

Scientific Response from Takeda Pharmaceutical U.S.A.

Date: 11/14/2019
Drug: VPRIV® (Velaglucerase alfa for injection)
Manufacturer: Takeda Pharmaceutical U.S.A., Inc.

On behalf of Takeda Pharmaceutical U.S.A. (formerly Shire), we would like to provide additional evidence-based scientific data for VPRIV (velaglucerase alfa) to the P&T committee for consideration as a first-line enzyme replacement therapy (ERT) for Gaucher disease type 1 (GD1) patients. Please refer to the VPRIV US prescribing information label for full safety and indication information. Below are additional evidence-based scientific data we would like to highlight for VPRIV (velaglucerase alfa):

- **Human Fibroblast Cell Line Based Derivative Resembling Glucocerebrosidase**
 - Velaglucerase alfa is the only ERT derived by gene activation technology in a human (fibroblast) cell line, therefore, it has exactly the same amino acid sequence as that of naturally occurring glucocerebrosidase¹⁻⁵
 - It contains predominantly high-mannose-type glycans, which facilitates target cell uptake via mannose receptors, resulting in greater in vitro internalization relative to imiglucerase^{3,4}
- **Low Anti-Drug Immunogenicity in GD1 Patients on ERT**
 - Velaglucerase alfa has a low immunogenicity potential, as demonstrated across clinical studies¹⁻⁶.
 - One in 54 (2%) enzyme treatment-naïve patients in clinical studies treated with velaglucerase alfa developed anti-drug IgG-class antibodies⁵.
 - Seroconversion observed in 1% of all patients (n=82) from multiple Phase III clinical trials⁷.
 - Development of anti-drug antibodies to velaglucerase alfa showed a very low incidence of 2%⁸ relative to the incidence of 15% anti-drug antibodies reported for imiglucerase in treatment-naïve patients⁹, relative to 53% for taliglucerase alfa in treatment-naïve patients, and 14% in patients who switched from imiglucerase to taliglucerase alfa¹⁰.
- **Clinical Biomarkers Improvement**
 - Plasma chitotriosidase and plasma CCL18 declined in ERT patients switched to velaglucerase alfa at 12 months with mean percentage changes of -28.1% and -16.4%, respectively¹¹.
 - 52% reduction in lyso-Gb1 levels at Week 161 in ERT patients switched to velaglucerase alfa¹².
- **Hematologic Improvements**
 - Significant increases in the blood hemoglobin level (primary endpoint) and in platelet count with decreases in spleen volume and liver volume^{11,13}.
 - Sustained clinical stability in hematological parameters over 5 years of treatment¹⁴.
- **Bone Improvements in BMD and BMB**
 - Improvements in mean lumbar spine and femoral neck bone mineral density (BMD) from baseline to Month 24 and Month 33, respectively¹⁵.
 - Reduced lumbar spine bone marrow burden (BMB) by at least 2 points, from baseline to Month 57, as exploratory endpoints in a Phase I/II study¹⁵.
 - BMB maintained improvement over approximately 7 years (duration of 9-month controlled trial (n=12) and subsequent extension study [n=10]¹⁵. BMD maintained improvement over 24 to 69 months (n=10).¹⁵
 - 87% of Treatment-naïve patients (≥ 18 years of age) showed improvements in bone mineral density, lumbar spine bone mineral density after 4 years of treatment.¹⁵

- **Long-Term Post-Marketing Clinical Experience – Gaucher Outcomes Survey (GOS) Registry**
 - The Gaucher Outcome Survey (GOS) is an international registry for patients with confirmed GD regardless of type or treatment status. It collects data during patients' routine care, and provides an opportunity for long-term analysis of patients receiving velaglucerase alfa¹⁶. The objectives of the registry include to evaluate the safety and long-term effectiveness of velaglucerase alfa.
- **Treatment Considerations**
 - Currently, ERTs such as VPRIV, imiglucerase, and taliglucerase alfa are recommended as first-line therapy for type 1 Gaucher disease. Substrate reduction therapy (SRT), such as miglustat, is limited to use only in adults with mild to moderate type 1 Gaucher disease for whom ERT is not an option due to constraints such as allergy, hypersensitivity, or poor venous access^{5,10,17,18}.
- **Dosage and administration**
 - VPRIV administered under the supervision of an HCP comprises a 60-minute intravenous infusion for enzyme therapy-naïve patients 4 years and older: 60 Units/kg administered every other week (EOW). Patients currently being treated with imiglucerase for type 1 Gaucher disease can be switched to VPRIV. Patients previously treated on a stable dose of imiglucerase are recommended to begin treatment with VPRIV at that same dose upon switch from imiglucerase to VPRIV two weeks after last imiglucerase dose. Dosage adjustments can be based on achievement and maintenance of each patient's therapeutic goals⁵.
- **VPRIV Clinical Benefits**
 - The VPRIV clinical development program included 5 Phase II/III clinical trials that evaluated the efficacy and safety of velaglucerase alfa and exposed 94 patients with type 1 Gaucher disease (intent-to-treat [ITT] population) to doses ranging from 15 Units/kg to 60 Units/kg every other week (EOW)^{2,5,11,13,19}. Diverse patient populations with type 1 Gaucher disease were studied in the VPRIV clinical trials. These included adult and pediatric patients (4 years of age and older), splenectomized and nonsplenectomized patients, patients with different ethnicities and genotypes and treatment-naïve and patients switched from imiglucerase.

References:

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Cambridge, November 7th, 2019

To

Roger A. Citron, RPh
Sarah Servid, PharmD
Oregon State University
500 Summer Street NE, E35
Salem, Oregon 97301-1079

Dear Drs. Citron and Servid,

Thank you for the opportunity to review and provide comments on “Drug Class Review: Target Therapies for Gaucher Disease”. Sanofi Genzyme Medical acknowledges the validity of the core scientific arguments and kindly request your consideration of some specific comments and references described below.

We believe more recent clinical data, including eliglustat and imiglucerase new real-world evidence, long-term bone and quality of life data, are critical for the development of a set of guidelines that will enrich the quality of patient care in Oregon. Key points are summarized below; we would ask you to refer to the original publications as well.

Our comments will address each of the three parts of the recently released “OSU Drug Class Review: Target Therapies for Gaucher Disease”.

Part 1. Regarding the level of scientific evidence in the rare disease space, with a focus on the eliglustat clinical development program, long-term clinical practice with imiglucerase and the International Gaucher Registry.

Acknowledging the difficulties of developing large randomized control trials in a very small population, Sanofi Genzyme would like to emphasize:

The eliglustat clinical development program is the largest ever developed in Gaucher disease, enrolling almost 400 patients over four clinical trials, including both treatment naïve and patients stable on ERT. Long-term data from this program confirming the finding of different primary analyses are available for up to 8 years (Lukina E. ERT al, *Am J Hematologists*. 2019; 94:29-38 and Cox T. *Blood*. 2017; 129(17):2375-2383).

Imiglucerase is the longest studied enzyme replacement therapy (ERT) in Gaucher disease. Since its approval 25 years ago in the US, its safety and efficacy in the treatment of GD1 patients have been evaluated in both randomized clinical trials (*Ann Intern Med*. 1995;122(1):33-39) and long-term observational studies (*Am J Hematol*. 2008;83(12):890-895)). The historical lack of awareness and the overall rarity of the disease made the International Collaborative Gaucher Group (ICGG) Gaucher Registry, sponsored by Sanofi Genzyme, an essential part of the imiglucerase clinical development program allowing extensive analysis over the last two decades. The Gaucher Registry is the world’s largest cooperative, observational database for Gaucher disease, providing data on more than 6000 patients worldwide (*Am J Hematol*. 2015;90(Suppl 1): S2-S5).

1.A. OHA observations on the ENCORE study; a single non-inferiority trial with patients switching from imiglucerase to eliglustat (Cox T. ERT al, Lancet 2015;385:2355-62):

OHA questions ENCORE's quality of evidence and the chosen non-inferiority margin.

ENCORE is a phase 3, randomized, multinational, open-label, non-inferiority trial enrolling 160 adult patients with Gaucher disease who have received ERT for 3 or more years. Non-inferiority is an appropriate design to establish the safety and efficacy of a novel treatment.

Following this primary analysis period, patients entered a long-term extension phase in which all received eliglustat. Long-term safety and efficacy data from 157 patients who received eliglustat in the ENCORE trial have been published (Blood. 2017; 129(17):2375-2383); data is also available for 46 patients who received eliglustat for four years.

Additional Discussion on Non-Inferiority Margin

Supplementary information for the rationale and statistical methodology provided to other HTAs during their evaluation to confirm the validity of the -25% non-inferiority margin.

As published by Cox et al. (*Lancet. Jun 13 2015;385(9985):2355-2362*) the composite primary efficacy endpoint of the non-inferiority ENCORE trial was the percentage of patients whose **all FOUR parameters**, two hematological (platelet count and hemoglobin concentration) AND two organ volumes (liver and spleen) remained stable after 12 months of treatment.

A composite endpoint is legitimate when a particular disease manifests itself in a multifaceted form of the same underlying cause (*Stat Med. Dec 10 2017;36(28):4437-4440*). In the ENCORE trial, the conservative definition of disease stability was not arbitrarily set but mainly defined as per the widely accepted published therapeutic goals in Gaucher disease (*Semin Hematol. Oct 2004;41(4 Suppl 5):4-14*) and as per the criteria established from patients with Gaucher disease type 1 receiving maintenance treatment with imiglucerase (*Mol Genet Metab. 2009;96(1):164-170*). To be classified as a success with respect to the composite endpoint, individual patients in the ENCORE trial – stabilized with ERT for at least 3 years – had thus to meet all four stability criteria listed below:

- Hemoglobin concentration that did not decrease by more than 1.5 g/dL;
- Platelet count that did not decrease by more than 25%;
- Spleen volume (in non-splenectomized subjects expressed as multiples of normal [MNs]) that did not increase by more than 25%;
- Liver volume (MN) that did not increase by more than 20% from baseline.

The patients enrolling in ENCORE had good disease control at baseline, including liver volumes ~1 MN and spleen volumes of ~3 MN. This means that relatively small absolute increases in liver or spleen volumes would be likely to result in failure to meet stability criteria, defined in terms of percent growth. The 25% non-inferiority margin was based on a 95% imiglucerase (Cerezyme) response rate and an 85% eliglustat response rate (established by phase 2 results) (*Lancet. Jun 13 2015;385(9985):2355-2362*). The margin thus allowed for a 10% difference between imiglucerase and eliglustat, and an additional 15% for inherent variability in estimation of the difference between these treatments. This margin of 25% is also half the expected difference of approximately 50% that would exist between Cerezyme treatment and

discontinuation of Cerezyme treatment for 1 year, based on data from a matched group of GD1 patients from the ICGG Gaucher Registry (SANOFI GENZYME Canada. Data on File. Cerdelga Common Technical Documents. 2018).

In addition, this margin has been discussed with the FDA and the Committee for CHMP. The reason for the 25% margin versus the 20% margin was due to the rarity of the patient population, the size of the study and the required statistical power. Accordingly the power to demonstrate non-inferiority using the assumptions used at the ENCORE study design stage regarding the stability rates of Cerezyme (95%) and CERDELGA® (85%) using the observed number of per-protocol population patients for Cerezyme (n = 47) and CERDELGA® (n = 99) is shown in Table for different non-inferiority margins.

Table 1: Power to Demonstrate Non-inferiority in the ENCORE Study Per-protocol Population for Different Margins

| Non-inferiority margin | Power (%) * |
|------------------------|-------------|
| -25% | 91 |
| -20% | 61 |
| -15% | 21 |

* Power using the non-stratified Agresti-Caffo method. Similar results are obtained with the Newcombe test.

Despite this caveat, the ENCORE trial reported that the lower bound of the 95% CI for the observed difference between eliglustat and imiglucerase treatment arms were within the 20% recommended CHMP margin and within the 25% agreed FDA margin demonstrating non-inferiority to imiglucerase in maintaining the stability of hematological characteristics and organ volumes in adults with GD1.

Worth mentioning, for each parameter taken separately from the composite end-point, stability was achieved in 93% to 96% of eliglustat treated patients i.e., spleen volume 96%; liver volume 96%; hemoglobin level 95% and platelet count 93%.

Summary

- The appropriate way to evaluate the benefit of eliglustat is to look at the composite endpoint, which integrates clinical efficacy across visceral and hematological parameters; the ENCORE study met the primary composite end-point with eliglustat deemed non-inferior to imiglucerase in maintaining overall disease control in adult patients with GD1
- >90% of patients receiving eliglustat met the individual pre-specified therapeutic goals at Year 1 and each year of the ENCORE extension study.

From Cox T. ERT al; Blood. 2017: "Clinical stability assessed by composite and individual measures was maintained in adults with Gaucher Disease type 1 treated with eliglustat who remained in the ENCORE trial for up to 4 years."

Additional Data from Real-World Clinical Practice on GD1 Patients stable on ERT that switched to eliglustat: 2 years eliglustat data from the ICGG Gaucher Registry

This section describing the ICGG Registry is an excerpt from the Statistical Analysis Plan (SAP) that was submitted as a post-marketing commitment report to the regulatory authorities in Europe. It has been modified to reflect the methodology used for peer-reviewed publication, which is not the same as for regulatory reports. The complete SAP is included with this submission as an example of how data from the registry are used.

Two Years of Effectiveness of Oral Eliglustat in Treatment-Naïve and Switch Patients Enrolled in the International Collaborative Gaucher Group Gaucher Registry (Abstract, *WORLD Symposium 2019, Orlando, Florida 2019*)

This analysis provides real-world data of two years of effectiveness of oral eliglustat in treatment-naïve and ERT-switch patients enrolled in the ICGG Gaucher Registry (NCT00358943/Sanofi Genzyme).

As of July 2018, there were 400 eliglustat-treated patients in the Registry. Of these, 238 patients had baseline and 2-year data for at least one of the following: spleen volume, liver volume, hemoglobin, platelets, bone pain or bone crisis. Overall, 213 (**89%**) were from the US (the first country to approve eliglustat); 82% had at least 1 N370S mutation (34% homozygous); and 91% were CYP2D6 extensive, intermediate or poor metabolizers. 223 patients were switch, including 43 who were splenectomized. The mean age in switch and naïve patients was 45 years (range: 15–78).

Hematologic and Visceral Response

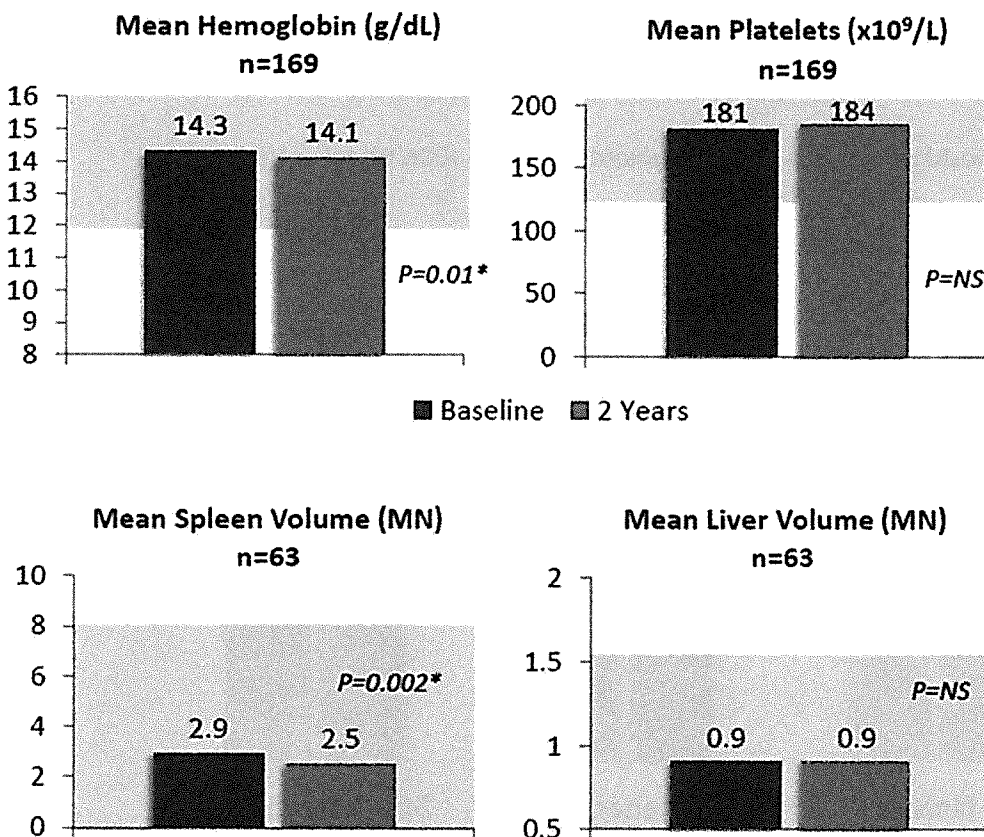
In non-splenectomized switch patients (figure 1):

- mean hemoglobin remained normal (14.3 at baseline vs 14.1 g/dL after eliglustat; $p=0.01$, $n=169$).
- mean platelet count remained normal (181 vs 184 $\times 10^9/L$; $n=169$).
- mean spleen volume decreased (2.9 to 2.5 MN; $p=0.002$, $n=63$).
- mean liver volume was stable at 0.9 MN ($n=63$).

In summary, mean values for all clinical parameters were within therapeutic goal ranges at baseline and remained with the therapeutic goal at the 2-year follow-up for non-splenectomized patients that switched from ERT to eliglustat. Additional information about anemia and thrombocytopenia status can be found in the poster that is included in this submission.

Figure 1: 2-year Eliglustat Response in Non-splenectomized Switch Patients from the ICGG Gaucher Registry

Hematologic and Visceral Response



*P value is from a paired t test comparing 2-year parameters to baseline

Shaded areas indicate values within long-term therapeutic goal thresholds for non-splenectomized GD1 patients:
Hemoglobin ≥ 11 g/dL for women and ≥12 g/dL for men; Platelets: ≥120 x 10⁹/L; Spleen volume ≤8 MN; Liver volume ≤1.5MN²;
MN: multiples of normal

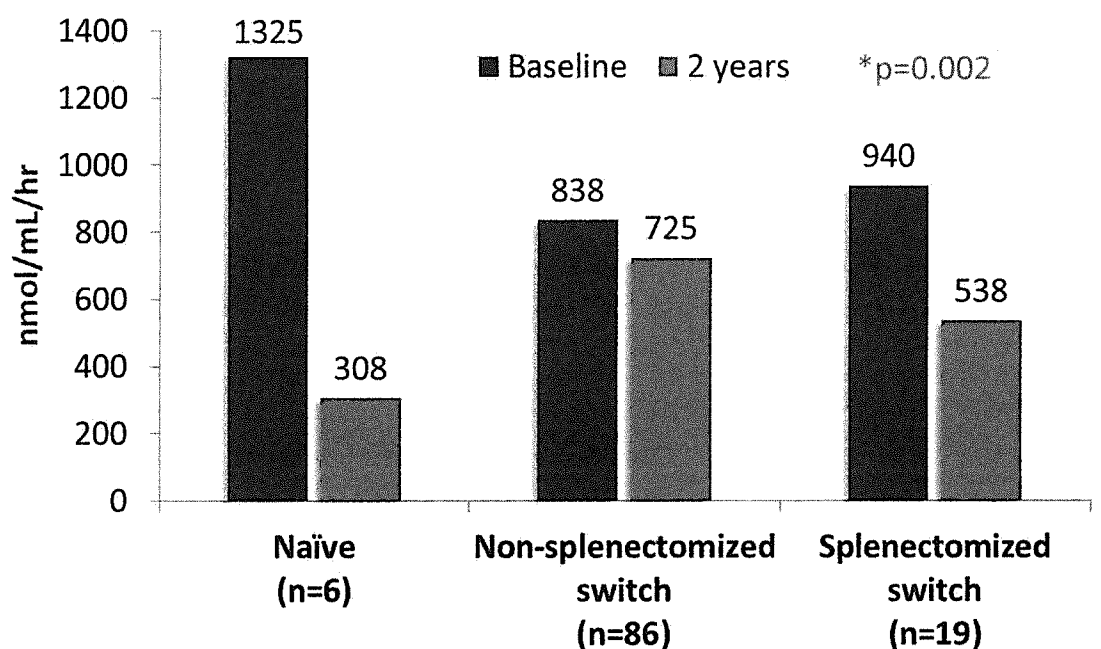
Source: 1) Mistry PM et al. Poster World 2019; 2) Pastores et al. Semin Hematol (suppl 5):4-14. 2004

Overall, switch patients had mean final visceral and hematologic values within GD1 therapeutic goal thresholds established for long-term ERT (hemoglobin ≥11 g/dL for women, ≥12 g/dL for men; platelet count ≥120 x10⁹/L; spleen volume <8 MN; liver volume <1.5 MN).

Chitotriosidase Response

Chitotriosidase is a biochemical marker for patients with Gaucher disease. Elevated levels of chitotriosidase activity reflect excess lipid storage and may be useful in monitoring the treatment of Gaucher disease. Mean chitotriosidase levels decreased 77% in naïve (1325 to 308 nmol/mL/hr, $p=0.03$, $n=6$), 13% in non-splenectomized-switch (838 to 725 nmol/mL/hr; $p=0.002$, $n=86$) and 43% in splenectomized-switch (940 to 538 nmol/mL/hr, NS, $n=19$) patients (Figure 2).

Figure 2: 2-Year chitotriosidase response in GD1 patients from the ICGG Gaucher Registry



* P value is from a Signed Rank test (nonparametric), comparing 2-year parameters to baseline

**NS=Not Significant; statistical significance was not achieved for this group

Source: Mistry PM et al. Poster World 2019.

Authors' Conclusion

ICGG Gaucher Registry demonstrated that:

- After 2 years of eliglustat, switch patients remained stable with respect to hemoglobin, platelets, spleen, and liver.
- Final mean values for switch patients were within GD1 therapeutic goal thresholds.
- These real-world results from the ICGG Gaucher Registry are consistent with those reported in eliglustat clinical trials.

1.B. OHA observations on the ENGAGE trial; a phase 3, double-blind, placebo-controlled trial conducted at 18 sites in 12 countries; enrolling 40 previously untreated adult patients with Gaucher disease type 1.

OHA comments on lack of improvement in bone parameters and symptoms.

Sanofi-Genzyme calls OHAs attention to the results of Eliglustat in different trials enrolling previous untreated GD1 patients.

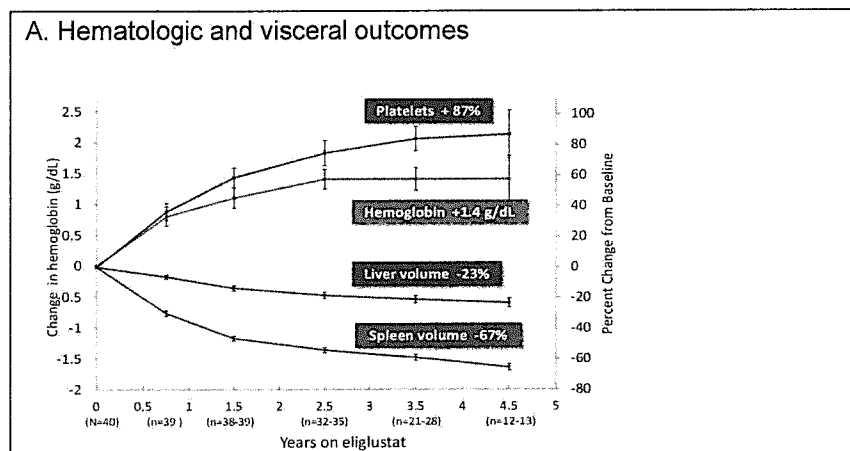
The achievement in different endpoints in Gaucher disease should take into consideration the baseline disease severity and time from treatment initiation. ENGAGE trial followed patients for nine months, which is generally considered to be insufficient to observe relevant changes in bone mineral density, especially in comparison to a mild bone loss at baseline. From Mistry P. et al. JAMA. 2015; 313(7):695-706: "Most patients in both treatment groups had unrestricted mobility and minimal or mild bone pain at baseline and 9 months". Nevertheless, investigators found a significant statistical improvement in total Bone Marrow Burden (BMB) at nine months in the eliglustat arm compared to placebo (mean difference -1.1, P=0.002), and all other markers of bone disease showed trends towards improvement, including lumbar spine Bone Mineral Density (BMD) and biomarker MIP-1 β . Additionally, after nine months, eliglustat resulted in significant improvement in the physical functioning domains compared to the placebo.

Based on the patient population and time to follow-up, Sanofi Genzyme refers to phase 2 study (Lukina E. ERT al, Am J Hematologists. 2019; 94:29-38), where treated naïve patients receiving eliglustat for up to 8 years achieved increase in mean lumbar spine T-score by 0.96, moving from osteopenia to the normal range. Mean quality of life score, including Fatigue Severity Score (FSS) and mean SF-36 domain, mostly below normal at baseline, also moved into ranges seen in healthy adults.

Long-term Data on visceral-hematological parameter and bone response in eliglustat Clinical Trials among naïve GD1 patients

Final data from the ENGAGE trial represent up to 4.5 years of eliglustat treatment (*Mol Genet Metab.* 2017;120(1):S97-S99). All patients previously randomized to placebo for the Primary Analysis Period (PAP) were switched to eliglustat. After the PAP, dose adjustments were permitted based on plasma trough concentration levels (dose escalation up to 150 mg BID was allowed). The results for the hematologic, visceral, and bone measures for patients who received eliglustat for up to 4.5 years show continued improvement in all parameters (Figure 3).

Figure 3. ENGAGE: Long-term Efficacy Measures up to 4.5 Years



Data points are mean \pm SEM

SOURCE: Mistry et al, 2015²⁶; Mistry et al, 2017²⁵

The longitudinal data show that patients treated for 8 years with eliglustat had early and significant improvements in both hematologic and visceral measures, which continued or were maintained over time. As a reminder, clinically meaningful and statistically significant improvements were observed after 13 weeks of treatment for hemoglobin levels and after 6 months for platelet counts and spleen and liver volumes (*Blood*. Aug 12 2010;116(6):893-899).

Figure 4: Hematologic and Visceral Improvements in 8 years follow-up Phase 2 study

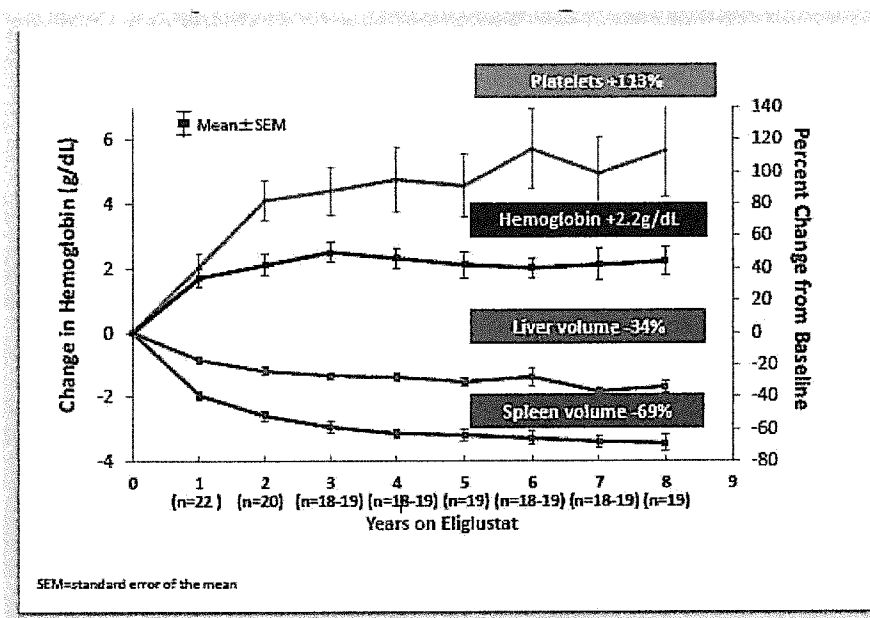
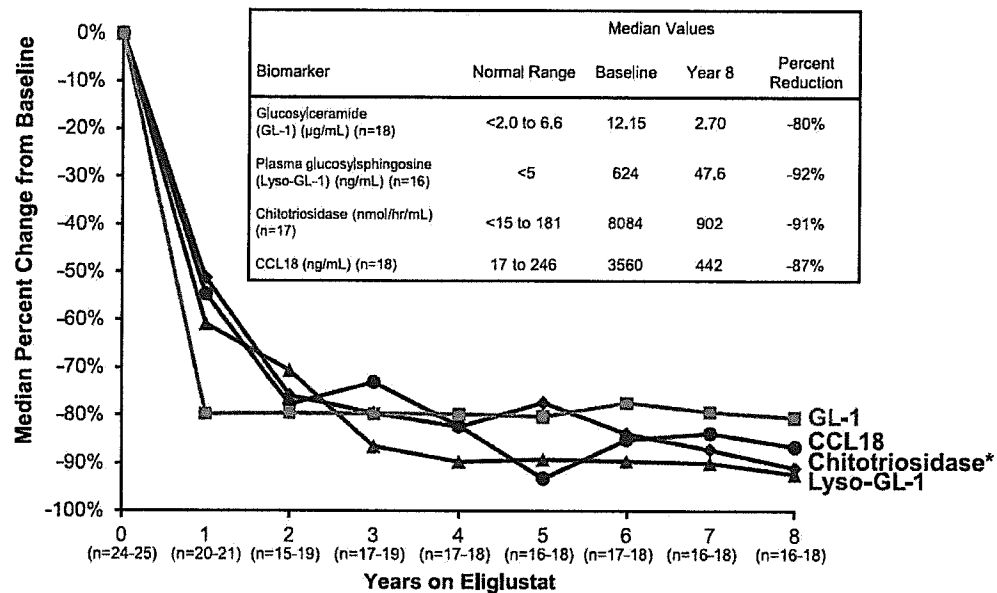


Figure 51: Decrease in Gaucher Disease Biomarkers in the Phase 2 Trial – 8 years Follow-up



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.

Additional Data from Real-World Clinical Practice on Naïve GD1 Patients: 2 years eliglustat data from the ICGG Gaucher Registry (Abstract, WORLDSymposium 2019, Orlando, Florida 2019)

Fifteen patients were treatment-naïve, all with intact spleens; The mean age in switch and naïve patients was 45 years (range: 15–78).

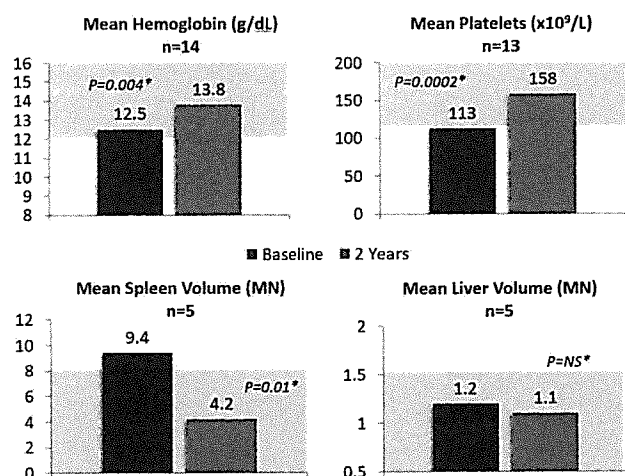
Hematologic and Visceral Response

In naïve patients (Figure 6):

- mean hemoglobin increased (12.5 to 13.8 g/dL, $p=0.004$, $n=14$);
- the mean value of hemoglobin at baseline is above the therapeutic goal threshold described by Pastores *et al.* (11 g/dL for women and 12 g/dL for men) and significantly improves at the 2-year follow-up.
- mean platelet count increased (113 to 158 $\times 10^9/L$, $p=0.0002$; $n=13$);
- the mean platelet count at baseline is below the therapeutic goal threshold described by Pastores *et al.* (120×10^9) and significantly improves at the 2-year follow-up.
- mean spleen volume decreased (9.4 to 4.2 multiples of normal [MN], $p=0.01$, $n=5$);
- the mean spleen volume at baseline is above the therapeutic goal threshold described by Pastores *et al.* (≤ 8) and significantly improves at the 2-year follow-up.
- mean liver volume was unchanged (1.2 vs 1.1 MN; $n=5$).
- the mean liver volume at baseline is below the therapeutic goal threshold described by Pastores *et al.* (≤ 1.5) and remains below this threshold at the 2-year follow-up.

In summary, the final mean values for all clinical parameters are within therapeutic goal thresholds established for long-term ERT.

Figure 6: 2 –Year Eliglustat response in naïve patients from ICGG Gaucher Registry



*P value is from a paired t test comparing 2-year parameters to baseline

Shaded areas indicate values within established long-term therapeutic goal thresholds²: Hemoglobin ≥ 11 g/dL for women and ≥ 12 g/dL for men; Platelets: $\geq 120 \times 10^9/L$; Spleen volume ≤ 8 MN; Liver volume ≤ 1.5 MN.

MN: multiples of normal

Source: 1) Mistry PM *et al.* Poster World 2019; 2) Pastores *et al.* Semin Hematol (suppl 5):4-14. 2004

Table 2: Disease Severity at Baseline and After 2-years of Eliglustat in Individual Treatment-naïve Patients

| Age (Years) | Sex | Hemoglobin (g/dL) | | Platelet Count (x 10 ⁹ /L) | | Spleen (MN) | | Liver (MN) | |
|---------------------|-----|------------------------|---------|---------------------------------------|---------|--------------------|---------|----------------------|---------|
| | | Baseline | 2 Years | Baseline | 2 Years | Baseline | 2 Years | Baseline | 2 Years |
| 18–30 | F | 8.8 | 12.1 | 196 | 219 | 7.5 | 3.9 | 1.3 | 1.4 |
| | M | 14.5 | 14.5 | 88 | 121 | | | | |
| | M | 13.7 | 14.5 | 89 | 132 | | | | |
| | M | 13.8 | 13.9 | 90 | 136 | | | | |
| >30 to 50 | M | 13.4 | 13.8 | 136 | 149 | | | | |
| | M | 16.7 | 17.0 | 74 | 154 | | | | |
| | F | 12.0 | 12.5 | | | | | | |
| | F | 11.4 | 12.9 | 86 | 185 | 8.5 | 3 | 1.2 | 0.9 |
| >50 to 60 | F | 14.3 | 14.0 | 211 | 204 | | | | |
| | F | 11.3 | 14.1 | 85 | 144 | 14 | 6.4 | 1.6 | 1.3 |
| | F | 11.9 | 12.2 | 71 | 93 | | | | |
| >60 to 80 | M | 8.7 | 12.0 | 91 | 146 | | | | |
| | F | 13.4 | 14.6 | 94 | 183 | 4.6 | 3.4 | 1.2 | 1.2 |
| | M | 11.3 | 14.4 | 159 | 194 | 12.5 | 4.5 | 1 | 0.9 |
| Severity categories | | ≥12 (men); ≥11 (women) | | None: >150 Mild: 100 to ≤150 | | None/Mild: ≤ 5 | | None/Mild: ≤ 1.25 | |
| | | <12 (men); <11 (women) | | Moderate: 50 to <100 | | Moderate: >5 to 15 | | Mod.: >1.25 to ≤ 2.5 | |

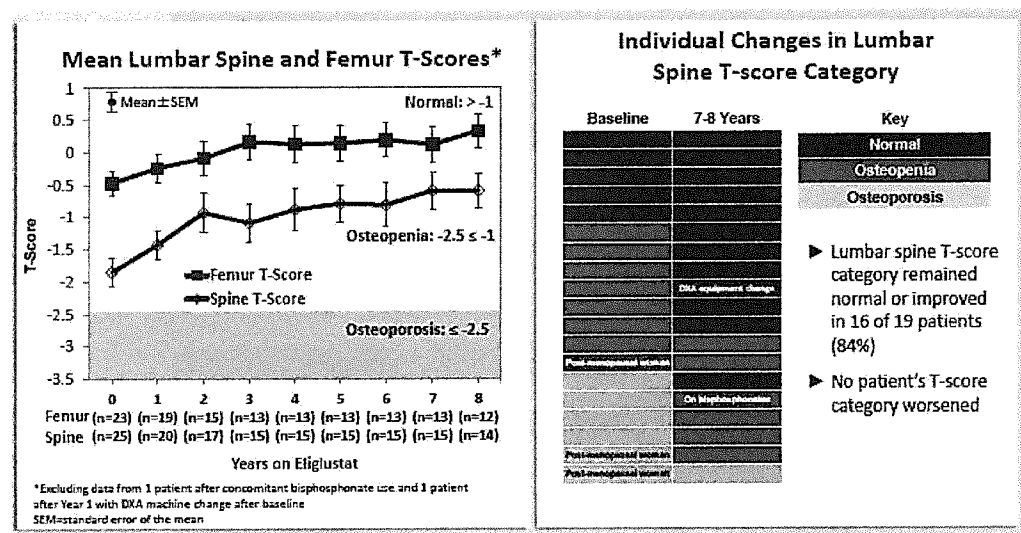
Eliglustat Bone Data

Phase 2 Study Long-term analysis

All patients who were normal at baseline remained normal throughout the trial. Results from this analysis demonstrated that after 8 years of eliglustat, the lumbar spine T-score remained normal or improved in 16 (84%) of 19 patients. No patient's osteopenia category worsened; 2 patients had persistent osteopenia; 1 patient (post-menopausal woman) had persistent osteoporosis.

Mean lumbar spine T-score moved from the osteopenic range at baseline to the normal range within 2-3 years and remained normal with continued improvement for up to 8 years. Patients who had normal values at baseline remained normal, and most patients with osteopenia or osteoporosis at baseline improved.

Figure 8: Bone parameters - Lumbar spine and Femur T-scores (Lau H. et al. WORLD Symposium San Diego, US2018)

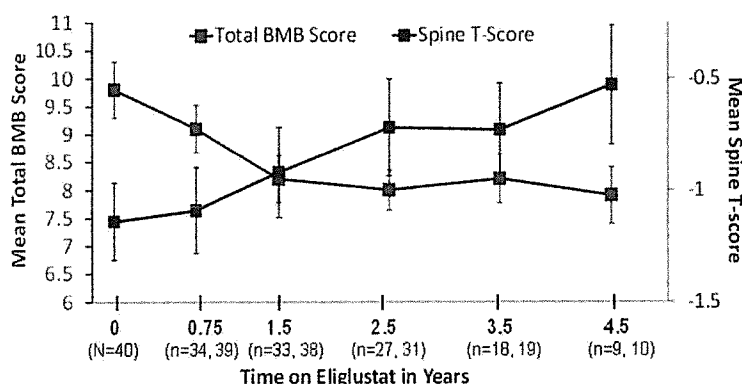


ENGAGE Study and Extension (up to 4.5 years of eliglustat treatment)

In the ENGAGE study and extension, patients were followed for up to 4.5 years on eliglustat (*Mol Genet Metab.* 2017;120(1):S97-S99). Bone measures and Gaucher disease biomarker levels improved significantly, with a 21% increase in mean spine T-scores, an 82% decrease in chitotriosidase, a 79% decrease in GL-1, and a 71% decrease in MIP-1 β after 4.5 years of eliglustat.

As in the Phase 2 study, BMD lumbar spine T-scores were in the osteopenic range at baseline and moved into the normal range after 2-3 years of eliglustat treatment, with further improvement for the duration of the trial.

Figure 9: ENGAGE - Long-term Bone Data



BMB=bone marrow burden; BMD=bone mineral density; SEM=standard error of the mean
SOURCE: Mistry et al, 2015; Mistry et al, 2017

1.C. OHA observation of lack of RCTs to evaluate clinical bone-related outcomes, mortality and quality of life in patients with Gaucher disease type 1.

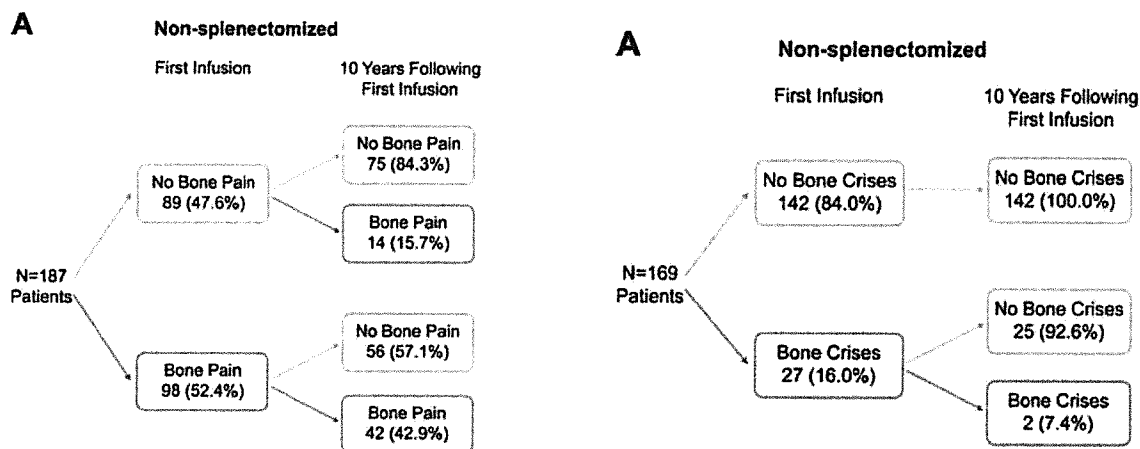
Sanofi Genzyme acknowledges the natural limitations of data coming from the ICGG Gaucher Registry. Registry data are challenging to control for confounding factors. Nevertheless, registries are still an essential informative tool in the Rare Disease space (Frieden TR. N Engl J Med 2017;377:465-75).

The ICGG is an international, multicenter, longitudinal, observational, and voluntary program designed to collect uniform and meaningful clinical data related to the onset, progression, and treated course of patients with Gaucher disease. ICGG is the largest rare disease registry with data collected from over 6300 patients with Gaucher disease worldwide and should reflect the real-world clinical care of type 1 Gaucher patients.

Sanofi Genzyme refers to relevant imiglucerase publications from the ICGG Registry that may address some of the raised concerns.

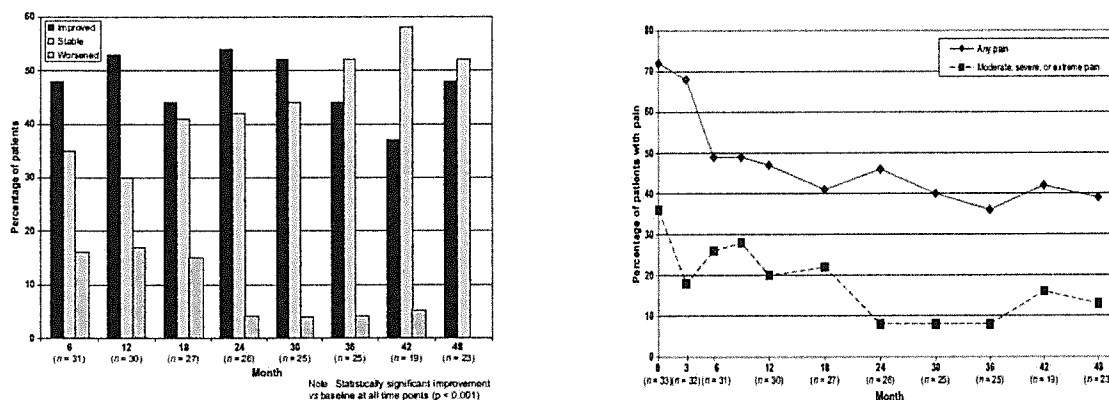
Weinreb N et al. (*J Inherit Metab Dis.* 2013;36(3):543-553) have retrospectively analyzed hematological, visceral and bone parameters of 757 patients receiving imiglucerase over 10 years. Both splenectomized and non-splenectomized patients showed statistically significant improvement in visceral, hematological and bone manifestations, with a 57% reduction in reported bone pain and a 93% reduction in the reported bone crisis.

Figure 10 shows changes in bone pain ($P < 0.0001$) and bone crisis ($p < 0.0001$) from the first infusion of imiglucerase to 10 years in non-splenectomized GD1 patients.



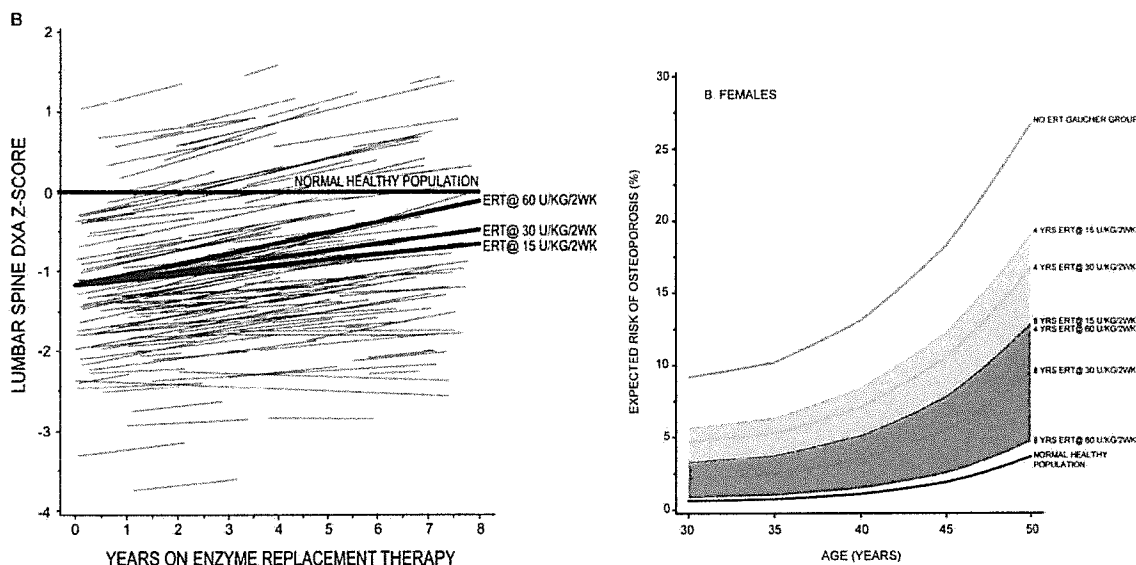
Charrow J et al. (Clin Genet. 2007;71(3):205-211) retrospectively analyzed the Gaucher Registry data on patients with bone crisis and/or one pain data for 1 year prior to imiglucerase treatment and each year for 3 years after imiglucerase treatment initiations. The year before treatment was considered as baseline. The study showed statistically significant ($P < 0.0001$) improvement in skeletal manifestations.

Figure 11 shows bone pain over time – self-reported pain levels over time. The percentage of patients with any pain or moderate, severe or extreme pain was determined and graphed over time.



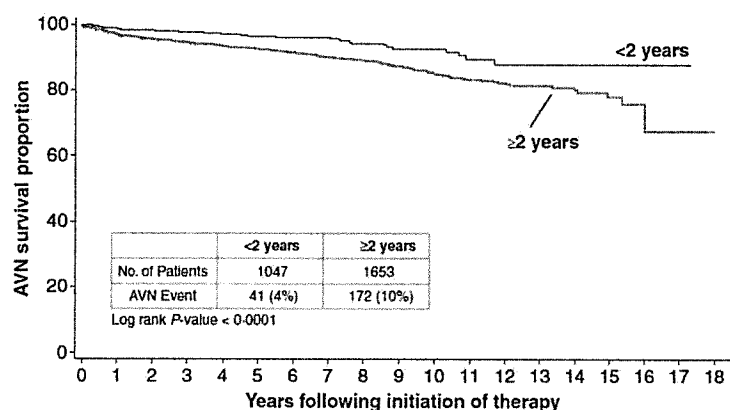
Wenstrup RJ et al. (J Bone Miner Res. 2007;22(1):119-126) have analyzed all patients with type 1 Gaucher disease enrolled in the ICGG Gaucher Registry for whom lumbar spine BMD were available. "In this analysis, untreated patients showed no improvement or a slight decline in BMD over time. Patients treated by ERT with imiglucerase showed significant improvements in BMD over time, with significant dose-related increases in lumbar spine Z scores that approached the normal reference population."

Figure 12 shows changes in LS BMD accordingly to imiglucerase dose over time and the risk of developing osteoporosis according to different dose regimes.



Mistry et al. (*Br J Haematol.* 2009;147(4):561-570) analyzed the relationship between enzyme replacement therapy with imiglucerase and incidence of avascular necrosis (AVN) in type 1 Gaucher disease. "The risk of AVN was reduced among patients who initiated ERT within 2 years of diagnosis, compared to initiating treatment ≥ 2 years after diagnosis. A higher risk of AVN was observed among patients who had previously undergone splenectomy".

Figure 13: Describes Kaplan-Myer curve for Avascular Necrosis over several years of imiglucerase initiation



From Mistry P. et al. "Avascular necrosis is a severe and irreversible complication of GD1 that frequently leads to functional disability (Wolfe & Taylor-Butler, 2000). Even after acute debilitating symptoms subside, patients suffer from chronic joint destruction, pain and progressive immobility"

Andersson H, et al. (*Pediatrics*. 2008;122(6):1182-1190) investigated the long-term effect of imiglucerase on 884 pediatric patients with type 1 Gaucher disease. "Patients demonstrated significant improvement in height z score over the 8-year treatment period". "The treatment effect (follow-up value at 8 years, compared with baseline value) was an improvement of 1.9 and 0.5 z score units for patients in the 5th and 95th percentiles at baseline, respectively". "Among the 440 patients with no reported bone crises before initiation of ERT, 2.5% (11 patients) reported a bone crisis during the follow-up period. Of the 90 patients who reported a bone crisis before initiation of ERT, 16.3% (15 patients) reported a bone crisis during follow-up monitoring. After 2 years of ERT, there were no new bone crises among patients who reported an event before initiation of ERT".

Figure 13 shows changes in height Z score and pain crisis over imiglucerase treatment.

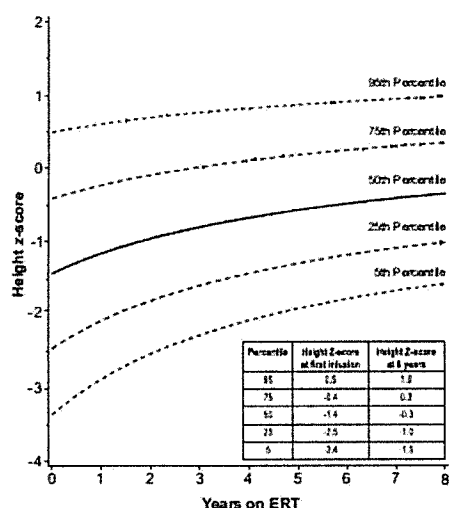


FIGURE 1
Changes in height z scores with years of ERT treatment.

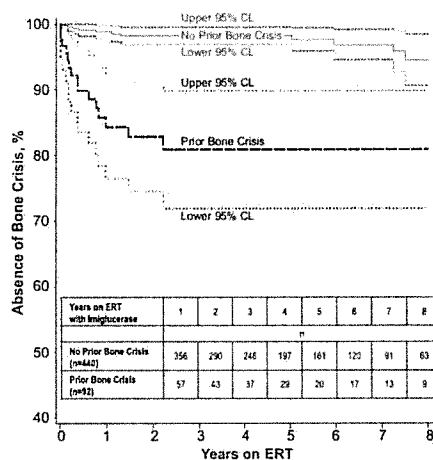


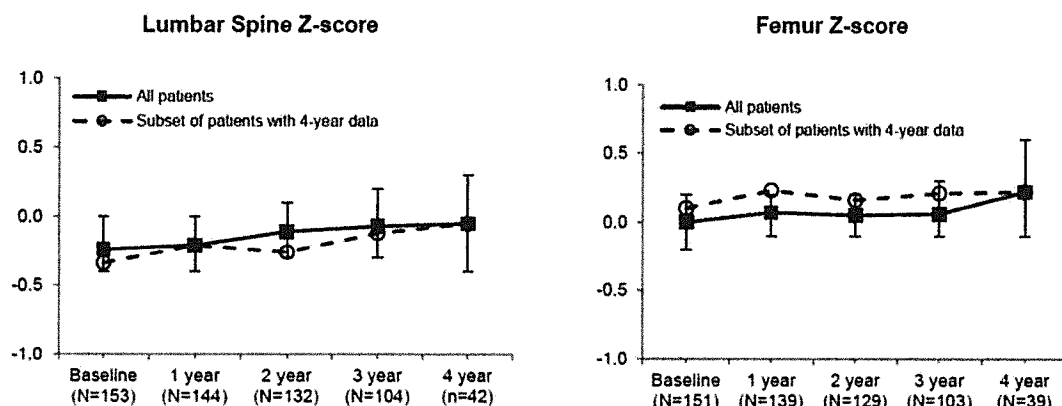
FIGURE 7
Numbers of bone crises with years of ERT treatment. CL indicates confidence limit.

Additionally, Sanofi-Genzyme would like to call attention to specific Bone data from phase 3 studies with Eliglustat in stable GD1 patients switched from ERT.

ENCORE Study – eliglustat on GD1 patients stable on ERT

Within the ENCORE study, BMD scores for most patients were within the normal range at baseline, and Z-scores (for lumbar spine and femur) were maintained for up to 4 years (Figure 2) (*Blood. 2017;129(17):2375-2383*).

Figure 2. ENCORE: long-term efficacy for bone endpoints



*Eliglustat dose started at Day 1 for the eliglustat group and after Year 1 for imiglucerase-to-eliglustat group. Error bars indicate exact 95% confidence interval

SOURCE: Cox et al 2017²⁸

Repeated measures mixed model analysis revealed a small but statistically significant increase in total spine Z-score through 4 years of eliglustat treatment (Table 3). This analysis also revealed a small increase in total femur Z-score over 4 years, which was significant at some time points (*Blood. 2017;129(17):2375-2383*).

Table 3. ENCORE: Long-term Efficacy Results After Up to 4 Years of Eliglustat Therapy (LS Means for Spinal Z-scores From Repeated-measures Mixed Model)

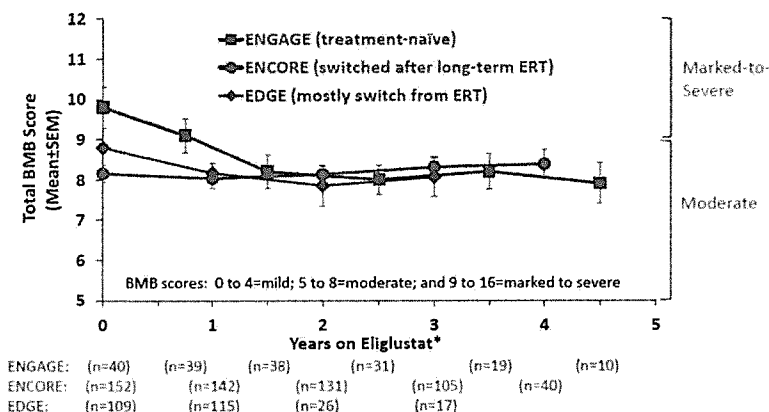
| Total spinal Z-score | LS mean (95% CI) | P value vs baseline |
|----------------------|---------------------|---------------------|
| Baseline (n=153) | -0.3 (-0.3, -0.2) | — |
| Year 1 (n=144) | -0.2 (-0.2, -0.1) | 0.002 |
| Year 2 (n=132) | -0.1 (-0.2, -0.09) | <0.0001 |
| Year 3 (n=104) | -0.09 (-0.1, -0.04) | <0.0001 |
| Year 4 (n=42) | 0.04 (-0.04, 0.1) | <0.0001 |

CI=confidence interval; LS=least squares

SOURCE: Cox et al²⁸

Bone Marrow Burden in Phase 3 Eliglustat Clinical Trials

Figure 15: Total Bone Marrow Burden (BMB) Score in all Eliglustat Phase 3 Trials (Cox T et al. WORLD Symposium. Orlando, Florida 2019)

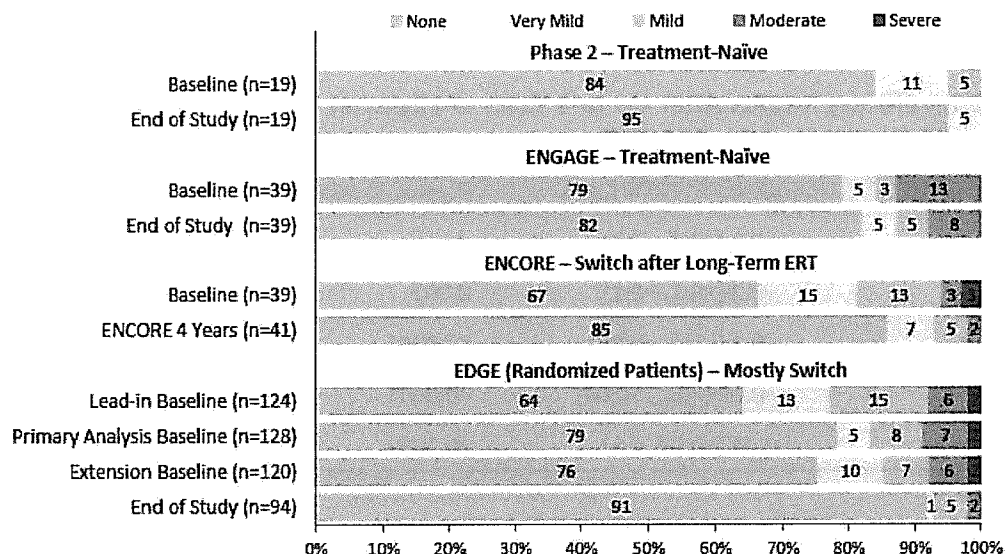


*Excludes eliglustat treatment in the EDGE Lead-in Period, which ranged from 6 to 18 months

Bone pain and bone crises in all eliglustat clinical trials

In all trials, patients periodically rated bone pain in the previous 4 weeks and reported bone crises

Overall, the frequency and severity of bone pain decreased in both naïve and switch trials with increasing time on eliglustat (Figure 16). No bone crises occurred in treatment-naïve patients treated with eliglustat; in switch patients, bone crises were infrequent and decreased overtime on eliglustat.



Patient-relevant Outcomes

While ERT is an effective and well-accepted treatment, unmet needs still exist. There are several considerations that still need to be addressed in order to fill a medical need for patients with GD1.

Except for eliglustat, all current first-line treatment options require regular, lifetime intravenous infusions, which are often burdensome to patients and caregivers. The burden of ERT involves factors beyond the cost and time of IV infusion therapy (*Br J Nurs. Mar 23-Apr 12 2006;15(6):330-333*).

Perceived benefits of oral treatment for patients could thus include:

- better continuity of activities of daily living (work, attend university or social events)
- increase productivity by decreasing absenteeism in professional life
- fewer family life disruptions
- greater overall mobility without the need to get infusions
- less involvement in medical care

In the phase 2 trial, clinically significant improvements in quality of life measures were observed after 2-3 years of eliglustat treatment and sustained for up to 8 years (*Am J Hematol. 2019;94(1):29-38; WORLD Symposium San Diego, US2018; International Congress of Inborn Errors of Metabolism. Rio de Janeiro, Brazil 2017*). Quality of life indices showed improvement with eliglustat treatment. At baseline, mean values for 6 of the 8 SF-36 domain scores were abnormal. After 8 years of eliglustat all 8 domain scores were in the normal range.

Fatigue Severity Scale score moving into the normal range, and the validated Gaucher Disease Severity total score moving from the moderate disease range to the borderline to mild disease range.

Figure 17: Improvements in Patient Quality of Life

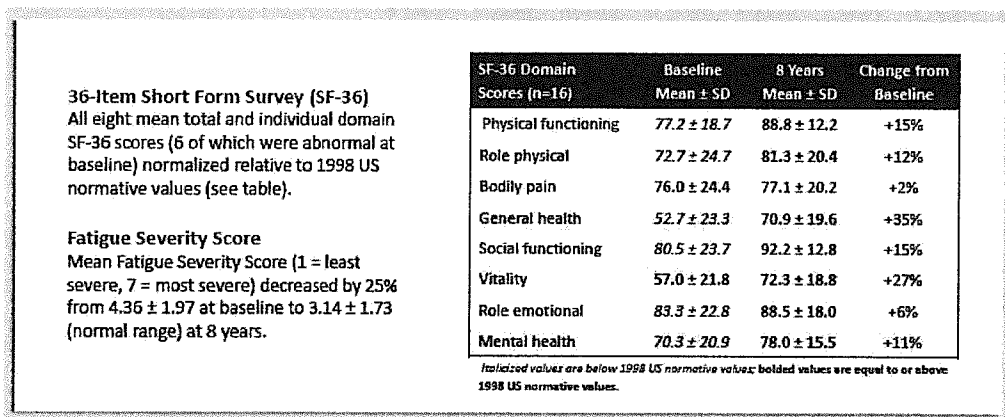


Figure 18: Normalization of SF-36 Scores After 8 Years

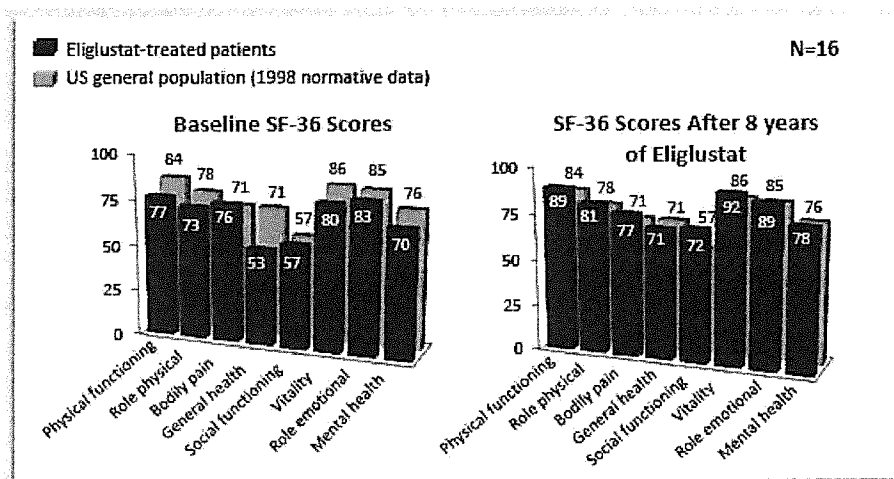
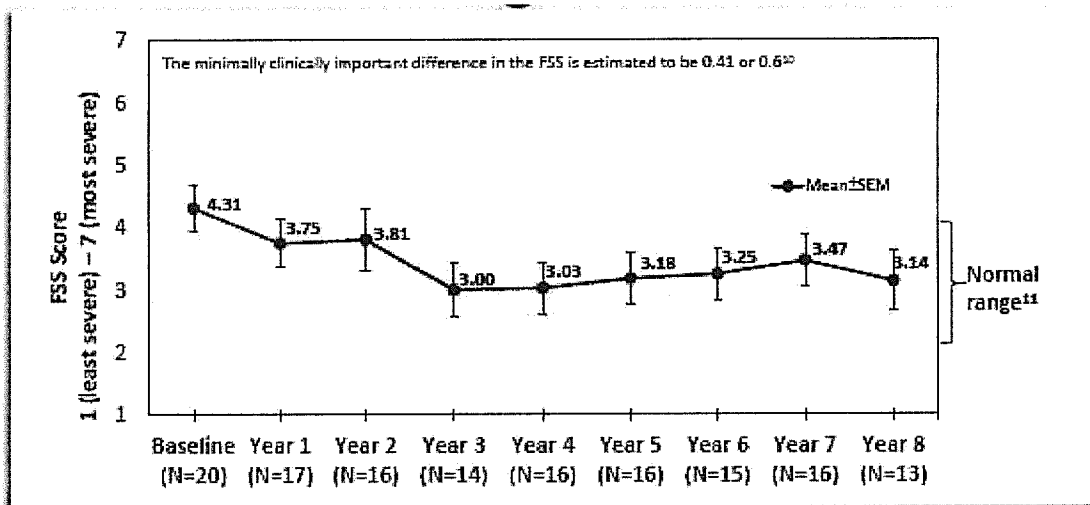


Table 1: Mean Fatigue Severity Scale (FSS) Score Through 8 Years



ENGAGE study

Eliglustat led to significant improvement in the physical functioning domain of the Short Form 36 (SF-36) compared with placebo ($p=0.01$) (*JAMA. Feb 17 2015;313(7):695-706*). After 9 months, the mean total DS3 score was significantly reduced in the eliglustat group compared to placebo (least-squares mean treatment difference = -0.3, $p=0.0452$) with most improvements occurring in the bone and visceral sub-scores (*JAMA. Feb 17 2015;313(7):695-706*).

ENCORE study

The patient population included in the ENCORE trial had by definition stable Gaucher disease and thus had mild disease burden at baseline. On all measures evaluated, patients treated with eliglustat for up to

4 years maintained the quality of life they had achieved on ERT⁵⁰(Note: the mean number of years patients in the ENCORE trial were on ERT prior to randomization was ~10 years).⁵

Over 4 years of eliglustat therapy, the patients in ENCORE, who had previously achieved a near-normal quality of life through years of treatment with ERT maintained their quality of life as measured by the FSS, SF-36, BPI (Brief Pain Inventory), DS3, and mobility status.^{28,51}

In a patient survey, 98% of patients preferred oral treatment to IV treatment after 1 year of eliglustat (*Blood*. 2017;129(17):2375-2383).

In summary, improvement in patient-relevant outcomes has been demonstrated in eliglustat clinical studies. Eliglustat can thus provide a valuable treatment option for both treatment naïve patients (first-line therapy) and patients switched from their current ERT.

Part 2. Guidelines – OHA states no high-quality guidelines were identified which met quality inclusion criteria.

Sanofi Genzyme refers to the following publication:

Balwani M et al. (Mol Genet Metabol, 2016;117:95-1-3). Recommendations for the use of eliglustat in the treatment of adults with type 1 Gaucher disease in the United States.

From Balwani M et al. “The decision to treat and choice of therapy should be based on the presence of GD symptoms, patient characteristics, individual patient's needs and/or preferences for therapy, and access to each type of therapy. Eliglustat is currently approved only for adults older than 18 years with GD1, whereas ERT is approved for both children and adults”. “Symptomatic children should be started on ERT and should not wait to start treatment until they are old enough for eliglustat. Early treatment of symptomatic patients has been shown to improve outcomes, including reversal of organomegaly, anemia, and thrombocytopenia, amelioration of bone pain and bone crises, reversal of osteopenia, prevention of avascular necrosis, acceleration of retarded growth in children, and better quality of life.”

Part 3. OHA suggested Approval Criteria.

Comment on approval criteria #9 & #11 regarding Eliglustat.

Sanofi Genzyme kindly requests the author to reconsider approval criteria #9 and #11 based on eliglustat's approval as first-line therapy for GD1 patients without prior consideration of ERT.

The efficacy and safety of eliglustat, as first-line treatment for Gaucher disease were established in an extensive clinical trial program including almost 400 patients with GD1 (Phase 2³, ENGAGE⁴, ENCORE⁵, and EDGE⁶). This is the largest clinical development program in Gaucher disease⁷ to date. Data from these 4 clinical trials represent 1,400 patient-years of exposure to eliglustat with a mean treatment duration of 3.6 years (maximum: 9.3 years) (*ASH Annual Meeting 2018; San Diego US*).

In addition, to up to 8 years of experience with CERDELGA® in clinical trials⁹, there is now 4.5 years¹⁰ of experience of CERDELGA® use in the real-world setting in a number of treated patients around the globe.

This generated real-world evidence confirming the efficacy and safety of CERDELGA®, which is in line with data reported in the eliglustat clinical trials. Moreover, several clinical and post-authorization phase 4 studies are ongoing and continue to evaluate the long-term efficacy and safety of CERDELGA® in adults and children (Elibone², Elisafe, Exoskel, EliPro, Elikids).

To date, eliglustat is approved in over 55 countries worldwide as first-line therapy for GD1 adult patients with eligible metabolizer phenotypes (>90% of patients). Over 1000 patients are currently on treatment with CERDELGA® (SANOFI GENZYME. Data on File. 2019).

About CYP2D6 Testing:

- The CYP2D6 testing is a required prior to initiation of treatment with eliglustat.
- Sanofi Genzyme sponsors CYP2D6-metabolizer testing through LabCorp.
- The Program is available to patients free of charge at any of the 1700 LabCorp draw stations in the US.

Sanofi Genzyme kindly requests a review of two additional points:

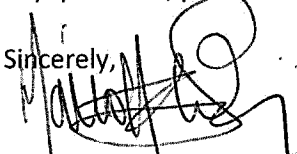
Item 5: The characterization of bone involvement in Gaucher disease limiting a T-score lower than - 2.5 SD.

Sanofi Genzyme suggests reviewing the criterion as a lower T-score and lower Trabecular Bone Score (TBS) have been correlated with a higher incidence of avascular necrosis in Gaucher disease (Baldini M et al. Blood Cell Mol Dis 2018; 68:148-152). Treatment postponement based on low T-scores may jeopardize the ability of available treatments to affect bone outcomes in patients with Gaucher disease.

Item 8 and 14: Duration of therapy approval for up to six months.

Table 2 (page 3) of the “Drug Class Review” describes the select short-term goals for patients with type 1 Gaucher disease. Sanofi Genzyme would suggest a minimum of 12 months to re-access at least some of the therapeutic goals addressed in table 2.

Thank you again for the opportunity to comment on your review of Gaucher Treatments. If you have any questions, please do not hesitate to contact us.

Sincerely,


Mario Aguiar, Medical Director

Rare Disease Medical - Sanofi-Genzyme North America
50 Binney Street, Cambridge, MA, 02142