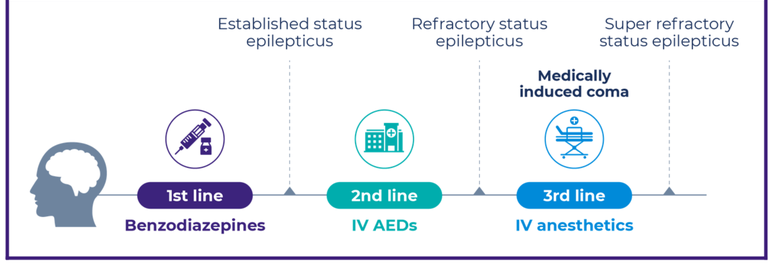
# A Double-Blind, Randomized, Placebo-controlled Study to Evaluate the Efficacy and Safety of Intravenous Ganaxolone in Status Epilepticus (RAISE)

## Introduction

### Refractory Status Epilepticus

- Status epilepticus (SE) is a neurological emergency and one of the most severe seizure disorders
- In SE, persistent or recurring seizures result from either failure of mechanisms that terminate seizures or initiation of mechanisms that abnormally prolong seizures[1,2]
- SE may become refractory to treatment. Patients who fail to respond to 1st line benzodiazepines (BZD) and 2nd line antiepileptic drugs (AED) may progress to intravenous anesthetic 3rd line agents to abort the status[3] (Figure 1)
- Therapeutic coma has been associated with poorer outcomes after SE, higher infection rates and longer hospitalizations[4,5]

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



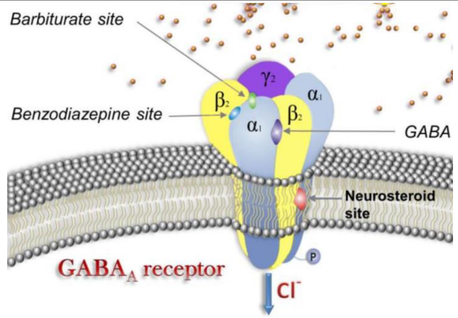

AED, existing antiepileptic drugs; IV, intravenous.

- Ongoing seizures rapidly modify neuronal activity and synaptic function[6].
  - Synaptic $GABA_A$ receptors ($GABA_AR$) become functionally inactive through receptor internalization[7]
- Reduced inhibitory neurotransmission mediated by $GABA_AR$ is proposed to be a mechanism of the self-sustaining and progressive nature of SE
- Extrasynaptic $GABA_AR$ remain functional during ongoing seizures; therapies that target these receptors may offer benefit over existing treatments

### Ganaxolone in Refractory Status Epilepticus

- Ganaxolone (GNX) is a synthetic analog of endogenous allopregnanolone and a potent positive allosteric modulator (PAM) of $GABA_AR$
  - GNX binds to $GABA_AR$ at a site distinct from that of the BZD or barbiturate sites (Figure 2)
- GNX binds to both synaptic and extrasynaptic $GABA_AR$ and has shown efficacy in terminating resistant seizures in an animal model[8] and a phase 2 open-label dose escalation clinical study[9]
- The Phase 2 study evaluated intravenous (IV) GNX in 17 patients with RSE added to standard of care
  - IV GNX achieved rapid (median 5 minutes) seizure cessation with durability of seizure control
  - No patients progressed to IV anesthetics during the first 24 hours of treatment
  - IV GNX showed an acceptable safety profile in patients with RSE
  - Safety profile was consistent with GNX mechanism of action
- These data supported further development of IV GNX for RSE in a Phase 3 study

**Figure 2. $GABA_A$ Receptor Structure**




Schematic of $GABA_A$ receptor. Figure adapted from *Psychopharmacology*, from "Neurosteroid interactions with synaptic and extrasynaptic GABA(A) receptors: regulation of subunit plasticity, phasic and tonic inhibition, and neuronal network excitability." Carver CM, Reddy DS; 230(2);2013

## RAISE Phase 3 Study

### Objectives

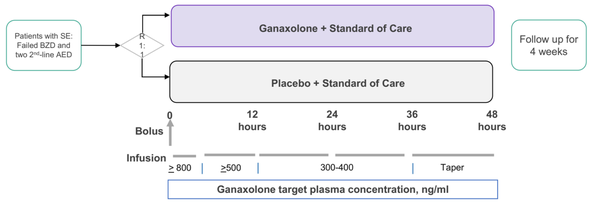
- To establish the efficacy and safety of GNX in the treatment of refractory SE, by initiating IP after failure of a benzodiazepine and 2 second-line AEDs prior to initiation of IV anesthesia

### Methods

Phase 3 Study Design (Figure 3)

- The RAISE study (NCT04391569) is a double-blind, randomized, placebo-controlled study to evaluate the efficacy and safety of IV GNX in SE
- Investigational product (GNX or placebo) will be added to standard of care before IV anesthetic during the treatment of SE
- This phase 3 study is currently active and looking to enroll patients at participating sites (visit https://clinicaltrials.gov/ for additional information)

**Figure 3. RAISE Study Design**




### Primary outcome measures

- **SE Cessation:** Proportion of participants with status epilepticus cessation within 30 minutes of IP initiation without medications for the acute treatment of status epilepticus. SE cessation is determined by clinical and EEG findings
- **Progression to IV anesthesia:** Proportion of participants with no progression to IV anesthesia for 36 hours following IP initiation

### Key Secondary Endpoints*

- No progression to IV anesthesia for 72 hours following IP initiation
- Time to SE cessation following IP initiation
- Proportion of patients who develop Super Refractory SE (SRSE) through the final study follow-up visit

### Key Safety Assessments*

- Adverse events
- Laboratory safety parameters
- Vital signs
- ECG

* additional assessments will be included

### Subjects

**Key inclusion criteria:***

- Male or female subjects age ≥12 who have clinical and/or electrographic SE# and failed first line benzodiazepine AND at least 2 IV AEDs at therapeutic concentrations

**#SE criteria:**

- Documented clinical seizures (convulsive SE) greater than 5 minutes in duration and without clear trend for improvement within 30 minutes prior to IP initiation
  or
- EEG consistent with modified Salzburg criteria without clear trend toward improvement and for 30 minutes prior to IP

**Key exclusion criteria*:**

- Life expectancy of less than 24 hours
- Anoxic brain injury for an uncontrolled metabolic condition as primary cause of SE
- Uncontrolled metabolic condition
- Treatment of current SE episode with IV anesthetics
- Patient who, in the investigator's judgment, would be unlikely to require IV anesthetics to treat SE or if the treatment would be medically contraindicated


### Summary

- The RAISE study (NCT04391569) is a phase 3, double-blind, randomized, placebo-controlled study to evaluate the efficacy and safety of IV GNX in SE after failure of first-line benzodiazepines and two second-line IV antiepileptic drugs
- The study is currently active and open to enroll patients at participating study sites
- For more information on the RAISE study, please contact SE-Study@marinuspharma.com



**References**

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