Refractory Status Epilepticus Teach-In

April 30, 2019
RSE Overview

- Status Epilepticus is the most life-threatening occurrence within the spectrum of epileptic disorders
  - Continuous seizures lasting >5 min for convulsive seizures; >30 minutes for non-convulsive seizures
  - Heterogenous patient population with various/unknown etiologies
  - SE caused by: Tumor, Infection, TBI, Stroke, Alcoholism
  - 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

- No approved therapies for RSE or Super Refractory Status Epilepticus (SRSE)
Care Continuum: Vision for Treating Patients with SE

- 1st line: Established Status Epilepticus (ESE) - Benzodiazepine Administered
- 2nd line: Refractory Status Epilepticus (RSE) - IV AED’s
- 3rd line: Severe Refractory Status Epilepticus (SRSE) - IV Anesthetics
- 4th line: IV Ketamine and others

40% death rate when progressing to 3rd line treatment
### Clinical Course of SE and Treatment Options

<table>
<thead>
<tr>
<th>Early Phase</th>
<th>Established SE</th>
<th>RSE</th>
<th>SRSE</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st line benzos</td>
<td>2nd line IV AEDs</td>
<td>3rd line IV anes.</td>
<td>4th line</td>
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<tr>
<td>Lorazepam</td>
<td>Phenytoin</td>
<td>Propofol</td>
<td>IV ketamine</td>
</tr>
<tr>
<td>Diazepam</td>
<td>Phosphoryntoin</td>
<td>Thiopental</td>
<td>Immunotherapy</td>
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<tr>
<td>Clonazepam</td>
<td>Valproate</td>
<td>Pentobarbital</td>
<td>Magnesium</td>
</tr>
<tr>
<td>Phenobarbital</td>
<td>Levetiracetam</td>
<td>Midazolam</td>
<td>Topiramate</td>
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<tr>
<td></td>
<td>Lacosamide</td>
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#### Treatment Options

- **1st line benzodiazepines** lose effectiveness in established SE and are suboptimal for long-term anti-seizure management.
- **2nd line**: narrow therapeutic window, hypotension, arrhythmia, and bleeding disorders.
- **3rd line IV anesthetics**: hemodynamic complications, prolonged hospitalization and monitoring, and ~40% death rate.
RSE Market Assessment

TJ Lyons
VP, Corporate & Business Development and Commercial Planning
Status Epilepticus (SE) - U.S. Hospital Incidence

Marinus is in the process of sizing and segmenting the SE/RSE markets both primary and secondary data as well as with KOL and advisory inputs.

75K Total SE Pats - 23 ICD-10 codes within SE
- 2,700 codes in ICD-9 vs. 86,000 codes in ICD-10 (2015)
- ICD-10 5 digit vs. 3 ICD-9 3 digit coding - greater specificity
- 55% are primary vs. 45% secondary diagnosis of SE

12K-38K Potential RSE Patients
- Patients coded as “intractable” in ICD-10 = 12.5K Patients
- Med lit indicates higher incidence of refractory (30%-60%)
- MR and clinicians also corroborate higher refractory pats.

Marinus mining secondary data to quantify RSE
- Cross referencing ICD-10 with additional patient records
- Identifying patient record “proxies” for refractory pops
- Variables to include ICU, IV anesthetics, intubation etc.
Strong GNX clinical value proposition of mitigating need for sedation, decreasing intubation, and lowering mortality rates supports substantial pricing levels for GNX

## RSE Costs & Pharmacoeconomic Drivers

<table>
<thead>
<tr>
<th>RSE Treatment Costs &amp; Mortality</th>
<th>Cost Per Event</th>
<th>Units</th>
<th>Cost Per Case ($)</th>
<th>Total U.S. Hospital Cost ($MM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug Costs &amp; Med Services (6)</td>
<td>$1,192</td>
<td>2</td>
<td>$2,384</td>
<td>$90</td>
</tr>
<tr>
<td>Hospital LOS (4, 2)</td>
<td>$2,000</td>
<td>17</td>
<td>$14,400</td>
<td>$543</td>
</tr>
<tr>
<td>ICU LOS (5, 2)</td>
<td>$4,000</td>
<td>9</td>
<td>$37,200</td>
<td>$1,402</td>
</tr>
<tr>
<td><strong>Total (1)</strong></td>
<td></td>
<td></td>
<td><strong>$53,984</strong></td>
<td><strong>$2,035</strong></td>
</tr>
</tbody>
</table>

SRSE Mortality Rate (1) 38%

| Total SE Hospital Cases/Year (3) | 75,375 |
| Potential % Refractory SE (7)   | 50%    |
| Refractory Cases                | 37,688 |

(3) ICD-10 based SE incidence estimation based upon hospital discharge records factored by medical literature refractory occurrence
(4) Becker’s Hospital review - https://www.beckershospitalreview.com/finance/average-cost-per-inpatient-day-across-50-states.htm
(6) Interpolated calculation implied by cited statistics
(7) Canaccord Geniiy Sage Coverage - Oct 2014
Refractory Status Epilepticus
Clinician Market Research

Prepared by DiCicco Research, LLC.
Qualitative research was executed to understand current RSE management strategies, unmet need, and reception to GNX concept.

30 MDs were interviewed across two research phases representing a mix of Neurology, Epileptology, Emergency Medicine, Hospitalist specialties.

Interviews lasted roughly 60 minutes each, and were conducted by a third-party moderator in Feb & April, 2019.
SE & RSE Treatment Goals

SE & RSE treatment goals as reported by intensivist and ER physician respondents in RSE qualitative MR conducted in February & April, 2019

01
Stop the seizure
High rates of morbidity and mortality (especially in CSE) increase urgency to control SE quickly and effectively

02
Identify, resolve
MDs need time in some cases to pinpoint the root of the problem, and employ corrective measures

03
Discharge
Depending on nature of status, will seek to discharge patient quickly to reduce cost/infection risk
Overview of Current RSE Management

- Management of RSE follows a stepwise approach
  
  i. Benzodiazepine
  
  ii. AED (typically fosphenytoin or levetiracetam)
  
  iii. General sedation
  
  iv. Additional AED(s) until adequate response
  
  v. Neuro typically discharges on regimen that was effective inpatient

- MDs emphasize the importance of time in above steps – the earlier action and onset the better
  
  "The faster the better. The brain starts suffering neuronal loss 30 minutes after continuous seizures. You want it to stop immediately. That is why you need to go for the IV sedating drugs, which generally do the trick." Epileptologist
MDs express significant dissatisfaction with current Txs

- MDs struggle to articulate what is going "well" in RSE Tx, but are quick to point out challenges and unmet needs

- Current AEDs are critiqued as often ineffective in controlling RSE, not FDA approved, and associated with SEs

- General sedation is associated with numerous downsides
  - Significant morbidity and mortality, infection, intubation risk, long LOS
  - High cost to patient and system
  - Inability to perform physical evaluation when sedated
Opportunity for Novel Treatments in Refractory Status Epilepticus
A qualitative methodology was used to assess potential opportunities for new treatments in refractory status epilepticus (RSE)

Marinus and Evolution Consulting developed a screening instrument to recruit:

Hospital **Pharmacy Directors** and **Neurologists** who are members of their institution’s P&T committee

**Medical Directors** and a **Pharmacy Benefit Manager** who make medication formulary decisions for large national/regional insurance plans

Key screening criteria included:

- All respondents must be involved in CNS medication formulary decisions
- All respondent types must be “Extremely qualified or comfortable” discussing their organization’s treatment of RSE

60-minute in-depth web-assisted telephone interviews (TDIs)

*TDIs conducted April 9th – April 19th, 2019

Respondents specified their required minimum and ideal clinical and pharmaco-economic outcomes for a novel RSE treatment to be added to hospital formularies

*As with all qualitative research, findings should be interpreted with caution and may not be projectable to the total market*
RSE offers a unique opportunity for drug development: The current standard of care is risky to patients and expensive for hospitals

Pharmacy directors, hospital physicians, and payers agree there is a tremendous clinical and economic unmet need for a novel RSE treatment

- Medically-induced coma is initiated in status epilepticus patients who fail to respond to an infused benzodiazepine followed by an infused anti-epileptic
- Refractory patients are intubated, moved to the ICU, and then receive either propofol, midazolam, or pentobarbital
- Treating RSE with sedation is associated with significant rates of morbidity and mortality
- The median hospital stay for RSE patients is about 8-12 days with approximately 4-6 days in the ICU
- Treatment costs for RSE patients will often run close to $50,000; ranging from about $30,000 to $75,000
  - Treatment costs vary as a function of hospital setting (i.e., community hospital vs. tertiary center) and specific patient presentation

Standard treatment for RSE patients is a “last resort” option that is outdated, expensive, and fraught with morbidity concerns
Novel treatment options must combine clinical benefits for RSE patients with substantial pharmaco-economic benefits for hospitals and payers

Hospital P&T committee members would be **universally enthusiastic** about a novel FDA-approved RSE treatment **despite** anticipating that this agent would be **priced significantly higher** than generic benzodiazepines and anti-epileptic drugs (AEDs)

**Physicians:** champion novel agents that provide essential clinical benefits

**Pharmacy Directors:** champion less expensive agents to conserve hospital budget

**Target benefits for a novel RSE treatment**

- Rapid and durable seizure control **minus** intubation and close patient monitoring =
  - Shorter hospital stays
  - Shorter ICU stays
  - Reduced incidence of pneumonia, infection, renal and cardiovascular events =

**Significant cost-savings**
Most of the $50,000 treatment expense for RSE treatment comes from the cost of hospital facilities, rather than drug costs.

### Hospital facility costs

- **ER**: $10,000/day
- **ICU**: $2,500-$10,000; 1:1 nurse to patient
- **Step-down unit**: $2,000-$3,000/day; 2:1 nurse to patient
- **Hospital floor**: $1,000-$3,000/day; 4:1 nurse to patient
- **Post-coma rehab**: physical/occupational therapy
- **Specialty consults**: potential consults: infectious disease, pulmonology, cardiology, nephrology, neurology
- **Imaging/testing**: to address respiratory, cardiovascular, renal, or CNS-related adverse events
- **Infused nutrition**: if coma extends beyond 48 hours

### Infused medication costs

- **Benzodiazepines** (including midazolam) and **AEDs** (IV): inexpensive; available as generic
- **Propofol**: inexpensive; available as generic (Teva)
- **Pentobarbital**: one Pharm D indicated that the price of pentobarbital increased recently

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<table>
<thead>
<tr>
<th>Stay</th>
<th>Few hours</th>
<th>4-6 days</th>
<th>2-3 days</th>
<th>2-3 days</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cost/day</strong></td>
<td>ER</td>
<td>ICU</td>
<td>Step-down unit</td>
<td>Hospital floor</td>
</tr>
<tr>
<td><strong>$10,000</strong></td>
<td>up to $10,000</td>
<td>$3,000</td>
<td>$2,000</td>
<td></td>
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</table>
Pharm Ds and NEUROs: a novel RSE treatment that reduces hospital costs by 20% would be quickly added to the hospital formulary

### Pharmaco-economic benefit

- **Shorten hospital stay**
  - Rapid and sustained seizure control
  - No recovery/rehab from sedation

- **Bypass ICU**
  - Bolus delivery suitable for the ER
  - No need for intubation
  - No intensive cardiovascular monitoring

- **Reduce adverse events**
  - Avoid frequent complications associated with intubation/ventilator/ICU

### RSE clinical benefits

- Rapid and sustained seizure control
- No recovery/rehab from sedation
- Bolus delivery suitable for the ER
- No need for intubation
- No intensive cardiovascular monitoring
- Avoid frequent complications associated with intubation/ventilator/ICU

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"If you can save $15,000 and offer other benefits then it’s a no-brainer for the P&T committee." Pharmacy Director

A novel RSE treatment that does not require ICU-level care could reduce the patient’s length of hospital stay and provide significant cost-savings to the hospital.

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**POTENTIAL RSE HOSPITAL STAY**

(Given availability of novel agent)

- Few hours
- 2 days
- 2 days

**Cost/day**

- ER: $10,000
- Step-down unit: $3,000
- Hospital Floor: $2,000

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SE/RSE Market Research Summary

SE/RSE Market Size & Structure – Secondary Research
- ICD-10 codes provide most comprehensive, empiric view of actual hospital diagnoses
- 75,000+ Status Epilepticus cases across 23 ICD-10 codes occur in US hospital each year
- Marinus in process of mining additional procedural codes to quantify RSE population

SE/RSE Clinician Interviews – Primary Research
- Primary treatment SE/RSE treatment goal is to stop seizures as quickly as possible
- Physicians seeking a drug to stop seizures and decrease intubation in refractory pats
- No distinction between convulsant and non-convulsant in terms of treatment

SE/RSE Payer Interviews - Primary Research
- Cost of SE/RSE is $50K+, driven by hospital LOS and various complications
- P&T members cite a tremendous need to address SE/RSE clinical and economic issues
- Pricing to reflect total costs savings and reduced morbidity as supported by PE ($25K+)
Ganaxolone Phase 2 in RSE

Dr. Maciej Gasior,
Executive Director, Clinical Development
Phase 2 RSE Proof-of-Concept Clinical Trial

Evaluate safety, tolerability, efficacy, and pharmacokinetics of GNX IV in RSE patients

Design:

• Open-label, PK group, dose-finding
• Up to 20 patients
• ~10-15 sites in US
• GNX IV adjunctive to SOC; currently available IV AEDs
• Dosing: loading dose followed-by continuous infusion on Day 1. Potential for additional infusions on Day 2-4 followed by taper
• Efficacy Objectives: time to onset and # patients who do not require an IV anesthetic drug within the first 24 hours
GNX Phase 2 Open-Label Trial Design

**Screening**

**Treatment Period**

<table>
<thead>
<tr>
<th>Loading Dose</th>
<th>Maintenance</th>
<th>Taper</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bolus plus continuous infusion</td>
<td>Potential for 2-4 day infusion</td>
<td>12 hour taper</td>
</tr>
</tbody>
</table>

**Follow up Period**

<table>
<thead>
<tr>
<th>Day After</th>
<th>3 Week FU</th>
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<tbody>
<tr>
<td>24hr in patient FU</td>
<td>Weeks 2,3,4 FU</td>
</tr>
</tbody>
</table>

**RSE Patients**

- Failed 1st line benzodiazepines (not required)
- Failed one 2nd line IV AED
- Significant challenge with patient identification and informed consent
Rationale For Use of Ganaxolone in RSE

- GNX works on extrasynaptic GABA-A receptors, which are still functional after prolonged seizures with RSE
- Efficacy seen in benzodiazepine-resistant SE rat model
- Evidence of rapid effects on EEG after IV infusion (propofol-like effects) - PK/PD study in healthy volunteers
- Lower risk of respiratory depression (unlike propofol) - large therapeutic window in both animals and healthy volunteers
- Several IV formulations of AEDs but none approved in RSE
## Key Differences of Sage SRSE Trial Vs. Marinus RSE Trial

<table>
<thead>
<tr>
<th>Patient Population</th>
<th>BRX: medically more difficult to treat than RSE; seizures less likely to respond than RSE patients</th>
<th>GNX: More likely to respond than SRSE patients via engagement of the GABA receptor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment Algorithm</td>
<td>On IV anesthetics with goal to remove IV anesthetics</td>
<td>Failed one 2\textsuperscript{nd} line IV AED. Goal is to prevent proceeding to IV anesthetics</td>
</tr>
<tr>
<td>Dose w/ targeted plasma level</td>
<td>~50-100ng/mL</td>
<td>&gt;~100ng/mL</td>
</tr>
<tr>
<td>Primary Endpoint</td>
<td>Prevent relapse to IV anesthetics</td>
<td>Block seizures and prevent progression of treatment</td>
</tr>
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Marinus RSE Program Summary

Strong rationale for targeting 2\textsuperscript{nd} line RSE
\begin{itemize}
  \item Receptor targeting for maximal efficacy
  \item Synergistic effects with benzodiazepines
  \item Potential to reduce need and duration for intubation, CV monitoring
  \item Avoid significant morbidity and mortality associated with 3\textsuperscript{rd} line treatments
\end{itemize}

Treatment success defined
\begin{itemize}
  \item Improve proportion of patients with 2\textsuperscript{nd} line treatment seizure control
  \item Provide meaningful period of status cessation to focus on underlying cause
\end{itemize}

Differentiated approach compared to SAGE program
\begin{itemize}
  \item Treating earlier in disease continuum
  \item Goal is to stop progression to IV anesthetic
  \item Higher dosing
  \item Less severe patient population
\end{itemize}

Data set to include
\begin{itemize}
  \item Up to 20 patients, multiple ascending dose
  \item EEG confirmation through duration of GNX infusion
  \item Follow-up to 24 hours
\end{itemize}
Thank you