FULL-LENGTH ORIGINAL RESEARCH

Randomized, double-blind, placebo-controlled phase 2 study of ganaxolone as add-on therapy in adults with uncontrolled partial-onset seizures

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Summary

Objective: **To evaluate the efficacy and safety of ganaxolone as adjunctive therapy in adults with uncontrolled partial-onset seizures despite taking up to three concomitant antiepileptic drugs (AEDs).**

Methods: **Adults aged 18–69 years and refractory to conventional AEDs were enrolled in a multicenter, double-blind, placebo-controlled trial. After an 8-week baseline period, patients were randomized 2:1 to ganaxolone 1,500 mg/day or placebo for a 10-week treatment period (2-week forced titration and 8-week maintenance) followed by either tapering or entry into an open-label extension study. The primary endpoint was mean weekly seizure frequency. Secondary endpoints included the proportion of patients experiencing ≥50% reduction in seizure frequency (responder rate), percent change in mean weekly seizure frequency, seizure-free days, and quality of life. Safety and tolerability assessments included adverse events (AEs), treatment discontinuation, and clinical laboratory evaluations. Efficacy analyses were performed on the intent-to-treat population.**

Results: **Of 147 randomized patients (98 ganaxolone, 49 placebo), 131 completed the study; 95% of participants titrated up to 1,500 mg/day and 78% maintained this dose. From baseline to endpoint, mean weekly seizure frequency decreased with ganaxolone (6.5–5.2) versus placebo (9.2–10.8), representing an 11.4% decrease versus placebo ($p = 0.0489$, analysis of covariance [ANCOVA]). Mean percent change from baseline was −17.6% with ganaxolone versus 2.0% with placebo ($p = 0.0144$, Kruskal-Wallis test). Responder rates were 24% with ganaxolone versus 15% with placebo ($p = 0.19$). Discontinuation due to adverse events was similar with ganaxolone (7.1%) and placebo (6.1%). Common adverse events were mild to moderate in severity and included dizziness (16.3% vs. 8.2%), fatigue (16.3% vs. 8.2%), and somnolence (13.3% vs. 2.0%).**

Significance: **Ganaxolone 1,500 mg/day reduced partial-onset seizure frequency and was generally safe and well tolerated in this phase 2 study. These results support continued development of ganaxolone for adult patients with refractory partial-onset seizures.**

KEY WORDS: **Adjunctive therapy, Ganaxolone, Neurosteroid, Partial-onset seizures.**

Ganaxolone, 3-β-methylated synthetic analogue of the neurosteroid allopregnanolone, has a novel antiepileptic mechanism of action, and merits investigation as a treatment for seizures.[1] Ganaxolone binds to both synaptic and extrasynaptic γ-aminobutyric acid $(GABA)_A$ receptors and acts most potently and effectively at $GABA_A$ receptors containing the δ-subunits, potentiating both tonic and phasic inhibition. In contrast, benzodiazepines bind just to synaptic

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Key Points

- Ganaxolone, 3-β-methylated analogue of allopregnanolone, has a novel antiepileptic mechanism of action for treatment of seizures
- This phase 2 study evaluated ganaxolone as add-on therapy in adults with partial-onset seizures (POS) not controlled on a current AED regimen
- Ganaxolone 1,500 mg/day reduced partial-onset seizure frequency and was generally safe and well tolerated in this phase 2 study

$GABA_A$ receptors, are insensitive to δ-subunit containing $GABA_A$ receptors and are prone to habituation of anticonvulsant effects.[2] Ganaxolone, like allopregnanolone, acts on $GABA_A$ receptors but does not activate nuclear (classical) progesterone receptors. In vitro studies conducted with ganaxolone demonstrate protective activity in diverse rodent seizure models, including clonic seizures induced by pentylenetetrazol (PTZ) and bicuculline, limbic seizures in the 6 Hz model, amygdala-kindled seizures,[1,3–7] and lithium-pilocarpine-induced status epilepticus (data on file, Marinus Pharmaceuticals).

Following oral administration, ganaxolone is rapidly absorbed (T_{max} 1.5–2 h), followed by a sharp decrease in plasma levels over the first 12 h and then by a terminal half-life of approximately 20 h,[8] whereas allopregnanolone has low bioavailability and a half-life of approximately 30 min following intravenous administration.[5,7,9–11] Ganaxolone is metabolized via cytochrome P450 (CYP)3A4, and approximately 80% of a radiolabeled oral dose is recovered in the feces and 20% in the urine.[1]

Early clinical studies of both monotherapy and combination therapy with other antiepileptic drugs (AEDs) in adults and children with treatment-resistant epilepsy demonstrated antiseizure activity with an acceptable tolerability profile.[8,12–14] However, the previous formulation had low oral bioavailability and its absorption was affected by administration with food. The present phase 2 study evaluated the safety, tolerability, and efficacy of ganaxolone as add-on therapy in adults with partial-onset seizures (POS) not controlled on the current AED regimen using a new formulation of ganaxolone with improved absorption and bioavailability after oral administration.

Methods

The study was conducted in accordance with Good Clinical Practices and with the International Conference on Harmonisation and the ethical principles of the Declaration of Helsinki. The study protocol, amendments, and informed consent documents were reviewed and approved by institutional review boards for each study site. All patients or legal representatives provided written informed consent prior to any study-related procedures. The study was registered at clinicaltrials.gov: NCT00465517.

Study design

This was an 18-week, double-blind, placebo-controlled, randomized clinical trial of ganaxolone administered as add-on therapy in adults with uncontrolled POS. The study was conducted between April 3, 2007 and October 28, 2008, at 24 clinical sites in the United States. Baseline seizure frequency was determined by the daily recording of the total number and type of seizure(s) during the 8-week prospective baseline period. Eligible patients were randomized to ganaxolone or placebo added to existing AED therapy of up to three antiepileptic drugs, which were maintained at a stable dose for at least 30 days prior to enrollment. Ganaxolone dose titration started at 600 mg/day for 2 days, followed by 900 mg/day for 2 days, 1,200 mg/day for 2 days, and then 1,500 mg/day, administered in three divided doses daily. The target dose of 1,500 mg/day was continued for the 8-week maintenance period. One to three doses of benzodiazepines could be used over a 24-h period for rescue therapy during the titration and maintenance periods.

Patient selection criteria

Men or women ages 18–69 years inclusive were eligible if they had a diagnosis of epilepsy with POS with or without secondarily generalized seizures (SGS) according to the International League Against Epilepsy (ILAE) Classification of Epileptic Seizures (1981).[15] The study design did not contain any preference for gender of participants. Computed tomography (CT) or magnetic resonance imaging (MRI) of the brain was used to rule out progressive structural lesions.

During the 8-week baseline period, patients had to have ≥3 POS in a 28-day period with no more than 21 consecutive seizure-free days. Eligible seizure types included complex partial seizures (CPS) with or without secondary generalization or simple partial seizures with motor manifestations.

Patients had to be treated with a stable dose of one to three AEDs for ≥30 days prior to screening. Vigabatrin was not permitted. Felbamate was allowed only if the patient had been treated for at least 18 months and had stable laboratory tests. Vagus nerve stimulator (VNS) was allowed if it had been in place for at least 12 months prior to study entry, with stimulation parameters unchanged for at least 30 days prior to screening. VNS counted as one of the three permitted concomitant "AEDs." Women of childbearing potential were required to use a medically acceptable form of birth control and have negative serum pregnancy test at screening.

Patients were excluded if they had only non-motor simple partial seizures (SPS); a history of pseudoseizures in the past 5 years; generalized epilepsy; >40 seizures during the

4-week baseline period; a history of repetitive seizures within the past 12 months; past use of vigabatrin without stable visual fields over the 12 months since the last dose; seizures secondary to drug or alcohol use or any other medical condition; status epilepticus within the past year; history of suicide attempt within 5 years or ideation within 6 months; or any significant medical, psychiatric, or surgical condition that could interfere with the conduct of the study. Women who were pregnant or breastfeeding were excluded.

Study procedures

At screening, patients had a medical history and physical and neurologic examination with vital signs, 12-lead electrocardiography (ECG), clinical laboratory testing (chemistry, hematology, and urinalysis), and serum pregnancy test for women. Physical and neurologic examinations and clinical laboratory testing were repeated at baseline (week 0) and at weeks 2, 4, 7, and 10. Vital signs were recorded at each study visit. Patients recorded daily seizure frequency and type in a diary beginning with the 8-week prospective baseline period and continuing throughout the study. ECG was repeated at weeks 2 and 10. Serum pregnancy test was repeated at baseline and week 10. Home ovulation tests and menstrual log were reviewed weekly during titration and maintenance. The Seizure Severity Questionnaire and Quality of Life in Epilepsy Inventory-31 (QOLIE-31)[16,17] were administered at baseline and week 10.

Study outcomes

The primary efficacy variable was change in mean weekly seizure frequency for all seizure types including complex POS, simple POS with motor manifestations, and secondarily generalized seizures (but excluding non-motor simple partial seizures) during the titration plus maintenance periods (weeks 1–10). Secondary efficacy outcome measures included the following: (1) change in mean weekly seizure frequency during the maintenance period; (2) change and percent change from baseline of mean weekly seizure frequency during the maintenance period and titration plus maintenance period; (3) weekly seizure frequency for each week after dosing (titration plus maintenance period); (4) mean weekly seizure frequency and change and percent change from baseline during the titration plus maintenance period for each seizure subtype (CPS, generalized tonic–clonic seizure [GTCS], and SPS-motor); (5) responder rate (≥50% reduction from baseline in mean weekly seizure frequency during the titration plus maintenance period from baseline); (6) number of seizure-free days during the titration, maintenance, and titration plus maintenance periods; and (7) number of seizure-free subjects and seizure-free rate during the titration, maintenance, and titration plus maintenance periods. In addition, the Seizure Severity Questionnaire[17] and QOLIE-31 were exploratory endpoints.[16]

Post hoc analyses were conducted to evaluate the impact of concomitant use of CYP3A4-inducing AEDs for mean and change from baseline in weekly seizure frequency and responder rate (≥50% reduction of seizures from baseline).

Statistical analysis

The sample size was initially calculated using a common standard deviation (SD) of 0.43, as reported by Glauser et al.,[18] and power fixed at 85%. One hundred forty-one evaluable patients (94 ganaxolone and 47 placebo) were needed for a two-sided *t*-test on the difference between the two groups, with $\alpha = 0.05$ to detect a difference of 0.2304, corresponding to a 20% reduction from placebo in seizure frequency per week. After nearing the target number of evaluable patients, the sponsor decided to close enrollment. This resulted in a final SD of 0.503, and power fixed at 78%.

The intent-to-treat (ITT) population included all randomized patients who received at least one dose of study drug and provided at least one post dose evaluation and was used for all efficacy and safety analyses. Mean weekly seizure frequency was analyzed using analysis of covariance (ANCOVA) on transformed data with treatment as a factor and baseline weekly seizure frequency as a covariate. Differences between treatments were compared using least squares (LS) mean with a lower one-sided 95% confidence interval (CI) for percent reduction with ganaxolone versus placebo.

A Kruskal-Wallis test was used for between-group comparisons for change and percent change in mean weekly seizure frequency and for the number of seizure-free days during the titration period, maintenance period, and titration plus maintenance period. A Cochran–Mantel–Haenszel (CMH) analysis was used for comparison between treatment groups of response rate and for the number and proportion of seizure-free patients. Response rate analysis used pooled site as a stratification factor. Statistical analyses were performed using SAS Version 9.1.

Results

Of 147 patients who were randomized to treatment (98 ganaxolone and 49 placebo) and included in the ITT population, 131 (89.1%) completed the maintenance period (Fig. 1). Twelve (12.2%) of 98 patients on ganaxolone and four (8.2%) of 49 on placebo discontinued the study (Fig. 1). The majority of randomized patients were female (68.0%) and Caucasian (87.8%). Baseline demographic and clinical characteristics were similar between treatment groups (Table 1). The female predominance was likely due to the perceived benefit for women who have catamenial epilepsy based on the ganaxolone's mechanism of action. The mean illness duration since epilepsy diagnosis was approximately 25 years, and >75% patients were receiving at least two AEDs. The most frequent concomitant AEDs were lamotrigine (31.3%), levetiracetam (27.9%), and

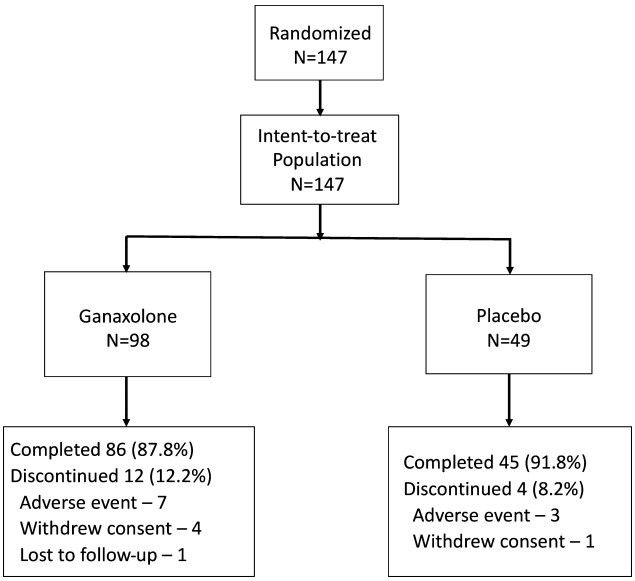

Figure 1.
Patient disposition.
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Table 1. Baseline demographic and clinical characteristics

Variable	Number (%) of patients: Ganaxolone (N = 98)	Placebo (N = 49)
Female, n (%)	64 (65.3)	36 (73.5)
Race, n (%)		
White	87 (88.8)	42 (85.7)
Black/African American	8 (8.2)	4 (8.2)
Other	3 (3.0)	3 (6.1)
Age, years[a]	39.1 (11.7)	40.2 (11.1)
Weight, kg[a]	81.7 (22.4)	82.4 (21.5)
Mean years since diagnosis	25.2	24.7
History of VNS, n (%)	29 (29.6)	13 (26.5)
Baseline weekly seizure frequency[a]	6.5 (11.3)	9.2 (30.5)
Weekly seizure frequency range	0.5–74.5	0.5–210.3
Seizure subtype, n (%)		
Complex partial	96 (98.0)	47 (95.9)
Secondarily generalized tonic–clonic	23 (23.5)	14 (28.6)
Simple partial seizures—motor	37 (37.8)	21 (42.9)
Concomitant AED use, n (%)		
1	24 (24.5)	10 (20.4)
2	57 (58.2)	30 (61.2)
3	17 (17.3)	9 (18.4)

[a]Mean (standard deviation).

Table 2. Mean change and mean percent change from baseline for mean weekly seizure frequency, and seizure-free days and seizure-free patients by treatment phase (ITT population)

	Ganaxolone (N = 98)	Placebo (N = 49)	p-Value[a]
Weekly seizure frequency[b]			
Maintenance phase			
Mean change	−1.1 (3.9)	2.5 (20.2)	0.148
Mean % change	−12.1 (54.3)	4.6 (71.9)	0.117
Titration + maintenance phase			
Mean change	−1.3 (3.6)	1.4 (15.1)	0.025
Mean % change	−17.6 (48.9)	2.0 (63.2)	0.014
Seizure-free days[b]			
Titration	10.3 (4.4)	10.0 (3.8)	0.601
Maintenance	37.1 (18.5)	38.5 (16.2)	0.633
Titration + maintenance	45.9 (22.1)	46.8 (20.6)	0.719
Seizure-free patients, n (%)			
Titration	16 (16.8)	4 (8.3)	0.089
Maintenance	0	1 (2.2)	0.143
Titration + maintenance	1 (1.0)	0	0.450

[a]Kruskal-Wallis test for mean seizure weekly frequency and seizure-free days; Cochran-Mantel-Haenszel test for seizure-free days.
[b]Mean (standard deviation).

carbamazepine (26.5%). Current or past use of VNS occurred in 29 (29.6%) patients with ganaxolone and 13 (26.5%) patients with placebo.

Efficacy

For titration plus maintenance phases combined, there was a significant reduction in mean weekly seizure frequency in ganaxolone-treated patients compared with placebo (17.6% reduction in ganaxolone treated patients compared with 2% increase in placebo-treated patients, $p = 0.014$, Table 2). A significant effect was not noted during the maintenance phase alone. Decreases from baseline in mean weekly seizure frequency were observed in all weeks except week 7 in the ganaxolone group and in weeks 1–5 in the placebo group (Fig. 2). Mean changes for ganaxolone versus placebo were significant at weeks 1, 5, and 10 ($p < 0.05$, ANCOVA). Responder rates were 23.5% and 14.6% for ganaxolone and placebo, respectively, for the titration plus maintenance period ($p = 0.249$, CMH test), and 26.3% and 13.0% with ganaxolone and placebo, respectively, for the maintenance period ($p = 0.076$, CMH test) regardless of pooled site stratification (Fig. 3). No significant difference in seizure-free days was observed between the groups (Table 2). A post hoc analysis found that taking an enzyme-inducing AED with ganaxolone did not influence response.

For the QOLIE-31 overall score, median scores at baseline and end of the maintenance period were similar for both groups: 58.0 and 56.4 for ganaxolone and 57.7 and 61.5 for placebo.

Safety and tolerability

At least one treatment-emergent AE was reported by 82 patients (83.7%) on ganaxolone and 38 (77.6%) on placebo. Treatment-related AEs occurred in 54 patients (55.1%) on ganaxolone and 16 (32.7%) on placebo. The most common AEs were dizziness and fatigue, somnolence, headache, impaired coordination, convulsion, fall, and

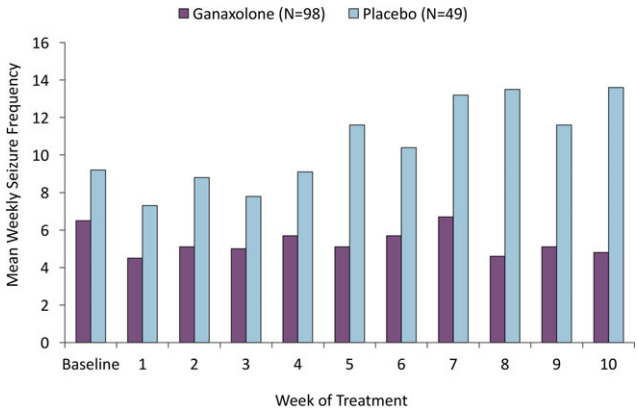

Figure 2.
Mean weekly seizure frequency for ganaxolone and placebo (ITT population).
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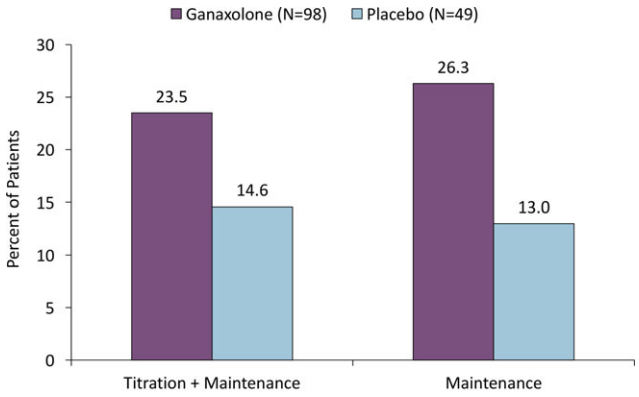

Figure 3.
Response rate (≥50% decrease in seizure frequency) during titration + maintenance phase and during maintenance only phase (ITT population).
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Table 3. Incidence of treatment-emergent adverse events occurring in least 5% of patients in the ganaxolone group

	Number (%) of patients	
Adverse event	Ganaxolone (N = 98)	Placebo (N = 49)
At least one AE	82 (83.7)	38 (77.6)
Dizziness	16 (16.3)	4 (8.2)
Fatigue	16 (16.3)	4 (8.2)
Somnolence	13 (13.3)	1 (2.0)
Headache	8 (8.2)	6 (12.2)
Coordination abnormal	6 (6.1)	3 (6.1)
Convulsion	5 (5.1)	4 (8.2)
Fall	5 (5.1)	6 (12.2)
Nasopharyngitis	5 (5.1)	5 (10.2)

nasopharyngitis (Table 3). Most AEs were of mild or moderate intensity; however, 12 patients (12.2%) in the ganaxolone group (dry mouth, nausea, stomach discomfort, fatigue, irritability, fall, hemothorax, joint dislocation, arthralgia, convulsion, dizziness, dysarthria, epilepsy, headache, lethargy, memory impairment, depression) and 6 (12.2%) in the placebo group (enteritis, fatigue, upper respiratory infection, coordination abnormal, dizziness, headache, hypoesthesia) experienced an AE rated as severe by the primary site. Nervous system disorders (dizziness, headache, somnolence, convulsion, coordination abnormal) occurred in 47 (48.0%) with ganaxolone and 19 (38.8%) with placebo. Severe nervous system disorders occurred in 8.2% of patients in each group (convulsion, coordination abnormal, dizziness, dysarthria, hypoesthesia, headache, lethargy, memory impairment, and somnolence).

Seven patients (7.1%) on ganaxolone and three (6.1%) on placebo discontinued treatment because of AEs. The most frequently reported AEs that led to discontinuation were headache, lethargy, and tremor with ganaxolone, and postictal psychosis, headache, dizziness, and convulsion with placebo. Four patients (4.1%) receiving ganaxolone discontinued due to rash considered related to study drug, and two (2.0%) discontinued due to eye disorders (diplopia in a placebo patient and eye swelling in a ganaxolone patient); both events were considered by the investigators to be related to the study drug. Five patients (5.1%) on ganaxolone and four (8.2%) on placebo experienced serious AEs. Three serious AEs reported by ganaxolone patients were considered by the treating investigator as related to therapy: one event each of rash, arthralgia, and convulsion.

Most clinical laboratory values (hematology, chemistry, and urinalysis) were normal at all measurement time points. One patient taking ganaxolone had mild thrombocytopenia, which was considered possibly related to drug therapy. The platelet count was 148,000 mm^3 at baseline and decreased to 126,000 mm^3 at week 10. Although thrombocytopenia persisted, ganaxolone was continued, and no action was required. No notable changes in vital signs or physical or neurologic examinations findings were observed. No postdose ECG abnormalities were detected that were considered clinically significant.

Discussion

In this cohort with treatment-resistant POS, therapy with this new formulation of ganaxolone at a dose of 1,500 mg/day resulted in a significant reduction in mean weekly seizure frequency compared to placebo over the 10-week titration and maintenance period. Weekly seizure frequency was reported in this study to explore treatment effects of ganaxolone in more detail. A weekly comparison was used instead of monthly to understand how soon an effect would occur after the 2-week dose titration. This also allowed the consistency of the effect to be assessed over the duration of the study using more frequent assessment time points. In an earlier open-label study of pediatric and adolescent patients with refractory seizures, four patients (25%) were

considered responders (≥50% reduction in seizure frequency) and two (13%) were considered moderate responders (25% and 50% reduction).[14]

The treatment effect with a fixed dose of ganaxolone was similar to that obtained in phase 2 studies with other AEDs. The placebo-adjusted reduction in seizure frequency for ganaxolone was 16% median and 20% mean. For comparison, placebo-adjusted seizure frequency rates with other AEDs included eslicarbazepine (5–30% mean),[19] lacosamide (30% [400 mg] median),[20] and levetiracetam (16–18% mean).[21] The response rate likely reflected the severity of illness of patients in this study who were quite refractory to drug treatment; they had a mean duration of epilepsy of 24 years and continued seizures despite treatment (68% of patients were currently taking two or more AEDs, and 20% of patients had VNS).

Ganaxolone modulates neuronal excitability through the inhibitory GABA system by binding to a neurosteroid binding site on the $GABA_A$ receptor that is distinct from other allosteric GABA receptor modulators such as benzodiazepines and barbiturates.[4,10,22,23] No evidence of a loss of effect was observed when ganaxolone was combined with other AEDs as a result of potential drug interactions, which can complicate treatment with AEDs.[24–26] Ganaxolone is metabolized by CYP3A4, and plasma levels were approximately 40% lower in subjects treated with an enzyme-inducing AED, but this reduction had no obvious effect on efficacy.

Ganaxolone was well tolerated with no clinically relevant laboratory or ECG changes during the study. Discontinuation rates because of AEs were comparable with results from studies with other AEDs.[27,28] As expected, central nervous system (CNS) side effects were the most common. The incidence of behavioral AEs was similar with ganaxolone and placebo.

This phase 2 study was conducted to evaluate the safety and efficacy of a new formulation of ganaxolone after the product had been dormant for many years. Prior formulations of ganaxolone showed an effect of administration with food that reduced bioavailability by up to 15-fold (data on file, Marinus Pharmaceuticals). The new sub-micron formulation also replaced the β-cyclodextrin and 2-hydroxypropyl β-cyclodextrin vehicles, which had daily dose limitations due to toxicity. Taken together, the food effect coupled with sub-optimal bioavailability and a potential for a broad use of ganaxolone prompted the creation of a sub-micron dosage form.

The placebo-controlled, phase 2 study reported here was conducted using the new formulation with a design similar to that of a registration study for adjunctive POS control (i.e., 8-week prospective baseline followed by 10 weeks of treatment using seizure diaries), to ascertain the effect size needed for a larger study and to determine the minimally effective dose. It has demonstrated that this formulation can be used, although because of the modest effect size with 1,500 mg/day, a higher dose of 1,800 mg/day is being evaluated in a phase 3 study.

Limitations of this study are the short duration of treatment and the limited number of patients that were treated with active drug. Although many phase 2 studies employ 12 weeks of maintenance therapy, the 10-week design of this study was sufficient to examine the efficacy and safety/tolerability of a single dose of ganaxolone. The results of the present study provide support for further studies with ganaxolone in patients with refractory seizure disorders.

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Conflict of Interest

Dr. Sperling has received research contracts as principal investigator through Thomas Jefferson University from UCB Pharma, Eisai, Sunovion, SK Life Sciences, GlaxoSmithKline, Marinus Pharmaceuticals, Acorda, Lundbeck, Pfizer, Neurelis, Medtronic, Brain Sentinel, and Upsher Smith. He also has received research support from Defense Advanced Research Projects Agency and National Institutes of Health (NIH) through Thomas Jefferson University. He has consulted for Medtronic and Medscape. Dr. Klein has served on a speaker's bureau for Eisai, Sunovion, and UCB Pharma and on an advisory board for UCB Pharma and Lundbeck; has received research support from Lundbeck and Eisai; and has performed contracted research for SK Life Sciences, Marinus Pharmaceuticals, Acorda Therapeutics, Upsher-Smith, and UCB Pharma. Dr. Tsai is a full time employee of Marinus Pharmaceuticals. We 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.

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