Received: 20 July 2018 | Revised: 20 September 2018 | Accepted: 24 September 2018

DOI: 10.1002/ajh.25300

WILEY AJH

RESEARCH ARTICLE

Outcomes after 8 years of eliglustat therapy for Gaucher disease type 1: Final results from the Phase 2 trial

Elena Lukina[1] | Nora Watman[2] | Marta Dragosky[3] | Heather Lau[4] | Elsa Avila Arreguin[5] | Hanna Rosenbaum[6] | Ari Zimran[7] | Meredith C. Foster[8] | Sebastiaan J. M. Gaemers[9] | M. Judith Peterschmitt[10]

[1]Department of Orphan Diseases, National Research Center for Hematology, Moscow, Russia

[2]Division of Hematology, Hospital Ramos Mejia, Buenos Aires, Argentina

[3]Department of Hematology, IMAI-Research, Buenos Aires, Argentina

[4]Department of Neurology, New York University School of Medicine, New York, New York

[5]Department of Hematology, Instituto Mexicano del Seguro Social Hospital de Especialidades, Col. La Raza, Mexico

[6]Hematology Department, Rambam Medical Center, Haifa, Israel

[7]Gaucher Clinic, Department of Medicine, Shaare Zedek Medical Center, Jerusalem, Israel

[8]Global Medical Communications, Sanofi Genzyme, Cambridge, Massachusetts

[9]Global Pharmacovigilance, Sanofi Genzyme, Naarden, The Netherlands

[10]Rare Diseases Clinical Development, Sanofi Genzyme, Cambridge, Massachusetts

Correspondence
M. Judith Peterschmitt, Sanofi Genzyme, 50 Binney Street, Cambridge, MA 02142.
Email: judith.peterschmitt@sanofi.com

Funding information
Sanofi Genzyme

Abstract

Eliglustat is a first-line oral therapy for adults with Gaucher disease type 1 (GD1) and poor, intermediate or extensive CYP2D6-metabolizer phenotypes (>90% of patients). We report the final results of a Phase 2 trial and extension (NCT00358150) in previously untreated adult GD1 patients who had splenomegaly with thrombocytopenia and/or anemia and received 50 or 100 mg eliglustat tartrate (equivalent to 42 or 84 mg eliglustat) twice daily for 8 years. In total, 19 of 26 patients completed the trial. After 8 years of eliglustat, mean spleen and liver volumes decreased by 69% and 34%, respectively. Mean hemoglobin concentration and platelet count increased by 2.2 g/dL and 113%, respectively. All patients met at least 3 of 4 therapeutic goals established for patients on long-term enzyme replacement therapy. Mean final values for patients with severe splenomegaly (n = 6), moderate-to-severe anemia (n = 6), or severe thrombocytopenia (n = 8) were similar to patients with milder disease at baseline and within long-term therapeutic goal thresholds. Biomarker median percent changes from baseline were -91% for chitotriosidase, -87% for CCL18, -92% for glucosylsphingosine, and -80% for plasma glucosylceramide. Mean lumbar spine T-score increased by 0.96, moving from the osteopenic to the normal range. Mean quality-of-life scores, mostly below normal at baseline, moved into ranges seen in healthy adults. Eliglustat was well-tolerated; 98% of adverse events were mild or moderate and 94% were considered unrelated to treatment. Clinically meaningful improvements in all parameters continued or were maintained over 8 years, with the largest margins of improvement seen in the most severely affected patients.

1 | INTRODUCTION

Eliglustat (Cerdelga, Sanofi Genzyme) is an oral substrate reduction therapy approved in many countries worldwide, including the United States, Europe, and Japan, as a first-line therapy for adults with Gaucher disease type 1 (GD1) who have poor, intermediate, or extensive CYP2D6-metabolizer phenotypes (>90% of patients[1,2]). In Gaucher disease, inherited mutations in the acid β-glucosidase gene (OMIM 606463) result in deficient activity of the enzyme acid β-glucosidase (glucocerebrosidase) and pathogenic accumulation of its substrates, primarily glucosylceramide, in the spleen, liver, bone marrow, and occasionally the lungs.[3,4] If untreated, substrate accumulation leads to hepatosplenomegaly, thrombocytopenia, anemia, skeletal disease, chronic bone pain, and growth failure (in children).[3] Eliglustat

works by partially inhibiting glucosylceramide synthase to reduce synthesis of its major substrate, glucosylceramide, thereby restoring balance between substrate production and degradation.

The safety, efficacy, and tolerability of eliglustat therapy have been demonstrated in Phase 3 trials of previously untreated GD1 patients, as well as patients previously treated with enzyme replacement therapy (ERT) infusions, the historical standard of care. In the ENGAGE randomized, double-blind, placebo-controlled trial, eliglustat therapy improved hematologic, visceral, and skeletal disease parameters relative to placebo in treatment-naïve patients after 9 months,[5] and these improvements continued with up to 4.5 years of eliglustat therapy in the open-label trial extension.[6,7] In the ENCORE trial of GD1 patients whose disease had been stable after a mean of 10 years on ERT, eliglustat was noninferior to imiglucerase ERT,[8] and the majority of patients maintained stable hematologic, visceral, and skeletal disease parameters for up to 4 years of eliglustat therapy.[9]

As Gaucher disease requires lifelong therapy, long-term safety and efficacy of therapies are of paramount importance. We report the final 8-year outcomes of previously untreated adults with GD1 who completed the open-label, Phase 2 trial of eliglustat (NCT00358150, Sanofi Genzyme). These data represent the longest eliglustat therapy experience to date. They build on the 1-year outcomes, in which the primary endpoint of improvement in at least 2 of the 3 main efficacy parameters (spleen volume, hemoglobin level, and platelet count) was met,[10] as well as the 2- and 4-year data showing sustained improvements in hematologic parameters, organ volumes, disease-related biomarkers, and measures of bone health.[11–13]

2 | METHODS

The full methodology, inclusion and exclusion criteria, and 1-year primary endpoint analysis of this Phase 2 trial were published previously.[10] In summary, adult GD1 patients who had splenomegaly with thrombocytopenia and/or anemia were enrolled between June 2006 and October 2007 and received 50 or 100 mg eliglustat tartrate (equivalent to 42 or 84 mg eliglustat) twice daily, dosed according to plasma trough levels. The primary endpoint was improvement from baseline after 1 year of eliglustat therapy in at least 2 of the 3 main efficacy parameters (spleen volume, hemoglobin level, and platelet count) that met inclusion criteria for abnormal at baseline. Following the 1-year primary analysis period, patients who entered the trial extension period had quarterly visits. Measurements of long-term efficacy parameters were assessed every 3 months (hemoglobin and platelets), 6 months (spleen volume, liver volume, Gaucher disease assessments for mobility, bone crisis, and bone pain), or annually (disease-related biomarkers, quality of life, and spine and femur bone mineral density) until the trial ended on December 30, 2015 or the patient withdrew from the trial. Blood samples for pharmacokinetic testing were obtained at 3, 9, 12, 15, 18, 21, and 24 months, and annually thereafter.

For this long-term analysis, efficacy endpoints included changes from baseline to 8 years in spleen and liver volumes, hemoglobin and platelet levels, disease-related biomarkers, skeletal disease markers, quality-of-life indices, and Gaucher Disease Severity Scoring System (DS3). Eight-year values were defined as the value measured closest to 8 years during follow-up, with a window of ±6 months (ie, 7.5-8.5 years). Spleen and liver volumes were measured in multiples of normal (MN) and derived from volumetric magnetic resonance imaging (MRI) or spiral computed tomography (CT) and reviewed by a central MRI/CT laboratory. Hemoglobin concentrations, platelet counts, and levels of the disease-related blood biomarkers glucosylceramide, glucosylsphingosine, chitotriosidase, and chemokine (C-C motif) ligand 18 (CCL18), were analyzed at central laboratories. Skeletal disease was assessed based on lumbar and femur bone mineral density (g/cm^2), T-scores, and Z-scores using dual-energy X-ray absorptiometry (DXA) and MRI. Quality-of-life indices included the 8 individual domain components from the Short Form-36 Health Survey (SF-36),[14] the Fatigue Severity Scale,[15] and the validated Gaucher DS3.[16,17] In addition, we evaluated the achievement at 8 years of therapeutic goals established for patients on long-term ERT: spleen volume ≤8 MN or ≥50% decrease from baseline; liver volume ≤1.5 MN or ≥30% decrease from baseline; hemoglobin ≥11.0 g/dL for women and ≥12.0 g/dL for men; and platelet count ≥120 × 10^9/L or double the baseline value for patients with platelet count <60 × 10^9/L at baseline.[18]

Long-term safety was assessed through continuous monitoring of adverse events during the 8-year follow-up period. Adverse events and serious adverse events are summarized and categorized based on severity and relatedness to eliglustat therapy.

Baseline demographic and clinical characteristics are summarized for all patients (n = 26) and separately for patients who completed the trial (n = 19) as counts with proportions for categorical characteristics and means with standard deviations (SD) for continuous characteristics (medians, 25th and 75th percentiles for biomarkers). Changes in each parameter over time are expressed as mean values with either SDs or standard error of the mean (SEM). Baseline and 8-year values for spleen volume, liver volume, hemoglobin, and platelet count are also analyzed in subgroups according to baseline disease severity, defined as: Splenomegaly: mild/moderate (spleen volume ≤15 MN) vs severe (spleen volume >15 MN); Hepatomegaly: mild (liver volume <1.25 MN) vs moderate/severe (liver volume ≥1.25 MN); Anemia: none/mild (hemoglobin ≥11 to <12 g/dL males; ≥10 to <11 g/dL females) vs moderate/severe (hemoglobin ≥9 to <11 g/dL males; ≥9 to <10 g/dL females); Thrombocytopenia: none/mild/moderate (platelet count ≥60 × 10^9/L) vs severe (platelet count <60 × 10^9/L).

3 | RESULTS

3.1 | Patients

Of 26 GD1 patients enrolled and treated with eliglustat in this trial, 22 completed the 1-year primary analysis and 20 entered the trial extension. Median time on eliglustat therapy for all patients was 8.5 years (range 1 day to 9.3 years). One patient was withdrawn after 2 years on eliglustat and the remaining 19 patients completed the trial after 7.5-9.3 years on treatment, depending on the date that each patient enrolled. Among these 19 patients, 4 received final twice-daily doses of 50 mg, 14 received 100 mg, and 1 received 150 mg. In total

TABLE 1 Baseline demographics and clinical characteristics

	All patients (*n* = 26)	Patients who completed the trial (*n* = 19)
Sex, *n* (%)		
Male	10 (38)	9 (47)
Female	16 (62)	10 (53)
Ethnicity, *n* (%)		
Caucasian, Ashkenazi Jewish	7 (27)	3 (16)
Caucasian, non-Jewish	16 (62)	14 (74)
Hispanic	3 (11)	2 (11)
Age at start of eliglustat (years)	34 ± 13 (19, 60)	34 ± 12 (19, 56)
Age at diagnosis (years)	24 ± 15 (6, 59)	24 ± 14 (6, 52)
Hemoglobin (g/dL)	11.1 ± 1.7 (8.1, 14.6)	11.3 ± 1.5 (8.8, 14.6)
Platelet count ($\times 10^9$/L)	66.4 ± 20.1 (39.0, 105.5[a])	68.7 ± 21.2 (39.0, 105.5)
Spleen volume (MN)	20.0 ± 12.8 (8.2, 59.7[a])	16.8 ± 9.5 (8.2, 49.2)
Liver volume (MN)	1.8 ± 0.6 (0.8, 3.9)	1.7 ± 0.5 (0.81, 2.47)
Chitotriosidase (normalized),[b,c] (nmol/hr/mL)	8543 (2081, 23 759)	8084 (3924, 23 759)
	n = 24	*n* = 17
Chemokine ligand 18 (CCL18),[c] (ng/mL)	3385 (1070, 6563)	3560 (1280, 6563)
	n = 24	*n* = 18
Plasma glucosylceramide (μg/mL)[c]	12.0 (5.9, 21.7)	12.15 (5.9, 21.7)
	n = 25	*n* = 18
Glucosylsphingosine (ng/mL)[c]	597 (146, 1570)	587 (146, 1570)
	n = 24	*n* = 17
Total Gaucher DS3 score	5.0 ± 2.2 (1.4, 9.0)	4.9 ± 2.4 (1.4, 9.0)

Abbreviations: DS3, Disease Severity Scoring System; MN, multiples of normal.
Unless otherwise noted, continuous characteristics are presented as mean values ± standard deviations (minimum, maximum) or median (minimum, maximum) and categorical characteristics as *n* (%).
[a] Exceptions were granted for some patients with baseline platelet counts and spleen volumes outside the range established for inclusion criteria.
[b] Excludes 2 patients with absent chitotriosidase (CHIT) activity due to a homozygous null mutation in the *CHIT1* gene.
[c] Normal ranges: chitotriosidase: <15-181 nmol/h/mL, chemokine ligand 18: 17-246 ng/mL, glucosylceramide: <2.0-6.6 μg/mL, glucosylsphingosine: <5 ng/mL.

7 of the 26 enrolled patients prematurely discontinued the trial: 3 due to adverse events, 1 of which was considered related to treatment; 3 due to pregnancy (2 during the first year, 1 after completion of the primary analysis period), and 1 for administrative reasons (patient was not able to continue in the trial under an amended protocol since the study site had not yet approved the amendment extending the trial beyond 2 years). As shown in Table 1, baseline demographic and clinical characteristics were similar for the 26 patients who entered the trial and the 19 patients who completed 8 years of eliglustat therapy. All but one patient had an extensive CYP2D6 metabolizer phenotype; the remaining patient (a trial completer) had a poor metabolizer phenotype.

3.2 | Long-term efficacy

Improvements in spleen volume, liver volume, hemoglobin concentration, and platelet count, from baseline to 1 and 2 years of treatment continued or were maintained during 8 years of eliglustat therapy. Mean and individual patient values for each parameter are shown in Figure 1. After 8 years of eliglustat, mean (± SD) spleen and liver volumes decreased by 69% (from 16.8 ± 9.5 to 4.9 ± 3.2 MN) and 34% (from 1.7 ± 0.5 to 1.1 ± 0.3 MN), respectively. Hemoglobin concentration and platelet count increased by 2.2 ± 1.7 g/dL (from 11.3 ± 1.5 to 13.5 ± 1.2 g/dL) and 113% (from 68.7 ± 21.2 to 135.3 ± 56.6 × 10^9/L), respectively. All patients achieved at least 3 of the 4 long-term therapeutic goals established for patients on ERT.[18] Overall, 100% of patients met the spleen volume goal, 95% met the liver volume goal, 95% met the hemoglobin goal, and 63% met the platelet goal (Supporting Information Figure SA). All 19 trial patients showed clinically significant improvements, with larger margins of improvement seen in patients with the most severe baseline disease (Supporting Information Figure SB). Mean final values achieved for patients with severe baseline splenomegaly, moderate to severe hepatomegaly, moderate to severe baseline anemia, or severe baseline thrombocytopenia were similar to those in patients with milder disease at baseline (Figure 2) and were within long-term therapeutic goal thresholds. Mean spleen volume for patients with severe baseline splenomegaly (*n* = 6) decreased by 80% (from 26.8 to 5.7 MN) and by 63% (from 12.2 to 4.5 MN) for patients with mild or moderate baseline splenomegaly (*n* = 13). Mean liver volumes for patients with moderate to severe baseline hepatomegaly (*n* = 15) decreased by 37% (from 1.81 to 1.12 MN) and by 22% (from 1.08 to 0.85 MN) for patients with absent or mild baseline hepatomegaly (*n* = 4). Mean hemoglobin values increased by 3.5 g/dL (from 9.6 to 13.1 g/dL) among patients with moderate to severe baseline anemia (*n* = 7) and by 1.4 g/dL (from 12.3 to 13.7 g/dL) in patients with absent or mild baseline anemia (*n* = 12). Mean platelet counts increased by 164% (from 50 to 128 × 10^9/L) for patients with severe baseline

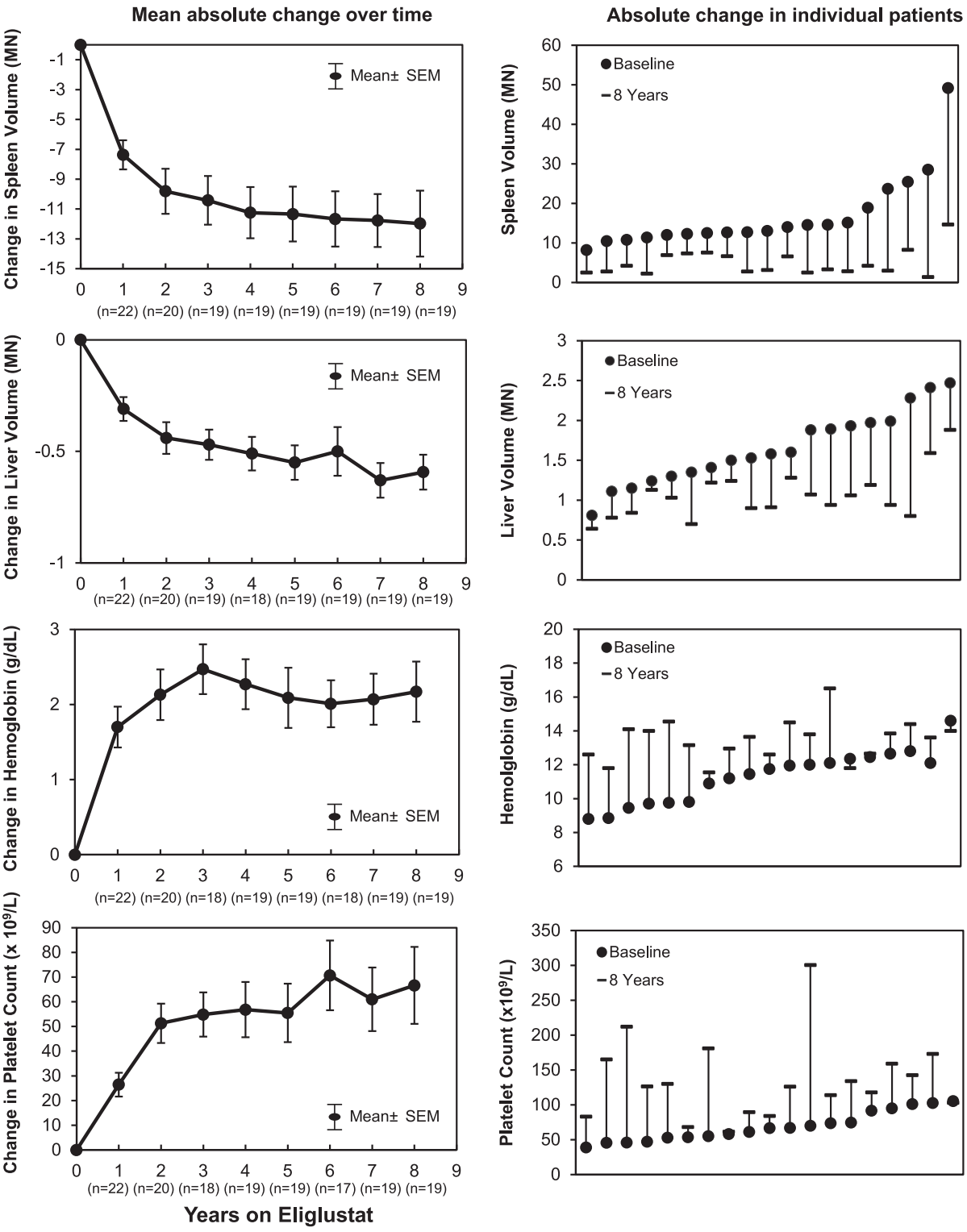

FIGURE 1 Changes from baseline in spleen volume, liver volume, hemoglobin concentration, and platelet count during 8 years of eliglustat therapy

thrombocytopenia (n = 8) and by 75% (from 83 to 140 × 10^9/L) for patients with absent, mild, or moderate baseline thrombocytopenia (*n* = 11).

As shown in Figure 3A, mean lumbar spine T-scores increased during the first 3-4 years of eliglustat therapy and these improvements were maintained or continued through 8 years. In patients who completed 8 years of eliglustat therapy and had measurements at baseline and Year 8, mean (±SD) total lumbar spine bone mineral density increased by 0.12 ± 0.15 g/cm^2 (13%), mean Z-score increased by 0.89 (from −1.17 ± 0.97 to −0.29 ± 1.09) and mean T-score by 0.96 (from −1.55 ± 1.05 to −0.59 ± 1.29), moving from the osteopenic to the normal range. Mean (±SD) femur bone mineral density was in the normal range at baseline and increased by 0.03 ± 0.10 g/cm^2, mean Z-score increased by 0.24 (from 0.40 ± 0.55 to 0.64 ± 0.69) and mean T-score by 0.21 (from 0.13 ± 0.69 to 0.33 ± 0.91). After 8 years of eliglustat therapy, most patients

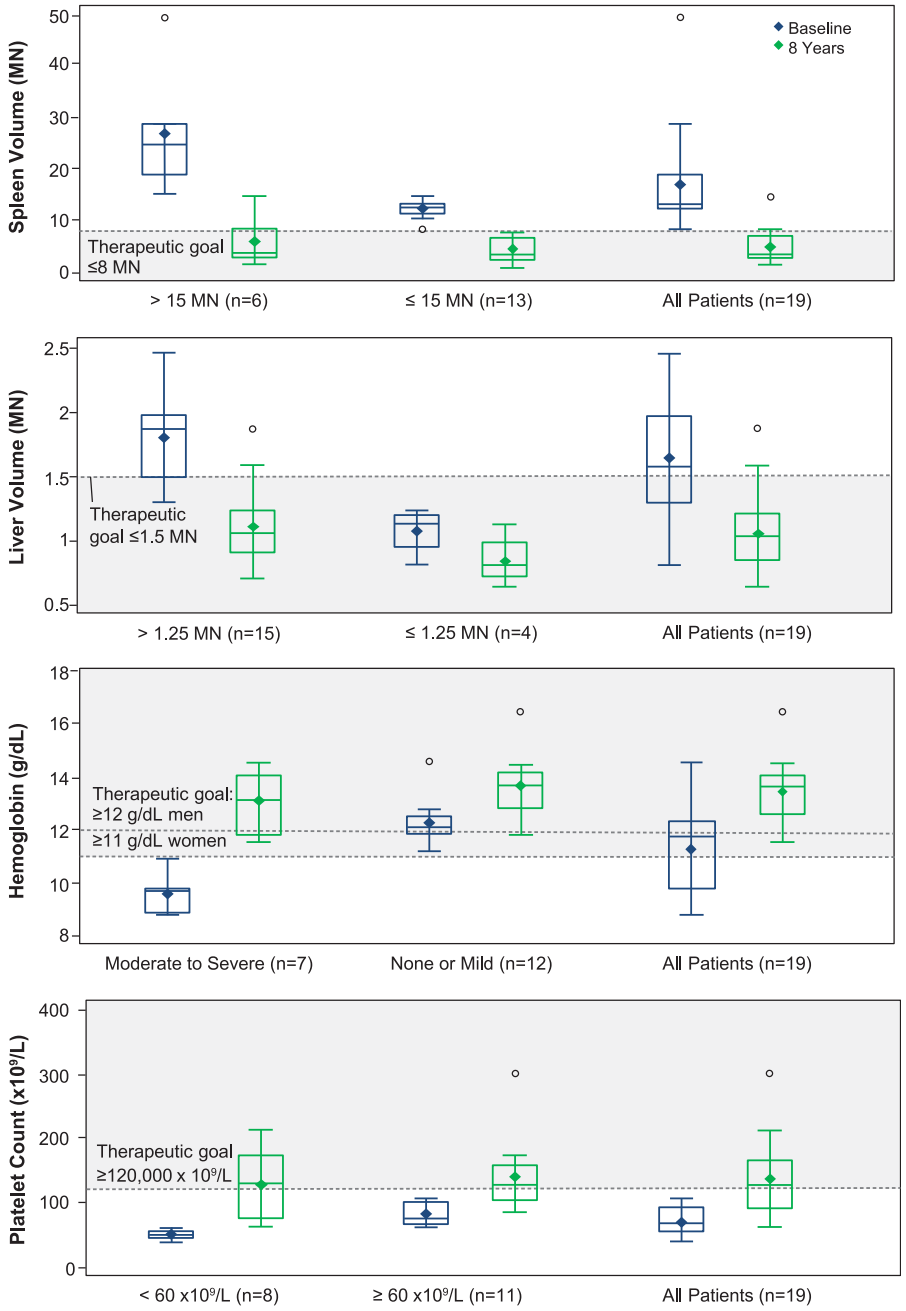

FIGURE 2 Baseline and 8-year values for spleen volume, liver volume, hemoglobin concentration, and platelet count in patients who completed the trial, overall and by baseline disease severity. Hemoglobin values are stratified by anemia category, which is sex-specific as indicated. MN: Multiples of normal. Bottom and top edges of box indicate 25th and 75th percentiles. Whiskers encompass data points within 1.5 times the interquartile range from the edge of the box; circles indicate outlier values. Diamonds indicate mean values. The line inside the box indicates the median value. Gray shading indicates the therapeutic goal ranges established for patients after long-term ERT[18]

showed improvements in lumbar spine (Figure 3B) and femur (Figure 3C) T-scores. Patients with normal lumbar spine T-scores at baseline remained in the normal range, and lumbar spine T-scores remained normal or improved in 16 of 19 patients (84%). Two patients had persistent osteopenia, one of which was a postmenopausal woman; another postmenopausal woman had persistent osteoporosis. A third postmenopausal woman had a T-score in the osteoporosis range at baseline, which improved to the osteopenic range. All patients with normal femur T-scores at baseline remained in the normal range after 8 years; among the 5 patients with femur T-scores in the osteopenia range at baseline, all improved and 2 were in the normal range after 8 years of eliglustat therapy. There were no new fractures, osteonecroses, lytic lesions, or bone infarctions during 8 years of eliglustat therapy (with the exception of a possible new infarct reported in 1 patient at 4 years, which subsequently resolved[12]), and existing lesions remained stable. There were no clinically significant changes in bone pain. At baseline, 3 patients reported bone pain, all very mild or mild; at 8 years, 1 patient reported very mild bone pain. There were no bone crises in any patient for the duration of the trial.

Mean quality-of-life and disease severity measures improved over the first 3-4 years of eliglustat therapy with sustained values

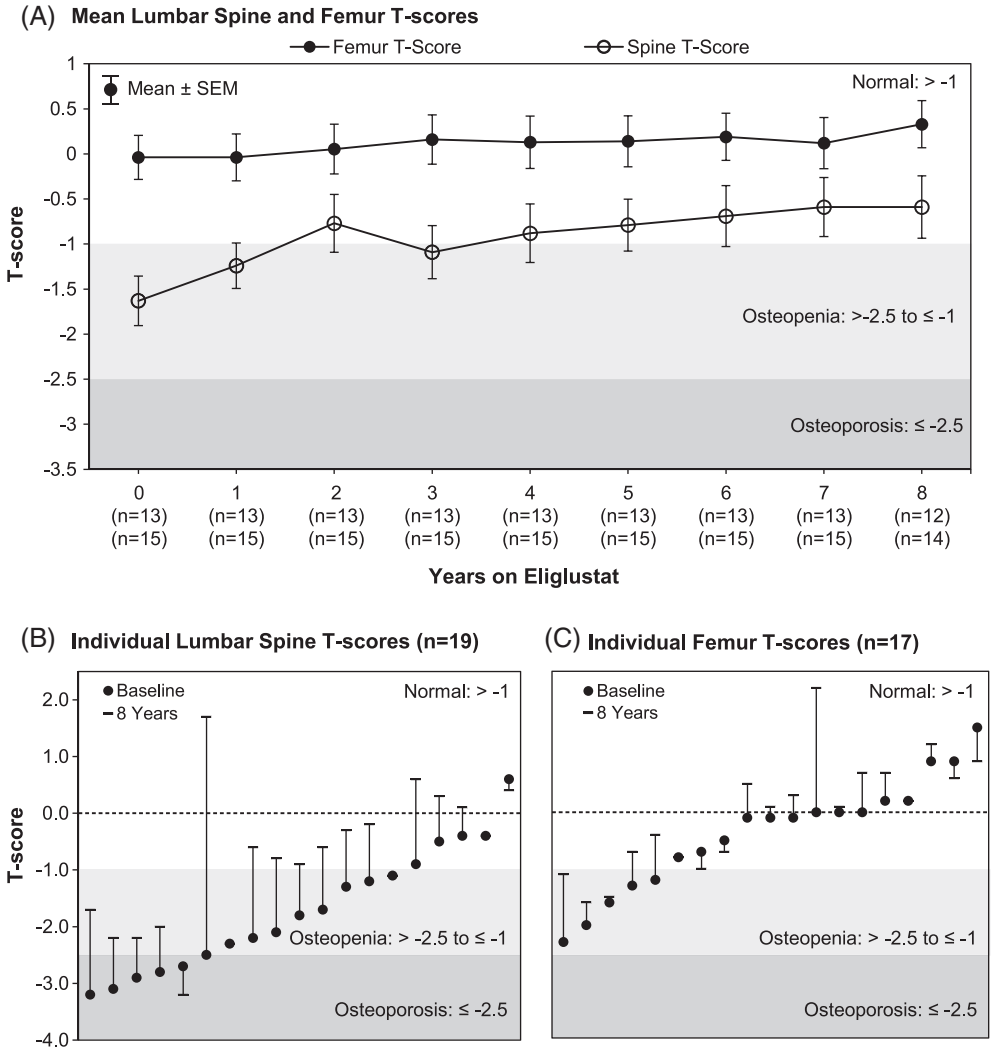

FIGURE 3 Lumbar spine and femur T-scores during 8 years of eliglustat therapy. A, Mean T-scores over time. B,C, individual patient lumbar spine and femur T-scores at baseline and 8 years. Panel A, shows patients with DXA data up to at least 7 years where baseline and follow-up DXA were performed on the same machine and patients were not taking bisphosphonates. In panel B, (lumbar spine) and panel C, (femur), individual patients are ranked by baseline T-score. Osteopenia and osteoporosis ranges are indicated by light and medium gray shading, respectively.

for the remainder of the trial with minor fluctuations (data not shown). All 8 individual SF-36 domain scores (6 of which were abnormal at baseline) were normalized relative to 1998 US normative values[14] after 8 years (Supporting Information Table SA). Among the 16 patients with baseline and 8-year values, the mean (±SD) Fatigue Severity Score (1 = least severe, 7 = most severe) had decreased by 24% from 4.44 ± 1.79 to 3.28 ± 1.62 at 8 years. Among the 16 patients with baseline and 8-year values, the mean (±SD) total Gaucher DS3 Score (0 = best, 19 = worst) decreased by 40% from the moderate range (4.71 ± 2.62) to the borderline-to-mild range (2.83 ± 1.81). Individual patient Gaucher DS3 scores at baseline and 8 years are shown in Supporting Information Figure SB.

3.3 | Long-term biomarker response

The primary storage lipids (glucosylceramide and glucosylsphingosine) and established biomarkers (chitotriosidase and CCL18) of Gaucher disease were highly elevated at baseline. The marked reductions observed at 1 year continued or were maintained through 8 years of eliglustat therapy (Figure 4). After 8 years, median percent changes from baseline were -91% for chitotriosidase, -87% for CCL18, -92% for glucosylsphingosine, and -80% for plasma glucosylceramide. The median plasma glucosylceramide level normalized within 6 months of starting eliglustat therapy and remained in the low-normal range for the duration of the trial.

3.4 | Long-term safety

This long-term trial represents a total of 169 patient-years of eliglustat exposure. In total, 98% of adverse events were mild or moderate and 94% were considered unrelated to eliglustat. Adverse events are summarized in Supporting Information Table SB. There were no treatment-emergent deaths reported during the trial. One patient died from complications (hypovolemic shock due to spleen laceration) following a laparoscopic cholecystectomy approximately 7 months after

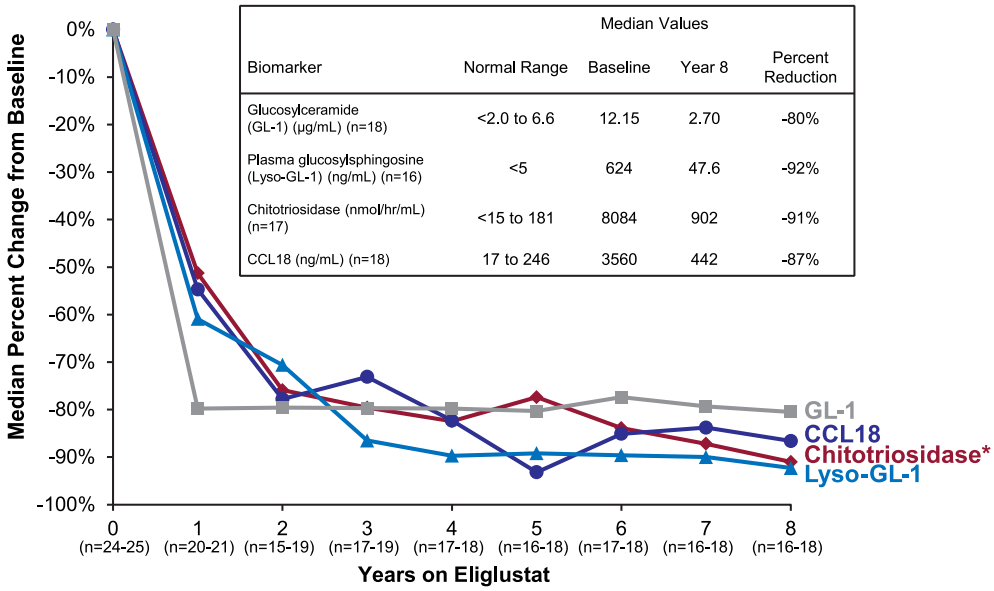

FIGURE 4 Percent change from baseline in disease-related biomarkers during 8 years of eliglustat therapy. Percent reductions are based on patients who had data at both baseline and each timepoint. Baseline and year 8 values are based on patients who had data at both timepoints. *Chitotriosidase analysis excludes 2 patients with absent chitotriosidase (CHIT) activity due to homozygous null mutation in the CHIT1 gene.

she had stopped eliglustat therapy and had withdrawn from the trial at the end of the 1-year primary analysis due to pregnancy. The death was considered by the investigator to be unrelated to eliglustat. In total 5 patients reported 8 serious adverse events, including one that was considered by the investigator to be possibly related to eliglustat (a short run of asymptomatic nonsustained ventricular tachycardia [NSVT]) and assessed as serious due to prolonged hospital stay on day 1 for a protocol-mandated 36-h cardiac telemetry for safety monitoring (from 12 h before through 24 h after the first dose), which was uneventful.[10] The 7 unrelated serious adverse events in the other 4 patients were as follows: ovarian cyst ruptured (severe); abortion spontaneous (severe) and 2 events of radiation exposure during pregnancy (mild) in the same patient; radiation exposure during pregnancy (moderate); and inguinal hernia (severe) and cholecystitis (severe) in the same patient. As reported previously,[10] 3 patients withdrew from the trial due to 4 adverse events: 1 patient after 1 year for a moderate event of osteonecrosis retrospectively identified as present at baseline (considered unrelated to treatment) and 2 patients after day 1 for 3 events of asymptomatic NSVT detected during protocol-mandated 36-h ECG monitoring on day 1, 1 of which (also noted above) was considered possibly related to eliglustat by the investigator. In both patients, plasma eliglustat levels were undetectable at the time of the event.

Overall 5, patients reported 6 adverse events that were severe. All were considered unrelated to eliglustat: ovarian cyst ruptured (1 patient), hiatus hernia (1 patient), thrombocytopenia (1 patient), spontaneous abortion (1 patient), and inguinal hernia and cholecystitis (1 patient). Overall, 20 adverse events considered related to treatment were reported in 10 patients; 18 of these events were mild and 2 were moderate. Each related adverse event was reported once in 1 patient except for abdominal pain, diarrhea, and abnormal nerve conduction studies, which were reported twice in 2 patients.

4 | DISCUSSION

Final 8-year data from this open-label Phase 2 trial confirm and extend the safety and efficacy of eliglustat reported at the 1-, 2-, and 4-year time points,[10–13] and are consistent with 9-month, 18-month, and 4.5 year data from the Phase 3 ENGAGE placebo-controlled trial, also in treatment-naïve patients.[5–7] The long-term stability observed in this trial is also consistent with the Phase 3 ENCORE trial, in which the same hematologic and visceral parameters remained stable for up to 4 years among patients who had switched from long-term ERT to eliglustat.[9] All patients in this 8-year Phase 2 trial achieved at least 3 of the 4 long-term therapeutic goals established for patients on ERT,[18] and no patient showed clinical decline over the course of the trial (Supporting Information Figure SB). Of note, the largest margins of improvement were seen in patients with the most severe disease at baseline, with these patients attaining final values for all clinical parameters that were similar to patients whose disease was less severe at baseline. Overall, the clinical values achieved after 8 years of eliglustat therapy are comparable to those seen after 10 years of imiglucerase therapy among a large cohort of non-splenectomized patients enrolled in the International Collaborative Gaucher Group Gaucher Registry.[19]

The therapeutic goal thresholds used for comparison in this study[18] have been the mainstay of assessing treatment effects in Gaucher disease for more than a decade. These thresholds, which were developed based on real-world clinical outcomes data from the International Collaborative Gaucher Group Gaucher Registry, are aimed primarily at alleviating florid disease manifestations of anemia, thrombocytopenia, hepatosplenomegaly, skeletal pathology, and impaired growth (in children). Recently, a consensus panel of experts, with input from patients, developed a revised set of management guidelines that expands upon these parameters to include improvement in patient-reported outcomes, such as quality of life, fatigue and

social participation, as well as refractory elements of Gaucher disease, complications, and co-morbidities.[20] The thresholds for improvement in hemoglobin and hepatosplenomegaly remain essentially unchanged; whereas the platelet goal for nonsplenectomized patients was lowered from ≥120 × 10^9/L (achieved by 63% of patients in our study) to ≥100 × 10^9/L (achieved by 74% of patients in our study). In addition, 17 of 19 patients (89%) achieved platelet counts >80 × 10^9/L, which is considered sufficient to prevent surgical, obstetric, and spontaneous bleeding. Persistent thrombocytopenia in some nonsplenectomized patients with severe baseline thrombocytopenia has been reported after 4, 5, or even 10 years of ERT, but the etiology remains unclear.[19,21,22] In our earlier analysis of 4-year platelet data from this trial, mean platelet counts did not correlate significantly with severity of thrombocytopenia, splenomegaly, or splenic filling defects at baseline; however, they did correlate with mean trough plasma concentrations of eliglustat.[13]

The increase in mean and individual lumbar spine and femur T-scores during the first 3-4 years of eliglustat therapy is in keeping with the therapeutic goals developed for GD1 patients on ERT, which call for increasing bone density within 3-5 years of starting treatment.[18] Long-term maintenance or continued improvement in these bone measures through 8 years is comparable to the long-term stability seen in the Phase 3 ENCORE trial, in which least square mean lumbar spine Z-score was not only stable but slightly improved ($P < .0001$) during 4 years after patients switched to eliglustat following a mean of 10 years of prior ERT.[9] Similar to imiglucerase therapy, in which attainment of normal or near-normal bone mineral density can take up to 8 years on average,[23] the mean lumbar spine T-score in this Phase 2 trial population moved from the osteopenic to the normal range after 4 years and remained normal during the remaining 4 years of the trial.

The long-term safety data from this trial extend the safety and tolerability profile of eliglustat reported among treatment-naïve patients during 1.5 years in the Phase 3 ENGAGE trial,[7] ERT switch patients during 4 years in the Phase 3 ENCORE trial,[9] and mostly ERT switch patients in the EDGE trial comparing once- vs twice-daily dosing of eliglustat.[24] These 4 trials represent a total of 393 eliglustat-treated patients and 1400.3 patient-years of eliglustat exposure, with a mean duration of 3.6 years on eliglustat.[25] Nineteen of the 20 patients who entered the Phase 2 trial extension after the 1-year primary analysis completed the trial, with just one withdrawal at 2 years for administrative reasons.

This 8-year analysis provides new insights into long-term biomarker responses to eliglustat. The established Gaucher disease biomarkers, chitotriosidase and CCL18, both of which were highly elevated at baseline, were reduced by >85%. As seen in other trials of eliglustat, levels of the primary substrate glucosylceramide normalized within several months and remained in the low-normal range for the duration of the trial. Levels of the substrate glucosylsphingosine were reduced by 92%. This minor substrate of acid β-glucosidase is increasingly recognized as a highly specific and sensitive biomarker of Gaucher disease with direct involvement in disease pathogenesis.[26–29] These findings suggest that eliglustat therapy may reverse the pathological glycosphingolipid accumulation in Gaucher disease.

This is the first trial to show long-term, clinically significant improvements in quality of life and Gaucher disease severity with eliglustat therapy in previously untreated GD1 patients with moderate to severe baseline disease. In total, 6 of the 8 SF-36 domain scores were abnormal at baseline, and after 8 years of eliglustat therapy, all 8 scores were in the normal range established for the United States general population.[14] The SF-36 domain score improvements were similar to those reported with imiglucerase ERT.[14] Similarly, the mean Fatigue Severity Score was elevated at baseline (4.44), similar to that reported for patients with multiple sclerosis (4.8) and systemic lupus erythematosus (4.7), and decreased to 3.28, near the range observed in healthy adults (2.3-3.00[15,30]). Mean total scores for the validated Gaucher Disease Severity Score moved from the moderate to the mild-to-borderline disease range after 8 years of eliglustat. In the ENCORE trial, these same measures remained stable and in the normal range for 4 years after patients switched from long-term ERT to eliglustat.[9]

Although this article provides important insights into how patients on eliglustat fare over the long term, our analysis does have limitations. This small open-label trial in previously untreated adults with GD1 did not include a comparator arm, such as placebo-treated or ERT-treated patients. It served as a precursor to the larger, confirmatory Phase 3 trials, including the randomized, double-blind, placebo-controlled ENGAGE trial of 40 previously untreated GD1 patients[5] and the ENCORE trial of eliglustat compared with imiglucerase in 159 patients who switched from long-term ERT.[8] It should be noted that the study findings reflect outcomes for patients with intact spleens and relatively mild skeletal involvement at treatment initiation. The study was initiated before widespread use of the bone marrow burden score and, therefore, does not include this important assessment of skeletal disease involvement.

In summary, clinically meaningful improvements in hematologic, visceral, bone, and biomarker parameters were achieved in previously untreated patients with GD1 as early as the first year of treatment with eliglustat.[10] These improvements continued or were maintained over the course of 8 years of eliglustat therapy. Quality-of-life measures also showed clinically significant improvements after 8 years of eliglustat. Eliglustat was generally safe and well tolerated with only 1 withdrawal due to an adverse event considered possibly related to eliglustat.

ACKNOWLEDGMENTS

This trial was sponsored by Sanofi Genzyme. The authors thank the patients and health-care professionals who participated in the eliglustat Phase 2 trial; Laurie LaRusso (Chestnut Medical Communications) for medical writing support funded by Sanofi Genzyme; Lisa Underhill (Medical Affairs, Sanofi Genzyme) for medical writing support and critical review of the manuscript; and Yaoshi Wu (Biostatistics, Sanofi Genzyme) and Regina Tayag (Prometrika LLC) for biostatistical analyses.

CONFLICT OF INTEREST

EL was a principal investigator in the Sanofi Genzyme-sponsored eliglustat Phase 2, ENGAGE, ENCORE, and EDGE trials. She receives honoraria and travel reimbursement and participates on advisory

boards for Sanofi Genzyme and Shire. NW was a principal investigator in the Sanofi Genzyme-sponsored eliglustat Phase 2 and ENCORE trials. MD, EAA, and HR were principal investigators in the Sanofi Genzyme-sponsored eliglustat Phase 2 trial; HR has also received honoraria and travel reimbursement from Sanofi Genzyme. HL was a principal investigator in the Sanofi-Genzyme-sponsored Phase 2 and ENGAGE trials. She has also been a consultant to Actelion, Amicus, BioMarin, Pfizer, Prevail Therapeutics, Sanofi Genzyme, Shire and Ultragenyx and has received grant/research support from Sanofi Genzyme, Amicus, BioMarin, Pfizer, Shire, Sangamo, and Ultragenyx. AZ was a principal investigator in the Sanofi Genzyme-sponsored eliglustat Phase 2 trial. He receives honoraria and travel reimbursement from Shire and Pfizer, has participated in advisory boards for Shire, Sanofi Genzyme and Pfizer, and is a consultant of Shire and Targeted Cell Therapies LLC. His clinic receives research grants from Shire and Pfizer, as well as support from Shire, Sanofi Genzyme and Pfizer for participation in their respective registries. SJMG, MCF, and MJP are employees of Sanofi Genzyme. MJP designed the clinical trial protocol for this study.

ORCID

Elena Lukina https://orcid.org/0000-0002-8774-850X
Ari Zimran https://orcid.org/0000-0003-0077-8608

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

How to cite this article: Lukina E, Watman N, Dragosky M, et al. Outcomes after 8 years of eliglustat therapy for Gaucher disease type 1: Final results from the Phase 2 trial. *Am J Hematol*. 2019;94:29–38. https://doi.org/10.1002/ajh.25300