Intravenous Ganaxolone Achieves Rapid and Dose-Dependent Sustained Improvement in EEG Seizure Burden in Patients with Refractory Status Epilepticus

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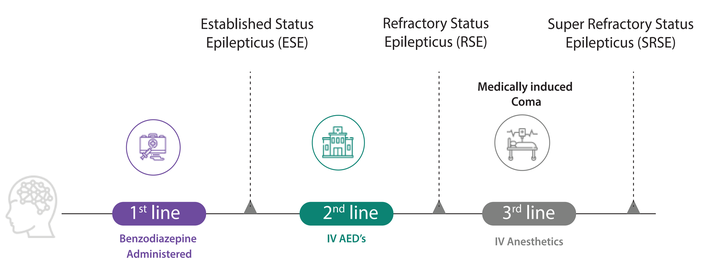
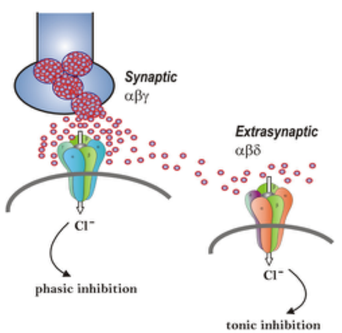
GOALS OF A NEW THERAPY FOR THE TREATMENT OF SE



Goals of a new treatment for SE

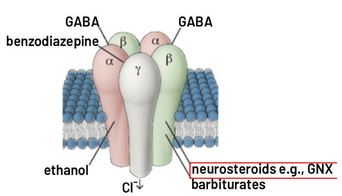
- Prevent patient progression towards escalation of treatment (IV anesthetics)
- Rapid cessation of SE
- Maintenance of seizure control over study period

GANAXOLONE (GNX) MECHANISM OF ACTION



- GNX acts on both synaptic and extrasynaptic $GABA_A$-receptors to maximize inhibitory signaling as well as maintain activity when synaptic receptors are down-regulated.

- GNX is a synthetic analog of endogenous allopregnanolone and a potent positive allosteric modulator of $GABA_A$-receptors.
- GNX targets unique binding sites on $GABA_A$-receptors that are not susceptible to tolerance build up (e.g., benzodiazepines).



PHASE 2 TRIAL OF IV GANAXOLONE IN RSE

Study Design

Objectives: Evaluate safety, tolerability, efficacy, and pharmacokinetics of IV Ganaxolone in RSE patients

RSE Patients

Diagnosis of convulsive or non-convulsive SE
Failed at least one 2nd line IV AED but not progressed to 3rd line IV anesthetics

Screening →

Treatment Period		
Loading Dose	Maintenance	Taper
Bolus plus continuous infusion	2-4 day infusion	18 hour taper

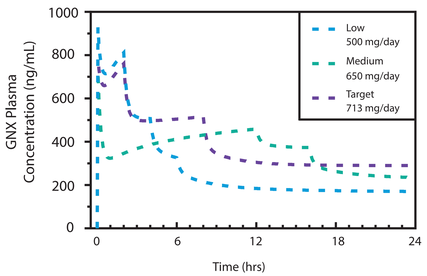
Cohort	Dose of GNX/day	N
Low	500mg/day	5
Medium	650mg/day	4
Target	713mg/day	8

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
EEG assessments: EEG's were retrospectively evaluated by an independent, central reading group. Seizure burden (defined below) was analyzed pre and post-GNX treatment.

$$\text{Seizure burden} = \frac{\text{Cumulative time with electrographic seizures within epoch}}{\text{Total epoch duration}}$$

Modeled PK Curves for Dosing Groups
Target Dose Achieves ≥=500 ng/mL for ~8 hours



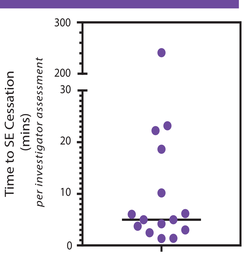
Baseline Characteristics

Gender	8 males, 9 females Age (mean) 56.9 (range: 23-88)
Varied reasons for RSE	brain tumors, vascular (stroke, hemorrhage), metabolic, autoimmune, alcohol withdrawal, illicit drug overdose
Type of SE	5 (29%) convulsive SE 11 (65%) non-convulsive, 1 (6%) convulsive SE progressing to non-convulsive SE
History of epilepsy	7 (41%) had history of epilepsy 10 (59%) no history of epilepsy
Mean # of failed IV AEDs including benzodiazepines	2.9 (range: 2-5)
Mean # of failed 2nd line IV AEDs	2.1 (range: 1-4) All 17 patients (100%) failed levetiracetam or lacosamide before receiving GNX

IV GNX Efficacy

Cohort	No escalation to IV anesthetics within 24 hrs from infusion initiation **(Primary Endpoint)**	Status-free through 24 hrs from infusion initiation	No escalation to additional IV AEDs or IV anesthetics for status relapse at any time through 24hrs after GNX discontinuation	SE Relapse at anytime during the 4-wk follow up period
Target (713 mg/day); (n=8)	**100%** (8 of 8)	**88%** (7 of 8)	**100%** (8 of 8)	**0%** (0 of 8) *1ET, 1 died*
Medium (650 mg/day); (n=4)	**100%** (4 of 4)	**100%** (4 of 4)	**75%** (3 of 4)*	**33%** (1 of 3) *1 ET*
Low (500 mg/day); (n=5)	**100%** (5 of 5)	**100%** (5 of 5)	**60%** (3 of 5)*	**50%** (1 of 2) *1 died*

Target dose: One patient had status relapse @ Day 1, which resolved during the ganaxolone infusion without treatment escalation
Medium dose: One patient escalated to additional IV AED @ Day 1 for seizure relapse. **One patient experienced status relapse @ Day 2 (during taper).
Low Dose: Two patients escalated to 3rd line therapy for seizure relapse @ Day3

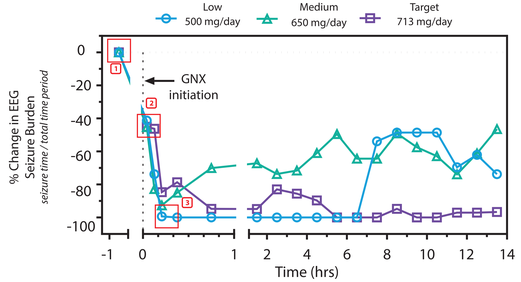


SE cessation occurred rapidly in all dose groups at a median of 5 minutes

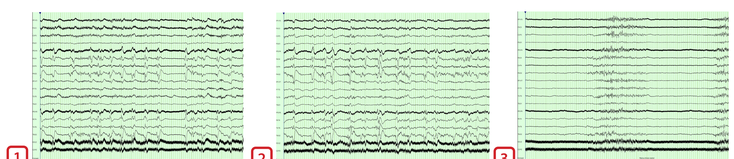
EEG Seizure Burden

n=15 evaluable patients
Baseline seizure burden (average seizure burden 60 minutes prior to GNX administration):

- Low cohort: 0.71
- Medium cohort: 0.97
- Target cohort: 0.51



Percent change in EEG seizure burden in RSE patients administered IV GNX in various dosing cohorts. Percent seizure burden change is calculated based on each patients seizure burden in the 60 minutes prior to GNX administration.



Representative EEG's from a patient at timepoint 1, 2, and 3 (above) correlating to high, medium, and low seizure burden, respectively

CONCLUSIONS

	No patients progressed to IV anesthetics during first 24 hours Median time to SE cessation = 5 minutes (3.4-14.4 minutes 25th-75th percentile) (n=15 evaluable) Durable response throughout study period in target dose cohort including retrospective EEG seizure burden analysis
	Patients failed mean of 2.1 second line IV AEDs Highly heterogeneous underlying cause of status
	Target patient population and dose identified for Ph. 3 study
	Ganaxolone shows an acceptable safety profile in patients with RSE
	Planning EOP2 meeting in 01 2020