Conversion to eslicarbazepine acetate monotherapy
A pooled analysis of 2 phase III studies

ABSTRACT
Objective: To assess the efficacy and safety of eslicarbazepine acetate (ESL) monotherapy.
Methods: This post hoc pooled analysis of 2 randomized double-blind studies (093-045 and -046) included adults with partial-onset seizures medically uncontrolled by 1 or 2 antiepileptic drugs (AEDs). Following the baseline period (8 weeks), eligible patients were randomized 2:1 to receive ESL 1,600 mg or 1,200 mg once daily for 18 weeks; the primary endpoint was study exit by meeting predefined exit criteria (signifying worsening seizure control). In each study, treatment was considered effective if the upper 95% confidence limit for exit rate was lower than the historical control threshold (65.3%).
Results: Pooled exit rates were as follows: ESL 1,600 mg 520.6% (95% confidence interval: 15.6%–26.8%); ESL 1,200 mg 530.8% (23.0%–40.5%). Use of 2 baseline AEDs or rescue medication, US location, epilepsy duration 20 years, and higher maximum baseline seizure frequency were associated with higher exit risks. Median percent reductions in standardized seizure frequency between baseline and the 18-week double-blind period were as follows: ESL 1,600 mg 543.2%; ESL 1,200 mg 535.7%; baseline carbamazepine use was associated with smaller reductions. Safety profiles were similar between ESL doses.
Conclusions: Exit rates for ESL monotherapy (1,600 mg and 1,200 mg once daily) were lower than the historical control threshold, irrespective of baseline AED use and region, with no additional safety concerns identified. Clinical factors and location clearly influence treatment responses in conversion-to-monotherapy trials.

Classification of evidence: This pooled analysis provides Class IV evidence that for adults with medically uncontrolled partial-onset seizures, ESL monotherapy is well tolerated and effective.

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GLOSSARY
AE = adverse event; AED = antiepileptic drug; CI = confidence interval; ESL = eslicarbazepine acetate; ITT = intent-to-treat; KM = Kaplan–Meier; MADRS = Montgomery-Åsberg Depression Rating Scale; POS = partial-onset seizure; QOLIE-31 = 31-item Quality of Life in Epilepsy; SAE = serious adverse event; SSF = standardized seizure frequency; TEAE = treatment-emergent adverse event; UCL = upper 95% confidence limit.

Antiepileptic drug (AED) monotherapy for epilepsy compares favorably with polypharmacy, often with fewer side effects and fewer drug–drug interactions.1,2 There is a need for effective and well-tolerated AEDs for use in the monotherapy setting.

Eslicarbazepine acetate (ESL) (Aptiom; Sunovion Pharmaceuticals Inc., Marlborough, MA) is a once-daily oral AED, approved by the US Food and Drug Administration for the treatment of partial-onset seizures (POS) as monotherapy or adjunctive therapy, and by Health Canada as adjunctive therapy of POS in patients with epilepsy who are not satisfactorily controlled with conventional therapy. ESL (Zebinix; BIAL – Portela & Cª., S.A., S. Mamede do Coronado,
Portugal) is approved by the European Medicines Agency as adjunctive therapy of POS in adults. Eslicarbazepine, the active metabolite of ESL, is thought to inhibit sodium currents by stabilizing the inactivated state of voltage-gated sodium channels.\(^3\)

The results of 2 ESL monotherapy studies (093-045 and 093-046) have been reported previously.\(^4,5\) ESL monotherapy (1,600 mg and 1,200 mg once daily) was found to be effective (superior to a historical control) and well tolerated. A combined analysis of these studies allowed a more thorough evaluation of ESL monotherapy; pooling data from identically designed studies provides greater statistical power for the assessment of treatment effects in patient subgroups of interest. This analysis evaluates the relationships between various factors (including geographic region, number and type of baseline AEDs, benzodiazepine use, and presence of secondarily generalized seizures) and the efficacy and safety of ESL monotherapy.

**METHODS** The study design (including inclusion and exclusion criteria, exit criteria, and randomization technique) and statistical methods (including sample size determination) were identical for both studies.\(^4,5\)

**Classification of evidence.** The primary research question was whether the rate of study exit (by meeting predefined exit criteria signifying worsening seizure control) for patients taking ESL (1,600 mg or 1,200 mg) was lower than the historical control threshold. This pooled analysis provides Class IV evidence that for adults with medically uncontrolled POS, ESL monotherapy is well tolerated and effective.

**Standard protocol approvals, registrations, and patient consents.** The 2 studies (093-046 [NCT01091662] and 093-045 [NCT00866775], both registered at ClinicalTrials.gov) were conducted between 2009 and 2013 at sites in the United States, Canada, Bulgaria, Serbia, the Ukraine, and the Czech Republic, in accordance with the principles of the Declaration of Helsinki, the International Conference on Harmonisation guidelines, and all national, state, and local laws of the pertinent regulatory authorities. Approval was received from the relevant independent ethics committees/institutional review boards, and all patients provided informed consent.

**Patients.** Patients aged 16 to 70 years with a diagnosis of localization-related (focal) epilepsy (defined by the International League Against Epilepsy, 1981)\(^6\) and a history of POS were localization-related (focal) epilepsy (defined by the International League Against Epilepsy, 1981)\(^6\) and a history of POS were included. Patients aged 18 to 70 years with a diagnosis of POS and the efficacy and safety of ESL monotherapy periods).

**Seizure data were obtained using seizure diaries, completed daily by the patients or their caregivers throughout the study. The primary efficacy endpoint was seizure exit by meeting \(0.1\) of 5 prospectively defined exit criteria (signifying worsening seizure control), between the start of the AED conversion period and the end of the monotherapy period.

**Secondary endpoints.** The key secondary efficacy endpoint was the percentage of patients who achieved seizure freedom (defined by baseline AED use (those AEDs used by \(\geq 15\%\) of patients) and region (US vs non-US). Effects of subgroup factors were also evaluated separately, using a Cox proportional hazards regression model.

**Safety and tolerability.** Investigators recorded adverse events (AEs) at each clinic visit. AEs were coded using the Medical Dictionary for Regulatory Activities, version 13.1. Treatment-emergent AEs (TEAEs) were defined as AEs that occurred on or after the first dose of study drug. Serious AEs (SAEs) were reported separately; classification of AEs as “serious” was at the judgment of the investigators. Summary statistics for TEAEs were calculated for each study period (titration, AED conversion, and ESL monotherapy periods).

**Statistical analyses.** Both studies used a historical control comparator, as proposed by French et al.\(^8\) The historical control exit rate was determined from the placebo/pseudo-placebo groups of 8 historical conversion-to-monotherapy trials. The lower bound of the 95% prediction interval of the overall exit rate (i.e., 65.3% at 112 days)\(^9\) was used as the exit threshold for a scenario involving a single study. Similarly to the individual studies, pooled cumulative exit rates and 95% confidence intervals (CIs) at 112 days were estimated using Kaplan–Meier (KM) methodology for each ESL treatment group. Methods for censoring and patient reassessment have been previously reported.\(^3\)

Exit rates and 95% CIs were estimated for patient subgroups defined by baseline AED use (these AEDs used by \(\geq 15\%\) of patients) and region (US vs non-US). Effects of subgroup factors were also evaluated separately, using a Cox proportional hazards regression model.

A worst-case scenario analysis was conducted to evaluate the potential confounding effect of benzodiazepine use: patients who took benzodiazepine derivatives during the AED conversion

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\(^3\) ELF monotherapy (1,600 mg and 1,200 mg once daily) was found to be effective (superior to a historical control) and well tolerated. A combined analysis of these studies allowed a more thorough evaluation of ESL monotherapy; pooling data from identically designed studies provides greater statistical power for the assessment of treatment effects in patient subgroups of interest. This analysis evaluates the relationships between various factors (including geographic region, number and type of baseline AEDs, benzodiazepine use, and presence of secondarily generalized seizures) and the efficacy and safety of ESL monotherapy.

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**Table 1** Selected demographics and baseline clinical characteristics for the pooled efficacy population (US and non-US subgroups)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>US (n = 211)</th>
<th>Non-US (n = 121)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Patient demographics</strong></td>
<td></td>
<td></td>
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<tr>
<td>Race, %</td>
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<td></td>
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<tr>
<td>White</td>
<td>74.4</td>
<td>99.2</td>
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<td>Black or African American</td>
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<tr>
<td>Asian</td>
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<td>0.8</td>
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<tr>
<td>Weight, kg, mean (SD)</td>
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<td>72.9 (14.3)</td>
</tr>
<tr>
<td>BMI &gt;30 kg/m², %</td>
<td>46.4</td>
<td>10.7</td>
</tr>
<tr>
<td><strong>Clinical characteristics</strong></td>
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<tr>
<td>Duration of epilepsy, y, median</td>
<td>17.0</td>
<td>11.0</td>
</tr>
<tr>
<td>Duration of epilepsy ≥20 y, %</td>
<td>43.6</td>
<td>28.1</td>
</tr>
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<td>AEDs used by ≥15% of patients, %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>26.5</td>
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<td>Lamotrigine</td>
<td>11.8</td>
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<tr>
<td>Levetiracetam</td>
<td>31.8</td>
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<td>Valproic acid</td>
<td>10.9</td>
<td>35.5</td>
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<tr>
<td>Taking 1 AED, %</td>
<td>68.7</td>
<td>69.4</td>
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<tr>
<td>Partial seizures evolving to secondarily generalized seizures, %</td>
<td>25.1b</td>
<td>39.7c</td>
</tr>
<tr>
<td>Maximum consecutive 2-d seizure rate, mean (SD)</td>
<td>3.7 (2.6)b</td>
<td>2.2 (1.3)c</td>
</tr>
<tr>
<td>Maximum consecutive 28-d seizure rate, mean (SD)</td>
<td>13.4 (9.1)b</td>
<td>10.0 (7.2)d</td>
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<td>Maximum consecutive 28-d seizure rate &gt;15/mo, %</td>
<td>31.3b</td>
<td>14.9c</td>
</tr>
<tr>
<td>Benzodiazepines used, %</td>
<td>10.0</td>
<td>2.5</td>
</tr>
</tbody>
</table>

Abbreviations: AED = antiepileptic drug; BMI = body mass index; US = United States. Percentages are calculated based on the number of patients with available data in the efficacy population in each subgroup.

*An AED was considered to be used at baseline if it was started at any time before the first dose of study drug and continued into the titration period.

$^a$n = 210.

$^b$n = 120.

Period, after the first dose of study medication, were considered to have met the study exit criteria at the time of use. The relationship between QOLIE-31 overall score and reduction in SSF from baseline was evaluated via Pearson correlation. All statistical procedures were performed using SAS version 9.2 (SAS Institute, Cary, NC). All statistical tests were 2-sided.

**Study populations.** The pooled intent-to-treat (ITT) population comprised all randomized patients in the 2 trials who received ≥1 dose of study drug. The ITT population was used to evaluate patient disposition, baseline demographics and characteristics of the overall population, and safety outcomes. Efficacy analyses and comparisons of baseline demographics and characteristics between US and non-US patients used the pooled efficacy population (i.e., all ITT patients who entered the AED conversion period).

**RESULTS Patients.** The ITT population comprised 365 patients (ESL 1,600 mg, n = 242; ESL 1,200 mg, n = 123; figure e-2). Baseline demographic and clinical characteristics were generally well balanced between dose groups (table e-1) and comparable to those of the historical control comparator group (Jacobson et al., 2015 [table S2]).

The efficacy population comprised 332 patients (ESL 1,600 mg, n = 218; ESL 1,200 mg, n = 114; US, n = 211; non-US, n = 121). There were some notable differences in demographics and clinical characteristics between the US and non-US subgroups (table 1). The US subgroup had a longer median duration of illness, more levetiracetam use, and less valproic acid and lamotrigine use, as well as higher proportions of obese individuals, and black, Asian, and Hispanic patients, than the non-US subgroup. Compared with the non-US subgroup, the US subgroup also had higher maximum 2- and 28-day seizure rates and more benzodiazepine use during the baseline period.

**Efficacy. Primary endpoint.** In the individual studies (045 and 046), the upper 95% confidence limits (UCLs) of exit rates for both ESL doses were lower than the historical control threshold (65.3%), indicating drug efficacy. The pooled KM-estimated exit rates at 112 days were 20.6% (95% CI: 15.6%–26.8%) for ESL 1,600 mg and 30.8% (23.0%–40.5%) for ESL 1,200 mg (figure 1).

Secondary analyses of the primary endpoint. US vs non-US patients. The KM-estimated exit rates for the US subgroup were greater than those for the non-US subgroup (figure 2A). Cox proportional hazard regression analysis confirmed that US patients were significantly more likely to exit the study ($p < 0.001$; figure 2C). The time to exit for US patients exhibited a dose-response relationship; the rate was lower with ESL 1,600 mg vs 1,200 mg. For US patients taking 2 baseline AEDs, or with secondarily generalized seizures before or during the baseline period, the difference in exit rates between dose groups was particularly marked. For all 4 subgroups (US and non-US patients taking ESL 1,600 and 1,200 mg), the UCLs of the exit rates were lower than the 65.3% historical control threshold.

**Baseline AEDs.** KM-estimated exit rates were also calculated for subgroups defined by baseline AED use (for AEDs taken by ≥15% of patients; figure 2B). Use of carbamazepine (n = 91), lamotrigine (n = 49), levetiracetam (n = 82), and valproic acid (n = 66) at baseline did not have statistically significant effects on risk of exit (figure 2C).

Overall, 31.0% of patients were taking 2 AEDs during the baseline period. The exit risk was significantly higher for patients taking 2 baseline AEDs (vs 1; figure 2C). In addition, exit risk was...
significantly lower for patients taking phenytoin at baseline (vs those not taking phenytoin; $p = 0.049$), although the sample size was small (only 30 patients were taking baseline phenytoin).

**Benzodiazepine use.** Patients who used benzodiazepines had a higher risk of study exit (figure 2C). Approximately 7.8% of patients had not used benzodiazepines before randomization but used them during the 18-week treatment period. In a sensitivity analysis of the primary endpoint, in which patients who used benzodiazepines after the start of the AED conversion period, but not before the first dose of study medication, were deemed to have met the exit criteria, the UCLs of exit rates for both ESL dose groups were also lower than the 65.3% historical control threshold (1,600 mg: 24.2% [95% CI: 18.9%–30.8%]; 1,200 mg: 32.6% [24.6%–42.4%]).

**Disease characteristics.** Exit risk was also found to be higher for patients with a duration of epilepsy $\geq 20$ years, for patients with a higher baseline seizure rate (maximum consecutive 2-day rate), for those who used vagal nerve stimulation during baseline, and for those who used rescue medication (figure 2C).

**Secondary endpoints.** The proportion of patients who achieved seizure freedom during the entire 10-week monotherapy period was similar for the 2 ESL dose groups (ESL 1,600 mg: 8.7% [95% CI: 5.3%–13.3%]; ESL 1,200 mg: 7.9% [CI: 3.7%–14.5%]). Seizure frequency was calculated as SSF per 28 days. The median percent reduction from baseline in SSF for the 18-week treatment period was 43.2% with ESL 1,600 mg and 35.7% with ESL 1,200 mg (figure 3); for the 10-week monotherapy period, the median percent reduction was 46.3% and 47.1% with ESL 1,600 mg and 1,200 mg, respectively. Responder rates (proportion of patients with $\geq 50\%$ reduction in SSF) during the 18-week treatment period were 42.7% for ESL 1,600 mg and 36.0% for ESL 1,200 mg. Reductions in seizure frequency occurred in patients taking different AEDs at

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**Figure 1** Kaplan–Meier analysis of exit rates (efficacy population): Pooled population (A) and individual studies and pooled population (B)

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CI = confidence interval; ESL = eslicarbazepine acetate; QD = once-daily; US = United States.
Figure 2 Subgroup analyses of exit rates (pooled efficacy population): Influence of geographic region on exit rate (US vs non-US regions) (A), of baseline AED use (AEDs used by ≥15% of patients) on exit rate (B), and of patient characteristics on risk of study exit (pooled efficacy population) (C).

Note that for age, baseline body weight, and maximum 2- or 28-day seizure rate, the hazard ratio is displayed for a single unit change; otherwise, it is shown for the referenced group compared to those without the stated factor. VPA included all dosage forms combined unless otherwise stated (including VPA, sodium valproate, divalproex sodium, etc.). BZD derivatives used before study treatment (prior), after initiation of the AED conversion period as rescue or emergency medication (after), or only after study treatment (not prior, after). AED = antiepileptic drug; B/L = baseline; BZD = benzodiazepine; CBZ = carbamazepine; CI = confidence interval; CP = complex partial seizure; duration = duration of epilepsy; ESL = eslicarbazepine acetate; LEV = levetiracetam; LTG = lamotrigine; OXC = oxcarbazepine; PHT = phenytoin; SGTC = secondarily generalized tonic-clonic seizures (also referred to as complex partial seizures with secondary generalization); sz = seizure; TOP = topiramate; US = United States; VNS = vagal nerve stimulator; VPA = valproic acid.
baseline, but the magnitude of reduction was less for patients who were taking carbamazepine at baseline than for those who were not (figure 3).

For patients who continued into the monotherapy period, overall QOLIE-31 scores increased between baseline and the end of the monotherapy period (ESL 1,600 mg, 5.7-point median increase; ESL 1,200 mg, 3.3 point median increase; calculated for the 252 patients who had QOLIE-31 scores for both the baseline and monotherapy periods). Of note, there was a statistically significant correlation ($p = 0.001$) between reduction in SSF from baseline and the increase in overall QOLIE-31 score. Similarly, MADRS total scores decreased by a median of 1 point with ESL 1,600 mg and were unchanged with ESL 1,200 mg (calculated for the 267 patients who had MADRS scores for both periods).

Completion rates for the 18-week treatment period were 71.6% (95% CI: 65.1%–77.4%) for ESL 1,600 mg and 61.4% (51.8%–70.4%) for ESL 1,200 mg. For the 10-week monotherapy period, completion rates were 86.2% (95% CI: 80.3%–90.9%) for ESL 1,600 mg and 75.3% (65.2%–83.6%) for ESL 1,200 mg.

Safety. TEAEs reported for $\geq 5\%$ of patients during each treatment period are shown in table 2. Headache, dizziness, somnolence, and fatigue were the most frequently reported TEAEs. There was no clear relationship between incidence of these TEAEs and ESL dose. Depression was reported in 2.5% and 0.8% of patients taking ESL 1,600 mg and 1,200 mg, respectively, and “suicidal ideation” in 2 patients (1.6%) taking ESL 1,200 mg. Serum sodium $\leq 125$ mEq/L was recorded in 7 patients taking ESL 1,600 mg (2.9%) and 5 patients taking ESL 1,200 mg (0.8%). TEAEs led to discontinuation in 15.3% and 8.1% of patients taking ESL 1,600 mg and 1,200 mg, respectively. Events leading to discontinuation included hyponatremia (1.4%), skin and subcutaneous tissue disorders (ESL 1,600 mg, 2.9%; ESL 1,200 mg, 0.8%), and drug rash with eosinophilia and systemic symptoms (ESL 1,600 mg, 1 patient).

During the 18-week treatment period, SAEs occurred in 21 patients (5.8% overall: ESL 1,600 mg, 6.6%; ESL 1,200 mg, 4.1%). The most frequent SAEs were hyponatremia (ESL 1,600 mg, 1.2% [3 patients]; ESL 1,200 mg, 0%), complex partial seizures (0.8% [2 patients]; 0%), and partial seizures with secondary generalization (0.4% [1 patient]; 0.8%
s patients. The authors thank Rebecca Thair of FireKite, an Ashfield company, for assistance with editing the manuscript for nonintellectual content.

AUTHOR CONTRIBUTIONS

M. Sperling was involved in the acquisition, analysis, and interpretation of data, and in drafting and revising the manuscript for content. J. French was involved in the development of the study concept/design, and in drafting and revising the manuscript for content. M. Jacobson was involved in the acquisition, analysis, and interpretation of data, and in drafting and revising the manuscript for content. T. Grinnell was involved in the development of the study concept/design, in the acquisition, analysis, and interpretation of data, and in drafting and revising the manuscript for content. M. Gough was involved in the development of the study concept/design, in the acquisition, analysis, statistical analysis, and interpretation of data, and in drafting and revising the manuscript for content. L. Pazdera was involved in the acquisition, analysis, and interpretation of data, and in drafting and revising the manuscript for content. M. Sperling was involved in the acquisition, analysis, and interpretation of data, and in drafting and revising the manuscript for content. L. Pazdera was involved in the acquisition, analysis, statistical analysis, and interpretation of data, and in drafting and revising the manuscript for content. T. Grinnell was involved in the development of the study concept/design, in the acquisition, analysis, and interpretation of data, and in drafting and revising the manuscript for content. M. Gough was involved in the development of the study concept/design, in the acquisition, analysis, statistical analysis, and interpretation of data, and in drafting and revising the manuscript for content. L. Pazdera was involved in the acquisition, analysis, statistical analysis, and interpretation of data, and in drafting and revising the manuscript for content.
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DISCLOSURE
M. Sperling has received consultancy honoraria for UCB Pharma, honorary from Wiley for serving as associate editor for Epilepsia 2013–2014, and has been the editor-in-chief of Epilepsia from 2014 to present (no honorarium). M. Sperling has also served as site principal investigator from Sunovion Pharmaceuticals Inc., UCB Pharma, SK Life Sciences, Eisai, Lundbeck, Acorda, Upsher-Smith, Medtronic, Brain Sentinel, Visualase, and GlassSmithKline, for research contracted and paid to Thomas Jefferson University, and has received federal funding from NIH and the Defense Advanced Research Projects Agency. J. French has consulted for Acorda, Anavex, Braeburn Pharma, BioPharm Solutions, Eisai, GlassSmithKline, GW Pharma, Impax, Johnson & Johnson, Marinus, Neurontics, Novartis, Pfizer, Sage, Sunovion Pharmaceuticals Inc., SK Life Sciences, Supernus, Takeda, UCB Pharma, Upsher-Smith, Ultradynex, Vertex, Zogenix, and Zynadex. All consulting was on behalf of the Epilepsy Study Consortium, and fees are paid to the consortium, New York University receives salary support from the consortium. J. French has also received grants and research support from Acorda, Alexza, LCGH, Eisai, Lundbeck, Pfizer, SK Life Sciences, UCB Pharma, Upsher-Smith, Vertos, Zogenix, and Zynadex. M. Sperling has received honoraria from Sunovion Pharmaceuticals Inc., and research support from Lundbeck, Sunovion Pharmaceuticals Inc., Sage Therapeutics, and Marinus. L. Pandera is an employee of Vestra Clinics and has received research support from Sunovion Pharmaceuticals Inc. M. Gough is an employee of FireKite, and was funded by Sunovion Pharmaceuticals Inc. and research support from Sunovion Pharmaceuticals Inc. M. Gough is an employee of FireKite, and was funded by Sunovion Pharmaceuticals Inc. M. Gough is an employee of Sunovion Pharmaceuticals Inc. T. Grinnell is an employee of Sunovion Pharmaceuticals Inc. D. Blum is an employee of Sunovion Pharmaceuticals Inc. Go to Neurology.org for full disclosures.

REFERENCES
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