthase inhibitor might potentially be effective for additional glycosphingolipid storage disorders, including Fabry disease, GM1 gangliosidosis and Tay-Sachs disease, where globotriaosylceramide, ganglioside GM1 and ganglioside GM2 accumulate, respectively.

A search was undertaken for such an inhibitor. The first glucosylceramide synthase inhibitor identified was empirically identified based on the structural similarity between chloramphenicol and glucosylceramide (17). This compound, DL-2-decanoylamino-3-morpholino-propiophenone, was an irreversible inhibitor with a relatively poor IC_{50} of 300 μM. However, with reduction of the ketone, a more potent and reversible inhibitor was identified. D-*threo*-1-Phenyl-2-decanoylamino-3-morpholinepropanol (PDMP) inhibited glucosylceramide formation with an IC_{50} of 20 μM. PDMP contains three functional groups: a fatty acid in amide linkage, an aromatic group and a cyclic amine (18). Following the delineation of a pharmacophore required for inhibition of glucosylceramide synthase, substitutions at each group were made. Empiric changes at the fatty acyl group demonstrated a modest increase in inhibitory activity with increasing fatty acyl chain lengths (19). Applying a similar strategy, the replacement of the morpholino with a pyrrolidino group further

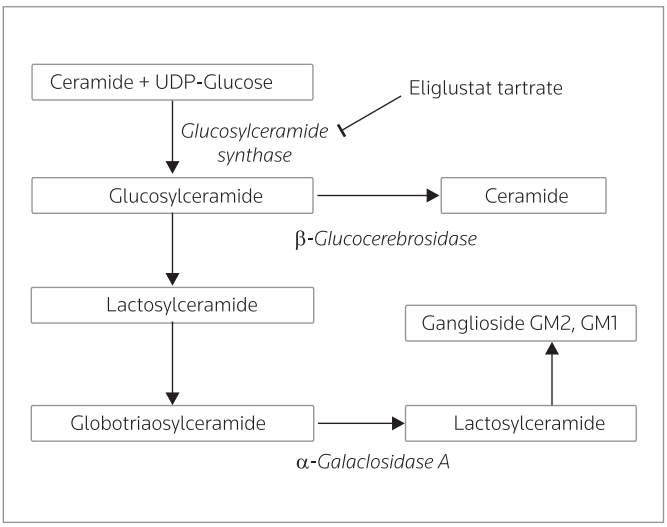


Figure 1. Pathways for simple glycosphingolipid synthesis and degradation. In Gaucher disease glucosylceramide accumulates due to a decrease or loss of activity of β-glucocerebrosidase; in Fabry disease globotriaosylceramide accumulates due to a loss or decreased activity of β-galactosidase A. Conventional enzyme replacement therapy directly restores deficient enzyme through i.v. infusion of the respective glycosidase. Eliglustat tartrate blocks the first step in glycosphingolipid synthesis, glucosylceramide synthase. In the presence of eliglustat tartrate, all glucosylceramide-based glycosphingolipids are inhibited, including globotriaosylceramide.

increased the activity (20). Ultimately, the use of Hansch analysis as a more rational design strategy for alternative aromatic groups led to the identification of an ethylenedioxyphenyl-substituted compound with a markedly lower IC_{50} of 11 nM (21). The resulting compound, D-*threo*-1-(3,4-ethylenedioxyphenyl)-2-(palmitoylamino)-3-(1-pyrrolidinyl)propanol (EtDO-P4), was subsequently employed for in vivo proof-of-concept studies. Importantly, in cells treated with the ethylenedioxyphenyl homologue depletion of glucosylceramide was dissociated from accumulation of ceramide. This observation supported the view that glycolipid depletion could occur at a concentration range of glucosylceramide synthase inhibition over which ceramide toxicity would not be rate-limiting.

Proof-of-principle studies were initially performed in models of Fabry disease, a glycosphingolipidosis in which globotriaosylceramide accumulates in the vasculature and kidneys secondary to a loss of β-galactosidase A activity. The Fabry models were chosen because at the time the only suitable mouse model for Gaucher disease was associated with early neonatal death. EtDO-P4 rapidly reduced the glucosylceramide and globotriaosylceramide content of transformed lymphoblasts from Fabry disease patients (22). Additionally, EtDO-P4 treatment of β-galactosidase A-null mice resulted in the depletion of globotriaosylceramide in the kidney, liver and heart, without apparent toxicity (23). Based on these studies, the PDMP-based glucosylceramide inhibitors were licensed to Genzyme by the University of Michigan for further clinical development.

cLogP is a measure of the differential solubility of a compound based on its partitioning between octanol and water. EtDO-P4 has a high cLogP (9.1), consistent with a very high degree of hydrophobicity. Thus, despite its excellent activity, early studies evaluated the effect of fatty acyl chain substitutions of EtDO-P4 on activity, bioavailability and half-life. The C8-substituted homologue eliglustat tartrate, or Genz-112638, was found to have the most suitable pharmacokinetic profile, with limited loss of inhibitory activity (cLogP of 4.8).

PRECLINICAL PHARMACOLOGY

Eliglustat tartrate was designed and developed to inhibit glucosylceramide synthase, the enzyme that catalyzes the formation of glucosylceramide from UDP-glucose and ceramide. The IC_{50} of the drug against the glucosylceramide synthase from MDCK cell homogenates was 115 nM and the IC_{50} in intact MDCK cells was 20 nM. The difference in activity relates to its high degree of lipophilicity and ability to concentrate within cells. The inhibition of glucosylceramide synthase by eliglustat tartrate is highly specific. Eliglustat tartrate displays limited or no activity against a variety of glycosidases (24). The enzyme specificities (IC_{50}) for these enzymes include β-glucosidase I and II (> 2500 μM), lysosomal glucocerebrosidase (> 2500 μM), non-lysosomal glycosylceramidase (1600 μM) and glycogen debranching enzyme (> 2500 μM). Additionally, no inhibition of sucrase or maltase was observed at drug concentrations up to 10 μM. Miglustat, an imino-based sugar inhibitor of glucosylceramide synthase, inhibits β-glucosidase I and II and digestive disaccharidases at concentrations close to its IC_{50}. Miglustat also binds to lysosomal glucocerebrosidase (25) and has been suggested to act as a chemical chaperone (26).

Preclinical studies in normal mice, rats and dogs with i.v. and oral administration demonstrated significant dose-related decreases in spleen, kidney and liver glucosylceramide content, consistent with prior observations with the palmitoyl homologue. The *gba* knockout mouse has not proven useful for inhibitor studies because these mice suffer from a skin permeability defect and die shortly post partum. Therefore, the $gba^{D409V/null}$ mouse, a knockin model that retains low basal activity of β-glucocerebrosidase, was employed to assess the efficacy of eliglustat in a Gaucher model (27). Young mice (10 weeks of age) and older mice (7 months of age) were dosed with 75 or 150 mg/kg/day p.o. of eliglustat for up to 10 weeks (26). No weight loss was observed in the treated mice compared to the vehicle-treated controls. Dose-dependent decreases in tissue glucosylceramide content were observed in the young mice, with a significant decline in the number of hepatic Gaucher (foam) cells. In the older mice, the age-dependent accumulation of glucosylceramide was arrested in the kidney, spleen and liver, and a decrease in Gaucher cell number was similarly observed.

PHARMACOKINETICS AND METABOLISM

Following a dose of 5 mg/kg i.v., the elimination half-life in mice, rats and dogs was 16, 24 and 68 min, respectively, with a clearance of 6.3, 8.9 and 4.4 L/h/kg, respectively. The volume of distribution was approximately four times the normal body water. The oral bioavailability in rats and dogs was 39% and 44%, respectively.

Absorption, distribution, metabolism and excretion studies with radiolabeled drug confirmed the oral bioavailability and demonstrated that the majority of the drug is eliminated in the feces. High concentrations of drug were observed in the kidney, liver and adrenal gland. Little radioactivity was observed in the brain, and most was associated with the pituitary gland. Microsomal enzyme assays demonstrated that eliglustat metabolism is primarily catalyzed by cytochrome P450 CYP2D6. Eliglustat tartrate is a P-glycoprotein substrate, possibly accounting for its poor distribution into the brain.

SAFETY

Traditional safety studies evaluating the effects of eliglustat tartrate on renal, CNS, gastrointestinal and respiratory function were conducted. In general, the drug was well tolerated. Specifically, no adverse effects were observed in rats on the behavioral or physiological neurological responses at single oral doses of up to 400 mg/kg. Below 400 mg/kg no changes in respiratory rate or tidal volume were noted. At 400 mg/kg a depression in respiratory rate was observed. Similarly, below 400 mg/kg no change in renal function was seen. At 400 mg/kg an increase in urinary pH and decrease in potassium and chloride excretion were observed, without changes in urinary volume or sodium excretion. At 100 and 400 mg/kg p.o. decreases in gastrointestinal transit time and gastric emptying were observed.

Eliglustat tartrate had no acute effects on heart rate or blood pressure in dogs at doses up to 80 mg/kg. At 80 mg/kg there was a tendency for increased heart rate and a decrease in the R-R interval. No effect on Q-T interval was observed at doses up to 80 mg/kg. However, a dose-dependent increase in QRS duration and P-R interval was observed between 10 and 80 mg/kg. These changes are consistent with a potential effect on sodium channels.

Acute and repeat-dose toxicity testing was performed in rats and dogs. In rats the drug was well tolerated, without any observable untoward effects at 5 mg/kg/day. The no observable adverse effect level in rats was determined to be 50 mg/kg/day and in dogs 2.5 mg/kg b.i.d. Genotoxicity was evaluated in vitro. Both the Ames bacterial mutagenicity test and clastogenic assay for chromosome damage were negative.

Reproductive toxicity was assessed in rats and rabbits. The no observable adverse effect level for systemic toxicity and fertility in rats was determined to be 100 mg/kg/day. The no observable effect level for embryofetal development in both rats and rabbits was determined to be 100 mg/kg/day.

CLINICAL STUDIES

Allometric scaling was employed to determine an equivalent ED_{50} in humans. Based on a comparison of the ED_{50} for measured hepatic glucosylceramide depletion in mice, rats and dogs, an equivalent dose of 0.6 mg/kg b.i.d. was extrapolated.

Three phase I clinical studies were subsequently conducted. To date, these have been reported as abstracts and oral presentations (28). However, a paper detailing these findings is in press (29). The phase Ia study was a single-dose, dose-escalating study designed to evaluate the safety, tolerability and pharmacokinetic profile in healthy male volunteers. Based on predictions of where dose-limiting toxicity (DLT) would be observed, the original protocol included five cohorts receiving drug at doses of 0.01, 0.03, 0.1, 0.3 and 1.0 mg/kg. Because no DLT was observed, eight additional cohorts were dosed at levels up to 30 mg/kg. The C_{max} of eliglustat tartrate measured as the free base was attained within 1-2 h after oral administration. A dose-dependent increase in plasma concentrations was observed for single doses between 0.3 and 30 mg/kg. The observed mean values for C_{max} and AUC also increased in a dose-dependent manner. A dose of 1 mg/kg resulted in a C_{max} of 10 ng/mL, a concentration predicted to inhibit glucosylceramide synthase based on allometric scaling. Adverse events were reported in 76 of 99 subjects (76.8%). These included 9 of 25 individuals in the placebo group and 67 of 74 individuals in the treatment group. Sixty-one subjects were identified as having drug-related adverse effects defined as possibly, probably or definitely related to the drug. The majority of these were CTC grade 1. The most common complaints included dysgeusia, throat irritation and dizziness. Only one subject receiving 30 mg/kg drug reported a single CTC grade 3 adverse event (dizziness). A dose of 30 mg/kg was thus identified as being associated with DLT. 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. The cardiac changes were not observed in subjects receiving doses of 5 mg/kg or less.

A phase Ib feeding study was conducted to assess the safety, bioavailability and pharmacokinetics of eliglustat tartrate under fed and fasted conditions. A single 300-mg dose of drug was administered to 24 male subjects under fed or fasted conditions. Each subject was re-evaluated in a crossover design following a 6-day washout period. Under fed conditions, a lower C_{max} (mean of 79.1 ng/mL) was observed compared to fasted conditions (mean of 88.3 ng/mL). The median time to maximum concentration (t_{max}) was longer in the fed state (3 h) compared to the fasted state (2 h). AUC analyses demonstrated equivalence between the fed and fasted conditions, suggesting that the food effect was due to a decrease in the rate but not the degree of absorption.

A multiple-dose phase Ib study was also conducted to ascertain the safety, tolerability and pharmacokinetic profiles in separate cohorts of healthy female and male subjects receiving 50, 200 or 350 mg b.i.d. of eliglustate tartrate over 12 days. The subjects received single doses of drug on days 1, 2 and 12 and twice-daily dosing on days 3 through 11. Steady-state plasma concentrations of eliglustat free base were attained by 60 h after the start of b.i.d. dosing and remained constant through the end of day 12. However, the pharmacokinetic profile was nonlinear and drug accumulation was greater than predicted following the measurement of plasma levels after the first dose. Interestingly, the plasma concentrations in the female subjects were consistently higher than in the male subjects. Subjects were genotyped for variants in the *CYP2D6* gene. A correlation was observed between *CYP2D6* genotype (classified as poor to ultra-rapid metabolizers) and drug exposure. 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. This probably reflected a smaller dose range and significantly lower C_{max} than observed in the dose-ranging phase Ia study. Ninety-two percent of subjects treated with drug and 75% of subjects treated with placebo reported at least one adverse event. The vast majority of these were grade 1 and gastrointestinal in origin. There were no subjects with serious (grade 3) adverse events.

The results from the initial 52 weeks of a phase II study in patients with type 1 Gaucher disease treated with eliglustat tartrate were recently reported (30). The primary goals of this study were to evaluate the efficacy, safety and pharmacokinetics in type 1 Gaucher disease patients receiving either 50 or 100 mg of eliglustat tartrate for a period of 52 weeks. The trial design was open-label and single-arm. Pharmacokinetic analysis was performed on day 1 following a single dose of 50 mg. The analysis was repeated on day 10 and subjects with trough concentrations of < 5 ng/mL had dose increased from 50 to 100 mg b.i.d. Eligibility requirements for entry into the study included age 18-65 years, confirmation of β-glucocerebrosidase deficiency, spleen size > 10 times a multiple of normal, and either thrombocytopenia (platelet count between 45,000 and 100,000/mm^3) or anemia (hemoglobin levels between 8.0 and 10.0 g/dL for females or 8.0 and 11.0 g/dL for males). Subjects were excluded if they had prior splenectomy, were treated with miglustat or imiglucerase during the prior 12 months, received bisphosphonates within the prior 3 months, had documented anemia from other causes, suffered from new bone crises or skeletal pathology in the prior 12 months, had documented varices, neurological or pulmonary disease, structural or functional cardiac disease, pregnancy or lactation. Fifty patients were screened and 26 were enrolled. Three primary efficacy endpoints were evaluated. These included a reduction in spleen size of at least 15% as measured by MRI or CT scan, an increase in hemoglobin of 0.5 g/dL or greater and a 15% increase in platelet count. Collectively, these were defined as a composite endpoint. Secondary endpoints were also measured and included liver volume, plasma biomarkers (chitotriosidase, CCL18, ACE and TRAP), plasma glucosylceramide and ganglioside GM3 levels, and skeletal changes. The skeletal changes were monitored by following mobility, the occurrence of bone crises, dual energy x-ray

absorptiometry and MRI of femurs. The average age of the subjects was 34 years, with a mean age at diagnosis of 24 years. Among the study subjects, acidic β-glucocerebrosidase activity was < 10% of normal on average. Sixty-two percent of the patients were female. Twenty-two of 26 subjects completed 52 weeks of treatment. Two subjects were withdrawn on day 1 due to nonsustained ventricular tachycardia believed to be unrelated to the drug. Two additional subjects withdrew at weeks 17 and 26 due to pregnancy. The composite primary efficacy endpoint was achieved in most participants. By intention-to-treat analysis 20 of 26 subjects (77%) achieved the endpoint; among completer subjects, 91% achieved the endpoint. Four of the 6 intention-to-treat failures were early withdrawals from the study. The other two failures showed declines in platelet counts, although the endpoint was met for reduction in spleen volumes. When statistically grouped together, highly significant increases in hemoglobin (1.62 mg/dL; $P < 0.001$) and platelet counts (40.3%; $P < 0.001$) were observed. Organ volumes declined significantly as well, with a 38.5% reduction in spleen size ($P < 0.001$) and a 17.0% reduction in liver size ($P < 0.001$). Significant improvements in bone densities were also observed, as measured by BMD or dark marrow involvement. Plasma biomarker levels, which were significantly elevated at baseline, declined by 35-50% with treatment. Plasma glucosylceramide and ganglioside GM3 levels declined to the normal range. Pharmacokinetic measurements failed to demonstrate gender-specific differences. The mean t_{max} and $t_{½}$ were 2.3 and 6.8 h, respectively. The C_{mean} was 12.9 ng/mL. This was within the predicted therapeutic range of 6-14 ng/mL. During the 52 weeks of treatment, 75 adverse events were reported, but only 7 events in 6 patients were considered to be treatment-related. These included abdominal pain, diarrhea, palpitations and headache. Five serious adverse events were reported involving three patients. Four events involved the two pregnant patients and were deemed unrelated to treatment. These included radiation exposure and a spontaneous abortion. Two patients were withdrawn from the study because of asymptomatic nonsustained ventricular tachycardia diagnosed by Holter monitoring. Subsequent evaluation determined that these events were unrelated to treatment. This was based on their occurrence on the first day of treatment at a time when drug levels were not detectable in the plasma. Both subjects had preexisting mild cardiac valvular abnormalities. No significant ECG abnormalities as measured by changes in P-R intervals, QRS intervals or $Q\text{-}T_{cF}$ were observed in any of the study subjects.

Twenty of the 22 completers elected to continue in the phase II extension trial. Data on the year two extension have been reported in abstract form (31). Continued improvement across all outcomes was observed in this cohort. Specifically, spleen size continued to decrease by a mean of 52% and liver volume by a mean of 26%. Hemoglobin levels were increased by a mean of 2.1 g/dL and platelet counts by a mean of 81% over baseline by 24 months. Nineteen subjects have elected to continue into a third year of the study.

The phase II study was not designed to directly compare the efficacy of eliglustat tartrate with either imiglucerase or miglustat. However, based on comparisons to the historical response of type 1 Gaucher patients to enzyme replacement, the clinical response to eliglustat tartrate, as measured by reductions in spleen size and improvements in hemoglobin and platelet counts, is comparable to imiglucerase (32). By contrast, the clinical responses clearly exceed those reported for miglustat. Importantly, the untoward effects reported for miglustat, most notably weight loss and tremor, were not observed with eliglustat tartrate. Thus, the gastrointestinal and neuropathic complications of miglustat are likely the result of actions unrelated to glucosylceramide synthase inhibition.

Based on these results, two phase III trials of eliglustat tartrate have been initiated. The first trial (the ENGAGE study) is a randomized, double-blind, placebo-controlled, multicenter study designed to confirm the efficacy and safety of eliglustat tartrate (50 or 100 mg b.i.d.) in patients with type 1 Gaucher disease. The primary outcome measure is a change in the spleen volume from baseline to 39 weeks of treatment compared to placebo. Secondary outcomes, also assessed at 39 weeks, include a change in hemoglobin level from baseline, percent change in liver volume and percent change in platelet counts. The anticipated total enrollment is 36 patients. Eligible patients are 16 years or older. The inclusion criteria include a confirmed diagnosis of type 1 Gaucher disease, a negative pregnancy test and use of contraceptives in female patients of childbearing potential. The exclusion criteria include a partial or total splenectomy, prior treatment with miglustat or pharmacological chaperones within 6 months, or enzyme replacement therapy within the prior 9 months, a diagnosis or suspected diagnosis of type 2 or 3 Gaucher disease, the presence of a coexisting significant other clinical disease, pregnancy or lactation, HIV, hepatitis B or hepatitis C positivity, or use of another investigational product within 30 days. The estimated completion date for this study is December 2011.

The second trial (the ENCORE study) is a randomized, multicenter, open-label comparator study designed to evaluate the efficacy and safety of eliglustat tartrate (50, 100 or 150 mg b.i.d.) in type 1 Gaucher patients who have been stabilized with imiglucerase. The primary outcome to be evaluated is the percent of patients who remain clinically stable for 52 weeks on eliglustat tartrate compared to imiglucerase. Outcome measures will include absolute changes in BMD, absolute changes in hemoglobin levels, percent change in platelet counts, percent change in spleen volume and percent change in liver volume. The anticipated enrollment is 186 patients. The inclusion criteria are identical to the ENGAGE trial, with the following differences. Patients are to be no older than 65 years of age. The patient is to have received imiglucerase for at least 3 years at a prescribed dose of 20 U/kg or more to 60 U/kg or less every 2 weeks during the last year of treatment. The patient is to have clinically stable Gaucher disease prior to randomization. The exclusion criteria are the same as for the ENGAGE study. The anticipated primary completion date is also December 2011.

DRUG INTERACTIONS

Presently, no formal studies have been conducted to assess interactions between eliglustat tartrate and other drugs. Because eliglustat tartrate is metabolized by CYP2D6, potential toxicity might be observed in patients concurrently treated with known CYP2D6 inhibitors (33, 34). Commonly used CYP2D6 inhibitors include, but are not limited to, albuterol, amiodarone, bupropion, chlorpheniramine, cimetidine, diphenhydramine, fluoxetine, haloperidol, hydroxyzine, metoclopramide, paroxetine, sertraline and thioridazine. Known inducers of CYP2D6 include phenobarbital, rifampin and dexamethasone.

CONCLUSIONS

Eliglustat tartrate is an orally active specific inhibitor of glucosylceramide synthase. The drug has good oral bioavailability, a high therapeutic index and limited toxicity. Pending the results of currently active phase III trials, eliglustat tartrate may emerge as a preferred alternative to enzyme replacement therapy. The advantages of eliglustat tartrate would include its oral as opposed to i.v. administration and lower cost. Alternatively, because eliglustat tartrate lowers cellular glucosylceramide content by a mechanism that is distinct from enzyme replacement, the potential use of both eliglustat and β-glucocerebrosidase as synergistic therapies will undoubtedly be considered. While no clinical data have yet been generated, studies in the *gba*$^{D409V/null}$ mouse support this approach (35). Alternatively, Gaucher patients might be "debulked" of their glucosylceramide by enzyme replacement and then maintained on the oral drug.

The inhibition of glycosphingolipid synthesis may be a useful strategy beyond the treatment of Gaucher disease. Because the original "proof-of-concept" studies were performed in models of Fabry disease, these patients should be considered for eliglustat tartrate therapy as well. However, due to its poor penetration into the CNS, other lysosomal storage disorders including Tay-Sachs disease, type 2 and 3 Gaucher disease and GM1 gangliosidosis will require the development of eliglustat homologues that cross the blood–brain barrier. Beyond lysosomal storage disorders, there may be a role for glycosphingolipid synthesis reduction in other clinical settings. Experimental data have been reported in support of glucosylceramide synthase inhibition with eliglustat tartrate or other structural homologues of PDMP for the treatment of insulin-resistant diabetes (36, 37), cancer (38), AIDS (39) and polycystic kidney disease (40).

SOURCE

Genzyme Corp. (US).

DISCLOSURES

James A. Shayman is an inventor on patents covering the composition of matter, synthesis and uses of eliglustat tartrate and related compounds. These patents are held by the University of Michigan and licensed to Genzyme. As an employee of the University of Michigan, the author has recused himself from participation in the clinical trials on eliglustat tartrate to avoid the potential for a conflict of interest.

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