Original Investigation

Effect of Oral Eliglustat on Splenomegaly in Patients With Gaucher Disease Type 1
The ENGAGE Randomized Clinical Trial

Pramod K. Mistry, MD, PhD, FRCP; Elena Lukina, MD; Hadhami Ben Turkia, MD; Dominick Amato, MD; Hagit Baris, MD; Majed Dasouki, MD; Marwan Ghosn, MD; Atul Mehta, MD; Seymour Packman, MD; Gregory Pastores, MD; Milan Petakov, MD; Sarit Assouline, MD; Manisha Balwani, MD, MS; Sumita Danda, DM; Evgueniy Hadjiev, MD; Andres Ortega, MD; Suma Shankar, MD, PhD; Maria Helena Solano, MD; Leorah Ross, MD, PhD; Jennifer Angell, SCM; M. Judith Peterschmitt, MD

IMPORTANCE Gaucher disease type 1 is characterized by hepatosplenomegaly, anemia, thrombocytopenia, and skeletal disease. A safe, effective oral therapy is needed.

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

DESIGN, SETTING, AND PARTICIPANTS Phase 3, randomized, double-blind, placebo-controlled trial conducted at 18 sites in 12 countries from November 2009 to July 2012 among eligible patients with splenomegaly plus thrombocytopenia and/or anemia. Of 72 patients screened, 40 were enrolled.

INTERVENTIONS Patients were stratified by spleen volume and randomized 1:1 to receive eliglustat (50 or 100 mg twice daily; n = 20) or placebo (n = 20) for 9 months.

MAIN OUTCOMES AND MEASURES The primary efficacy end point was percentage change in spleen volume in multiples of normal from baseline to 9 months; secondary efficacy end points were change in hemoglobin level and percentage changes in liver volume and platelet count.

RESULTS All patients had baseline splenomegaly and thrombocytopenia (mostly moderate or severe), most had mild or moderate hepatomegaly, and 20% had mild anemia. Least-square mean spleen volume decreased by 27.77% (95% CI, −32.57% to −22.97%) in the eliglustat group (from 13.89 to 10.17 multiples of normal) vs an increase of 2.26% (95% CI, −2.54% to 7.06%) in the placebo group (from 12.50 to 12.84 multiples of normal) for an absolute treatment difference of −30.03% (95% CI, −36.82% to −23.24%; $P < .001$). For the secondary end points, the least-square mean absolute differences between groups all favored eliglustat, with a 1.22-g/dL increase in hemoglobin level (95% CI, 0.57-1.88 g/dL; $P < .001$), 6.64% decrease in liver volume (95% CI, −11.37% to −1.91%; $P = .007$), and 41.06% increase in platelet count (95% CI, 23.95%-58.17%; $P < .001$). No serious adverse events occurred. One patient in the eliglustat group withdrew (non–treatment related); 39 of the 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.

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Author Affiliations: Author affiliations are listed at the end of this article.

Corresponding Author: Pramod K. Mistry, MD, PhD, FRCP, Yale University School of Medicine, 333 Cedar St, New Haven, CT 06520 (pramod.mistry@yale.edu).

In Gaucher disease type 1, biallelic mutations in *GBA* (OMIM 606463) result in defective acid β-glucosidase (glucocerebrosidase) and cause lysosomal accumulation of glucosylceramide and glucosylsphingosine, primarily in the monocyte-macrophage cell lineage.[1] Consequently, lipid-laden macrophages (Gaucher cells) infiltrate spleen, liver, bone marrow, and lungs, leading to hepatosplenomegaly, pancytopenia, skeletal disease, chronic bone pain, and growth failure. Patients exhibit high clinical variability.[2]

Untreated Gaucher disease type 1 is a chronic and progressive disorder associated with 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 Gaucher disease type 1[1,3,4] but requires lifelong biweekly intravenous infusions. Moreover, systemwide involvement beyond the monocyte-macrophage system may underlie unmet treatment needs in bone, lung, and the immune system.[5]

Eliglustat, a novel oral substrate reduction therapy (SRT), was recently approved by the US Food and Drug Administration and the European Commission for use in Gaucher disease type 1.[6] Whereas ERT supplements acid β-glucosidase activity in the lysosomes of mononuclear phagocytes, eliglustat is a ceramide analog that is a potent and specific inhibitor of glucosylceramide synthase (IC_{50} = 24 nM [concentration of drug needed to inhibit enzyme activity by 50%]), thereby reducing glucosylceramide production to match its impaired rate of degradation.[6] The first oral SRT approved for Gaucher disease type 1 was miglustat. However, its risk-benefit profile and tolerability issues restrict it to second-line therapy for a small subset of adults with mild or moderate Gaucher disease type 1 in whom ERT is not an option.[7-9]

BMB *bone marrow burden*
BMD *bone mineral density*
ERT *enzyme replacement therapy*
MRI *magnetic resonance imaging*
SRT *substrate reduction therapy*

In an uncontrolled phase 2 trial of 26 untreated adult patients with Gaucher disease type 1, eliglustat reduced glucosylceramide accumulation and ameliorated major disease manifestations.[10-12] We report the results of ENGAGE, a randomized, double-blind, placebo-controlled trial designed to determine the effect of eliglustat on spleen volume, hemoglobin level, liver volume, and platelet count in untreated patients with Gaucher disease type 1 and splenomegaly.

Methods

Patient Eligibility

Eligibility criteria included age 16 years or older, Tanner stage 4 or higher, a diagnosis of Gaucher disease type 1 confirmed by deficient activity of acid β-glucosidase in blood leukocytes and/or *GBA* mutation analysis, and major clinical manifestations of the disease as defined by (1) hemoglobin level of 8.0 to 11.0 g/dL (women/girls) or 8.0 to 12.0 g/dL (men/boys) and/or platelet count of 50 to 130 × 10^9/L based on the mean of 2 screening measurements obtained at least 24 hours apart; (2) splenomegaly with spleen volume 6 to 30 multiples of normal (normal spleen volume = 0.2% of body weight[3]); and (3) if hepatomegaly was present, liver volume less than 2.5 multiples of normal (normal liver volume = 2.5% of body weight[3]).[2,13] 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 with treatment within 3 months prior to randomization.

Written informed consent was obtained from each patient 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 (available in Supplement 1) was reviewed and approved by the institutional review board or independent ethics committee at each study site.

Study Drug

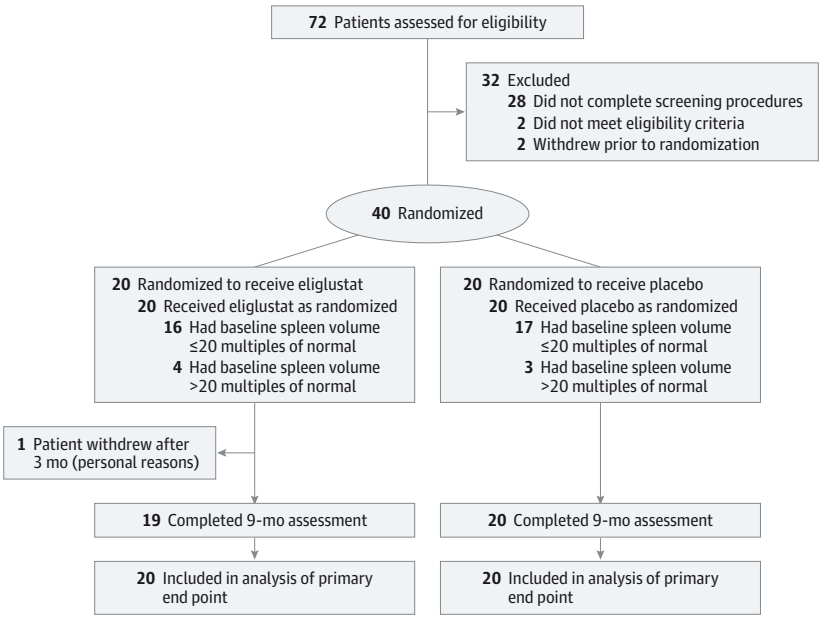
Patients were randomized to receive either eliglustat tartrate (previously Genz-112638, Genzyme) or a placebo capsule containing 50% microcrystalline cellulose (Avicel PH101) and 50% lactose monohydrate USP/Ph-Eur.

Study Design

A placebo-controlled trial design was chosen to minimize patient and physician bias and provide the clearest determination of the magnitude of the treatment effect and tolerability in treatment-naive patients. A 9-month study with change in spleen volume as the primary end point was considered acceptable to assess clinical efficacy and minimize the risk of acute or irreversible deterioration in patients receiving placebo, who were eligible to receive eliglustat during the trial's open-label extension. A study with ERT as the comparator would have required at least twice as many treatment-naive patients and posed prohibitive enrollment challenges given the rarity and heterogeneity of Gaucher disease and the commercial availability of effective treatment. Furthermore, a separate trial, now completed, was undertaken comparing imiglucerase with eliglustat in adults whose Gaucher disease type 1 had been stabilized by 3 years or longer of ERT (ENCORE; clinicaltrials.gov identifier: NCT00943111).

Eligible patients were stratified by spleen volume (≤20 vs >20 multiples of normal) to ensure that treatment groups were balanced with respect to number of patients with very large spleens, then randomized 1:1 to receive 9 months of treatment with eliglustat or placebo (**Figure 1**). The complete randomization list was computer generated prior to enrollment of the first patient in blocks of 4 within strata of spleen volume and was delivered using a central interactive voice response or interactive web response system administered by the sponsor's Clinical Pharmacy Research Services. Blinded study

Figure 1. Flow of Participants in the ENGAGE Trial



medication kits were provided to each patient. Dose adjustment based on eliglustat pharmacokinetic results (described 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, patients in the eliglustat group 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 of 5 ng/mL or higher continued to receive 50 mg twice daily; the dose was increased to 100 mg twice daily if the 2-week trough concentration was lower than 5 ng/mL. This dosing regimen was selected based on results of a phase 2 study of eliglustat in patients with Gaucher disease type 1.[10] To maintain the blind, patients were administered 2 identical-appearing capsules twice daily of placebo, placebo plus eliglustat tartrate (50-mg dose), or eliglustat tartrate alone (100-mg dose).

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

Study Assessments

The primary efficacy end point was the least-square mean percentage change in spleen volume by magnetic resonance imaging (MRI) from baseline to 9 months in the eliglustat group compared with the placebo group. An independent core laboratory (BioClinica, Newtown, Pennsylvania) performed central blinded analysis of all imaging data. Secondary efficacy end points were the between-group absolute differences in change in hemoglobin level, percentage change in liver volume by MRI, and percentage change in platelet count from baseline to 9 months. Tertiary efficacy end points included the percentage or absolute change from baseline to 9 months in activity of the serum biomarker chitotriosidase (*CHIT1* [OMIM 600031]; chitotriosidase genotypes were established for all patients with respect to the common 24-base pair duplication at baseline so that values could be normalized or excluded for analysis)[14-16]; spine and femur bone mineral density (BMD) expressed in grams per square centimeter, T score, and *z* score; bone marrow burden (BMB) score (lumbar spine plus femur); Gaucher disease assessments (mobility, bone crises, and bone pain); and quality-of-life scores (Brief Pain Inventory,[17-19] Fatigue Severity Scale,[20,21] and 36-Item Short Form Health Survey).[22] The MRI-based 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.[23,24] Exploratory efficacy end points included a Gaucher disease severity scoring system,[25] a validated overall disease severity score, and investigational plasma biomarker measurements, including glucosylceramide, GM3 ganglioside, ceramide, sphingomyelin, and macrophage inflammatory protein 1β.

Safety assessments included continuous monitoring of adverse events with characterization by severity, relatedness to treatment, seriousness, and medical events of interest from the time of informed consent through completion of the safety follow-up period (30-37 days after the last dose of study drug). Medical events of interest were defined as clinically significant cardiac arrhythmias detected by electrophysiological monitoring that did not meet serious adverse event criteria as well as syncope due to any cause irrespective of seriousness criteria. Other safety assessments included 12-lead electrocardiography; 24-hour dual-lead Holter monitoring; physical ex-

aminations; body weight, body mass index, and vital sign measurements; neurological examinations; the Mini-Mental State Examination; and standard clinical laboratory tests (ie, hematology, serum chemistry, urinalysis). Plasma eliglustat concentrations were measured for pharmacokinetic analysis as described previously.[26]

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 disease assessments, and quality-of-life assessments at weeks 26 and 39; and neurologic examination, Mini-Mental State Examination, Gaucher disease severity score, echocardiogram, spine x-ray, and dual-energy x-ray absorptiometry 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. Ethnicity information is relevant in Gaucher disease because of the 50-fold greater incidence in Ashkenazi Jewish individuals related to the high carrier frequency of the N370S mutation.[27]

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 end point using a 2-sided, 2-sample *t* test with an α=.05 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 the treatment response, the primary efficacy end-point analysis was performed in the intention-to-treat population with the last-value-carried-forward method using an analysis-of-covariance model fitted with treatment and baseline spleen severity and an α=.05 level of significance. Analysis of covariance uses least-square 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 an α=.05 level of significance. If the primary end point was met, sequential testing of the secondary end points using the same analysis of covariance method was permitted in a prespecified order (hemoglobin level, liver volume, platelet count), which required demonstration of statistical significance of each preceding end point. For all efficacy end points, significance testing was 2-sided and the last-value-carried-forward method was used if a result at 9 months was unavailable. Safety analyses were performed for all patients who received at least 1 dose of placebo or eliglustat. Analyses were performed using SAS software, version 9.0 or higher (SAS Institute Inc).

Results

Patient Characteristics

For this multinational study, 72 patients were screened at 26 centers in 18 countries during a 2-year enrollment period. Of these, 40 met the inclusion criteria and were randomized 1:1 to receive eliglustat (n = 20) or placebo (n = 20) 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 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 5% of the eliglustat group, were carried forward from the patient's last visit at 3 months for all efficacy analyses; because spleen and liver volumes were measured only at baseline and at 6 and 9 months, the baseline values were carried forward for these measures. The remaining 39 patients had both baseline and 9-month data for all primary and secondary end points.

Baseline demographics and patient characteristics are shown in **Table 1**. eTable 1 in Supplement 2 summarizes the Gaucher (*GBA*) and chitotriosidase (*CHIT1*) genotypes for all patients. The study population included equal numbers of male and female patients, was predominantly white 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 (hemoglobin <12 g/dL [male] or <11 g/dL [female]) 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 had similar *GBA* mutations (eTable 1 in Supplement 2) and residual acid β-glucosidase activity. Five patients (eliglustat, n=2; placebo, n=3) had received prior ERT with imiglucerase or alglucerase; 4 of these patients (eliglustat, n=1; placebo, n=3) had also received prior SRT with miglustat (none was received within 9 months [ERT] or 6 months [SRT] before randomization).

Adherence to the assigned treatment regimen was at least 90% in all but 3 patients: 2 in the placebo group (adherence, 80.3% and 86.3%) and 1 in the eliglustat group (adherence, 61.6%).

Primary End Point

Changes in the primary and secondary efficacy end points from baseline to 9 months are shown in **Figure 2** and **Figure 3** and eTable 2 in Supplement 2. Mean spleen volume (primary end point; Figure 2) decreased by 27.77% (95% CI, −32.57% to −22.97%) in the eliglustat group (from 13.89 to 10.17 multiples of normal) in contrast to an increase of 2.26% (95% CI, −2.54% to 7.06%) in the placebo group (from 12.50 to 12.84 multiples of normal) for an absolute treatment difference of −30.03% (95% CI, −36.82% to −23.24%; $P < .001$).

Table 1. Demographics and Baseline Patient Characteristics

Characteristics	Eliglustat (n = 20)	Placebo (n = 20)
Age at study day 1, mean (SD), y	31.6 (11.55)	32.1 (11.26)
Sex, No. (%)		
Male	8 (40)	12 (60)
Female	12 (60)	8 (40)
Race/ethnicity, No. (%)		
White, Ashkenazi Jewish	3 (15)	8 (40)
White, non-Ashkenazi Jewish	14 (70)	12 (60)
Hispanic	2 (10)	0
Asian	1 (5)	0
Acid β-glucosidase activity, nmol/h/mg[a]		
Mean (SD)	2.29 (3.38)	2.04 (3.79)
Median (range)	1.40 (0.0 to 15.7)	0.50 (0.0 to 15.5)
Spleen volume, multiples of normal		
Mean (SD)	13.89 (5.93)	12.50 (5.96)
Median (range)	12.09 (5.94 to 28.39)	11.05 (6.32 to 25.27)
Liver volume, multiples of normal		
Mean (SD)	1.44 (0.35)	1.36 (0.28)
Median (range)	1.36 (0.93 to 2.18)	1.29 (0.93 to 1.98)
Hemoglobin level, g/dL		
Mean (SD)	12.1 (1.8)	12.8 (1.6)
Median (range)	12.1 (8.15 to 15.25)	12.9 (9.65 to 16.30)
Platelet count, $\times 10^9$/L		
Mean (SD)	75.05 (14.10)	78.48 (22.61)
Median (range)	78.75 (50.5 to 98.5)	76.25 (50.5 to 128.5)
Chitotriosidase activity, nmol/h/mL[a,b]		
Mean (SD)	13 313 (8151)	11 118 (8313)
Median (range)	14 229 (2298 to 35 106)	11 031 (724 to 35 960)
Plasma glucosylceramide, μg/mL[a]		
Mean (SD)	12.7 (4.8)	9.6 (3.8)
Median (range)	11.7 (6.3 to 27.9)	8.4 (5.6 to 18.4)
Bone marrow burden score[c]		
Mean (SD)	10.9 (2.6)	9.8 (2.8)
Median (range)	10.8 (6.0 to 16.0)	9.5 (4.7 to 16.0)
Lumbar spine bone mineral density T score[d]		
Mean (SD)	−1.1 (0.8)	−1.1 (1.2)
Median (range)	−1.2 (−2.3 to 0.6)	−1.2 (−3.2 to 1.6)
Femur bone mineral density T score[d]		
Mean (SD)	−0.3 (0.8)	−0.5 (1.2)
Median (range)	−0.4 (−1.5 to 1.3)	−0.6 (−2.4 to 2.3)

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

[b] Normalized chitotriosidase values; values were doubled for 6 patients with a heterozygous chitotriosidase genotype and excluded for 1 eliglustat patient with a homozygous mutation and no expected chitotriosidase activity.[14-16]

[c] Bone marrow burden score is the sum of lumbar spine and femur bone marrow burden scores and ranges as follows: 0-4, mild; 5-8, moderate; 9-16: marked to severe.[23,24]

[d] For placebo, n = 18; for eliglustat, n = 17; 2 placebo and 2 eliglustat patients were excluded from T-score analyses because they were younger than 19 years and had no normative data; 1 additional eliglustat patient had no baseline bone mineral density value.

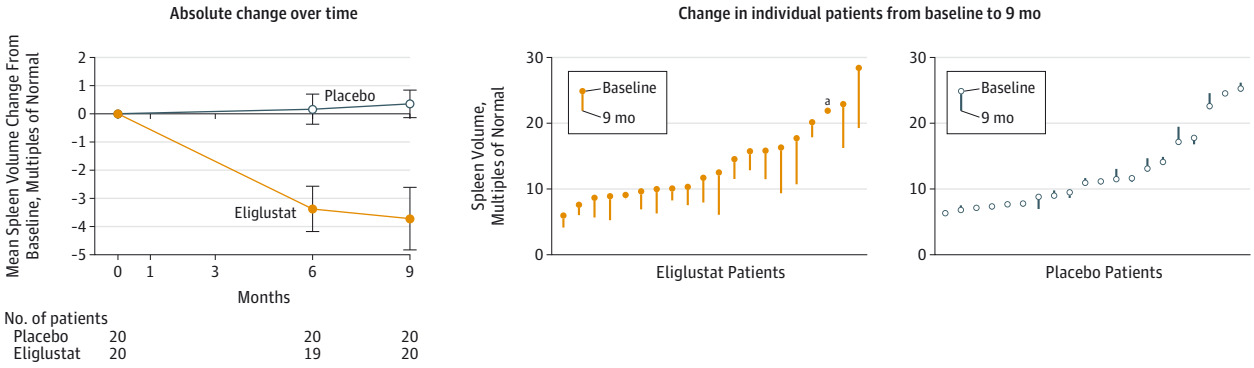
Secondary End Points

Mean hemoglobin level 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 absolute treatment difference of 1.22 g/dL (95% CI, 0.57-1.88 g/dL; $P < .001$). Mean liver volume decreased in the eliglustat group (−5.2%) and increased in the placebo group (+1.4%) for an absolute treatment difference of −6.64% (95% CI, −11.37% to −1.91%; $P = .007$). Mean platelet count increased in the eliglustat group (+32.0%) and decreased in the placebo group (−9.1%), resulting in an absolute treatment difference of 41.06% (95% CI, 23.95%-58.17%; $P < .001$). As shown in Figure 3, the largest improvements tended to be seen in the most severely affected patients.

Tertiary and Exploratory End Points

Outcomes related to tertiary and exploratory bone and biomarker end points are shown in **Table 2**. Eliglustat treatment resulted in a statistically significant improvement in mean total BMB score and there was no change in the placebo treatment group, for an absolute decrease of 1.1 (95% CI, −1.7 to −0.4; $P = .002$). Other markers of bone disease, including BMD, showed no significant change (Table 2). All disease-related biomarkers reflecting different aspects of Gaucher disease pathophysiology showed mean reductions with eliglustat treatment compared with placebo, except for sphingomyelin, which increased slightly but remained in the normal range, due to increased bioavailability of ceramide with treatment (Table 2).

Figure 2. Changes in the Primary End Point of Spleen Volume in the Intention-to-Treat Population



For absolute mean changes in spleen volume, error bars indicate 95% CIs. For individual baseline and 9-month values for each patient, patients are ordered in each graph from the lowest to the highest baseline value. Mean baseline values for spleen volume were as follows: for eliglustat, 13.9 multiples of normal, and placebo, 12.5 multiples of normal.

[a] Indicates the single patient who withdrew from the trial; this patient in the eliglustat group withdrew for personal reasons at 3 months and had no 6-month or 9-month assessments. For the final efficacy assessments, change for this patient was determined by last observation carried forward; thus, for spleen volume, the baseline value was carried forward.

These included a biomarker of Gaucher cells (tertiary end point of chitotriosidase, −44.4%; 95% CI, −64.1% to −24.8%; $P < .001$), biomarkers of substrate accumulation (the exploratory end points of plasma glucosylceramide [−66.9%; 95% CI, −78.2% to −55.5%; $P < .001$] and GM3 ganglioside [−46.3%; 95% CI, −61.6% to −31.0%; $P < .001$]), and a biomarker of inflammation (exploratory end point of macrophage inflammatory protein 1β, −43.5%; 95% CI, −55.8% to −31.2%; $P < .001$]).

With respect to Gaucher disease assessments, most patients in both treatment groups had unrestricted mobility and minimal or mild bone pain at baseline and at 9 months (eTable 3 in Supplement 2). Quality-of-life analyses showed few significant treatment-related changes in this 9-month trial (eTable 4 in Supplement 2). There was a mean improvement in the 36-Item Short Form Health Survey physical functioning domain with eliglustat (75.3 to 79.0) compared with placebo (88.3 to 77.8), for an absolute treatment difference of 13.2 (95% CI, 0.45 to 26.01; $P = .01$); changes in the other 9 domains did not reach statistical significance. There was a statistically significant mean improvement in the Fatigue Severity Scale score in the placebo group (3.53 to 2.96), which was attributable to large decreases in two patients, compared to no change in the eliglustat group (3.84 to 3.87), for an absolute treatment difference of 0.7 (95% CI, 0.02 to 1.33; $P = .04$).

The exploratory end point of Gaucher disease severity score (eTable 5 in Supplement 2) showed a small but statistically significant mean reduction with eliglustat (from 4.70 to 4.24) compared with placebo (from 4.43 to 4.37), for an absolute treatment difference of −0.3 (95% CI, −0.67 to −0.01; $P = .045$).

Safety Analyses

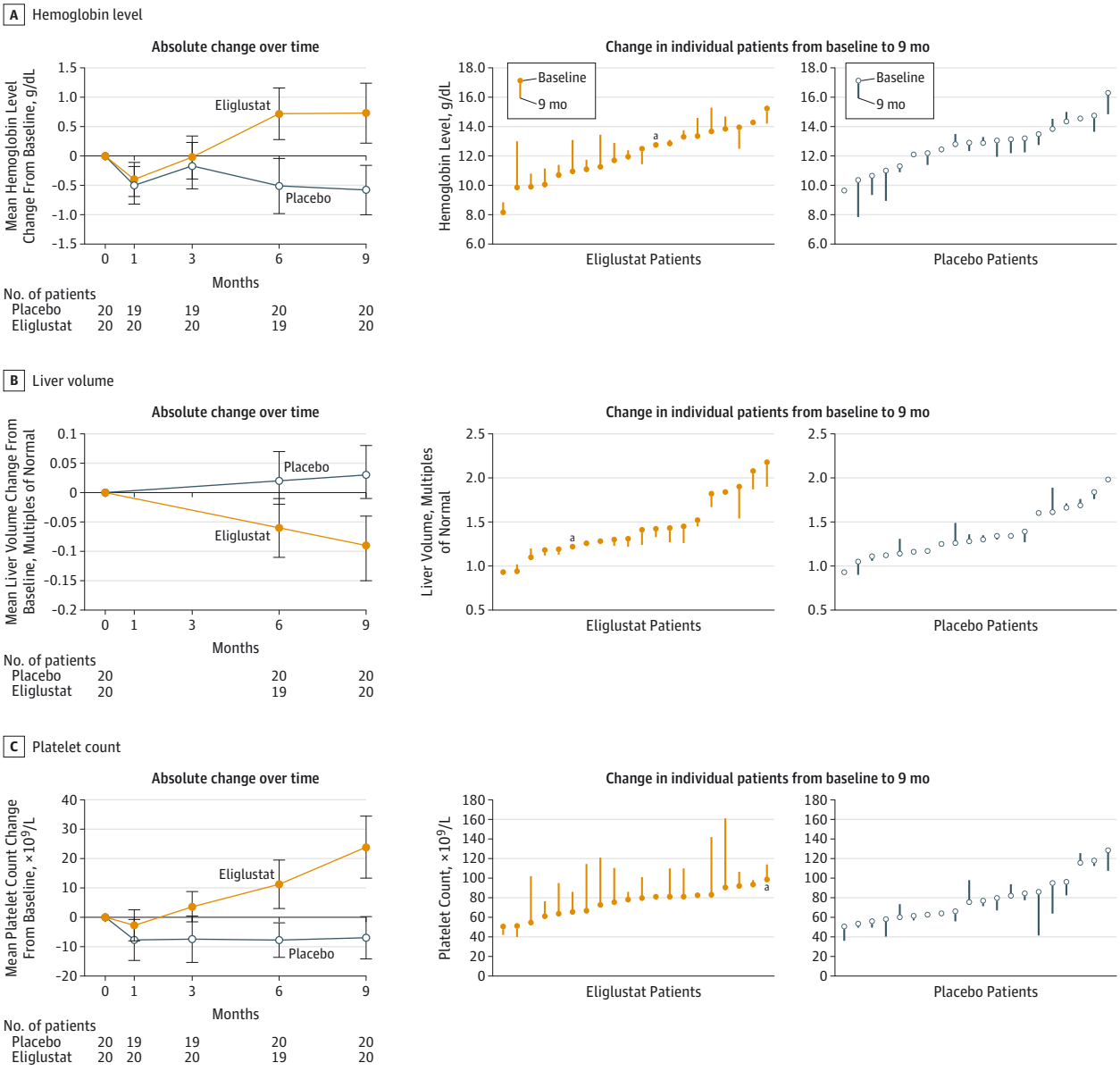
Adverse events are summarized in **Table 3**. There were no deaths or serious adverse events, and no patients discontinued treatment because of a treatment-emergent adverse event. All treatment-emergent adverse events were graded as mild or moderate, and most were considered by the investigator to be unrelated to the study drug. One medical event of interest consisting of mild, nonsustained ventricular tachycardia was reported in a patient in the placebo group. Arthralgia, nasopharyngitis, headache, migraine, nasal obstruction, and pyrexia occurred in at least 10% more patients receiving eliglustat (≥2 patients) than receiving placebo. No patients in either group had clinically significant worsening in any non-disease-related laboratory measurements, vital signs, echocardiogram findings, or neurologic examination findings. Mean Mini-Mental State Examination scores at baseline and 9 months did not differ between treatment groups.

Discussion

Eliglustat, orally administered for 9 months, resulted in a statistically significant and clinically meaningful absolute reduction in spleen volume of approximately 30% compared with placebo, as well as statistically significant absolute 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 (glucosylceramide and GM3 ganglioside). Moreover, chitotriosidase, a serum biomarker indicative of the bodily burden of Gaucher cells, was substantially reduced, as was macrophage inflammatory protein 1β, an inflammatory biomarker secreted by phagocytic cells surrounding Gaucher cells.[14] No patient discontinued treatment over the course of the 9-month study because of a treatment-emergent adverse event.

Eliglustat differs from the oral SRT miglustat, a second-line therapy for Gaucher disease type 1, in its structural and pharmacologic properties. Eliglustat resembles the ceramide moiety of glucosylceramide and is a potent and highly specific inhibitor of glucosylceramide synthase (in vitro IC_{50} = 24 nM).[28] Miglustat, an *N*-butyl iminosugar, resembles the glucose moiety of glucosylceramide and is a

Figure 3. Changes in the Secondary End Points of Hemoglobin Level, Liver Volume, and Platelet Count in the Intention-to-Treat Population



For absolute mean changes in hemoglobin level, liver volume, and platelet count, error bars indicate 95% CIs. For individual baseline and 9-month values for each patient, patients are ordered in each graph from the lowest to the highest baseline value. Mean baseline values were as follows: for hemoglobin level, eliglustat, 12.1 g/dL, and placebo, 12.8 g/dL; for liver volume, eliglustat, 1.4 multiples of normal, and placebo, 1.4 multiples of normal; for platelet count, eliglustat, 75 × 10^9/L, and placebo, 79 × 10^9/L.

[a] Indicates the single patient who withdrew from the trial; this patient in the eliglustat group withdrew for personal reasons at 3 months and had no 6-month or 9-month assessments. For the final efficacy assessments, change for this patient was determined by last observation carried forward; thus, for liver volume, the baseline value was carried forward, and for hemoglobin level and platelet count, the 3-month value was carried forward.

nonspecific and weak inhibitor of glucosylceramide synthase (in vitro IC_{50} = 50 µM).[29] In addition, miglustat crosses the blood-brain barrier whereas eliglustat effectively does not. Miglustat is known to inhibit a wide range of glucosidases with a resultant high incidence of gastrointestinal disturbance and new neurologic symptoms,[7,9,30] which have been linked to poor tolerability in clinical studies.[9,30,31]

In this cohort with Gaucher disease type 1 and substantial disease manifestations, the slight decrease 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.

Table 2. Changes in Bone and Biomarker End Points From Baseline to 9 Months

End-Point Measures	Eliglustat (n = 20)	Placebo (n = 20)	Difference[a]	*P* Value
Tertiary end points				
Bone marrow burden score[b]	(n = 20)	(n = 20)		
Baseline, mean (SD)	10.9 (2.6)	9.8 (2.8)		
9 mo, mean (SD)	9.8 (2.6)	9.8 (2.8)		
Absolute change, LS mean (95% CI)	−1.1 (−1.5 to −0.6)	0.0 (−0.5 to 0.5)	−1.1 (−1.7 to −0.4)	.002
Lumbar spine bone mineral density, g/cm^2	(n = 19)[c]	(n = 20)		
Baseline, mean (SD)	0.991 (0.172)	1.037 (0.152)		
9 mo, mean (SD)	0.995 (0.160)	1.027 (0.151)		
Absolute change (SD)	0.004 (0.031)	−0.010 (0.039)		
% Change, LS mean (95% CI)	0.4 (−1.17 to 2.0)	−0.8 (−2.38 to 0.71)	1.2 (−0.97 to 3.47)	.26
Lumbar spine T score[d]	(n = 17)[c,e]	(n = 18)[e]		
Baseline, mean (SD)	−1.1 (0.8)	−1.1 (1.2)		
9 mo, mean (SD)	−1.0 (0.8)	−1.2 (1.1)		
Absolute change, LS mean (95% CI)	0.0 (−0.1 to 0.2)	−0.1 (−0.2 to 0.03)	0.1 (−0.1 to 0.3)	.14
Lumbar spine *z* score[f]	(n = 19)[c]	(n = 20)		
Baseline, mean (SD)	−1.1 (0.9)	−1.2 (1.2)	−0.7	
9 mo, mean (SD)	−1.1 (0.9)	−1.3 (1.2)		
Absolute change, LS mean (95% CI)	0.1 (−0.1 to 0.2)	−0.1 (−0.2 to 0.02)	0.2 (−0.01 to 0.4)	.06
Femur bone mineral density, g/cm^2	(n = 19)[c]	(n = 20)		
Baseline, mean (SD)	0.967 (0.146)	0.981 (0.161)		
9 mo, mean (SD)	0.961 (0.149)	0.982 (0.163)		
Absolute change, mean (SD)	−0.006 (0.023)	0.001 (0.03)		
% Change, LS mean (95% CI)	−0.7 (−2.19 to 0.76)	0.1 (−1.29 to 1.57)	−0.9 (−0.01 to 0.36)	.66
Femur T score[d]	(n = 17)[c,e]	(n = 18)[e]		
Baseline, mean (SD)	−0.3 (0.8)	−0.5 (1.2)		
9 mo, mean (SD)	−0.3 (0.8)	−0.4 (1.2)		
Absolute change, LS mean (95% CI)	−0.1 (−0.2 to 0.04)	0.0 (−0.1 to 0.1)	−0.1 (−0.3 to 0.04)	.15
Femur *z* score[f]	(n = 18)[c]	(n = 20)		
Baseline, mean (SD)	−0.1 (0.7)	−0.4 (1.2)		
9 mo, mean (SD)	−0.2 (0.7)	−0.4 (1.2)		
Absolute change, LS mean (95% CI)	0.0 (−0.1 to 0.1)	0.0 (−0.1 to 0.1)	0.0 (−0.2 to 0.1)	.57
Serum chitotriosidase activity, nmol/h/mL[g]	(n = 19)[h]	(n = 20)		
Baseline, mean (SD)	12 648 (8473)	11 118 (8313)		
9 mo, mean (SD)	8204 (6340)	10 950 (7345)		
Absolute change, mean (SD)	−4677 (3658)	−167 (3333)		
% Change, LS mean (95% CI)	−39.0 (−53.0 to −25.0)	5.4 (−8.3 to 19.0)	−44.4 (−64.1 to −24.8)	<.001

(continued)

Table 2. Changes in Bone and Biomarker End Points From Baseline to 9 Months (continued)

End-Point Measures	Eliglustat (n = 20)	Placebo (n = 20)	Difference[a]	*P* Value
Exploratory end points				
Plasma glucosylceramide, μg/mL[g]	(n = 20)	(n = 20)		
Baseline, mean (SD)	12.7 (4.8)	9.6 (3.8)		
9 mo, mean (SD)	3.5 (2.2)	8.9 (3.5)		
Absolute change, mean (SD)	−9.2 (3.5)	−0.6 (2.5)		
% Change, LS mean (95% CI)	−71.7 (−79.5 to −64.0)	−4.9 (−12.6 to 2.9)	−66.9 (−78.2 to −55.5)	<.001
Plasma GM3 ganglioside, μg/mL[g]	(n = 14)[i]	(n = 14)[i]		
Baseline, mean (SD)	27.7 (5.3)	22.6 (7.0)		
9 mo, mean (SD)	12.0 (6.4)	20.7 (4.6)		
Absolute change, mean (SD)	−15.7 (7.3)	−1.9 (4.7)		
% Change, LS mean (95% CI)	−54.0 (−64.4 to −43.7)	−7.7 (−18.1 to 2.7)	−46.3 (−61.6 to −31.0)	<.001
Plasma macrophage inflammatory protein 1β, pg/mL[g]	(n = 20)	(n = 20)		
Baseline, mean (SD)	277 (101)	287 (143)		
9 mo, mean (SD)	134 (76)	255 (120)		
Absolute change, mean (SD)	−143 (78)	−32 (58)		
% Change, LS mean (95% CI)	−51.6 (−60.3 to −42.9)	−8.0 (−16.7 to 0.6)	−43.5 (−55.8 to −31.2)	<.001
Plasma ceramide, μg/mL[g]	(n = 20)	(n = 20)		
Baseline, mean (SD)	3.5 (0.95)	3.6 (0.84)		
9 mo, mean (SD)	3.1 (0.68)	3.3 (1.08)		
Absolute change, mean (SD)	−0.4 (1.20)	−0.3 (1.12)		
% Change, LS mean (95% CI)	−4.7 (−16.9 to 7.5)	−3.2 (−15.4 to 9.0)	−1.5 (−18.7 to 15.8)	.86
Plasma sphingomyelin, μg/mL[g]	(n = 20)	(n = 20)		
Baseline, mean (SD)	247 (69.4)	234 (47.5)		
9 mo, mean (SD)	280 (50.2)	230 (39.4)		
Absolute change, mean (SD)	33 (78.8)	−4 (42.2)		
% Change, LS mean (95% CI)	21 (12.5 to 29.4)	−2 (−10.5 to 6.4)	23 (11 to 35)	<.001

[a] Change from baseline was analyzed using analysis-of-covariance methods evaluating differences in least-square (LS) means, 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 LS means calculated using the analysis-of-covariance methods. Only patients who had baseline data were included in these analyses; as specified in the Methods section of the text, last values were carried forward for the 1 eliglustat patient who withdrew from the trial at 3 months; all other patients with baseline data also had 9-month data.

[b] Bone marrow burden score is the sum of lumbar spine and femur bone marrow burden scores (each ranging from 0-8) and categorized as follows: 0-4, mild; 5-8, moderate; and 9-16, marked to severe.[23,24]

[c] One eliglustat patient lacked baseline bone mineral density data and is excluded from all bone mineral density analyses.

[d] T-score bone density categories: normal, score >−1; osteopenia, score −2.5 to ≤−1; and osteoporosis, score ≤−2.5.

[e] Two patients in each treatment group were younger than 19 years and were excluded from the lumbar spine and femur T-score analyses because normative data are not available for this age group.

[f] Bone density categories: normal, *z* score >−2; below normal, *z* score ≤−2.

[g] Normal ranges: chitotriosidase, <15 to 181 nmol/h/mL; glucosylceramide, <2.0 to 6.6 μg/mL; GM3 ganglioside, 5 to 21 μg/mL; macrophage inflammatory protein 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 1 patient with a homozygous *CHIT1* null mutation expected to result in inactive enzyme and were doubled for 6 patients who were heterozygous for the *CHIT1* null mutation.[14-16] Percentage change was not calculated for the patient with the homozygous *CHIT1* mutation.

[h] One eliglustat patient was omitted from the analysis because of a null mutation rendering the enzyme inactive.

[i] Baseline values are missing for 6 patients in each group because this assessment was added as a protocol amendment (amendment 3; February 25, 2010) after these patients had enrolled in the trial and had begun treatment.

Table 3. Summary of Treatment-Emergent Adverse Events

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

[a] One medical event of interest (nonsustained ventricular tachycardia) was reported in a patient in the placebo group; none were reported in the eliglustat group.

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 patients with Gaucher disease type 1 twice daily in 50-mg or 100-mg doses based on plasma drug concentrations.[10] The patients in the phase 2 study had more advanced Gaucher disease type 1 compared with the patients studied 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.[32] 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. Although, to our knowledge, ENGAGE is the first placebo-controlled trial in patients with Gaucher disease type 1 and the largest randomized trial in treatment-naive patients with Gaucher disease type 1 conducted to date, 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 end points and minimized the number of patients exposed to placebo. Because this was a 9-month study in untreated adult patients with Gaucher disease type 1, information about longer-term exposure or in different patient populations, including those whose disease is currently stabilized with ERT, cannot be extrapolated. Nine months is generally an insufficient follow-up period to observe changes in BMD, 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 increased 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 with placebo; however, the

Fatigue Severity Scale score improved in placebo patients and was unchanged in eliglustat patients. Longer-term treatment may result in improvements in other domains of quality of life in a population reporting a relatively small burden of quality-of-life impairment at baseline. This study was not designed to compare the efficacy of eliglustat with other therapies for Gaucher disease type 1. Although the improvements observed with eliglustat were consistent with what can be expected from ERT, further eliglustat studies, such as the ENCORE trial, are intended to assess how eliglustat compares with ERT in patients whose disease has been stabilized with 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 ERT as well as longer-term follow-up.

ARTICLE INFORMATION

Author Affiliations: Yale University School of Medicine, New Haven, Connecticut (Mistry); Hematology Research Center, Moscow, Russia (Lukina); Hôpital La Rabta, Tunis, Tunisia (Ben Turkia); Mount Sinai Hospital, Toronto, Ontario, Canada (Amato); Rabin Medical Center, Petach Tikvah, and Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel (Baris); University of Kansas Medical Center, Kansas City (Dasouki); Hôtel-Dieu de France University Hospital, Beirut, Lebanon (Ghosn); The Royal Free Hospital, London, England (Mehta); University of California, San Francisco, School of Medicine, San Francisco (Packman); New York University School of Medicine, New York, New York (Pastores); Clinical Center of Serbia, University of Belgrade School of Medicine, Belgrade, Serbia (Petakov); Jewish General Hospital, Montreal, Quebec, Canada (Assouline); Icahn School of Medicine at Mount Sinai Hospital, New York, New York (Balwani); Christian Medical College, Vellore, India (Danda); University Hospital Alexandrovska, Sofia, Bulgaria (Hadjiev); OCA Hospital, Monterrey, Mexico (Ortega); Emory University, Atlanta, Georgia (Shankar); Hospital de San Jose-Fundacion Universitaria de Ciencias de la Salud San Jose, Bogota, Colombia (Solano); Genzyme, Cambridge, Massachusetts (Ross, Angell, Peterschmitt).

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Study concept and design: Peterschmitt.
Acquisition, analysis, or interpretation of data: All authors.
Drafting of the manuscript: Mistry, Turkia, Hadjiev, Shankar, Angell, Peterschmitt.
Critical revision of the manuscript for important intellectual content: Mistry, Lukina, Amato, Baris, Dasouki, Ghosn, Mehta, Packman, Pastores, Petakov, Assouline, Balwani, Danda, Ortega, Shankar, Solano, Ross, Peterschmitt.
Statistical analysis: Angell.
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Administrative, technical, or material support: Amato, Baris, Dasouki, Ghosn, Mehta, Packman, Pastores, Balwani, Shankar, Ross.
Study supervision: Dasouki, Mehta, Petakov, Assouline, Shankar.

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