Genetics in Medicine (2022) ■, 100329

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Genetics in Medicine
An Official Journal of the ACMG

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ARTICLE

Long-term effects of eliglustat on skeletal manifestations in clinical trials of patients with Gaucher disease type 1

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ARTICLE INFO

Article history:
Received 12 June 2022
Received in revised form
18 October 2022
Accepted 19 October 2022
Available online xxxx

Keywords:
Acid β-glucosidase deficiency
Eliglustat
Gaucher disease type 1
Skeletal manifestations
Substrate reduction therapy

ABSTRACT

Purpose: Most patients with Gaucher disease have progressive and often disabling skeletal manifestations. We examined the long-term effect of eliglustat treatment on bone outcomes in clinical trials in adults with Gaucher disease type 1.

Methods: Data from 4 completed phase 2 and 3 trials were evaluated in treatment-naïve patients or patients switching to eliglustat from enzyme replacement therapy (ERT).

Results: Overall, 319 of 393 (81%) eliglustat-treated patients remained in their trials until completion or commercial eliglustat became available. Mean eliglustat treatment duration ranged from 3.3 to 6.5 years. In treatment-naïve patients and ERT-switch patients, frequency and severity of bone pain decreased during eliglustat treatment. Mean lumbar spine T-scores shifted from abnormal to normal in treatment-naïve patients and remained in the healthy reference range or improved modestly in ERT-switch patients. Mean total bone marrow burden score shifted from marked-to-severe to moderate in treatment-naïve patients and remained moderate in ERT-switch patients. MIP-1β (marker of active bone disease) was elevated at baseline and decreased to the healthy reference range in treatment-naïve patients and remained in the healthy reference range among ERT-switch patients.

Conclusion: These findings confirm the long-term efficacy of eliglustat on skeletal complications of Gaucher disease in treatment-naïve and ERT-switch patients.

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doi: https://doi.org/10.1016/j.gim.2022.10.011

Introduction

In Gaucher disease (OMIM 230800), organs with abundant populations of mononuclear phagocytes, including the bone marrow, liver, and spleen, are infiltrated by activated glycosphingolipid-laden macrophages, termed Gaucher cells.[1] In the non-neuronopathic variant of Gaucher disease (type 1) the principal manifestations are anemia, thrombocytopenia, hepatosplenomegaly, and skeletal disease.[1]

This rare, inherited lysosomal disorder results from pathogenic variants in *GBA1* (OMIM 606463), which encodes acid β-glucosidase, the lysosomal enzyme that hydrolyzes glucosylceramide and glucosylsphingosine to ceramide and sphingosine, respectively.[1] Accumulation of activated macrophages engorged with glucosylceramide has pathological effects in the liver and spleen and occasionally the lung: these so-called Gaucher cells displace the normal bone marrow. Imbalanced osteoclastic-osteoblastic activity occurs and is associated with fragility fractures as well as osteonecrosis.[1,2]

Skeletal disease affects up to 90% of patients with Gaucher disease.[3] The associated pain and, for some patients, disability and orthopedic intervention markedly impair quality of life.[4-7] The complex skeletal manifestations include progressive bone mineral loss in all ages and both sexes, with increased risk of pathologic fractures. Bone pain varies from chronic, dull, achy, nonspecific pain to intense or localized acute pain—the latter often described as a bone crisis (an episode of severe pain, usually with fever and an elevated white blood cell count) that accompanies osteonecrosis. Osteonecrosis, sometimes termed avascular necrosis, may be a presenting feature of Gaucher disease; it is an irreversible and disabling complication that predominantly affects the femoral head, proximal humerus, and vertebrae and may lead to subchondral joint collapse.[8] Even in the absence of overt skeletal symptoms, most patients with Gaucher disease have radiologic evidence of bone disease.[8,9]

Displacement of healthy adipocytes in adult marrow by pathologic Gaucher cells is accompanied by abnormal bone modeling, reduced bone density, osteonecrosis, osteolytic lesions, and, less commonly, plasma cell dyscrasias.[2] In addition, exposure to excess bioactive glycosphingolipids appears to affect hematopoiesis and the balance of osteoblast and osteoclast numbers and activity.[2] This imbalance between bone formation and breakdown induces disordered trabecular and cortical bone modeling, cortical bone thinning, fragility fractures, and osteolytic lesions.[2] Although Gaucher-specific treatment can prevent or alleviate skeletal disease, it cannot reverse secondary changes, such as fracture deformity, osteonecrosis, lytic lesions, and the consequences of bone injury, such as osteoarthritis.[2] It is therefore essential to institute disease-modifying therapy that will prevent irreversible skeletal injury as early as possible. This includes measures that enable patients to achieve peak bone mass while they are young, thereby mitigating the risk of fragility fractures. Gaucher-specific therapies reverse the splenomegaly and cytopenias so that splenectomy, which is associated with a greatly increased risk of recurrent osteonecrosis, as well as fragility fractures, can be avoided.[10-18]

First-line therapies for Gaucher disease type 1 include enzyme replacement therapy (ERT) infusions with recombinant acid β-glucosidase (imiglucerase [Cerezyme, Sanofi], velaglucerase alfa [VPRIV, Takeda Pharmaceuticals U.S.A., Inc], or taliglucerase alfa [Elelyso, Pfizer]), and substrate reduction therapy using an oral glucosylceramide synthase inhibitor (eliglustat [Cerdelga, Sanofi]). Enzyme therapy augments residual activity of acid β-glucosidase to promote degradation of its endogenous substrates, whereas substrate reduction therapy partly inhibits glucosylceramide synthase activity to balance glucosylceramide production with its impaired rate of degradation.[19] Eliglustat is approved in the United States, Europe, Japan, and other countries as a first-line therapy for adults with Gaucher disease type 1 who have poor, intermediate, or extensive CYP2D6-metabolizer phenotypes (>90% of patients[20,21]). Therapeutic response of skeletal disease to either of these treatment modalities is slower than in the visceral and hematological compartments, but the salutary effects continue for at least 7 to 8 years.[2]

We report long-term skeletal outcomes in adults with Gaucher disease type 1 who participated in the phase 2 and phase 3 clinical trials of eliglustat.

Materials and Methods

Data sources

Data were obtained from the 4 clinical trials of eliglustat in adults with Gaucher disease type 1: the phase 2, single-arm study in treatment-naïve patients (NCT00358150);[16,22-24] the phase 3, randomized, double-blind, placebo-controlled trial in treatment-naïve patients (ENGAGE, NCT00891202);[17,25,26] the phase 3, randomized, imiglucerase-controlled trial in patients already stable on ERT (ENCORE, NCT00943111);[15,27] and the phase 3, randomized, double-blind trial of once-daily vs twice-daily eliglustat dosing (same total daily dose) primarily in patients already stable on ERT (EDGE, NCT01074944).[14]

Table 1 summarizes key features of the trial designs and patient populations. The phase 2 and ENGAGE trials in treatment-naïve patients and the ENCORE trial in ERT-switch patients stipulated that participants had no symptomatic bone disease nor bone crises within the year before enrollment. In contrast, the EDGE trial in mostly ERT-switch patients allowed those with recent bone crises to enroll.

Assessments

In all 4 trials, parameters of skeletal disease were assessed at least annually.

Table 1 Phase 2 and 3 eliglustat clinical trials

	Treatment-Naïve		Switch or Predominantly Switch	
Study Parameter	Phase 2[16,22-24] $N = 26$	Phase 3 ENGAGE[17,25,26] $N = 40$	Phase 3 ENCORE[15,27] $N = 159$[a]	Phase 3 EDGE[14] $N = 170$
Study design	Open-label, single-arm, 1-year primary analysis + extension	Randomized, placebo-controlled 9-month primary analysis + extension	Randomized, imiglucerase-controlled, noninferiority 1-year primary analysis + extension	Randomized noninferiority, once- vs twice-daily dosing, Lead-in period of 0.5-1.5 years 1-year primary analysis + extension
Participant age range, mean (SD), y	19-60, 34.5 (12.96)	16-63, 31.8 (11.26)	18-69, 37.5 (14.37)	18-75, 37.7 (15.1)
Bone exclusions	No active bone lesion, no bone crises within last year			Could have recent bone crisis
Disease status	Moderate to severe	Mild to moderate	Stable, achieved specified therapeutic goals	Stable to mild/moderate
Prior treatment	None	None	≥3 years of ERT (mean = 10 y)	Mixture—87% had prior ERT for variable duration
Mean time on eliglustat[28] (range), y	6.5 (0.0-9.3)	3.9 (0.5-6.0)	3.3 (0.2-5.3)	3.3 (0.1-5.0)
Patients who remained in trial until switched to commercial eliglustat or trial end[28]	19/26 (73%)	34/40 (85%)	129/159 (82%)	137/170 (81%)

ERT, enzyme replacement therapy.

[a]A total of 157 patients were treated with eliglustat; 2 patients treated with imiglucerase in the primary analysis did not enter the open-label extension.

Bone mineral density (BMD) was measured in the lumbar spine and femur using dual x-ray absorptiometry. The total BMD (g/cm^2), T-scores, and z-scores for spine and femur were calculated.

Bone marrow infiltration was assessed using magnetic resonance imaging (MRI) in all 4 trials. In addition, we used the bone marrow burden (BMB) score as a validated MRI-based measure of bone marrow infiltration by Gaucher cells and an indicator of skeletal response to treatment.[29,30] The BMB score was assessed in the ENGAGE, ENCORE, and EDGE trials but was not assessed in the phase 2 trial, which started before the procedure was incorporated into international clinical practice. MRI images of the lumbar spine and femur were scored by 2 blinded central readers and adjudicated by a third reader if there was a >1-point discrepancy in scores between the 2 original readers. An average of all reader values at each time point was calculated. BMB scoring ranged from 0 to 16, in which 0 to 4 was classified as mild, 5 to 8 moderate, and 9 to 16 marked-to-severe.[31]

The Gaucher disease-related assessments of self-reported bone pain (none, very mild, mild, moderate, severe, or extreme), bone crises (presence or absence) in the previous 4 weeks, and investigator-assessed mobility (current mobility status: unrestricted mobility, walks with difficulty, walks with orthopedic aid, wheelchair, or bedridden) were available from all 4 trials. Bone crisis was defined in the trials as bone pain with acute onset requiring immobilization of the affected area, narcotics for pain relief, and possibly accompanied by periosteal elevation, elevated white blood cell count, fever, and/or debilitation for >3 days. In addition, the bone subdomain score of the Gaucher Disease Severity Scoring System (DS3)[32,33] was available from the phase 2, ENGAGE, and ENCORE trials. The DS3 bone subdomain score contains 5 items each scored individually by the evaluating physician: (1) new lytic lesions, avascular necrosis, or pathological fractures within the last 12 months, (2) bone/joint pain in the last 30 days, (3) number of bone crises in the last 12 months, (4) bone marrow infiltration, and (5) BMD z-score. The domain score was tabulated by averaging the scores for all items within the domain. The maximum total disease severity score in DS3 is 19, of which 8 are ascribed to the bone subdomain.[33]

MIP-1β is produced by inflammatory phagocytes surrounding Gaucher cells and has been proposed as a marker of active bone disease.[34] As a relatively new biomarker, MIP-1β was measured in plasma only in the phase 3 trials. Chitotriosidase is an established biomarker of Gaucher disease reflecting burden of alternatively activated lipid-laden macrophages. Chitotriosidase activity was measured in all 4 trials and in phase 2, ENGAGE, and ENCORE, it was normalized based on *CHIT1* genotype by excluding patients who were homozygous for the common null variant (24-base pair duplication in exon 10) of *CHIT1* (ie, expected to have no chitotriosidase activity) and by doubling the plasma activity in patients who were heterozygous for this variant (ie, expected to have half the normal chitotriosidase activity).[35] Chitotriosidase genotyping was not performed in EDGE; patients who had zero chitotriosidase activity (ie, likely homozygous

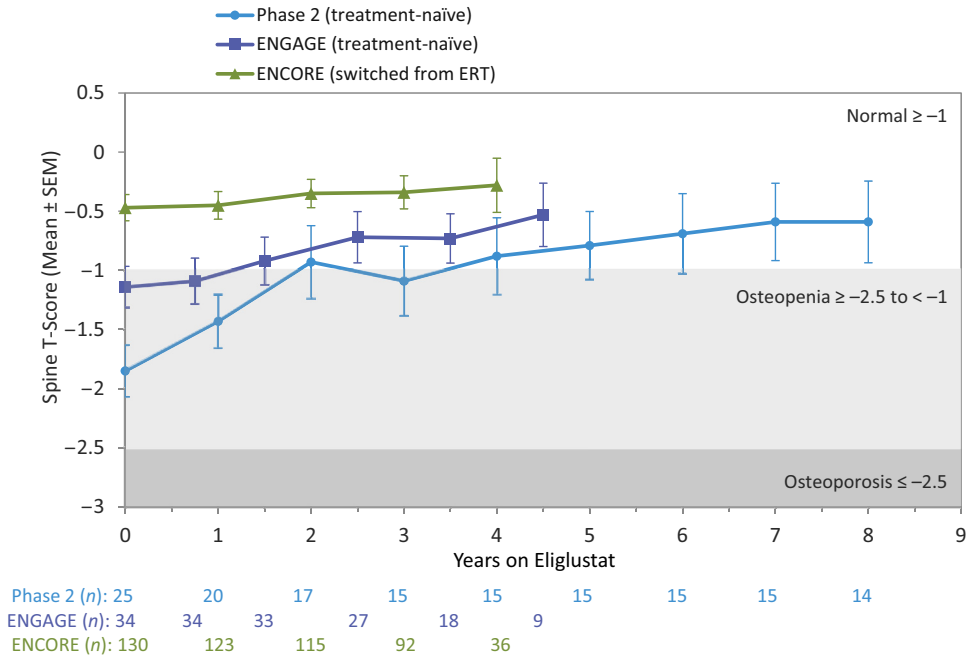

Figure 1 **Vertebral T-scores over time in treatment-naïve and ERT-switch patients**. One patient in the Phase 2 trial was excluded from bone analyses after starting bisphosphonate treatment (after Year 1). SEM, standard error of the mean; ERT, enzyme replacement therapy.

for the *CHIT1* null variant) were excluded from the chitotriosidase analysis. Glucosylsphingosine (a sphingolipid directly derived from glucosylceramide and a highly specific biomarker of Gaucher disease[36-38]) was measured in the phase 2 and ENCORE trials (retrospectively from frozen plasma samples collected during the trials) and the ENGAGE trial (prospectively, after protocol amendment, from plasma samples collected during the trial) by extraction from the plasma and analysis using ultraperformance liquid chromatography coupled with tandem mass spectrometry using the method described by Dekker et al.[39]

Statistical analyses

Results from each study are presented separately and identified as either treatment-naïve (phase 2, ENGAGE, EDGE-treatment-naïve) or ERT-switch (ENCORE, EDGE-switch) populations. The EDGE trial included ERT-switch patients and treatment-naïve patients. Mean ± SEM or median were assessed over time for continuous bone assessments and are presented for all timepoints in each study for which the sample size was ≥8 patients. For post hoc analysis of proportion of patients experiencing bone pain at baseline and follow-up, we used the latest timepoint for which baseline and follow-up data were available for ≥70% of the baseline population and/or represented ≥30 patients. This approach allowed for comparison of the same group of patients at baseline and follow-up and excluded later time points where small sample sizes could skew the results.

Results

The study population of 393 eliglustat-treated patients included 26 patients from the phase 2 trial, 40 patients from the ENGAGE trial, 157 patients from the ENCORE trial, and 170 patients from the EDGE trial (Table 1). In total, 319 patients (81%) remained in their respective trials until completion or availability of commercial eliglustat in their regions, no patient discontinued treatment because of lack of efficacy, and 9 (2.3%) patients discontinued because of adverse events that were considered drug-related.[28] Among the 74 patients who actively withdrew from a trial (ie, not including the US patients who switched to commercial eliglustat when it became available), 25 withdrew because of an adverse event (9 because of events considered drug-related, 16 because of events considered unrelated to drug), 25 wished to withdraw (reasons not specified but could include women who wished to become pregnant), 15 withdrew because of pregnancy, 3 because of noncompliance, 3 were lost to follow-up, and 3 because of other reasons. Mean duration of eliglustat exposure in each trial ranged from 3.3 to 6.5 years (Table 1).[28]

BMD and BMB

The mean lumbar spine BMD T-scores shifted from abnormal to the healthy reference range in treatment-naïve patients and remained stable within the reference range or improved modestly in ERT-switch patients (Figure 1). The

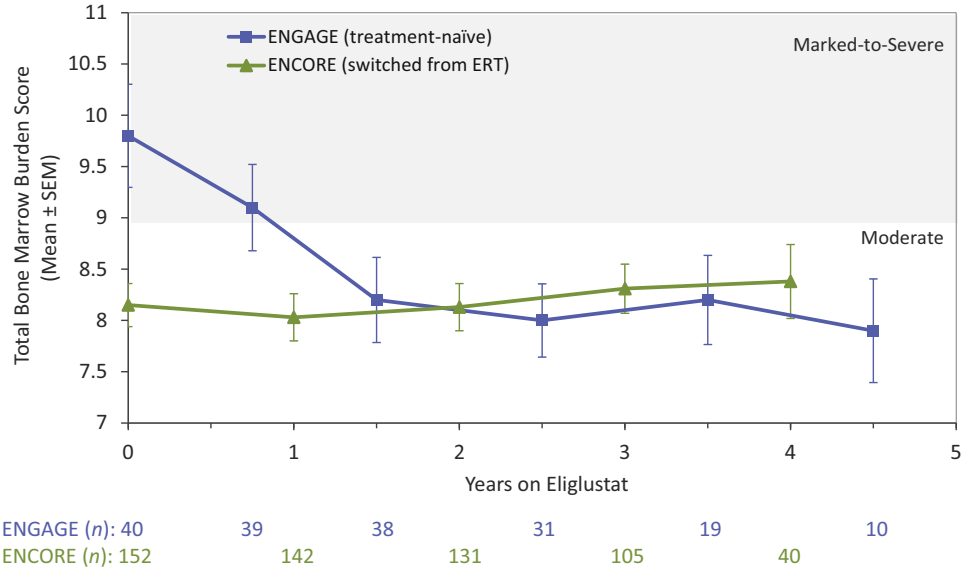

Figure 2 **Bone marrow burden score over time in treatment-naïve and switch patients.** ERT, enzyme replacement therapy.

trajectories for mean *z*-scores were similar (data not shown). In addition, an earlier least-squares mean analysis of lumbar spine *z*-score in the ENCORE ERT-switch trial showed a statistically significant improvement of 0.29 ($P < .0001$) after 4 years of eliglustat,[27] which is consistent with the trends observed in this analysis.

The mean total BMB score shifted from the marked-to-severe range at baseline to the moderate range with eliglustat treatment in treatment-naïve ENGAGE patients; it remained stable in the moderate range in ERT-switch patients (Figure 2).

Gaucher assessments (bone pain, bone crises, and mobility)

Among treatment-naïve patients, 84% and 95% of patients in the phase 2 trial reported no bone pain at baseline and follow-up, respectively; 79% and 78% in the ENGAGE trial reported no bone pain at baseline and follow-up, respectively; and 86% and 87% in the EDGE treatment-naïve population reported no bone pain at baseline and follow-up, respectively. Among ERT-switch patients, 67% and 87% of patients in the ENCORE trial reported no bone pain at baseline and follow-up, respectively, and 66% and 77% in the EDGE-switch population reported no bone pain at baseline and follow-up, respectively. In both treatment-naïve and ERT-switch populations, bone pain followed a trend from the higher to lower severity categories, as shown in Figure 3. Analysis of baseline to 2.5 years in 119 ENCORE patients (data not shown) was consistent with the 4-year outcomes in 41 patients depicted in Figure 3.

Bone crises were very infrequent in these trials but decreased over time on eliglustat. In the phase 2 and ENGAGE trials of treatment-naïve patients (none of whom had recent bone crises at baseline), no patient had a bone crisis while taking eliglustat and 1 placebo-treated ENGAGE patient had a bone crisis. In the ENCORE trial of patients who switched to eliglustat after a mean 10 years on ERT (none of whom had recent bone crises at baseline), 3 (2%) had a bone crisis during eliglustat treatment: 1 was retrospectively identified in baseline images and 1 bone crisis occurred during imiglucerase treatment. In the EDGE trial (the only trial that allowed enrollment of patients with recent bone crises), 11 of 163 patients (7%) with available data reported bone crises at baseline, and the number decreased during the time on eliglustat: 3 patients at 6 months, 1 at 1 year, 1 at 1.5 years, and 1 at 2.5 years. After 3 years of eliglustat treatment, no patients in the EDGE trial reported a bone crisis.[14]

Mobility of nearly all patients was unrestricted at baseline and throughout their respective studies. In ENGAGE, 93% of patients reported unrestricted mobility at baseline and that number remained ≥90% throughout 4.5 years of follow-up. In the phase 2 trial, 92% of patients had unrestricted mobility at baseline, which increased to 100% at 1 year and all patients were fully mobile at 8 years. In ENCORE, 95% of patients reported unrestricted mobility at baseline, and this proportion remained between 95% and 97% year to year.[27] In EDGE, 90% of patients had unrestricted mobility at baseline and ≥90% continued to have unrestricted mobility for up to 3 years.

Among treatment-naïve patients, there was a downward trend in the DS3 bone domain disease severity score, indicating improvement over time. Eight points for scoring are assigned to the bone domain. Among patients with scores at baseline and 3.5 years in ENGAGE ($n = 17$), the mean bone domain score improved from 2.26 at baseline to 1.92 at 3.5 years. Among patients with scores at baseline and 7 years in the phase 2 study ($n = 19$), the mean bone domain score improved from 2.83 at baseline to 2.03 at 7 years. Among ERT-switch patients (ENCORE only), the score was 2.10 at baseline and remained between 1.93 and 2.15 during the study.

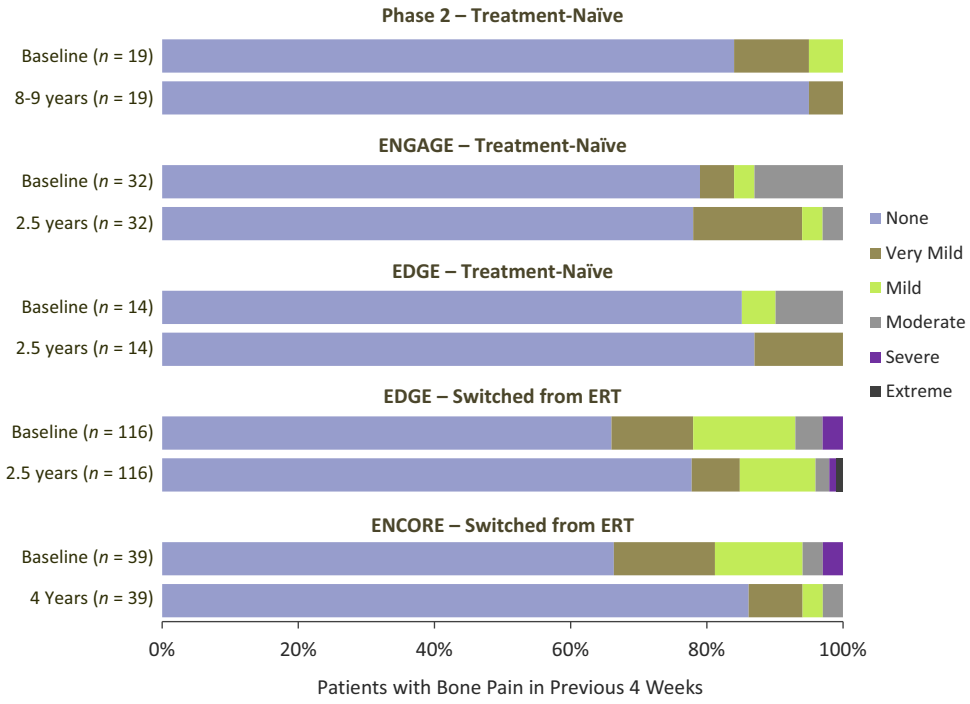

Figure 3 **Symptomatic bone pain before and after eliglustat treatment**. ERT, enzyme replacement therapy.

Gaucher disease biomarkers

Biomarkers of Gaucher disease were elevated at baseline, decreased consistently in treatment-naïve patients and remained stable or decreased further in ERT-switch patients. In treatment-naïve patients, median MIP-1β was approximately 3 times the upper reference limit at baseline, decreased into the normal range within 1 to 1.5 years of eliglustat treatment, and remained in the normal range throughout treatment (Figure 4A). In previously ERT-treated patients, median MIP-1β was normal or near-normal at baseline and remained within the healthy reference range over the duration of eliglustat treatment (Figure 4A). Median plasma chitotriosidase activity and glucosylsphingosine concentrations were highly elevated at baseline in treatment-naïve patients, decreased markedly within 1 to 1.5 years of eliglustat treatment, and remained low throughout treatment but did not normalize (Figure 4B and C). Among ERT-switch patients, chitotriosidase activity and glucosylsphingosine concentrations were moderately elevated at baseline and decreased modestly with eliglustat treatment (Figure 4B).

Discussion

Prolonged treatment with eliglustat had salutary effects on the skeletal manifestations of non-neuronopathic (type 1) Gaucher disease. Therapeutic benefit was seen in patients who were formerly naïve to treatment but also in those who otherwise had stable disease while taking enzyme therapy but had switched to eliglustat. In summary, eliglustat restored BMD to within the healthy reference range, diminished disease burden in the bone marrow, reduced the severity and frequency of bone pain, and prevented bone crises. Beyond improvements in these clinically relevant parameters, alleviating the complex skeletal manifestations of Gaucher disease is likely to prevent disability arising from decreased bone density and contribute to long-term maintenance of health and individual wellbeing.

Before the advent of macrophage-targeted enzyme therapy with tissue-derived alglucerase and recombinant human imiglucerase, disabling bone crises were frequent in patients of all ages suffering from Gaucher disease,[18,40,41] splenectomy was often performed for severe cytopenias related to hypersplenism, and bone events (bone pain, bone crises and ischemic events) were more prevalent among splenectomized patients.[40] Over the 3 decades since enzyme therapy has become widely available, a residue of painful and disabling events due to the effects of Gaucher disease on bone remain, but the prevalence of splenectomy and irreversible skeletal complications has markedly declined—arguably as a consequence of earlier introduction of definitive treatment.[40] A recent real-world analysis of patients with Gaucher disease in the United Kingdom found that splenectomy was associated with a greatly increased hazard of fragility fractures, in addition to osteonecrosis and orthopedic surgery; there were also marked sex differences in fracture risk over time since splenectomy.[18] Treatment goals for adults with Gaucher disease type 1 were developed in the context of ERT before the development and approval of eliglustat.[42] With regard to skeletal disease, the goals of treatment are to lessen or eliminate bone pain within 1 to 2

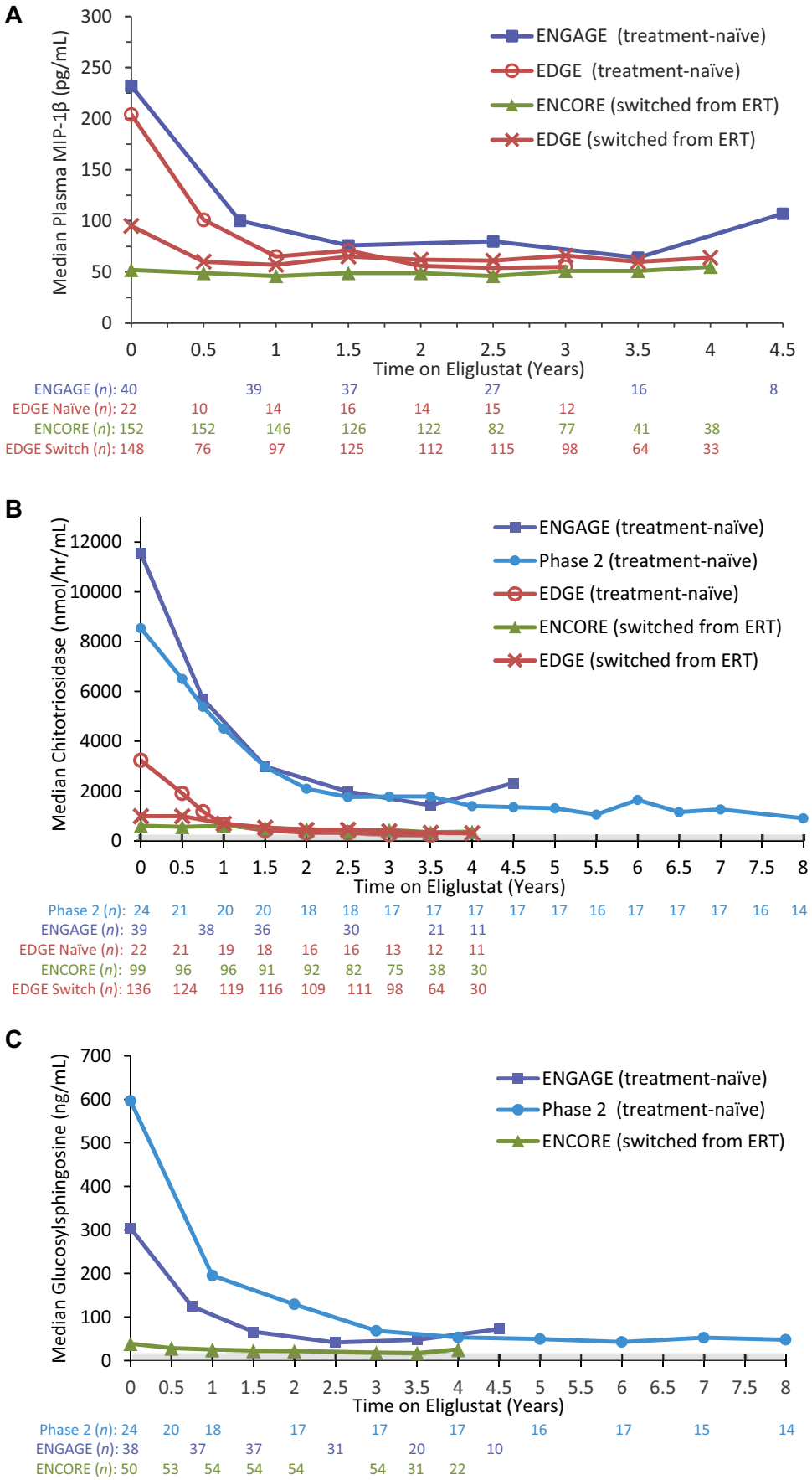

Figure 4 Gaucher disease biomarker values over time in treatment-naïve and switch patients. A. MIP-1β. B. Chitotriosidase. C. Glucosylsphingosine. Gray areas denote normal ranges. Reference ranges for healthy subjects in plasma: MIP-1β: 22 to 77 pg/mL; chitotriosidase in phase 2, <15 to 181 nmol/h/mL and in ENGAGE, ENCORE, and EDGE, 4 to 120 nmol/h/mL; glucosylsphingosine: <5 ng/mL. ENCORE data excludes patients who received imiglucerase during the first year of the trial. ERT, enzyme replacement therapy.

years, prevent bone crises, prevent osteonecrosis and subchondral joint collapse, improve BMD, and increase trabecular BMD by 3 to 5 years. An analysis from the International Collaborative Gaucher Group (ICGG) Gaucher Registry between 1991 and 2006 reported significant improvements in BMD over time and lumbar spine *z*-scores approaching the healthy reference population in imiglucerase-treated patients compared with untreated patients.[43] The authors noted that 8 or more years of ERT with imiglucerase may be required to achieve near-normal BMD. ICGG Gaucher Registry analyses after 10 and 20 years of imiglucerase treatment showed a decrease in bone pain and bone crises among patients who reported these symptoms before starting treatment, and prevention of bone pain and bone crises for most patients who did not report these symptoms at baseline.[11,13] More recently, it has become clear that BMD is an imperfect predictor of fracture risk; other factors, including conformation and geometry, trabecular microarchitecture (especially in the vertebrae), and mineralization and turnover, determine bone strength and solidity—aspects that have yet to be fully explored in the protean skeletal effects of Gaucher disease.[2]

The improvements in parameters of skeletal disease observed with eliglustat treatment in the clinical trials are generally consistent with those in these registry analyses of real-world imiglucerase treatment. Furthermore, a 2-year analysis of eliglustat treatment in the ICGG Gaucher Registry showed improvement in BMD with eliglustat treatment in the ERT-switch population comparable to the ERT-switch population in the ENCORE trial.[44]

Marked reduction of plasma MIP-1β in treatment-naïve patients and stability of MIP-1β in ERT-switch patients are consistent with the effects of eliglustat activity on this marker of metabolic inflammation that is increased in patients with Gaucher disease but does not originate from the pathognomic macrophages.[34,45] In addition, identical trends in plasma chitotriosidase activity and glucosylsphingosine concentrations reflect the ability of eliglustat to reduce the burden of activated lipid-engorged Gaucher macrophages and decrease the release of a glycosphingolipid metabolite that is derived directly in the lysosome from the primary accumulating substrate and congener, glucosylceramide.[38] Patients with Gaucher disease who have skeletal manifestations tend to have higher plasma MIP-1β concentrations than those without skeletal disease.[45] Although in many patients with Gaucher disease, plasma MIP-1β decreases in response to ERT, in those with ongoing skeletal disease despite enzyme therapy, MIP-1β remains elevated above a critical threshold of 85 pg/mL.[45]

The mechanisms by which the Gaucher-specific therapies, ERT and eliglustat, may correct or prevent Gaucher-related bone pathophysiology, including bone marrow infiltration by Gaucher cells, aberrant bone mineralization, and osteonecrosis, remain uncertain. Bone marrow infiltration occurs as glycolipid-laden Gaucher cells progressively and centrifugally displace normal, triglyceride-rich adipocytes from the adult marrow, leading to abnormal quantities and distribution of dark marrow (ie, areas of reduced bone marrow signal intensity on T_1-weighted MRI), usually starting in the axial skeleton and eventually extending to the appendicular skeleton.[2] An MRI analysis of bone marrow infiltration in the eliglustat phase 2 trial showed at least some dark marrow present at baseline in the femurs of 18 of 19 patients (95%); after 4 years of eliglustat treatment, 10 patients (56%) showed decreased dark marrow compared with baseline and the other 8 patients (44%) had stable dark marrow.[46] Although bone marrow infiltration appears to respond rapidly to treatment, it is not yet clear whether improvements in BMB score reflect decreased risk of bone events. Inadequate bone mineralization arising from pathological imbalances in osteoblastic-osteoclastic activity, possibly brought about by effects of excess bioactive glycosphingolipids on hematopoiesis, lead to increased fracture risk.[2] Treatment increases BMD, but whether this improvement translates into lower fracture risk remains to be seen. Osteonecrosis and osteolytic lesions arise from impaired blood supply to the bone resulting from disturbances in microcirculation related to the underlying marrow.[47] In addition, bone fracture, osteonecrosis, and inflammation are all characterized by excessive osteocyte death. Two mechanistic papers have characterized the relationships among the pattern recognition receptor macrophage-inducible C-type lectin (mincle), osteocyte death, osteoclast activity, endogenous glycolipids, and osteonecrosis.[48,49] Mincle acts as an immunostimulatory factor in response to cell damage; it senses pathogens and damaged cells, including the endogenous glycolipid β-glucosylceramide derived from damaged cells, such as necrotic osteocytes.[45,46] Strongly increased mincle expression after exposure to dead osteocytes stimulated by damage-associated molecular patterns has been reported to trigger osteoclast formation and metabolic activation.[49]

Effective treatment of skeletal disease would probably depend upon the dispersal of Gaucher-specific glycosphingolipids driving mincle activation in the marrow cavity.[45] However, the unitary steps that link pathological glycosphingolipids to impaired microcirculation in the bone and marrow tissues responsible for osteonecrosis, are unclear.[47,49] One possibility is that by enhancing osteoclast migration, activation of mincle by β-glucosylceramides may distract the cells from their coupled physiological role in remodeling bone, thereby leading to obstruction of capillaries in the growth plate. This phenomenon might explain the apparent paradox between osteoporosis related to imbalanced osteoclast/osteoblast activity and the frequent Erlenmeyer modeling deformity with undertubulated long bones due to impaired endochondral resorption at the metaphases.

Long-term analysis of skeletal outcomes across different eliglustat trials has limitations. On account of the distinct study designs that explored therapeutic activity of eliglustat in different subpopulations of patients with Gaucher disease, we evaluated the trials separately. In addition, the phase 2, ENGAGE, and ENCORE populations probably had a lower risk for bone events because of the exclusion of patients with

bone crises or active bone lesions during the year before enrolment (only the EDGE trial did not exclude patients with recent bone crises) and exclusion of splenectomy (a known risk factor for bone events[18,40]) in phase 2 and ENGAGE. Because these were adult populations, there were too few adolescents and young adults for analysis of changes in skeletal parameters over the transition from adolescence into adulthood. Of note, the entry criteria for the treatment-naïve trials required participating patients to have an intact spleen, because reduction in spleen volume was the primary end point for the efficacy evaluation of eliglustat.

Finally, not only did each trial have a different duration (Table 1) but also the number of patients available for analysis in ENGAGE, ENCORE, and EDGE declined, sometimes by ≥50%, during long-term follow-up. It should be noted however, that almost without exception, the patients became unavailable for evaluation because the trial extensions ended on a specific date rather than after a prespecified duration of treatment. Patients who enrolled early in the 2-year enrollment period, and were randomized to eliglustat (for ENGAGE or ENCORE[26,27]) and were not switched to commercial eliglustat after drug approval (United States only) could remain in these trials for up to 3 years longer than patients who enrolled later. These latter subjects were randomized to placebo or imiglucerase and switched to commercial eliglustat after drug approval (United States only). The data are, therefore, presented descriptively with the number of patients evaluated at each time point provided. For the bone pain analysis (Figure 3), timeframes were chosen to represent the latest time points with sufficient numbers of patients with baseline and follow-up data. The one objective measure of skeletal disease in our study, BMD, is a surrogate marker for bone health and should be interpreted in the larger context of other skeletal parameters, such as fractures, bone pain, bone crises, and mobility. It will be important to evaluate long-term skeletal effects of eliglustat treatment in real-world populations and the effect of eliglustat treatment on risk of fragility fractures. The Gaucher Risk Assessment for Fracture, a composite risk score for assessing adult fracture risk in imiglucerase-treated patients with Gaucher disease type 1, may prove helpful for this effort.[50] Two recent long-term, real-world analyses of ERT-treated patients in the ICGG Gaucher Registry[50] and the United Kingdom[18] have documented increased risk of fragility fractures, osteonecrosis,[18] and orthopedic surgery[18] among patients with splenectomy, as well as marked sex differences in fracture risk over time since splenectomy.[18,50] On account of patients with splenectomy being excluded from the phase 2 and ENGAGE trials and the lack of baseline BMD data in the EDGE trial, we were unable to explore these relationships.

Conclusion

With eliglustat treatment, markers of skeletal disease and degree of bone pain improved for treatment-naïve patients and remained stable for patients who switched from ERT to eliglustat. These findings extend the demonstrated long-term safety[28] and efficacy of eliglustat to ameliorate hematologic, visceral, and bone manifestations in treatment-naïve patients and its ability to maintain the stability of these parameters in patients switching from enzyme therapy.[14-17,22-27]

Data Availability

Qualified researchers may request access to patient-level data and related documents. Patient-level data will be anonymized, and study documents will be redacted to protect the privacy of trial participants. Further details on Sanofi's data sharing criteria, eligible studies, and process for requesting access can be found at https://www.clinicalstudydatarequest.com/

Acknowledgments

The eliglustat clinical trials were sponsored by Sanofi. The authors thank the participating patients, who were compensated for travel expenses, and health care professionals, whose institutions received funding for clinical trial-related expenses from Sanofi. We also thank Laurie LaRusso of Chestnut Communications for medical writing support funded by Sanofi, Lisa Underhill (Director of Scientific Communications and Publications for eliglustat, Sanofi Global Medical Affairs) for writing assistance and critical review of the manuscript, and Sebastiaan J.M. Gaemers (Sanofi, Global Pharmacovigilance) for critical review of the manuscript.

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Ethics Declaration

All 4 studies were approved by the institutional review boards or independent ethics committees at each trial site and 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.

Conflict of Interest

T.M.C. was a principal investigator on the Sanofi-sponsored eliglustat ENCORE trial and has received honoraria, travel

reimbursement, and grant/research support from Takeda, Shire Pharmaceuticals and Sanofi. J.C. was a principal investigator on the Sanofi-sponsored eliglustat EDGE trial; has received honoraria for consultation and advisory board participation from Sanofi, Synageva, Shire, BioMarin, National Gaucher Foundation, and Pfizer/Protalix; and has received lecture fees or honoraria for speaking at the invitation of Sanofi and SIMD North American Metabolic Academy. E.L. was a principal investigator on the Sanofi-sponsored eliglustat phase 2, ENGAGE, ENCORE, and EDGE trials and has received honoraria and travel reimbursement and participates on advisory boards of Sanofi and Shire. P.K.M. was a principal investigator on the Sanofi-sponsored eliglustat ENGAGE trial, is a member of the International Collaborative Gaucher Group (ICGG) Gaucher Registry North American Advisory Board, and has received research support, honoraria, and travel reimbursement from Sanofi. M.J.P. and M.C.F. are employees of Sanofi and own shares and/or stock options in the company.

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