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Once- versus twice-daily dosing of eliglustat in adults with Gaucher disease type 1: The Phase 3, randomized, double-blind EDGE trial

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ABSTRACT

Eliglustat is a first-line oral therapy for adults with Gaucher disease type 1 (GD1) with compatible CYP2D6-metabolizer phenotypes (> 90% of patients). The randomized, double-blind EDGE trial (NCT01074944, Sanofi Genzyme) evaluated once-daily eliglustat dosing compared with the approved twice-daily regimen at the same total daily dose in adults with GD1. Subjects received twice-daily dosing during a 6- to 18-month lead-in period. Only subjects who attained prespecified treatment goals for hemoglobin, platelet count, spleen and liver volumes, and bone symptoms during the lead-in period were randomized to once- or twice-daily dosing. Of 170 enrolled patients, 156 completed the lead-in period and 131 met all requirements to enter the double-blind treatment period. To achieve the composite primary endpoint in the double-blind period, patients had to maintain clinical stability relative to baseline on all five endpoints (hemoglobin, platelet count, spleen and liver volumes, and bone symptoms) and meet pharmacokinetic and other tolerability requirements as determined by the investigator after 1 year of eliglustat treatment. After 1 year, 80.4% (95% CI: 67.6, 89.8) of once-daily patients were stable compared with 83.1% (95% CI: 71.0, 91.6) of twice-daily patients. The 95% CI for the mean difference of −2.7% between groups was −17.7, 11.9. Because the lower bound of the CI exceeded the predefined non-inferiority margin of −15%, once-daily dosing could not be declared non-inferior to twice-daily dosing. Both once-daily and twice-daily patients maintained mean values for hematologic and visceral measures within established therapeutic goals during the double-blind treatment and long-term extension periods. Eliglustat was generally well-tolerated during this long-term trial (mean treatment duration: 3.3 years), with just four withdrawals (2%) for related adverse events (AE), and similar AE profiles for both dosing regimens. Patients on twice-daily eliglustat showed more stability overall, and this dose regimen was better tolerated, confirming the dosing regimen for most patients specified in the drug label.

1. Introduction

In Gaucher disease type 1 (GD1), inherited mutations in the acid β-glucosidase gene (*GBA*, OMIM 606463) result in deficient lysosomal acid β-glucosidase activity. The enzyme substrates, mainly glucosylceramide, accumulate in lysosomes of macrophages, primarily in the spleen, liver, bone marrow, and sometimes, the lungs [1,2]. Untreated, the accumulation of lipid-laden macrophages (Gaucher cells) in these organ systems results in hepatosplenomegaly, anemia, thrombocytopenia, skeletal disease, chronic bone pain, and growth retardation [1]. GD1 is estimated to affect 1 in 40,000 in the general population and 1 in 850 among those of Ashkenazi Jewish ancestry [3].

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For more than two decades, intravenous infusions of macrophage-targeted enzyme replacement therapy (ERT) with recombinant human acid β-glucosidase has been used to safely and effectively reverse or prevent numerous manifestations of GD1 [4–9]. In recent years, the oral substrate reduction therapy, eliglustat (Cerdelga, Sanofi Genzyme, Cambridge, MA, USA), has been approved in many countries worldwide, including the United States, Europe, and Japan, as a first-line treatment for adults with GD1. Because eliglustat is metabolized primarily by cytochrome P450 (CYP) 2D6 and, to a lesser extent, CYP3A, its use is limited to patients whose CYP2D6 genotypes are classified as extensive, intermediate, or poor metabolizers, which is true for > 90% of patients [10,11]. It is approved at a dose of 84 mg twice-daily for extensive or intermediate metabolizers, as well as a reduced dose of 84 mg once-daily for poor metabolizers and for patients taking certain concomitant medications also metabolized by these pathways [12–15]. The approved dose of 84 mg eliglustat (active moiety) is equivalent to the 100 mg eliglustat tartrate used in the clinical trials. In treatment-naïve GD1 patients, eliglustat has been shown to improve hemoglobin, platelets, and spleen and liver volumes at 9–12 months [16,17], with improvements maintained out to 4 [18,19] and 8 years [20], as well as improved bone mineral density after 1 year of therapy [17,21,22] with continued improvement out to 4 [19,21] and 8 years [20]. In GD1 patients already stable on ERT, eliglustat maintained stability of hematologic parameters and organ volumes at 1 year [23], with stability maintained up to 4 years [24].

Here we present the results of the EDGE trial (NCT01074944, Sanofi Genzyme, Cambridge, MA, USA), which evaluated the efficacy and safety of once-daily eliglustat dosing compared with the approved twice-daily regimen in patients already stable on twice-daily eliglustat.

2. Methods

2.1. Study design

EDGE was a Phase 3, randomized, double-blind, parallel-group, non-inferiority study evaluating the efficacy and safety of once-daily versus twice-daily eliglustat in patients with GD1 who demonstrated clinical stability on twice-daily dosing during a lead-in period. The study consisted of a screening period, an open-label lead-in period, a double-blind treatment period, an open-label long-term treatment period for randomized patients continuing in the trial, and an extended open-label treatment period for patients who completed the lead-in period but were not randomized to the double-blind treatment period (Fig. 1). Eligible subjects entered a lead-in period, during which they received eliglustat twice daily for 6–18 months. The starting dose was 50 mg twice daily with dose adjustment at Week 4 to maintain $C_{trough} \geq 5$ ng/mL. If the eliglustat C_{trough} was ≥ 5 ng/mL, the patient stayed at 50 mg twice daily; if the eliglustat C_{trough} was < 5 ng/mL, the patient was dosed at 100 mg twice daily. Those who met the five prespecified therapeutic goals and two additional randomization criteria (see below) at the 6-, 12-, or 18-month assessment entered the double-blind treatment period. Patients who did not qualify for the double-blind period could continue to receive twice-daily eliglustat in the extended treatment period for up to 42 months.

Patients who entered the double-blind period were stratified in two groups depending on the dose they were receiving at the end of the lead-in period (50 or 100 mg twice daily). Each group was randomized 1:1 by an Interactive Voice Response System/Interactive Web Response System (IVRS/IWRS) to receive eliglustat either once daily or twice daily for 1 year at the same total daily dose they were receiving at the end of the lead-in period. All patients received identical blister packs containing two capsules for morning dosing (two eliglustat for once-daily patients; one eliglustat and one matching placebo for twice-daily patients) and one capsule for evening dosing (eliglustat for twice-daily patients; placebo for once-daily patients).

Patients who did not meet tolerability criteria (see criteria in Section 2.4) during the double-blind period were returned to their twice-daily lead-in dose but continued to have scheduled assessments. All other patients continued at the same dose until they completed the double-blind period. Patients who completed the double-blind period could continue in the open-label long-term treatment period for up to 42 months; those who had met the composite primary endpoint and tolerability criteria (see below) received eliglustat once daily at the same total daily dose as their last twice-daily, lead-in regimen, regardless of their randomized treatment assignment. Patients who did not meet the composite primary endpoint during the double-blind period received their twice-daily lead-in dose until study end.

2.2. Study population

Patients eligible for screening were men and nonpregnant, non-lactating women ≥ 18 years old with GD1 confirmed by deficient acid β-glucosidase activity by enzyme assay. They could be previously treated or untreated with ERT and had to meet the following clinical entry criteria: hemoglobin level ≥ 9 g/dL (mean of two measurements); platelet count $\geq 70 \times 10^9$/L (mean of two measurements); spleen volume ≤ 25 multiples of normal (MN); and liver volume ≤ 2.0 MN. Patients were not eligible if they had participated in another Phase 3 eliglustat trial, took miglustat within 6 months before starting the study, had partial or total splenectomy within 3 years before starting the study, or had any of the following medical conditions: neurologic or pulmonary involvement of GD; deficiency of iron, vitamin B12, or folate not currently controlled with treatment; esophageal varices or liver infarction or clinically significant elevation of liver enzymes; clinically significant coronary artery disease (including history of myocardial infarction, ongoing signs or symptoms consistent with cardiac ischemia or heart failure, clinically significant arrhythmias or conduction defect such as second or third degree atrioventricular block, complete bundle branch block, prolonged QTc interval, or sustained ventricular tachycardia); or any clinically significant disease other than GD1.

2.3. Therapeutic goals and randomization criteria

To enter the double-blind treatment period, patients had to meet the following five therapeutic goals during the lead-in period: hemoglobin level ≥ 11 g/dL if female and ≥ 12 g/dL if male; platelet count $\geq 100 \times 10^9$/L; liver volume ≤ 1.5 MN; spleen volume ≤ 10 MN (non-splenectomized patients); and no more than one bone crisis and freedom from other symptomatic bone disease (such as bone pain attributable to osteonecrosis and/or pathological fractures) during the previous 6 months in the lead-in period. To be randomized, patients also had to have peak eliglustat plasma concentration < 50 ng/mL and maintained a dose of 50 mg or 100 mg eliglustat twice-daily for at least 4 months.

2.4. Efficacy assessments

The primary efficacy endpoint was the percentage of patients who remained stable relative to baseline (defined as the last assessment prior to randomization) after 1 year in the double-blind period with respect to all five of the following measures: no decrease in hemoglobin concentration > 1.5 g/dL (based on two successive measurements); no decrease in platelet count > 25%; no increase in spleen volume (MN) > 25%; no increase in liver volume (MN) > 20%; and no more than two bone crises and free of other clinically symptomatic bone disease (such as bone pain attributable to osteonecrosis and/or pathological fractures). Patients could fail the stability endpoint at any time during the double-blind period due to any of three additional non-tolerability measures: “non-tolerance” as determined and reported by the investigator (not defined in the protocol), plasma concentration of eliglustat that exceeded 150 ng/mL (a conservative alert level chosen to avoid plasma concentrations that could cause concern in the worst case