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Letter to the Editor

# Safety, efficacy, and authorization of eliglustat as a first-line therapy in Gaucher disease type 1

ARTICLE INFO

Editor: Mohandas Narla

To the Editor,

The editorial by Zimran et al. titled “Should eliglustat be first line therapy for patients with type 1 Gaucher disease? Definitions of safety and efficacy” [1] makes specious claims about eliglustat safety, efficacy and prescribing information that may mislead physicians in their decisions and inappropriately alarm patients. As principal investigators in the clinical trials of eliglustat, authors of eliglustat clinical trial manuscripts, clinicians with extensive experience treating patients with eliglustat, and medical representatives of the drug sponsor involved in the design and conduct of the trial program, we are obliged to address these inaccuracies. In contrast to the opinions represented by Dr. Zimran and colleagues, we feel that the eliglustat clinical trial program has set a new bar for evaluation of drugs in rare diseases, and was conducted with transparency, integrity, and rigor.

Eliglustat is approved as a first-line therapy by the United States (US) Food and Drug Administration (FDA), the European Medicines Agency (EMA), and regulatory authorities in many other countries, for adults with Gaucher disease type 1 who have CYP2D6 extensive, intermediate, or poor metabolizer phenotypes (> 90% of patients) [2–4]. Approvals were based on evaluation of safety and efficacy data from 393 patients—the largest clinical trial program ever conducted in Gaucher disease — as well as independent analyses of clinical trial results conducted by regulatory bodies.

The Phase 3 ENGAGE and ENCORE trials of eliglustat, including endpoints and comparator arms, were designed after consultation with the US FDA and EMA, with input from Gaucher patient groups. Primary results were published in *JAMA* [5] and the *Lancet* [6], respectively, after rigorous editorial and peer review. We reject the allegation that the results of these trials were presented “in a novel and potentially misleading manner”: the primary ENGAGE manuscript and online supplement [5] provide not only the results of the prospectively defined efficacy endpoints, but also absolute change from baseline and percent change from baseline. Individual baseline and final spleen, liver, hemoglobin, and platelet values are shown for all 40 trial patients, as well as outcomes for all tertiary and exploratory endpoints. The results are similarly presented in the primary ENCORE manuscript and online supplement [6], although the large trial size (159 patients) precluded inclusion of individual data.

In referring to changes from baseline in four 6- to 12-month trials of enzyme replacement therapies and miglustat in treatment-naïve patients [7–10], Zimran et al. [1] are mistaken in describing the efficacy of eliglustat as comparatively “inferior.” Disparities in the cited trials and the patients recruited do not allow strict comparison, particularly with regard to the highly variable baseline burden of disease, which largely determines the magnitude of the therapeutic response [5,8,11,12]. In Table 1, we set out the absolute baseline and final values attained, as well as change from baseline in these four trials [7–10] and the eliglustat Phase 2 and Phase 3 ENGAGE trials [5,11,13]. With the exception of the miglustat study [9], where the improvements were inferior, these show highly comparable clinical improvements in all measures. As expected, more severe baseline disease was associated with the greatest proportional improvement but less favorable mean absolute values achieved after treatment.

Although a trial comparing eliglustat with ERT in treatment-naïve Gaucher patients would be a practical impossibility, Ibrahim et al. [14] compared 1-year outcome data from the Phase 2 and ENGAGE eliglustat trials with similar imiglucerase-treated patients from the International Collaborative Gaucher Group Gaucher Registry (this article was cited mistakenly as Balwani et al. in the editorial by Zimran et al. [1]). While such a comparison lacks the rigor of a randomized, active, concurrent-controlled trial, the post hoc analysis showed that therapeutic response to eliglustat was comparable in rate as well as the magnitude of response to that achieved after treatment with imiglucerase.

With respect to Gaucher patients switching from ERT to eliglustat, we disagree with Zimran et al. [1] that the stability endpoint of the ENCORE trial was weak and overly generous compared with other switch trials in Gaucher patients. ENCORE enrolled 159 patients, was randomized with an active control, and was powered for a primary composite endpoint comprising spleen, liver, hemoglobin, and platelet components. As set out by Cox et al. [6], the thresholds chosen for these four components were based on data from a clinical trial of patients with Gaucher disease stabilized on ERT [15], as well as reported variability in organ volume measurement. It was necessary for patients to meet all four endpoints simultaneously – a bar that was achieved by 85% of all eliglustat-treated patients in the 1-year primary analysis, and in 91% of patients who remained in the trial for 4 years. Of the 15 eliglustat patients who did not achieve the primary composite endpoint, 14 missed on a single criterion. All three of the switch trials cited by Zimran et al. [1] as more rigorous than ENCORE ($N$ = 159 adults) enrolled far fewer patients ($N$ = 31–40), had less rigorous entry criteria, and had no primary efficacy endpoint or an endpoint with fewer components and lacked justification for the efficacy cutoffs or margins. The uncontrolled velaglucerase alfa trial enrolled children and adults and the primary endpoint was safety [16]. The taliglucerase alfa switch trial [17] was also uncontrolled and included both children and adults: the endpoints were separately reported without statistical analysis. The 2-year miglustat trial [18] was not registered and was carried out at a single center without prespecified endpoints; there were three

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**Table 1**
Treatment response in four studies of treatment-naïve Gaucher patients cited by Zimran et al. [1] and in the eliglustat ENGAGE and Phase 2 Trials[a].

| Drug | N | Months of treatment | Mean spleen volume | | Mean liver volume | | Mean hemoglobin concentration (g/dL) | | Mean platelet count ($\times 10^9$/L) | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | Baseline | After Tx (change) | Baseline | After Tx (change) | Baseline | After Tx (change) | Baseline | After Tx (change) |
| Enzyme replacement therapies | | | | | | | | | | |
| Alglucerase [7] | 12[b] | 6 | 49.9 MN[c] | 27.2 MN[c] (−40%) | 2.37 MN[e] | 1.86 MN[c] (−20%) | 8.85 | 11.9 (+3.0) | 100 | 131 (+45%) |
| Alglucerase [8] | 15 | 9 | 23.7 MN[c] | 15.1 MN[c,d] (−32%) [6 months] | 1.83 MN[d] | 1.61 MN[c,d] (−11%) [6 months] | 10.8 | 13.1 (+2.3) | 71 | 99 (+53%) |
| Imiglucerase [8] | 15 | | 19.3 MN[c] | 11.5 MN[c,d] (−37%) [6 months] | 1.65 MN[d] | 1.39 MN[c,d] (−13%) [6 months] | 10.7 | 13.1 (+2.5) | 72 | 99 (+43.5%) |
| Taliglucerase alfa [10] 30 U/Kg[f] | 16 | 9 | 15 MN | ~11 MN (−27%) | 1.7 | ~1.52 MN (−11%) | 12.2 | 13.8 (+1.6) | 75 | 92 (+18%) |
| Taliglucerase alfa [10] 60 U/Kg | 16 | | 17 MN | ~11 MN[e] (−38%) | 1.6 | ~1.42 MN[e] (−11%) | 11.4 | 13.6 (+2.2) | 65 | 107 (+73%) |
| Substrate reduction therapies | | | | | | | | | | |
| Miglustat [9] | 28[f] | 12 | 1.64 L 12.0 O/E[g] | 1.325 L (−20% in L) | 2.39 L 1.7 O/E[g] | 2.11 L (−12% in L) | 12.0 | 12.3 (+0.3) | 77 | 85 (+12%) |
| Eliglustat [11] (Phase 2) | 26 | 12 | 20.0 MN | 12.7 (−39%) | 1.80 MN | 1.41 MN (−17%) | 11.1 | 12.6 (+1.6) | 66 | 93 (+40%) |
| Eliglustat [5,13] (ENGAGE)[h] | 40 | 9 | 13.4 MN | 9.2 MN (−30%) | 1.4 MN | 1.32 MN (−6%) | 12.1 | 12.9 (+0.8) | 73 | 99 (+36%) |

[a] Values reported in this table are taken directly from the published reference or are derived from individual patient data included in the reference. In trials for which spleen and liver volumes are reported volumetrically, volume was converted to multiples of normal (MN) where possible to allow for comparisons across trials.

[b] Included children and adults.

[c] Multiples of normal (MN) were calculated by the following formulas: Spleen MN = spleen volume in cc/(body weight in Kg × 2); Liver MN = liver volume in cc/(body weight in Kg × 25). These equations assume that a normal spleen has 2 mL volume for each Kg body weight and that a normal liver has 25 mL volume for each Kg body weight.

[d] Multiples of normal (MN) after treatment for liver and spleen could be calculated only for 6-month values as there were no individual values provided for the 9-month timepoints.

[e] Final values for liver and spleen were estimated by multiplying the percent reduction given in Figure 2 of the cited manuscript [10] by the baseline value, and subtracting this number from the baseline value.

[f] 7 patients were splenectomized and 6 had previous enzyme replacement therapy.

[g] Observed/Expected (O/E) are reported for spleen and liver volumes at baseline in the published reference. O/E is similar to MN but uses a slightly different formula: for liver volume, expected organ volume was 2.14% of body weight; for spleen, expected organ volume was 0.2% of body weight.

[h] 9-month eliglustat treatment response was determined for all 40 patients (all former placebo patients entered the trial extension during which all patients received eliglustat). Baseline was at trial entry for patients randomized to eliglustat and immediately before the switch to eliglustat treatment in patients randomized to placebo for the primary analysis.

treatment arms and 58% of the patients discontinued the trial.

No patient in ENCORE was withdrawn due to clinical deterioration. Of the 15 eliglustat-treated patients who did not meet the composite primary endpoint, 13 (80%) maintained absolute clinical values that met established therapeutic goal thresholds for Gaucher disease recommended by Pastores et al. for patients receiving ERT [19]. This was possible because changes were assessed relative to each patient's baseline. For example, one patient who failed the primary endpoint and the platelet endpoint due to a 25% fall in platelet count had a final count of $292 \times 10^9$/L, which is well within the therapeutic goal threshold as well as the reference range for healthy adults (Sanofi Genzyme data on file).

Zimran et al. [1] suggest that ENCORE and other switch trials should have a placebo comparator arm, since they claim that patients can remain clinically stable after treatment is stopped. In fact, several studies including one by Zimran et al. in this journal during the imiglucerase supply shortage firmly refute this claim [20]. Most measures of disease burden (organ volumes, hematological parameters, biomarker values) worsen within 3–6 months of stopping enzyme therapy [20–26].

We contend that if eliglustat had been inferior to ERT, patients would have started to deteriorate during the 1-year primary exposure period in ENCORE and worsened during the prolonged trial extension. In contrast, > 90% of ENCORE patients maintained absolute values for spleen, liver, hemoglobin and platelets within prospectively defined therapeutic goal thresholds for up to 4 years. Furthermore, least-square mean spleen volume, liver volume, and lumbar spine *Z*-score showed statistically significant improvements; mean values for chitotriosidase activity and other biomarkers decreased, and quality-of-life scores were also maintained in the normal or near-normal reference range [27]. These findings further underscore the efficacy of eliglustat in switch patients.

Zimran et al. [1] characterize the safety profile of eliglustat as “problematic especially with respect to cardiac events.” Final safety data from the completed Phase 2 and Phase 3 eliglustat trials encompass 1400 patient-years of eliglustat exposure in 393 patients, with a mean treatment duration of 3.6 years (maximum of 9.3 years) [28]. Overall, > 80% of patients remained in their respective trials until eliglustat became commercially available or the study was completed. About 2% of patients receiving eliglustat permanently discontinued as a result of adverse events considered drug-related by the investigator. The most commonly reported adverse events considered to be drug-related were: dyspepsia (6%), headache (5%), upper abdominal pain (5%), and dizziness (5%). Most of these events were mild or moderate, transient and occurred only once per patient [28].

Two years of additional treatment experience with eliglustat in the postmarketing “real world” setting confirm the benign adverse reaction profile of the clinical trial experience [29]. Naturally we recognize that “real world” safety should continue to be carefully monitored, as with any new drug.

With regard to cardiac safety, Zimran et al. [1] inflate and misrepresent the adverse event data reported in Peterschmitt et al. [3] and also misrepresent the risk of arrhythmia described in the drug prescribing information [30,31]. Zimran et al. state that 17% of patients in eliglustat clinical trials had a cardiac adverse event (AE); they arrived at this inflated figure by double-counting palpitations (a subset of the MedDRA System Organ Class [SOC] “Cardiac Disorders”) and including syncope, which is not classified under this SOC. Moreover, no syncopal event in the eliglustat clinical trials was considered to be of cardiac origin and none led to trial discontinuation. As reported by Peterschmitt et al., 5% of patients had a cardiac AE considered related to eliglustat, and 6% of patients had cardiac AEs that were considered unrelated.

Based on preclinical in vitro data suggesting the potential for QT prolongation and regulatory recommendations, extensive cardiac monitoring was carried out in the clinical trials. Most cardiac events were detected in asymptomatic patients during periodic 24-h Holter monitoring, were mild or moderate, were considered unrelated to eliglustat, and did not lead to either trial discontinuation or dose adjustment. In eliglustat Phase 2 and Phase 3 clinical studies, no clinically significant prolongations of the QTcF, PR, or QRS intervals were observed at therapeutic concentrations [3,28]. Increases in $C_{max}$ were not associated with cardiac events or electrocardiographic abnormalities; the highest $C_{max}$ observed was 261 ng/mL (due to a medication error), which was well below the threshold of concern.

Neither the US nor the EU eliglustat (Cerdelga) drug label notes an increased risk of arrhythmia in patients who take eliglustat as recommended (i.e., patients without preexisting cardiac disease and patients not taking certain concomitant medications). Both labels note a theoretical risk of arrhythmia in patients with pre-existing cardiac disease (none of whom were enrolled in the clinical trials) or with coadministration of drugs that are contraindicated in patients taking eliglustat. This theoretical risk is not based on data from Phase 2 or any other trial of eliglustat, as incorrectly stated by Zimran et al., but on data from a negative thorough QT study conducted in healthy volunteers. This study showed that at therapeutic and supratherapeutic concentrations, the effects of eliglustat on QTcF were below the level of concern as defined in the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) E14 guidelines [32]. Pharmacokinetic/pharmacodynamic modeling of the data from this study predicted that eliglustat would cause mild increases in the mean PR, QRS, and QTc intervals at eliglustat plasma concentrations substantially above therapeutic levels (i.e., 11-fold the predicted human $C_{max}$ per EU label [30] or at 500 ng/mL per US label [31]). Such exposures are mitigated by mandatory CYP2D6 genotyping before eliglustat initiation and by scrutinizing concomitant medication use, as recommended in the eliglustat label.

Finally, we feel that it is a disservice to patients with Gaucher disease to characterize their condition as “benign,” as described by Zimran et al. [1] The disease can be disabling and life-shortening [33,34] and can significantly compromise quality of life [35–38]. Gaucher disease is very heterogeneous, even among the three subtypes. The well-characterized subgroup of patients with type 1 disease who are homozygous for the N370S mutation may not show florid manifestations of Gaucher disease and can present late in adult life. However, even this subgroup can also have severe disease manifestations [39]. Furthermore, patients with this genotype are not necessarily representative of the global population of patients with Gaucher disease type 1. Outside the United States, Europe, and Australasia, patients with Gaucher disease type 1 tend to have more severe disease [40–42], and the proportion of Gaucher patients with types 2 and 3 is much greater [35–37].

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