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Effect of Oral Eliglustat vs Placebo on Spleen Volume in Patients with Splenomegaly and Gaucher Disease Type 1: The ENGAGE Randomized Clinical Trial

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Author contributions

Pramod K Mistry recruited patients, conducted the study research, participated in writing the manuscript. He and Judith Peterschmitt had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Elena Lukina, Hadhami Ben Turkia, Dominick Amato, Hagit Baris, Majed Dasouki, Marwan Ghosn, Atul Mehta, Seymour Packman, Gregory Pastores, Milan Petakov, Sarit Assouline, Manisha Balwani, Sumita Danda, Evgueniy Hadjiev, Andres Ortega, Suma Shankar, and Maria Helena Solano all recruited patients, conducted the study research, and reviewed and edited initial and final versions of the manuscript. Leorah Ross analyzed the safety data and reviewed and edited initial and final versions of the manuscript. Jennifer Angell performed the biostatistical analyses and reviewed and edited initial and final versions of the manuscript. M. Judith Peterschmitt designed the study and reviewed and edited initial and final versions of the manuscript. All authors jointly decided to submit the manuscript for publication and all reviewed and approved the submitted version of the manuscript.

Conflict of Interest Disclosures

Principal investigators received no compensation for their role in the study or the development of this manuscript; however, their institutions as study sites received compensation to cover the costs of performing study assessments. Pramod Mistry is a principal investigator in the eliglustat ENGAGE and ENCORE trials and has received research grants, honoraria, and travel reimbursement from Genzyme.

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Abstract

Importance—In Gaucher disease type 1, inherited deficiency of acid-β-glucosidase underlies accumulation of glucosylceramide in lysosomes of macrophages and resultant hepatosplenomegaly, anemia, thrombocytopenia, and skeletal disease. The standard of care is lifelong intravenous enzyme replacement therapy. A safe, effective oral therapy appropriate for a broad spectrum of patients is an important unmet need.

Objective—To determine whether eliglustat, a novel oral substrate-reduction therapy, safely reverses clinical manifestations in previously untreated adults with Gaucher disease type 1.

Design, Setting, and Participants—Phase-3, randomized, double-blind, placebo-controlled, multinational trial conducted from November 2009 to July 2012 in eligible untreated patients with Gaucher disease type 1 who had splenomegaly plus thrombocytopenia and/or anemia.

Interventions—Patients were stratified by spleen volume and randomized 1:1 to receive eliglustat (50 or 100 mg twice daily) or placebo for 9 months.

Main Outcome and Measures—The primary efficacy endpoint was percent change in spleen volume from baseline to 9 months; secondary efficacy endpoints were change in hemoglobin and percent changes in liver volume and platelet count.

Results—Of 72 patients screened, 40 patients from 12 countries and 18 sites were enrolled. All had baseline splenomegaly and thrombocytopenia (mostly moderate or severe), most had mild to moderate hepatomegaly and moderate to severe bone marrow infiltration, and 20% had mild anemia. Least square mean spleen volume decreased by 27.8% (95% CI: −32.57, −22.97) in the eliglustat group (13.89 MN to 10.17 MN) compared to an increase of 2.3% (95% CI: −2.54, 7.06) in the placebo group (12.50 MN to 12.84 MN), for an overall treatment difference of −30% (95% CI: −36.82, −23.24, $P<0.001$). For the secondary endpoints, the least squares mean difference between groups all favored eliglustat over placebo with a 1.2 g/dL increase in hemoglobin level (95% CI: 0.57, 1.88, P<0.001), 6.6% decrease in liver volume (95% CI: −11.37, −1.91, P<0.007), and 41% increase in platelet count (95% CI: 23.95, 58.17, P<0.001). No serious adverse events occurred. The most common adverse events, all mild or moderate, were (eliglustat, placebo patients): arthralgia (45%, 10%), headache (40%, 30%), diarrhea (15%, 20%), and upper respiratory tract infection (5%, 20%). One eliglustat patient withdrew (non-treatment-related); 39/40 patients transitioned to an open-label extension study.

Conclusions and Relevance—Among previously untreated adults with Gaucher disease type 1, treatment with eliglustat compared with placebo for 9 months resulted in significant improvements in spleen volume, hemoglobin level, liver volume, and platelet count. The clinical significance of these findings is uncertain and more definitive conclusions about clinical efficacy and utility will require comparison with the standard treatment of enzyme replacement therapy, as well as longer-term follow-up.

Trial Registration—ENGAGE; NCT00891202, EudraCT 2008-005222-37, CTRI/2009/091/000689 (India)

Keywords

Gaucher disease; eliglustat; substrate reduction therapy; clinical trial

Introduction

In Gaucher disease type 1 (GD1), biallelic mutations in *GBA* (OMIM #606643) result in defective acid-β-glucosidase (glucocerebrosidase) and cause lysosomal accumulation of glucosylceramide and glucosylsphingosine, primarily in cells of monocyte/macrophage lineage.[1] The metabolic defect results in proliferation of lipid-laden macrophages (“Gaucher cells”) in spleen, liver, bone marrow and lungs, causing hepatosplenomegaly, pancytopenia,

skeletal disease, chronic bone pain, and growth failure. Severity of individual organ involvement varies.[2]

Untreated GD1 is a chronic and progressive, resulting in disability, reduced life-expectancy and, in some patients life-threatening complications. The standard of care, macrophage-targeted enzyme replacement therapy (ERT), reverses and prevents numerous manifestations of GD1.[1,3] but requires lifelong, bi-weekly, intravenous infusions. Moreover, system-wide involvement beyond the monocyte-macrophage system may underlie unmet treatment needs in bone, lung, and immune system.[4]

Eliglustat, a novel oral substrate reduction therapy (SRT), was recently approved by the United States Food and Drug Administration for the treatment of GD1.[5] Unlike ERT, which supplements acid β-glucosidase activity in the lysosomes of mononuclear phagocytes, eliglustat is a potent and specific ceramide-analog inhibitor (IC_{50} 24nM) of glucosylceramide synthase. Eliglustat reduces synthesis of glucosylceramide to compensate for its impaired degradation[5] The only other oral SRT approved for GD1 is miglustat. However, because of its risk-benefit profile and tolerability, miglustat is a second-line therapy for a small subset of adults with mild or moderate GD1 for whom ERT is not an option.[6,7,8,9]

In a Phase 2 trial of 26 untreated adult GD1 patients, eliglustat reduced glucosylceramide accumulation and ameliorated major disease manifestations.[10–12] A Phase 3 trial found eliglustat non-inferior to imiglucerase in 159 GD1 patients stabilized after ≥3 years of ERT. [lancetinpress] We report the results of a randomized, placebo-controlled trial (ENGAGE), designed to determine the effect of eliglustat on spleen volume, hemoglobin level, liver volume, and platelet count in in untreated patients with splenomegaly and GD1.

Methods

A placebo-controlled trial was chosen to minimize patient and physician bias and provide the clearest determination of the magnitude of the treatment effect and tolerability in treatment naïve patients. A 9-month study with spleen volume as the primary endpoint was considered to be sufficient to assess clinical efficacy without resulting in acute or irreversible deterioration for patients on placebo, all of whom would be eligible to receive eliglustat during the open-label extension phase of the trial. To conduct a non-inferiority study with ERT as the comparator would have required at least twice as many treatment-naïve patients, which would have posed significant enrollment challenges given the rarity and heterogeneity of Gaucher disease and the availability of an effective treatment; enrollment in the eight other clinical trials conducted to date in treatment naïve Gaucher patients has ranged from 12 to 34 patients[refs]). Furthermore, a second phase 3 trial (ENCORE) comparing eliglustat to imiglucerase in patients whose disease had been stabilized by at least 3 years of ERT was also underway and has now been completed [ref lancet].

Patient Eligibility

Eligibility criteria included age ≥16 years, Tanner Stage ≥4, with a diagnosis of GD1 confirmed by deficient activity of acid β-glucosidase activity in blood leukocytes and/or

GBA mutation analysis and major clinical manifestations of the disease as defined by: hemoglobin 8.0 to 11.0 g/dL (females) or 8.0 to 12.0 g/dL (males) and/or platelet count 50 to 130 × 10^9/L based on the mean of two screening measurements obtained at least 24 hours apart; splenomegaly with spleen volumes 6 to 30 multiples of normal (MN; normal spleen volume 0.2% body weight[3]); and, if hepatomegaly was present, liver volume <2.5 MN (normal liver volume 2.5% of body weight[3]). Patients were eligible only if they had not received treatment with SRT within 6 months or ERT within 9 months before randomization. Additional exclusion criteria included a history of splenectomy (partial or total), evidence of neurologic or pulmonary involvement, current symptomatic bone disease, bone crises within 12 months before randomization, transfusion-dependence, and non-Gaucher-related anemia that was untreated or not stabilized on treatment within 3 months prior to randomization.

Written informed consent was obtained from each patient and/or legal guardian. This study was conducted in accordance with Good Clinical Practice as defined by the International Conference on Harmonisation, the principles defined in the Declaration of Helsinki and its amendments, and all applicable national and international laws. The study protocol was reviewed and approved by the institutional review board or independent ethics committee at each study site.

Study Drug

Patients received either eliglustat tartrate (previously Genz-112638, Genzyme, a Sanofi company, Cambridge, MA) or a placebo capsule containing 50% Avicel PH101 and 50% Lactose Monohydrate USP/Ph-Eur.

Study Design

Eligible patients were stratified by spleen volume (≤ or > 20 MN) to ensure that treatment groups were balanced with respect to number of patients with very large spleens, and then randomized 1:1 to receive 9 months of treatment with eliglustat or placebo. The complete randomization list was computer-generated prior to enrolment of the first patient, in blocks of four, within strata of spleen volume and was delivered using a central interactive voice-response (IVRS) or interactive web-response (IWRS) system administered by the sponsor's Clinical Pharmacy Research Services. Blinded study medication kits were provided to each patient. Dose adjustment based on eliglustat pharmacokinetic results (explained below) was performed by an independent pharmacology consultant at a central laboratory. Patients, investigators, and the sponsor’s clinical team were blinded to treatment allocation until all patients completed the 9-month, double-blind treatment primary analysis period.

During the first 4 study weeks (Day 1 to Week 4), patients randomized to eliglustat received a single 50-mg dose on Day 1 and doses of 50 mg twice daily from Day 2 to Week 4. From post-Week 4 to 9 months, eliglustat patients received either 50 or 100 mg twice daily, dosed on the basis of trough plasma concentrations of eliglustat at Week 2. Patients with a trough concentration ≥5 ng/mL continued to receive 50 mg twice daily; the dose was increased to 100 mg twice daily if the 2-week trough concentration was <5 ng/mL. This dosing regimen was selected based on results of a Phase 2 study of eliglustat in GD1 patients.[10] To maintain the blind, patients were administered two identical-appearing capsules twice daily of

placebo, placebo plus eliglustat tartrate (50-mg dose), or eliglustat tartrate alone (100-mg dose).

Patient compliance with the treatment regimen was determined by counting and recording the number of remaining capsules at each study site visit. Acceptable drug compliance was defined as at least 90% between each study visit.

Study Assessments

The primary efficacy endpoint was the least-square mean percentage change in spleen volume by MRI from baseline to 9 months in the eliglustat group compared with the placebo group. An independent core laboratory (BioClinica, Newtown, PA) performed central blinded analysis of all imaging data. Secondary efficacy endpoints were absolute change in hemoglobin level, percentage change in liver volume by MRI, and percentage change in platelet count from baseline. Tertiary efficacy endpoints included the percentage or absolute change from baseline to 9 months in the plasma biomarker chitotriosidase activity (*CHIT1* [OMIM #600031]); spine and femur bone mineral density (BMD) expressed in g/cm^2, T-score, and Z-score; bone marrow burden (BMB) score (lumbar spine plus femur); Gaucher disease assessments (mobility, bone crisis, and bone pain); and quality of life (QOL) scores (Brief Pain Inventory [BPI],[13] Fatigue Severity Scale [FSS],[14] 36-Item Short Form Health Survey [SF-36 v2]).[15] The BMB score has been validated as a measure of bone marrow infiltration by Gaucher cells and as an indicator of the skeletal response to ERT.[16,17] Exploratory efficacy endpoints included Gaucher Disease Severity Score [DS3][18], a validated overall disease severity score, and the investigational plasma biomarkers including glucosylceramide (GL-1), GM3 ganglioside (GM3), ceramide, sphingomyelin, and macrophage inflammatory protein 1-beta (MIP-1β).

Safety assessments included continuous monitoring of adverse events (AEs) with characterization by severity, relatedness to treatment, seriousness (SAEs), and medical events of interest (MEOIs) from the time of informed consent through completion of the safety follow-up period (30–37 days after the last dose of study drug). MEOIs were defined as clinically significant cardiac arrhythmias detected by electrophysiological monitoring that did not meet SAE criteria as well as syncope from any cause irrespective of seriousness criteria. Other safety assessments included 12-lead electrocardiogram (ECG); 24-hour dual-lead Holter monitoring; physical examinations; body weight, body mass index (BMI), and vital sign measurements; neurological examinations; Mini Mental State Examination (MMSE); and standard clinical laboratory tests (i.e., hematology, serum chemistry, urinalysis). Plasma eliglustat concentrations were measured for pharmacokinetic analysis as described previously.[19]

After screening assessments for all disease indicators, follow-up assessments included: urinalysis, hematology, and biomarkers at Weeks 4, 13, 26, and 39 (9 months); spleen and liver volumes, Gaucher assessments, and QOL assessments at Weeks 26 and 39; and neurologic exam, MMSE, DS3, echocardiogram, spine X-ray, and DXA and MRI of the spine and femur at 9 months.

As required by regulatory authorities, race and ethnicity data were collected via patient self-report. Because Gaucher disease has a 50-fold higher prevalence in Ashkenazi Jews, who tend to have less severe disease (largely attributed to the common N370S mutation)[ref], we report this information to help the reader assess burden of disease in each treatment group.

Statistical Analysis

Sample size calculation estimated enrollment of at least 36 patients to provide 92% power to detect a 20% mean treatment difference between eliglustat and placebo in the primary efficacy endpoint using a 2-sided, 2-sample t-test with a 5% level of significance, assuming decreases in spleen volume from baseline to 9 months of 25% and 5% for eliglustat and placebo, respectively, a standard deviation of 15%, and a dropout rate of 20%.

Because baseline spleen volume is an important predictor of the expected magnitude of change in response to treatment, the primary efficacy endpoint analysis was performed in the intent-to-treat population with the last value carried forward method using an analysis of covariance (ANCOVA) model fitted with treatment and baseline spleen severity and a 5% level of significance. ANCOVA analysis uses least squares means linear regression to evaluate changes from baseline, while adjusting for the covariates included in the model. Normal distribution of the residuals was confirmed using the Shapiro-Wilk test at a 5% level of significance. If the primary endpoint was met, sequential testing of the secondary endpoints using the same ANCOVA method was permitted in a pre-specified order (hemoglobin, liver volume, platelets), which required demonstration of statistical significance of each preceding endpoint. Significance testing for all endpoints was 2-sided. Safety analyses were performed on all patients who received at least one dose of placebo or eliglustat. Data analyses were performed by the sponsor, but the lead author had full access to the data and all authors jointly decided to submit this paper for publication. Analyses were performed using SAS for Windows, Version 9.0 or higher (SAS Institute Inc., Cary, NC).

Results

Patient Characteristics

For this multinational study, 72 patients were screened from 26 centers in 18 countries over the course of 2 years. Of these, 40 met inclusion criteria and were randomized 1:1 to eliglustat (n=20) or placebo (n=20) treatment at 18 sites in 12 countries (Bulgaria, Canada, Colombia, India, Israel, Lebanon, Mexico, Russia, Serbia, Tunisia, United Kingdom, and United States). The first patient consented in November of 2009 and the last patient visit was in July, 2012. Thirty-nine patients completed the primary analysis period of the study (Figure 1) and continued to the open-label extension period. One patient in the eliglustat group withdrew after Week 13 for personal reasons not related to an adverse event. As specified in the protocol, data from this patient, who represented 1/20 (5%) of the eliglustat group, were carried forward from the patient's last visit at 3 months for all efficacy analyses; since spleen and liver volume were measured only at baseline and at 6 and 9 months, baseline values were carried forward for these measures whereas 3-month values were

carried forward for hemoglobin and platelets. The remaining 39 patients had both baseline and 9-month values for all primary and secondary endpoints.

Baseline demographics and patient characteristics are shown in Table 1. Supplemental table A lists the Gaucher genotypes of all patients. The study population included equal numbers of males and females, was predominantly Caucasian and of non-Jewish descent, and ranged in age from 16 to 63 years (mean 32 years). At baseline, all patients had splenomegaly and thrombocytopenia (mostly moderate or severe) and the majority had mild to moderate hepatomegaly. Anemia (defined as hemoglobin of <12 g/dL in males and <11 g/dL in females) was present in 20% of patients and was generally mild. A majority of patients had moderate to severe marrow infiltration indicated by BMB score and approximately 50% of patients had osteopenia of the lumbar spine. The eliglustat and placebo groups were well-matched on baseline patient characteristics, with the exception of a higher mean plasma glucosylceramide level in the eliglustat group. Overall, disease-related biomarkers were elevated in both treatment groups. Moreover, the eliglustat and placebo groups were matched for *GBA* mutations and residual acid β-glucosidase activity (Table 1). Five patients (two eliglustat, three placebo) had received prior ERT with imiglucerase or alglucerase; four of these patients (one eliglustat, three placebo) had also received prior SRT with miglustat.

Compliance with the assigned treatment regimen was at least 90% in all but three patients: two in the placebo group (compliance 80.3% and 86.3%) and one in the eliglustat group (compliance 61.6%).

Efficacy Analyses

Changes in primary and secondary efficacy endpoints from baseline to 9 months are shown in Figure 2 and supplementary Table B. Mean spleen volume (primary endpoint) decreased by 27.8% in the eliglustat group in contrast to an increase of 2.3% in the placebo group, for an overall relative treatment difference of −30% (95% CI: −36.82, −23.24, $P<0.001$). Mean hemoglobin level (secondary endpoint) (least-squares mean) increased in the eliglustat group (0.69 g/dL) in contrast to a decrease in the placebo group (−0.54 g/dL), resulting in an overall relative treatment difference of 1.2 g/dL (95% CI: 0.57, 1.88, P<0.001). Mean liver volume (secondary endpoint) decreased in the eliglustat group (−5.2%) and increased in the placebo group (+1.4%), for an overall relative treatment difference of −6.6% (95% CI: −11.37, −1.91, P<0.01). Mean platelet count (secondary endpoint) increased in the eliglustat group (+32.0%) and decreased in the placebo group (−9.1%) resulting in an overall relative treatment difference of 41.1% (95% CI: 23.95, 58.17, P<0.001). As shown in Figure 2, the largest improvements tended to be seen in the most severely affected patients.

Outcomes related to tertiary and exploratory bone and biomarker endpoints are shown in Table 5. Eliglustat treatment resulted in statistically significant improvement in mean total BMB score (−1.1) (tertiary endpoint), with no change in the placebo treatment group (P=0.002). Most patients in both treatment groups had minimal or mild bone pain and unrestricted mobility at baseline and all subsequent time-points. Other markers of bone disease, including BMD, (tertiary endpoint), showed no significant change. All disease-related biomarkers reflecting different aspects of Gaucher disease pathophysiology showed mean reductions with eliglustat treatment compared with placebo (Table 3). These included

the tertiary biomarkers of substrate accumulation (plasma glucosylceramide, −67% and GM3, 46%), Gaucher cells (chitotriosidase, −44%) (tertiary endpoints), and inflammation (MIP-1β, −44%) (exploratory endpoint) (P<0.001).

Quality of life analyses showed few significant treatment-related changes in this 9-month trial (Supplemental tables C and D). There was a mean improvement in the SF-36 v2 physical functioning domain (tertiary endpoint) with eliglustat (75.25 to 79.00) compared with placebo. (88.25 to 77.75), for an overall treatment difference of 13.2 (95% CI: 0.45, 26.01, P=0.01), whereas changes in the other 9 domains did not reach statistical significance.

The DS3 Gaucher severity score (exploratory endpoint) showed a small but statistically significant mean reduction with eliglustat (4.70 to 4.24) compared with placebo (4.43 to 4.37), for an overall treatment difference of −0.3 (P=0.045).

Safety Analyses

Adverse events are summarized in Table 6. There were no deaths or SAEs, and no patients discontinued treatment because of a treatment-emergent adverse event (TEAE). All TEAEs were graded as mild or moderate, and most were considered by the investigator to be unrelated to the study drug. One MEOI consisting of mild, non-sustained ventricular tachycardia was reported in a placebo patient. Arthralgia, nasopharyngitis, headache, migraine, nasal obstruction, and pyrexia occurred in at least 10% more eliglustat patients (at least two patients) than placebo patients. No patients in either group had clinically significant worsening in any non-disease-related laboratory parameters, vital signs, echocardiogram findings, or neurologic exam findings. Mean MMSE scores at baseline and 9 months did not differ between treatment groups.

Discussion

Orally administered eliglustat for 9 months resulted in a statistically significant and clinically meaningful 30% reduction in spleen volume compared with placebo, and statistically significant improvements in hemoglobin level (1.2 g/dL), liver volume (−6.6%), and platelet count (41%). These clinical findings were accompanied by improvement in the BMB score and reductions in circulating substrate levels (GL-1 and GM3). Moreover, chitotriosidase, the plasma biomarker indicative of the body burden of Gaucher cells, was substantially reduced as was MIP-1β, an inflammatory biomarker secreted by phagocytic cells surrounding Gaucher cells.[20] No patients discontinued treatment over the course of the 9-month study due to a TEAE.

Eliglustat differs from the oral SRT miglustat, a second-line therapy for GD1, in its structural and pharmacologic properties. Eliglustat resembles the ceramide moiety of glucosylceramide and is a potent and highly specific inhibitor of glucosylceramide synthase (IC_{50} = 24nM).[21] Miglustat, an N-butyl iminosugar, resembles the glucose moiety of glucosylceramide and is a non-specific and weak inhibitor (Ki 7μM) of glucosylceramide synthase. Miglustat is known to inhibit a wide range of glucosidases with a resultant high

incidence of gastrointestinal disturbance and new neurologic symptoms,[9,22,23] which have been linked to poor tolerability in clinical studies.[22,24]

In this GD1 cohort with substantial disease manifestations, the downward trend in clinical status of patients in the placebo group over 9 months underscores the progressive nature of Gaucher disease. By reducing substrate influx, eliglustat significantly improved disease manifestations in patients with existing visceral and hematologic involvement. The magnitude of the improvements observed suggests that eliglustat alone may have the potential to effectively restore balance in the production and degradation of glucosylceramide without prior reconstitution of the macrophage system with exogenous acid β-glucosidase. The United States Food and Drug Administration recently approved eliglustat as a first-line oral therapy for adults with GD1.[reference]

The observed efficacy of eliglustat therapy after 9 months in this Phase 3 clinical study is consistent overall with the results observed in an uncontrolled Phase 2 study, in which oral eliglustat was administered to 26 GD1 patients twice daily in 50- or 100-mg doses based on plasma drug concentrations.[10] The patients in the Phase 2 study had more advanced GD1 compared to the study herein, with lower mean hemoglobin levels and platelet counts, greater splenomegaly, and lower residual acid β-glucosidase at baseline. In that study, significant improvements after 1 year were observed for change in mean spleen volume (−38.5%), liver volume (−17.0%), hemoglobin level (1.62 g/dL), and platelet count (40.3%),[10] with continued improvements during the second year of treatment.[25] After 4 years of treatment, there was a mean 65% reduction in spleen volume, 28% reduction in liver volume, 2.3 g/dL increase in hemoglobin level, and 95% increase in platelet count.[12]

The findings of our study should be interpreted with some limitations in mind. To our knowledge, ENGAGE is the only placebo-controlled trial done in patients with GD1 and the largest randomized trial in treatment-naïve patients with GD1 conducted to date; however, it is still a small trial with only 40 patients. Because of the large treatment effects observed with eliglustat, the study was adequately powered to detect statistically significant differences in the primary and all secondary endpoints, and minimized the number of patients exposed to placebo. As this was a 9-month study in untreated adult GD1 patients, information about longer-term exposure or in different patient populations, including those currently stable on ERT, cannot be extrapolated. Nine months is generally an insufficient follow-up period to observe changes in bone mineral density, especially in patients with comparatively mild bone loss at baseline. Longer follow-up of the patients in this trial is needed to confirm the BMD improvements reported in the Phase 2 study, in which mean lumbar spine T-score went from the osteopenic range at baseline to the normal range after 4 years of treatment.[11] After 9 months, eliglustat resulted in significant improvement in the physical functioning domain compared to placebo; however other quality-of-life measures did not reach statistical significance. Longer-term treatment may result in improvements in other domains of QOL in a population reporting a relatively small burden of QOL impairment at baseline. This study was not designed to compare the efficacy of eliglustat with other therapies for GD1. Although the improvements observed with eliglustat were consistent with what can be expected from ERT, further eliglustat studies, such as the

ENCORE trial (NCT00943111), are in progress to assess how eliglustat compares to ERT in patients whose disease has stabilized on ERT.

Conclusions

Among previously untreated adults with Gaucher disease type 1, treatment with eliglustat compared with placebo for 9 months resulted in significant improvements in spleen volume, hemoglobin level, liver volume, and platelet count. The clinical significance of these findings is uncertain and more definitive conclusions about clinical efficacy and utility will require comparison with the standard treatment of enzyme replacement therapy, as well as longer-term follow-up.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Role of the Sponsor

This trial was funded by Genzyme, a Sanofi company. The Genzyme project team developed the design and set-up of the trial in collaboration with study investigators and regulatory authorities and was involved in the conduct of the study and the collection, management, analysis, and interpretation of the data. Study data were monitored by clinical research associates contracted by Genzyme in each study region. Analyses were carried out by the Genzyme Biomedical Data Science and Informatics division. An independent Data Monitoring Committee (DMC) provided additional oversight of patient safety through periodic and ad-hoc reviews of study data, and review of information on patient discontinuations/withdrawals. Genzyme provided funding for assistance with manuscript writing. All authors concurred with submission of this manuscript. In addition to the coauthors who are Genzyme employees (Drs Ross, Angell, and Peterschmitt), three Genzyme employees from Genzyme Global Medical Affairs (Gerald Cox, MD, PhD, Raymond Mankoski, MD, PhD, and Lisa Underhill, MS) reviewed the manuscript and provided non-binding suggestions to the authors for their consideration. All final decisions regarding content and the decision to submit were made solely by the coauthors.

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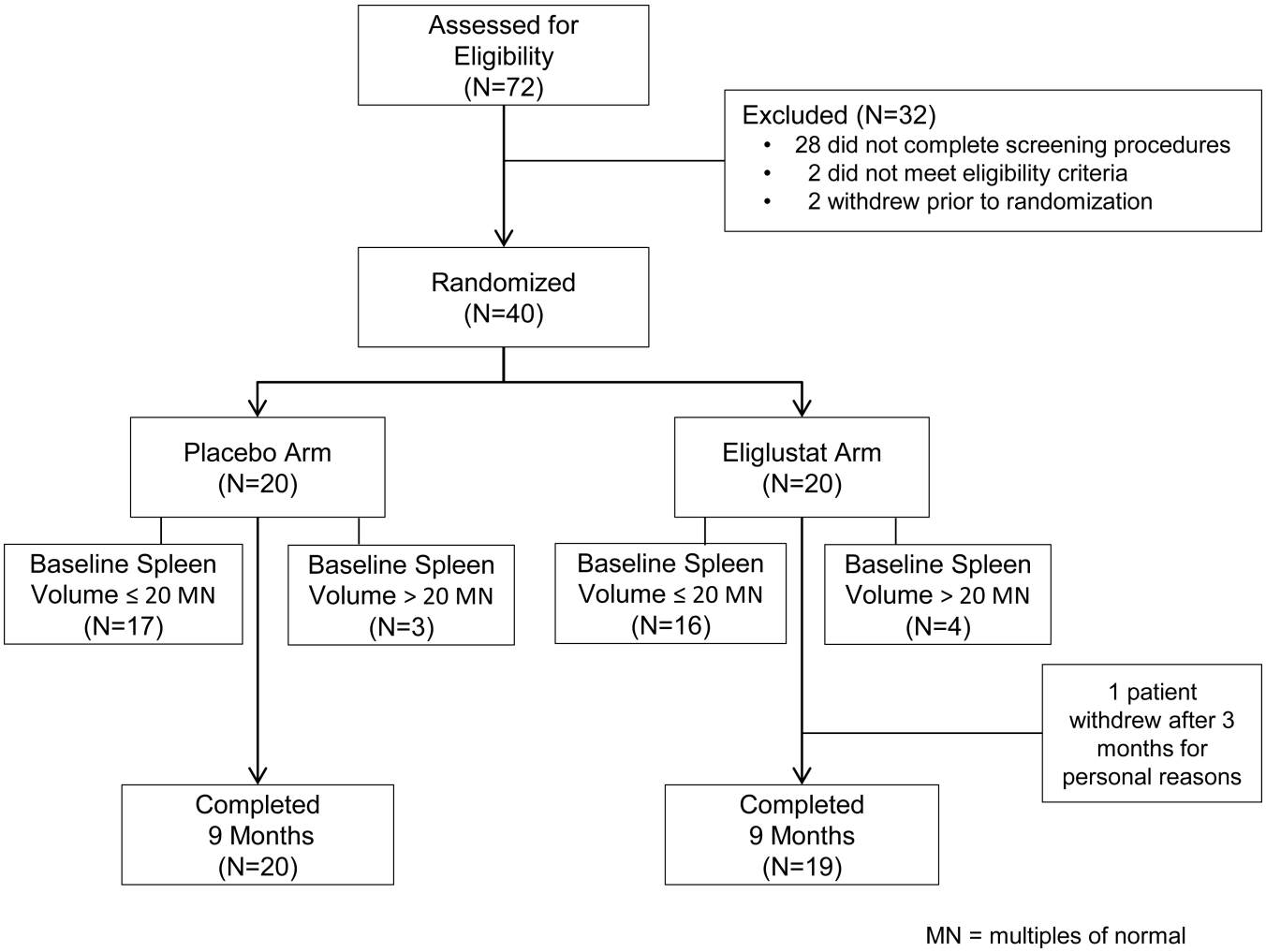

Figure 1.

Patient Disposition for the Double Blind Primary Analysis Period

MN denotes multiples of normal.

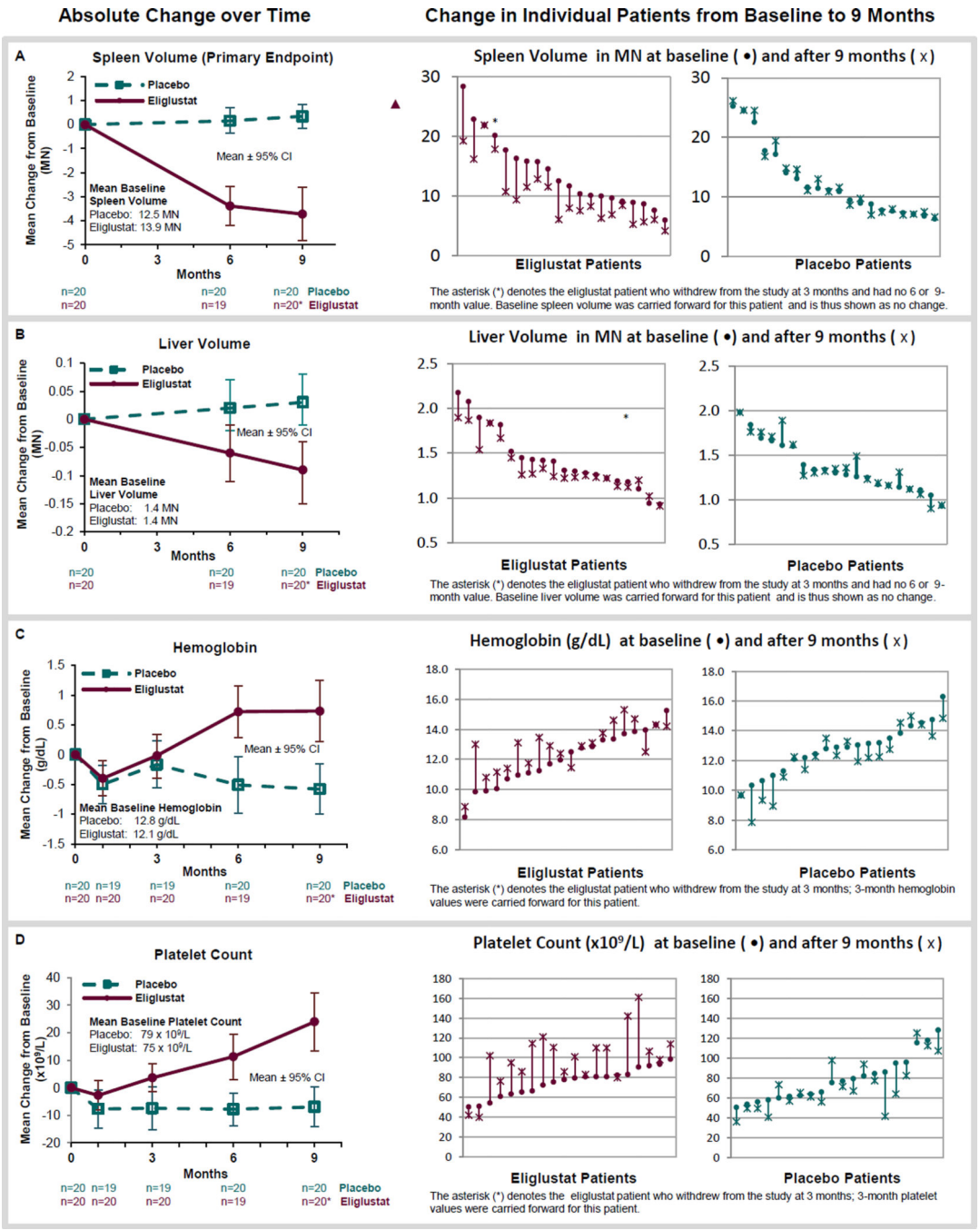

Figure 2.

Change in Spleen, Hemoglobin, Liver, and Platelets: Intent to Treat Population

Panels A, B, C, and D show absolute mean changes in spleen volume, liver volume, hemoglobin level, and platelet count, respectively (error bars denote 95% confidence intervals), as well as individual baseline and 9-month values for each patient on these four parameters. All patients are shown in ascending order within each treatment group with respect to most to least normal value for that parameter (i.e., lowest to highest spleen and liver volumes, and highest to lowest values for hemoglobin level and platelet count). The

asterisk (*) denotes the single patient who withdrew from the trial; this eliglustat patient withdrew for personal reasons at 3 months and had no 6- or 9-month assessments. For the final efficacy assessments, change for this patient was determined by last observation carried forward; thus for liver and spleen, the baseline value was carried forward and for hemoglobin and platelets, the 3 month value was carried forward. All other patients had both baseline and 9 month values for all parameters. MN denotes multiples of normal.

Table 1

Demographics and Baseline Patient Characteristics

Parameter	Placebo (N=20)	Eliglustat (N=20)
Age at Day 1 in years, mean (SD)	32.1 (11.26)	31.6 (11.55)
Sex, n (%)		
Male	12 (60)	8 (40)
Female	8 (40)	12 (60)
Race/ethnicity, n (%)		
Caucasian, Ashkenazi Jewish	8 (40)	3 (15)
Caucasian, Non- Ashkenazi Jewish	12 (60)	14 (70)
Hispanic	0	2 (10)
Asian	0	1 (5)
GBA mutations, n (%)		
N370S/Other	8 (40)	8 (40)
N370S/N370S	6 (30)	5 (25)
N370S/L444P	4 (20)	2 (10)
L444P/Other	1 (5)	3 (15)
Other/Other	1 (5)	2 (10)
Acid β-glucosidase activity (nmol/hr/mg)[a], mean (SD)	2.04 (3.79)	2.29 (3.38)
median	0.50	1.40
(min, max)	(0.0, 15.5)	(0.0, 15.7)
Spleen volume (multiples of normal), mean (SD)	12.50 (5.96)	13.89 (5.93)
median	11.05	12.09
(min, max)	(6.32, 25.27)	(5.94, 28.39)
Liver volume (multiples of normal), mean (SD)	1.36 (0.28)	1.44 (0.35)
median	1.29	1.36
(min, max)	(0.93, 1.98)	(0.93, 2.18)
Hemoglobin level (g/dL), mean (SD)	12.8 (1.6)	12.1 (1.8)
median	12.9	12.1
(min, max)	(9.65, 16.30)	(8.15, 15.25)
Platelet count (10^9/L), mean (SD)	78.48 (22.61)	75.05 (14.10)
median	76.25	78.75
(min, max)	(50.5, 128.5)	(50.5, 98.5)
Chitotriosidase activity (nmol/hr/mL)[a,b], mean (SD)	11 118 (8313)	13 313 (8151)
median	11 031	14 229
(min, max)	(724.0, 35960.0)	(2298.0, 35106.0)
Plasma glucosylceramide (μg/mL)[a], mean (SD)	9.6 (3.8)	12.7 (4.8)
median	8.4	11.7
(min, max)	(5.6, 18.4)	(6.3, 27.9)
Bone marrow burden score[c], mean (SD)	9.8 (2.8)	10.9 (2.6)
median	9.5	10.8

Parameter	Placebo (N=20)	Eliglustat (N=20)
(min, max)	(4.7, 16.0)	(6.0, 16.0)
Lumbar spine bone mineral density T-score[d], mean (SD)	−1.1 (1.2)	−1.1 (0.8)
median	−1.2	−1.2
(min, max	(−3.2, 1.6)	(−2.3, 0.6)
Femur bone mineral density T-score[d], mean (SD)	−0.5 (1.2)	−0.3 (0.8)
median	−0.6	−0.4
(min, max)	(−2.4, 2.3)	(−1.5, 1.3)

[a]Normal ranges: acid β-glucosidase: 5.79–9.12 nmol/hr/mg; chitotriosidase: <15 to 181 nmol/hr/mL; glucosylceramide: <2.0 to 6.6 μg/mL

[b]Normalized chitotriosidase values; values were doubled for six patients with heterozygous chitotriosidase genotypes and excluded for one patient with homozygous mutation with no expected chitotriosidase activity.[add ref?]

[c]Bone marrow burden score is the sum of spine and femur BMB scores and ranges from 0 to 4: mild; 5 to 8: moderate; 9 to 16: marked to severe.

[d]T-scores are reported only for patients who had data at both baseline and specified time point; (n=18 for placebo; n=17 for eliglustat).

Table 2

Changes in Primary and Secondary Efficacy Endpoints from Baseline to 9 Months

	Placebo (N=20)	Eliglustat (N=20)	Difference	P Value
Spleen Volume (MN) (Primary)				
Baseline	12.5 (5.96)	13.9 (5.93)		
9 Months				
Absolute Value, mean (SD)	12.84 (6.4)	10.17 (5.07)		
Absolute Change, mean (SD)	0.35 (1.05)	−3.72 (2.38)		
(95% CI for absolute change)	(−0.14, 0.84)	(−4.83, −2.61)		
Percent Change, LS mean	2.26	−27.77	−30.03	<0.001
(95% CI for Percent Change)	(−2.54, 7.06)	(−32.57, −22.97)	(−36.82, −23.24)	
Hemoglobin (g/dL) (Secondary)				
Baseline, mean (SD)	12.75 (1.63)	12.05 (1.82)		
9 Months				
Absolute Value, mean (SD)	12.17 (2.01)	12.78 (1.56)		
Absolute Change, mean (SD)	−0.58 (0.89)	0.73 (1.09)		
(Absolute change 95% CI)	(−1.00, −0.16)	(0.22, 1.24)		
Absolute Change, LS mean	−0.54	0.69	1.22	<0.001
(95% CI Absolute Change LS mean)	(−1.00, −0.08)	(0.23, 1.14)	(0.57, 1.88)	
Liver Volume (MN) (Secondary)				
Baseline, mean (SD)	1.36 (0.28)	1.44 (0.35)		
9 Months				
Absolute Value, mean (SD)	1.39 (0.31)	1.35 (0.28)		
Absolute Change, mean (SD)	0.03 (0.11)	−0.09 (0.11)		
(95% CI for absolute change)	(−0.02, 0.07)	(−0.15, −0.04)		
Percent Change, LS mean	1.44	−5.2	−6.64	
(95% CI for percent change)	(−1.89, 4.78)	(−8.53, −1.87)	(−11.37, −1.91)	0.0072
Platelet Count (10^9/L) (Secondary)				
Baseline, mean (SD)	78.48 (22.61)	75.05 (14.10)		
9 Months				
Absolute Value, mean (SD)	71.50 (25.16)	98.95 (28.37)		
Absolute Change, mean (SD)	−6.98 (15.39)	23.90 (22.6)		
(95% CI)	(−14.18, 0.23)	(13.33, 34.47)		
Percent Change, LS mean	−9.06	32.00	41.06	<0.001
(95% CI for percent change)	(−21.12, 3.00)	(19.94, 44.06)	(23.95, 58.17)	

Change from baseline was analyzed using ANCOVA methods evaluating differences in least squares mean, adjusted for treatment group, baseline spleen severity group and a continuous variable for the baseline observation. Means and SDs are calculated arithmetically, unless specifically noted to be least-square means calculated using the ANCOVA methods. As per the trial protocol, missing values were imputed with last value carried forward. One patient withdrew from the trial at 3 months, for this patient, baseline spleen and liver values and 3 month hemoglobin and platelet values were carried forward. Both baseline and 9-month data were available for all other patients for all four endpoints.

Table 3

Changes in Bone and Biomarker Endpoints from Baseline to 9 Months

	Placebo (N=20)	Eliglustat (N=20)	Difference*	P Value
Tertiary Endpoints				
Bone marrow burden score§				
Baseline, mean±SD (n)	9.8±2.8 (20)	10.9±2.6 (20)		
9 Months, mean±SD (n)	9.8±2.8 (20)	9.8±2.6 (20)		
Absolute change, LS Mean ; 95% CI (n)	0.0; −0.5, 0.5 (20)	−1.1; −1.5, −0.6 (20)	−1.1; −1.7, −0.4	0.002
Lumbar spine bone mineral density (g/cm^2)				
Baseline, mean±SD (n)	1.037±0.152 (20)	0.991±0.172 (19)		
9 Months, mean± SD (n)	1.027±0.151 (20)	0.995±0.160 (19)		
Absolute change±SD (n)	−0.010±0.039 (20)	0.004±0.031 (19)		
Percent change, LS Mean ; 95% CI (n)	−0.8; −2.38, 0.71 (20)	0.4; −1.17, 2.0 (19)	1.2; −0.97, 3.47	0.26
Lumbar spine T-score**				
Baseline, mean±SD (n)	−1.1±1.2 (18)	−1.1±0.8 (17)		
9 Months, mean±SD (n)	−1.2±1.1 (18)	−1.0±0.8 (17)		
Absolute change, LS Mean; 95% CI (n)	−0.1; −0.2, 0.03 (18)	0.0; −0.1, 0.2 (17)	0.1; −0.1, 0.3	0.14
Lumbar spine Z-score††				
Baseline, mean±SD (n)	−1.2±1.2 (20)	−1.1±0.9 (19)	−0.7	
9 Months, mean±SD (n)	−1.3±1.2 (20)	−1.1±0.9 (20)		
Absolute change, LS Mean; 95% CI (n)	−0.1; −0.2, 0.02 (20)	0.1; −0.1, 0.2 (20)	0.2;-0.01, 0.4	0.06
Femur bone mineral density (g/cm^2)				
Baseline, mean±SD (n)	0.981±0.161 (20)	0.967±0.146 (19)		
9 Months, mean±SD (n)	0.982±0.163 (20)	0.961±0.149 (19)		
Absolute change, mean±SD (n)	0.001±0.03 (20)	−0.006±0.023 (19)		
Percent change, LS Mean ; 95% CI (n)	0.1; −1.29, 1.57 (20)	−0.7; −2.19,0.76 (19)	−0.9; −0.01, 0.36	0.66
Femur T-score**				
Baseline, mean±SD (n)	−0.5±1.2 (18)	−0.3±0.8 (17)		
9 Months, mean±SD (n)	−0.4±1.2 (18)	−0.3±0.8 (17)		
Absolute change, LS Mean; 95% CI (n)	0.0; −0.1, 0.1 (18)	−0.1;-0.2, 0.04 (17)	−0.1; −0.3, 0.04	0.15
Femur Z-score††				
Baseline, mean±SD (n)	−0.4±1.2 (20)	−0.1±0.7 (18)		
9 Months, mean (SD)	−0.4±1.2 (20)	−0.2±0.7(18)		
Absolute change; LS Mean, 95% CI (n)	0.0; −0.1, 0.1 (20)	0.0± −0.1, 0.1(18)	0.0; −0.2, 0.1	0.57
Plasma chitotriosidase activity (nmol/hr/mL)†				
Baseline, mean±SD (n)	11 118±8313 (20)	12648±8473 (19)		
9 Months, mean±SD (n)	10950±7345 (20)	8204±6340 (19)		
Absolute change, mean±SD (n)	−167±3333 (20)	4443±3711 (19)		
Percent change, LS Mean ; 95% CI (n)	5.4; −8.3, 19.0 (20)	−39.0; −53.0, −25.0 (19)	−44.4; −64.1, −24.8	<0.001
Exploratory Endpoints				

	Placebo (N=20)	Eliglustat (N=20)	Difference*	P Value
Plasma glucosylceramide (μg/mL)†				
Baseline, mean±SD (n)	9.6±3.8 (20)	12.7±4.8 (20)		
9 Months, mean±SD (n)	8.9±3.5 (20)	3.5±2.2 (20)		
Absolute change, mean±SD (n)	−0.6±2.5(20)	−9.2±3.5 (20)		
Percent change, LS Mean ; 95% CI (n)	−4.9; −12.6, 2.9(20)	−71.7; −79.5, −64.0(20)	−66.9; −78.2, −55.5	<0.001
Plasma GM3 (μg/mL)†				
Baseline, mean±SD (n)	22.6±7.0 (14)	27.7±5.3 (14)		
9 Months, mean±SD (n)	20.7±4.6 (14)	12.0±6.4(14)		
Absolute change, mean±SD (n)	−1.9±4.7 (14)	−15.7±7.3(14)		
Percent change, LS Mean ; 95% CI (n)	−7.7; −18.1, 2.7 (14)	−54.0; −64.4, −43.7 (14)	−46.3; −61.6, −31.0	<0.001
Plasma MIP-1β (pg/mL)†				
Baseline, mean±SD (n))	287±143 (20)	277±101 (20)		
9 Months, mean±SD (n)	255±120 (20)	134±76 (20)		
Absolute change, mean±SD (n)	−32±58 (20)	143±78 (20)		
Percent change, LS Mean ; 95% CI (n)	−8.0; −16.7, 0.6 (20)	−51.6; −60.3, −42.9 (20)	−43.5;-55.8, −31.2	<0.001
Plasma ceramide (μg/mL)†				
Baseline, mean±SD (n)	3.6 ±0.84 (20)	3.5±0.95 (20)		
9 Months, mean±SD (n)	3.3±1.08 (20)	3.1±0.68 (20)		
Absolute change, mean±SD (n)	−0.3±1.12 (20)	−0.4±1.20 (20)		
Percent change, LS Mean ; 95% CI (n)	−3.2; −15.4, 9.0 (20)	−4.7; −16.9, 7.5 (20)	−1.5; −18.7, 15.8	0.862
Plasma sphingomyelin (μg/mL)†				
Baseline, mean±SD (n)	234±47.5 (20)	247±69.4 (20)		
9 Months, mean±SD (n)	230±39.4 (20)	280±50.2 (20)		
Absolute change, mean±SD (n)	−4±42.2 (20)	33±78.8 (20)		
Percent change, LS Mean ; 95% CI (n)	−2; −10.5, 6.4 (20)	21; 12.5, 29.4 (20)	23; 11, 35	0.0002

*Change from baseline was analyzed using ANCOVA methods evaluating differences in least squares mean, adjusted for treatment group, baseline spleen severity group and a continuous variable for the baseline observation. Means and SDs are calculated arithmetically, unless specifically noted to be least-square means calculated using the ANCOVA methods.

†Normal ranges: chitotriosidase: <15 to 181 nmol/hr/mL; GL-1: <2.0 to 6.6 μg/mL; GM3 = 5 to 21 μg /mL; MIP-1β = 27.3 to 77.2 pg/mL; Ceramide = 1.8 to 6.5 μg/mL; Sphingomyelin ≥200 to 703 μg/mL. Chitotriosidase values were set equal to zero for one patient with a homozygous *CHIT1* null mutation expected to result in inactive enzyme and were doubled for six patients who were heterozygous for the *CHIT1* null mutation. Percentage change not calculated for the patient with the homozygous *CHIT1* mutation.

§BMB Score is the sum of spine and femur BMB scores (each ranging from 0–8) and categorized as follows: 0 to 4, mild; 5 to 8, moderate; and 9 to 16, marked to severe.

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

††Z-score bone density categories: normal (score > −2) and below normal (score ≤ −2). T-scores reported only for patients with data at both baseline and specified time point; (n=18 for placebo; n=17 for eliglustat).

Table 4

Changes in Bone and Biomarker Endpoints from Baseline to 9 Months

	Placebo (N=20)	Eliglustat (N=20)	Difference*	P Value
Tertiary Endpoints				
Bone marrow burden score§				
Baseline, mean±SD (n)	9.8±2.8 (20)	10.9±2.6 (20)		
9 Months, mean±SD (n)	9.8±2.8 (20)	9.8±2.6 (20)		
Absolute change, LS Mean ; 95% CI (n)	0.0; −0.5, 0.5 (20)	−1.1; −1.5, −0.6 (20)	−1.1; −1.7, −0.4	0.002
Lumbar spine bone mineral density (g/cm^2)				
Baseline, mean±SD (n)	1.037±0.152 (20)	0.991±0.172 (19)		
9 Months, mean± SD (n)	1.027±0.151 (20)	0.995±0.160 (19)		
Absolute change±SD (n)	−0.010±0.039 (20)	0.004±0.031 (19)		
Percent change, LS Mean ; 95% CI (n)	−0.8; −2.38, 0.71 (20)	0.4; −1.17, 2.0 (19)	1.2; −0.97, 3.47	0.26
Lumbar spine T-score**				
Baseline, mean±SD (n)	−1.1±1.2 (18)	−1.1±0.8 (17)		
9 Months, mean±SD (n)	−1.2±1.1 (18)	−1.0±0.8 (17)		
Absolute change, LS Mean; 95% CI (n)	−0.1; −0.2, 0.03 (18)	0.0; −0.1, 0.2 (17)	0.1; −0.1, 0.3	0.14
Lumbar spine Z-score††				
Baseline, mean±SD (n)	−1.2±1.2 (20)	−1.1±0.9 (19)	−0.7	
9 Months, mean±SD (n)	−1.3±1.2 (20)	−1.1±0.9 (20)		
Absolute change, LS Mean; 95% CI (n)	−0.1; −0.2, 0.02 (20)	0.1; −0.1, 0.2 (20)	0.2;-0.01, 0.4	0.06
Femur bone mineral density (g/cm^2)				
Baseline, mean±SD (n)	0.981±0.161 (20)	0.967±0.146 (19)		
9 Months, mean±SD (n)	0.982±0.163 (20)	0.961±0.149 (19)		
Absolute change, mean±SD (n)	0.001±0.03 (20)	−0.006±0.023 (19)		
Percent change, LS Mean ; 95% CI (n)	0.1; −1.29, 1.57 (20)	−0.7; −2.19,0.76 (19)	−0.9; −0.01, 0.36	0.66
Femur T-score**				
Baseline, mean±SD (n)	−0.5±1.2 (18)	−0.3±0.8 (17)		
9 Months, mean±SD (n)	−0.4±1.2 (18)	−0.3±0.8 (17)		
Absolute change, LS Mean; 95% CI (n)	0.0; −0.1, 0.1 (18)	−0.1;-0.2, 0.04 (17)	−0.1; −0.3, 0.04	0.15
Femur Z-score††				
Baseline, mean±SD (n)	−0.4±1.2 (20)	−0.1±0.7 (18)		
9 Months, mean (SD)	−0.4±1.2 (20)	−0.2±0.7(18)		
Absolute change; LS Mean, 95% CI (n)	0.0; −0.1, 0.1 (20)	0.0± −0.1, 0.1(18)	0.0; −0.2, 0.1	0.57
Plasma chitotriosidase activity (nmol/hr/mL)†				
Baseline, mean±SD (n)	11 118±8313 (20)	12648±8473 (19)		
9 Months, mean±SD (n)	10950±7345 (20)	8204±6340 (19)		
Absolute change, mean±SD (n)	−167±3333 (20)	4443±3711 (19)		
Percent change, LS Mean ; 95% CI (n)	5.4; −8.3, 19.0 (20)	−39.0; −53.0, −25.0 (19)	−44.4; −64.1, −24.8	<0.001
Exploratory Endpoints				

	Placebo (N=20)	Eliglustat (N=20)	Difference*	P Value
Plasma glucosylceramide (μg/mL)†				
Baseline, mean±SD (n)	9.6±3.8 (20)	12.7±4.8 (20)		
9 Months, mean±SD (n)	8.9±3.5 (20)	3.5±2.2 (20)		
Absolute change, mean±SD (n)	−0.6±2.5(20)	−9.2±3.5 (20)		
Percent change, LS Mean ; 95% CI (n)	−4.9; −12.6, 2.9(20)	−71.7; −79.5, −64.0(20)	−66.9; −78.2, −55.5	<0.001
Plasma GM3 (μg/mL)†				
Baseline, mean±SD (n)	22.6±7.0 (14)	27.7±5.3 (14)		
9 Months, mean±SD (n)	20.7±4.6 (14)	12.0±6.4(14)		
Absolute change, mean±SD (n)	−1.9±4.7 (14)	−15.7±7.3(14)		
Percent change, LS Mean ; 95% CI (n)	−7.7; −18.1, 2.7 (14)	−54.0; −64.4, −43.7 (14)	−46.3; −61.6, −31.0	<0.001
Plasma MIP-1β (pg/mL)†				
Baseline, mean±SD (n))	287±143 (20)	277±101 (20)		
9 Months, mean±SD (n)	255±120 (20)	134±76 (20)		
Absolute change, mean±SD (n)	−32±58 (20)	143±78 (20)		
Percent change, LS Mean ; 95% CI (n)	−8.0; −16.7, 0.6 (20)	−51.6; −60.3, −42.9 (20)	−43.5;-55.8, −31.2	<0.001
Plasma ceramide (μg/mL)†				
Baseline, mean±SD (n)	3.6 ±0.84 (20)	3.5±0.95 (20)		
9 Months, mean±SD (n)	3.3±1.08 (20)	3.1±0.68 (20)		
Absolute change, mean±SD (n)	−0.3±1.12 (20)	−0.4±1.20 (20)		
Percent change, LS Mean ; 95% CI (n)	−3.2; −15.4, 9.0 (20)	−4.7; −16.9, 7.5 (20)	−1.5; −18.7, 15.8	0.862
Plasma sphingomyelin (μg/mL)†				
Baseline, mean±SD (n)	234±47.5 (20)	247±69.4 (20)		
9 Months, mean±SD (n)	230±39.4 (20)	280±50.2 (20)		
Absolute change, mean±SD (n)	−4±42.2 (20)	33±78.8 (20)		
Percent change, LS Mean ; 95% CI (n)	−2; −10.5, 6.4 (20)	21; 12.5, 29.4 (20)	23; 11, 35	0.0002

*Change from baseline was analyzed using ANCOVA methods evaluating differences in least squares mean, adjusted for treatment group, baseline spleen severity group and a continuous variable for the baseline observation. Means and SDs are calculated arithmetically, unless specifically noted to be least-square means calculated using the ANCOVA methods.

†Normal ranges: chitotriosidase: <15 to 181 nmol/hr/mL; GL-1: <2.0 to 6.6 μg/mL; GM3 = 5 to 21 μg /mL; MIP-1β = 27.3 to 77.2 pg/mL; Ceramide = 1.8 to 6.5 μg/mL; Sphingomyelin ≥200 to 703 μg/mL. Chitotriosidase values were set equal to zero for one patient with a homozygous *CHIT1* null mutation expected to result in inactive enzyme and were doubled for six patients who were heterozygous for the *CHIT1* null mutation. Percentage change not calculated for the patient with the homozygous *CHIT1* mutation.

§BMB Score is the sum of spine and femur BMB scores (each ranging from 0–8) and categorized as follows: 0 to 4, mild; 5 to 8, moderate; and 9 to 16, marked to severe.

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

††Z-score bone density categories: normal (score > −2) and below normal (score ≤ −2). T-scores reported only for patients with data at both baseline and specified time point; (n=18 for placebo; n=17 for eliglustat).

Table 5

Changes in Tertiary and Exploratory Endpoints from Baseline to 9 Months

	Placebo (N=20)	Eliglustat (N=20)	Difference*	P Value
Plasma Chitotriosidase activity (nmol/hr/mL)†				
Baseline, mean (SD)	11 118 (8313)	12648 (8473)		
9 Months, mean (SD)	10950 (7345)	8204 (6340)		
Absolute change, mean (SD)	−167 (3333)	4443(3711)		
Percent change (LS mean 95% CI)	5.4 (−8.3, 19.0)	−39.0 (−53.0, −25.0)	−44.4 (−64.1, −24.8)	<0.001
Plasma glucosylceramide (μg/mL)†				
Baseline, mean (SD)	9.6 (3.8)	12.7 (4.8)		
9 Months, mean (SD)	8.9 (3.5)	3.5 (2.2)		
Absolute change, mean (SD)	−0.6 (2.5)	−9.2 (3.5)		
Percent change (LS Mean, 95% CI)	−4.9 (−12.6, 2.9)	−71.7 (−79.5, −64.0)	−66.9 (−78.2, −55.5)	<0.001
Plasma GM3 (μg/mL)†				
Baseline, mean (SD)	22.6 (7.0)	27.7 (5.3)		
9 Months, mean (SD)	20.7 (4.6)	12.0 (6.4)		
Absolute change, mean (SD)	−1.9 (4.7)	−15.7 (7.3)		
Percent change (LS Mean, 95% CI)	−7.7 (−18.1, 2.7)	−54.0 (−64.4, −43.7)	−46.3 (−61.6, −31.0)	<0.001
Plasma MIP-1β (pg/mL)†				
Baseline, mean (SD)	287 (143)	277 (101)		
9 Months, mean (SD)	255 (120)	134 (76)		
Absolute change, mean (SD)	−32 (58)	143 (78)		
Percent change (LS Mean 95% CI)	−8.0 (−16.7, 0.6)	−51.6 (−60.3, −42.9)	−43.5 (−55.8, −31.2)	<0.001
Plasma ceramide (μg/mL)†				
Baseline, mean (SD)	3.6 (0.84)	3.5 (0.95)		
9 Months, mean (SD)	3.3 (1.08)	3.1 (0.68)		
Absolute change, mean (SD)	−0.3 (1.12)	−0.4 (1.20)		
Percent change (LS Mean 95% CI)	−3.2 (−15.4, 9.0)	−4.7 (−16.9, 7.5)		
Plasma sphingomyelin (μg/mL)†				
Baseline, mean (SD)	234 (47.5)	247 (69.4)		
9 Months, mean (SD)	230 (39.4)	280 (50.2)		
Absolute change, mean (SD)	−4 (42.2)	33 (78.8)	−1.5 (−18.7, 15.8)	0.862
Percent change (LS Mean, 95% CI)	−2 (−10.5, 6.4)	21 (12.5, 29.4)	23 (11, 35)	0.0002
Bone marrow burden score§				
Baseline, mean (SD)	9.8 (2.8)	10.9 (2.6)		
9 Months, mean (SD)	9.8 (2.8)	9.8 (2.6)		
Absolute change (LS Mean, 95% CI)	0.0 (−0.5, 0.5)	−1.1 (−1.5, −0.6)	−1.1 (−1.7, −0.4)	0.002
Lumbar spine bone mineral density (g/cm^2)				
Baseline, mean (SD)	1.037 (0.152)	0.991 (0.172)		
9 Months, mean (SD)	1.027 (0.151)	0.995 (0.160)		

	Placebo (N=20)	Eliglustat (N=20)	Difference*	P Value
Absolute change (SD)	−0.010 (0.039)	0.004 (0.031)		
Percent change (LS Mean, 95% CI)	−0.8 (−2.38, 0.71)	0.4 (−1.17, 2.0)	1.2 (−0.97, 3.47)	0.26
Lumbar spine T-score**				
Baseline, mean (SD)	−1.1 (1.2)	−1.1 (0.8)		
9 Months, mean (SD)	−1.2 (1.1)	−1.0 (0.8)		
Absolute change (LS Mean, 95% CI)	−0.1 (−0.2, 0.03)	0.0 (−0.1, 0.2)	0.1 (−0.1, 0.3)	0.14
Lumbar Spine Z-score††				
Baseline, mean (SD)	−1.2 (1.2)	−1.1 (0.9)	−0.7	
9 Months, mean (SD)	−1.3 (1.2)	−1.1 (0.9)		
Absolute change (LS Mean, 95% CI)	−0.1 (−0.2, 0.02)	0.1 (−0.1, 0.2)	0.2 (−0.01, 0.4)	0.06
Femur bone mineral density (g/cm^2)				
Baseline, mean (SD)	0.981 (0.161)	0.967 (0.146)		
9 Months, mean (SD)	0.982	0.961		
Absolute change (SD)	0.001 (0.03)	−0.006 (0.023)		
Percent change (LS Mean 95% CI)	0.1 (−1.29, 1.57)	−0.7 (−2.19,0.76)	−0.9 (−0.01, 0.36)	0.66
Femur T-score**				
Baseline, mean (SD)	−0.5 (1.2)	−0.3 (0.8)		
9 Months, mean (SD)	−0.4 (1.2)	−0.3 (0.8)		
Absolute change (LS Mean, 95% CI)	0.0(−0.1, 0.1)	−0.1 (−0.2, 0.04)	−0.1 (−0.3, 0.04)	0.15
Femur Z-score††				
Baseline, mean (SD)	−0.4 (1.2)	−0.1 (0.7)		
9 Months, mean (SD)	−0.4 (1.2)	−0.2 (0.7)		
Absolute change (LS Mean, 95% CI)	0.0 (−0.1, 0.1)	0.0 (−0.1, 0.1)	0.0 (−0.2, 0.1)	0.57

*Change from baseline was analyzed using ANCOVA methods evaluating differences in least squares mean, adjusted for treatment group, baseline spleen severity group and a continuous variable for the baseline observation. Means and SDs are calculated arithmetically, unless specifically noted to be least-square means calculated using the ANCOVA methods.

†Normal ranges: chitotriosidase: <15 to 181 nmol/hr/mL; GL-1: <2.0 to 6.6 μg/mL; GM3 = 5 to 21 μg /mL; MIP-1β = 27.3 to 77.2 pg/mL; Ceramide = 1.8 to 6.5 μg/mL; Sphingomyelin ≥200 to 703 μg/mL. Chitotriosidase values were set equal to zero for one patient with a homozygous *CHIT1* null mutation expected to result in inactive enzyme and were doubled for six patients who were heterozygous for the *CHIT1* null mutation. Percentage change not calculated for the patient with the homozygous *CHIT1* mutation.

§BMB Score is the sum of spine and femur BMB scores (each ranging from 0–8) and categorized as follows: 0 to 4, mild; 5 to 8, moderate; and 9 to 16, marked to severe.

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

††Z-score bone density categories: normal (score > −2) and below normal (score ≤ −2). T-scores reported only for patients with data at both baseline and specified time point; (n=18 for placebo; n=17 for eliglustat).

Table 6

Summary of Treatment-Emergent Adverse Events

Parameter	Placebo (N=20)		Eliglustat (N=20)	
	No. of patients	No. of events	No. of patients	No. of events
Adverse events (AE)	14	95	18	137
Serious adverse events (SAE)	0	0	0	0
Medical events of interest (MEOI) *	1	1	0	0
Treatment-related AEs	9	25	8	31
AE-related withdrawals	0	0	0	0
Severity of AEs				
Mild	14	85	16	94
Moderate	6	10	15	43
Severe	0	0	0	0
AEs in ≥ 10% of patients (listed alphabetically)	No. of patients (%)	No. of events	No. of patients (%)	No. of events
Abdominal pain	2 (10)	2	1 (5)	1
Arthralgia	2 (10)	4	9 (45)	11
Contusion	3 (15)	3	2 (10)	4
Cough	2 (10)	2	0 (0)	0
Diarrhea	4 (20)	5	3 (15)	6
Dizziness	2 (10)	2	1 (5)	2
Fatigue	2 (10)	2	1 (5)	2
Flatulence	1 (5)	1	2 (10)	3
Headache	6 (30)	13	8 (40)	23
Influenza	2 (10)	2	0 (0)	0
Migraine	0 (0)	0	2 (10)	2
Nasal obstruction	0 (0)	0	2 (10)	3
Nasopharyngitis	0 (0)	0	3 (15)	3
Nausea	1 (5)	1	2 (10)	2
Oropharyngeal pain	1 (5)	1	2 (10)	2
Pruritus	2 (10)	3	0 (0)	0
Pyrexia	0 (0)	0	2 (10)	2
Sinusitis	1 (5)	1	2 (10)	2
Toothache	3 (15)	3	1 (5)	2
Vomiting	2 (10)	2	1 (5)	1
Upper respiratory tract infection	4 (20)	4	1 (5)	1

* 1 MEOI (nonsustained ventricular tachycardia) reported in 1 patient in the placebo group; none reported for eliglustat