

Phase 1 Study to Determine the Pharmacokinetics, Pharmacodynamics, and Safety of IV Ganaxolone in Healthy Adults

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INTRODUCTION & BACKGROUND

Saralodine (2 α -hydroxy-3 β -methyl-5 α -pregnan-20-one; GNX) is a positive allosteric modulator of the GABA_A receptor. It is a 3 β -methylpregnane analog of the endogenous progesterone metabolite, allopregnanolone, which binds to and activates GABA_A receptors, potentiates their function, but without nuclear progesterone receptor activity, and thus eliminates the potential for steroidal effects with chronic dosing. GNX has been studied in a broad range of animal seizure models (Carter et al. 1997; Reddy and Rogawski 2012), and unlike other GABA_A receptor modulators, GNX does not show tolerance or dependence, nor does it show any evidence of abuse or abuse potential (Carter et al. 2012).

Figure 1: Ganaxalone is a Synthetic Analog of Allopregnanolone

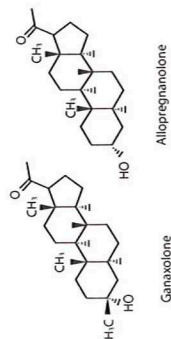
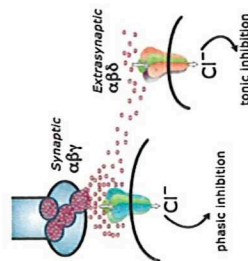
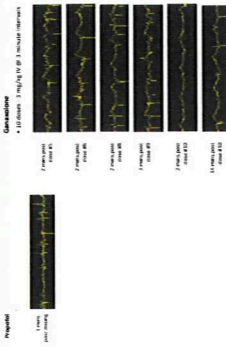


Figure 2. GNX is designed to modulate both synaptic and extrasynaptic GABA_A receptors to decrease activity of overexcited neurons



GNX is currently being developed in three different dose forms (intravenous [IV], capsule and liquid suspension) to maximize therapeutic reach to adult and pediatric patient populations in both acute and chronic care settings. Targeted indications for ganaxolone include status epilepticus (SE), genetic behavioral and seizure disorders, and postpartum depression.

Figure 3. GNX Induces Similar EEG Changes to Propofol in Healthy Rats



METHODS

This study was a single site study conducted at the Duke Clinical Research Unit, Duke University Medical Center, Durham, North Carolina.

Study Design

This was a sequential cohort evaluation of IV GNX in healthy participants. The study consists of 2 stages. The study investigated the safety, PK, and PD of IV GNX administered as an ascending bolus dose (Stage 1) and as a bolus dose followed by a continuous infusion (Stage 2).

Neurophysiologic PD variables in this study were qualitative and quantitative EEG and BIS, particularly the timing and severity of EEG slowing in relation to the administered as an ascending bolus dose (Figure 1) and a bolus dose showing a continuous infusion (Figure 2).

to the 2 stages of the study: a total of up to 5 cohorts (up to 4 in Stage 1 and 1 cohort in Stage 2) were enrolled:

Table 1. Stage, Cohort Design, and Sample Size

Study Phase	N (Placebo Control)	Dose
Stage 1 (bolus dose)		
Cohort A	6	Subtherapeutic dose based on GNX focal onset seizure study (FOS); over 5 minutes
Cohort B	6 (2)	Therapeutic dose based on GNX (FOS); over 2 min
Cohort C	6 (2)	Explore additional doses and infusion duration
Cohort D	6 (2)	Explore additional doses and infusion duration
Stage 2 (bolus dose + continuous infusion for up to 4 hours)		
Cohort A	6	PK, PD of bolus + continuous infusion

For all cohorts, safety, PK, and clinical PD parameters were measured at scheduled intervals and participants received continuous ECG, EEG, and BIS monitoring throughout the infusion. EEG and BIS monitoring continued for at least 30 minutes after the start of study drug administration or until they normalized following the infusion.

An interim PK analysis was conducted after each cohort and this PK data was used to predict the PK to inform dose and infusion rate in subsequent cohorts, as well as dosing in Stage 2.

RESULTS

Subject Disposition

Table 2. Subject Disposition

Category	All Subjects (N=36)
Randomized (ITT population)	36
Started study drug (safety population)	36 (100.0%)
Completed study	35 (97.2%)
Discontinued study	1 (2.7%)
Reason for discontinuation: Withdrawal by subject	1 (2.7%)

Table 3. Summary of Adverse Events

All Subjects (N=36)					
	Stage 1 Cohort A (N=6)	Stage 1 Cohort B (N=8)	Stage 1 Cohort C (N=8)	Stage 1 Cohort D (N=8)	Stage 2 Cohort A (N=6)
Category					
Subjects with ≥ 1 adverse events (AEs)	0	4 (50.0%)	3 (37.5%)	0	0
Subjects with ≥ 1 treatment-emergent AEs (TEAEs) [1]	0	3 (37.5%)	3 (37.5%)	0	0
Subjects with ≥ 1 study drug related AEs	0	1 (12.5%)	0	0	0
Subjects with ≥ 1 serious adverse events (SAEs)	0	0	0	0	0
Subjects who died	0	0	0	0	0

Table 5. The Modified Observer's Assessment of Alertness/Sedation

Score	Responsiveness
5	Responds readily to name spoken in normal tone (alert)
4	Lethargic response to name spoken in normal tone
3	Responds only after name is called loudly and/or repeatedly
2	Responds only after mild prodding or shaking
1	Does not respond to mild prodding or shaking

Figure 4. BIS and MOAA Score of Subject in Stage 2 Cohort A

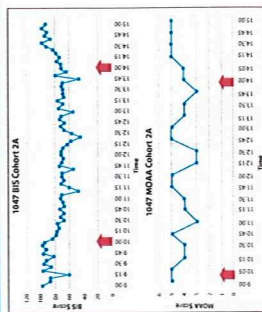


Figure 5. EEG and BIS Changes Consistent with Sedative/Anesthetic Effects

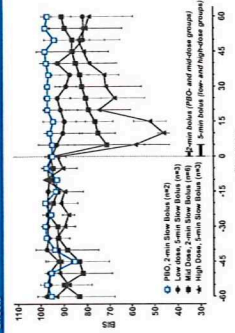
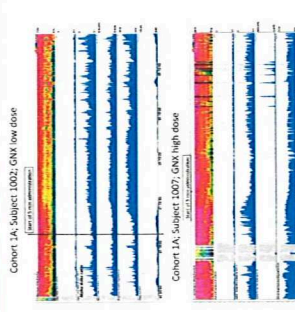


Figure 6. EEG-Alpha Delta Ratio Changes in Low and High Dose GNX



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MARINUS
PHARMACEUTICALS

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INTRODUCTION & BACKGROUND

Ganaxolone (3 α -hydroxy-3 β -methyl-5 α -pregnan-20-one; GNX) is a positive allosteric modulator of the GABA_A receptor. It is a 3 β -methylated synthetic analog of the endogenous progesterone metabolite, Allopregnanolone, but without nuclear progesterone receptor activity, and thus eliminates the potential for steroid effects with chronic dosing. GNX has been studied in a broad range of animal seizure models (Carter et al. 1997; Reddy and Rogawski 2012), and unlike other GABA_A receptor modulators, GNX does not show tolerance to anticonvulsant activity.

Figure 1: Ganaxolone is a Synthetic Analog of Allopregnanolone

Ganaxolone and Allopregnanolone Structures

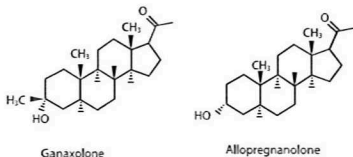


Figure 2: GNX is Designed to Modulate Both Synaptic and Extrasynaptic GABA_A Receptors to Decrease Activity of Over-Excited Neurons

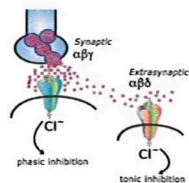
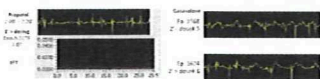
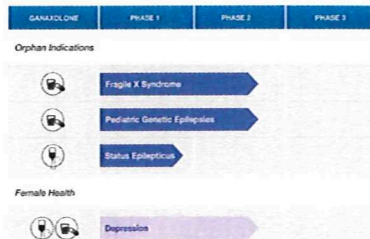


Figure 3: GNX Induces Similar EEG Changes to Propofol in Healthy Rats



- GNX and propofol administered in sedating dose levels
- GNX animals still breathing spontaneously after dose #10
- PK obtained after dose #10

• Ganaxolone
• 10 mg/kg @ 15 min
• 1 mg/kg IV dose



GNX is currently being developed for orphan indications including status epilepticus (SE), genetic behavior and seizure disorders, as well as depression in females.

Three different dose forms (intravenous [IV], capsule and liquid suspension) are being developed for ganaxolone to maximize therapeutic reach to adult and pediatric patient populations in both acute and chronic care settings. The recent addition of the IV formulation is intended for patients in SE. The availability of both IV and oral formulation allow for continuity of care for patients recovering from SE and when transitioning from hospital to outpatient settings.

OBJECTIVES

Primary

- To evaluate the safety and pharmacokinetics (PK) of IV GNX administered as a bolus dose and continuous infusion in healthy participants.

Secondary

- To evaluate the pharmacodynamics (PD) effect of IV GNX on electroencephalogram (EEG) parameters
- To evaluate the PD effect of IV GNX on Bispectral Index (BIS) parameters
- To evaluate the effect of IV GNX on clinical sedation scores
- To evaluate the PD effect of IV GNX on ventilation

MATERIALS

- Investigational Medicinal Product: Intravenous GNX Solution 1 mg/ml in Captisol® FID5404 diluted in saline
- Active Control: Intravenous Captisol® FID5404 diluted in saline

METHODS

This study is a single site study conducted at the Duke Clinical Research Unit, Duke University Medical Center, Durham, North Carolina.

Study Design

This was a sequential cohort evaluation of IV GNX in healthy participants. The study consists of 2 Stages. The study investigated the safety, PK, and PD of IV GNX administered as an ascending bolus dose (Stage 1) and as a bolus dose followed by a continuous infusion (Stage 2).

Neurophysiologic PD variables in this study are qualitative and quantitative EEG and BIS, particularly the timing and severity of EEG slowing in relation to the doses administered. The study also assessed the safety profile of IV GNX on electrocardiogram (ECG) parameters, vital signs, physical examination findings, and adverse events. Given the potential for sedative effects of IV GNX, an anesthesiologist was present for all dosing to maintain participant safety.

In the 2 Stages of the study, a total of up to 5 cohorts (up to 4 in Stage 1 and 1 cohort in Stage 2) was enrolled.

Table 1. Stage, Cohort Design, and Sample Size

Study Phase	N (PBO Control)	Dose
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Cohort A	6	PK, PD of bolus + continuous infusion

For all cohorts, safety, PK, and clinical PD parameters were measured at scheduled intervals and participants received continuous ECG, EEG, and BIS monitoring throughout the infusion. EEG and BIS monitoring continued for at least 30 minutes after the start of study drug administration or until they normalized following the infusion.

An interim PK analysis was conducted after each cohort and this PK data will be used to predict the PK to inform dose and infusion rate in subsequent cohorts, as well as dosing in Stage 2.

Study Population

The subject population was typical for a Phase 1 study. They were healthy male and females between 18 and 50 yrs. old with no concomitant medications and no somatic illnesses or laboratory, vital signs, EEG, ECG abnormalities.

RESULTS

Subject Disposition

Category	All Subjects (N=36)
Randomized (ITT population)	36
Started study drug (safety population)	36 (100.0%)
Completed study	35 (97.2%)
Discontinued study	1 (2.7%)
Reason for discontinuation:	
Withdrawal by Subject	1 (2.7%)

Safety

Table 3. Summary of Adverse Events

All Subjects (N=36)					
	Stage 1 Cohort A (N=6)	Stage 1 Cohort B (N=6)	Stage 1 Cohort C (N=6)	Stage 1 Cohort D (N=6)	Stage 2 Cohort A (N=6)
Category					
Subjects with ≥ 1 adverse events (AEs)	0	4 (50.0%)	3 (37.5%)	0	0
Subjects with ≥ 1 treatment-emergent AEs (TEAEs)[1]	0	3 (37.5%)	3 (37.5%)	0	0
Subjects with ≥ 1 study drug related AEs	0	1 (12.5%)	0	0	0
Subjects with ≥ 1 serious adverse events (SAEs)	0	0	0	0	0
Subjects who died	0	0	0	0	0

Table 4. Summary of Blinded Treatment-Emergent AEs by System, Organ Class and Preferred Term

System Organ Class Preferred Term	All Subjects (N=36)
Subjects with at least one TEAE	6 (16.6%)
Gastrointestinal disorders	2 (5.5%)
Constipation	1 (2.8%)
Nausea	1 (2.8%)
Investigations	1 (2.8%)
Lipase increased	1 (2.8%)
Metabolism and nutrition disorders	1 (2.8%)
Hypertiglyceridaemia	1 (2.8%)
Nervous system disorders	1 (2.8%)
Headache	1 (2.8%)
Skin and subcutaneous tissue disorders	1 (2.8%)
Rash maculo-papular	1 (2.8%)

- TEAEs were all mild in severity and all resolved without intervention
- Only headache was considered possibly related to study drug
- No subject discontinued due to AE and no SAEs were reported
- No changes in physical exams, vital signs, ECGs, and laboratory values that would prevent reaching potentially anti-convulsant target plasma concentrations in a short period of time (minutes)

Pharmacodynamics

Changes in BIS and Modified Observer's Assessment of Alertness/Sedation (MOAA) score were evident within 5-15 minutes of infusion start and the majority returned to baseline within 30 minutes post-dose.

Table 5. The Modified Observer's Assessment of Alertness/Sedation Score

Responsiveness	Score
Responds readily to name spoken in normal tone (alert)	5
Lethargic response to name spoken in normal tone	4
Responds only after name is called loudly and/or repeatedly	3
Responds only after mild prodding or shaking	2
Does not respond to mild prodding or shaking	1
Does not respond to deep stimulus	0