Ganaxolone for the Treatment of RSE

September 26, 2019

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RSE Overview

Status Epilepticus (SE) is the most life-threatening occurrence within the spectrum of epileptic disorders

Continuous seizures lasting >5 min for convulsive seizures or >30 minutes for non-convulsive seizures

Heterogenous patient population with various/unknown etiologies

Prolonged seizure activity can result in permanent neuronal damage and contribute to the high morbidity and mortality rates associated with SE

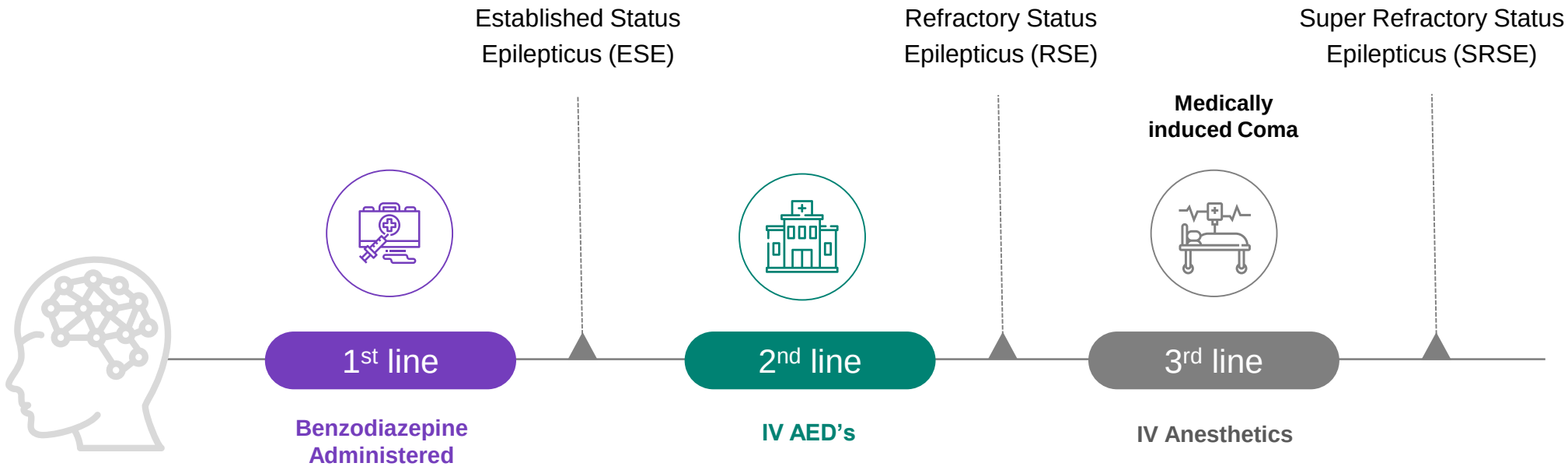
SE becomes more difficult to control as its duration increases and is associated with increased mortality

RSE defined as failure of at least one 2nd line intravenous (IV) anti-epileptic drug (AED)

Super Refractory Status Epilepticus (SRSE) is SE that continues or recurs 24hrs or more after the onset of IV anesthetics or failure to wean off IV anesthetics

No approved therapies for RSE globally

Goals of a New Therapy for the Treatment of RSE



Goals of a new treatment for RSE

Prevent patient progression towards escalation of treatment (IV anesthetics)

Rapid cessation of SE

Maintenance of seizure control over study period

Refractory Status Epilepticus is a Neurological Emergency

Increased duration of SE leads to neuronal damage, pharmacoresistance, and generally worse outcomes[1,2]

Mortality

Overall mortality is ~17-39% in RSE patients[3,7]

Mean RSE duration (in hrs.) between survivors and non-survivors was found to be 88.9 and 120.3 (p=0.002)[3]

Hospital stay

Patients that achieve SE cessation within 1 or 12 hours (convulsive or non-convulsive SE, respectively) spent significantly less days in the hospital (p<0.001)[5]

General Outcomes

Mean RSE duration between patients that had a 'good' or 'bad' outcomes were 7 and 14 days (p=0.003)[4]

3rd line IV anesthetics are generally effective at achieving SE cessation however are associated with significant complications[6]

More infections during SE (p<0.0001)

~2.9x increased relative risk for death

Increased hospital stay (29 days vs. 19 days, p=0.0005)

Increased ICU stay (14 days vs. 5 days, p<0.0001)

[1] Betjemann JP & Lowenstein DH 2015 *Lancet Neurol*
[2] Sutter R *et al.* 2013 *Nature Reviews Neurology*
[3] Sutter R *et al.* 2013 *Epilepsia*
[4] Madžar D *et al.* 2016 *J. Neurol.*
[5] Kellinghaus C *et al.* 2019 *Ann. Neurol.* [7]Novy et al 2010
[6] Hockher SE *et al.* 2013 *JAMA Neurol.*

Rationale for IV Ganaxolone for the Treatment of RSE

Ganaxolone has demonstrated a broad range of anticonvulsant and psychotherapeutic responses

Benzodiazepines are effective in treating acute seizures but not RSE

Benzodiazepines are positive allosteric modulators of the synaptic (gamma subunit) $GABA_A$ receptor

These receptors down-regulate with prolonged seizures and explains why SE patients become refractory to benzodiazepines

These receptors also down-regulate with chronic benzodiazepine administration

Ganaxolone is a positive allosteric modulator of the synaptic and extrasynaptic (delta subunit) $GABA_A$ receptors

The extrasynaptic receptor does not down regulate with prolonged seizures and explains why SE patients remain responsive to ganaxolone

The extrasynaptic receptor does not down regulate with chronic GNX administration therefore patients should be responsive to ganaxolone with chronic dosing

Phase 2 RSE Trial Design

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 → Post-treatment Follow-up

Treatment Period			Post-treatment Follow-up	
Loading Dose	Maintenance	Taper	24 hr	Weeks 2, 3, 4
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

Baseline Characteristics

17 patients	8 males, 9 females, Mean Age 56.9 years (range: 23 – 88)
Varied reasons for RSE	(e.g., brain tumors, vascular (stroke, hemorrhage), metabolic, autoimmune, alcohol withdrawal, illicit drug overdose)
Types of SE	5 (29%) convulsive SE 11 (65%) non-convulsive, and 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

Phase 2 RSE Trial – Efficacy of IV Ganaxolone

Cohort	No escalation to IV anesthetics within 24 hours from infusion initiation (Primary Endpoint)	Status-free at 24 hours from infusion initiation	No escalation to additional IV AEDs or IV anesthetics for status relapse at any time through the follow up period*
Target (713 mg/day; n=8)	100% (8 of 8)	88% (7 of 8)	100% (8 of 8)
Medium (650 mg/day; n=4)	100% (4 of 4)	100% (4 of 4)	75% (3 of 4)
Low (500 mg/day; n=5)	100% (5 of 5)	100% (5 of 5)	60% (3 of 5)

One patient had status relapse @ Day 1, which resolved during the ganaxolone infusion without treatment escalation

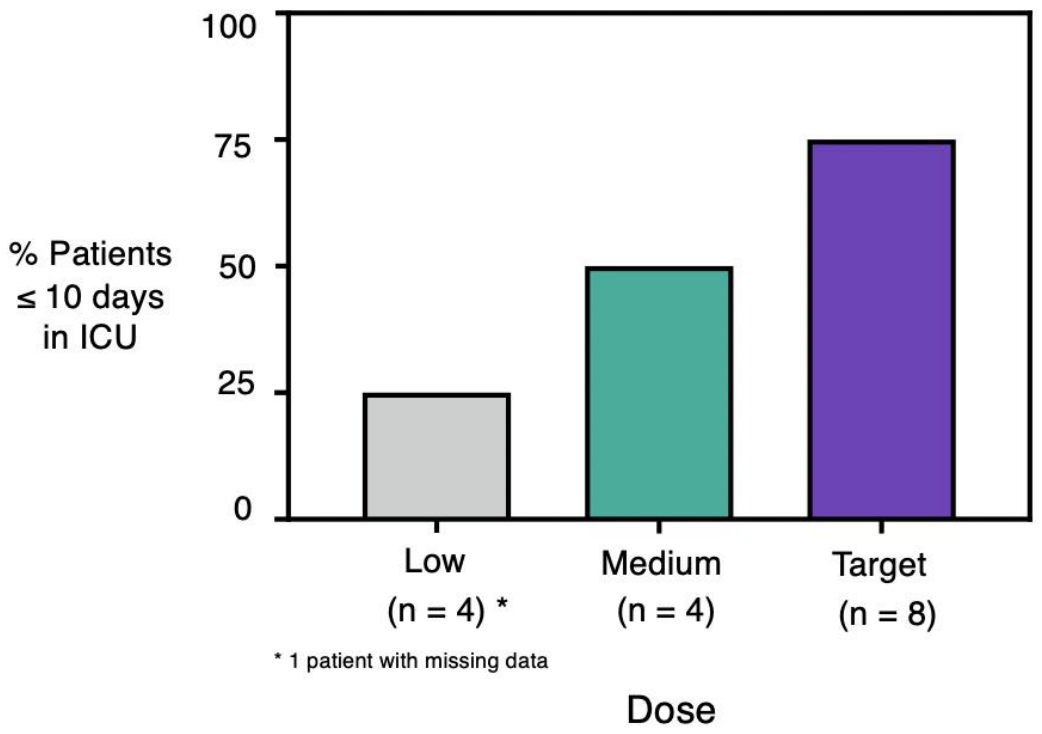
One patient escalated to additional IV AED @ Day 1 for seizure relapse.

One patient experienced status relapse @ Day 2 (during taper).

Two patients escalated to 3rd line therapy for seizure relapse @ Day3

*Follow up period equals end of taper to 24 hours post taper

Target Dose Provided Shorter ICU Time and Greater Improvements in CGI-I at Follow-up



CGI-I at Final Follow-up Visit (Target Dose)	
3: Minimally Improved	N=1
2: Much Improved	N=1
1: Very Much Improved	N=5

**1 patient in Target Dose died due to perforated bowel (not related)*

Phase 2 RSE Trial - IV Ganaxolone Safety Summary

10 SAEs in 6 patients (also included in AEs)

2 related in 2 patients

- 2 severe sedation

8 non-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

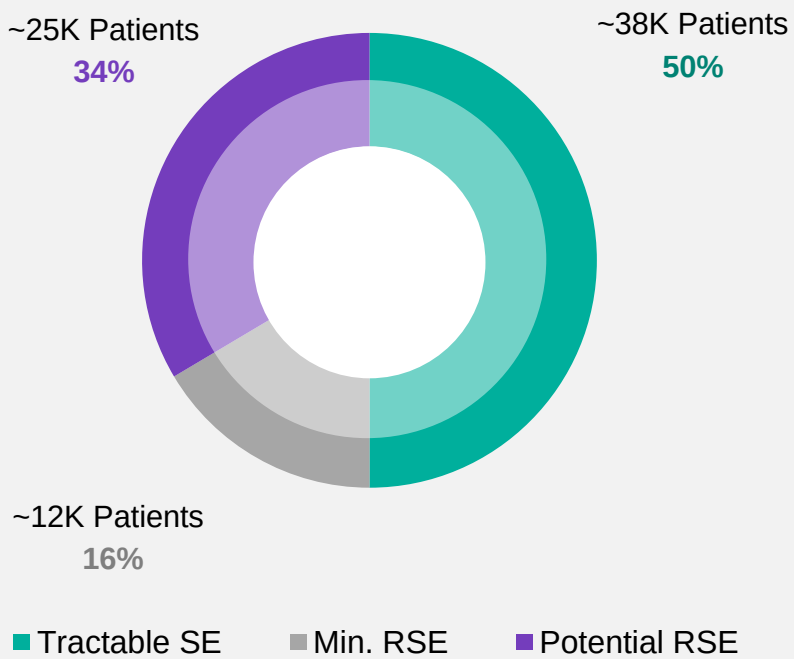
- 20 mild
- 8 moderate (2 pain; 2 pneumonia, 2 dysphagia, 1 delirium, 1 hypertension)
- 9 severe (respiratory depression, death due to withdrawal of support, sepsis, embolic stoke, perforated bowel, fall, loss of consciousness, multiple fractures, pneumothorax)

Intubation

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

Status Epilepticus - U.S. Hospital Incidence

~75K Hospital SE Patients (ICD-10)



Both SE & RSE fall within
the orphan drug designation

75K Total SE Patients Annually in U.S.

- 23 unique ICD-10 codes with some reference to SE
- Refractory SE patient volumes range from 12.5K to 37.5K
  - *Minimum = patients coded as "intractable" in ICD-10 (understated)*
  - *Maximum = 30%-50% of patients cited as refractory in med literature*
- Primary market research & clinicians confirm refractory patients in range of medical literature

Current SE treatment approach is clinically deficient

- High level of mortality for refractory patients @ 40%
- High levels of morbidities with existing treatments
  - *Co-morbidities extend beyond SE to include infection, etc.*
- Average hospital length of stay for refractory = 7-17 days

SE presents a very high cost burden to HC system

- Average cost of therapy for case ranges from $50k-$75K
- DRG < average cost of treatment, many hospitals losing $$
- Primary cost of care drivers are ICU and treatment complications

Phase 2 RSE Trial - Conclusions

No patients progressed to IV anesthetics during first 24 hours
Median time to SE cessation = 5 minutes (n=15 evaluable)
Durable response throughout study period in target dose cohort

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 Q1 2020

Thank You