Neurosteroids in the Management of Status Epilepticus

Maciej Gasior, MD, PhD
Vice President, Clinical Development
Marinus Pharmaceuticals, Inc.

Intravenous Ganaxolone is an investigational product not yet approved by the United States Food and Drug Administration (FDA). Its safety and efficacy have not been established.

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Disclosures

- I am an employee of Marinus Pharmaceuticals. Views and opinions expressed are my own and do not necessarily represent the opinions of my employer

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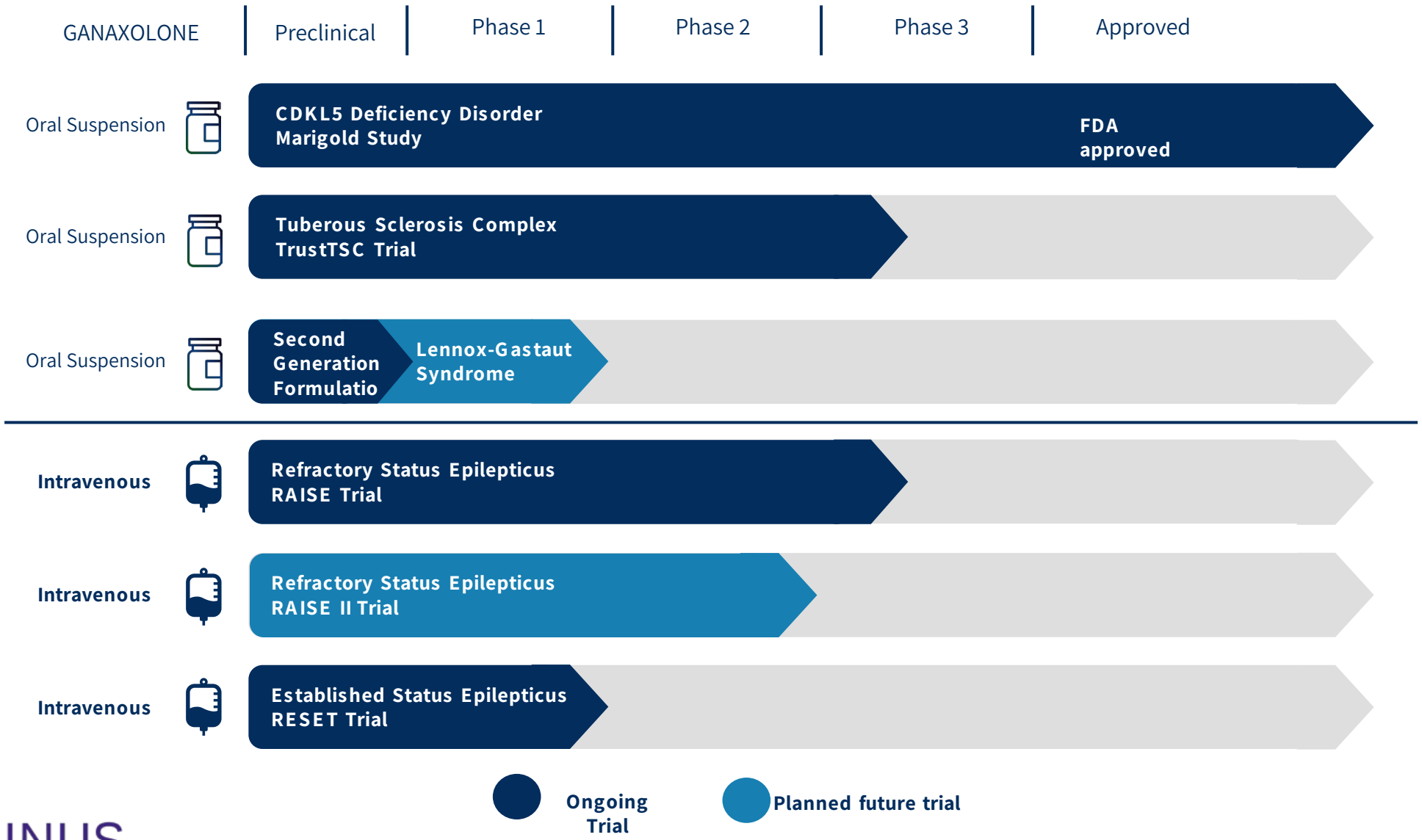
Marinus Pharmaceuticals, Inc. Pipeline



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Status Epilepticus is a Dynamic Condition Involving Multiple Biological Proces

ILAE Status Epilepticus Definition[1]

Condition resulting from either the failure of the mechanisms responsible for seizure termination or from the initiation of mechanisms which lead to

- abnormally prolonged seizures (after time point t_1)
- can have long-term consequences (after time point t_2)

Multiple distinct pathophysiological processes potentially involved in SE, not necessarily mutually exclusive[2-5]

Pro-convulsant processes may be co-occurring during the development of SE[6,7]

The longer a seizure continues, the less likely it is to stop it[8-10]
→ Seizure activity itself can exhaust seizure inhibitory mechanisms

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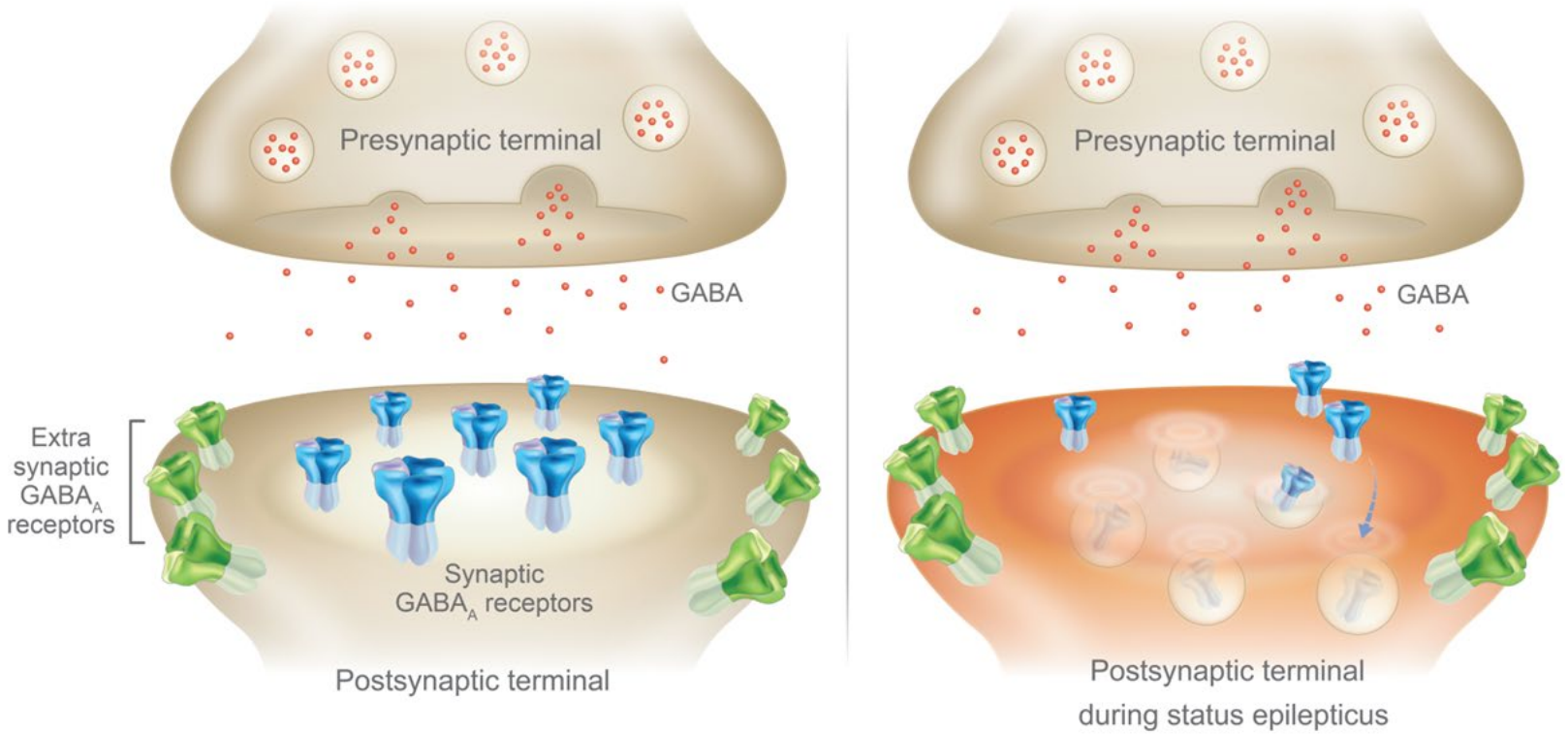
1. Trinka E et al. *Epilepsia*. 2015;56:1515-1523; 2. Goodkin HP et al, J. Neurosci. 28 (2008) 2527–2538; 3. Naylor DE et al. J. Neurosci. 25 (2005) 7724–7733; 4. Naylor DE et al. Neurobiol. Dis. 54 (2013) 225–238; 5. Rajasekaran K et al. Ann. Neurol. 72 (2012) 91–102; 6. Janigro et al. Epilepsia 54 (Suppl. 6) (2013) 30–32; 7.Liu H et al. Proc. Natl. Acad. Sci. U. S. A. 96 (1999) 5286–5291; 8. Shinnar S, et al. Ann. Neurol. 49 (2001) 659–664; 9. DeLorenzo RJ et al. Epilepsia 40 (1999) 164–169.; 10. Mazarati AM et al. Brain Res. 814 (1998) 179–185.

Attenuation of $GABA_A$ Receptor Mediatednhibition in SE

Synaptic $GABA_A$ receptors have been found to **internalize during ongoing SE** whereas extrasynaptic $GABA_A$ receptors mainly remain on the surface[1,2]



Loss of benzodiazepines potency as SE continues is partly due to the internalization of synaptic (γ-subunit) containing GABAA receptors[1-3]

GNX, ganaxolone; BDZ, benzodiazepine; Rec, receptor.

1. Goodkin HP et al. ,J.Neurosci.28(2008)2527–2538. 2. Naylor Deet al. J.Neurosci.25(2005)7724–7733. 3. Kapur J, Macdonald RL. Neurosci.17(1997)7532–7540.

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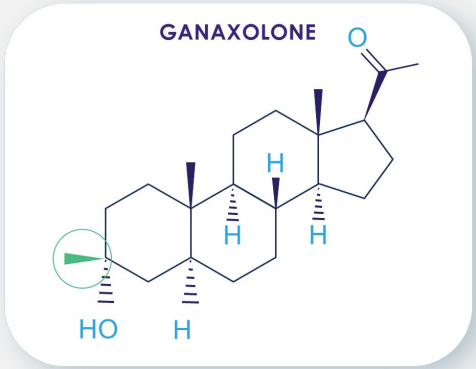
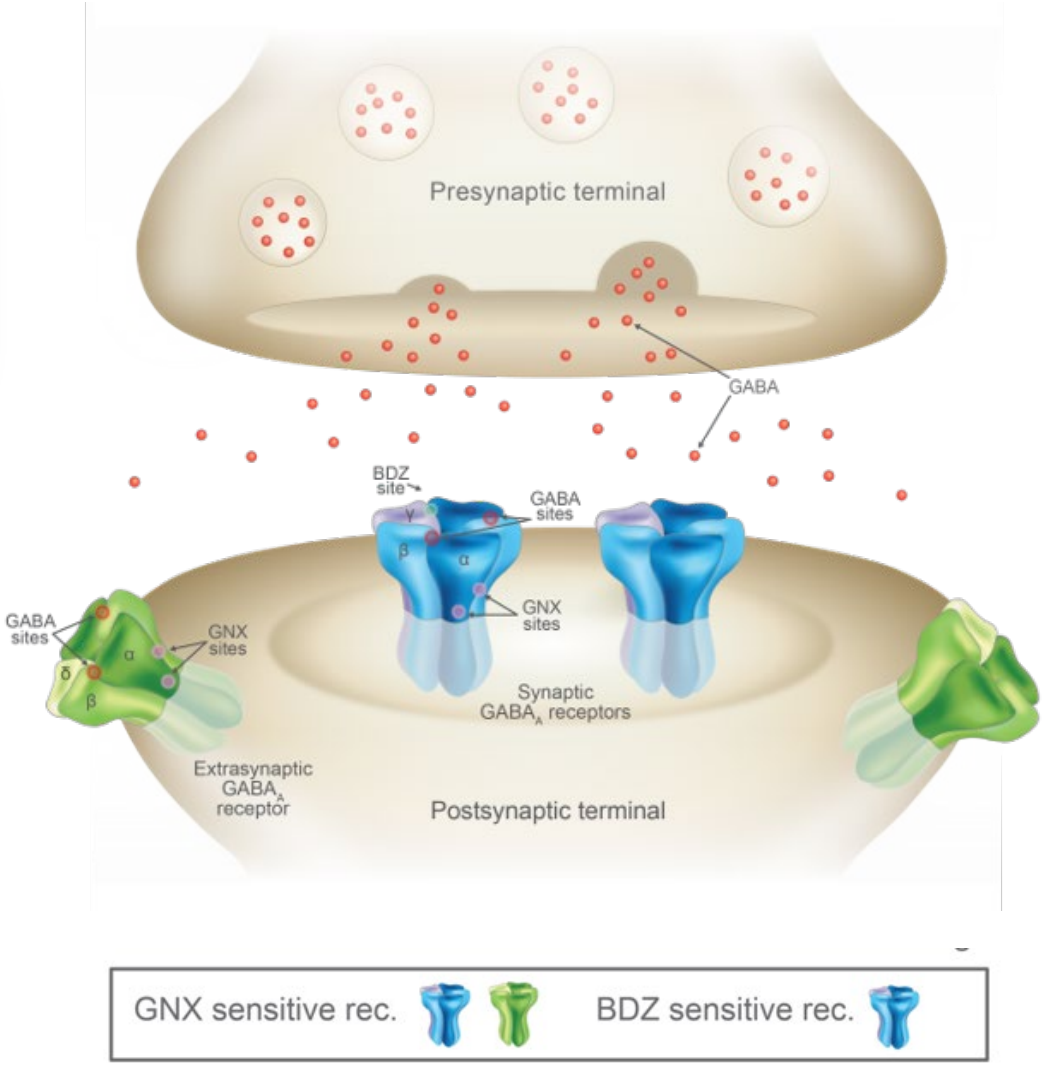
Ganaxolone Engages Both Synaptic and Extrasynaptic $GABA_A$ Receptors

Ganaxolone, a synthetic analog of endogenous neuroactive steroid allopregnanolone, **targets binding sites on $GABA_A$ receptors** that are distinct from the benzodiazepine site and other GABAergic molecules[1-3]



Ganaxolone modulates both synaptic and extrasynaptic $GABA_A$ receptors to maximize inhibitory tone[1-5]

- **Potentiates dual inhibitory signaling, transient (phasic) and continuous (tonic)[1,3]**



Cl^-, chloride ion; NAS, neuroactive steroids

1. Reddy DS and Woodward R. *Drugs Fut.* 2004;29(3):227-242. 2. Reddy DS, Estes WA. *Trends Pharmacol Sci.* 2016;37(7):543-561. 3. Carver CM, Reddy DS. *Psychopharmacology (Berl).* 2013;230(2):151-188. 4. Reddy DS. *Front Cell Neurosci.* 2013;7:115. 5. Reddy DS, Rogawski MA. Jasper's Basic Mechanisms of the Epilepsies [Internet]. 4th edition; **6.** Paul SM, Purdy RH. *Neuroactive steroids*, Faseb J 1992; 6(6):2311-22.

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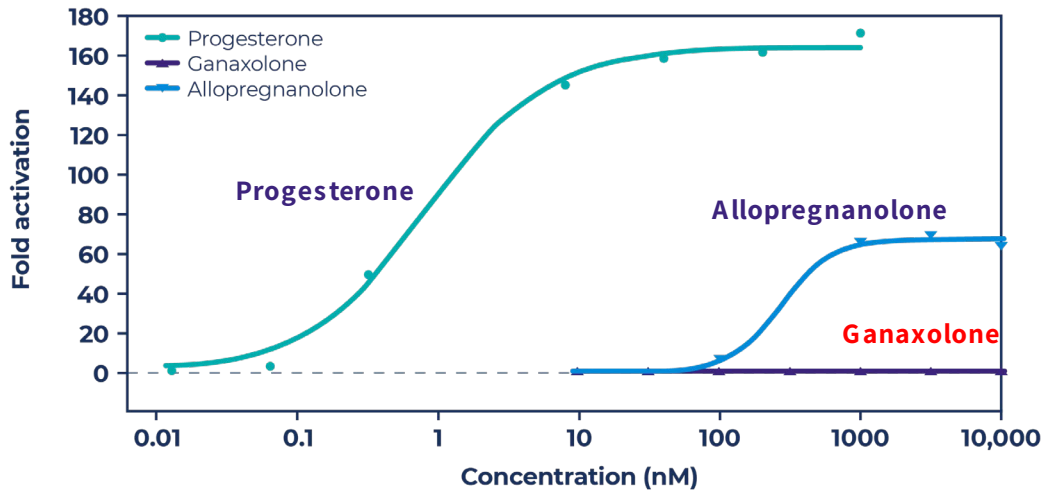
Ganaxolone is Inactive at Off-target Receptors

Ganaxolone is inactive (IC_{50}>10µM) at various off-target receptors tested[1]

Cytosolic Steroid	Inhibitory Amino Acid	Excitatory Amino Acid	Adenosine Peptide
Estrogen Androgen Glucocorticoid Mineralocorticoid Progesterone	$GABA_B$ Glycine	NMDA-associated Glycine NMDA PCP AMPA Kainate Sigma	A_2 A_{II} ANF V1 Bombesin CCK EGF Substance K Neurotensin NGF NPY Somatostatin Substance P VIP

Monoamine	Channel Protein	Second Messenger
DA_1 DA_2 $5\text{-}HT_1$ $5\text{-}HT_2$	Calcium Potassium	Adenylate Cyclase IP3 Protein Kinase

Activity of Progesterone, Allopregnanolone, and Ganaxolone at the Nuclear Progesterone Receptor[2]



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1. Carter RB et al. JPET 1997; 280: 1284-1295 2. AES 2022 Marinus Scientific Exhibit

Ganaxolone Confers Antiseizure Activity in Diverse Preclinical Models

Ganaxolone exhibited broad-spectrum antiseizure activity in preclinical models[1-12]

- ✓ Chemically and electrically induced seizures
- ✓ Acute and Chronic kindling models
- ✓ Benzodiazepine-resistant model of status epilepticus

Antiseizure profiles of neuroactive steroids based on ED_{50} values in preclinical seizure models

Seizure Model	Allopregnanolone*	Ganaxolone
Electroshock Models		
Maximal electroshock	✓[1]	✓[6]
6-Hz stimulation	✓[1]	✓[7]
Chemoconvulsant Models		
Cocaine	✓[9]	✓[9]
Pentylenetetrazol	✓[1]	✓[6]
Bicuculline	✓[1]	✓[6]
Picrotoxin	✓[1]	ND
N-methyl-D-aspartate	X[1]	X[9]
4-Aminopyridine	X[1]	ND
Kindling Models		
Amygdala kindling	✓[1]	✓[4]
Hippocampus kindling	✓[1]	✓[5]
Cocaine kindling	✓[11]	✓[11]
Pentylenetetrazol kindling	✓[12]	✓[10]
Status Epilepticus Models		
Pilocarpine	✓[1]	✓[3]
Kainic acid	x[1]	ND

ND - not determined; ✓ - active; X - inactive.
*Allopregnanolone is not FDA approved to treat seizures.

1. Reddy DS, Woodward R. *Front Endocrinol (Lausanne).* 2011;2:1-11. **2.** Kapur J, MacDonald RL. *J Neurosci.* 1997;17:7532-7540. **3.** Saporito MS et al. *J Pharmacol Exp Ther.* 2019;368:326-337. **4.** Reddy DS, Rogowsky MA. *Epilepsy Res.* 2010;89:254. **5.** Chuang SH, Reddy DS. *J Pharmacol Exp Ther.* 2020;372:285. **6.** Carter RB et al. *J Pharmacol Exp Ther.* 1997;280:1284-1295. **7.** Kaminski RM et al. *Epilepsia.* 2004;45:864. **8.** Yum MI et al. *Epilepsy Res.* 2014;108:1492. **9.** Gasior M et al. *J Pharmacol Exp Ther.* 1997; 282:543-553. **10.** Gasior M et al. *Neuropharmacology* 2000; 39: 1184-1196. **11.** Kaminski RM et al. *Eur J Pharmacol.* 2003; 474: 217-22. **12.** Kumari P et al. *IJEP*; 2016: 68-74

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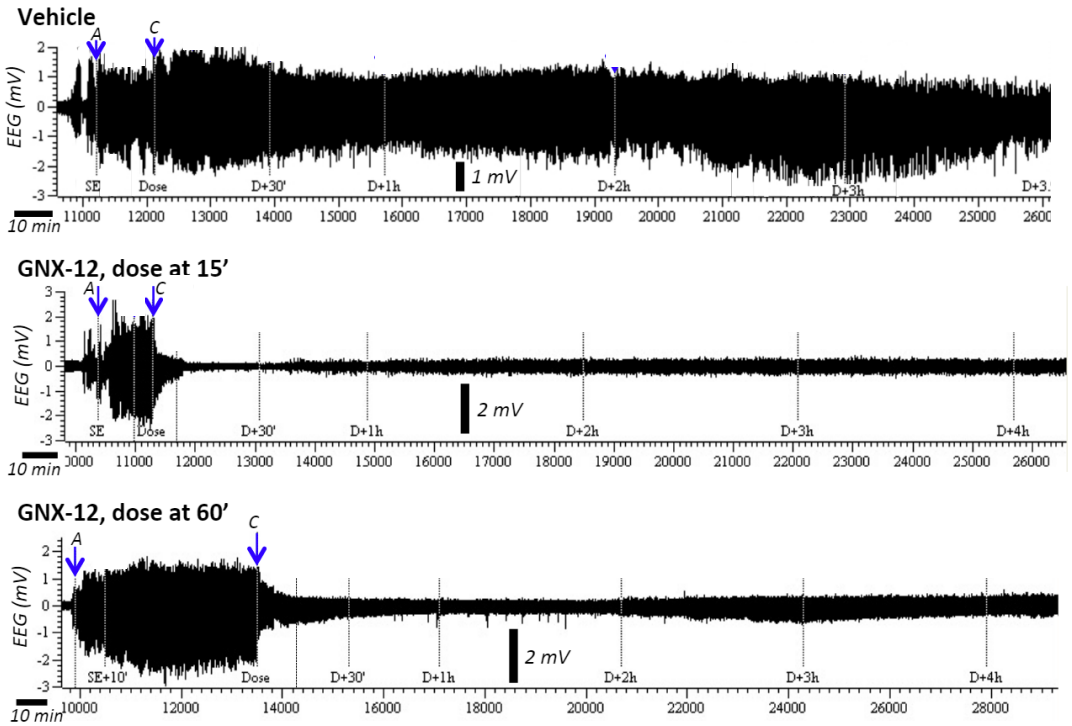
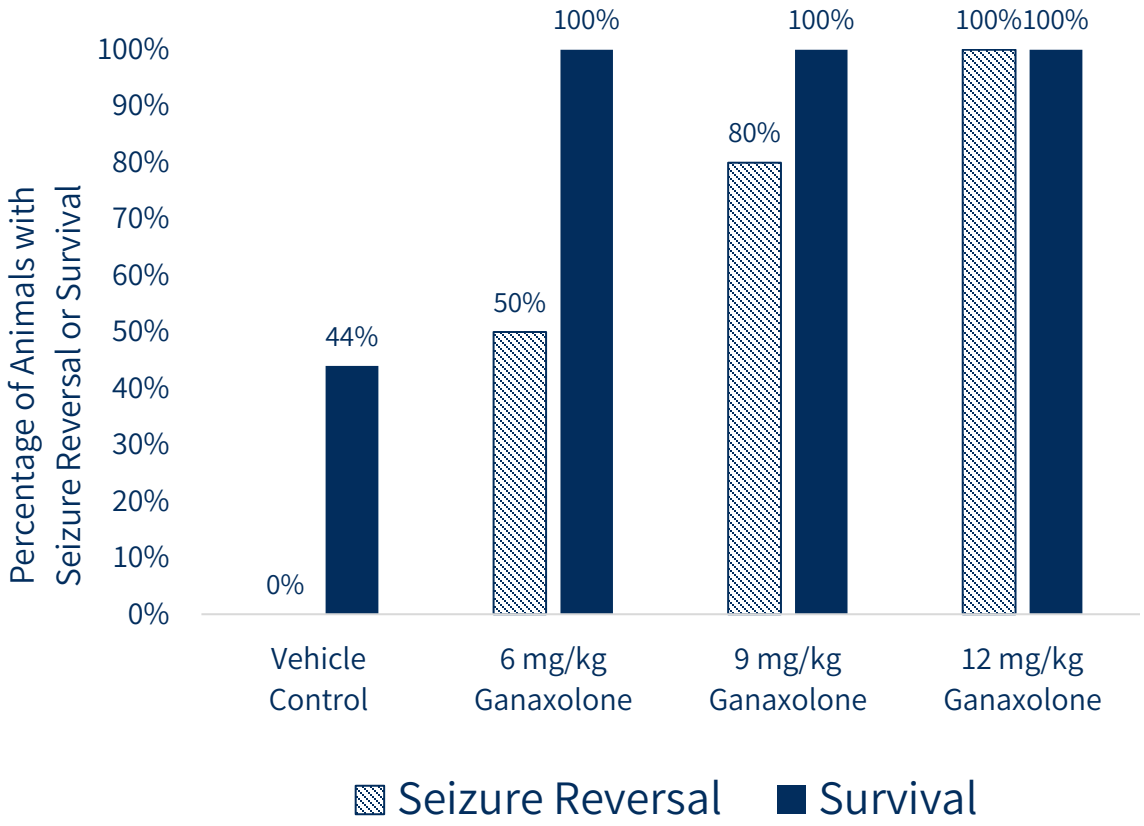
Preclinical Data of Ganaxolone in Status Epilepticus

Ganaxolone Showed Anticonvulsant Response on EEG when Administered both 15 or 60 minutes after SE-onset



(A) SE-onset; (C) IP dosing

IV Ganaxolone Showed Dose-Dependent Reversal of Seizure and Improved Survival at 60-minutes after Convulsive SE Onset

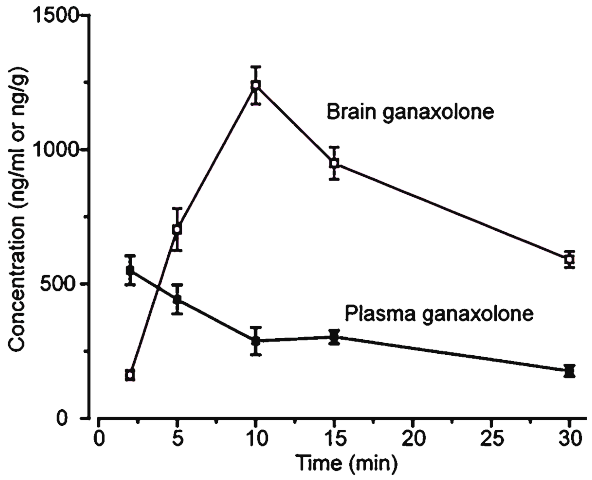


1. Saporito MS et al. *JPET*. 2019; 368(3): 327-336

PK/PD of IV Ganaxolone Well Suited for Acute SE Treatment

Experimental PK[1]

Brain and plasma concentration:
ganaxolone 3 mg/kg IM in mice



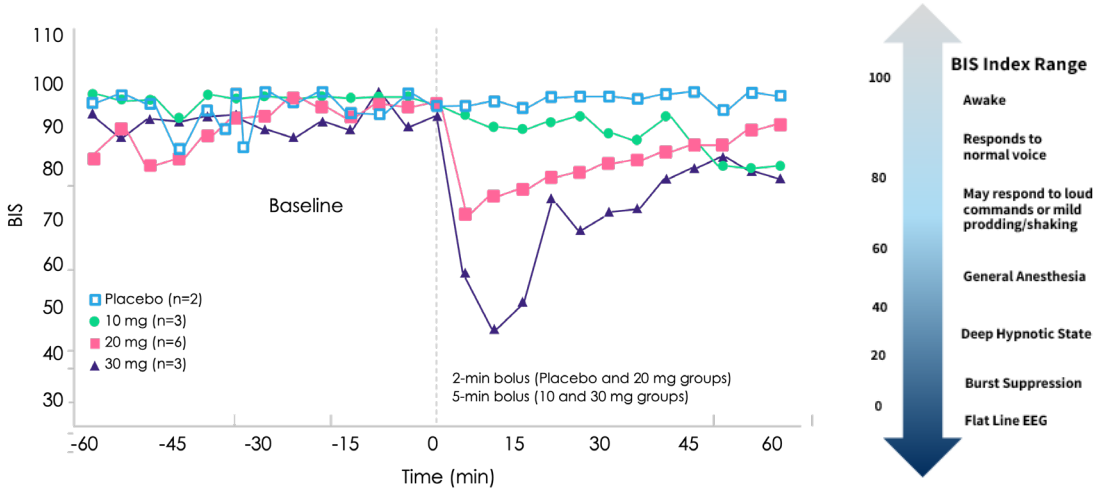
Human PK[2]

30 mg IV ganaxolone bolus
(over 5 minutes):

C_{max} 1,240 ng/mL
T_{max} ~ 5 minutes

Human PD[2]

EEG bispectral index
following IV ganaxolone bolus



Ganaxolone pharmacokinetics well suited to SE treatment
Rapid attainment of plasma and brain concentrations
Human PD correlates with experimental evidence of early brain penetration

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PD, Pharmacodynamics; PK, Pharmacokinetics.

1. Zolkowska D et al. *Epilepsia*. 59(suppl 2):220-227. 2. Marinus Pharmaceuticals. AES 2022.

3rd-line IV Anesthesia Treatments are Associated with Increased Morbidity and Mortality in S

Third-line IV anesthetics in refractory SE have been associated with[1-8]

- ↑ infectious complications
- Severe hypotension &need for vasopressor treatment
- Mechanical ventilation
- Unfavorable outcomes and new disability
- Longer ICU and hospital stays
- Increased mortality

Limitations with current treatment options:

- Minimal data from controlled, randomized trials to guide pharmacotherapy in refractory phases of SE
- Limited guidance on choice(s) of therapeutic agent(s) beyond 1st and 2nd lines of treatment
- Ideal duration and depth of therapeutic coma with IVanesthetics remains unknown

ICU, intensive care unit; IV, intravenous; SE, status epilepticus

1. Kowalski RG et al. *Crit Care Med*. 2012;40:2677-2684. **2.** Sutter R et al. *Neurology*. 2014;25;82:656-664. **3.** Marchi NA et al. *Crit Care Med*. 2015;43:1003-1009. **4.** Sutter R et al. *CNS Drugs*. 2017;31:65-74. **5.** Claassen J et al. *Epilepsia*. 2002;43:146-153. **6.** Hocker S et al. *Curr Neurol Neurosci Rep*. 2014;14:452. **7.** Hawkes MA et al. *Crit Care Med*. 2019;47:1226-1231. **8.** Muhlhofer WG et al. *Epilepsia*. 2019;60:921-934.

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Phase 2 Refractory Status Epilepticus Trial (RSE) Design

SE Patients

Screening

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

Treatment Period			Post-Treatment Follow-up	
Loading Dose	**Maintenance**	**Taper**	**24 hour**	**Weeks 2, 3, 4**
Bolus plus continuous infusion	2-4 day infusion	18-hour taper		

Cohort	Dose of ganaxolone/day	No. Patients
Low	500 mg/day	5
Medium	650 mg/day	4
High	713 mg/day	8

Endpoints:

Primary — Percent of patients who did not require escalation of treatment to IV anesthetic within the first 24 hours after ganaxolone initiation

Secondary — Additional efficacy, safety, and tolerability

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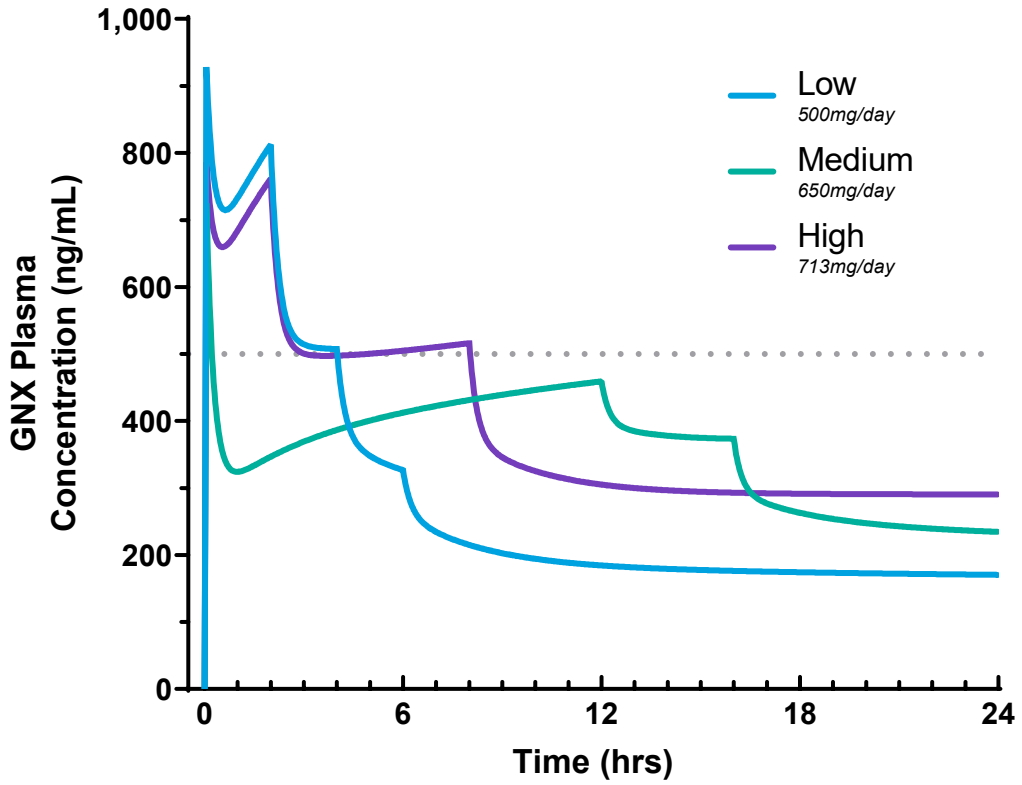
1. Vaitkevicius H et al. *Epilepsia.* 2022; 63(9): 2381-2391

Phase 2 Refractory Status Epilepticus Trial (RSE) Modeled Pharmacokine

Modeled Pharmacokinetic Curves for All Dose Groups



Initial bolus of IV ganaxolone resulted in rapid plasma ganaxolone levels **(~900 ng/mL)** designed to terminate SE

High-dose ganaxolone achieved and maintained target plasma levels ⩾ 500 ng/mL for **≈ 8 hours**

Low-dose ganaxolone achieved and maintained target plasma levels ≥ 500 ng/mL for **≈ 4 hours**

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1. Vaitkevicius H et al. *Epilepsia.* 2022; 63(9): 2381-2391

Phase 2 RSE Trial: Baseline Characteristics

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

Types of SE
- 5 (29%) CSE, 11 (65%) NCSE, 1 (6%) CSE→NCSE

History of epilepsy
- 9 (53%)

Mean # of failed IV ASM (including benzodiazepines)
- 3 (range: 2-5)

Mean # of failed second-line IV ASMs
- 2 (range: 1-4), all failed LEV or LAC
- All prior ASMs were administered within recommended dosing guidelines

SE Etiology*

Acute (76.5%)

** Includes various conditions: brain tumors, stroke, neurodegenerative disorders, intracranial hemorrhage, alcohol withdrawal, illicit drug use, metabolic disturbances, infection, autoimmune disorders, epilepsy, traumatic brain injury)*

Progressive (11.8%)

Remote (11.8%)

SE in defined electroclinical syndromes (11.8%)

*More than one etiology could be selected

CSE, convulsive status epilepticus; IV, intravenous; ASM, antiseizure drug; LAC, lacosamide; LEV, levetiracetam; NCSE, nonconvulsive status epilepticus; SE, status epilepticus

1. Vaitkevicius H et al. *Epilepsia.* 2022; 63(9): 2381-2391

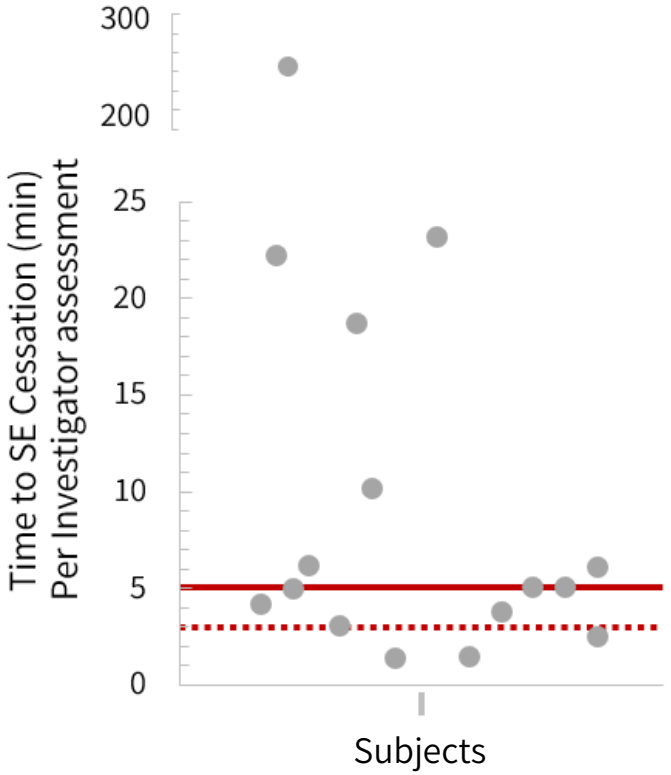
Phase 2 RSE Trial: Results

Dose cohort	No IV anesthesia for 24 hours	Status-free through 24 hours*	No treatment escalation for 24 hours	No SE Relapse during 4-week follow up
High (713 mg/day) (n=8)	**100%** (8 of 8)	**88%** (7 of 8)	**100%** (8 of 8)	**100%** (6 of 6) (1ET, 1 death)
Medium (650 mg/day) (n=4)	**100%** (4 of 4)	**100%** (4 of 4)	**75%** (3 of 4)	**67%** (2 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 death)

* Investigator determined

High dose provided sustained reduction (>80%) in seizure burden throughout entire analysis window

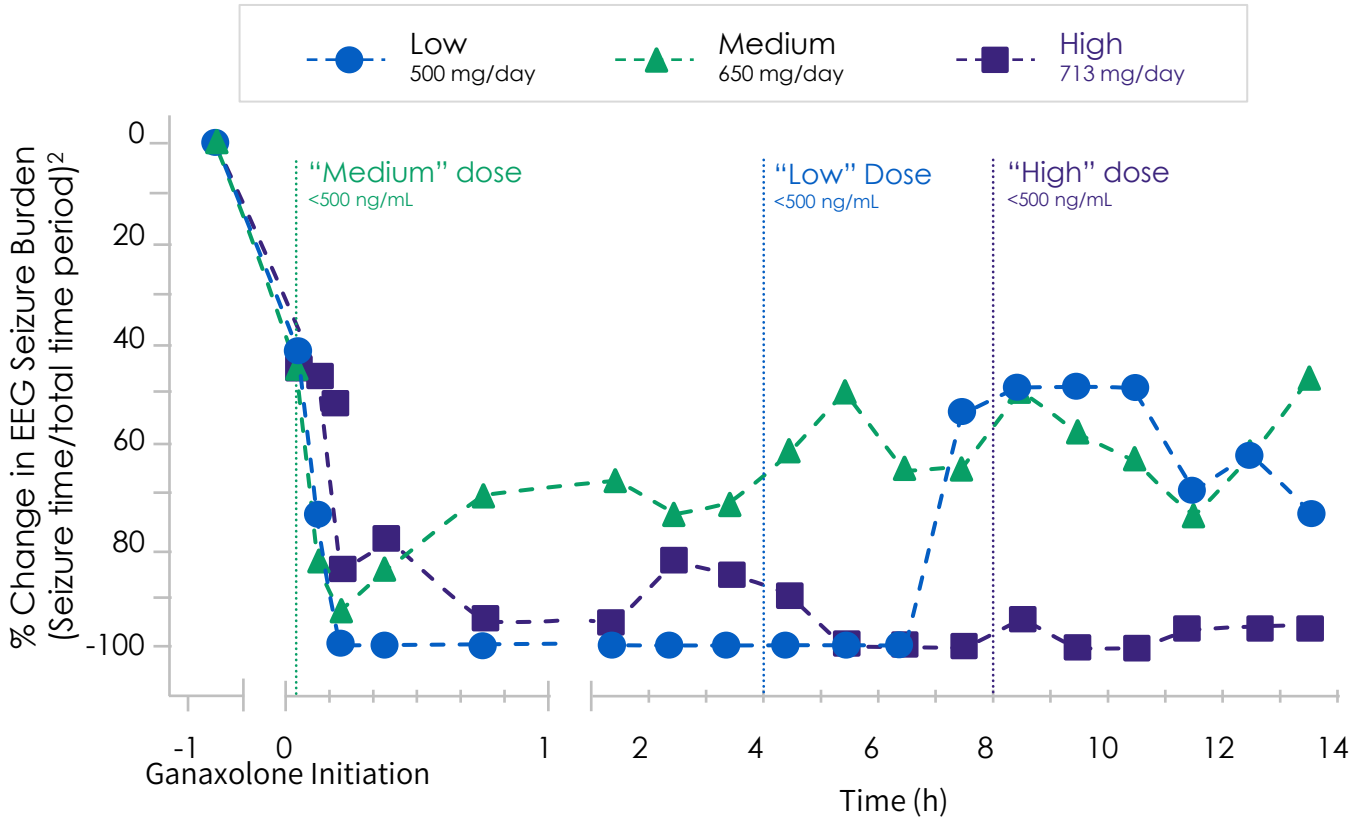
Median time to SE cessation:
5 minutes



1. Vaitkevicius H et al. *Epilepsia.* 2022; 63(9): 2381-2391

Phase 2 RSE Trial: Results

Seizure Burden Reduction Occurred Rapidly in All Dose Groups



High dose provided sustained reduction (>80%) in seizure burden throughout entire analysis window

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Phase 2 RSE Trial: Safety and Tolerability

Summary of related adverse events based on safety population[1]

Treatment emergent AEs	Overall (N=17) n (%)
Any treatment emergent AE	9 (52.9)
Somnolence*	5 (29.4)
Sedation	2 (11.8)
Leukocytosis	1 (5.9)
Leukopenia	1 (5.9)
Neutrophilia	1 (5.9)
Hematuria	2 (11.8)
Urinary retention	1 (5.9)
Blood urea increased	1 (5.9)
Lymphocyte percentage decreased	1 (5.9)
Neutrophil percentage increased	1 (5.9)
Hypercapnia	2 (11.8)
Hypotension	2 (11.8)
Hypocalcemia	1 (5.9)
Hypokalemia	1 (5.9)

AE, adverse event.
*Somnolence was reported twice in 1 subject.

Total of 23 related AEs in 9 subjects

Severity of related AEs[2]
- 16 mild, 5 moderate, and 2 severe

2 related serious AEs in 2 patients (included in AEs)[2]
- 2 severe sedation

Intubation[2]
- 9 patients were not intubated upon enrollment
  - 6 remained intubation-free during the ganaxolone treatment period
  - 3 were intubated during the ganaxolone treatment period

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1. Vaitkevicius H et al. *Epilepsia.* 2022; 63(9): 2381-2391

RAISE Trial Design: Overview

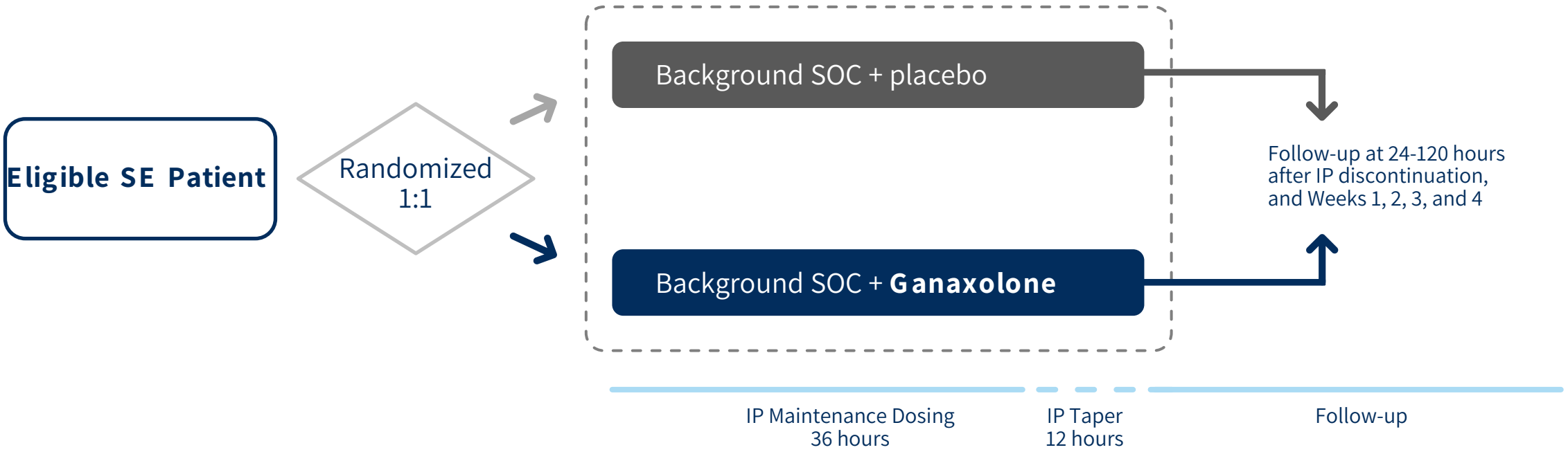
Study Objective: To establish efficacy and safety of IV ganaxolone for the treatment of status epilepticus (SE) after failure of 2 or more antiseizure medications (ASMs)

 **Geography/Site Numbers**	North America and Australia, up to **80** clinical sites
 **Patient Population**	**Status epilepticus** participants aged **≥12 years** (n=124) who have **failed 2 or more antiseizure treatments** for the acute treatment of SE (either a benzodiazepine and 1 IV ASM or 2 IV ASMs)
 **Co-primary Endpoints**	1. **Onset of Action:** Proportion of participants with SE cessation within 30 minutes of study drug initiation without medications for the acute treatment of SE[§] 2. **Durability of Effect:** Proportion of participants with no progression to IV anesthesia for 36 hours following study drug initiation
 **Key Secondary Endpoints**	1. No progression to IV anesthesia for 72 hours following study drug initiation 2. Time to SE cessation following study drug initiation

[§] Medications for the acute treatment of SE are defined as ASMs administered to abort ongoing SE or prevent imminent recurrence of SE based on clinical or EEG evidence. This definition excludes maintenance doses of ASMs or medications with anticonvulsant properties used for other reasons, such as procedural sedation.

RAISE Trial: Study Design

Intent of the study design: Not to change SOC!



IP, investigational product; SE, status epilepticus; SOC, standard of care

RAISE Trial: Key Eligibility Criteria

Key Inclusion Criteria

- Patients **12 years of age or older**
- **SE** with or without prominent motor features based on clinical and EEG findings
- **Failed ≥2 antiseizure treatments** for the current episode of SE
  - Either a benzodiazepine and at least 1 second-line IV ASM or 2 or more second-line IV ASMs*
- **IV anesthesia** would be the **next step in escalation of care for SE**

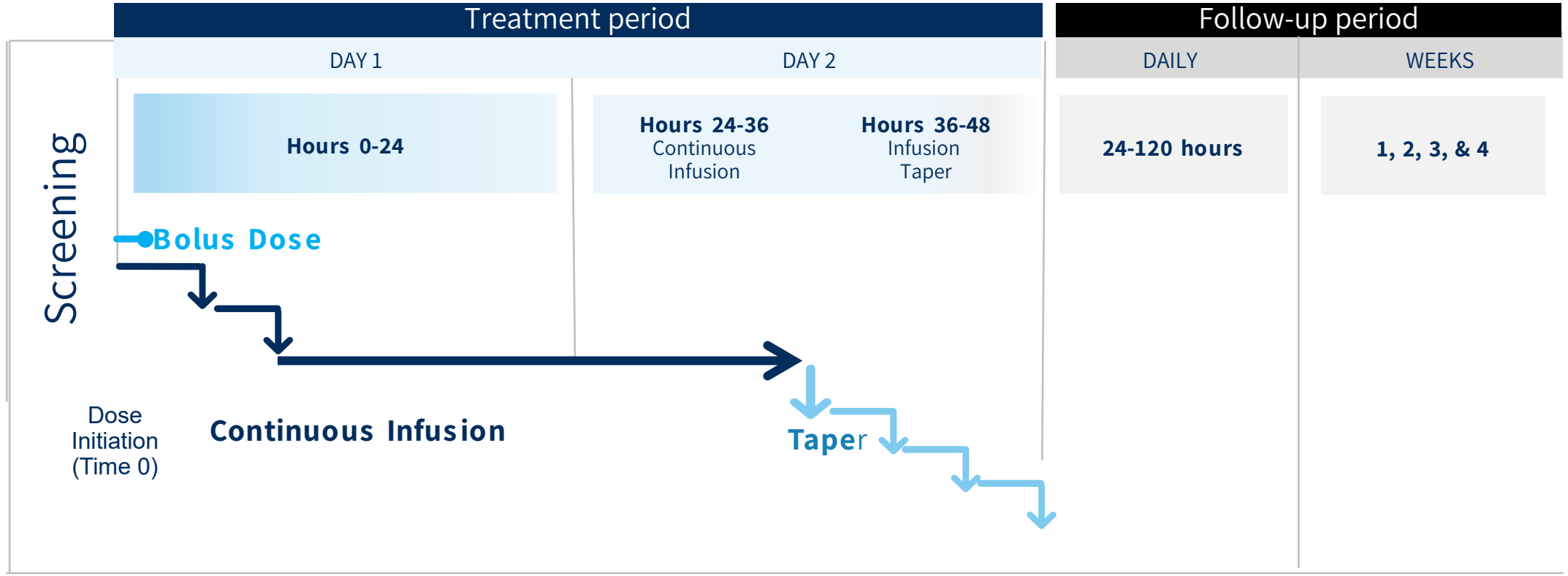
Key Exclusion Criteria

- **Life expectancy** <24 hours
- **SRSE**: More than 18 hours of high-dose IV anesthesia during the current episode of SE or continue to have clinical or electrographic evidence of persistent seizures while receiving high-dose IV anesthetics
- **Anoxic brain injury** or **uncorrected rapidly reversal metabolic condition** as primary cause of SE

*IV ASMs: IV fosphenytoin/phenytoin, IV levetiracetam, IV valproic acid, IV lacosamide, IV brivaracetam, IV phenobarbital
SE, status epilepticus; SRSE, super refractory status epilepticus; IV, intravenous; ASM, antiseizure medication

RAISE Trial: Study Design and Flow Diagram

Study Design Flow Chart



Treatment is planned to be 2 days (including a 12-hour taper).
Upon IP discontinuation (with or without taper), participant will continue into the Follow-up period.
Total participation is expected to be approximately 4 weeks.

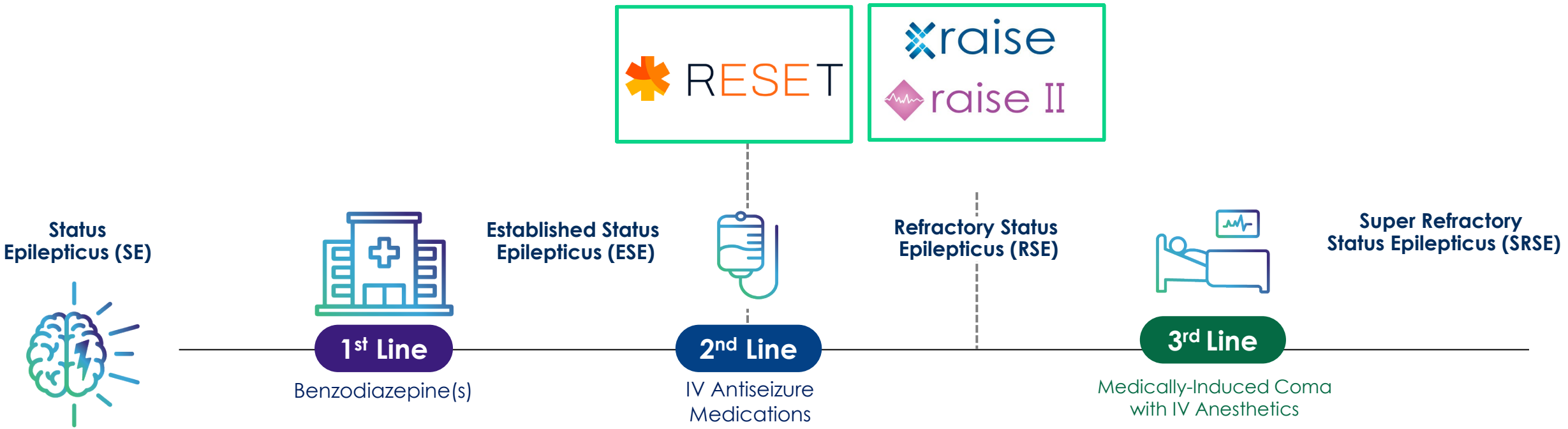
Key Differences Between Ganaxolone and Brexanolone Trials

	Brexanolone Phase 3 Trial [1,2] STATUS TRIAL	Ganaxolone Phase 3 Trial [3,4] Xraise
Patient Population	**SRSE**	**RSE**
Treatment Objective	Goal **to wean from IV anesthetics** while on brexanolone	Goal **to rapidly stop SE and prevent escalation to IV anesthesia** for SE treatment
Primary Endpoint	Prevent relapse of seizures/SE within 24 hours after weaning off IV anesthetics	1. Achieve SE cessation within 30 minutes 2. Prevent progression to IV anesthetics
Drug Dosing (Target plasma level)	**~50-100 ng/mL**	**≥500 ng/mL** (12 hours)

SRSE, super-refractory status epilepticus; RSE, refractory status epilepticus; IV, intravenous; SE, status epilepticus

1. ClinicalTrials.gov. https://clinicaltrials.gov/ct2/show/NCT02477618. Updated May 2, 2019. Accessed February 5, 2021.
2. Rosenthal ES et al. *Ann Neurol.* 2017;82:342-352. 3. Vaitkevicius H et al. AES 2020. 4. Marinus Pharmaceuticals. AES 2020.

IV Ganaxolone Clinical Trials in Status Epilepticus



	RESET	raise II
Trial Phase	Phase 2/3 Clinical Trial in United States	Phase 3 Clinical Trial in European Union
Target patient population	Failure of benzodiazepine (ESE, n=120)	Failure of benzodiazepines and at lease one IV ASM (RSE, n=70)
Comparator	Ganaxolone vs. Placebo with **concurrent IV ASM initiation**	Ganaxolone vs. Placebo with **concurrent IV ASM initiation**
Primary endpoint	SE cessation within 30 minutes	**Responder analysis**: SE cessation within 30 minutes **AND** no escalation of care within 36 hours

ASM, antiseizure medication; IV, intravenous;

1. The RESET Study. Marinus Pharmaceuticals, Inc. Retrieved from: https://theresetstudy.com/. **2.** Corporate Presentation. Marinus Pharmaceuticals, Inc. January 2023

Key Takeaways

- **Intravenous ganaxolone is an investigational neuroactive steroid that targets unique binding sites on both synaptic and extrasynaptic $GABA_A$ receptors**
  - Ability to maintain GABAergic modulatory effects even when the synaptic receptors are internalized during prolonged SE

- **Preliminary efficacy, safety, tolerability, and pharmacokinetics of IV ganaxolone given in patients with RSE was assessed in an open-label phase 2 study showing:[1]**
  - No patients progressed to IV anesthetics for the treatment of RSE during the first 24 hours (primary endpoint)
  - IV ganaxolone was generally well tolerated in patients with RSE

- **The primary objective of the ongoing Phase 3 RAISE Trial is to establish efficacy and safety of IV ganaxolone for the treatment of SE after failure of at least 2 antiseizure treatments**

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IV, intravenous; SE, status epilepticus; RSE, refractory status epilepticus

1. Vaitkevicius H et al. *Epilepsia.* 2022; 63(9): 2381-2391

