TrustTSC

TrustTSC Study:

Enrolling children and adults with TSC-associated seizures

TReating Uncontrolled Seizures in Tuberous Sclerosis Complex

This presentation is for U.S. audiences

Hosted by:

TSC Alliance

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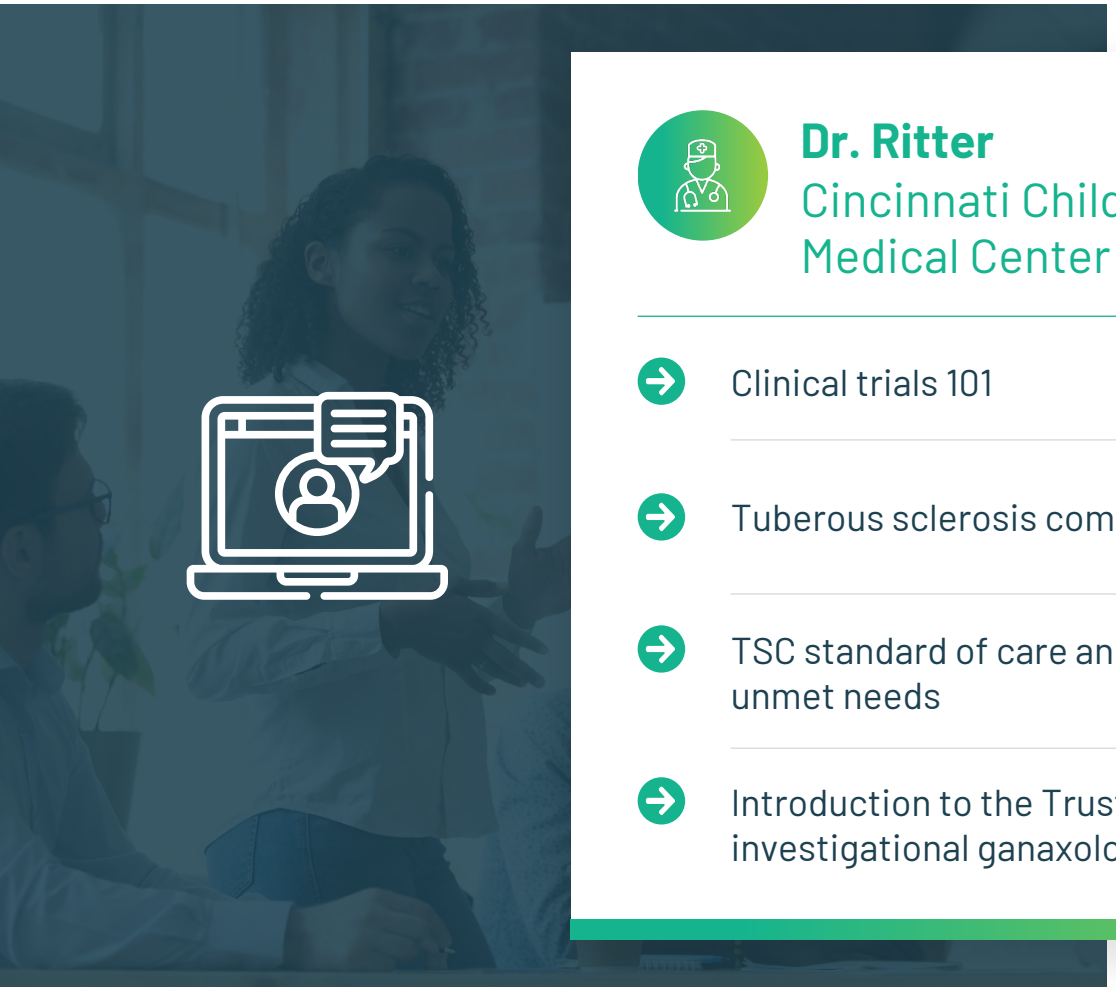
Speakers & Agenda



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

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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

TSC Alliance Webinar - 4/25/23

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

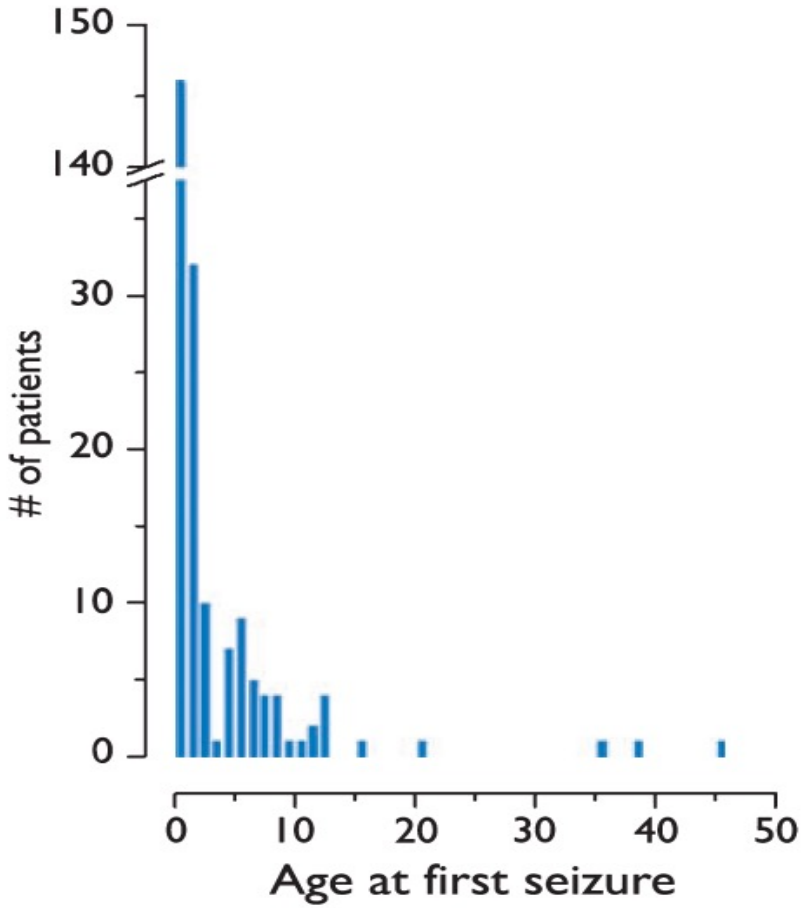
Sources: https://www.nih.gov/health-information/nih-clinical-research-trials-you/basics; https://www.fda.gov/patients/drug-development-process/step-3-clinical-research#phases

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

Tuberous Sclerosis Complex (TSC) and Epilepsy



- 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

	TSC1 (%)	*TSC2* (%)	NMI (%)
History of seizure[a]	51/60 (85)	112/123 (91.0)	34/48 (70.8)
Refractory epilepsy	27/51 (52.9)	76/112 (67.9)	20/34 (58.8)
Epilepsy remission[a]	17/50 (34.0)	34/122 (27.9)	18/31 (54.5)

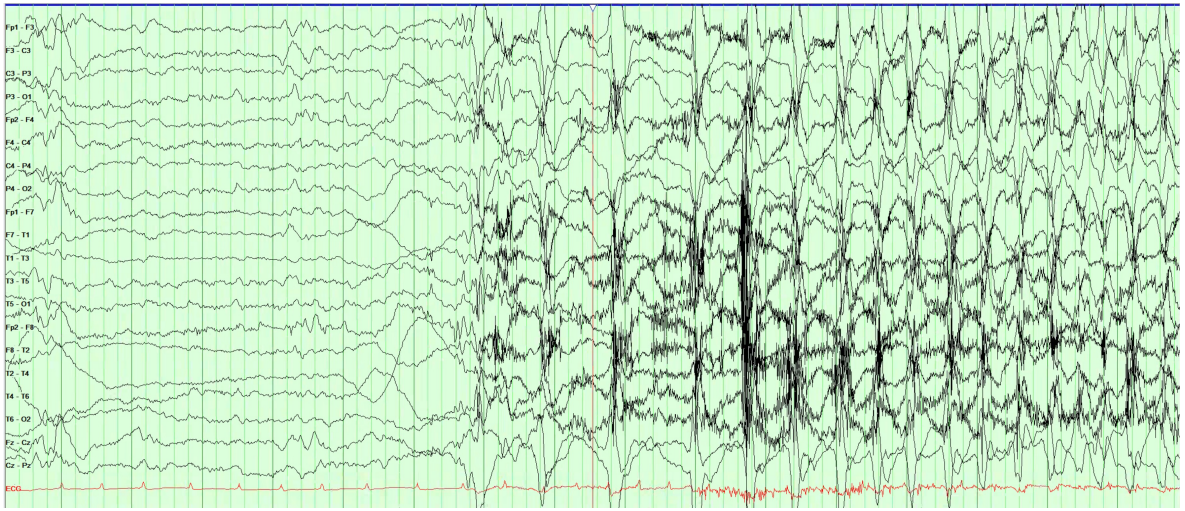
[a]Denotes statistically significant comparison.

Chu-Shore et al. *Epilepsia* 2010; 51:1236-1241.
Capal *et al. Epilepsy and Behavior* 2017; 70:245-252..

Why Conduct Clinical Trials in TSC-related Seizures

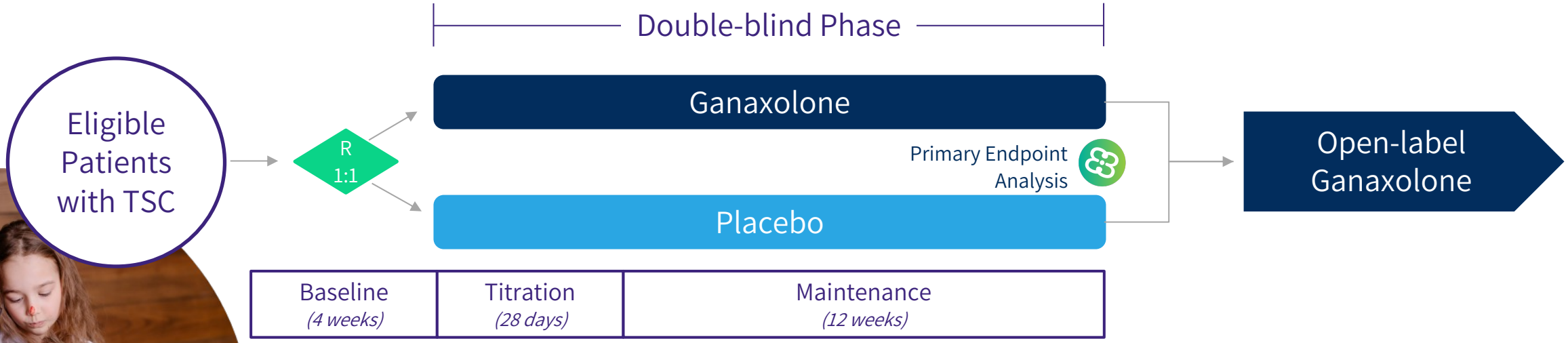
Current medications do not work for everyone with TSC-related seizures, so:

1. We need to prove that a new medication/treatment is safe
2. We need to show that a new medication/treatment works



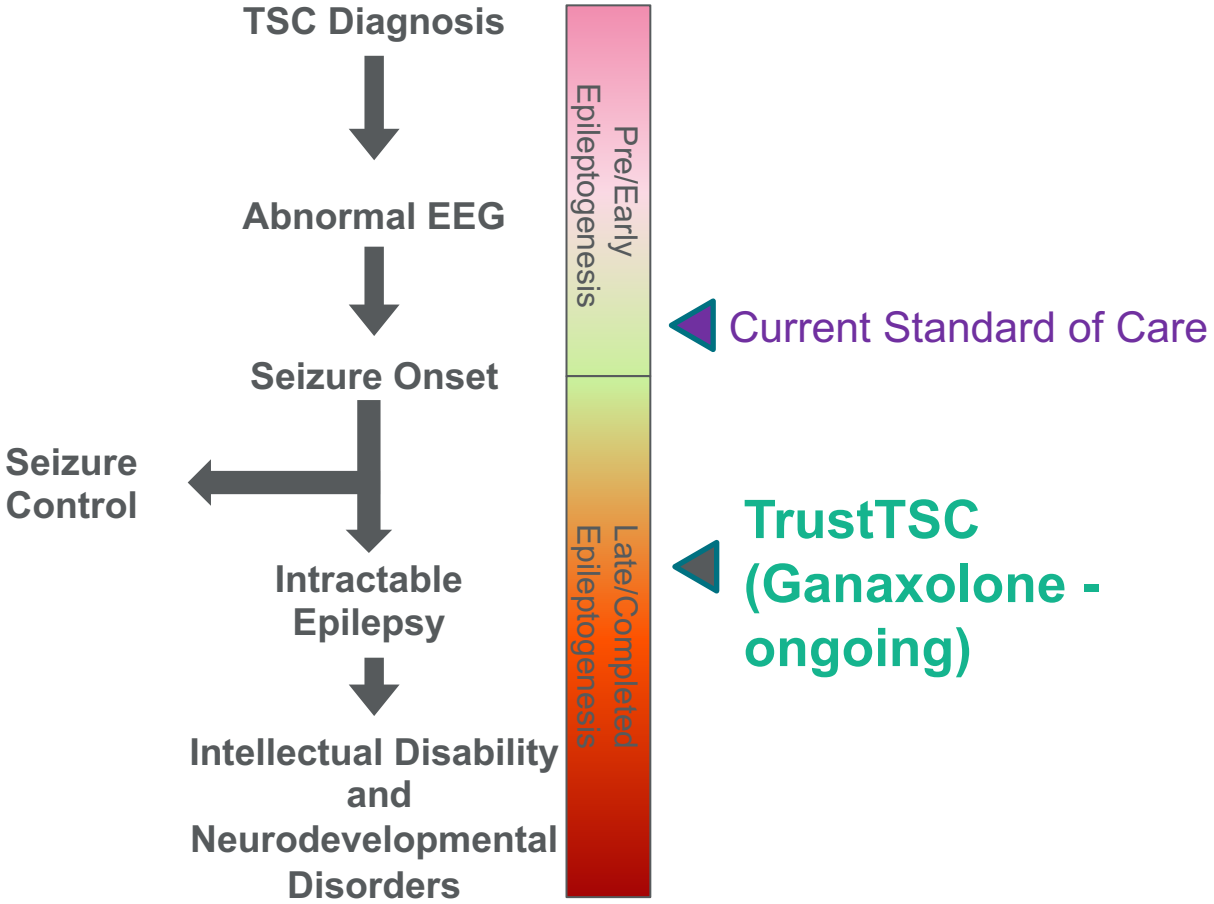
TrustTSC: Ongoing Phase 3 Study of Ganaxolone

TrustTSC



From Marinus Pharmaceuticals

Where Ganaxolone Fits in TSC 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?

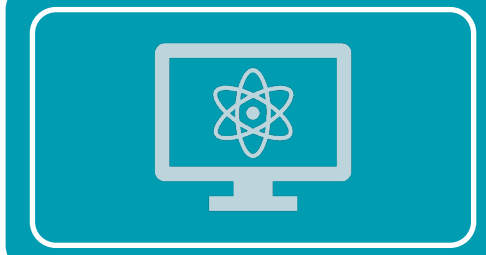
Key Inclusion Criteria:

- 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

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The TrustTSC Study

Ian Miller, M.D.
VP, Clinical Development
Marinus Pharmaceuticals

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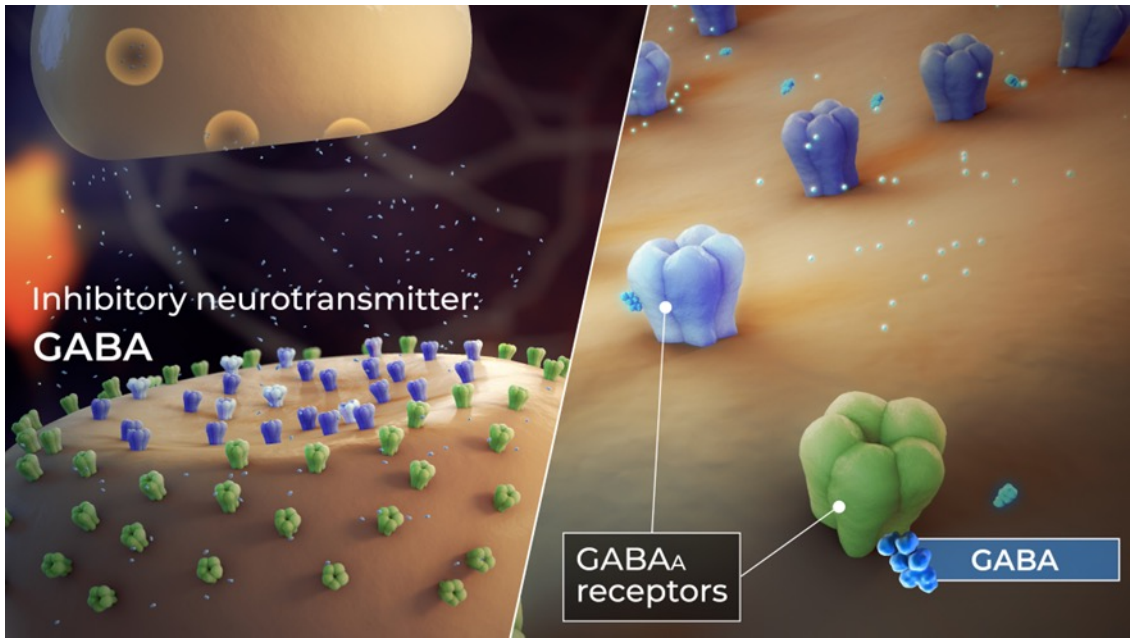
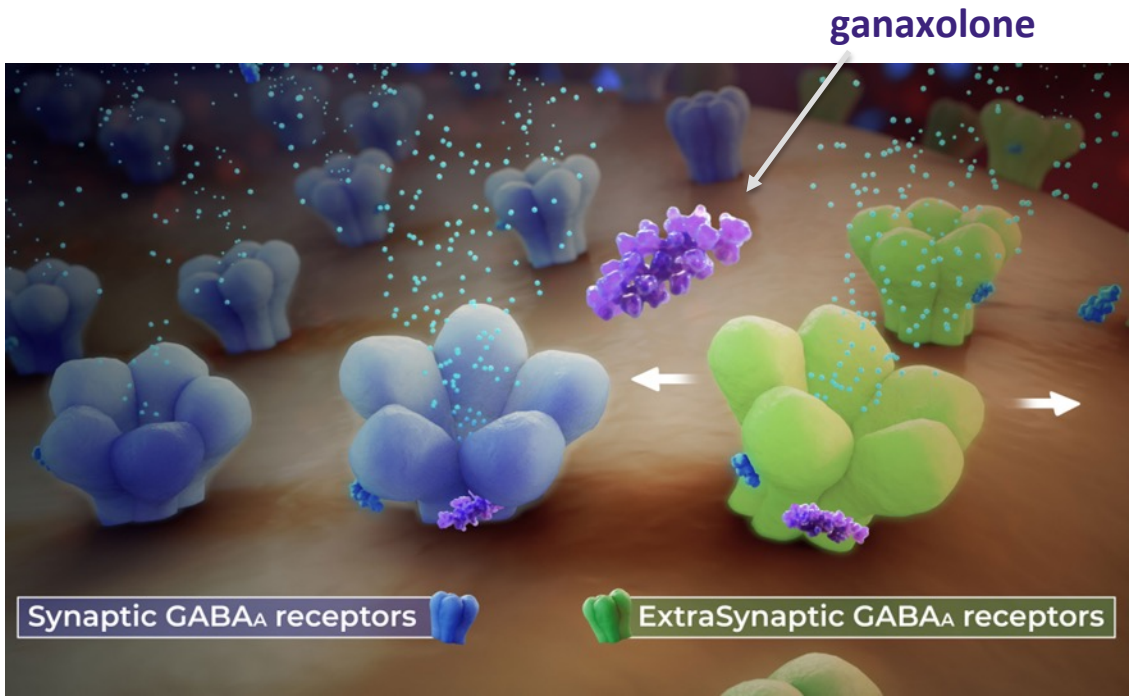
Ganaxolone Targets Synaptic & Extrasynaptic $GABA_A$ Receptors

Ganaxolone is a positive allosteric $GABA_A$ 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 $GABA_A$ receptors to calm over-excited neurons.

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Ganaxolone Development Pipeline

Ongoing trial Planned future trial

Ganaxolone is a positive allosteric $GABA_A$ receptor modulator with a well-defined MOA designed to treat patients suffering from seizure disorders. Ganaxolone is designed to modulate both synaptic and extrasynaptic $GABA_A$ receptors to calm over-excited neurons.

GANAXOLONE	Preclinical	Phase 1	Phase 2	Phase 3	Approved	Anticipated Milestones
Administered		Seizure Disorders				

Oral Suspension	CDKL5 Deficiency Disorder Marigold Study	**FDA approved**	EU CHMP opinion Q2 2023
Intravenous	Refractory Status Epilepticus RAISE Trial		Topline data 2H 2023
Oral Suspension	Tuberous Sclerosis Complex TrustTSC Trial		Topline data Q1 2024
Intravenous	Refractory Status Epilepticus RAISE II Trial		Enroll first patient 2H 2023
Intravenous	Established Status Epilepticus RESET Trial		First cohort data year end 2023
Oral Suspension (Second Gen. Formulation)	Second Generation Formulation Lennox-Gastaut Syndrome		Initiate multiple ascending dose trial Q2 2023

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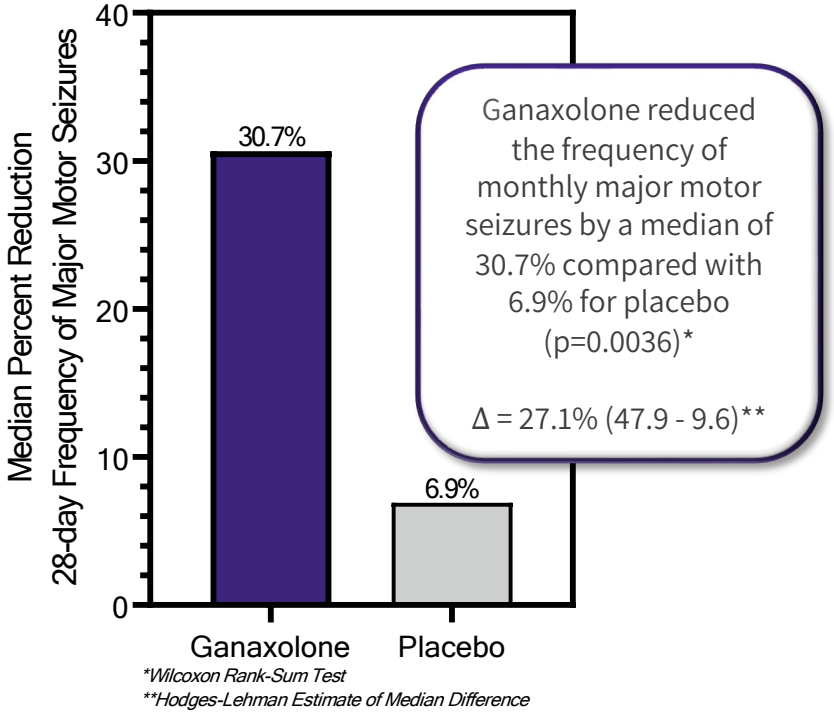
CDKL5 Deficiency Disorder: Phase 3 Marigold Trial and Open Label Extension Data

Marigold Study
CDKL5 Deficiency Disorder

Phase 3 Marigold data published in ***The Lancet Neurology***

First international CDKL5 guidelines published in ***Frontiers in Neurology***

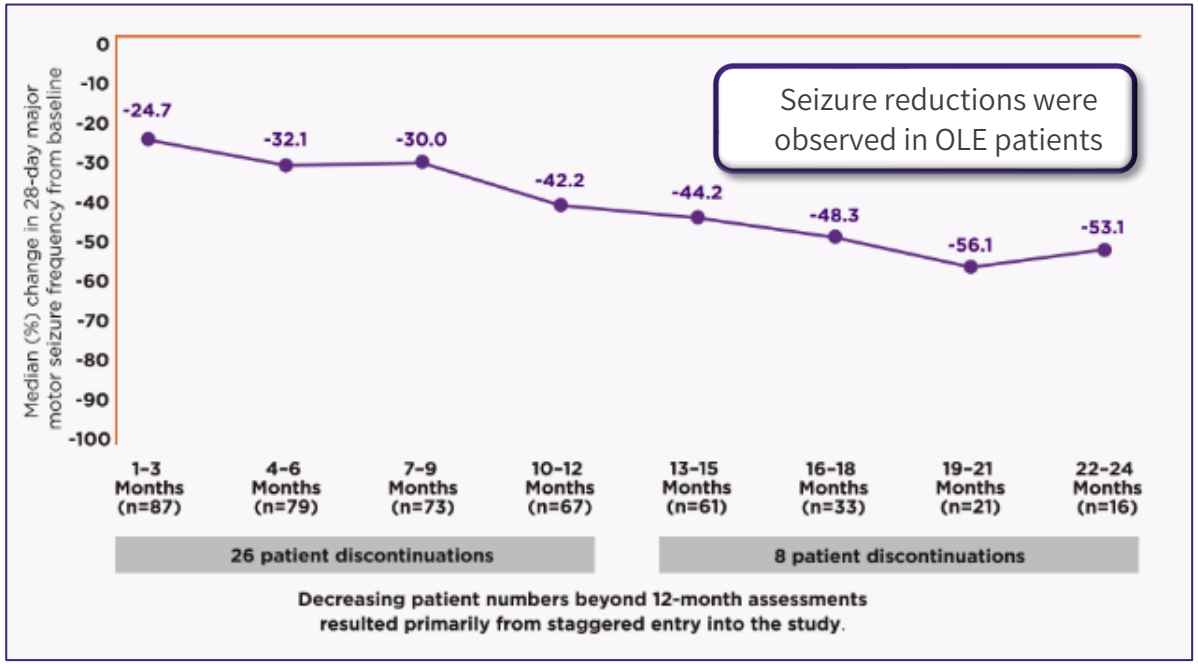
Patients taking ganaxolone experienced a significant reduction in seizure frequency



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

Δ = 27.1% (47.9 - 9.6)**

Reduction in monthly major motor seizure frequency over 24 months in OLE



Seizure reductions were observed in OLE patients

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.

*Hodges-Lehmann estimate of median difference (95% confidence interval);
**Wilcoxon rank-sum test
Data as of June 22, 2021
LOCF=last observation carried forward.
LAR=legally authorized representative.

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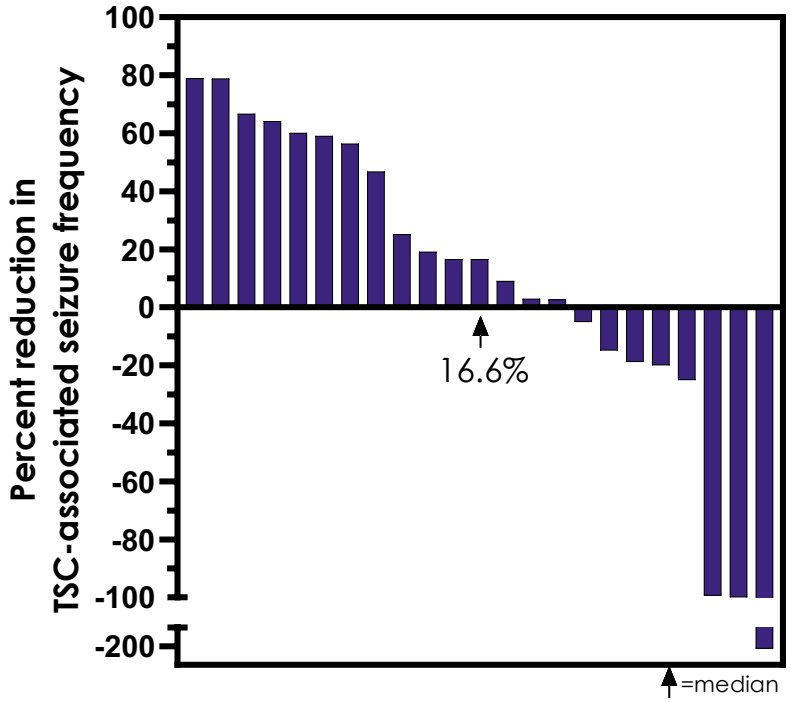
Not for promotional

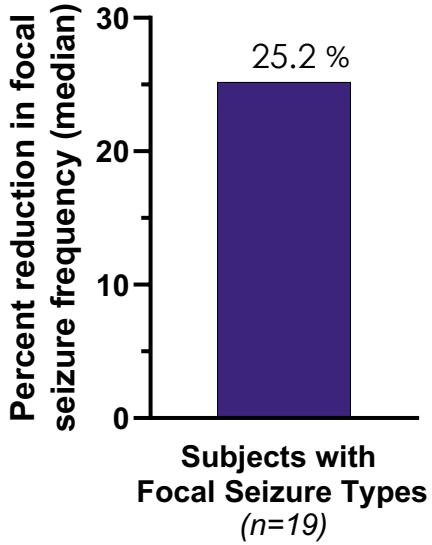
TSC Phase 2 Trial Results

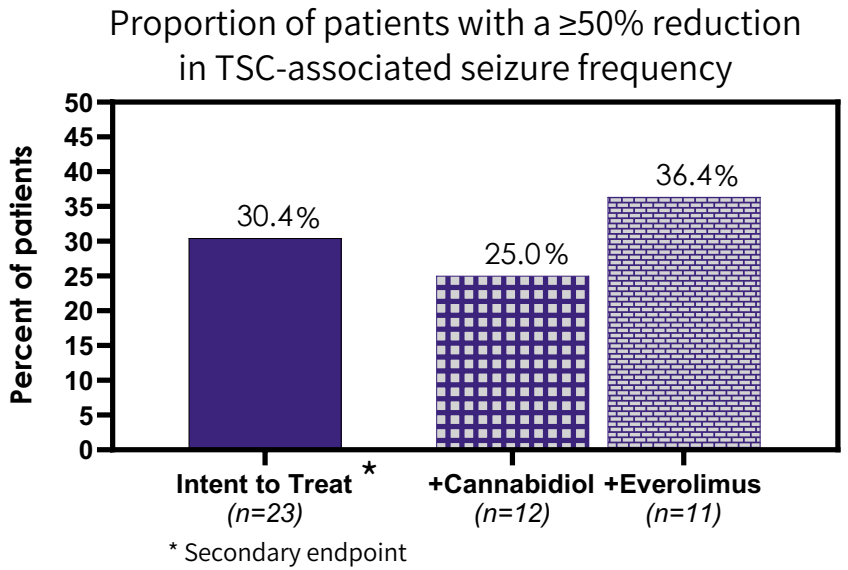
CALM STUDY
TSC-Related Epilepsy (ganaxolone)

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

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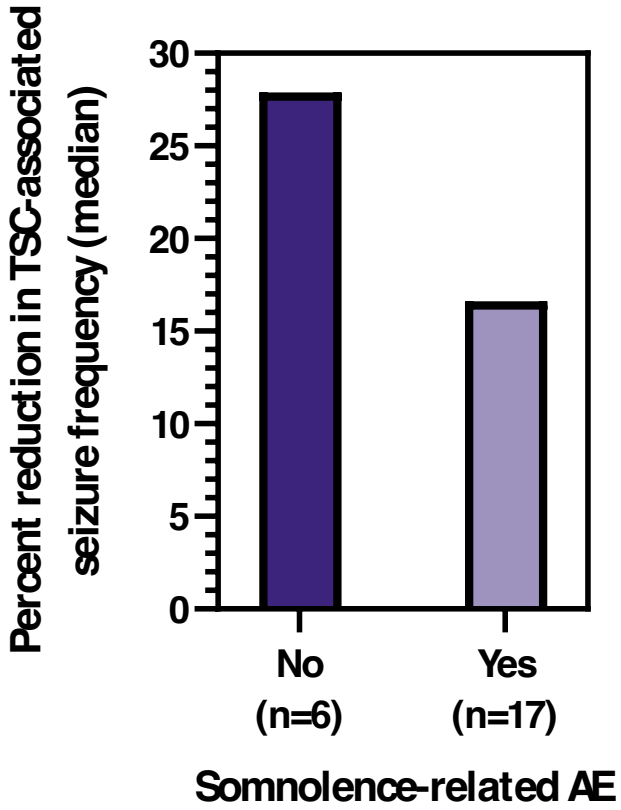
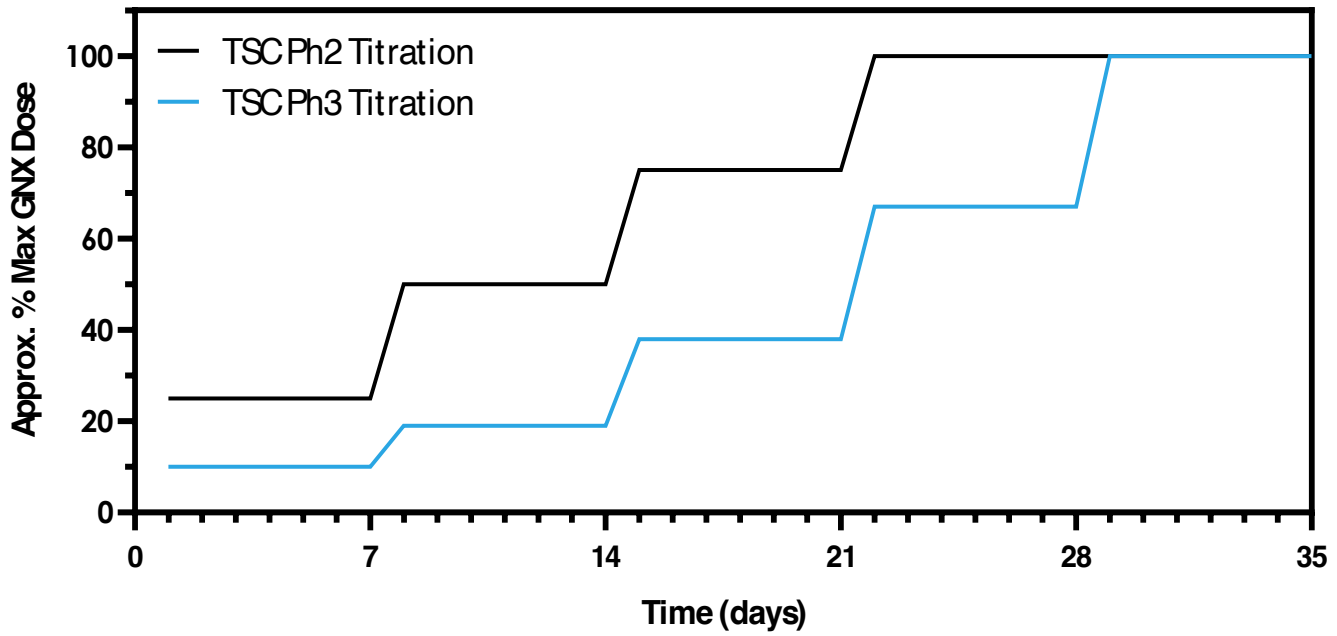
Phase 3 Protocol Refinements Informed by Phase 2

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)

TEAE	All Doses of GNX (n=1168)	Placebo (n= 853)
Somnolence	278 (23.8%)	66 (7.7%)
Dizziness	142 (12.2%)	30 (3.5%)
Fatigue	131 (11.2%)	41 (4.8%)
Headache	74 (6.3%)	59 (6.9%)

TEAE: Treatment-emergent adverse events

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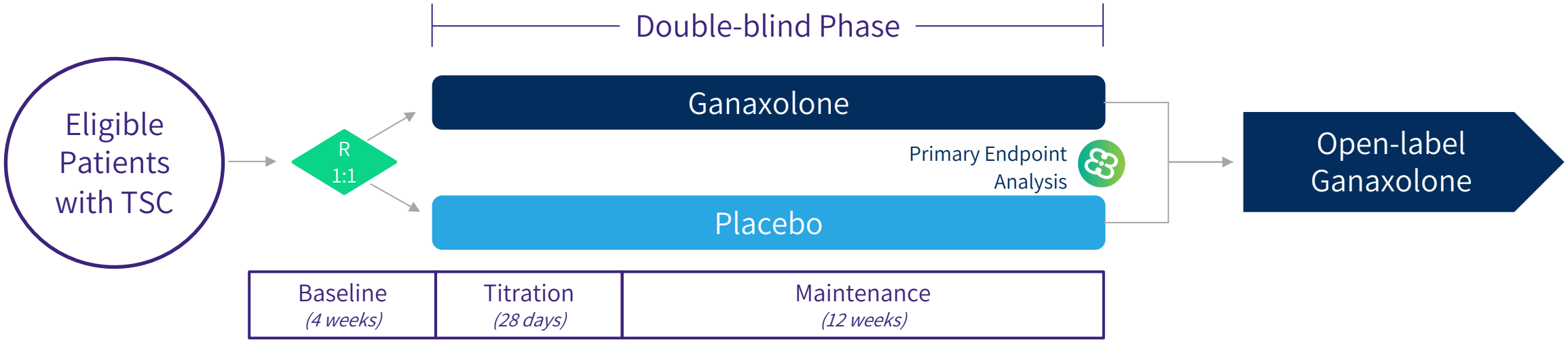
Phase 3 TrustTSC Trial Overview



- 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.

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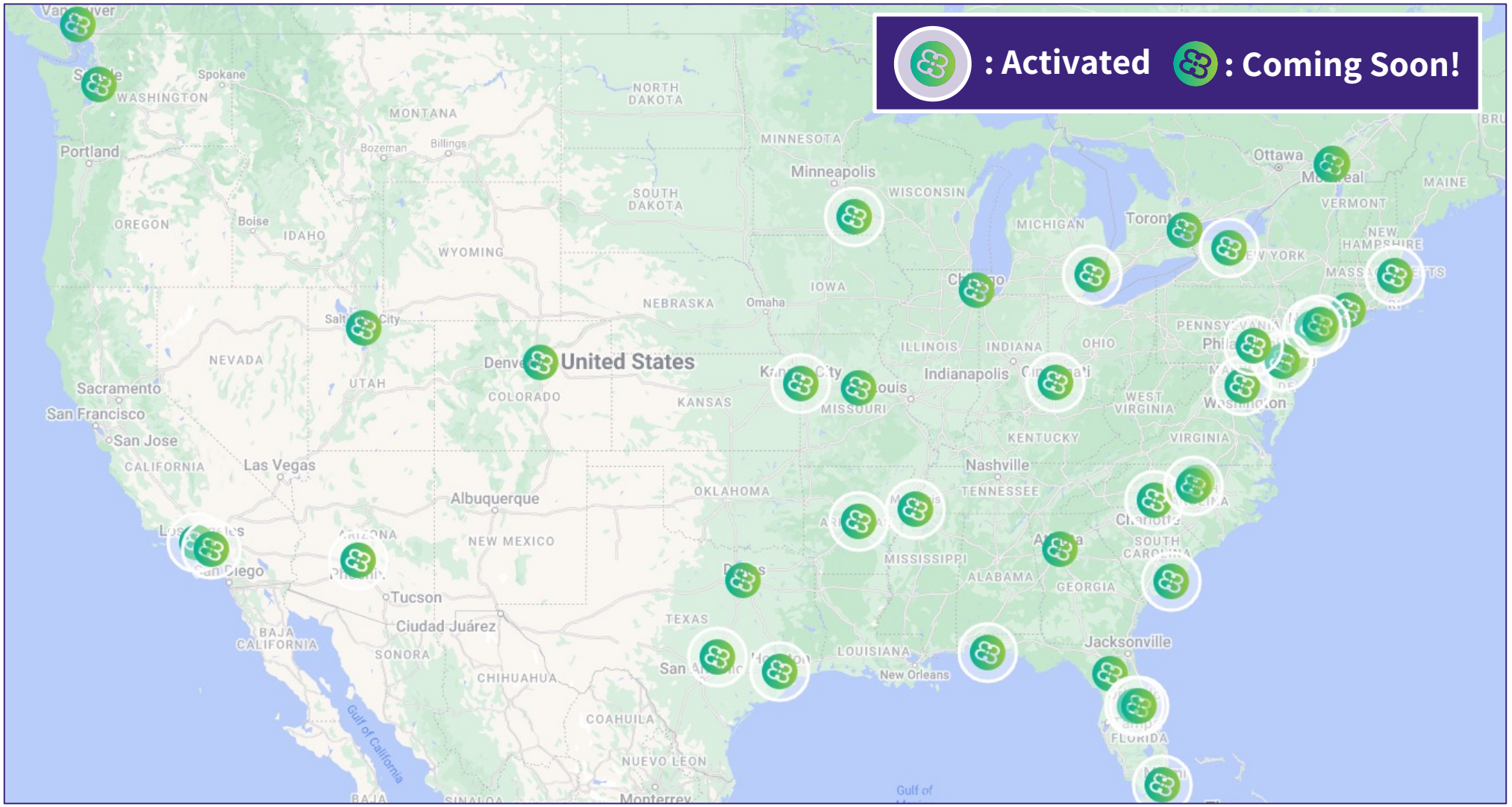
Do I Qualify?

Children and adults must meet the following criteria to be eligible for the study:

- Clinical or mutational TSC diagnosis (TSC1 or TSC2 mutation confirmed by your doctor)
- 1-65 years old (2-65 years old in EU, Australia and Israel)
- Inadequate seizure control
- Treated with at least two prior antiseizure medications
- Not currently enrolled in any other clinical studies

Participation in the Trust TSC Study is completely voluntary. Ask your doctor if being in this study is right for your child.

U.S. TrustTSC Site Locations (As of 4/20/23)



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To learn more and find a clinical study site near you, visit TrustTSCTrial.com or scan this QR code:

You can also contact Marinus' Medical Affairs team at medinfo@marinuspharma.com

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