Safe Harbor Statement

To the extent that statements contained in this presentation are not descriptions of historical facts regarding Marinus, they are forward-looking statements reflecting the current beliefs and expectations of management made pursuant to the safe harbor provisions of the Private Securities Litigation Reform Act of 1995. Words such as “may”, “will”, “expect”, “anticipate”, “estimate”, “intend”, “believe”, and similar expressions (as well as other words or expressions referencing future events, conditions or circumstances) are intended to identify forward-looking statements. Examples of forward-looking statements contained in this presentation include, among others, statements regarding our expected revenue and operating expenses for 2021; our clinical development plans for ganaxolone; expected dosing in our clinical trials; the clinical development schedule and milestones; our expected timing to begin and complete enrollment in our clinical trials; the expected trial design, target patient population and endpoints for our clinical trials; interpretation of scientific basis for ganaxolone use; timing for availability and release of data; the potential safety and efficacy and therapeutic potential of ganaxolone; timing and expectations regarding regulatory communications and submissions; our commercialization plans and the expected timing thereof; expectations regarding our agreement with BARDA; expectations regarding the potential market opportunities for our product candidates, including oral ganaxolone; potential commercial alliances; and our expectations regarding the effect of the COVID-19 pandemic on our business and clinical development plans. Forward-looking statements in this presentation involve substantial risks and uncertainties that could cause our clinical development programs, future results, performance or achievements to differ significantly from those expressed or implied by the forward-looking statements. Such risks and uncertainties include, among others, uncertainties and delays relating to the design, enrollment, completion, and results of clinical trials; interpretation of results of clinical trials; unanticipated costs and expenses; early clinical trials may not be indicative of the results in later clinical trials; clinical trial results may not support regulatory approval or further development in a specified indication or at all; actions or advice of the FDA or other regulatory agencies may affect the design, initiation, timing, continuation and/or progress of clinical trials or result in the need for additional clinical trials; our ability to obtain and maintain regulatory approval for our product candidate; our ability to obtain and maintain patent protection for our product candidates; the potential negative impact of third party patents on our ability to commercialize ganaxolone; delays, interruptions or failures in the manufacture and supply of our product candidate; our ability to raise additional capital; the effect of the COVID-19 pandemic on our business, the medical community and the global economy; and the availability or potential availability of alternative products or treatments for conditions targeted by us that could affect the availability or commercial potential of our product candidate. Marinus undertakes no obligation to update or revise any forward-looking statements. For a further description of the risks and uncertainties that could cause actual results to differ from those expressed in these forward-looking statements, as well as risks relating to the business of the Company in general, see filings Marinus has made with the Securities and Exchange Commission. You may access these documents for free by visiting EDGAR on the SEC web site at www.sec.gov.
**Ganaxolone (GNX) Targets Synaptic & Extrasynaptic \( \text{GABA}_A \) Receptors**

| **Ganaxolone** | a positive allosteric \( \text{GABA}_A \) receptor modulator with a well-defined MOA designed to treat patients suffering from epilepsy and neuropsychiatric disorders. GNX is designed to modulate both synaptic and extrasynaptic \( \text{GABA}_A \) receptors to calm over-excited neurons |
| **Clinical development** | focused on status epilepticus and rare genetic epilepsies that have few or no treatment options |
| **Multiple dose formulations** | IV and oral – to meet the needs of adult and pediatric patients in acute and chronic care settings |
| **Extensive safety record** | in more than 1,600 patients both pediatric and adult, at therapeutically relevant dose levels for up to two years |

The main inhibitory neurotransmitter in the brain is “GABA”. By binding to specific receptors, GABA can bring about decreased seizure activity.

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Evaluation of IV and Oral Opportunities

Building Upon Status Epilepticus (SE)
- Expand clinical opportunities to broader status epilepticus indications
- Build U.S. commercial strategy
- Execute global development plan
- Develop pharmacoeconomic, value proposition and outcomes assessment

Maximizing Value for Orphan Epilepsies
- CDKL5 deficiency disorder (CDD) commercialization strategy
- Advance tuberous sclerosis complex (TSC) clinical development
- Research scientifically based expansion opportunities
- Global integrated commercialization strategy

Leveraging GNX Molecule
- Explore opportunities to improve bioavailability, PK profile & clinical outcomes
- Engage in strategic collaborations on novel technologies & formulations
- Evaluate new indications based on unmet need, and scientific rationale
- Establish strategic commercial collaborations to expand geographic footprint
Ganaxolone Development Pipeline

<table>
<thead>
<tr>
<th>Administered</th>
<th>Seizure Disorders</th>
<th>Anticipated Milestones</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral Suspension</td>
<td>CDKL5 Deficiency Disorder (CDD)</td>
<td>NDA submission Mid-2021 MAA submission Q3 2021</td>
</tr>
<tr>
<td>Oral Suspension</td>
<td>Tuberous Sclerosis Complex (TSC)</td>
<td>PH2 Data Q3 2021 PH3 Patient enrollment Q4 2021</td>
</tr>
<tr>
<td>Intravenous Clinical Development</td>
<td>Refractory Status Epilepticus (RSE)</td>
<td>Data 1H-2022</td>
</tr>
<tr>
<td>Intravenous Clinical Development</td>
<td>Refractory Status Epilepticus (RSE): European Trial</td>
<td>PH3 trial to begin 1H 2022</td>
</tr>
<tr>
<td>Intravenous Clinical Development</td>
<td>Established Status Epilepticus (ESE)</td>
<td>1st patient enrolled 1H 2022 Data Mid-2023</td>
</tr>
<tr>
<td>Oral Suspension</td>
<td>Lennox-Gastaut Syndrome (LGS)</td>
<td>PH2 trial to begin mid-2022</td>
</tr>
</tbody>
</table>
Orphan Epilepsy Franchise
CDKL5 Deficiency Disorder

“CDKL5 is painful. It’s a hard, sad at times, thing that we face. When you have a relationship with people like Marinus and their researchers, you are able to help be a driving force behind that work.”

- Karen Utley, Mother to Samantha, President of International Foundation for CDKL5 Research
# CDKL5 Deficiency Disorder (CDD)

<table>
<thead>
<tr>
<th><strong>Cause</strong></th>
<th>Mutation of the cyclin-dependent kinase-like 5 (CDKL5) gene, located on the X chromosome</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Symptoms</strong></td>
<td>Early-onset, treatment refractory seizures, &amp; severe neuro-developmental delay  &lt;br&gt; Most can’t walk, talk or care for themselves  &lt;br&gt; Suffer from scoliosis, visual impairment, gastrointestinal difficulties &amp; sleeping disorders</td>
</tr>
<tr>
<td><strong>Incidence</strong></td>
<td>1:40,000 live births(^1); approx. 75-100 newborn in US and EU5  &lt;br&gt; Predominantly affects females  &lt;br&gt; Genetic testing available  &lt;br&gt; Orphan Disease</td>
</tr>
<tr>
<td><strong>Treatments</strong></td>
<td>No disease-specific treatments are approved</td>
</tr>
<tr>
<td><strong>Rationale</strong></td>
<td>Potential GABAergic dysfunction, achieved Primary endpoint in Marigold Phase 3 study</td>
</tr>
</tbody>
</table>

\(^1\)Symonds JD 2019 Brain

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## Completed Global Phase 3 Trial Design

### Trial Details

Evaluated the use of oral ganaxolone in children and young adults

Global, double-blind, placebo-controlled, clinical trial enrolled 101 patients between the ages of 2 and 19 with a confirmed disease-related CDKL5 gene variant

Ages 2-19, ≥16 major motor seizures/month; up to 4 concomitant AEDs

### Endpoints

Primary endpoint of the trial was percent change in 28-day major motor seizure frequency *

Non-seizure secondary outcome measures: Behavioral/neuropsychiatric changes correlated with domains of attention & sleep

* Major motor seizures were defined as bilateral tonic, generalized tonic-clonic, atonic/drop, bilateral clonic, or focal to bilateral tonic-clonic
Marigold Baseline Clinical Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Placebo (n=51)</th>
<th>Ganaxolone (n=50)</th>
<th>Total (n=101)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline Primary Seizure Frequency, per 28 days (median, IQR)</td>
<td>49.2 (18.7 – 120.0)</td>
<td>54.0 (31.3 – 147.3)</td>
<td>-</td>
</tr>
<tr>
<td>Number of AED Medications Taken Prior (median)</td>
<td>7</td>
<td>7</td>
<td>7</td>
</tr>
<tr>
<td>Concomitant AED Medications, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Valproate</td>
<td>16 (31.4)</td>
<td>18 (36.0)</td>
<td>34 (33.7)</td>
</tr>
<tr>
<td>Levetiracetam</td>
<td>13 (25.5)</td>
<td>13 (26.0)</td>
<td>26 (25.7)</td>
</tr>
<tr>
<td>Clobazam</td>
<td>13 (25.5)</td>
<td>12 (24.0)</td>
<td>25 (24.8)</td>
</tr>
<tr>
<td>Vigabatrin</td>
<td>12 (23.5)</td>
<td>10 (20.0)</td>
<td>22 (21.8)</td>
</tr>
</tbody>
</table>

Baseline seizure burden and AED history highlights unmet need
Ganaxolone Achieved Primary Efficacy Endpoint in Seizure Reduction and Secondary Endpoint for Seizure Severity

Ganaxolone Placebo
0 10 20 30 40
Median Percent Reduction
28-day Frequency of Major Motor Seizures
30.7%
6.9%
\( \Delta = 27.1\% (47.9 - 9.6)* \\
p = 0.0036**

*Hodges-Lehman Estimate of Median Difference
**Wilcoxon Rank-Sum Test

Caregiver Global Impression of Change in Seizure Intensity / Duration (CGI-CSID)

\[p=0.015^*\]

*Logistic Regression
Marigold Cumulative Response Curve

Percent Reduction 28-day Frequency of Major Motor Seizures

% of Patients

≥ 0% ≥ 5 ≥ 10 ≥ 15 ≥ 20 ≥ 25 ≥ 30 ≥ 35 ≥ 40 ≥ 45 ≥ 50

Ganaxolone
Placebo

p = 0.064^a

Δ = 14.7 (-4.7, 33.8)^b

24.5%

9.8%

*p<0.05^a

^aFisher's Exact

^bDifference (95% CI)
Consistent Efficacy Signal Across the Broader CDD Population

- Ganaxolone demonstrated a similar efficacy signal across multiple subgroups related to baseline demographics and seizure frequency
  - Supports beneficial effect in the U.S. patient population

U.S. AU/FR/IL/IT/UK RU/PL

\[ \Delta^a = 34.2\% \]

\[ \Delta^a = 25.2\% \quad \text{Hodges-Lehman Estimate of Median Difference} \]

Female Male

\[ \Delta^a = 12.5\% \]

Baseline Major Motor Seizure Frequency

[Per 28 days]
## Phase 3 Safety Summary

### Treatment Emergent Adverse Events (TEAE)

<table>
<thead>
<tr>
<th>Preferred Term</th>
<th>Placebo (n=51)</th>
<th>Ganaxolone (n=50)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any TEAE, n (%)</td>
<td>45 (88.2)</td>
<td>43 (86.0)</td>
</tr>
<tr>
<td>Somnolence</td>
<td>8 (15.7)</td>
<td>18 (36.0)</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>4 (7.8)</td>
<td>9 (18.0)</td>
</tr>
<tr>
<td>Upper Respiratory Tract Infection</td>
<td>3 (5.9)</td>
<td>5 (10.0)</td>
</tr>
<tr>
<td>Constipation</td>
<td>3 (5.9)</td>
<td>3 (6.0)</td>
</tr>
<tr>
<td>Salivary Hypersecretion</td>
<td>1 (2.0)</td>
<td>3 (6.0)</td>
</tr>
<tr>
<td>Sedation</td>
<td>2 (3.9)</td>
<td>3 (6.0)</td>
</tr>
</tbody>
</table>

*Includes AEs that occurred >5% of subjects in ganaxolone arm and ganaxolone > placebo*

### Serious Treatment Emergent Adverse Events

<table>
<thead>
<tr>
<th>Preferred Term</th>
<th>Placebo (n=51)</th>
<th>Ganaxolone (n=50)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any Serious TEAE, n (%)</td>
<td>5 (9.8)</td>
<td>6 (12.0)</td>
</tr>
<tr>
<td>Bronchitis</td>
<td>0 (0.0)</td>
<td>1 (2.0)</td>
</tr>
<tr>
<td>Rhinovirus Infection</td>
<td>0 (0.0)</td>
<td>1 (2.0)</td>
</tr>
<tr>
<td>Urinary Tract Infection</td>
<td>0 (0.0)</td>
<td>1 (2.0)</td>
</tr>
<tr>
<td>Pneumonia Mycoplasmal</td>
<td>1 (2.0)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Pneumonia Viral</td>
<td>1 (2.0)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Respiratory Syncytial Virus Bronchiolitis</td>
<td>1 (2.0)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Oxygen Saturation Decreased</td>
<td>0 (0.0)</td>
<td>1 (2.0)</td>
</tr>
<tr>
<td>Food Refusal</td>
<td>0 (0.0)</td>
<td>1 (2.0)</td>
</tr>
<tr>
<td>Pneumonia Aspiration</td>
<td>0 (0.0)</td>
<td>1 (2.0)</td>
</tr>
<tr>
<td>Hypoxia</td>
<td>1 (2.0)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Faecaloma</td>
<td>1 (2.0)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Hypotonia</td>
<td>1 (2.0)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Seizure</td>
<td>1 (2.0)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Unresponsive to Stimuli</td>
<td>1 (2.0)</td>
<td>0 (0.0)</td>
</tr>
</tbody>
</table>
Ganaxolone’s Potential to Provide Durable Seizure Improvements in the Open Label Extension

- Seizures associated with CDD are often refractory to treatment with existing AEDs and improvements may be short-lived (<3 months).¹
- Preliminary analysis* of the open-label extension (OLE) provides insights into the extended duration effects of ganaxolone (GNX) in CDD

Patients treated with ganaxolone for at least 12 months experienced a median 49.6% reduction in major motor seizure frequency

Patients transitioning from placebo to ganaxolone demonstrated seizure frequency improvements

No new safety findings emerged in the OLE to date


*Data as of February 24, 2021
Average Ganaxolone Levels Correlate with Seizure Reduction

- Logarithms of plasma GNX level and percentage change in major motor seizure frequency were negatively correlated.
- Patients in the Medium and High GNX level groups had an average GNX concentration of 120 ng/mL and a median 38.5% reduction in seizure frequency.
  - Incidence of CNS-related adverse events was similar across GNX dose level groups.

![Graph showing the correlation between loge GNX level and percent change in major motor seizure frequency.](image)

- **Pearson correlation**
  - Equivalent GNX Level (ng/mL)
  - Loge GNX Level (ng/mL)
  - Loge Percent Change Major Motor Seizure Frequency
  - Percent Change in Major Motor Seizure Frequency

<table>
<thead>
<tr>
<th>Equivalent GNX Level (ng/mL)</th>
<th>Loge GNX Level (ng/mL)</th>
<th>Loge Percent Change Major Motor Seizure Frequency</th>
<th>Equivalent % Change in Major Motor Seizure Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>20.1</td>
<td>3.0</td>
<td>0</td>
<td>-100</td>
</tr>
<tr>
<td>33.1</td>
<td>3.5</td>
<td>25</td>
<td>-75</td>
</tr>
<tr>
<td>54.6</td>
<td>4.0</td>
<td>50</td>
<td>-50</td>
</tr>
<tr>
<td>90.0</td>
<td>4.5</td>
<td>75</td>
<td>-25</td>
</tr>
<tr>
<td>148</td>
<td>5.0</td>
<td>100</td>
<td>0</td>
</tr>
<tr>
<td>245</td>
<td>5.5</td>
<td>125</td>
<td>25</td>
</tr>
<tr>
<td>403</td>
<td>6.0</td>
<td>150</td>
<td>50</td>
</tr>
</tbody>
</table>

- **Kruskal-Wallis Test**
- **p = 0.01**
- Mean GNX level within Group
- Mean GNX level withingroup

Loge percentage change in major motor seizure frequency was calculated as loge(percentage change + 100).

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PK Analysis: Adult Focal Onset Seizure Trial vs. Marigold

Adults Focal Onset Phase 3 Trial vs. Phase 1 PK

<table>
<thead>
<tr>
<th>Age Group</th>
<th>AUC$_{24}$ (ng*hr/mL)</th>
<th>$C_{\text{min}}$ (ng/mL)</th>
<th>$C_{\text{max}}$ (ng/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 to &lt;6 years</td>
<td>3903</td>
<td>85</td>
<td>247</td>
</tr>
<tr>
<td>6 to &lt;12 years</td>
<td>3998</td>
<td>84</td>
<td>269</td>
</tr>
<tr>
<td>12 to &lt;18 yrs</td>
<td>4106</td>
<td>84</td>
<td>293</td>
</tr>
<tr>
<td>≥18 years</td>
<td>4100</td>
<td>84</td>
<td>292</td>
</tr>
</tbody>
</table>

Abbreviations: AUC$_{24}$=24-hour area under the ganaxolone plasma concentration time curve; $C_{\text{max}}$=maximum ganaxolone plasma concentration; $C_{\text{min}}$=minimum ganaxolone plasma concentration.

Lower levels than predicted from Ph1

Marigold Trial PK

Adult focal onset program was discontinued as noted in the 10-Q
“Many individuals with TSC continue to experience uncontrolled seizures despite a cocktail of multiple antiepileptic drugs. Because new options are always needed, the TSC community welcomes clinical evaluation of new epilepsy treatments”

- Kari Luther Rosbeck, President & CEO of the Tuberous Sclerosis Alliance
# Tuberous Sclerosis Complex (TSC)

<table>
<thead>
<tr>
<th><strong>Cause</strong></th>
<th>Defect or mutation of TSC1 and/or TSC2 genes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Symptoms</strong></td>
<td>Benign tumors, seizures, cognitive impairment, behavioral problems, skin abnormalities</td>
</tr>
<tr>
<td><strong>Incidence</strong></td>
<td>1:6,000 live births</td>
</tr>
<tr>
<td><strong>Prevalence</strong></td>
<td>~25K-40K refractory TSC patients in the U.S.*</td>
</tr>
<tr>
<td><strong>Treatments</strong></td>
<td>Despite available treatments, continued unmet medical need</td>
</tr>
</tbody>
</table>
| **Mechanistic Rationale** | Potential neurosteroid deficiency¹  
Pathophysiology may involve GABAergic dysfunction |

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*Failure of two prior antiseizure medications with ongoing, frequent seizures.
### TSC - Phase 2 Open-Label Clinical Trial Design

<table>
<thead>
<tr>
<th><strong>PART A</strong></th>
<th><strong>PART B</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Baseline</strong> (4 Weeks)</td>
<td><strong>Open-Label Extension (OLE)</strong> (24 Weeks)</td>
</tr>
<tr>
<td><strong>GNX Titration</strong> (4 Weeks)</td>
<td><em>Available to patients that respond to GNX as defined per protocol</em></td>
</tr>
<tr>
<td><strong>GNX Maintenance</strong> (8 Weeks)</td>
<td></td>
</tr>
</tbody>
</table>

**Baseline Period**
- Screening Visit

**Treatment Period**
- Baseline Treatment Visit

**OLE Period**
- 2-week taper upon GNX discontinuation (if not continuing to Part B)

**Primary Seizure Types**
- Focal motor seizures without impairment of consciousness or awareness
- Focal seizures with impairment of consciousness or awareness
- Focal seizures evolving to bilateral generalized convulsive seizures
- Generalized seizures with a motor component that are countable

**Design**
- **n = Approx. 25**
- **8 U.S. sites**
- **Electronic diaries** will be used for data capture
- **At least 8 seizures per month**
- **Primary efficacy endpoint**: % change in 28-day primary seizure frequency through the end of 12-week treatment period relative to 4-week baseline period
- Patient enrollment to be completed March 2021
- **Top-line data expected Q3 2021**
Trial Details

Evaluates the use of oral ganaxolone in children and adults with seizures associated with TSC

Global, double-blind, placebo-controlled clinical trial

Aims to enroll ~160 total patients between the ages of 1 and 65 (1:1 randomization)

Up to 60 sites, including ex-US (e.g., EU, Canada, Australia, Russia).

Projected first patient enrolled in Q4

Primary Efficacy Endpoint

Percent change in 28-day primary endpoint seizure frequency*

* Primary endpoint seizure types: focal motor seizures without impairment of consciousness or awareness, focal seizures with impairment of consciousness or awareness, focal seizures evolving to bilateral generalized convulsive seizures, and generalized seizures with a motor component that are countable
Formulation Development
Efforts to Improve Ganaxolone Exposure in Chronic Epilepsies

▶ **Dosing regimen:** Marigold Study was the first Phase 3 trial of ganaxolone to evaluate three times a day (TID) dosing
  - Predicted pharmacokinetic (PK) curves for TID and two times a day (BID) dosing demonstrate increase trough GNX levels which may provide improved seizure control

▶ Support the continued study of ganaxolone TID dosing in other epilepsies

▶ **Formulation development:** new oral ganaxolone formulations in development that aim to improve PK properties to better achieve target ganaxolone levels

<table>
<thead>
<tr>
<th>Dose regimen</th>
<th>( C_{\text{max}} ) (ng/mL)</th>
<th>( \text{AUC}_{0-24} ) (ng ( \cdot ) h/mL)</th>
<th>% time (&gt;100 ng/mL GNX)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TID</td>
<td>281</td>
<td>3763</td>
<td>78</td>
</tr>
<tr>
<td>BID</td>
<td>286</td>
<td>3135</td>
<td>53</td>
</tr>
</tbody>
</table>
Ganaxolone Formulation Work in Progress for Second Generation Candidate

- Exploring opportunities to improve bioavailability and PK profile
- Potential expansion into new indications and into new therapeutic areas
- Targeting IV-to-oral step down for patients that may benefit from continued therapy
Commercial Opportunity
Commercialization Preparedness

- Refining and Optimizing Value Proposition for Market Testing with key stakeholders – Providers, Payers
- Developing organizational and infrastructure needs – home office, field, systems and processes
- Readying supply chain to support patient services, channel strategy and scale up needs
- Evaluating Life Cycle plans to scale up Access, Scientific Affairs and Commercial teams
- Key Objectives is to create operational leverage across indications
### Key Findings from Recently Conducted Market Research Show that Ganaxolone is Well Suited for Broad Clinical Adoption Across Indications

<table>
<thead>
<tr>
<th>Mechanism of Action</th>
<th>Ganaxolone’s extrasynaptic mechanism of action well understood and viewed as differentiable</th>
</tr>
</thead>
<tbody>
<tr>
<td>TPP Reactions</td>
<td>Many HCPs are excited about the opportunity to use ganaxolone, especially for CDD, given favorable reactions to its efficacy and durability data, and safety profile</td>
</tr>
</tbody>
</table>
| Primary Usage Drivers | • Disease-specific indication, response rate, and durability of response in a highly refractory patient population  
• Ability to be used with antiseizure medications across mechanisms (i.e., sodium channel blockers, GABA transmission inhibitors, cannabidiol) in refractory patients |
| Awareness           | Neurologists who treat both CDD and TSC patients had high awareness of ganaxolone |

Source: ZS Associates Primary Research and Analysis (N=35 HCP Interviews), (TPP – May 2020; other market research – June 2020)
Status Epilepticus
Status Epilepticus (SE): Definition and Epidemiology

**Background**

- Prolonged continuous seizures
- Heterogenous patient population with various etiologies, including glioblastoma, vascular disease, encephalitis, drug or alcohol withdrawal or overdose
- Pre-existing epilepsy in less than half of SE cases
- Status epilepticus can result in permanent neuronal damage and contribute to high morbidity and mortality
- Becomes more treatment refractory with progression

SE is the second most common neurologic emergency in the U.S.¹

150,000 SE patients²

---

1. Anaesthesia and Intensive Care Medicine, February 02, 2018, Update on the management of status epilepticus
Goals of a New Therapy for the Treatment of SE

1st line
Benzodiazepine Administered

Established Status Epilepticus (ESE)

Medically induced Coma

2nd line
IV AED's (antiepileptic drugs)

Refractory Status Epilepticus (RSE)

Super Refractory Status Epilepticus (SRSE)

3rd line
IV Anesthetics

IV GNX
Pharmacokinetics/Pharmacodynamics Well Suited for Acute SE Treatment

Ganaxolone activates the extrasynaptic GABA_A receptor, is associated with high brain concentrations, and delivers a rapid onset of action.

### Experimental PK – plasma and brain

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

*Human PK*^2^ Following 20 mg ganaxolone bolus (over 2 minutes):

- $C_{\text{max}}$ 1,240 ng/mL
- $T_{\text{max}}$ 0.08 hrs

### Human PD – EEG changes

EEG bispectral index in healthy volunteers following IV ganaxolone

---

2. Data on file, Marinus Pharmaceuticals, Inc.
Phase 2 RSE Trial Design

Evaluate IV ganaxolone in refractory SE patients

SE Patients → Screening → Diagnosis of convulsive or non-convulsive SE
Failed at least one 2nd line IV AED but had not progressed to 3rd line IV anesthetics → Treatment Period → Post-treatment Follow-up

<table>
<thead>
<tr>
<th>Treatment Period</th>
<th>Loading Dose</th>
<th>Maintenance</th>
<th>Taper</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Bolus plus continuous infusion</td>
<td>2-4 day infusion</td>
<td>18-hour taper</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Cohort</th>
<th>Dose of GNX/day</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>500mg/day</td>
<td>5</td>
</tr>
<tr>
<td>Medium</td>
<td>650mg/day</td>
<td>4</td>
</tr>
<tr>
<td>High</td>
<td>713mg/day</td>
<td>8</td>
</tr>
</tbody>
</table>

Goals of a new treatment
Rapid cessation
Maintenance of seizure control
Prevent progression to IV anesthetics

Limitations of current treatments
1st line Benzodiazepines ineffective in 45%-50%; limited by cardiovascular and respiratory side effects
2nd line Ineffective in over 50% of established SE; further decreased response in refractory SE
3rd line IV Anesthetics: high morbidity, mortality ~35%; increased duration of hospitalization and costs of care

Endpoints
Primary: Percent of patients who did not require escalation of treatment with IV anesthetic within the first 24 hours after ganaxolone initiation
Secondary: Additional efficacy, safety and tolerability
## Patient Demographics of Phase 2 Trial

### History of Epilepsy
- 7 (41%) yes, 10 (59%) no

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

### Mean # of failed 2nd-line IV AEDs
- 2.1 (range: 1-4), all failed LEV or LAC
- 14/17 patients failed two or more 2nd-line AEDs
- All prior AEDs were administered within recommended dosing guidelines

### Etiologies
- 7 Vascular
- 4 Tumor
- 2 Autoimmune
- 2 Drug overdose
- 2 Unknown

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

### Mean # of failed first-and-second line IV AEDs (including benzodiazepines)
- 2.9 (range: 2-5)
Phase 2 Trial Results Demonstrated Rapid Onset And Durability of Effect

<table>
<thead>
<tr>
<th>Cohort</th>
<th>Status-Free Through 24 Hours From Infusion Initiation (Investigator Determination)</th>
<th>No Escalation to Additional IV AEDs or IV Anesthetics for Status Relapse at Any Time Through 24 Hours After Ganaxolone Discontinuation</th>
<th>No SE Relapse at Anytime During the 4-Wk Follow Up Period</th>
</tr>
</thead>
<tbody>
<tr>
<td>High (713 mg/day) (n=8)</td>
<td>88% (7 of 8)</td>
<td>100% (8 of 8)</td>
<td>100% (6 of 6) (1ET, 1 died)</td>
</tr>
<tr>
<td>Medium (650 mg/day) (n=4)</td>
<td>100% (4 of 4)</td>
<td>100% (4 of 4)</td>
<td>75% (3 of 4)</td>
</tr>
<tr>
<td>Low (500 mg/day) (n=5)</td>
<td>100% (5 of 5)</td>
<td>100% (5 of 5)</td>
<td>50% (1 of 2) (1 died)</td>
</tr>
</tbody>
</table>

Immediate Prior AED Administered 4 Hours (mean) to Ganaxolone Treatment

SE Cessation Occurred Rapidly in All Dose Groups (median = 5 minutes)
PK/PD Relationship and Rationale for Target Dose

Modeled PK Curves for All Dose Groups

- High Dose Achieves Target Range ≥ 500 ng/mL for ~8 hours

Seizure Burden Reduction Occurred Rapidly in All Dose Groups

- Only High Dose Provided Sustained Reduction (>80%) Throughout Entire Analysis Window

Data presented at AES 2019

PK: Pharmacokinetics / PD: Pharmacodynamic
## 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 patients

13 related in 7 patients
- 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 patients
- 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 stroke, 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.

---

AE: adverse event / SAE: serious adverse event

Data presented at AES 2019

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# Overview of U.S. Phase 3 RSE RAISE Trial Design

<table>
<thead>
<tr>
<th>Trial design</th>
<th>• Randomized, placebo-controlled (adjunctive to standard-of-care) clinical trial</th>
</tr>
</thead>
<tbody>
<tr>
<td>Target patient population</td>
<td>• Status epilepticus patients (n=124) who have failed benzodiazepines and ≥ 2 IV AEDs</td>
</tr>
</tbody>
</table>
| Dosing | • 36-hour infusion followed by a 12-hour taper (48-hour treatment)  
• Phase 2 dose paradigm and extends ganaxolone plasma exposure ≥ 500 ng/mL for 12 hours |
| Co-primary endpoints | • Proportion of participants with SE cessation within 30 minutes of study drug initiation without medications for the acute treatment of SE  
• Proportion of participants with no progression to IV anesthesia for 36 hours following study drug initiation |
| Secondary endpoints | • No progression to IV anesthesia for 24 hours off study drug (i.e., 72 hours)  
• Time to SE cessation  
• Healthcare utilization metrics (eg, length of stay, # of days in the ICU)  
• Functional outcomes  
• Safety measures |
RSE Phase 3 RAISE Clinical Planning

Phase 3 Target Plasma Concentration

- 1:1 randomized, double-blind, placebo-controlled trial
- Failure of a benzodiazepine and 2 second-line IV AEDs
- 3-minute bolus, 36-hour infusion, 12-hour taper
- Approx. 125 randomized patients
- 80-100 sites

Currently recruiting patients
Topline data expected 1H 2022

<table>
<thead>
<tr>
<th>Treatment Period</th>
<th>Follow-up Period</th>
</tr>
</thead>
<tbody>
<tr>
<td>Daily</td>
<td>Daily</td>
</tr>
<tr>
<td>Hours 0-24</td>
<td>Weeks 1, 2, 3, 4</td>
</tr>
<tr>
<td>Day 2</td>
<td></td>
</tr>
<tr>
<td>Hours 24-36</td>
<td></td>
</tr>
<tr>
<td>Hours 36-48</td>
<td></td>
</tr>
<tr>
<td>24-120 hours</td>
<td></td>
</tr>
<tr>
<td>Continuous Infusion</td>
<td>Taper</td>
</tr>
<tr>
<td>Infusion Taper</td>
<td></td>
</tr>
</tbody>
</table>

Treatment is planned to be 2 days (including a 12-hour taper).
Surveyed PI's at selected RAISE Trial sites to learn more about their standard of care natural history progression to IV anesthesia following the failure of one versus more than one 2nd-line IV AEDs.

Of those that escalate to 3rd-line IV anesthesia, they do so in ~2.5 hours following failure of the second 2nd-line IV AED.

Clear unmet medical need in patients that fail two or more 2nd line IV AEDs.

Guides site selection and approximates placebo response for escalation to IV anesthesia co-primary.

Patients with non-convulsive status epilepticus (NCSE)
Commercial Opportunity
The Phase 3 trial of ganaxolone in refractory SE aims to demonstrate rapid onset of action capable of preventing escalation to IV anesthetics, and downstream associated clinical outcomes.

Treatment with IV anesthetics has been reported to lead to increased length of hospital admission and risk of infections, new disability, and death\textsuperscript{1-3}.

Pharmacoeconomic opportunity to quantify cost of care and characterize clinical outcomes based on treatment progression to IV anesthetics.

To support value-based economics / approach will be a key tool with reimbursement experts.
# High Cost of Care Currently Associated with RSE Population

Ganaxolone may provide an opportunity to reduce hospital costs and save lives by altering how medicine is practiced.

## Clinical Outcomes

<table>
<thead>
<tr>
<th>Metric</th>
<th>Cohort 1 (≤ 1 IV AED)</th>
<th>Cohort 2 (&gt; 1 IV AED)</th>
<th>Cohort 3 (≥ 1 IV anesthetic)</th>
<th>All</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unique RSE patient encounter, N (%)</td>
<td>14,694 (33.4)</td>
<td>10,140 (23.1)</td>
<td>19,154 (43.5)</td>
<td>43,988 (100)</td>
</tr>
<tr>
<td>Discharge disposition (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Expired*</td>
<td>4.6</td>
<td>6.3</td>
<td>18.9</td>
<td>11.2</td>
</tr>
<tr>
<td>Hospital-acquired condition (%Y)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Catheter-associated UTI (%)</td>
<td>12.0</td>
<td>17.4</td>
<td>18.3</td>
<td>16.0</td>
</tr>
<tr>
<td>Miscellaneous infection* (%)</td>
<td>1.6</td>
<td>1.7</td>
<td>4.3</td>
<td>2.8</td>
</tr>
<tr>
<td>Vascular catheter-associated infection* (%)</td>
<td>0.2</td>
<td>0.2</td>
<td>0.4</td>
<td>0.3</td>
</tr>
<tr>
<td>Mechanical ventilator-associated complication (%)</td>
<td>0.2</td>
<td>0.2</td>
<td>1.6</td>
<td>0.8</td>
</tr>
</tbody>
</table>

## Utilization and Cost Outcomes

<table>
<thead>
<tr>
<th>Metric</th>
<th>Cohort 1 (≤ 1 IV AED)</th>
<th>Cohort 2 (&gt; 1 IV AED)</th>
<th>Cohort 3 (≥ 1 IV anesthetic)</th>
<th>All</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unique RSE patient encounter, N (%)</td>
<td>14,694 (33.4)</td>
<td>10,140 (23.1)</td>
<td>19,154 (43.5)</td>
<td>43,988 (100)</td>
</tr>
<tr>
<td>Hospital length of stay (LOS) (days)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean*</td>
<td>4.7</td>
<td>7.2</td>
<td>12.0</td>
<td>8.4</td>
</tr>
<tr>
<td>Median*</td>
<td>3</td>
<td>4</td>
<td>8</td>
<td>5</td>
</tr>
<tr>
<td>ICU LOS (for ICU patients only)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean*</td>
<td>2.7</td>
<td>3.1</td>
<td>6.6</td>
<td>5.4</td>
</tr>
<tr>
<td>Median*</td>
<td>2</td>
<td>2</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>Total hospital cost* ($USD)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean*</td>
<td>$11,532</td>
<td>$18,328</td>
<td>$41,858</td>
<td>$26,304</td>
</tr>
<tr>
<td>Median*</td>
<td>$6,812</td>
<td>$10,592</td>
<td>$24,105</td>
<td>$13,201</td>
</tr>
</tbody>
</table>

Marinus estimates that safe and effective therapeutics that prevent progression to SRSE (i.e., treatment with IV anesthetics) may reduce mortality rates and hospital costs.

Source: Guteran EL 2021 JAMA Neurol.
Status Epilepticus
Development Plan
Status Epilepticus Patient Populations & Development Plan

Drugs Administered

- Established SE
- Refractory SE
- Super-Refractory SE

ESE Phase 2 Trial

Convulsive SE
(45% of total SE population)¹

Non-Convulsive SE/ Focal SE
(55% of total SE population)¹

~15% transition to NCSE/Focal SE

Benzodiazepines

IV AED’s

IV Anesthetics

Emergency Dept. / ICU

ICU

1. Leitinger M. 2019 Epilepsia

IV Ganaxolone’s clinical development programs address patient populations in different treatment settings across the SE continuum.
Additional Commercial Opportunities Along SE Continuum

Potential to leverage future hospital sales force to address > 3x patient population in ESE & SRSE

Treatment of Refractory Status Epilepticus

Failure of Benzodiazepines and Initial Second Line AEDs

Failure of Benzodiazepines and Two or More Second Line AEDs

- Ganaxolone can be initiated earlier in the course of RSE
- Patient population failing benzodiazepine and initial second line AED
Proposed Phase 3 Trial in Refractory SE (RAISE II)

► Trial Goals:
  • Support potential European approval in RSE
  • Potential indication expansion opportunity (relative to the RAISE study population)

<table>
<thead>
<tr>
<th>Trial Attributes</th>
<th>RAISE II</th>
<th>RAISE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trial Population</td>
<td>Failure of benzodiazepines and at least one IV AED’s (RSE) (n=70)</td>
<td>Failure of benzodiazepines and at least two IV AED’s (RSE) (n=124)</td>
</tr>
<tr>
<td>Comparator</td>
<td>Ganaxolone vs. Placebo with concurrent IV AED initiation</td>
<td>Ganaxolone vs. Placebo in patients receiving background standard of care</td>
</tr>
<tr>
<td>Primary Endpoint</td>
<td>Responder analysis: SE cessation within 30 min and no escalation of care within 36 hrs</td>
<td>Co-primary: (1)SE cessation within 30 min (2) no escalation to IV anesthesia within 36 hrs</td>
</tr>
<tr>
<td>Geographic Location</td>
<td>EU/UK/US</td>
<td>US only</td>
</tr>
</tbody>
</table>
Established Status Epilepticus – Potential Use of Ganaxolone in Emergency Room

• Unique Environment:
  - No EEG
  - Risk of rapid escalation of care
  - Convulsive patients: new dosing paradigm – bolus and short infusion time (2-24 hours)
Established Status Epilepticus – Potential Use of Ganaxolone in Emergency Room

**Proposed ESE Clinical Trial Design**

- **Pilot:** N = 4-5 per cohort
  - Failed benzodiazepine → Open → Bolus → IV ganaxolone infusion
  - Standard of care IV AED

- **Blinded:** N = 40 per arm
  - Failed benzodiazepine → 1:1 → Bolus → IV ganaxolone
  - Placebo bolus → Placebo
  - Standard of care IV AED

- **Screening** <30 min
- **Randomization**
- **Double-blind treatment (2-24h)** 2-24h

- **Not enough time for consent**
  - Exception from Informed Consent (EFIC) / Community consent activities
- **First patient expected to be enrolled in 1H of 2022**
Financial Update
Credit Financing Overview

Credit financing agreement with **Oaktree Capital Management**, a leader among investment managers specializing in alternative investments

Financing has potential to provide incremental cash of **up to $125 million total** through 2023* (gross proceeds before fees)

**$75 million** available to be drawn through 2H 2022 based on anticipated regulatory milestones associated with the CDKL5 Deficiency Disorder indication

Marinus has option to draw the final **$50 million** based on additional ganaxolone milestones*.

The loan will mature in May 2026 and includes an interest only period for the initial three years of the agreement

Transaction proceeds enable continued investment in commercialization, R&D, and manufacturing scale up

Monetization of the anticipated Priority Review Voucher is permitted and Marinus maintains ability to execute a U.S. synthetic royalty monetization deal

Morgan Stanley & Co. LLC acted as lead placement agent and H. C. Wainwright & Co. acted as co-placement agent on the transaction

*Availability subject to meeting of certain regulatory, clinical, financing, and revenue thresholds

**15 million drawn at closing in May 2021
Updated 2021 Guidance

• Revenue
  • FY 2021 projected to be between $9 - $12 million

• Operating Expenses
  • FY 2021 loss from operations of between $113 - $118 million
  • Total includes approximately $16 million of non-cash stock-based compensation

Financial Summary (at March 31, 2021):  
• $123.5 million in cash and cash equivalents
• $0 in debt
• 36.6 million shares outstanding
• 5.4 million options, RSUs & convertible preferred stock outstanding

Investor Relations – Nasdaq: MRNS

Analyst Coverage*:  
• Cantor Fitzgerald: Alethia Young
• Cowen: Joseph Thome, Ph.D.
• H.C. Wainwright & Co: Douglas Tsao
• Jefferies: Andrew Tsai
• JMP Securities: Jason N. Butler, Ph.D.
• Ladenburg Thalman: Michael Higgens
• Leerink: Marc Goodman
• Oppenheimer: Jay Olson
• Truist: Joon Lee, M.D., Ph.D.
• RW Baird: Brian Skorney

* Note: Opinions, estimates, and forecasts of the individual analysts regarding Marinus do not represent opinions, estimates, and forecasts of Marinus. The listing above does not imply endorsement or concurrent with their information, conclusions, or recommendations.
BARDA Contract – Refractory Status Epilepticus

Key Contract Parameters

► BARDA to contribute $21 million in base contract to support the Phase 3 RAISE clinical trial in RSE and preclinical studies of ganaxolone in nerve agent exposure animal models.

► BARDA may contribute up to an additional $30 million in support of manufacturing, supply chain, clinical, regulatory and toxicology activities based on favorable clinical and pre-clinical outcomes.

► Total contract value = $84 million; $51 million BARDA / $33 million Marinus - if all options are undertaken.

► On successful development, BARDA and Marinus may negotiate for a supply of ganaxolone for a potential response to nerve gas exposure threats.
Intellectual Property
Multiple Layers Of Potential Protection

<table>
<thead>
<tr>
<th>Patent/Patent Applications</th>
<th>Expiration Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>IV formulations containing exclusively in-licensed proprietary Captisol® product</td>
<td>2033</td>
</tr>
<tr>
<td>SE – patent application pending on IV formulations and methods of use</td>
<td>2036</td>
</tr>
<tr>
<td>SE – patent application pending on clinical treatment regimen</td>
<td>2040</td>
</tr>
<tr>
<td>Oral Formulations – nanoparticulate formulations (2026 + up to 5 Year PTE)</td>
<td>2031</td>
</tr>
<tr>
<td>CDD &amp; PCDH19 – patent application pending on methods of use, patient stratification</td>
<td>2038</td>
</tr>
<tr>
<td>TSC – patent application pending on methods of use</td>
<td>2040</td>
</tr>
<tr>
<td>Oral Formulations containing cyclodextrin</td>
<td>2042</td>
</tr>
</tbody>
</table>

Orphan drug designations for CDD and PCDH19 provide 7 and 10 years regulatory exclusivity in US and EU, respectively. Orphan drug designation for SE provides 7 years regulatory exclusivity in US.
Thank You
Appendix
CDKL5 Deficiency Disorder
# Subject Baseline Demographics & Country Enrollment in Marigold Study (CDD)

<table>
<thead>
<tr>
<th>Demographic</th>
<th>Placebo (n=51)</th>
<th>Ganaxolone (n=50)</th>
<th>Total (n=101)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age, median</strong></td>
<td>7.0</td>
<td>5.0</td>
<td>6.0</td>
</tr>
<tr>
<td><strong>Gender, n (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>10 (19.6)</td>
<td>11 (22.0)</td>
<td>21 (20.8)</td>
</tr>
<tr>
<td>Female</td>
<td>41 (80.4)</td>
<td>39 (78.0)</td>
<td>80 (79.2)</td>
</tr>
<tr>
<td><strong>Ethnicity, n (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hispanic or Latino</td>
<td>6 (11.8)</td>
<td>4 (8.0)</td>
<td>10 (9.9)</td>
</tr>
<tr>
<td>Not-Hispanic or Latino</td>
<td>43 (84.3)</td>
<td>44 (88.0)</td>
<td>87 (86.1)</td>
</tr>
<tr>
<td>Unknown</td>
<td>1 (2.0)</td>
<td>1 (2.0)</td>
<td>2 (2.0)</td>
</tr>
<tr>
<td>Not reported</td>
<td>1 (2.0)</td>
<td>1 (2.0)</td>
<td>2 (2.0)</td>
</tr>
<tr>
<td><strong>Race, n (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>47 (92.2)</td>
<td>46 (92.0)</td>
<td>93 (92.1)</td>
</tr>
<tr>
<td>Asian</td>
<td>3 (5.9)</td>
<td>2 (4.0)</td>
<td>5 (5.0)</td>
</tr>
<tr>
<td>Other</td>
<td>1 (2.0)</td>
<td>2 (4.0)</td>
<td>3 (3.0)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Country</th>
<th>Count</th>
</tr>
</thead>
<tbody>
<tr>
<td>US</td>
<td>42</td>
</tr>
<tr>
<td>IT</td>
<td>15</td>
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<tr>
<td>RU</td>
<td>14</td>
</tr>
<tr>
<td>PL</td>
<td>10</td>
</tr>
<tr>
<td>UK</td>
<td>7</td>
</tr>
<tr>
<td>FR</td>
<td>6</td>
</tr>
<tr>
<td>AU</td>
<td>6</td>
</tr>
<tr>
<td>IL</td>
<td>1</td>
</tr>
</tbody>
</table>
Responder Analysis – Marigold Study

Percent Reductions in Major Motor Seizure Frequency

- ≥ 25%
- ≥ 50%
- ≥ 75%

% of Patients

Ganaxolone
Placebo

57.1%
23.5%
24.5%
9.8%
10.2%
3.9%

p=0.064

Fisher's Exact Test

p=0.001

Percent Reduction 28-day Frequency of Major Motor Seizures

≥ 25% 23.5%
≥ 50% 9.8%
≥ 75% 3.9%

aFisher's Exact Test
Tuberous Sclerosis Complex
Unmet Need in TSC Epilepsy and Scientific Rationale for Ganaxolone

► Epilepsy present in ~90% of individuals affected with TSC
► Existing treatments fail to control seizures in ~60% of individuals with TSC-associated epilepsy
► Uncontrolled seizures, especially early in life, may lead to developmental delays and cognitive dysfunction

Clear need to evaluate treatments with a differentiated mechanism of action

Data generated in collaboration with the TS Alliance and utilization of their biosample repository

SHORT REPORT

GABA<sub>A</sub> receptor active steroids are altered in epilepsy patients with tuberous sclerosis

F di Michele, M Verdecchia, M Dorofeeva, L Costamagna, G Bernardi, P Curatolo, E Romeo

J Neural Neurosurg Psychiatry 2009;74:667-670

2. ChuShore CJ et al Epilepsia_The natural history of epilepsy in TSC.
Status Epilepticus
### Details on Baseline Patient Characteristics for Phase 2 SE Trial

<table>
<thead>
<tr>
<th>Patient</th>
<th>Dosing Cohort</th>
<th>Etiology</th>
<th>History of Epilepsy</th>
<th>Type of SE</th>
<th>Failed Antiseizure Medications Prior to GNX*</th>
<th>Dose of Last IV AED Administered Prior to GNX (Recommended Dose)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Low</td>
<td>Vascular</td>
<td>No</td>
<td>NCSE</td>
<td>LAC, LEV</td>
<td>200mg (200-600mg)</td>
</tr>
<tr>
<td>2</td>
<td>Low</td>
<td>Unknown</td>
<td>Yes</td>
<td>NCSE</td>
<td>fPHT, LEV</td>
<td>1,000mg (1000-3000mg)</td>
</tr>
<tr>
<td>3</td>
<td>Low</td>
<td>Vascular</td>
<td>No</td>
<td>NCSE</td>
<td>LOR, LAC, LEV</td>
<td>600mg (200-600mg)</td>
</tr>
<tr>
<td>4</td>
<td>Low</td>
<td>Tumor</td>
<td>No</td>
<td>NCSE</td>
<td>LOR, LAC, LEV</td>
<td>600mg (200-600mg)</td>
</tr>
<tr>
<td>5</td>
<td>Low</td>
<td>Vascular</td>
<td>No</td>
<td>CSE</td>
<td>LOR, LAC, LEV</td>
<td>2,000mg (1000-3000mg)</td>
</tr>
<tr>
<td>6</td>
<td>Medium</td>
<td>Vascular</td>
<td>No</td>
<td>NCSE</td>
<td>LOR, LAC, LEV</td>
<td>600mg (200-600mg)</td>
</tr>
<tr>
<td>7</td>
<td>Medium</td>
<td>Drug Overdose / Withdrawal</td>
<td>Yes</td>
<td>CSE</td>
<td>LOR, LEV</td>
<td>1,000mg (1000-3000mg)</td>
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<tr>
<td>8</td>
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<td>Unknown</td>
<td>Yes</td>
<td>CSE → NCSE</td>
<td>LOR, LAC, LEV</td>
<td>1,000mg (1000-3000mg)</td>
</tr>
<tr>
<td>9</td>
<td>Medium</td>
<td>Tumor</td>
<td>Yes</td>
<td>NCSE</td>
<td>LAC, LEV, PHT</td>
<td>200mg (100mg)</td>
</tr>
<tr>
<td>10</td>
<td>Target</td>
<td>Vascular</td>
<td>Yes</td>
<td>CSE</td>
<td>LOR, LAC, VPA</td>
<td>400mg (200-600mg)</td>
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<tr>
<td>11</td>
<td>Target</td>
<td>Drug Overdose / Withdrawal</td>
<td>No</td>
<td>CSE</td>
<td>LOR, LAC, LEV</td>
<td>400mg (200-600mg)</td>
</tr>
<tr>
<td>12</td>
<td>Target</td>
<td>Tumor</td>
<td>Yes</td>
<td>NCSE</td>
<td>LOR, LEV, VPA</td>
<td>700mg (1000-3000mg)</td>
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<tr>
<td>13</td>
<td>Target</td>
<td>Autoimmune</td>
<td>No</td>
<td>NCSE</td>
<td>LOR, LEV</td>
<td>1,000mg (1000-3000mg)</td>
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<tr>
<td>14</td>
<td>Target</td>
<td>Vascular</td>
<td>No</td>
<td>NCSE</td>
<td>LOR, LAC, LEV, PHT</td>
<td>200mg (200-600mg)</td>
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<td>15</td>
<td>Target</td>
<td>Vascular</td>
<td>Yes</td>
<td>CSE</td>
<td>LOR, LEV</td>
<td>1,000mg (1000-3000mg)</td>
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<tr>
<td>16</td>
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<td>No</td>
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<td>17</td>
<td>Target</td>
<td>Autoimmune</td>
<td>No</td>
<td>NCSE</td>
<td>LOR, fPHT, LAC, LEV, VPA</td>
<td>200mg (200-600mg)</td>
</tr>
</tbody>
</table>

NCSE: Non-convulsive status epilepticus  
CSE: Convulsive status epilepticus  
LAC: Lacosamide  
LEV: Levetiracetam  
PHT: Phenytoin  
fPHT: Fosphenytoin  
VPA: Valproic Acid

*Bolded, underlined IV AED’s were the last ones administered prior to GNX.*
Potential Launch Into the Hospital Setting Designed to be Driven by Data, Customer Collaboration & Protocolization of Ganaxolone in RSE

Critical Success Factors for RSE Launch

**Clinical and Economic Evidence**
- Phase 3 data to support clinical adoption and budget model
- Clear clinical benefit e.g., SE cessation, IV escalation
- Economic advantage – LOS*, ICU duration, clinical outcomes

**Compelling Clinical and HEOR* Data**

**Society Guideline & Account Protocol Inclusion**
- Partner with KOLs and societies to update RSE treatment guidelines
- Collaborative approach to protocol augmentation with health systems and local hospitals

**Clinical Adoption**

**Access**
- Early engagement with hospital stakeholders to best understand and frame value proposition
- Determine formulary process and requirements
- Reimbursement, logistics and operational processes

**C-Suite, Pharmacy, & Admin Engagement**

**Experience Hospital Sales Force**
- Identify, navigate and influence unique hospital decision makers
- Educate and generate customer usage data
- Collaborate internally to protocolize usage and translate success

**Pull-Through**

*LOS – Longer length of stay
*HEOR – Health economics and outcomes research
PCDH19 Related Epilepsy
**Biomarker Stratified Proof of Concept (POC) Study in PCDH19**

**Trial Details**

- Ages 1-17 with 8 or more seizures in 8 weeks, failed 2 or more AEDs
- Completed double-blind portion of the trial with 21 patients
- Primary efficacy analysis based on change in seizure frequency in all patients
- Stratify patients into one of two biomarker groups based on baseline allopregnanolone sulfate levels and randomized (ganaxolone or placebo) within each stratum

**Primary efficacy analyses conducted using all patients**

- Pre-baseline Screening
- Baseline 12 weeks
- Titration 4 weeks
- Maintenance 13 weeks
- Titration 4 weeks
- Open-Label Phase (52 weeks) *not drawn to scale*
Ganaxolone Demonstrates Directional Improvement in Change in Seizure Frequency

Primary endpoint seizure types are defined as countable focal seizures with impaired awareness or generalized seizure with a clear motor component.

Baseline Primary Endpoint
28-day Seizure Frequency (median)

**Ganaxolone**
14.5

**Placebo**
17.7

<table>
<thead>
<tr>
<th>Percent Reduction in Primary Endpoint Seizure Frequency (per 28 days)</th>
<th>Ganaxolone (n=10)</th>
<th>Placebo (n=11)</th>
</tr>
</thead>
<tbody>
<tr>
<td>p=0.17</td>
<td></td>
<td></td>
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<tr>
<td>61.5%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>24.0%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Proportion of Patients (%)

- **Ganaxolone**
  - ≥ 25%: 80.0%
  - ≥ 50%: 45.5%
  - ≥ 75%: 36.4%

- **Placebo**
  - ≥ 25%: 50.0%
  - ≥ 50%: 36.4%
  - ≥ 75%: 36.4%