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RESEARCH ARTICLE

# Intravenous ganaxolone for the treatment of refractory status epilepticus: Results from an open-label, dose-finding, phase 2 trial

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## Abstract

**Objective:** Patients with refractory status epilepticus (RSE) have failed treatment with benzodiazepines and ≥1 second-line intravenous (IV) antiseizure medication (ASM). Guidelines recommend IV anesthesia when second-line ASMs have failed, but potential harms can outweigh the benefits. Novel treatments are needed to stop and durably control RSE without escalation to IV anesthetics. Ganaxolone is an investigational neuroactive steroid in development for RSE treatment. This study's objective was to determine the appropriate dosing for IV ganaxolone in RSE and obtain a preliminary assessment of efficacy and safety.

**Methods:** This was an open-label, phase 2 trial conducted from February 19, 2018 to September 18, 2019, at three sites in the United States. Patients were aged ≥12 years, had convulsive or nonconvulsive SE, and failed to respond to ≥1 second-line IV ASM. Twenty-one patients were screened; 17 were enrolled. Patients received IV ganaxolone added to standard-of-care ASMs. Ganaxolone infusion was initiated as an IV bolus (over 3 min) with continuous infusion of decreasing infusion rates for 48–96 h followed by an 18-h taper. There were three ganaxolone dosing cohorts: low, 500 mg/day; medium, 650 mg/day; and high, 713 mg/day. The primary end point was the number of patients not requiring escalation to IV anesthetic treatment within 24 h of ganaxolone initiation.

**Results:** Most of the 17 enrolled patients (65%) had nonconvulsive SE, and had failed a median of three prior ASMs, including first-line benzodiazepine and second-line IV ASM therapy. Median time to SE cessation following ganaxolone initiation was 5 min. No patient required escalation to third-line IV anesthetics during the 24-h period following ganaxolone initiation. Two treatment-related serious adverse events (sedation) were reported. Of the three deaths, none

Henrikas Vaitkevicius's was affiliated with 1 at the time the trial was conducted.

**Clinical Trial Registration**: NCT03350035.

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was considered related to ganaxolone; all occurred 9–22 days after completing ganaxolone.

**Significance:** IV ganaxolone achieved rapid and durable seizure control in patients with RSE, and showed acceptable safety and tolerability.

**KEYWORDS**

antiseizure medications, clinical trial, critical care, neurosteroids, seizure

## 1 | INTRODUCTION

Status epilepticus (SE) is a neurologic emergency that can result from either the failure of mechanisms that terminate seizures or the initiation of mechanisms that abnormally prolong seizures.[1,2] SE is associated with substantial morbidity and mortality.[3-5]

Antiseizure medications (ASMs) are used to terminate clinical and electrical seizure activity.[5,6] Typically, patients with SE are initially administered a benzodiazepine (eg, lorazepam, midazolam, diazepam),[5] but 30%–57% of patients fail to respond to first-line treatment.[3,7] Patients who fail to respond to benzodiazepines are considered to have established SE and are then administered one or more second-line intravenous (IV) ASMs such as fosphenytoin, valproate, or levetiracetam.[8] However, 53%–55% of patients with SE do not respond to either first- or second-line treatment and therefore meet criteria for refractory SE (RSE).[8] Patients with RSE either receive additional second-line IV ASMs or are placed in a pharmacologically induced coma using IV anesthetic agents such as midazolam, propofol, or barbiturates.[5,9] Patients with RSE have a worse prognosis, longer hospitalization, and decreased likelihood of returning to baseline clinical function compared to those without RSE.[3,10,11] Mortality rates associated with RSE are as high as 35%, and nearly half of the surviving patients have subsequent neurologic deficits.[12] Patients who continue to be in SE after 24 h of IV anesthetics or in whom SE recurs upon the reduction or withdrawal of the IV anesthetic are defined as being in super-refractory SE (SRSE).[13]

IV anesthetic drugs have a high risk of complications, including infections, hypotension, organ failure, and increased mortality.[14–16] Because general anesthesia depresses respiratory function, patients who are placed in a pharmacologically induced coma must receive prolonged ventilatory support, which is an independent risk factor for morbidity and mortality.[17,18] The optimal duration of IV anesthesia in controlling RSE is not known, and prematurely weaning patients may lead to SE recurrence. Moreover, prolonged hospital and intensive care unit (ICU) stays increase the cost and economic burden of RSE.[19–21] Thus there is a need for an RSE treatment that rapidly stops SE and maintains seizure control, mitigating the need to escalate to third-line IV anesthesia and preventing progression to SRSE.

**Key points**

- Ganaxolone may mitigate the need for third-line intravenous anesthetics by maintaining seizure control in patients with refractory status epilepticus (RSE)
- In this open-label study in RSE, no patient required escalation to third-line intravenous anesthetics within 24 h of initiating ganaxolone
- The results suggest that ganaxolone may be an effective treatment for RSE. A phase 3 trial of ganaxolone in RSE is ongoing

A decline in γ-aminobutyric acid type A ($GABA_A$) receptor–mediated inhibition is one proposed mechanism by which SE begins and becomes self-sustained.[22–25] As seizures progress, synaptic $GABA_A$ receptors become functionally inactive through receptor internalization,[23,24,26] which may be responsible for the resistance to first-line benzodiazepines that only act at synaptic receptors.[27,28] In addition to the effects of prolonged SE, chronic benzodiazepine exposure also promotes the internalization of synaptic $GABA_A$ receptors, which may further contribute to benzodiazepine resistance.[29] In contrast, levels of extrasynaptic $GABA_A$ receptors are stable, or even increased, during SE.[15,23,28]

Ganaxolone is a synthetic neuroactive steroid that acts as a positive allosteric modulator of both synaptic and extrasynaptic $GABA_A$ receptors,[30–32] binding at a site distinct from that of benzodiazepines or barbiturates.[30,31,33,34] By binding to both types of $GABA_A$ receptors, ganaxolone can potentiate both phasic and tonic inhibition.[32] Neuroactive steroids, such as ganaxolone, have the potential to increase GABAergic signaling when synaptic $GABA_A$ receptors are internalized and benzodiazepines are less effective, such as in RSE.[35]

In multiple preclinical seizure models, including treatment-resistant SE, ganaxolone exhibited

anticonvulsant activity[30,31,36–40] without inducing treatment tolerance.[40]

Ganaxolone has pharmacokinetic/pharmacodynamic properties suited to the treatment of SE. This neuroactive steroid is highly lipophilic and achieved brain exposure ~3-fold greater than plasma in a preclinical study of refractory SE.[37] IV ganaxolone has a triphasic decline in plasma levels following cessation of drug administration. The pharmacodynamic effects of IV ganaxolone were assessed in a phase 1 study of 36 healthy volunteers.[41] In this study, IV ganaxolone showed pharmacodynamic effects consistent with its GABAergic mechanism of action. IV ganaxolone affected quantitative electroencephalography (EEG) in a dose-dependent manner, with changes seen within 5–15 min of infusion and generally returning to baseline 30 min post-dose.

In this report, we describe the preliminary results from an open-label, dose-finding, phase 2 trial exploring the efficacy and safety of IV ganaxolone when added to the standard-of-care in patients with RSE.

## 2 | MATERIALS AND METHODS

### 2.1 | Trial design and patients

This multicenter, open-label, dose-finding, phase 2 trial (NCT03350035) was performed at three sites in the United States between February 19, 2018, and September 18, 2019. The primary objective was to identify the treatment regimen (dose and duration of infusion) for ganaxolone in RSE and to obtain a preliminary assessment of the efficacy, safety, and feasibility of IV ganaxolone administration in this patient population.

Eligible participants were adolescents (≥12 years of age) and adults with convulsive or nonconvulsive SE who failed ≥1 second-line IV ASMs, specifically fosphenytoin/phenytoin, valproate, levetiracetam, or lacosamide. Patients with SE had to satisfy one of the following criteria: 10 min of continuous clinical or EEG seizure activity; intermittent seizure activity (ie, seizure burden) in >50% of the previous 60 min; or if <60 min of baseline period was available, intermittent seizure activity must have been present for >50% of the available duration, and the seizure activity must have been ≥10 min when taken in aggregate. Salzburg criteria[42,43] were used to confirm an ictal EEG pattern for nonconvulsive seizures. For this study, modified criteria were utilized, which excluded confirmation of nonconvulsive SE based on the response to an IV ASM challenge and the presence of fluctuations without definite evolution of the EEG pattern. Exclusion criteria included the use of IV anesthetics for SE control, life expectancy <24 h, and anoxic brain injury or recent (<24 h) traumatic brain injury as the primary cause of SE.

This trial was conducted in compliance with the International Conference on Harmonization Guidelines for Good Clinical Practice and applicable national and local regulatory requirements. The trial protocol was approved by the independent ethics committee/institutional review board at each participating site, and all patients (or their guardian or legal representative) provided written informed consent.

### 2.2 | Treatment

Patients received IV ganaxolone in addition to ongoing treatment with second-line IV ASMs. Investigators were instructed to confirm that dosing of ASMs was consistent with the Internal League Against Epilepsy's (ILAE's) generally recommended loading/maintenance doses of ASMs.[5] The formulation of ganaxolone used in this trial was solubilized by Captisol® (betadex sulfobutyl ether sodium), which had a daily exposure limit up to 50 g/day at the time the trial was conducted. As per protocol, patients who were ≥40 kg were to receive a fixed dose of ganaxolone; those <40 kg were to receive mg/kg dosing. Because no patients weighed <40 kg, ganaxolone was studied in the following three dose cohorts: 500 mg/day (low), 650 mg/day (medium), and 713 mg/day (high, the most ganaxolone that could be administered while staying within the daily Captisol® limit) (Figure 1). In all dose cohorts, ganaxolone infusion was initiated as an IV bolus (over 3 min) with continuous infusion of decreasing infusion rates for 48–96 h followed by an 18-h taper (see Table S1 for details). Additional as-needed boluses were allowed in the Medium Cohort. These infusion parameters allowed for rapid loading of ganaxolone (plasma concentration ~ 900 ng/ml) designed to abort SE, followed by maintenance doses aimed at sustaining seizure control (Figure 2). If, in the opinion of the investigator, the patient was deriving continuing benefit, ganaxolone infusion could have been extended for an additional 48 h (total of 96 h), followed by a taper. Once the ganaxolone infusion was completed, patients were subject to in-person 24-h, 48-h, and 72-h assessments and to additional visits at weeks 2, 3, and 4 (follow-up), which were conducted in-person or via telephone.

### 2.3 | Outcomes and assessments

The primary end point was the number of patients who did not require escalation to a third-line IV anesthetic for RSE control within the first 24 h of ganaxolone initiation.

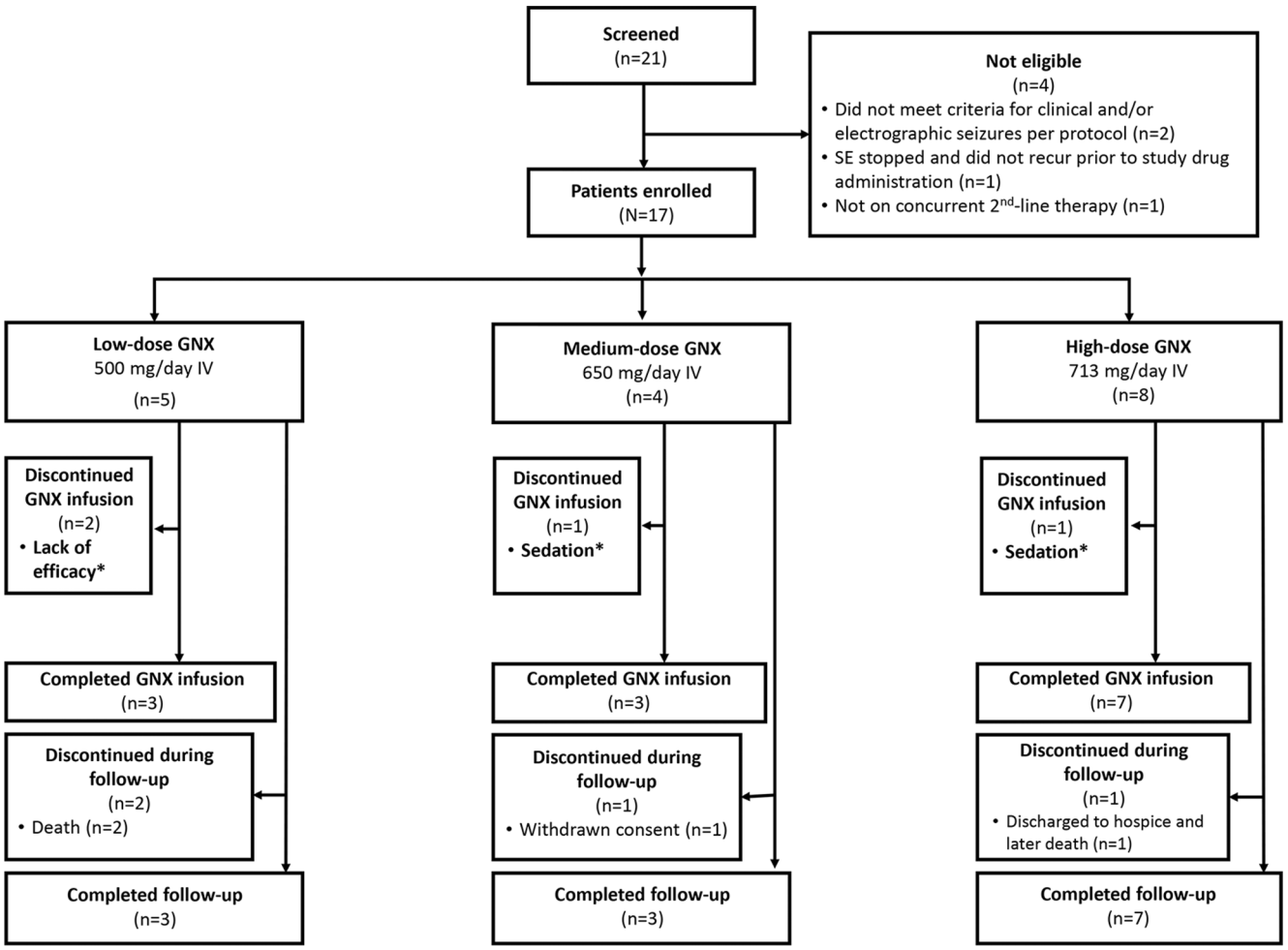


**FIGURE 1** Trial flow diagram. GNX, ganaxolone; SE, status epilepticus. *Patients who discontinued GNX infusion early were to enter the follow-up.

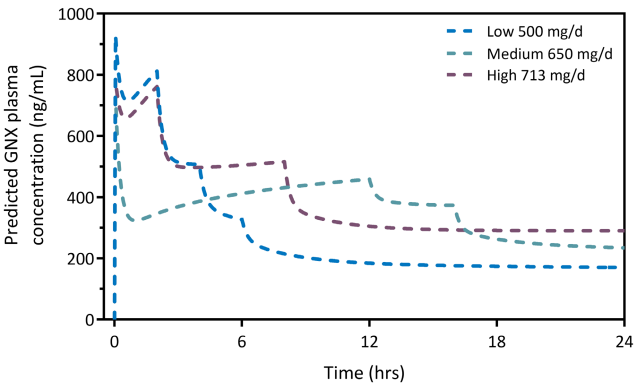


**FIGURE 2** Modeled pharmacokinetic curves for all dose groups. The initial bolus of IV GNX resulted in rapid plasma GNX levels (~900 ng/ml), designed to terminate SE. High-dose GNX achieves and maintains target plasma levels (≥500 ng/ml) for ~8 h, designed to sustain SE cessation. GNX, ganaxolone; IV, intravenous; SE, status epilepticus.

Secondary end points included the number of patients who maintained SE cessation 24 h after ganaxolone taper and at week 4, time to cessation of SE, and ganaxolone safety/tolerability and pharmacokinetics. Patients were monitored via continuous EEG prior to and during ganaxolone use. SE cessation was determined by trial investigators on the basis of clinical and EEG assessments, the latter annotated by investigators to indicate the start and stop of seizure activity. Interpretations of investigator-annotated EEGs were verified by a central EEG reader to confirm consistency of seizure identification and ictal burden calculations. Both trial-site investigators and the central reader received pre-trial training on the specifics of identifying seizure onset and cessation. Any discrepancies were reviewed with onsite staff and resolved by consensus. SE cessation was defined as the end of the last clinical or electrographic seizure after which the SE criteria defined above and observed during the baseline period was no longer met.

Patients were administered the Status Epilepticus Severity Score (STESS)[44] and the Clinical Global Impression-Severity (CGI-S) scale[45] at baseline. STESS is a prognostic score relying on four outcome predictors (age, history of seizures, seizure type, and extent

of consciousness impairment). The CGI-S is a seven-point Likert-like scale that assesses the patients' overall health and functional status. In addition, the Glasgow Coma Scale (GCS)[46] and the Clinical Global Impression-Improvement (CGI-I)[45] were used to assess the patients' state of consciousness and improvement/functional status, respectively, throughout the study (reported at three timepoints: at baseline [GCS only], 48 h, and follow-up; see Table S1). The Richmond Agitation and Sedation Scale (RASS)[47] was also used to evaluate the patients' sedation level throughout the study (reported at four timepoints: at baseline, 24 h, 48 h, and follow-up; see Figure S1).

Safety/tolerability was evaluated throughout the trial, with adverse events (AEs) coded to the Medical Dictionary for Regulatory Activities (version 20.1).

### 2.4 | Statistics

The efficacy population comprised patients who received ganaxolone and had ≥1 efficacy assessment following ganaxolone initiation. All patients receiving ganaxolone were included in the safety population. Efficacy and safety outcomes were summarized using descriptive statistics.

## 3 | RESULTS

### 3.1 | Patients

Of the 21 patients screened across three US clinical sites, 17 were enrolled (low dose, $n = 5$; medium dose, $n = 4$; high dose, $n = 8$). The mean (range) age of the trial population was 56.9 (23–88) years, and 53% of patients were female (Table 1). The trial population was heterogeneous, with the majority of the patients having acute SE (Table 1) caused by various conditions, including brain tumors, stroke, neurodegenerative disorder, intracranial hemorrhage, alcohol withdrawal, illicit drug use, metabolic disturbance, infection, autoimmune disorder, epilepsy, and traumatic brain injury. Approximately 50% of patients had a history of seizure or epilepsy (excluding recent SE episode; Table 1). The majority of patients (65%) had nonconvulsive SE, and one patient (6%) had been witnessed to progress from convulsive to nonconvulsive SE. Patients had failed a median (range) of 3 (2–5) prior ASMs, including first-line benzodiazepines and second-line IV ASMs. Furthermore, all 17 patients had failed second-line treatment with either levetiracetam or lacosamide, with 65% having failed both. Mean seizure burden was 61% in the last 60 min prior to administering ganaxolone. Additional patient baseline characteristics (ie, STESS and CGI-S) are provided in Table 1.

**TABLE 1** Baseline demographic and disease characteristics

| | Patients ($N = 17$) |
|---|---|
| Mean age, years (range) | 56.9 (23–88) |
| Female, *n* (%) | 9 (53) |
| Type of SE, *n* (%) | |
| Convulsive | 5 (29) |
| Nonconvulsive | 11 (65) |
| Convulsive progressing to nonconvulsive | 1 (6) |
| Etiology of SE[a], *n* (%) | |
| Acute | 13 (76.5) |
| Remote | 2 (11.8) |
| Progressive | 2 (11.8) |
| SE in defined electroclinical syndromes | 2 (11.8) |
| History of epilepsy[b], *n* (%) | 9 (53) |
| Median number of failed first- and second-line IV ASMs, including benzodiazepines, *n* (range) | 3 (2–5) |
| Median number of failed second-line IV ASMs[c], *n* (range) | 2 (1–4) |
| Seizure burden (%) baseline (pre-dose), mean (SD) | 61.4 (37.0) |
| STESS, mean (range) | |
| Overall | 2.8 (0–6) |
| CGI-S, mean (range) | |
| Overall | 4.9 (3–6) |

Abbreviations: ASM, anti-seizure medication; CGI-S, Clinician Global Impression-Severity; IV, intravenous; SE, status epilepticus. STESS, Status Epilepticus Severity Score.

[a]More than one etiology could be selected.

[b]Excluding current SE episode.

[c]All 17 patients failed levetiracetam or lacosamide before receiving ganaxolone, with 16 failing levetiracetam, 12 failing lacosamide, and 11 failing both.

Patients were receiving the following ASMs: levetiracetam ($n = 16$), lacosamide ($n = 12$), fosphenytoin/phenytoin ($n = 4$), and valproate ($n = 3$). Fourteen patients (82%) were receiving ≥2 IV ASMs, with the last IV ASM administered on average 6 h before ganaxolone initiation.

### 3.2 | Efficacy

All 17 patients were included in the efficacy population. No patient who received ganaxolone added to the standard-of-care ASMs required treatment with IV anesthetics within 24 h of ganaxolone initiation (Table 2).

**TABLE 2** Onset and durability of response to ganaxolone

| | Ganaxolone dose cohort | | |
|---|---|---|---|
| | **High (713 mg/day) (*n* = 8)** | **Medium (650 mg/day) (*n* = 4)** | **Low (500 mg/day) (*n* = 5)** |
| No escalation to third-line IV anesthetics during 24 h following infusion initiation (primary endpoint), *n* (%) | 8 (100) | 4 (100) | 5 (100) |
| Status-free during 24 h following infusion initiation (investigator determined), *n* (%) | 7 (88)[a] | 4 (100) | 5 (100) |
| No escalation to additional IV ASMs or to third-line IV anesthetics for status relapse during 24 h following infusion completion, *n* (%) | 8 (100) | 3 (75)[b] | 3 (60)[c] |

Abbreviations: ASM, anti-seizure medication; IV, intravenous.

[a]One patient had status relapse on day 1, which resolved during ganaxolone infusion without treatment escalation.

[b]One patient escalated to additional IV ASM on day 1 for seizure relapse.

[c]Two patients escalated to third-line IV anesthetics for seizure relapse on day 3.

Sixteen patients (94%) achieved and maintained SE cessation for 24 h following ganaxolone initiation as determined by trial-site investigator assessment (Table 2). The follow-up period after ganaxolone discontinuations was up to 4 weeks; during this period, 85% of evaluable patients did not have SE relapse ($N = 13$; 1 subject in the Low Cohort and 1 subject in the Medium Cohort had SE relapse). EEG data, reviewed by the trial site investigator, showed that one patient experienced several episodes of nonconvulsive seizures, including SE, between hour 8 and hour 18 of ganaxolone infusion. Seizure activity subsequently resolved during ganaxolone infusion without additional treatment, and the patient remained SE-free through the 72-h follow-up visit (day 3) without escalation of treatment.

Fourteen patients (82%) did not require treatment for SE with additional second-line IV ASMs or IV anesthetics through 24 h following completion of the ganaxolone infusion (Table 2). Of the three patients who did not achieve this secondary end point, one was enrolled in the medium-dose cohort and had an SE relapse after beginning the ganaxolone taper. The patient's family withdrew consent prior to the completion of the treatment regimen to transition to comfort care because of underlying disease-related morbidity. The other two patients, both of whom were enrolled in the low-dose cohort, had a seizure relapse that required escalation to IV midazolam on day 3.

Based on an analysis of 16 patients with evaluable data (one patient not included because of an absence of seizure in the 60 min immediately preceding ganaxolone initiation), the median time to SE cessation following initiation of ganaxolone infusion was 5 min. Of these patients, 15 (94%) achieved SE cessation within 30 min of initiating ganaxolone, and one (6%) at ~4 h postinitiation (Figure 3A). All three dose cohorts received a similar initial ganaxolone bolus (25–30 mg), resulting in rapid reductions in seizure burden within the first 15 min of infusion (Figure 3B). Although patients in the medium-dose cohort could receive up to 650 mg/day of ganaxolone, their overall daily infusion rate was lower than that for patients in the low- and high-dose cohorts to allow for additional boluses, if needed (Table S1). Sustained clinical response was associated with maintaining ganaxolone plasma concentrations ≥500 ng/ml. Ganaxolone plasma levels ≥500 ng/ml were achieved only briefly during the initial bolus for patients in the medium-dose cohort, whereas those in low- and high-dose cohorts maintained such levels for 4 and 8 h, respectively. The greatest decrease in seizure burden was seen when ganaxolone concentrations were maintained at ≥500 ng/m for at least 8 h.

Glasgow Coma Scale improved overtime following the initial bolus of ganaxolone; however, CGI-I scores remained relatively stable at 48 h and at follow-up (Table S2). As expected, RASS scores for sedation increased at 24 h, but they had returned to baseline levels by the follow-up visit (Figure S1).

## 3.3 | Safety

Fifteen patients (88%) experienced a total of 61 AEs (Table 3); 23 of these AEs (38%) were considered treatment-related, and all but 2 were mild or moderate in severity. The two severe treatment-related AEs were sedation ($n = 1$ each for medium- and high-dose cohorts), which led to ganaxolone discontinuation. These events occurred ~24 and 72 h after starting ganaxolone (ie, when plasma concentrations were <300 ng/ml). Six patients (35%) experienced a total of 10 serious AEs, 2 of which were considered treatment-related (the aforementioned reports of severe sedation). The eight non–treatment-related serious AEs corresponded to single events in two patients (sepsis and perforated bowel, both fatal), two events in one patient (respiratory depression and death

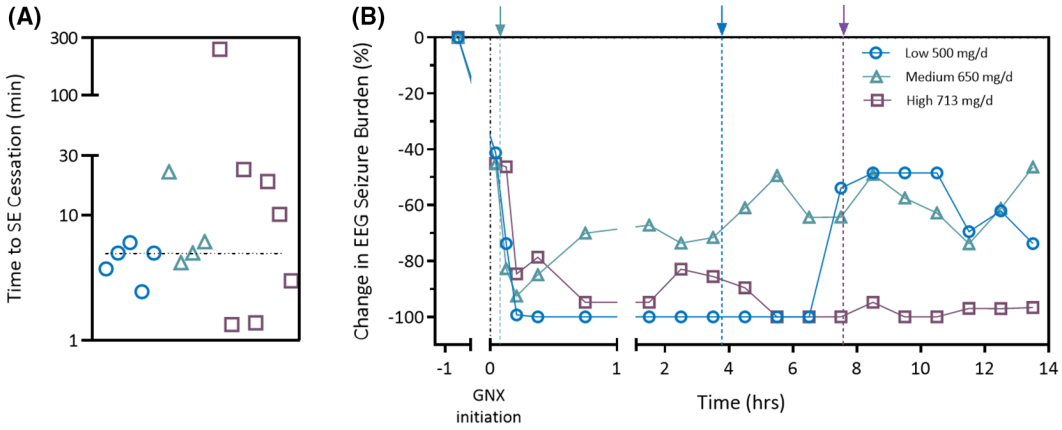


**FIGURE 3** Effects of ganaxolone infusion on seizure in patients with RSE. Patients were monitored via continuous EEG during GNX use. SE cessation was determined by trial investigators. (A) Time to cessation of SE following initiation of GNX, as determined by trial-site investigator assessment. SE cessation occurred rapidly in all dose groups (median, 5 min, dashed line). (B) Percentage change from baseline in seizure burden over time, as determined by central EEG review. Downward arrows indicate time points when GNX dosing targets were <500 ng/ml. EEG, electroencephalography; GNX, ganaxolone; RSE, refractory status epilepticus; SE, status epilepticus.

**TABLE 3** Safety summary

| | **Patients (*N* = 17)** |
|---|---|
| Patients with any AE, *n* (%) | 15 (88) |
| Total number of AEs, *n* | 61 |
| Treatment-related | 23 |
| Mild[a] | 16 |
| Moderate[b] | 5 |
| Severe[c] | 2 |
| Patients with any serious AE, *n* (%) | 6 (35) |
| Total number of serious AEs, *n* | 10 |
| Treatment-related serious AEs, *n* | 2[d] |
| Deaths, *n* (%) | 3 (18)[e] |

Abbreviation: AE, adverse event.

[a]The only treatment-related AEs reported as mild in intensity that occurred in more than 1 patient were hypotension ($n = 2$), somnolence ($n = 2$), and hematuria ($n = 2$).

[b]The 5 treatment-related AEs reported as moderate in intensity were somnolence ($n = 4$) and hypercapnia ($n = 1$).

[c]The two treatment-related AEs reported as severe in intensity were sedation.

[d]Both treatment-related serious AEs were sedation. One event was observed in the medium-dose cohort, and the other was observed in the high-dose cohort.

[e]The deaths were attributable to sepsis, perforated bowel, and withdrawal of life support. None was considered related to ganaxolone.

caused by withdrawal of life support) and four events in one patient (fall, loss of consciousness, multiple fractures, and pneumothorax). The three non–treatment-related serious AEs that led to death—perforated bowel (high-dose cohort), withdrawal of life support (low-dose cohort), and sepsis (low-dose cohort)—occurred 9, 16, and 22 days, respectively, after the completion of ganaxolone treatment.

Eight patients entered the study intubated; nine patients (53%) had not been intubated prior to initiating ganaxolone. Of these nine, three were intubated for airway protection ~4–12 h after starting the ganaxolone infusion. Two of these patients were extubated within 48 h, and the third required prolonged intubation because of underlying encephalitis but did require escalation of care to IV anesthetics. The other six nonintubated patients required no mechanical ventilation during ganaxolone treatment.

At the time of trial entry, one patient (6%) was receiving continuous IV vasopressors for blood pressure management. Of the 16 patients who entered the trial without having received vasopressors, five started continuous IV vasopressor treatment during ganaxolone treatment (four started on day 1 and one started on day 2). Of the six patients receiving vasopressors during ganaxolone treatment, three discontinued during ganaxolone treatment, two discontinued at the time of ganaxolone taper, and one discontinued following discontinuation of ganaxolone. Two patients in the low-dose cohort experienced mild hypotension unrelated to the study treatment; in the high-dose cohort, one patient experienced mild hypotension and one experienced moderate hypotension, both considered related to treatment. No patient had clinically meaningful changes in renal function during or following ganaxolone infusion.

## 4 | DISCUSSION

In this phase 2 trial assessing the preliminary efficacy and safety of IV ganaxolone in the treatment of RSE, none of the 17 enrolled patients had their treatment escalated to IV anesthesia within 24 h of ganaxolone

initiation (primary endpoint). Investigator assessments indicated that all but one patient maintained SE cessation during this 24-h period. The one patient had several episodes of nonconvulsive seizures (including SE) that resolved without treatment escalation. Furthermore, the antiseizure effect of ganaxolone was rapid, with a median time to SE cessation of 5 min. This is notable given that the trial population comprised patients who had failed multiple ASMs previously, including benzodiazepines and 1–4 second-line IV agents, and that successive treatments in patients with SE have been associated with diminishing efficacy.[5,9,48,49] The rapid onset of action of ganaxolone is supported by the preclinical and phase 1 data, which show that ganaxolone achieves peak brain concentrations within ~15 min of IV or intramuscular administration.[36,37,41]

These data support that the ganaxolone regimen administered in the high-dose cohort (713 mg/day) may reduce or prevent escalation of care to third-line IV anesthetics. This is clinically significant, as use of IV anesthesia in patients with RSE is associated with prolonged hospitalization, poorer functional outcomes, and increased mortality.[19,48,50] The complications associated with IV anesthetics—including respiratory depression, cardiac dysfunction (eg, arrhythmias, QT prolongation, depressed ejection fraction), hypotension, infection, and propofol infusion syndrome[6,51]—likely contribute to these adverse clinical outcomes.

It is notable that ganaxolone was shown to control seizure activity whether patients presented with or without convulsions. This finding is supported by data from a preclinical model of benzodiazepine-resistant SE, which demonstrated the ability of ganaxolone to both block convulsions and reduce EEG seizure activity.[36] It is important to note that SE did not recur in the majority of patients, even after discontinuation of ganaxolone infusion. Only three patients (18%) required an additional second-line IV ASM for SE treatment in the 24 h following tapering and discontinuation of ganaxolone.

Reductions in seizure burden occurred rapidly in all three ganaxolone dose cohorts. Patients in the high-dose cohort maintained ganaxolone plasma concentrations ≥500 ng/ml for 8 h following treatment initiation and demonstrated the most durable reductions in seizure burden. Although not studied in the present trial, maintaining ganaxolone levels ≥500 ng/ml for durations longer than 8 h may offer additional benefit and will be evaluated in future clinical studies.

Ganaxolone was generally well tolerated in patients with RSE. Incidence and severity of adverse events were comparable across the three dose cohorts. Increased sedation was recognized as a potential risk with ganaxolone, because of its GABAergic effects, particularly when administered concomitantly with other central nervous system depressants. There were two (12%) treatment-related cases of sedation that were considered severe and serious; these patients were receiving 4–5 concomitant ASMs. Notably, these events did not occur at the time of maximum ganaxolone plasma concentrations, and both resolved within minutes to hours following discontinuation of ganaxolone. There were no treatment-related deaths. Although we recognize this is an open-label study, these results suggest that ganaxolone has a manageable safety profile, an important attribute for use in patients who often have serious underlying illness and require treatment in an acute or intensive care setting.

The trial presented here differs from a previously reported phase 1/2 trial (study 547-SSE-201, NCT02052739)[52] evaluating the safety and efficacy of a neuroactive steroid, brexanolone, of similar molecular weight, structure, and mechanism of action.[53] First, the present phase 2 trial examined patients with RSE, whereas brexanolone was evaluated in patients with the more severe condition of SRSE. Second, with the goal of stopping SE, the target plasma concentration of even the lowest dose of ganaxolone in this trial was ~10-fold higher than that of brexanolone (~500 vs 47 ng/ml, respectively). Third, the primary outcome of the two studies differed: ganaxolone was studied for its ability to prevent escalation of care in RSE to third-line IV anesthetics, whereas brexanolone was studied for its ability to successfully wean patients with SRSE from IV anesthetics.

### 4.1 | Limitations

Limitations of this phase 2 trial include the lack of randomization, no comparator arm, heterogeneous patient population (with respect to SE etiologies and other comorbid conditions), small sample size, and the involvement of only three trial sites. The latter is of relevance because of a lack of generally accepted standard-of-care protocols to treat nonconvulsive SE.

## 5 | CONCLUSIONS

In conclusion, IV ganaxolone treatment resulted in rapid seizure cessation in RSE. Maintenance of higher plasma concentrations for a longer duration was associated with more substantial reductions in EEG seizure burden. In addition, ganaxolone had an acceptable safety and tolerability profile at the three dose levels studied. Collectively, these data suggest that ganaxolone has the potential to provide significant clinical benefit to patients with RSE, a condition for which there a paucity of evidence to guide

treatment. These phase 2 trial results also provide the rationale for further investigation of ganaxolone in RSE and informed the design of an ongoing, phase 3 trial (NCT04391569).

## AUTHOR CONTRIBUTIONS

**HV** participated in the design, conduct, and analysis of this study, as well as the preparation of the manuscript. **RER** participated in the conduct and analysis of this study, as well as the preparation of the manuscript. **CBS** participated in the conduct and analysis of this study, as well as the preparation of the manuscript. **AMH** participated in the conduct and analysis of this study, as well as the preparation of the manuscript. **AA** participated in the design, conduct, and analysis of this study, as well as the preparation of the manuscript. **MG** participated in the design, conduct, and analysis of this study, as well as the preparation of the manuscript.

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## AUTHOR DISCLOSURES

**Henrikas Vaitkevicius:** Dr. Vaitkevicius was a full-time employee at Brigham and Women's Hospital and Harvard Medical School during the conduct of the trial. Since completion of the trial, he joined Marinus Pharmaceuticals, Inc., as a full-time employee and currently owns stock in the company. **R. Eugene Ramsay**: Dr. Ramsay was a full-time employee at Ochsner Health System during conduct of the trial and has served on speaker's bureaus for UCB, Sunovion, Zogenix, and Neurelis. Since completion of the trial, he has served as a private consultant and owns no stock in Marinus Pharmaceuticals, Inc. **Christa B. Swisher:** Dr. Swisher was a full-time employee at Carolinas Medical Center during the conduct of the trial and has received consulting and advisory board fees from UCB and Eisai. **Aatif M. Husain:** Dr. Husain was a full-time employee at Duke Health during the conduct of the trial. He has served as a consultant for Jazz, BlackThorn, Eisai, and Neurelis; has been involved in both research and consultation for UCB, Sage, and Marinus Pharmaceuticals, Inc.; and has served as an editor and received publishing royalties from Wolters Kluwer, Springer Publishers, and Demos Medical Publishing. He owns no stock in Marinus Pharmaceuticals, Inc. **Alex Aimetti:** Dr. Aimetti is a full-time employee at Marinus Pharmaceuticals, Inc., and owns stock in the company. **Maciej Gasior:** Dr. Gasior is a full-time employee at Marinus Pharmaceuticals, Inc., and owns stock in the company. 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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## SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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