Evaluation of diazepam nasal spray in patients with epilepsy concomitantly using maintenance benzodiazepines: An interim subgroup analysis from a phase 3, long-term, open-label safety study.

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Evaluation of diazepam nasal spray in patients with epilepsy concomitantly using maintenance benzodiazepines: An interim subgroup analysis from a phase 3, long-term, open-label safety study

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Abstract

Objective: Diazepam nasal spray (Valtoco), indicated for acute treatment of frequent seizure activity (seizure clusters) in patients with epilepsy ≥6 years of age, is designed to be a rapid, noninvasive, socially acceptable route of administration. This interim analysis evaluated the safety profile of diazepam nasal spray in patients with and without concomitant use of benzodiazepines, with use of a second dose for a seizure cluster as a proxy for effectiveness.

Methods: A long-term, phase 3, open-label safety study enrolled patients with epilepsy who had seizures despite a stable antiseizure medication regimen.

Results: Among 175 patients enrolled by October 31, 2019, a total of 158 were treated with diazepam nasal spray (aged 6–65 years; 53.8% female). Of those, 119 (75.3%) received concomitant benzodiazepines (60, chronic; 59, intermittent); 39 (24.7%) did not. Use of a second dose was similar in patients using chronic concomitant benzodiazepines (second dose in 11.1% [144/1299]) and those with no concomitant benzodiazepines (second dose in 10.3% [41/398]). Treatment emergent adverse events (TEAEs) occurred for 80.0% with chronic use of concomitant benzodiazepines and 61.5% without. Cardiorespiratory depression was not reported, and no serious TEAEs were treatment related. Study retention was high: 83.3% in the chronic benzodiazepine group and 76.9% in the no-benzodiazepine group. Findings were similar in a sub-analysis of patients who were (n = 44) or were not (n = 75) taking clobazam.

Significance: This analysis of patients from a long-term study shows a similar safety profile of diazepam nasal spray in patients with and without concomitant benzodiazepines, and consistent with the established profile for diazepam. Use of a single dose of diazepam nasal spray and high study retention rates suggest the effectiveness of diazepam nasal spray in patients irrespective of chronic daily benzodiazepine use. Results were similar in the clobazam sub-analysis. These results support the safety
INTRODUCTION

Antiseizure medications are the mainstay of epilepsy management. For some patients with epilepsy these regimens may include benzodiazepines, which have played an important role in epilepsy management since the 1960s.1 However, even with maintenance treatment, seizure clusters may occur, resulting in increased morbidity and hospitalization as well as reduced quality of life.2,4 Benzodiazepines such as diazepam and midazolam are the primary treatment for seizure clusters.5 In other indications and doses, use of benzodiazepines has sometimes been associated with cardiorespiratory suppression6,7 as well as development of reduced effectiveness.8 Therefore, it is clinically relevant to understand how treatment with diazepam nasal spray for seizure clusters may be affected by concomitant use of other benzodiazepines as chronic and/or intermittent therapy.

Benzodiazepines modulate the γ-aminobutyric acid (GABA) A receptor, and produce sedative, anxiolytic, and anticonvulsive effects,9 with potential dose-related effects on respiratory and hemodynamic parameters.7,9 Cardiorespiratory adverse effects have been reported in the treatment of status epilepticus with intravenous anticonvulsants,7 and such effects have been observed in some studies of treatment for seizure clusters10 but were not observed in other studies.11

For more than two decades, diazepam rectal gel (Diastat) was the only US Food and Drug Administration (FDA)–approved rescue medication for seizure clusters, which allowed for out-of-hospital management of seizure clusters.5,12,13 However, this route of administration has limitations including invasiveness, limited ease of administration, and lack of social acceptability.14 More recently, two intranasal benzodiazepines (diazepam and midazolam) have been approved for this indication10,15-18. These two intranasal formulations have individual pharmacologic profiles, doses, and pediatric indications.10,15-18

Diazepam nasal spray (Valtoco) is a novel intranasal formulation designed to provide a rapid, noninvasive, and socially acceptable route of administration in patients 6 years of age and older with epilepsy for acute treatment of intermittent, stereotypic episodes of frequent seizure activity (ie, seizure clusters, acute repetitive seizures) that are distinct from a patient’s usual seizure pattern.17,19 As determined by the FDA for Orphan Drug Exclusivity, this route of administration provides a major contribution to patient care over the rectal route of administration by providing a significantly improved ease of use.20 Diazepam nasal spray is formulated with n-dodecyl-beta-δ-maltoside (Intravail A3), a nonionic surfactant used as an absorption enhancement agent that promotes transmucosal permeation and thus improves bioavailability of drugs21 and vitamin E to enhance the nonaqueous solubility of diazepam.18 Intransal administration of this formulation results in comparable bioavailability with less pharmacokinetic intrapatient variability than rectal diazepam.17 Diazepam nasal spray has the expected adverse event profile for rectal diazepam.18

This analysis used interim data from a long-term, phase 3, open-label safety study of diazepam nasal spray as rescue medication for treatment of seizure clusters. The objective of the analysis was to evaluate whether real-world effectiveness, using a second dose as a proxy, and safety profile, including key cardiorespiratory measures, were affected by chronic concomitant use of benzodiazepines as part of a patient’s antiseizure medication regimen and/or intermittent therapy.

and effectiveness of diazepam nasal spray in patients with concomitant benzodiazepine use.

KEYWORDS
antiseizure drug regimen, benzodiazepine, diazepam, intranasal, seizure cluster

Key Points
• Diazepam nasal spray is designed to be a rapid, noninvasive, socially acceptable route of administration
• Safety profile of diazepam nasal spray was similar in patients with and without concomitant benzodiazepines
• Low need for a second dose suggests the effectiveness of diazepam nasal spray in patients irrespective of chronic benzodiazepine use
• These results support the safety and effectiveness of diazepam nasal spray in patients with concomitant benzodiazepine use

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2 | METHODS

2.1 | Study design

This was an interim analysis of a phase 3, repeat dose, open-label study that evaluated the safety of diazepam nasal spray in patients with epilepsy, who, in the opinion of the investigator, could need benzodiazepine intervention for seizure control at least once every other month on average (ie, average 6 times a year). This study was approved by local institutional review boards and was conducted in accordance with the Declaration of Helsinki. All patients or their legal representatives provided written informed consent (Clinicaltrials.gov identifier: NCT02721069).

2.2 | Patients

Eligible patients were male or female and 6–65 years of age. Patients had a diagnosis of partial or generalized epilepsy with motor seizures or seizures with clear alteration of awareness; occurrence of seizures despite a stable antiseizure medication regimen; and availability of a qualified care partner or medical professional who could administer study medication in the event of a seizure. Patients also had no clinically significant abnormal findings in their medical history, or on physical examination, electrocardiography (QTcF <450 ms for males and QTcF <470 ms for females), or clinical laboratory results during screening. Female patients of childbearing potential agreed to use an approved method of birth control.

Key exclusion criteria were a history of major depression or a past suicide attempt or suicidal ideation; history of allergy or adverse response to diazepam; or history of a clinically significant medical condition that would jeopardize the safety of the patient.

2.3 | Treatment

Care partners and patients were trained on the proper use of the nasal spray device at screening and as needed during the treatment period. During patient follow-up of at least 1 year, diazepam nasal spray was administered at age- and weight-based doses of 5, 10, 15, or 20 mg, with a second dose administered, if needed, 4–12 h later, per the study protocol. Patients and care partners were instructed that treatment should not be repeated within 5 days of the prior treatment or be given more than 5 times a month. Investigators could adjust doses for efficacy or safety.

2.4 | Analysis

In an exploratory analysis, benzodiazepine use was classified as chronic or intermittent. For individual benzodiazepines in the concomitant medication database, chronic usage was defined using the “ongoing” flag as a filter. Patients with chronic usage had at least one “ongoing” benzodiazepine at least once in the database. All other patients with concomitant benzodiazepine use were included in the intermittent category. This analysis descriptively evaluated diazepam nasal spray utilization and safety profile in patients concomitantly using benzodiazepines as chronic therapy compared with patients not receiving benzodiazepines.

The proportion of seizure events that were treated with a second dose of diazepam nasal spray within a 24-h period also was assessed as a proxy for effectiveness. A sub-analysis of the concomitant benzodiazepines group specific to patients taking or not taking clobazam, which is used daily to treat seizures associated with Lennox-Gastaut syndrome, also was performed to assess potential differences in the utilization and safety profile of diazepam nasal spray in these subgroups. Group comparisons were not corrected for baseline differences.

2.5 | Data collection

Medical history was collected at screening and baseline. Use of concomitant medications was collected throughout the study. A diary was used to record dates and times of seizures and doses of diazepam nasal spray. Safety measures included occurrence of treatment-emergent adverse events (TEAEs) and results of physical/neurological examination, vital signs, and laboratory tests. TEAEs were recorded regardless of the investigator opinion of causality, noting severity and causal relationship to study drug. Retention rates in the study are reported.

3 | RESULTS

A total of 175 patients were enrolled; 158 received diazepam nasal spray as of October 31, 2019, and were included in the safety analysis. The remaining 17 patients did not have an event qualifying for use of diazepam nasal spray. The majority of patients were female (53.8%) and the mean age was 23.5 years.

A total of 119 patients (75.3%) received concomitant benzodiazepines (60 chronic, 59 intermittent) and 39 (24.7%) did not (Table 1). The mean age was 19.1 years in the chronic concomitant benzodiazepines group, 27.9 years in the intermittent group, and 23.7 years in the group without concomitant benzodiazepines. More patients in the group without concomitant benzodiazepines were female (61.5%) compared with the concomitant benzodiazepine group (chronic 50.0%; intermittent 52.5%). The most common concomitant benzodiazepines (≥5 patients) were clobazam (n = 40) and clonazepam (n = 19) in the chronic group and diazepam (n = 44),
lorazepam \((n = 32)\), and clonazepam \((n = 32)\) in the intermittent group, with some patients receiving two or more of these during the long-term study.

### 3.1 | Patient disposition

At the time of interim data cutoff, 34 of 60 patients (56.7%) in the chronic concomitant benzodiazepines group and 28 of 59 (47.5%) in the intermittent group remained in the study; 16 (26.7%) and 23 (39.0%), respectively, had completed the study; and 10 (16.7%) and 8 (13.6%), respectively, discontinued (Figure 1A,B). Reasons for discontinuation were loss to follow-up \((n = 1)\), withdrawal by subject from the study \((n = 6)\), chronic group; \(n = 5\), intermittent group), and other \((n = 4)\), chronic group; \(n = 2\) intermittent group). In the group without concomitant benzodiazepines, 22 of 39 patients (56.4%) remained in the study; 8 (20.5%) completed the study; 9 (23.1%) discontinued (Figure 1C). Reasons for discontinuation were loss to follow-up \((n = 2)\), withdrawal by subject \((n = 5)\), and other \((n = 2)\). No patient discontinued due to TEAEs. High retention rates were observed in both the chronic use of benzodiazepines group (83.3%) and the intermittent use group (86.4%), as well as those not receiving concomitant benzodiazepines (76.9%).

### 3.2 | Exposure

Most patients in the study had a duration of diazepam nasal spray exposure \(\geq 12\) months, with exposure modestly longer in the groups receiving concomitant benzodiazepines (Table 2). During the study, patients using chronic benzodiazepines were treated for 1299 seizure clusters and those using intermittent benzodiazepines for 1582 seizure clusters, whereas patients not receiving concomitant benzodiazepines recorded 398 treated seizure clusters. The percentage of patients with high-frequency usage of diazepam nasal spray (an average of 2-5 doses per month) was similar between the chronic (51.7%) and intermittent (52.5%) groups and lower for those not receiving concomitant benzodiazepines (46.2%). Likewise, the mean monthly dose was 2.5 doses in the chronic and 2.7 doses in the intermittent groups and 2.0 in the no concomitant benzodiazepines group (Table 2).

### 3.3 | Effectiveness in the chronic concomitant benzodiazepines and no concomitant benzodiazepines groups

Effectiveness, as measured by the percentage of seizure clusters for which a second dose was used within 24 h of the
first dose, was similar in the chronic concomitant benzodiazepines and the no concomitant benzodiazepines groups. A second dose was used in 144 of 1299 seizure clusters (11.1%) in patients receiving chronic concomitant benzodiazepines, and in 41 of 398 seizure clusters (10.3%) in those not receiving concomitant benzodiazepines.

3.4 | Safety in the chronic concomitant benzodiazepines and no concomitant benzodiazepines groups

The proportion of patients with a TEAE, irrespective of causality, was higher in the chronic use of concomitant benzodiazepines group (80.0%) compared with the group without concomitant benzodiazepines (61.5%; Table 3). Similarly, serious TEAEs (35.0% and 23.1%) were higher in the chronic use of concomitant benzodiazepines group. It is important to note that there were no occurrences of cardiorespiratory depression or sedation in any group, and no serious TEAEs were deemed related to treatment in either group. TEAEs deemed possibly related to treatment were more common in the chronic use of concomitant benzodiazepines group (16.7% compared with 10.3%; Table 3).

3.5 | Clobazam sub-analysis

In a sub-analysis, a total of 44 patients were taking clobazam (37.0%) and 75 patients were not (63.0%). Mean age was younger (17.4 years) in the clobazam group than in the no clobazam group (27.0 years); 54.5% were female in the clobazam group and 49.3% in the no clobazam group. The majority of the patients in both groups had duration of exposure to diazepam nasal spray of ≥12 months (clobazam group, 72.7%; no clobazam group, 77.3%). A higher proportion of patients in the clobazam group than the no clobazam group used two or more monthly doses of diazepam nasal spray (65.9% vs 54.7%, respectively). The proportion of seizure clusters for which a second dose was used was generally similar between the clobazam group (1032 seizure clusters; second dose, 9.6%) than the no clobazam group (1849 seizure clusters; second dose, 14.8%), as was the proportion of patients with TEAEs (clobazam: 81.8%; no clobazam: 78.7%). Proportions of serious TEAEs were higher in the clobazam group (40.9%, clobazam group; 24.0%, no clobazam group). Proportions of TEAEs that were deemed possibly treated related were similar between the groups (18.2%, clobazam group; 18.7%, no clobazam group).

4 | DISCUSSION

To our knowledge, this is the first analysis of a large, long-term study evaluating use of an intranasal benzodiazepine...
for seizure clusters in patients with epilepsy who received concomitant chronic or intermittent benzodiazepines, such as clobazam, which is an important part of the treatment algorithm for refractory childhood epilepsies. This is a relevant point, because some studies, including those for intranasal midazolam, have used concomitant benzodiazepine therapy for epilepsy as an exclusion criterion.

Maintenance benzodiazepines are generally reserved for management of refractory or difficult-to-treat epilepsy, and, in this study, the group of patients receiving concomitant benzodiazepines had a substantially higher seizure burden, as expected. Because of this, we hypothesize that those receiving chronic concomitant benzodiazepines were likely to have more severe epilepsy than those who do not use concomitant benzodiazepines. Patients in the concomitant benzodiazepines groups therefore received more doses of diazepam nasal spray, and they were also more likely to have been exposed to diazepam nasal spray >12 months. Even so, rates of second-dose use were similar for those using chronic concomitant benzodiazepines and those not using concomitant benzodiazepines, <12% of seizure clusters for both groups, which suggests that diazepam nasal spray maintained effectiveness.

The most common treatment-related TEAEs were primarily related to nasal discomfort, which was mild and transient. There were no serious TEAEs related to treatment, and there were no deaths. After the interim analysis cutoff date, one death was reported, which was deemed to be not treatment related. Notably, although benzodiazepines have the potential to impact cardiorespiratory function, reflected in a warning regarding usage in combination with other central nervous system depressants including other benzodiazepines in the prescribing information for diazepam nasal spray, there were no reported cases of respiratory depression or hypotension in this study. Furthermore, there were no discontinuations due to TEAEs, and the retention rates were high.

Similarly to the exclusion criteria in related studies, this study excluded patients with medical conditions that may bias against the potential occurrence of cardiorespiratory depression, which may be more likely to occur in patients with significant respiratory disease. In addition, these interim results from an ongoing, long-term, open-label, single-arm safety study did not control for baseline differences between the benzodiazepine subgroups or for total benzodiazepine dosages. However, the similarity of the overall results with those in the clobazam sub-analysis reinforces the generalizability of the present analysis. Taken together, these results show that diazepam nasal spray represents a potentially valuable treatment option for patients 6 years of age and older, irrespective of concomitant benzodiazepine use.

### 5 | CONCLUSIONS

Results from this long-term study support the use of intermittent diazepam nasal spray in patients with and without concomitant benzodiazepines as part of an antiseizure medication. Need for a second dose to control a seizure cluster was similarly low (<12%) in both groups, suggesting maintained effectiveness.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Chronic use of concomitant benzodiazepines</th>
<th>Intermittent use of concomitant benzodiazepines</th>
<th>No concomitant benzodiazepines group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n = 60)</td>
<td>(n = 59)</td>
<td>(n = 39)</td>
</tr>
<tr>
<td>Treatment exposure, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Duration of exposure</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;6 months</td>
<td>4 (6.7)</td>
<td>4 (6.8)</td>
<td>3 (7.7)</td>
</tr>
<tr>
<td>6 to &lt;12 months</td>
<td>15 (25.0)</td>
<td>6 (10.2)</td>
<td>10 (25.6)</td>
</tr>
<tr>
<td>≥12 months</td>
<td>41 (68.3)</td>
<td>49 (83.1)</td>
<td>26 (66.7)</td>
</tr>
<tr>
<td>Number of doses during the study</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1-2</td>
<td>5 (8.3)</td>
<td>6 (10.2)</td>
<td>12 (30.8)</td>
</tr>
<tr>
<td>3-10</td>
<td>20 (33.3)</td>
<td>14 (23.7)</td>
<td>15 (38.5)</td>
</tr>
<tr>
<td>11-20</td>
<td>8 (13.3)</td>
<td>12 (20.3)</td>
<td>4 (10.3)</td>
</tr>
<tr>
<td>21-40</td>
<td>14 (23.3)</td>
<td>15 (25.4)</td>
<td>7 (17.9)</td>
</tr>
<tr>
<td>&gt;40</td>
<td>13 (21.7)</td>
<td>12 (20.3)</td>
<td>1 (2.6)</td>
</tr>
<tr>
<td>Mean dose/month frequency</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Moderate: &lt;2</td>
<td>25 (41.7)</td>
<td>24 (40.7)</td>
<td>20 (51.3)</td>
</tr>
<tr>
<td>High: 2-5</td>
<td>31 (51.7)</td>
<td>31 (52.5)</td>
<td>18 (46.2)</td>
</tr>
<tr>
<td>Very high: &gt;5</td>
<td>4 (6.7)</td>
<td>4 (6.8)</td>
<td>1 (2.6)</td>
</tr>
<tr>
<td>Mean (SD) doses/month</td>
<td>2.5 (1.4)</td>
<td>2.7 (2.4)</td>
<td>2.0 (1.3)</td>
</tr>
</tbody>
</table>
effectiveness, and the retention rates were high. Moreover, use of benzodiazepines, including regular use of clobazam, did not have clinically relevant effects on the safety, including cardiorespiratory outcomes, of diazepam nasal spray.

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**DISCLOSURES**

Dr. Segal has received personal compensation for consulting, serving on a scientific advisory board, speaking, or other activities with Eisai, Lundbeck, Nutricia, Novartis, Greenwich, Epitel, Encoded Therapeutics, and Qbiomed, and is an advisor for Neurelis, Inc. Dr. Tarquinio has received personal compensation for consulting, serving on a scientific advisory board, speaking, or other activities with Marinus and Avexis. Dr. Miller has served as a consultant/advisor to GW Pharmaceuticals, Insys Therapeutics, Visualase, and NeuroPace, and as a study investigator for GW.

**TABLE 3** Adverse events

<table>
<thead>
<tr>
<th>Adverse event, n (%)</th>
<th>Chronic use of concomitant benzodiazepines (n = 60)</th>
<th>Intermittent use of concomitant benzodiazepines (n = 59)</th>
<th>No concomitant benzodiazepines group (n = 39)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any TEAE</td>
<td>48 (80.0)</td>
<td>47 (79.7)</td>
<td>24 (61.5)</td>
</tr>
<tr>
<td>Serious TEAE</td>
<td>21 (35.0)</td>
<td>15 (25.4)</td>
<td>9 (23.1)</td>
</tr>
<tr>
<td>Related to treatment</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Most common TEAEs (≥5% in any group)

- Seizure: 12 (20.0), 7 (11.9), 4 (10.3)
- Pneumonia: 8 (13.3), 1 (1.7), 2 (5.1)
- Pyrexia: 7 (11.7), 3 (5.1), 0
- Upper respiratory tract infection: 6 (10.0), 2 (3.4), 4 (10.3)
- Nasopharyngitis: 5 (8.3), 6 (10.2), 1 (2.6)
- Urinary tract infection: 5 (8.3), 2 (3.4), 0
- Vomiting: 5 (8.3), 0, 2 (5.1)
- Influenza: 4 (6.7), 4 (6.8), 0
- Constipation: 3 (5.0), 1 (1.7), 1 (2.6)
- Nasal discomfort: 3 (5.0), 5 (8.5), 1 (2.6)
- Rhinorrhea: 3 (5.0), 1 (1.7), 0
- Status epilepticus: 3 (5.0), 1 (1.7), 1 (2.6)
- Sinusitis: 2 (3.3), 3 (5.1), 1 (2.6)
- Somnolence: 2 (3.3), 2 (3.4), 3 (7.7)
- Dizziness: 1 (1.7), 4 (6.8), 2 (5.1)
- Fatigue: 1 (1.7), 2 (3.4), 2 (5.1)
- Headache: 1 (1.7), 5 (8.5), 1 (2.6)
- Contusion: 1 (1.7), 3 (5.1), 0
- Fall: 1 (1.7), 3 (5.1), 0
- Cough: 0, 2 (3.4), 2 (5.1)
- Gastroesophageal reflux disease: 0, 0, 2 (5.1)
- Nasal congestion: 0, 3 (5.1), 1 (2.6)
- Treatment-related TEAEs: 10 (16.7), 12 (20.3), 4 (10.3)

Most common treatment-related TEAEs (≥2 patients in any group)

- Nasal discomfort: 3 (5.0), 5 (8.5), 1 (2.6)
- Dysgeusia: 0, 2 (3.4), 0
- Headache: 0, 3 (5.1), 1 (2.6)
- Rhinalgia: 0, 2 (3.4), 0

Abbreviation: TEAE, treatment emergent adverse event.
Pharmaceuticals. Dr. Wheless has served as an advisor or consultant for: CombiMatrix; Eisai Inc.; GW Pharmaceuticals; Lundbeck, Inc.; Neuralis, Inc; NeuroPace, Inc.; Supernus Pharmaceuticals, Inc.; and Upsher-Smith Laboratories, Inc. Dr. Wheless has served as a speaker or a member of a speakers bureau for: Cyberonics, Inc.; Eisai Inc.; Lundbeck, Inc.; Mallinckrodt; Neuralis, Inc; Supernus Pharmaceuticals, Inc.; Upsher-Smith Laboratories, Inc., and has received grants for clinical research from: Acorda Therapeutics; GW Pharmaceuticals; INSYS Therapeutics, Inc.; Lundbeck, Inc.; Mallinckrodt; Neuralis, Inc.; NeuroPace, Inc.; Upsher-Smith Laboratories, Inc.; and Zogenix, Inc. Dr. Dlugos receives salary support from NIH/NINDS, Commonwealth of Pennsylvania Department of Health, Pediatric Epilepsy Research Foundation, and The Epilepsy Study Consortium. His institution receives research support for protocol development or studies from NIH; Commonwealth of PA Department of Health; Zogenix; GW Pharma; Greenwich Biosciences; UCB; Brain Sentinel; Neuralis, Inc.; Pfizer; Q-State; USL; Aqueactive; Sage; Bio-Pharm; Insys; SK Life Sciences; Encoded Therapeutics; CURE; Rett Syndrome Research Trust. He received travel expenses for protocol development or investigator meetings from Marinus, Ovid/Takeda, Ultragenyx, USL, Pfizer, Zogenix. Dr. Biton has nothing to disclose. Dr. Cascino has nothing to disclose. Dr. Desai has received research funding from the Epilepsy Foundation of Greater Los Angeles; Neuralis, Inc.; Novartis; Ovid; Aqueactive; and UCB. Dr. Hogan has received research support from UCB Pharmaceuticals, Neuralis, Inc; and Biogen Inc, and is an advisor for Neuralis, Inc. Dr. Liow has received research support from Intracellular Therapies, SK Life Sciences, Genentech, Biotie Therapies, Monosol, Aqueactive Therapeutics, Engage Therapeutics, Xenon, Lundbeck, Biogen, Eli Lilly, Pfizer, Novartis, Sunovion, Acorda, Eisai, UCB, Livanova, Axsome, and Acadia. Dr. Sperring has received personal compensation for speaking from Neurology Live and Eisai, is an advisor for Neuralis, Inc, and consulting with payments to Thomas Jefferson University from Medtronic. Dr. Sperring has received research support from Eisai; Medtronic; Neuralis, Inc.; SK Life Science; Takeda; Sunovion; UCB Pharma; Xenon; and Engage Pharmaceuticals. Dr. Vazquez is an advisor for Neuralis, Inc. Dr. Cook and Dr. Rabinowicz are employees of and have received stock options from Neuralis, Inc. Dr. Carrazana is an employee of and has received stock and stock options from Neuralis, Inc. Dr. Carrazana has received compensation for serving on the boards of directors of Marinus and Hawaii-Biotech.

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