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Impact of seizure frequency reduction on health-related quality of life among clinical trial subjects with refractory partial-onset seizures: A pooled analysis of phase III clinical trials of eslicarbazepine acetate

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ABSTRACT

Background: Subjects who received eslicarbazepine acetate (ESL) as adjunctive therapy experienced significantly greater seizure frequency reduction (SFR) than placebo in three phase III, randomized, double-blind trials. This analysis compared changes in health-related quality of life (HRQOL) between treatment responders and non-responders across the pooled, per-protocol population ($N = 842$) using the validated Quality of Life in Epilepsy Inventory-31 (QOLIE-31).

Methods: QOLIE-31 scores were calculated for Total Score (TS) and seven subscales; higher scores indicate better HRQOL. Mean changes from baseline were calculated. Analysis of covariance examined least square mean (LSM) differences in final scores between responders (≥50% and ≥75% SFR) and non-responders. Clinical significance was based on established minimal clinically important differences (MCIDs).

Results: Mean changes were greater among responders for TS (5.2 versus 1.4 for ≥50% SFR; 7.5 versus 1.9 for ≥75% SFR) and all subscales. Additionally, the percentage of subjects with changes meeting or exceeding MCIDs was higher among responders for TS (48.4% versus 33.9% for ≥50% SFR; 56.9% versus 35.8% for ≥75% SFR) and all subscales. Responders had significantly higher final scores for TS (LSM difference = 4.0 for ≥50% SFR; LSM difference = 5.7 for ≥75% SFR) and all subscales except emotional well-being at ≥50% SFR. LSM differences exceeded MCIDs at ≥75% SFR for TS and five of seven subscales, and two subscales at ≥50% SFR. In a subgroup analysis with placebo removed, LSM differences were larger overall.

Significance: In clinical trials of adjunctive ESL, higher levels of SFR were associated with greater improvements in HRQOL.

1. Introduction

The goal of treatment in epilepsy is to obtain seizure freedom with an absence of side effects, while maximizing quality of life. Therefore, an important consideration when deciding to change antiepileptic drug (AED) therapy is whether the anticipated reduction in seizure frequency and adverse effects will be accompanied by improved health-related quality of life (HRQOL) for the patient. It is reasonable to assume that HRQOL may be improved to a greater degree among patients whose seizure frequency is reduced by half or more than among those with a lesser response. Indeed, prior research into the role of seizure frequency and severity has shown that seizure freedom is critical to achieving meaningful improvements in HRQOL [1,2].

Components of HRQOL that can be measured in response to improvements in seizure frequency include the impact of treatment on adverse effects, comorbidities, mood, cognition, worry about seizures, and social functioning. In addition to improvements, favorable changes in some of these components can also impact overall HRQOL; in one study, an improvement in depression was shown to be a more

Abbreviations: ANCOVA, analysis of covariance; AED, antiepileptic drug; CF, cognitive functioning; EWB, emotional well-being; EF, energy/fatigue; ESL, eslicarbazepine acetate; HRQOL, health-related quality of life; LEV, levetiracetam; LSM, least square mean; ME, medication effects; MCID, minimal clinically important difference; OQOL, overall quality of life; QOLIE-31, Quality of Life in Epilepsy Inventory-31 instrument; SFR, seizure frequency reduction; SW, seizure worry; SF, social functioning; TS, total score.

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important factor for improvement in HRQOL than seizure reduction [3]. These aspects of patient perceptions can be assessed using a well-validated instrument, such as the Quality of Life in Epilepsy Inventory-31 (QOLIE-31) or the QOLIE-31–Problems [4,5]. In addition to statistical differences in instrument scores, the goal is to demonstrate minimal clinically important differences (MCID) with the addition of a new treatment. The MCIDs for the QOLIE-31 have been established for the total score and each subscale score in a similar population of clinical trial patients (total score: 5.19; CF: 5.34; EWB: 4.76; EF: 5.25; ME: 5.00; OQOL: 6.42; SW: 7.42; SF: 3.95) [6].

Eslicarbazepine acetate (ESL), a once-daily AED, is extensively converted to eslicarbazepine, which blocks the voltage-gated sodium channel, although the mechanism by which eslicarbazepine exerts anticonvulsant activity is not known [7]. In three phase III, randomized, double-blind clinical trials (studies 301, 302, and 304) [8–10], subjects with refractory partial-onset seizures who were treated with 800 mg/day ESL or 1200 mg/day ESL as adjunctive therapy experienced significantly greater seizure frequency reduction (SFR) than subjects treated with placebo. The objective of this analysis was to determine whether SFR across the three ESL trials also resulted in statistically-significant and clinically-meaningful improvement (i.e., exceeding the MCID) in HRQOL at two definitions of clinical response (≥50% SFR and ≥75% SFR).

2. Material and methods

Data from the three phase III, randomized double-blind ESL clinical trials in patients with refractory partial onset epilepsy were pooled. Each of the trial designs included an 8-week baseline period and a 14-week efficacy period (2-week dose escalation and 12-week maintenance therapy). Subjects treated with placebo or adjunctive ESL (800 mg/day or 1200 mg/day) and who had no major protocol violations were included in this analysis [8–10]. Standardized seizure frequency was the primary efficacy endpoint in these studies and those results are shown elsewhere [8–10].

The clinical studies were carried out according to the study protocols under the consideration of the International Conference on Harmonisation—Good Clinical Practice (ICH-GCP) guidelines, the Declaration of Helsinki, and the local laws of the countries where the studies were performed. Local independent ethics committees approved the protocols and all patients provided signed informed consent before initiating the study.

2.1. QOLIE-31 instrument

The QOLIE-31 was administered to all subjects in the three clinical trials at baseline and at the end of the 14-week efficacy period. The QOLIE-31, a validated instrument designed to evaluate changes in HRQOL, is comprised of seven subscales which measure the following concepts: cognitive functioning (CF), emotional well-being (EWB), energy/fatigue (EF), medication effects (ME), overall quality of life (OQOL), seizure worry (SW), and social functioning (SF) [4]. Each subscale includes two to five items used to create a score that ranges from 1 to 100, with higher values indicating better HRQOL. The QOLIE-31 total score is calculated as a weighted average of the subscale scores [4].

2.2. Analysis

Subjects from the ESL and placebo arms were categorized as responders or as non-responders based on the observed SFR between baseline and the end of the efficacy period. Two sets of analyses were conducted to examine differences between responders and non-responders. The first analysis defined responders as subjects with ≥50% SFR and the second defined responders as subjects with ≥75% SFR.

QOLIE-31 scores were calculated at baseline (baseline score) and at the end of the efficacy period (final score). Absolute change scores (final score minus baseline score) were calculated for each total score and each subscale score, along with the percentage of subjects with absolute change scores meeting or exceeding the respective MCIDs.

Analysis of covariance (ANCOVA) models were used to examine differences between responders and non-responders in least square mean (LSM) QOLIE-31 final scores for total score and each subscale score. Baseline scores were included in the ANCOVA models to account for differing baseline scores among the subjects [11]. Region also was included because the regional distribution differed across the three clinical trials. Statistical significance was established at an alpha level of 0.05. The LSM differences in QOLIE-31 final scores between responders and non-responders were also compared to MCIDs to examine whether the LSM differences were clinically meaningful. Lastly, a subgroup analysis was conducted that excluded subjects treated with placebo to examine the difference in HRQOL between responders and non-responders among only those subjects who received adjunctive ESL therapy.

3. Results

A total of 1251 subjects comprised the pooled population and were treated with either placebo or adjunctive ESL (800 mg/day or 1200 mg/day; the 400 mg/day group did not demonstrate significant clinical efficacy and was not included in the analysis). Among these subjects, 1006 had no major protocol deviations and 842 had usable baseline and final QOLIE-31 scores; thus, 842 subjects were included in this analysis (312 from the placebo arm, 287 from the 800 mg/day ESL arm, and 243 from the 1200 mg/day ESL arm). These subjects averaged 37.4 years of age, a body mass index of 25.5, and a disease duration of 20.6 years. Approximately half (51.8%) were male, and 77.6% were Caucasian. The subjects were distributed among Eastern Europe, Latin America, North America, Western Europe, and other regions (Table 1).

3.1. Absolute change in QOLIE-31 scores

At ≥50% SFR, 262 (31.1%) of 842 subjects were categorized as responders and 580 were categorized as non-responders. The mean absolute change scores for total score and all seven subscales were considerably greater among responders than non-responders with a mean absolute change in total score of 5.2 compared to 1.4 (Table 2).

At ≥75% SFR, 103(12.2%) of 842 subjects were categorized as responders and 739 were categorized as non-responders. Similar to the results at ≥50% SFR, mean absolute change scores for total score and all seven subscales were considerably greater for responders than non-responders with a mean absolute change in total score of 7.5 compared to 1.9 (Table 3).

Table 1
Demographics and baseline characteristics.

Characteristic	$N = 842$
Age (yrs), mean (SD)	37.4 (12.13)
Male, n (%)	436 (51.8)
Body mass index, mean (SD)	25.5 (5.41)
Duration of disease (yrs), mean (SD)	20.6 (13.13)
Region, n (%)	
Eastern Europe	283 (33.6)
Latin America	193 (22.9)
North America	160 (19.0)
Western Europe	88 (10.5)
Rest of World	115 (13.7)
Unknown	3 (0.4)
Race, n (%)	
Caucasian	653 (77.6)
Asian	87 (10.3)
Black	30 (3.6)
Hispanic	12 (1.4)
Other	57 (6.8)
Unknown	3 (0.4)

Abbreviations. SD: standard deviation.