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RESEARCH ARTICLE

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Outcomes after 18 months of eliglustat therapy in treatment-naïve adults with Gaucher disease type 1: The phase 3 ENGAGE trial

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Abstract

Eliglustat, an oral substrate reduction therapy, is a first-line treatment for adults with Gaucher disease type 1 (GD1) who are poor, intermediate, or extensive CYP2D6 metabolizers (>90% of patients). In the primary analysis of the Phase 3 ENGAGE trial (NCT00891202), eliglustat treatment for 9 months resulted in significant reductions in spleen and liver volumes and increases in hemoglobin concentration and platelet count compared with placebo. We report 18-month outcomes of patients who entered the trial extension period, in which all patients received eliglustat. Of 40 trial patients, 39 entered the extension period, and 38 completed 18 months. Absolute values and percent change over time were determined for spleen and liver volume, hemoglobin concentration, platelet count, bone mineral density, bone marrow burden, and Gaucher disease biomarkers. For patients randomized to eliglustat in the double-blind period, continuing treatment with eliglustat for 9 more months resulted in incremental improvement of all disease parameters. For patients randomized to placebo in the double-blind period, eliglustat treatment during the 9-month, open-label period resulted in significant decrease of spleen and liver volumes and

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significant increase of hemoglobin and platelets, with a similar rate of change to patients who had received eliglustat in the double-blind period. Eliglustat treatment was also associated with improvement in bone marrow burden score, bone mineral density, and established biomarkers of Gaucher disease, including reduction of the bioactive lipid, glucosylsphingosine. These findings underscore the efficacy of eliglustat in treatment-naïve patients. Eliglustat was well-tolerated, and there were no new safety concerns with longer-term exposure.

1 | INTRODUCTION

Gaucher disease type 1 (GD1) is an autosomal recessive lysosomal storage disorder caused by *GBA* mutations and defective acid-β-glucosidase.[1] The metabolic defect results in progressive accumulation of glucosylceramide and glucosylsphingosine in lysosomes, most conspicuously in the cells of macrophage/monocyte lineage. The accumulating lipids trigger metabolic inflammation and immune activation that is associated with increased synthesis of glucosylceramide via induction of glucosylceramide synthase, thus amplifying the primary metabolic defect[2,3]; hence, the typical phenotypic features of hepatosplenomegaly, cytopenia, and disabling skeletal complications.[1] Two treatment approaches have been used to lower pathological glucosylceramide accumulation in Gaucher disease. For the past two decades, the standard of care for GD1 has been enzyme replacement therapy (ERT) with biweekly infusions of macrophage-targeted recombinant acid β-glucosidase, which supplements enzyme activity in the macrophage system.[4] Substrate reduction therapy is predicated on partial inhibition of glucosylceramide synthase to decrease synthesis of glucosylceramide to balance residual activity of mutant acid β-glucosidase.[4]

Eliglustat (Cerdelga, Sanofi Genzyme, Cambridge, Massachusetts) is an oral substrate reduction therapy approved as a first-line treatment for adults with GD1 whose predicted CYP2D6 metabolizer status, as detected by an FDA-cleared test, is poor, intermediate, or extensive[5] (>90% of patients[6]). The Phase 3 ENGAGE trial (NCT00891202), the first placebo-controlled trial ever conducted in Gaucher disease, demonstrated significant reductions in spleen and liver volumes and increases in hemoglobin concentration and platelet count after 9 months of treatment in eliglustat-treated GD1 patients, while placebo-treated patients demonstrated slight worsening of these indicators of disease activity.[7] On completing the 9-month primary analysis period, all patients had the opportunity to continue in the open-label ENGAGE trial extension, in which all patients received eliglustat. We report the 18-month outcomes of the patients who entered the trial extension.

2 | METHODS

Clinical assessments in the ENGAGE trial were performed as described previously.[7] For eliglustat patients continuing on eliglustat and placebo patients who switched to eliglustat, absolute values and percent change over time were determined for spleen volume, liver volume, hemoglobin concentration, platelet count, bone mineral density, and bone marrow burden score. In addition, plasma levels of the acid β-glucosidase substrates, glucosylceramide and glucosylsphingosine, were measured. Biomarkers of Gaucher disease, serum chitotriosidase and plasma macrophage inflammatory protein 1β (MIP-1β), were also monitored. Moreover, we measured plasma levels of several sphingolipids to assess whether inhibition of glucosylceramide led to diversion of substrates through alternate pathways, namely, GM3 ganglioside, sphingomyelin, and ceramide. Safety data were collected as described previously[7] and assessed with regard to treatment group at baseline and duration of eliglustat treatment. Frequency of adverse events, serious adverse events, and severe adverse events are reported for all eliglustat-treated patients in the trial extension period and presented alongside data for the placebo-treated patients during their time in the 9-month primary analysis period.

3 | RESULTS

Baseline patient characteristics for the ENGAGE population were reported previously.[7] Of the 40 patients who entered the trial, 2 patients in the eliglustat-eliglustat group withdrew from the trial: one during the primary analysis period and one during the extension (Supporting Information Figure A). Neither withdrawal was due to adverse events.

Eliglustat treatment resulted in reversal of disease activity indicators in key affected organ systems. Hence, there were significant improvements in visceral (liver and spleen volume) and hematologic (hemoglobin concentration and platelet count) disease parameters (Figure 1). These consistent improvements were seen in patients taking eliglustat but not patients taking placebo. Patients randomized to eliglustat in the double-blind period demonstrated continued incremental responses during the open-label extension period for the next 9 months. The placebo-treated patients who switched to eliglustat (ie, placebo-crossover patients) demonstrated reversal of disease with similar time course and magnitude of improvement in spleen volume, liver volume, hemoglobin concentration, and platelet count over 9 months as was seen in the original eliglustat-treated patients during their first 9 months on eliglustat therapy (Figure 1). Bone mineral density and bone marrow infiltration indicated by bone marrow burden scores also improved in the placebo-crossover patients during their 9 months on eliglustat therapy with a time course and magnitude of improvement similar to the original eliglustat-treated patients (Supporting Information Figure B). Concomitantly, there was striking reduction in plasma concentrations of the primary storage lipids, glucosylceramide and glucosylsphingosine, as well as established biomarkers of Gaucher disease, serum chitotriosidase and plasma MIP-1β, all of which were elevated at baseline and decreased consistently in eliglustat-treated patients

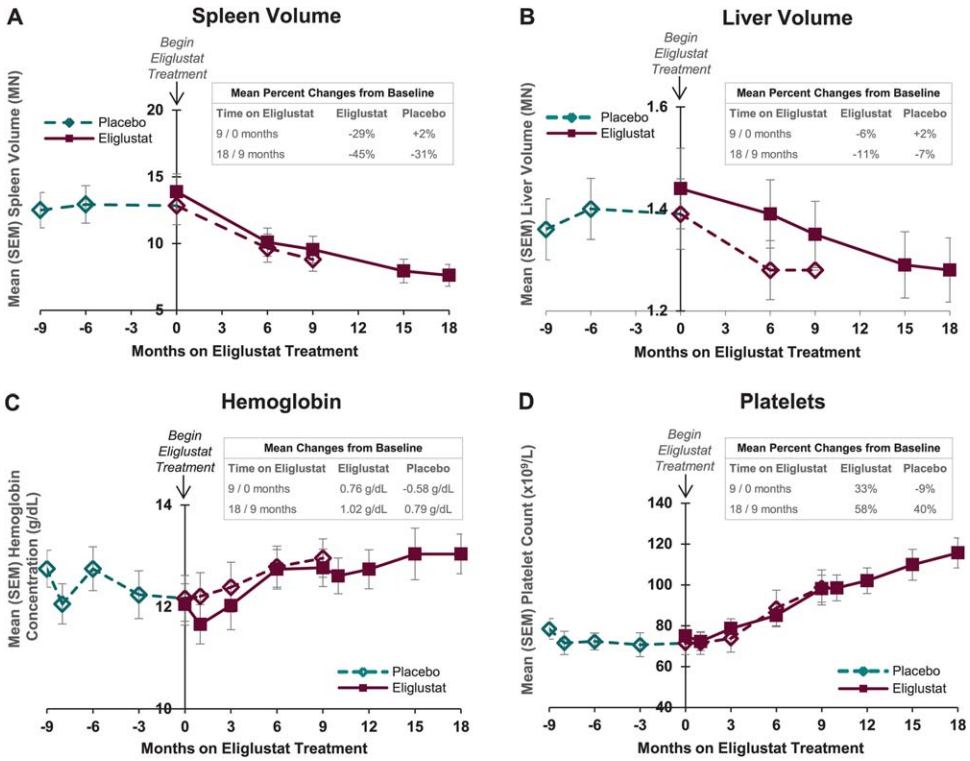

FIGURE 1 Effects of eliglustat on spleen volume (A), liver volume (B), hemoglobin concentration (C), and platelet count (D) through 18 months. Absolute mean values for patients initially randomized to placebo or eliglustat are depicted with reference to when they began eliglustat treatment rather than time in the trial. Change from baseline in the table insets is determined with respect to treatment baseline. For patients who received placebo for the first 9 months of the trial, the placebo baseline is when they entered the trial and the eliglustat baseline is when they switched to eliglustat. For patients randomized to eliglustat for the first 9 months, the treatment baseline is when they entered the trial. Abbreviations: MN, multiples of normal; SEM, standard error of the mean

(Figure 2), with similar reductions among placebo-crossover patients. In addition, patients randomized to eliglustat in the double-blind period showed consistent further reductions in these biomarkers during the 9-month extension period. Plasma sphingomyelin and ceramide, which were both in the normal range at baseline, remained well within the normal range (Figure 2, legend). Overall, patients who were treated with eliglustat for 18 months showed continued improvements in visceral, hematologic, bone, and biochemical parameters after their first 9 months on therapy.

The adverse event profile during the first 9 months of the extension trial was consistent with that reported during the primary analysis period (Table 1). There were no withdrawals due to adverse events and no deaths. During eliglustat treatment, 99% of adverse events were classified as mild or moderate. The two adverse events classified as severe were migraine (after 382 days on eliglustat) considered unlikely to be related to eliglustat and arthralgia (after 351 days on eliglustat) considered not related to eliglustat treatment as arthralgia is common in Gaucher disease. Adverse events reported in ≥15% of patients in any 9-month period are shown in Table 2.

During eliglustat treatment, 76% of adverse events were considered unrelated to eliglustat and all related adverse events were mild or moderate. The most common related adverse events, each reported in 2–3 patients (5.0%-7.5%) were: headache, diarrhea, nausea, abdominal distension, flatulence, abdominal pain, atrioventricular (AV) block second degree, dizziness, dyspepsia, and dry mouth (Table 3). Headache, diarrhea, abdominal distension, and abdominal pain were also reported as related events in 3, 4, 1, and 1 placebo-treated patients, respectively, during the 9-month primary analysis period.

In 1 patient, two serious adverse events were reported (AV block and Mobitz type 1 second-degree AV block) during the extension period in protocol-driven Holter monitoring. These two events were observed on a single Holter recording after 421 days on eliglustat. The patient was asymptomatic but per protocol was hospitalized for evaluation, hence triggering the classification as serious. Both events resolved without treatment, did not lead to study discontinuation, and were considered probably related to eliglustat by the investigator. The patient's dosage was lowered from 150 mg twice daily to 50 mg twice daily, and increased to 100 mg twice daily 4 weeks later. The external cardiac reviewer concluded that both episodes, which occurred in the early morning hours, were normal physiologic phenomena in a young individual related to nocturnal enhancement of vagal tone.

4 | DISCUSSION

The ENGAGE clinical trial was the first randomized placebo-controlled trial in GD1 and met its primary and all secondary endpoints: clinically meaningful and statistically significant improvements in hematologic

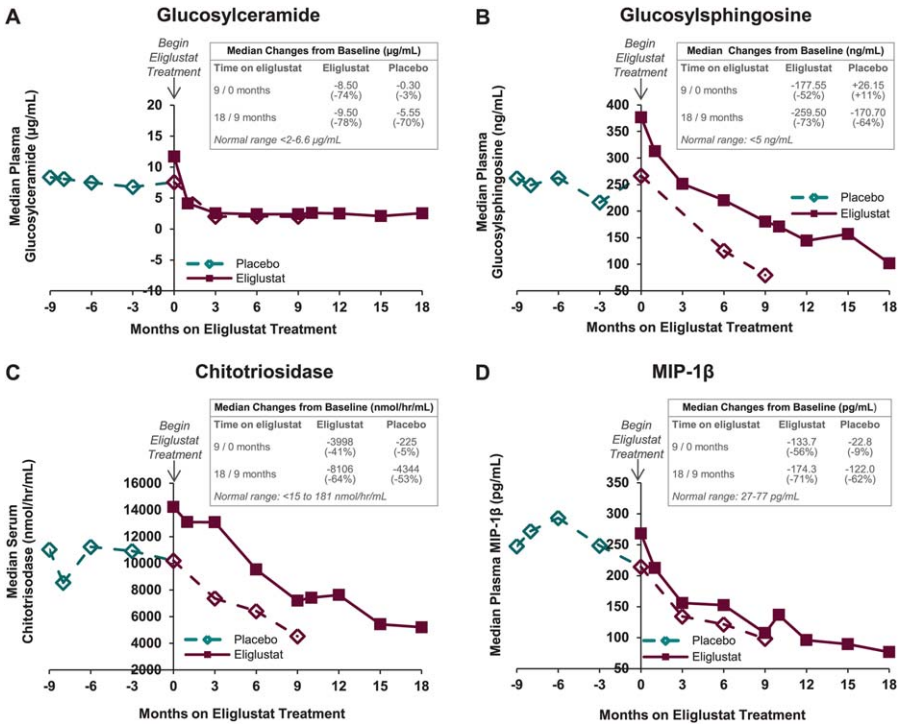

FIGURE 2 Effects of eliglustat on glucosylceramide (A), glucosylsphingosine (B), chitotriosidase (C), and MIP-1β (D) through 18 months. Median values for patients initially randomized to placebo or eliglustat are depicted with reference to when they began eliglustat treatment rather than time in the trial. Change from baseline in the table insets is determined with respect to treatment baseline. For patients who received placebo for the first 9 months of the trial, the placebo baseline is when they entered the trial and the eliglustat baseline is when they switched to eliglustat. For patients randomized to eliglustat for the first 9 months, the treatment baseline is when they entered the trial. Not shown: median ceramide remained in the normal range (1.8–6.5 μg/mL) from baseline (3.40 mg/L) to 18 months (4.42 mg/L) and median sphingomyelin remained in the normal range (200–703 μg/mL) from baseline (211.00 μg/mL) to 18 months (280.50 μg/mL)

and visceral indicators of disease activity were observed in eliglustat-treated patients compared with placebo-treated patients during the double-blind, primary analysis period.[7] Recently, eliglustat was approved as a first-line therapy for treatment of adults based on predicted CYP2D6 metabolizer status. Herein, we report the efficacy and safety in the first 9 months of the ENGAGE open-label trial extension. We found that placebo-crossover patients, who had shown no change or slight worsening of their indicators of Gaucher disease activity, when switched to eliglustat showed reversal of disease similar to the eliglustat-treated patients during the 9-month primary analysis. In fact, the rate of reversal of disease parameters paralleled that of patients initially randomized to eliglustat in the double-blind phase (Figure 1). Moreover, visceral, hematologic, and bone indicators of Gaucher disease activity in patients who were initially randomized to eliglustat showed incremental reversal of disease during the additional 9 months of open-label eliglustat treatment. These findings are consistent with

TABLE 1 Summary of adverse events

Adverse event	Primary analysis period (9 months)				Extension phase (9 months)					
	Eliglustat (*N* = 20)		Placebo (*N* = 20)		Eliglustat–eliglustat (*N* = 19)		Placebo–eliglustat (*N* = 20)		All adverse events on eliglustat[a] (*N* = 40)	
	Events	Patients (%)	Events	Patients (%)	Events	Patients (%)	Events	Patients (%)	Events	Patients (%)
Any AE	135	18 (90)	95	14 (70)	93	15 (79)	92	15 (75)	320	34 (85)
Related	32	9 (45)	25	9 (45)	25	8 (42)	19	9 (45)	76	21 (53)
Not related	103	18 (90)	70	14 (70)	68	13 (68)	73	12 (60)	244	31 (78)
Mild	93	16 (80)	85	14 (70)	67	14 (74)	85	13 (65)	245	31 (78)
Moderate	42	15 (75)	10	6 (30)	24	10 (53)	7	5 (25)	73	20 (50)
Severe	0	0	0	0	2	2 (11)	0	0	2	2 (5)
Serious	0	0	0	0	2	1 (5)	0	0	2	1 (3)
Led to withdrawal	0	0	0	0	0	0	0	0	0	0
Deaths	0	0	0	0	0	0	0	0	0	0

[a]Represents adverse events that occurred while on eliglustat treatment in either the primary analysis and/or the extension.

TABLE 2 Adverse events reported in ≥ 15% of patients during any 9-month period

Adverse event (preferred term)	Primary analysis period (9 months)				Extension phase (9 months)				All eliglustat-treated patients (9 or 18 months on eliglustat) (N = 40)	
	Eliglustat (N = 20)		Placebo (N = 20)		Eliglustat–eliglustat (N = 19)		Placebo–eliglustat (N = 20)			
	Events	Pt (%)	Events	Pt (%)	Events	Pt (%)	Events	Pt (%)	Events	Pt (%)
Headache	23	8 (40)	13	6 (30)	8	5 (26)	7	4 (20)	38	14 (35)
Nasopharyngitis	3	3 (15)	0	0	6	2 (11)	0	0	9	4 (10)
Diarrhea	6	3 (15)	4	4 (20)	1	1 (5)	1	1 (5)	8	5 (13)
Upper respiratory infection	1	1 (5)	4	4 (20)	3	3 (16)	4	3 (15)	8	7 (18)
Gastroesophageal reflux disease	0	0	0	0	1	1 (5)	4	3 (15)	5	4 (10)
Arthralgia	9	9 (45)	4	2 (10)	3	2 (11)	10	4 (20)	22	13 (33)

therapeutic responses demonstrated in the Phase 2 open-label trial of eliglustat in treatment-naïve patients.[8] After 1.5 years of eliglustat, Phase 2 patients (who had a greater disease burden at baseline than ENGAGE patients) had a 47% mean reduction in spleen volume compared to 45% in ENGAGE eliglustat-eliglustat patients in this analysis, a 20% mean reduction in liver volume versus 11% mean reduction in ENGAGE patients (most of whom had normal liver volume at baseline), a 63% mean increase in platelet count versus 58% in ENGAGE patients, and a 1.9 g/dL mean increase in hemoglobin versus 1.0 g/dL in ENGAGE patients (who had 1 g/dL higher baseline hemoglobin values). Taken together, these results further confirm the efficacy of eliglustat in treatment-naïve patients, even those with severe disease burden at baseline.

A notable finding in the open-label extension phase of the ENGAGE trial is the reversal of pathological glycosphingolipid accumulation. The primary sphingolipid accumulating in Gaucher disease is glucosylceramide, which leads to complement activation and metabolic inflammation. Interestingly, these effects lead to increased glucosylceramide synthase, thus increasing its synthesis and thereby amplifying the fundamental metabolic defect of Gaucher disease.[2] Accumulating glucosylceramide in Gaucher disease also triggers an alternative pathway of metabolism via acid ceramidase to generate glucosylsphingosine.[9,10] This minor substrate of acid β-glucosidase has been recently validated as the most specific biomarker of Gaucher disease, and it has been shown to trigger an immune response, resulting in NKT-cell-driven metabolic inflammation, B-cell proliferation and anti-lipid antibodies, key features of Gaucher disease pathophysiology.[11,12] Glucosylsphingosine has also been shown to be an osteoblast toxin in a mouse model of Gaucher disease.[3] Eliglustat treatment led to normalization of circulating glucosylceramide and a 73% decline in plasma concentrations of glucosylsphingosine. There was also a concomitant 71% reduction in plasma MIP-1β (Figure 2), a marker of metabolic

TABLE 3 Adverse events considered eliglustat-related in ≥ 2 patients during any 9-month period

Related adverse event (preferred term)	Eliglustat-eliglustat patients (18 months on eliglustat) (N = 20) Patients (events)	Placebo-eliglustat patients (9 months on eliglustat) (N = 20) Patients (events)	All eliglustat-treated patients (9 or 18 months on eliglustat) (N = 40) Patients (events)
Headache	3 (6)	1 (1)	4 (7)
Diarrhea	2 (5)	0 (0)	2 (5)
Nausea	1 (3)	1 (1)	2 (4)
Abdominal distension	2 (3)	0 (0)	2 (3)
Flatulence	2 (3)	0 (0)	2 (3)
Abdominal pain	2 (2)	0 (0)	2 (2)
Atrioventricular block second degree	1[a] (2)	1 (1)	2 (3)
Dizziness	1 (1)	1 (1)	2 (2)
Dyspepsia	1 (1)	1 (1)	2 (2)
Dry mouth	0 (0)	2 (2)	2 (2)

[a]Patient experienced "2:1 AV block" which was coded to "Atrioventricular block" but in this table counted as "Atrioventricular block second degree."

inflammation and skeletal involvement in Gaucher disease.[13] Moreover, serum chitotriosidase, a marker of glucosylceramide-laden Gaucher macrophages and an established biomarker of Gaucher disease in the clinic, was strikingly reduced by eliglustat treatment (Figure 2). Taken together, these findings suggest eliglustat reverses Gaucher disease pathophysiology involving macrophage activation and metabolic inflammation. Importantly, inhibition of glucosylceramide synthase was not apparently associated with diversion of lipid metabolic flux toward formation of ceramide or sphingomyelin, as plasma concentrations of these lipids remained within normal ranges (Figure 2 legend). Trends in biomarker reduction further support incremental reversal of disease indicators on prolonged eliglustat therapy. Thus, patients who were initially randomized to eliglustat in the double-blind period showed marked reduction from baseline in glucosylsphingosine (−52%), chitotriosidase (−41%), and MIP-1β (−56%) during their first 9 months of treatment and then further decreases in plasma concentrations of these biomarkers (−73%, −64%, and −71% from baseline, respectively) during the subsequent 9 months of treatment in the open-label period (Figure 2).

Skeletal complications are a major source of disability in Gaucher disease. Indicators of skeletal and marrow disease were also improved with eliglustat therapy. Pathological marrow infiltration, indicated by bone marrow burden score, fell during the first 9 months of eliglustat therapy and there was further improvement during the ensuing 9 months of treatment (Supporting Information Figure B). In patients on placebo, there was no change in bone marrow burden score during 9 months of placebo treatment, but after switching to eliglustat in the open-label period, there was progressive reduction. Similarly, osteopenia at baseline reversed in eliglustat-treated patients during the double-blind period and improved bone density was maintained during the succeeding 9 months in the open-label period. It should be noted that, compared with the Phase 2 clinical trial, which included patients with more severe disease, in the ENGAGE trial, patients with moderate disease were enrolled in an attempt to minimize risks to patients randomized to placebo in the double-blind period from developing complications while not receiving active treatment.

Eliglustat treatment for 9 to 18 months was generally well tolerated, with 95% of patients continuing on treatment. Most adverse events were non-serious, not drug-related and either mild or moderate in severity, and none resulted in patients discontinuing the study. The safety and tolerability data are consistent with what has been reported among both treatment-naïve[8,14,15] and ERT switch patients,[16,17] as well as a combined adverse event analysis that reported an overall continuation rate in clinical trials of 92% after a mean of 1.4 years on eliglustat.[6]

5 | CONCLUSIONS

In conclusion, the open-label extension period in the ENGAGE randomized, placebo-controlled clinical trial affirmed the efficacy of treatment and clearly demonstrated incremental reversal of visceral, hematologic and skeletal indicators, and pathophysiology of Gaucher disease. After switching from placebo to eliglustat treatment, patients experienced progressive improvement in visceral, hematologic, bone, and biomarker indicators of disease activity over 9 months similar in rate and magnitude to those initially treated with eliglustat. For patients continuing on eliglustat for 18 months, these same disease measures continued to improve, and no new safety concerns were identified with longer-term exposure to eliglustat. Future analysis will examine the effects of 4–5 years of eliglustat therapy in the ENGAGE trial.

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CONFLICT OF INTEREST

PKM is a principal investigator in the eliglustat ENGAGE and ENCORE trials and has received research grants, honoraria, and travel reimbursement from Sanofi Genzyme. PKM is supported by R01 AR 065932 from NIH NIAMS. EL is a principal investigator in the eliglustat ENGAGE, ENCORE, and EDGE trials and has received honoraria and travel reimbursement from Sanofi Genzyme and Shire. HBT is a principal investigator in the eliglustat ENGAGE trial and a coinvestigator in the HGT-GCB068 clinical trial at Shire. SPS, MG, SA, and AO are principal investigators in the eliglustat ENGAGE trial. SPS has also been site primary investigator in clinical trials and received research support and educational grants from Sanofi Genzyme, Shire, Protalix, Actelion, and Amicus. HB, AM, MP, SD, and EH are principal investigators in the eliglustat ENGAGE trial and have received travel reimbursement, honoraria, and/or research grants from Sanofi Genzyme. SP is a principal investigator in the eliglustat ENGAGE trial; has received research and programmatic support from Sanofi Genzyme, Shire HGT Corporation, Amicus Corporation, Actelion Corporation, and BioMarin Pharmaceutical; and is a member of the speaker's bureaus of Shire and Sanofi Genzyme. GP is a principal investigator in the eliglustat ENGAGE and ENCORE trials and has received honoraria and travel reimbursement from Sanofi Genzyme. MB is a principal investigator in the eliglustat ENGAGE and ENCORE trials, a member of the North American advisory board for the International Collaborative Gaucher Group Gaucher Registry, and has received honoraria and travel reimbursement from Sanofi Genzyme. RT is a paid biostatistical consultant for Sanofi Genzyme. MJP and SJMG are employees of Sanofi Genzyme.

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SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

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