

Intravenous Ganaxolone: Pharmacokinetics, Pharmacodynamics, Safety, and Tolerability in Healthy Adults

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Maciej Gasior¹, Aatif Husain², Megan E. Barra¹, Shruti M. Raja², David MacLeod²,
Jeffrey T. Guptill², Henrikas Vaitkevicius¹, and Eva Rybak¹

Abstract

Ganaxolone, a neuroactive steroid anticonvulsant that modulates both synaptic and extrasynaptic γ -aminobutyric acid type A (GABA_A) receptors, is in development for treatment of status epilepticus (SE) and rare epileptic disorders, and has been approved in the United States for treatment of seizures associated with cyclin-dependent kinase-like 5 deficiency disorder in patients ≥ 2 years old. This phase I study in 36 healthy volunteers evaluated the pharmacokinetics, pharmacodynamics, and safety of intravenous ganaxolone administered as a (i) single bolus, (ii) infusion, and (iii) bolus followed by continuous infusion. After a single bolus over 2 minutes (20 mg) or 5 minutes (10 or 30 mg), ganaxolone was detected in plasma with a median T_{max} of 5 minutes, whereas a 60-minute infusion (10 or 30 mg) or a bolus (6 mg over 5 minutes) followed by infusion (20 mg/h) for 4 hours achieved a median T_{max} of approximately 1 and 3 hours, respectively. C_{max} was dose and administration-time dependent, ranging from 73.8 ng/mL (10 mg over 5 minutes) to 1240 ng/mL (30 mg over 5 minutes). Bolus doses above 10 mg of ganaxolone markedly influenced the bispectral index score with a rapid decline; smaller changes occurred on the Modified Observer's Assessment of Alertness/Sedation scale and in quantitative electroencephalogram. Most adverse events were of mild severity, with 2 events of moderate severity; none were reported as serious. No effects on systemic hemodynamics or respiratory functions were reported. Overall, ganaxolone was generally well tolerated at the doses studied and demonstrated pharmacokinetic and pharmacodynamic properties suitable to treat SE.

Keywords

ganaxolone, pharmacokinetics, pharmacodynamics, intravenous, bispectral index, quantitative electroencephalogram, sedation

Ganaxolone (3 α -hydroxy-3 β -methyl-5 α -pregnan-20-one) is a synthetic methyl analog of the endogenous neuroactive steroid allopregnanolone (3 α -hydroxy-5 α -pregnan-20-one; 5 α , 3 α -P) that acts as a potent modulator of γ -aminobutyric acid type A (GABA_A) receptors in the central nervous system (CNS).¹ Ganaxolone binds to GABA_A receptors at a unique neuroactive steroid binding site distinct from those sites affected by other GABA_A receptor modulators (eg, benzodiazepines or barbiturates).¹ At lower (nanomolar) concentrations, ganaxolone is a positive allosteric modulator of GABA_A receptors and potentiates GABA-mediated inhibition by increasing the frequency and the duration of channel opening.^{2,3} At higher (micromolar) concentrations, ganaxolone exhibits a direct agonist effect at the GABA_A receptor. Modulation of GABA_A receptors by ganaxolone results in enhanced postsynaptic Cl[−] flux, subse-

quent hyperpolarization, and inhibition of nerve transmission.⁴

In animal models, ganaxolone demonstrated anti-seizure activity against both chemically and electrically induced seizures,^{1,5–8} including in benzodiazepine-resistant status epilepticus (SE).^{9,10} Ganaxolone is

¹ Marinus Pharmaceuticals Inc., Radnor, PA, USA

² Duke University School of Medicine, Durham, NC, USA

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Corresponding Author:

Maciej Gasior, MD, PhD, Clinical Development, Marinus Pharmaceuticals, Inc., 5 Radnor Corporate Center, 100 Matsonford Road, Suite 500, Radnor, PA 19087.
(e-mail: mgasior@marinuspharma.com)

Table 1. Dose Group Descriptions

Stage	Type	Ganaxolone dose	Total dose (mg)	Controls ^a	n
1	Bolus	10 mg over 5 minutes	10	–	3
	Bolus	30 mg over 5 minutes	30	2	3
	Bolus	20 mg over 2 minutes	20	2	6
	Infusion	10 mg/h over 1 hour	10	–	6
	Infusion	30 mg/h over 1 hour	30	2	6
2	Bolus + infusion	6 mg over 5 minutes + 20 mg/h over 4 hours	86	–	6

^a Controls received vehicle dosing similar to the respective ganaxolone group.

highly lipophilic (logP of 5.3) and achieves brain exposure equivalent to approximately 3-fold greater plasma exposure in preclinical studies of SE.^{9,10} Oral formulations of ganaxolone have been examined in phase 1-3 clinical trials across several disease states such as epilepsy and neuropsychiatric disorders.¹¹⁻¹⁷ Oral ganaxolone was recently approved in the United States for treatment of seizures associated with cyclin-dependent kinase-like 5 (CDKL5) deficiency disorder (CDD) in patients 2 years of age and older. In the European Union, ganaxolone was approved for the treatment of CDD in patients 2-17 years of age and may be continued in patients 18 years of age and older. Maximum plasma concentration of ganaxolone is reached 2-3 hours following administration of an oral suspension.¹⁸ $C_{\max}$ and AUC are 3- and 2-fold higher, respectively, when ganaxolone is administered after a high-fat meal compared with fasted conditions. Elimination occurs in a bimodal manner with a terminal half-life of 34 hours.^{18,19} Hepatic metabolism of ganaxolone is complex; the major metabolizing enzyme is CYP3A4/5, with additional involvement of CYP2B6, CYP2C19, and CYP2D6.¹⁸ Coadministration of ganaxolone with rifampin, a strong CYP3A4 inducer, reduced ganaxolone $C_{\max}$ and AUC by 57% and 68%, respectively.¹⁸ The intravenous (IV) formulation of ganaxolone is being developed to rapidly achieve and maintain therapeutic ganaxolone levels. Such a profile may have utility as a treatment for seizure emergencies, including SE. The purpose of this study was to assess the pharmacokinetics (PK), pharmacodynamics (PD), safety, and tolerability of IV ganaxolone in healthy adults.

Methods

Study Design

This single-site, sequential cohort evaluation of IV ganaxolone in healthy subjects was approved by the Duke Institutional Review Board. The safety, PK, and PD of IV ganaxolone were investigated by administering ascending bolus doses or infusions in different groups of subjects (stage 1) and as a bolus dose

followed by a continuous infusion (stage 2; Table 1). The study was conducted at the Duke Early Phase Clinical Research Unit at Duke University Medical Center (Durham, NC, USA) on behalf of Marinus Pharmaceuticals, Inc. (Radnor, PA, USA). Written informed consent was obtained prior to enrollment. The study was conducted in accordance with the ethical principles set forth in the Declaration of Helsinki and was designed, conducted, recorded, and reported in compliance with the principles of Good Clinical Practice guidelines.

Subjects

Planned enrollment was 36 healthy subjects. The main inclusion criteria were adults 18-50 years old with actual body weight of at least 50 kg and body mass index 18-33 kg/m², abstinence from smoking or nicotine-containing products for at least 6 months prior to study commencement, and deemed healthy at baseline screening with normal electroencephalography (EEG). Key exclusion criteria included clinically significant laboratory results outside the normal range, current drug or alcohol abuse, or history of major organ disease (including seizures) that might influence the study results. Subjects who were administered a prescription medication within 15 days or any over-the-counter medication or herbal/vitamin supplements within 7 days or 5 half-lives (whichever was longer) of study entry were excluded.

Treatment

Ganaxolone was supplied by Particle Sciences, Inc. (Bethlehem, PA, USA) as ganaxolone 3 mg/mL in Captisol (sulfobutylether- β -cyclodextrin) and diluted to 1 mg/mL for administration to study participants. Captisol control material (IV solution matching ganaxolone) was obtained from The Ligand Technology GMP production facility at the University of California.

A description of ganaxolone dosing cohorts is provided in Table 1. IV ganaxolone was administered as an ascending bolus dose or infusion (stage 1) or as a

bolus dose followed by a continuous infusion (stage 2). In stage 1, subjects ($n = 3$) were initially enrolled under open-label and received IV ganaxolone 10 mg administered over 5 minutes and were observed for 60 minutes postadministration. If this dose was tolerated, additional subjects ($n = 3$) received a higher open-label bolus dose of 30 mg administered over 5 minutes and were monitored for 60 minutes. Interim PK analyses were performed to define preliminary PK parameters for IV ganaxolone. These parameters were used to inform bolus dosing for the remainder of stage 1, as well as dosing in stage 2. Following the interim PK analysis, double-blind dosing was conducted in which additional subjects received IV ganaxolone as a single bolus 20-mg dose administered over 2 minutes ($n = 6$), a 10-mg infusion over 60 minutes ($n = 6$), or a 30-mg infusion over 60 minutes ($n = 6$). Six additional subjects were administered vehicle control ($n = 2$ for each treatment group). In stage 2, 6 subjects received open-label ganaxolone as a 6-mg bolus over 5 minutes followed by a ganaxolone infusion of 20 mg/h for 4 hours.

Pharmacokinetic Evaluation

Serial plasma PK sampling for stages 1 and 2 was performed from 15 minutes prior to start of dosing to 48 hours postdose (times specified in Figure 1). PK blood collections occurred within ± 2 minutes of the protocol-specified time points. Analytical assessment of all ganaxolone samples was conducted at QPS, LLC (Newark, DE, USA). Ganaxolone concentrations in K_2EDTA plasma were quantified using a reversed-phase ultra-performance liquid chromatography with atmospheric pressure chemical ionization tandem mass spectrometry method. Ganaxolone- d_6 was used as the internal standard. The method was validated for a range of 2–1000 ng/mL with an intraday precision (%CV) and accuracy (%RE) range of 0.9–4.1 and -0.4 –12.0, respectively, and an interday precision and accuracy range of 2.8–4.4 and 2.2–8.0, respectively. Samples were processed by a liquid-liquid extraction procedure using 2% isopropanol in hexanes. Samples were reconstituted in methanol:water 80:20 (v:v), and separated using an Acquity UPLC BEH C18 column (2.1×50 mm, 1.7 mm; Waters Corporation, Milford, MA, USA) maintained at a flow rate of 0.5 mL/min using mobile phases (A): water:formic acid 100:0.1 (v:v) and (B): methanol:formic acid 100:0.1 (v:v). Ganaxolone and ganaxolone- d_6 were monitored at m/z 315.3 $\rightarrow$ 297.3 and m/z 321.3 $\rightarrow$ 303.3, respectively.

PK was assessed in all subjects who received at least 1 dose and had at least 5 data points with a quantifiable plasma ganaxolone concentration value. Concentrations below the lower limit of quantitation were imputed as 0. PK parameters evaluated included maximum plasma concentration (C_{max}), time to maximum

concentration (T_{max}), area under the concentration-time curve from time 0 to last measurable concentration (AUC_{0-t}), area under the concentration-time curve from time 0 to infinity (AUC_{0-inf}), terminal half-life ($t_{1/2}$), clearance (CL), and volume of distribution (V_z).

Pharmacodynamic Evaluation

Prior to, during, and after ganaxolone administration, subjects were monitored for neurophysiologic PD changes using bispectral index (BIS) and quantitative EEG (qEEG) parameters,^{20,21} including relative alpha power, alpha/delta ratio, and spectral edge frequency (95%), and the Modified Observer's Assessment of Alertness/Sedation (MOAA/S) scale. qEEG and BIS are important PD variables for capturing the timing and severity of EEG slowing in relation to the doses administered. The MOAA/S scale is a validated 6-point scale used for assessing the subject's level of sedation and ranges from 0 to 5, with a score of 0 indicating lack of response to painful trapezius squeeze and presence of deep sedation and a score of 5 indicating the subject is readily responsive to their name spoken in a normal tone and no sedation present.^{22–24}

Safety and Tolerability

Safety was assessed in all subjects who received any amount of drug during the study. Safety analyses included descriptive statistics of vital signs, including noninvasive blood pressure, heart rate, respiratory rate, pulse oximetry saturation, and temperature; electrocardiogram parameters; frequency distributions of abnormal physical examinations; and summaries of treatment-emergent adverse events (TEAEs) (ie, those AEs that occurred after the start of study drug administration in the dosing period). Subjects were also monitored for incidence of suicidal ideations and behaviors using the Columbia Suicide Severity Rating Scale (C-SSRS), as required by the Food and Drug Administration for clinical trials of all anti-epileptic drugs.^{25,26} Changes from baseline in clinical laboratory tests (hematology, coagulation, biochemistry, and urinalysis) were also monitored.

Statistical Analysis

PK parameters for plasma concentrations of ganaxolone were derived for each subject using noncompartmental analysis methods with Phoenix WinNonlin PK software (v6.4, Certara USA, Princeton, NJ, USA). Summary values that required the use of the k_{el} for calculation were only considered valid if the concentration versus time regression R^2 value was ≥ 0.80 or the %AUCextrap was $\leq 20\%$. Summary statistics for all PK and PD parameters were generated using SAS version 9.3 (SAS Institute, Cary, NC, USA).

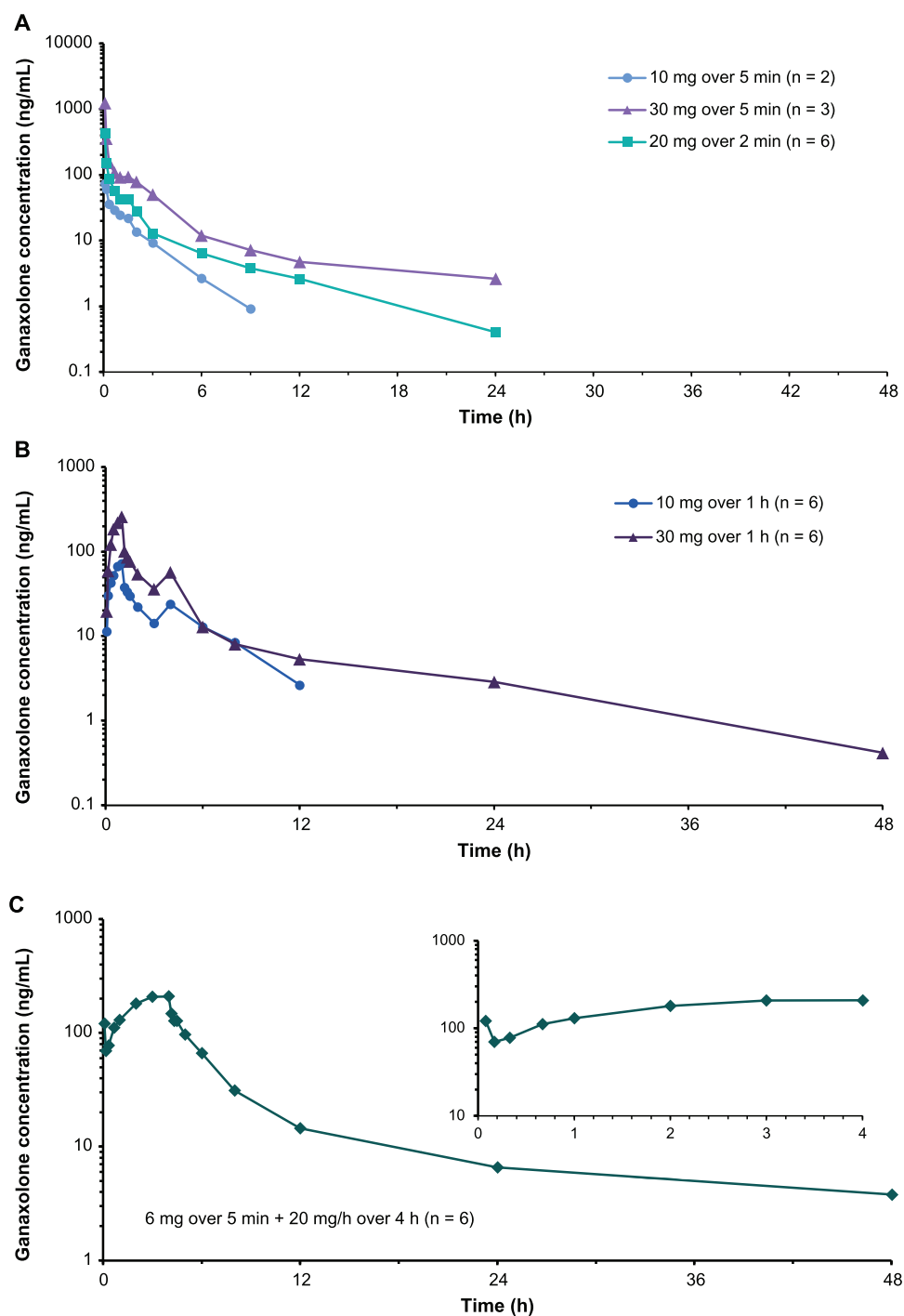


Figure 1. Plasma concentration versus time curves following IV administration of ganaxolone: (A) bolus doses of 10 mg over 5 minutes ($n = 2$), 30 mg over 5 minutes ($n = 3$), and 20 mg over 2 minutes ($n = 6$); (B) infused doses of 30 mg/h over 1 hours ($n = 6$) and 10 mg/h over 1 hour ($n = 6$); (C) bolus dose of 6 mg over 5 minutes followed by infused dose of 20 mg/h over 4 hours ($n = 6$). Mean values are plotted.

Results

Demographics

Subject demographics are provided in Table S1. Thirty subjects were enrolled in stage 1 and 6 subjects were enrolled in stage 2. One subject in stage 1 was excluded

from the PK analysis after withdrawal of consent. Subjects were predominantly male in stage 1 (80%) and predominantly female in stage 2 (66.7%). Mean age was 33.5 years for stage 1 subjects and 30.5 years for stage 2 subjects. For both stages, 25 subjects were Black or

Table 2. Key Pharmacokinetic Parameters Following IV Administration of Ganaxolone

Treatment	10 mg over 5 minutes		30 mg over 5 minutes		20 mg over 2 minutes		30 mg/h over 1 hour		10 mg/h over 1 hour		6 mg over 5 minutes + 20 mg/h over 4 hours	
Parameters	n	Mean ± SD	n	Mean ± SD	n	Mean ± SD	n	Mean ± SD	n	Mean ± SD	n	Mean ± SD
C _{max} (ng/mL)	3	73.8 ± 5.60	3	1240 ± 755	6	441 ± 188	5 ^a	257 ± 58.2	6	80.2 ± 21.4	6	215 ± 33.9
T _{max} (hour ^b)	3	0.08 (0.08, 0.17)	3	0.08 (0.08, 0.08)	6	0.08 (0.08, 0.08)	5 ^a	0.98 (0.98, 0.98)	6	0.98 (0.75, 4.00)	6	3.00 (0.08, 3.98)
AUC _{0-t} (ng·h/mL)	3	86.1 ± 26.1	3	547 ± 113	6	220 ± 32.8	5 ^a	494 ± 117	6	192 ± 163	6	1270 ± 206
AUC _{0-inf} (ng·h/mL)	3	93.5 ± 27.0	2 ^c	548 ± 140	5 ^c	247 ± 26.1	4 ^c	561 ± 113	6	210 ± 189	5 ^c	1360 ± 241
t _{1/2} (hour)	3	2.07 ± 0.193	2 ^c	10.4 ± 0.264	5 ^c	4.6 ± 0.855	4 ^c	11 ± 1.56	6	2.41 ± 0.702	5 ^c	18.2 ± 5.88
CL (L/h)	3	114 ± 36.5	2 ^c	56.6 ± 14.4	5 ^c	81.9 ± 8.75	4 ^c	54.8 ± 9.25	6	67.5 ± 29.3	5 ^c	64.9 ± 11.8
V _z (L)	3	344 ± 133	2 ^c	852 ± 238	5 ^c	546 ± 131	4 ^c	886 ± 246	6	216 ± 79.1	5 ^c	1710 ± 693

%AUC_{extrap}, percentage of extrapolated area under the concentration-time curve; AUC_{0-inf}, area under the concentration-time curve from time 0 to infinity; AUC_{0-t}, area under the concentration-time curve from time 0 to t hours; CL, total body clearance; C_{max}, maximum plasma concentration; SD, standard deviation; GNX, ganaxolone; t_{1/2}, terminal elimination half-life; T_{max}, time to reach maximum concentration; V_z, volume of distribution.

^aOne subject in this group withdrew consent after missing the day 3 visit and was excluded from the pharmacokinetic and statistical analysis.

^bT_{max} reported as median (minimum, maximum).

^cn = 1 removed from designated groups for analysis of AUC_{0-inf}, t_{1/2}, CL, and V_z due to adjusted R² value <0.80 or %AUC_{extrap} > 20%.

African American (69.4%). There were no notable differences in demographic variables between the 2 randomization groups.

Pharmacokinetic Results

Plasma concentration versus time curves for IV-administered ganaxolone are provided in Figure 1 and key PK parameters are provided in Table 2. Ganaxolone was detected rapidly in plasma following IV bolus administration over 2 or 5 minutes with a median T_{max} attained within approximately 5 minutes. When the IV ganaxolone dose was administered as an infusion over 60 minutes, T_{max} was reached at a median of approximately 1 hour; when administered as a bolus followed by an infusion for 4 hours, T_{max} was reached at 3 hours (Table 2). C_{max} appeared to be dose related; there was a stepwise elevation in C_{max} from 73.8 ng/mL at a dose of 10 mg over 5 minutes to 441 ng/mL at a dose of 20 mg over 2 minutes and to 1240 ng/mL at a dose of 30 mg over 5 minutes (Table 2). After the IV bolus dose, or cessation of the IV infusion dose, concentrations for ganaxolone in plasma declined in a multiphasic manner (Figure 1). A dose-response relationship was also observed after administration of an infusion, with administration of 30 mg ganaxolone over 60 minutes resulting in a greater C_{max} (257 ng/mL) compared with 10 mg over 60 minutes (C_{max} 80.2 ng/mL). A dose-response relationship in AUC was observed with increasing doses given over 2 or 5 minutes or given over a 60-minute infusion resulting in sequential increases in AUC_{0-t} and AUC_{0-inf} (Table 2). In stage 2, the combination of a 6-mg bolus dose and 20-mg/h infusion for 4 hours resulted in an initial rapid peak in plasma concentration of ganaxolone by the end of the 5-minute bolus (121 ng/mL), followed by a more sustained rise to C_{max} reached at an average of 3 hours (Figure 1C). V_z and t_{1/2} also appeared to be dose and exposure related. The shortest terminal t_{1/2} was observed when IV ganax-

olone was administered as a 10-mg bolus over 5 minutes (2.07 hours) and longest when it was administered as a bolus followed by an infusion for 4 hours (18.2 hours). A large V_z was observed for all IV ganaxolone cohorts (Table 2). CL ranged from 54.8 to 114 L/h across all the dosing cohorts.

Pharmacodynamic Results

Across all subjects, median baseline BIS was 97 (range 83-98). All 3 dosing regimens of ganaxolone elicited responses in the BIS index (Figure 2). After administration of an IV ganaxolone bolus, a rapid dose-dependent decline in BIS values was observed after administration of 20 mg over 2 minutes and 30 mg over 5 minutes. Following administration of a 30-mg bolus over 5 minutes, the median BIS score at 5 minutes was 54 (range 46-75) followed by a decrease to a median nadir of 44 (range 43-46) within 10 minutes (range 5-15). Across all cohorts in subjects with BIS <80 after IV ganaxolone, median time to recovery (BIS ≥80) was 30 minutes (range 20-45) postadministration (Figure 2A). Ganaxolone infusion over 60 minutes (10 mg over 60 minutes or 30 mg over 60 minutes) resulted in a dose-dependent decline in BIS values. Time to BIS nadir corresponded with administration duration, with a more gradual BIS decline compared to IV bolus over 2 or 5 minutes (Figure 2B). Administration of ganaxolone as a 6-mg IV bolus followed by 4-hour continuous infusion at the rate of 20 mg/h resulted in an initial rapid decline in BIS followed by a stable plateau. BIS decline was maintained for the duration of the continuous infusion (Figure 2C).

The median MOAA/S scores remained unchanged throughout all dosing cohorts. Most subjects were observed to have no or mild sedation throughout the monitoring period as determined by the MOAA/S scale (Figure S1). Across all cohorts, deep sedation (defined as an MOAA/S score of 0-1) was reported in a

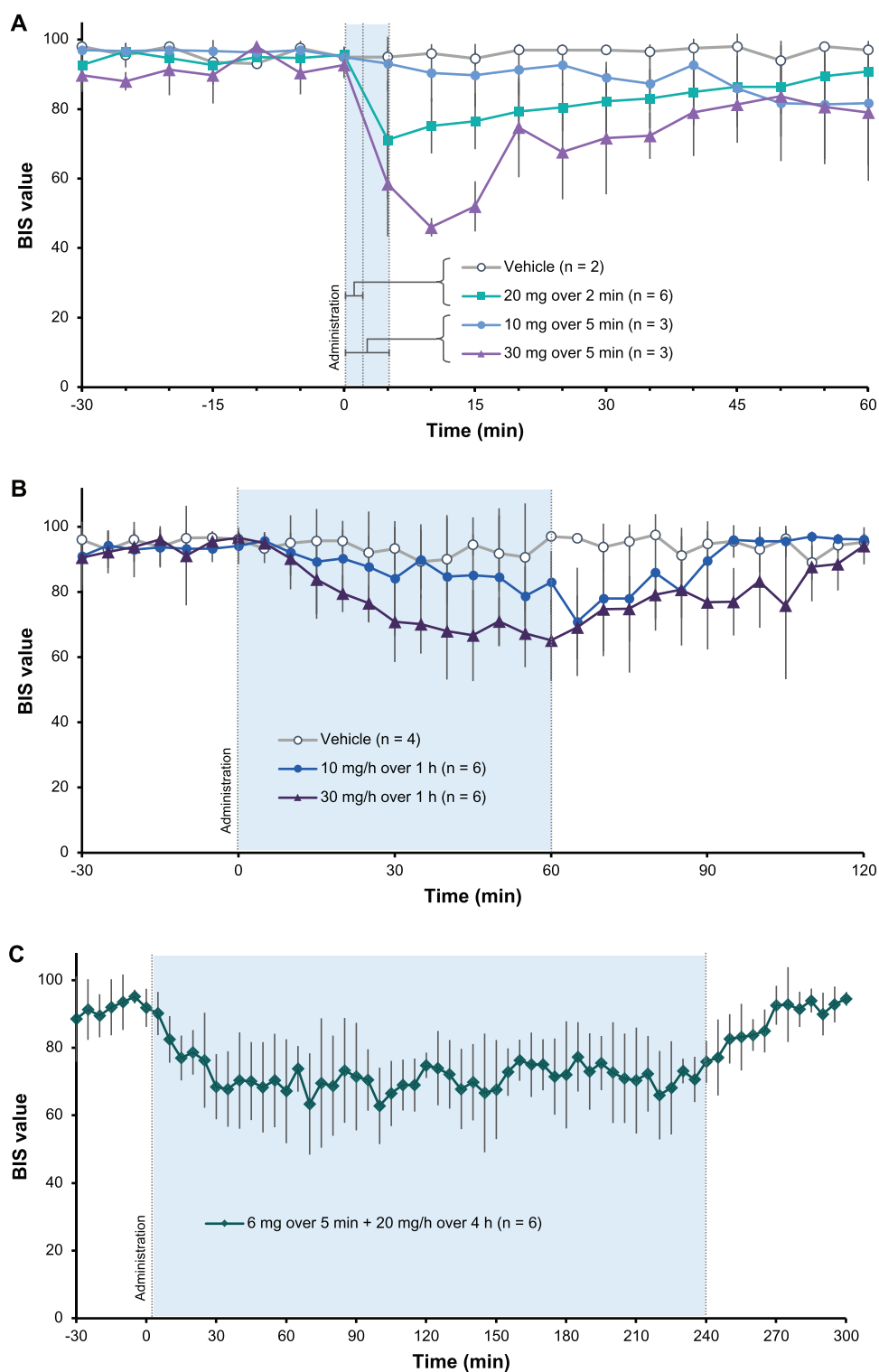


Figure 2. Effect of ganaxolone administration on BIS index: (A) bolus dosing of ganaxolone; (B) infusion dosing of ganaxolone; (C) bolus followed by an infusion of ganaxolone. Values are mean $\pm$ SD. Distance between dotted lines indicates dose duration. BIS, bispectral index; SD, standard deviation.

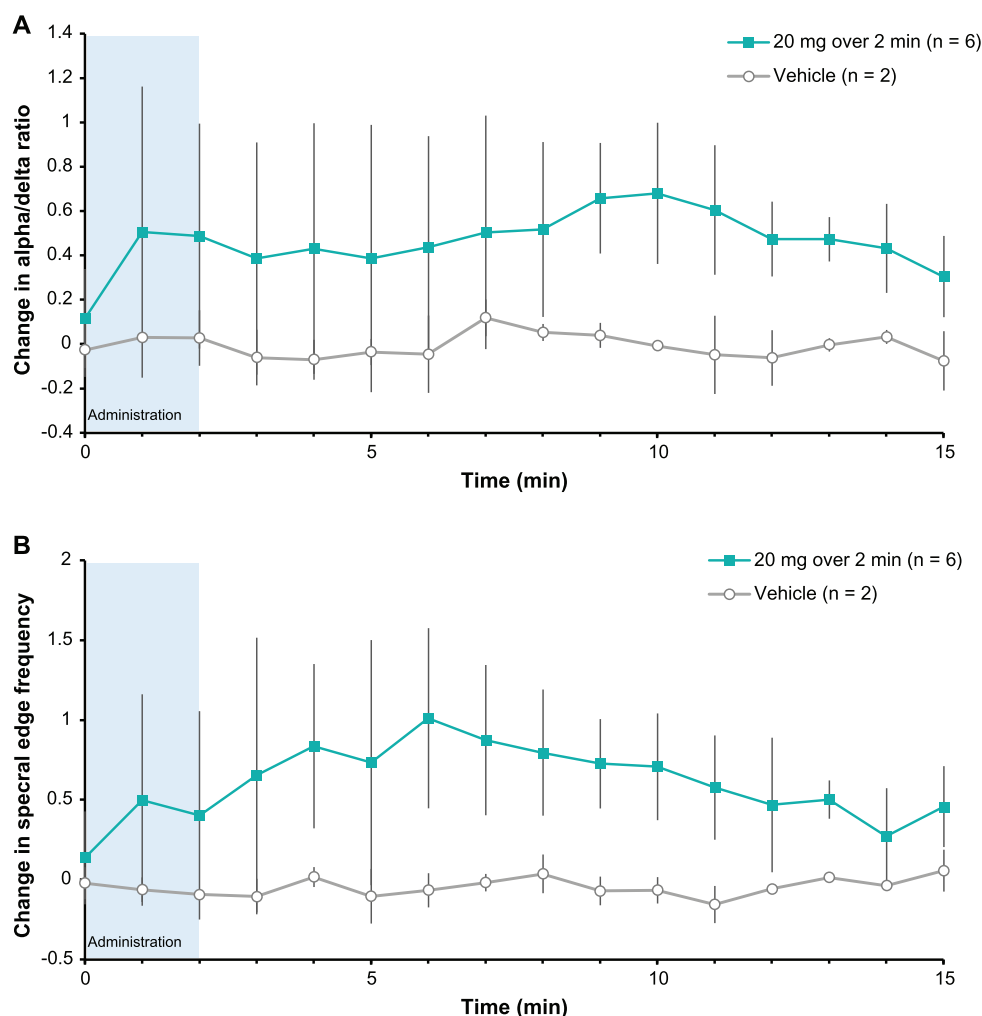


Figure 3. Effect of a bolus dose of ganaxolone 20 mg over 2 minutes on qEEG: (A) change in alpha/delta ratio; (B) change in spectral edge frequency. Values are mean $\pm$ SD. qEEG, quantitative electroencephalogram; SD, standard deviation.

single subject 5 minutes postadministration of a 30-mg IV bolus over 5 minutes with return to baseline arousal 15 minutes postadministration.

Modest changes in qEEG parameters were observed in this PD exploratory analysis with administration of IV ganaxolone. Overall, the changes seemed most evident in stage 1 with a bolus of 20 mg administered over 2 minutes. The mean alpha/delta ratio (Figure 3A) and spectral edge frequency (Figure 3B) appeared more informative than alpha power (data not shown). Lower bolus doses of ganaxolone (10 and 20 mg) resulted in an increase in faster frequencies (relative alpha power, alpha/delta ratio, and spectral edge frequency), whereas with a higher bolus dose (30 mg), delta frequencies also increased (relative alpha power and alpha/delta ratio decreased after initial increase).

Safety

All 36 subjects were evaluated for AEs in this study. No deaths, severe AEs, or serious AEs were reported. All AEs recorded in this study are shown in Table S2. Seven subjects (23.3%) and 1 subject (16.7%) reported at least 1 AE in stage 1 and stage 2, respectively. In stage 1, 6 of the 7 subjects reported AEs that were considered TEAEs. One subject in stage 2 reported 1 TEAE, following ganaxolone bolus followed by an infusion. TEAEs reported after receiving ganaxolone included headache (n = 1), elevated lipase (n = 1), and abdominal pain (n = 1). TEAEs reported after receiving vehicle infusion included constipation (n = 1), nausea (n = 1), decreased appetite (n = 1), hypertriglyceridemia (n = 1), and contact dermatitis (n = 1). No cardiovascular or respiratory AEs were observed for any subject. AEs

reported were primarily mild or moderate in severity and no TEAEs were considered definitely or probably related to study medication. A single report of mild headache was reported to be possibly related to study medication. No other clinically significant findings were reported for laboratory values, vital signs, electrocardiogram data, physical examinations, or C-SSRS.

Discussion

This study represents the first report of the PK/PD and safety of ganaxolone when administered to healthy volunteers by the IV route. Specifically, IV bolus administration of ganaxolone over 2 and 5 minutes resulted in rapid achievement of peak plasma concentrations, with a median $T_{\max}$ of 5 minutes, while addition of a continuous infusion allowed for sustained plasma concentrations. $C_{\max}$ was dose and administration-duration dependent, with the highest ganaxolone plasma concentration achieved after administration of 30 mg over 5 minutes, rapidly achieving plasma ganaxolone levels above 1000 ng/mL. This dose is within the expected therapeutic window for ganaxolone in the treatment of SE, and at which concentration it may exert direct agonist activity at GABA_A receptors. The onset of PD effects was also quickly observed on BIS monitoring when ganaxolone was administered as an IV bolus; this effect may be directly related to the high lipophilicity of ganaxolone and rapid attainment of brain concentrations (ie, a 3-fold increase in brain-to-plasma levels was previously reported).¹⁰ During ganaxolone continuous infusion over 4 hours, the PD response on BIS analysis was maintained for the duration of the infusion. The dose-related PK/PD findings from this study have informed the dosing of IV ganaxolone in clinical trials to achieve rapid and sustained control of SE.

Both $C_{\max}$ and AUC were found to be dose dependent after IV administration.¹¹ Increasing doses and duration of administration of IV ganaxolone were associated with dose- and exposure-related increases in $t_{1/2}$, AUC, and V_z . The terminal $t_{1/2}$ of IV ganaxolone ranged from approximately 2 to 10 hours over the dose range of 10 to 30 mg when administered as a bolus and up to 18.2 hours when administered as a 6-mg bolus followed by an infusion of 20 mg/h for 4 hours. The variability in $t_{1/2}$ may be attributed to a prolonged terminal elimination phase due to extravascular ganaxolone accumulation at higher doses and with longer exposures or could also be a result of incomplete characterization of the terminal elimination phase for the lower doses due to plasma concentrations rapidly falling below the lower limit of quantitation. Although the terminal elimination $t_{1/2}$ was reported to be up to 18.2 hours, the PD offset of effects of IV ganaxolone monitored with BIS was substantially shorter than what

the terminal $t_{1/2}$ would suggest. This is likely due to the high lipophilicity of ganaxolone with initial higher brain concentrations, followed by a rapid distribution phase out of the CNS and longer elimination phase after redistribution to body fat. Lastly, variable, context-sensitive PK parameters have been reported with prolonged infusion rates of other lipophilic molecules, despite consistency of PK parameters described with shorter infusion durations.²⁷⁻³⁰ Further evaluation of PK and PD parameters of varying dosing strategies with prolonged exposure in a larger cohort of critically ill subjects was conducted in a phase 2 trial³¹ and in the ongoing phase 3 RAISE study (NCT04391569).

Ganaxolone modulates both synaptic and extrasynaptic GABA_A receptors and its PD effects are thought to be related to GABA-mediated effects within the CNS. To assess the PD effects of IV ganaxolone, BIS and qEEG were utilized to characterize the effects on the EEG, while the MOAA/S scale was used to evaluate the clinician-observed level of alertness. A dose-dependent response on BIS monitoring was observed with IV ganaxolone. IV bolus of ganaxolone over 2 or 5 minutes was associated with a corresponding rapid decline in BIS values, while slower administration of IV ganaxolone as an infusion over 60 minutes resulted in more gradual BIS changes with sustained effects observed on BIS during a 4-hour continuous infusion. The time to maximal PD response on BIS monitoring was similar to $C_{\max}$ and $T_{\max}$ on PK evaluations, with the most rapid onset of effect noted with the 30-mg bolus administered over 5 minutes. The PD offset effects observed on BIS were shorter than terminal $t_{1/2}$, which may be due to rapid ganaxolone clearance out of the CNS. The PD effects of ganaxolone on BIS are consistent with the effects of other GABAergic medications.^{32,33} Rapid declines in BIS have been reported as PD markers of effect after initiation of propofol, barbiturates, and benzodiazepines.³²⁻³⁶

Consistent with the GABAergic mechanism of action of ganaxolone, sedation and sedation-related AEs were the most common AEs in previous clinical studies. The MOAA/S scale was used to assess the effects of variable dosing of ganaxolone on the clinically observed level of alertness. Across all dosing cohorts, most subjects were observed to have no to mild sedation throughout the entire monitoring period. Only 1 subject who received the 30-mg dose of ganaxolone as a bolus over 5 minutes was reported to have experienced deep sedation, with a MOAA/S score of 1. Although BIS monitoring is often used clinically as a tool to assess the depth of anesthesia,^{32,33} it has not been validated for all hypnotic drugs of differing mechanisms and sites of action.³⁷

There was a close temporal relationship observed between the 3 qEEG measures (relative alpha power,

alpha/delta ratio, and spectral edge frequency) and ganaxolone dose administered. Lower levels resulted in an increase in faster frequencies (higher relative alpha power, alpha/delta ratio, and spectral edge frequency); in contrast, the higher doses resulted in a rise in delta frequencies (relative alpha power and alpha/delta ratio decrease after initial increase). The PD effects of individual GABAergic agents on qEEG may vary depending on the concentration and localization of target receptor expression or distribution.^{38,39}

Of 36 subjects who participated in the current study, 8 reported at least one AE, which were mostly mild or moderate in severity. TEAEs were reported by 3 subjects assigned to receive ganaxolone and 4 subjects assigned to receive the vehicle control. All AEs resolved prior to the end of the study. No significant laboratory findings, vital signs, or C-SSRS assessment of suicidality findings were reported and there were no reported adverse effects on the cardiovascular or respiratory systems. Thus, AEs were minimal with all IV doses and administration times of ganaxolone administration.

Several neuroactive steroids have been evaluated for therapeutic use over the past several decades. A commercial formulation of alphaxolone and alphadolone was briefly available but withdrawn from the market in the 1970s due to toxicity associated with the product's excipient, cremophor, although it remains available for veterinary use.⁴⁰ Ganaxolone is formulated with sulfobutylether- β -cyclodextrin, a commonly used excipient with well-established safety in humans, to optimize solubility and stability.^{31,41} Ganaxolone received orphan drug designation for the treatment of various seizure disorders, including infantile spasms (1994), protocadherin 19 female epilepsy (2015), status epilepticus (2016), fragile X syndrome (2016), CDD (2017), tuberous sclerosis complex (2021), and Lennox–Gastaut syndrome (2023) to support the compound's ongoing clinical development. In this study of healthy volunteers, subjects maintained a baseline level of alertness with mean plasma concentrations up to 1240 ng/mL. These characteristics make ganaxolone an attractive option for continued clinical development in the treatment of seizure disorders.

The limitations of this analysis include the sample size in each treatment group, which, while sufficient for gaining a preliminary PK assessment of IV ganaxolone in healthy volunteers, provided insufficient statistical power for a careful analysis of the PD endpoints. Thus, further study with larger subject groups will be necessary to fully define the effects of ganaxolone on other qEEG parameters and degree of sedation. While the MOAA/S score was evaluated by investigators blinded to treatment during stage 1 in subjects administered IV ganaxolone or vehicle control over 2 minutes or over 60 minutes, MOAA/S scores were evaluated under open-

label administration during stage 1 in subjects who received 10 or 30 mg of IV ganaxolone over 5 minutes and in subjects enrolled in stage 2. As this study excluded subjects on baseline prescription or nonprescription medications or herbal supplements, the impact of concurrent therapies that may be coprescribed on PD and PK parameters was not evaluated and is an area for further study.

Conclusion

Ganaxolone administered as an IV bolus, an infusion over 60 minutes, or bolus with continuous infusion for 4 hours was generally safe and well tolerated in this phase 1 study. After administration of IV ganaxolone, a dose and administration-dependent response on PK and PD effects was observed. Ganaxolone was rapidly detected in plasma after administration over 2 or 5 minutes and achieved potentially direct GABA_A receptor agonistic activity and anticonvulsant plasma concentrations in a short period of time, especially with the 30-mg bolus over 5 minutes. More pronounced BIS and qEEG changes were observed following IV bolus administration of ganaxolone and indicated rapid brain penetration and clearance. BIS and qEEG changes also coincided with ganaxolone plasma concentrations, suggesting that ganaxolone was exerting GABA-mediated actions within the CNS. Overall, IV ganaxolone was generally well tolerated at the doses studied. The PK/PD findings from this study have been critical in guiding the clinical development of IV ganaxolone. Dosing in a completed phase 2 open-label study was based on the results from this phase 1 study, in which the observed median time to refractory SE cessation was 5 minutes after administering ganaxolone as an IV bolus followed by a continuous infusion of up to 5 days.³¹ A phase 3 trial in refractory SE with IV ganaxolone is ongoing (NCT04391569).

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Conflicts of Interest

M.G. is an employee of Marinus Pharmaceuticals, Inc. A.H. was a full-time employee at Duke Health during the conduct of the trial. He has served as a consultant for Jazz, BlackThorn, Eisai, Merck 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. M.B. Employee, Marinus Pharmaceuticals, Inc. S.R. None. D.M. None. J.G. Employee, argenx. H.V. Employee, Marinus Pharmaceuticals, Inc. E.R. Employee, Marinus Pharmaceuticals, Inc.

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