TrustTSC Study:  
Enrolling children and adults with TSC-associated seizures
Speakers & Agenda

**Dr. Ritter**
Cincinnati Children’s Hospital Medical Center

- Clinical trials 101
- Tuberous sclerosis complex & epilepsy
- TSC standard of care and existing unmet needs
- Introduction to the TrustTSC trial & investigational ganaxolone

**Dr. Miller**
Marinus Pharmaceuticals

- Ganaxolone’s mechanism of action
- Ganaxolone Phase 2 TSC study and safety summary
- TrustTSC travel info and inclusion/exclusion criteria
- TrustTSC site locations
Ganaxolone in TSC – why do we need a study?

David Ritter, MD, PhD
Assistant Professor of Pediatrics
Member Tuberous Sclerosis Clinic
Cincinnati Children’s Hospital Medical Center
University of Cincinnati College of Medicine
My Background

• Pediatric Neurologist
• Member of the TSC Center of Excellence at Cincinnati Children’s
• Help conduct clinical trials and research studies in TSC
• Assistant Professor at the University of Cincinnati College of Medicine
Phases of Clinical Trials

- Clinical trials look at new ways to treat disease, including studying investigational drugs to determine if they are safe and effective.
- They are conducted in a series of steps called “phases.” Each phase has a different purpose and helps researchers answer different questions.

**Phase 1 Trial**
- Purpose: Safety and dosage

**Phase 2 Trial**
- Purpose: Preliminary efficacy and side effects; dose selection

**Phase 3 Trial**
- Purpose: Confirm efficacy and monitor adverse reactions

Sources: [https://www.nih.gov/health-information/nih-clinical-research-trials-you/basics](https://www.nih.gov/health-information/nih-clinical-research-trials-you/basics); [https://www.fda.gov/patients/drug-development-process/step-3-clinical-research#phases](https://www.fda.gov/patients/drug-development-process/step-3-clinical-research#phases)
Terms in Clinical Trials Simplified

• **Active** – the main ingredient in a medicine that causes the desired effect
• **Placebo** – an inactive product that resembles the investigational drug, but without its treatment value
• **“Blinded” study** – designed to prevent members of the research team and study participants from influencing the results; allows the collection of scientifically accurate data
  • In a **double-blind study**, neither participants nor the research team are told what is being given (to reduce bias); only the pharmacist knows
• **Open label extension** – sometimes also called a long-term extension study. All subjects receive active drug and the main objective is safety

Sources: https://www.nih.gov/health-information/nih-clinical-research-trials-you/basics; https://www.fda.gov/patients/drug-development-process/step-3-clinical-research#phases
Seizures in TSC start early in life.
Epilepsy occurs in 80-90% of patients with TSC with most having seizures that are difficult to control.
The more seizures that occur, the higher the risk for cognitive problems.
Currently, antiseizure medications are the standard of care for seizures in TSC.

Table 3. Relationship of epilepsy prognosis to genetic mutation

<table>
<thead>
<tr>
<th></th>
<th>TSCI (%)</th>
<th>TSC2 (%)</th>
<th>NMI (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>History of seizure⁻</td>
<td>51/60 (85)</td>
<td>112/123 (91.0)</td>
<td>34/48 (70.8)</td>
</tr>
<tr>
<td>Refractory epilepsy</td>
<td>27/51 (52.9)</td>
<td>76/112 (67.9)</td>
<td>20/34 (58.8)</td>
</tr>
<tr>
<td>Epilepsy remission⁻</td>
<td>17/50 (34.0)</td>
<td>34/122 (27.9)</td>
<td>18/31 (54.5)</td>
</tr>
</tbody>
</table>

⁻Denotes statistically significant comparison.

Capal et al. *Epilepsy and Behavior* 2017; 70:245-252..
Why Conduct Clinical Trials in TSC-related Seizures

Current medications do not work for everyone with TSC-related seizures, so:

1. We need to prove that a new medication/treatment is safe
2. We need to show that a new medication/treatment works
TrustTSC: Ongoing Phase 3 Study of Ganaxolone

Eligible Patients with TSC

Double-blind Phase

Ganaxolone

Placebo

Primary Endpoint Analysis

Open-label Ganaxolone

Baseline (4 weeks) | Titration (28 days) | Maintenance (12 weeks)

From Marinus Pharmaceuticals
Where Ganaxolone Fits in TSC Care

Current Standard of Care

Common seizure medications and their targets

GABA:
- vigabatrin, clobazam, clonazepam, ganaxolone

Sodium channel:
- oxcarbazepine, carbamazepine, phenytoin, lacosamide

SV2a:
- levetiracetam, brivaracetam

mTOR:
- everolimus

Other or many targets
- valproic acid, topiramate, felbamate, perampanel, cannabidiol
Who Can Enroll in the TrustTSC Trial?

Key Inclusion Criteria:

- Male or female patients 1-65 years of age with TSC who have 8 seizures a month that include a motor component
- No changes in seizure medications for 1 month prior to coming into the study
- Willing to track seizures, report side effects, and continue on current medications until the end of the double-blind phase
- Failed at least two prior antiseizure medications
Participation in the Trial

- You will track seizures and medication administration more closely than normal
- You will have 6 office visits with some extra tests (blood draws, EKGs, surveys)
- You get the opportunity to have a role in TSC research
What if I Get Placebo?

You can enroll in the open label extension if you meet criteria at the end of the double-blind phase. In the open label extension:

• You for sure get ganaxolone
• You continue to track seizures and side effects
• You will have additional study visits
• Your provider will adjust medications as needed
Thanks for Your Support of TSC-Related Research!

If you have questions about enrolling in the TrustTSC trial at the Cincinnati Children’s site you can email Adrienne Victory at: 
adrienne.victory@cchmc.org

Questions in general about the trial or TSC you can email me at: david.ritter@cchmc.org
The TrustTSC Study

Ian Miller, M.D.
VP, Clinical Development
Marinus Pharmaceuticals
Ganaxolone Targets Synaptic & Extrasynaptic GABA<sub>A</sub> Receptors

**Ganaxolone** is a positive allosteric GABA<sub>A</sub> receptor modulator with a well-defined MOA designed to treat patients suffering from seizure disorders.

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

Ganaxolone is designed to modulate both synaptic and extrasynaptic GABA<sub>A</sub> receptors to calm over-excited neurons.
**Ganaxolone Development Pipeline**

**Ganaxolone** is a positive allosteric GABA<sub>A</sub> receptor modulator with a well-defined MOA designed to treat patients suffering from seizure disorders. Ganaxolone is designed to modulate both synaptic and extrasynaptic GABA<sub>A</sub> receptors to calm over-excited neurons.

<table>
<thead>
<tr>
<th>Ganaxolone</th>
<th>Preclinical</th>
<th>Phase 1</th>
<th>Phase 2</th>
<th>Phase 3</th>
<th>Approved</th>
<th>Anticipated Milestones</th>
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<tbody>
<tr>
<td>Administered</td>
<td>Seizure Disorders</td>
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<td>Oral Suspension</td>
<td>CDKL5 Deficiency Disorder Marigold Study</td>
<td>FDA approved</td>
<td>EU CHMP opinion Q2 2023</td>
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<td>Intravenous</td>
<td>Refractory Status Epilepticus RAISE Trial</td>
<td>Topline data 2H 2023</td>
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<tr>
<td>Oral Suspension</td>
<td>Tuberous Sclerosis Complex TrustTSC Trial</td>
<td>Topline data Q1 2024</td>
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<tr>
<td>Intravenous</td>
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<td>Enroll first patient 2H 2023</td>
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<tr>
<td>Intravenous</td>
<td>Established Status Epilepticus RESET Trial</td>
<td>First cohort data year end 2023</td>
<td></td>
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<tr>
<td>Oral Suspension (Second Gen. Formulation)</td>
<td>Second Generation Formulation Lennox-Gastaut Syndrome</td>
<td>Initiate multiple ascending dose trial Q2 2023</td>
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Patients taking ganaxolone experienced a significant reduction in seizure frequency.

**Ganaxolone reduced the frequency of monthly major motor seizures by a median of 30.7% compared with 6.9% for placebo (p=0.0036)**

\[ \Delta = 27.1\% (47.9 - 9.6) \]

All patients had the opportunity to remain in the OLE for at least 1 year (minimum duration of follow-up). 34 (38.6%) patients discontinued from the OLE primarily due to lack of efficacy (n=12), adverse event (n=10), and withdrawal by subject or parent/LAR (n=10). LOCF analyses showed similar findings during the minimum duration of follow-up in the OLE.
TSC Phase 2 Trial Results

Primary Endpoint Results:
16.6% median reduction in TSC-associated seizures

Secondary and Exploratory Analyses

Ganaxolone was generally well-tolerated with somnolence, sedation and fatigue reported as the most common adverse events; in addition, one treatment-related serious adverse event of seizure was reported in the trial.
Phase 3 Protocol Refinements Informed by Phase 2

Phase 2
Patients without somnolence related AEs experienced directionally better seizure reductions

Phase 3
Slower titration initially, designed to optimize tolerability and improve efficacy
Ganaxolone Safety Summary

Generally Well-tolerated

- Dosed in > 2,100 children and adults
- Most Frequently Reported TEAEs (in >5% of subjects)

<table>
<thead>
<tr>
<th>TEAE</th>
<th>All Doses of GNX (n=1168)</th>
<th>Placebo (n=853)</th>
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</thead>
<tbody>
<tr>
<td>Somnolence</td>
<td>278 (23.8%)</td>
<td>66 (7.7%)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>142 (12.2%)</td>
<td>30 (3.5%)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>131 (11.2%)</td>
<td>41 (4.8%)</td>
</tr>
<tr>
<td>Headache</td>
<td>74 (6.3%)</td>
<td>59 (6.9%)</td>
</tr>
</tbody>
</table>

TEAE: Treatment-emergent adverse events
Phase 3 TrustTSC Trial Overview

- Enrollment: ~162 patients, targeting 90 sites in the U.S., Europe, Canada, Israel, Australia and China
- Primary Endpoint: Percent change in 28-day TSC-associated seizure frequency
- Key Secondary Endpoints: Percent change in TSC-associated seizure frequency during 12-week maintenance period, 50% responder rate, and clinical global impression
Financial Support and Inclusion & Exclusion Criteria

If you require financial assistance to get to a required study visit, the sponsor will provide travel concierge services or reimbursement of reasonable travel expenses for the participant and caregiver.
U.S. TrustTSC Site Locations (As of 4/20/23)
To learn more and find a clinical study site near you, visit [TrustTSCTrial.com](http://TrustTSCTrial.com) or scan this QR code:

You can also contact Marinus' Medical Affairs team at [medinfo@marinuspharma.com](mailto:medinfo@marinuspharma.com)