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Health-related quality of life in patients treated with eslicarbazepine acetate monotherapy: Pooled analysis from two registered clinical trials

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ABSTRACT

Purpose: While antiepileptic drug (AED) treatment effectiveness is traditionally assessed based on seizure frequency reduction (SFR), the overall value of AEDs in managing epilepsy and associated sequelae may be best assessed by how patients feel and function in terms of overall health-related quality of life (HRQoL). We conducted a pooled analysis of the Quality of Life in Epilepsy-31 (QOLIE-31) questionnaire from two phase 3 trials to explore the effect of response to conversion to eslicarbazepine acetate (ESL) monotherapy on HRQoL.
Methods: Data were pooled from two multicenter, randomized, double-blind, historical control phase 3 trials examining conversion to ESL monotherapy in adults with inadequately controlled partial-onset seizures (POS). The relationship between HRQoL and ESL treatment response was examined through the analysis of week 18 QOLIE-31 scores between patients who met the SFR ≥50% threshold (responders) and patients with SFR <50% (nonresponders). The analysis was conducted in the efficacy population (intent-to-treat (ITT) patients who entered the AED taper/conversion period) and completer population (efficacy patients who completed the ESL monotherapy period) and was repeated using an SFR ≥75% threshold.
Results: In the efficacy population, week 18 QOLIE-31 total score least squares mean (LSM) was significantly higher for responders with ≥50% SFR (LSM difference: 3.0; 95% confidence interval (CI): 0.2–5.8; $p = 0.037$) and with ≥75% SFR (LSM difference: 7.0; 95% CI: 3.6–10.3; $p < 0.001$) than nonresponders. In the completer population, overall quality of life (QoL) (LSM difference: 5.1; 95% CI: 1.5–8.6; $p = 0.006$) and social functioning (LSM difference: 5.4; 95% CI: 0.1–10.7; $p = 0.046$) were significantly higher for responders with ≥50% SFR than nonresponders, and all domain LSMs were higher for responders with ≥75% SFR (all $p < 0.05$) than nonresponders.
Conclusions: This analysis of data from the phase 3 trials demonstrated significantly higher HRQoL among ESL responders with SFR of ≥75% and also at the lower SFR threshold of ≥50% compared with nonresponders.

1. Introduction

The chronic nature of epilepsy results in patients who suffer from it often having to live with its debilitating effects, which include physical, emotional, and social functioning effects, that can have a profound impact throughout their lives [1]. Additionally, given the spontaneous recurrent seizures and adverse effects of medications, persons with epilepsy also experience a variety of psychiatric disorders, most notably depression [2], which can further compound the issue of poor health-related quality of life (HRQoL) [2–4]. As a result of HRQoL decrements, patients with epilepsy also suffer from a significant adverse impact on the ability to gain meaningful employment, function in the workplace, and engage socially with others [2–4].

Traditionally, antiepileptic drug (AED) treatment effectiveness as it relates to seizure frequency reduction (SFR) has been the mainstay consideration in prescribing decisions by physicians. However, it is important to understand both AED effects on seizure control and how efficacy outcomes relate to HRQoL. In clinical trials of AED therapy, the most commonly used endpoint for assessing efficacy is the achievement of a ≥50% SFR while ≥75% SFR has been proposed as an alternative

Abbreviations: AED, antiepileptic drug; ANCOVA, analysis of covariance; CI, confidence interval; ESL, eslicarbazepine acetate; HRQoL, health-related quality of life; LSM, least squares mean; MCID, minimal clinically important difference; QoL, quality of life; POS, partial-onset seizure; QOLIE-31, Quality of Life in Epilepsy-31; SFR, seizure frequency reduction.

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measure that reflects a more stringent criteria for clinically meaningful improvement [5]. However, assessment of HRQoL based on the degree of SFR has not shown consistent results across different AEDs at either the 50% or 75% thresholds [5,6]. This suggests that seizure control may not directly and consistently translate to improved HRQoL for all AEDs.

Eslicarbazepine acetate (ESL) is a once-daily AED that was approved by the US Food and Drug Administration as an adjunctive therapy in 2013, as monotherapy in 2015, and for pediatric (age: ≥4 years) treatment in 2017 for the treatment of patients with partial-onset seizures (POS) [7,8]. Previously published studies of ESL have demonstrated that it is an efficacious adjunctive treatment for patients with POS, with statistically significant improvements in HRQoL measured using the Quality of Life in Epilepsy-31 (QOLIE-31) questionnaire [9–11]. A pooled analysis of three phase 3 randomized studies of ESL as adjunctive therapy demonstrated that higher levels of SFR were associated with greater improvements in HRQoL [12]. Likewise, ESL monotherapy trials have demonstrated favorable efficacy and HRQoL outcomes. In two phase 3 conversion to ESL monotherapy trials, patients with inadequately controlled seizures who converted to ESL monotherapy demonstrated a superior study exit rate, the primary endpoint, compared with the historical control. Secondary endpoints of improvement in SFR and improvement in HRQoL, as measured by QOLIE-31, were also achieved [13,14].

The two phase 3 trials evaluated change in QOLIE-31 [15] total score from baseline to the end of the ESL monotherapy period as a secondary endpoint. Treatment with ESL was associated with improved QOLIE total scores in both studies for the two doses evaluated [13,14]. Of the two ESL monotherapy trials, Jacobson et al. reported that ESL monotherapy was associated with a >4.0-point increase in QOLIE-31 total scores between baseline and the end of the ESL monotherapy period while Sperling et al. reported a >6.0-point increase in QOLIE-31 total score improvements between baseline and the end of the ESL monotherapy period. Although both ESL monotherapy trials reported statistically significant QOLIE-31 improvements after conversion to ESL monotherapy, it is estimated that a greater than 5-point improvement in QOLIE-31 total scores may be considered a minimal clinically important treatment difference [16].

Therefore, to further explore the effect of conversion to ESL monotherapy on HRQoL and to determine whether findings from the ESL adjunctive studies could be extended to responders, we conducted a pooled analysis of QOLIE-31 subscale and total scores from two phase 3 conversions to ESL monotherapy trials. Specifically, the objective of the current analysis was to examine the differences in the magnitude of HRQoL improvements between treatment responders (i.e., SFR ≥ 50% from baseline and ≥75%) and treatment nonresponders (i.e., SFR < 50% from baseline or SFR < 75%) to ESL monotherapy.

2. Methods

Data from two multicenter, randomized, double-blind, phase 3 trials using historical controls examining the conversion to ESL monotherapy in adults with inadequately controlled POS were pooled for this analysis [13,14]. Each trial included an 8-week baseline period (week 0), an 8-week ESL dose titration and baseline AED titration/conversion period (week 8; i.e., a 2-week titration followed by a 6-week AED withdrawal/conversion), and a 10-week ESL monotherapy efficacy period (week 18) (Appendix Fig. 1). Seizure frequency was measured at week 0 and at week 18. Patient-reported HRQoL was assessed using the QOLIE-31 questionnaire administered at week 0 and week 18 [13,14]. The baseline demographic characteristics of the intent-to-treat (ITT) population of the two individual trials, as well as their respective detailed efficacy results, are published elsewhere [13,14].

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 questionnaire

The QOLIE-31 questionnaire is a validated 31-item patient-reported outcome measure that evaluates changes in HRQoL in patients with epilepsy [6,15]. The seven subscale domains are the following: cognitive functioning (problem-solving, memory, concentration), emotional well-being (mood), energy/fatigue, medication effects (worry over physical/mental effects of medication), overall quality of life (QoL), seizure worry (worry/fear of seizures and their manifestations), and social functioning (social and leisure impact, driving, work limitations). Each domain includes two to six items used to create the domain scores, and a total 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 domain scores.

2.2. Analysis populations

The primary analysis population was the pooled efficacy population (ITT patients who *entered* the 8-week medication taper/conversion to ESL period). Only patients with available QOLIE-31 scores at both baseline and week 18 were included. Patients with ≥50% SFR from baseline to week 18 were classified as responders, and patients with <50% SFR were classified as nonresponders. A subgroup analysis was conducted in patients who *completed* the study through week 18 (completer population) to see whether results could be extended after excluding patients who did not complete the ESL monotherapy period. All analyses were repeated using the ≥75% SFR threshold for responders.

2.3. Statistical analysis

Descriptive statistics were used to describe patient demographics and characteristics (age, sex, body mass index, ethnicity, race, and region) at baseline. Analysis of covariance (ANCOVA) was used to examine differences in the week 18 QOLIE-31 scores between responders and nonresponders, adjusting for baseline QOLIE-31 score and the covariates of ESL dose, age, body mass index, sex, ethnicity, race, and region. Statistical significance of the covariates was assessed at the 0.15 alpha level for inclusion in the models using backwards selection [17]. Least squares means (LSMs) and corresponding 95% confidence intervals (CIs) were calculated for the week 18 QOLIE-31 total scores and

Table 1
Baseline characteristics of the analysis populations.

Characteristic	Efficacy (n = 252)	Completers (n = 211)
Age (years), mean (SD)	39.4 (11.92)	38.9 (11.96)
Male, n (%)	127 (50.4)	106 (50.2)
Body mass index (kg/m^2), mean (SD)	28.5 (7.20)	28.3 (7.21)
Hispanic or Latino, n (%)	25 (9.9)	20 (9.5)
Race, n (%)		
White	211 (83.7)	176 (83.4)
Black or African-American	21 (8.3)	18 (8.5)
Other and Multiple	20 (7.9)	17 (8.1)
Region, n (%)		
North America (United States & Canada)	151 (59.9)	120 (56.9)
Eastern Europe (Ukraine, Czech Republic, Bulgaria, & Serbia)	101 (40.1)	91 (43.1)

SD, standard deviation.

domain scores for responders and nonresponders. The z-test ($\alpha = 0.05$) was used to test for significant differences in the week 18 QOLIE-31 LSMs between responders and nonresponders.

3. Results

3.1. Patient demographics and baseline characteristics

Baseline characteristics of the pooled data for the primary analysis population (i.e., efficacy) and the subgroup of completers are reported in Table 1. The mean age of the pooled group was 39.4 (standard deviation [SD]: 11.92) years, and half (50.4%) were male. Additionally, the majority were white (83.7%) with very few of Hispanic/Latino (9.9%) origin. More than half of these patients were from North America (59.9%) compared with Eastern Europe (40.1%). Lastly, the pooled analysis population was overweight with a mean body mass index of 28.5 (SD: 7.2) kg/m^2. The completer population subgroup had similar characteristics.

3.2. Efficacy population

The final ANCOVA models developed to compare week 18 QOLIE-31 scores between responders and nonresponders included baseline QOLIE-31 score, responder/nonresponder, and ethnicity. All other covariates (ESL dose, age, body mass index, sex, race, and region) were removed during model selection.

Using the ≥50% SFR threshold, week 18 QOLIE-31 total score LSMs were significantly higher for responders than nonresponders (LSM difference: 3.0; 95% CI: 0.2–5.8; $p = 0.037$). Among the seven domains, four were significantly higher for responders than nonresponders: seizure worry (LSM difference: 6.1; 95% CI: 1.1–11.1; $p = 0.017$), overall QoL (LSM difference: 5.3; 95% CI: 1.9–8.7; $p = 0.002$), medication effects (LSM difference: 6.1; 95% CI: 0.3–11.9; $p = 0.038$), and social functioning (LSM difference: 6.2; 95% CI: 1.3–11.0; $p = 0.012$) (Table 2). Least squares mean differences were even greater using the ≥75% SFR threshold with responders having significantly higher LSMs than nonresponders for QOLIE-31 total score (LSM difference: 7.0; 95% CI: 3.6–10.3; $p < 0.001$) and for 6 of the 7 domain scores ($p < 0.05$ for all but emotional well-being) (Table 2).

3.3. Completer population

Using the ≥50% SFR threshold, week 18 QOLIE-31 LSMs were significantly higher for responders than nonresponders and, similar to the efficacy population, for overall QoL (LSM difference: 5.1; 95% CI: 1.5–8.6; $p = 0.006$) and social functioning (LSM difference: 5.4; 95% CI: 0.1–10.7; $p = 0.046$) (Table 3). Least squares mean differences were even greater using the ≥75% SFR threshold with responders having significantly higher LSMs than nonresponders, similar to the efficacy population, for QOLIE-31 total score (LSM difference: 6.6; 95% CI: 3.2–10.1; $p < 0.001$) and for all 7 domain scores ($p < 0.05$) (Table 3).

4. Discussion

These results demonstrate the incremental improvement in HRQoL as seizure frequency was reduced from >50% to >75% below baseline. Data from two clinical trials showed that conversion to ESL monotherapy resulted in improved HRQoL in patients with previously inadequately controlled seizures [13,14]. In this pooled analysis, we further explored the relationship between ESL and HRQoL by examining differences between patients who responded to ESL monotherapy and patients who did not respond. Depending on the threshold used for response (i.e., ≥50% or ≥75%), within the efficacy population, responders achieved a significant 3- to 7-point difference in QOLIE-31 total score above nonresponders with several domain scores also being significant. The most dramatic domain findings occurred in seizure worry (6.1-point to 10.5-point difference above nonresponders) and social functioning (6.2-point to 10.5-point difference above nonresponders). For the most part, similar results, particularly at SFR ≥ 75%, can be seen among the stricter completer population.

Unlike the results from analyses previously conducted to examine change from baseline, the results from this analysis show that the higher QOLIE-31 scores were specifically related to decreased seizure frequency using the commonly used responder threshold of SFR ≥ 50% as well as a more stringent cutoff of SFR ≥ 75%. When responders were defined by the SFR ≥ 50% cutoff, QOLIE-31 total score and 4 of the 7 domain scores appeared to be statistically related to SFR. When using the more stringent responder threshold of SFR ≥ 75%, QOLIE-31 total score

Table 2
Efficacy population: difference in week 18 QOLIE-31 scores between responders and nonresponders at week 18.[a]

QOLIE-31 domain	Responders LSM (95% CI)	Nonresponders LSM (95% CI)	LSM difference (95% CI)	p value[b]
≥50% SFR	n = 107	n = 144		
Total score	**68.7 (65.7–71.6)**	**65.7 (63.2–68.2)**	**3.0 (0.2–5.8)**	**0.037**
Seizure worry	**59.2 (54.0–64.5)**	**53.1 (48.7–57.6)**	**6.1 (1.1–11.1)**	**0.017**
Overall quality of life	**72.5 (69.0–76.1)**	**67.3 (64.2–70.3)**	**5.3 (1.9–8.7)**	**0.002**
Emotional well-being	75.3 (72.1–78.6)	74.8 (72.1–77.6)	0.5 (−2.6–3.6)	0.750
Energy/fatigue	65.8 (61.9–69.8)	65.2 (61.9–68.6)	0.6 (−3.2–4.3)	0.761
Cognitive functioning	67.5 (63.3–71.6)	66.8 (63.3–70.3)	0.7 (−3.3–4.6)	0.736
Medication effects	**68.3 (62.3–74.4)**	**62.2 (57.1–67.3)**	**6.1 (0.3–11.9)**	**0.038**
Social functioning	**69.1 (64.0–74.1)**	**62.9 (58.6–67.2)**	**6.2 (1.3–11.0)**	**0.012**
≥75% SFR	n = 51	n = 200		
Total score	**72.5 (68.9–76.1)**	**65.5 (63.2–67.9)**	**7.0 (3.6–10.3)**	**<0.0001**
Seizure worry	**64.0 (57.5–70.5)**	**53.5 (49.3–57.7)**	**10.5 (4.4–16.6)**	**0.0007**
Overall quality of life	**74.8 (70.3–79.3)**	**68.0 (65.1–70.9)**	**6.8 (2.6–11.0)**	**0.0014**
Emotional well-being	77.7 (73.7–81.7)	74.5 (71.9–77.1)	3.2 (−0.5–6.9)	0.0946
Energy/fatigue	**70.1 (65.2–74.9)**	**64.5 (61.4–67.7)**	**5.6 (1.0–10.1)**	**0.0159**
Cognitive functioning	**72.2 (67.1–77.3)**	**66.0 (62.7–69.3)**	**6.2 (1.5–11.0)**	**0.0102**
Medication effects	**71.1 (63.6–78.7)**	**62.9 (58.0–67.8)**	**8.2 (1.1–15.3)**	**0.0235**
Social functioning	**73.8 (67.5–80.0)**	**63.3 (59.2–67.3)**	**10.5 (4.7–16.3)**	**0.0004**

CI, confidence interval; LSM, least squares mean; QOLIE-31, Quality of Life in Epilepsy Inventory 31; SFR, seizure frequency reduction.
LSMs (CIs) with p values <0.05 are indicated in bold italics.
[a] Information on seizure frequency was not available for 1 patient, and information on overall quality of life was not available for another patient in the nonresponder group in each of the analysis populations.
[b] z-Test of difference in QOLIE-31 LSMs from ANCOVA model with baseline QOLIE-31 score and ethnicity in the model.

Table 3
Completer population: differences in week 18 QOLIE-31 scores between responders and nonresponders.[a]

QOLIE-31 domain	Responders LSM (95% CI)	Nonresponders LSM (95% CI)	LSM difference (95% CI)	p value[b]
≥50% SFR	n = 104	n = 106		
Total score	69.8 (66.7–72.9)	67.4 (64.5–70.2)	2.4 (−0.6–5.5)	0.116
Seizure worry	59.4 (53.8–65.0)	54.2 (49.1–59.3)	5.3 (−0.2–10.7)	0.058
Overall quality of life	**73.8 (70.1–77.5)**	**68.8 (65.4–72.1)**	**5.1 (1.5–8.6)**	**0.006**
Emotional well-being	76.9 (73.6–80.3)	76.0 (73.0–79.0)	1.0 (−2.3–4.2)	0.557
Energy/fatigue	66.5 (62.4–70.7)	66.2 (62.5–69.9)	0.3 (−3.6–4.3)	0.866
Cognitive functioning	68.5 (64.2–72.8)	68.9 (65.0–72.9)	−0.4 (−4.6–3.7)	0.836
Medication effects	70.2 (63.7–76.6)	64.4 (58.6–70.3)	5.7 (−0.6–12.0)	0.074
Social functioning	**70.4 (64.9–75.8)**	**65.0 (60.0–70.0)**	**5.4 (0.1–10.7)**	**0.046**
≥75% SFR	n = 55	n = 159		
Total score	**73.7 (69.9–77.4)**	**67.0 (64.4–69.6)**	**6.6 (3.2–10.1)**	**<0.001**
Seizure worry	**63.7 (57.0–70.4)**	**54.5 (49.8–59.2)**	**9.2 (3.0–15.4)**	**0.004**
Overall quality of life	**76.0 (71.5–80.5)**	**69.6 (66.5–72.7)**	**6.4 (2.2–10.5)**	**0.003**
Emotional well-being	**79.5 (75.5–83.4)**	**75.6 (72.8–78.4)**	**3.9 (0.2–7.6)**	**0.041**
Energy/fatigue	**70.8 (65.9–75.8)**	**65.2 (61.8–68.7)**	**5.6 (1.1–10.2)**	**0.015**
Cognitive functioning	**73.3 (68.1–78.5)**	**67.6 (64.0–71.2)**	**5.7 (0.9–10.5)**	**0.020**
Medication effects	**73.5 (65.6–81.3)**	**65.1 (59.6–70.5)**	**8.4 (1.1–15.7)**	**0.024**
Social functioning	**75.2 (68.7–81.7)**	**65.2 (60.6–69.8)**	**10.0 (4.0–16.1)**	**0.001**

CI, confidence interval; LSM, least squares mean; QOLIE-31, Quality of Life in Epilepsy Inventory 31; SFR, seizure frequency reduction.
LSMs (CIs) with p values <0.05 are indicated in bold italics.
[a] Information on seizure frequency was not available for 1 patient, and information on overall quality of life was not available for another patient in the nonresponder group in each of the analysis populations.
[b] z-test of difference in QOLIE-31 LSMs from ANCOVA model with baseline QOLIE-31 score and ethnicity in the model.

and 6 of the 7 domain scores appeared to be significantly associated with SFR. Responders to ESL monotherapy postconversion showed at least similar or higher LSMs in all subscales of QOLIE-31 than nonresponders. The results presented here show higher QOLIE-31 scores across an increasing number of domains as response to ESL conversion increases, as demonstrated by greater rates of reduction in seizure frequency.

In the subgroup analysis of the completer population, significantly higher QOLIE-31 scores were observed in overall QoL and social functioning for responders with SFR ≥ 50% and QOLIE-31 total score and all 7 domain scores for responders with SFR ≥ 75%, supporting the notion that better HRQoL coincided with SFR.

In general, differences in QOLIE-31 scores between responders and nonresponders were generally higher with the ≥75% SFR threshold than the ≥50% threshold, despite some variability between the efficacy and completer populations; better HRQoL correlated with improved SFR. Therefore, these results underscore the importance of effective seizure control in everyday activities, such as work, and other activities assessed by QOLIE-31 [15,18].

Prior research has shown that patients with POS whose seizures responded to other AED monotherapies have also experienced improvements in HRQoL across multiple domains. For example, in a single-arm study of oxcarbazepine monotherapy in pediatric patients with POS, those who achieved SFR ≥ 50% had statistically significant improvement in QOLIE-31 domains [19]. In a study of levetiracetam monotherapy conversion, patients with moderate to marked clinical improvement, defined by reduction in seizure control, showed ≥10% improvements from baseline in more QOLIE-31 domains than patients with mild clinical improvement [20]. Likewise, the current analysis demonstrated that responders to ESL monotherapy had statistically significant better HRQoL in several domains when compared with nonresponders.

Limitations of this study include the narrow analysis population and potential bias resulting from the study exit criteria. Patients who exited from the monotherapy conversion trial did so based on predefined criteria that signified worsening seizure control during the 16-week interval from AED conversion to the end of the monotherapy period (which includes the 6-week AED conversion period and the 10-week ESL monotherapy period). Also, some patients discontinued because of nonefficacy reasons such as unwillingness to continue the trial. Exclusion of those patients may select for patients whose seizures responded favorably to ESL treatment, thus biasing the findings, particularly in the efficacy analysis.

Additionally, there is the need to conduct further research to identify predictors for achievement of clinically meaningful change [16]. Prior assessment of QOLIE-31 minimal clinically important differences (MCIDs) with ESL adjunctive therapy in patients with POS suggested that the number of subscales meeting MCID thresholds increased among those with higher levels of response (SFR ≥ 75%) [12].

In conclusion, the current analysis of pooled data from clinical trials showed that greater seizure reduction with conversion to ESL monotherapy was associated with statistically significant higher HRQoL.

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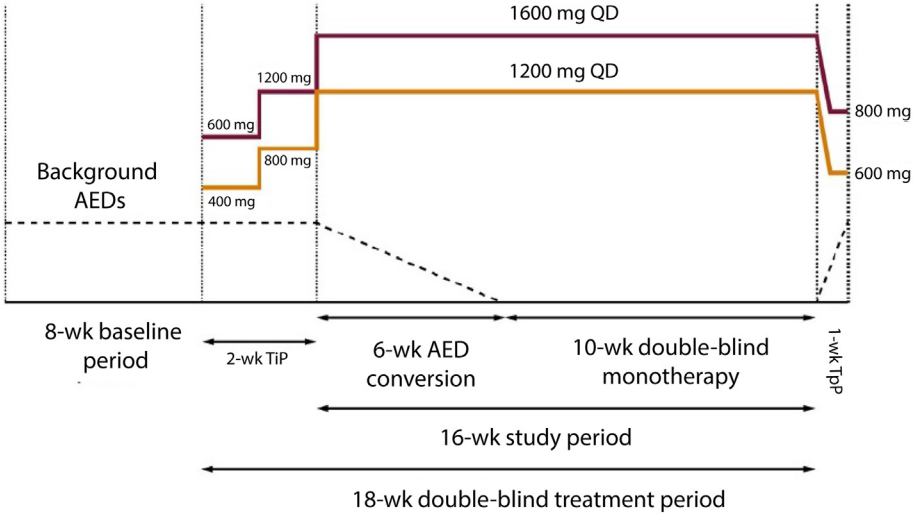
Disclosure of conflicts of interest

J. Cramer is a consultant for Sunovion, UCB, Eisai, and Irody. K. Rajagopalan was an employee of Sunovion Pharmaceuticals Inc. during the course of the study. K. P. Anastassopoulos is an employee of Covance, which was contracted by Sunovion to contribute to analyses in the study. D. Blum is an employee of Sunovion Pharmaceuticals Inc.

Ethical publication statement

All authors of this manuscript confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

Appendix A



Appendix Fig. 1. Study design.

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