Intravenous Ganaxolone for the Treatment of Refractory Status Epilepticus: Results From an Open-Label, Dose-Finding, Phase 2 Study

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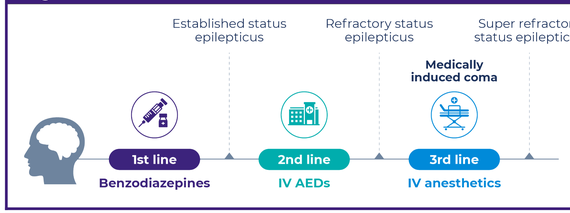
Introduction

- Status epilepticus (SE) is a neurological emergency and one of the most severe seizure disorders
  - Defined as continuous seizures lasting 5 minutes for convulsive seizures or 10 minutes for nonconvulsive seizures
  - Prolonged seizure activity can result in permanent neuronal damage and contribute to the high morbidity and mortality rates associated with SE
- Treatment with 3rd-line intravenous (IV) anesthetics (**Figure 1**) has been reported to lead to increased length of hospital admission and risk of infections, new disability, and death[1-3]
- Goals for new refractory status epilepticus (RSE) treatments:
  - Rapid cessation of SE
  - Avoid progression towards escalation of treatment with 3rd-line IV anesthetics

Figure 1. Current Status Epilepticus Standard of Care Treatment Progression and Clinical Definitions



AED, existing antiepileptic drugs; IV, intravenous.

Potential role for neuroactive steroids in RSE

- Neuroactive steroids (NAS) that act as positive γ-aminobutyric acid type A ($GABA_A$) receptor modulators exhibit broad-spectrum antiseizure effects
- Ganaxolone (GNX), a neuroactive steroid, is a synthetic analogue of endogenous allopregnanolone and a potent positive allosteric modulator of $GABA_A$ receptors
- GNX acts on both synaptic and extrasynaptic $GABA_A$ receptors
  - Synaptic $GABA_A$ receptors are known to downregulate during prolonged seizures, often leading to pharmacoresistance of existing GABAergic drugs (eg, benzodiazepines)[4]
- GNX exhibits rapid brain penetration, leading to early onset pharmacodynamic effects[5]

Methods

- Phase 2, open-label, dose-finding study of adjunctive IV GNX in RSE patients (NCT03350035)
- Evaluate safety, tolerability, efficacy, and pharmacokinetics of IV GNX in RSE patients

Key eligibility criteria

- Diagnosed with convulsive or nonconvulsive SE
- Failed at least one 2nd-line antiseizure medication but not progressed to 3rd-line IV anesthetics

Dosing

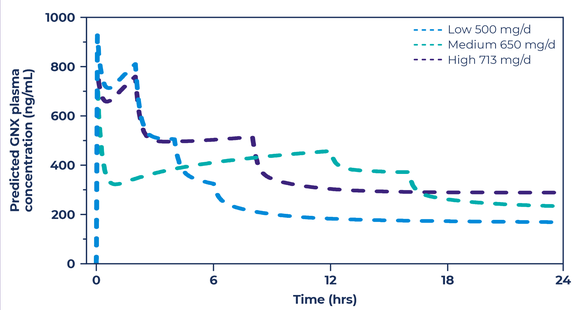
- Dosing includes bolus loading dose, 2- to 4-day maintenance infusion, 18-hour taper (**Table 1**, **Figure 2**)

Table 1. Dosing Cohorts

Cohort	Dose of GNX (mg/d)	≥500 ng/mL target GNX dose (hrs)
Low (n = 5)	500	4
Medium (n = 4)	650	0
High (n = 8)	713	8

GNX, ganaxolone.

Figure 2. Predicted GNX Plasma Concentrations



GNX, ganaxolone.

Clinical endpoints

- ***Primary:*** number of patients who do not require escalation of treatment with IV anesthetic within the first 24 hours after ganaxolone initiation
- ***Secondary:*** additional efficacy, safety, and tolerability

Results

Baseline characteristics

17 patients enrolled
- 8 males, 9 females
- Mean age: 57 years old (range, 23-88)

Types of SE
- 5 (29%) convulsive status epilepticus (CSE); 11 (65%) non-convulsive status epilepticus (NCSE); 1 (6%) CSE → NCSE

History of epilepsy
- 7 (41%) yes; 10 (59%) no

Mean number of failed IV existing antiepileptic drugs (AEDs) (including benzodiazepines)
- 2.9 (range, 2-5)

Mean number of failed 2nd-line IV AEDs
- 2.1 (range, 1-4), all failed levetiracetam or lacosamide
- Immediate AED administered on average 4 hours prior to GNX initiation
- **All prior AEDs were administered within recommended dosing guidelines**

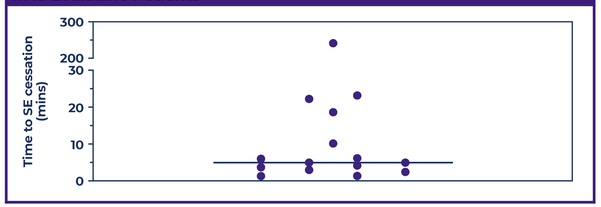
- All 17 patients avoided 3rd-line IV anesthetics at 24 hours following GNX initiation (primary endpoint) (**Table 2**)
- SE cessation occurred within 5 minutes (median) (**Figure 3**)
- High-dose patients did not require any escalation of SE treatment through 24 hours after GNX discontinuation and did not experience any SE relapse through 4 weeks of follow-up (**Table 2**)

Table 2. Summary Efficacy Results

	Cohort		
	High (713 mg/d) (n = 8)	Medium (650 mg/d) (n = 4)	Low (500 mg/d) (n = 5)
No escalation to IV anesthetics within 24 hrs from infusion initiation (primary endpoint)	100% (8 of 8)	100% (4 of 4)	100% (5 of 5)
Status-free through 24 hrs from infusion initiation (investigator determination)	88% (7 of 8)[a]	100% (4 of 4)	100% (5 of 5)
No escalation to additional IV AEDs or IV anesthetics for status relapse at any time through 24 hrs after GNX discontinuation	100% (8 of 8)	75% (3 of 4)[b]	60% (3 of 5)[d]
No SE relapse at anytime during the 4-wk follow-up period	100% (6 of 6) (1 ET, 1 died)	67% (2 of 3)[c] (1 ET)	50% (1 of 2) (1 died)

AED, existing antiepileptic drug; ET, early termination; GNX, ganaxolone; IV, intravenous; SE, status epilepticus.
[a]One patient had status relapse on day 1, which resolved during the ganaxolone infusion without treatment escalation.
[b]One patient escalated to additional IV AED on day 1 for seizure relapse.
[c]One patient experienced status relapse on day 2 (during taper).
[d]Two patients escalated to 3rd-line therapy for seizure relapse on day 3.

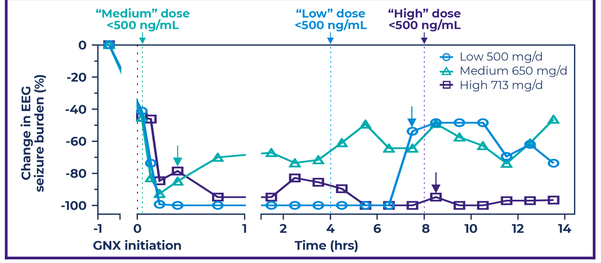
Figure 3. Investigator-Determined Time of Status Epilepticus Cessation in 15 Evaluable Patients



SE, status epilepticus.

- Seizure burden represents the time in electrographic seizures per total observation time
- All patients experienced a rapid electroencephalogram seizure burden reduction (>80% within 15 minutes) (**Figure 4**)
- Only high doses provided sustained reduction (>80%) throughout entire analysis window
  - Plasma GNX levels ≥500 ng/mL provide robust seizure control
- IV GNX showed an acceptable safety profile in patients with RSE (**Figure 5**)

Figure 4. Percentage Change in EEG Seizure Burden in Each Dose Cohort



EEG seizure burden was retrospectively determined by a central EEG reader blinded to GNX dose. Change in seizure burden = seizure time/total time period. Downward arrows indicate time points of seizure recurrence when GNX dosing targets were <500 ng/mL.
EEG, electroencephalogram; GNX, ganaxolone.

Figure 5. Safety Summary

10 SAEs in 6 patients (also included in AEs)

2 related in 2 patients
- 2 severe sedation

8 not related in 4 patients
- 1 death due to withdrawal of life support
  - 1 respiratory depression
- 1 bowel perforation (fatal)
- 1 sepsis (fatal)
- 1 fall
  - 1 loss of consciousness
  - 1 pneumothorax
  - 1 multiple fracture

50 AEs in 16 subjects

13 related in 7 subjects
- 6 mild (2 hypotension, 2 somnolence, 1 urinary retention, 1 hypercarbia)
- 5 moderate (4 somnolence, 1 hypercarbia)
- 2 severe (2 sedation)

37 not related in 12 subjects
- 20 mild
- 8 moderate (2 pain, 2 pneumonia, 2 dysphagia, 1 delirium, 1 hypertension)
- 9 severe (respiratory depression, death due to withdrawal of support, sepsis, embolic stroke, perforated bowel, fall, loss of consciousness, multiple fractures, pneumothorax)

Intubation
- Nine patients were not intubated upon enrollment. Of these, 6 remained intubation-free during the entire ganaxolone treatment period

AE, adverse event; SAE, serious adverse event.

Conclusions

- **No patients progressed to IV anesthetics during the first 24 hours (100% achievement of primary endpoint)**
- **IV GNX achieved SE cessation at 5 minutes (n = 15 evaluable patients), and ≈80% seizure burden reduction was achieved within 15 minutes**
- **High-dose group achieved >80% seizure burden reduction for the entire analysis time (24 hours), and no patients in this group experienced SE relapse during the 4-week follow-up period**
- **IV GNX showed an acceptable safety profile in patients with RSE**

References

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