TS Alliance Educational Webinar
Presenter: Mary Kay Koenig, MD
November 12, 2020

MARINUS PHARMACEUTICALS

CALM STUDY

TSC Related Epilepsy (ganaxolone)

2020

Agenda

- Presenter bio
- TSC background
- Options for treating TSC on the market
- Ganaxolone mechanism of action
- CALM study information
- CALM study design
- Eligibility criteria
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- Study assessment
- Study medication
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- Marigold Phase 3 positive results in a rare genetic epilepsy (CDKL5)
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Mary Kay Koenig, MD

- Neurologist for the University of Texas Tuberous Sclerosis Center
- Follow TSC patients & their families throughout their lifetime
- Multi-disciplinary:
  - Genetics: Hope Northrup, MD
  - Neurology: Mary Kay Koenig, MD
  - Nephrology: Joshua Samuels, MD
  - Dermatology: Adelaide Hebert, MD
  - LAM Center: Rosa Estrada-Y-Martin, MD
  - Neuropsychology: Deborah Pearson, PhD
  - Cardiology, Gastroenterology, Genetic Counseling, Endocrinology

TSC Background

Tuberous Sclerosis Complex – Rare, Serious Genetic Disorder

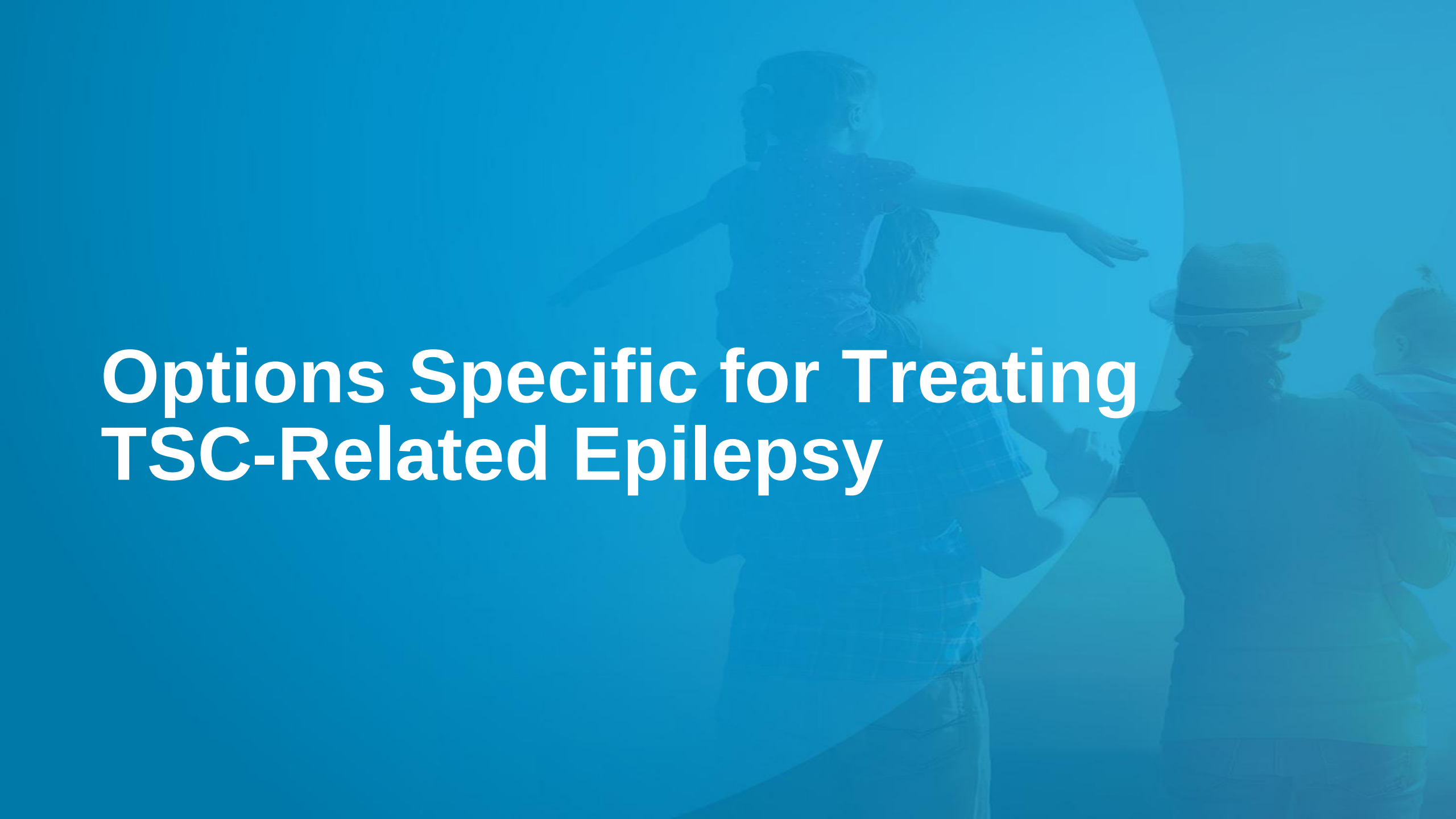
Cause	Defect of mutation of TSC1 and/or TSC2 genes (most common). ~10-15% of TSC patients have the clinical diagnosis without mutations in TSC1 or TSC2 genes but are still appropriately diagnosed patients.
Symptoms	Benign tumors, seizures, cognitive impairment, behavioral problems, skin abnormalities
Prevalence	TSC is a rare genetic disorder that affects 1 in 6,000 newborns in the United States. Approximately 40,000 to 80,000 people in the United States have TSC.
Treatments	Few products approved for symptoms
Mechanistic Rationale for GNX	$GABA_A$ receptor active steroids are altered[1]

[1] diMichele, et al, *J. Neuro Neurosurg Psychiatry*, 2003.

Seizures in Tuberous Sclerosis

- According to the recently reported TOSCA study (TuberOus Sclerosis registry to increase disease Awareness) looking at the data from 2216 TSC patients worldwide:
  - **Epilepsy** was reported in **83.6%** of patients
  - **38.9%** of those with seizures had **infantile spasms**
  - **79.3%** of patients were diagnosed with epilepsy **before the age of 2 years**
  - Focal seizures were **controlled in only 58.2%** of patients
  - **Control of seizures was associated with lower rates of intellectual disability**

Epilepsia Open. 2019;4:73–84.



Options Specific for Treating TSC-Related Epilepsy

Approved Options for Treating TSC-related Epilepsy on the Market

- Afinitor

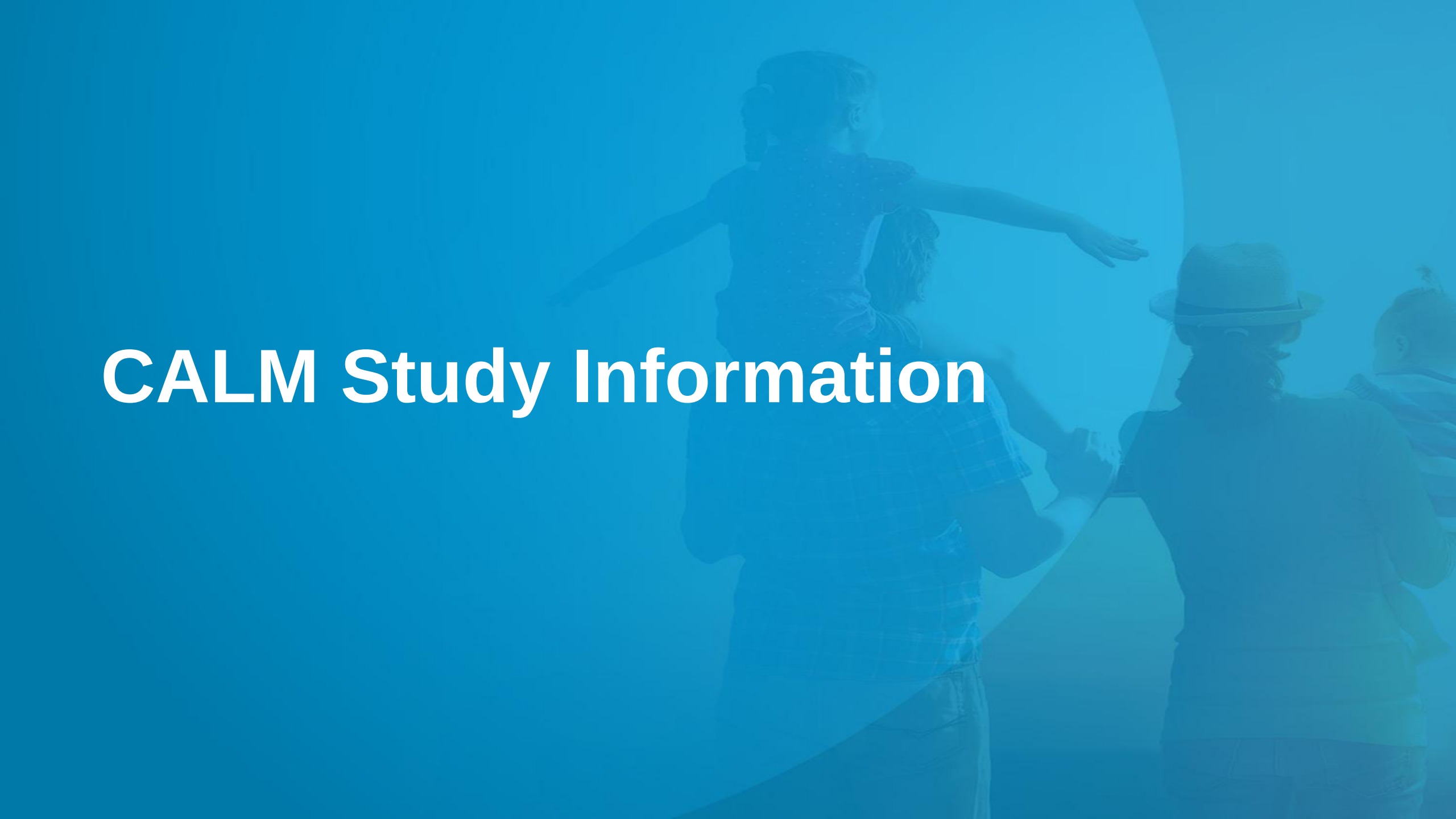
- Epidiolex

Mechanism of Action

Ganaxolone Mechanism of Action

https://www.youtube.com/watch?v=iU5MEmyEUuU&t=57s

CALM Study Information



About Clinical Trials

- You should discuss with your doctor and carefully consider the potential benefits and risks of participation in a clinical trial.
- If you qualify to participate in a clinical trial, the decision to participate is yours to make.
- A medical ethics committee oversees the clinical trial to ensure all participants are appropriately treated.
- If you are eligible and choose to participate in a clinical trial, an informed consent document will be presented to you.
- The informed consent document includes detailed information about the clinical trial, what you can expect as a participant and the potential benefits and risks associated with the clinical trial. If you are dissatisfied at any time during the conduct of a clinical trial, you are free to leave the clinical trial.

Study Information

- **Title:** A Phase 2 Open-Label 12-Week Trial of Adjunctive **Ganaxolone** Treatment (Part A) in Tuberous Sclerosis Complex-related Epilepsy followed by Long-term Treatment (Part B)
- Marinus Protocol Study Number: 1042-TSC-2001
- ClinicalTrials.Gov NCT Number: NCT04285346

- **Study Participants: Male or female aged 2-65**
- **Study Period: April 2020 – December 2021**

- Approximately **30 patients** with TSC-related epilepsy will be enrolled at 8 to 10 **sites across the United States**

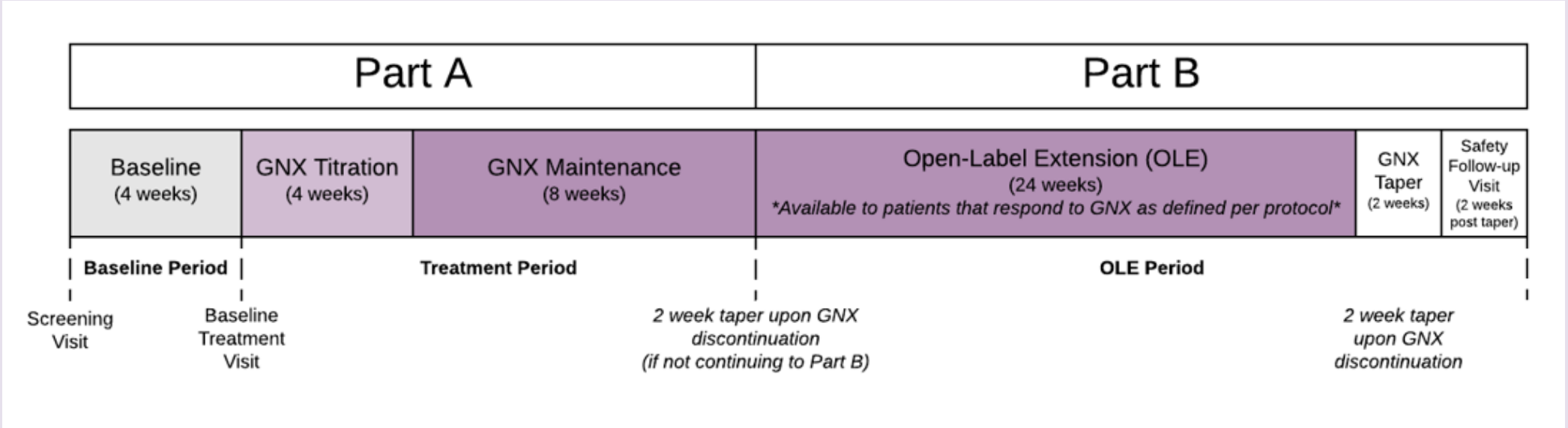
Study is currently enrolling, with a target to complete screening by the end of 2020.

CALM Study Trial Design

Phase 2 Open-Label Clinical Trial Design in TSC

To measure the change in the frequency of primary seizures

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, tonic-clonic seizures, and generalized motor seizures including tonic-clonic, bilateral tonic, bilateral clonic, and atonic/drop seizures



Eligibility Criteria

Inclusion/Exclusion

Inclusion Criteria

Major Inclusion Criteria include:

- Diagnosis of TSC
- Ages 2-65, male and female
- Unable to control seizures despite trial of **2 or more anti-seizure medications** (ASM) at therapeutic doses
- Patients should be on a stable regimen of ASMs for ≥ 1 month prior to the screening visit
- Willing to maintain an accurate and complete **daily seizure diary**
- Able and willing to take study drug three times per day with food
- Must use acceptable form of birth control, if of child-bearing potential

Exclusion Criteria

Major Exclusion Criteria include:

- If you have previously used ganaxolone
- If you are pregnant or breastfeeding
- Concurrent use of strong inducers or inhibitors of CYP3A4/5/7 is not permitted. Any strong inhibitor or inducer of CYP3A4/5/7 must be discontinued at least 28 days before Visit 2, study drug initiation. This does not include approved ASMs
- Patients who have been taking **felbamate** for < 1 year prior to screening
- **Patients with a positive result on tetrahydrocannabinol (THC) or non-approved cannabidiol (CBD) drug screen. Epidiolex with prescription is allowed.**
- Chronic use of oral steroid medications, ketoconazole (except for topical formulations), St. John's Wort, or other investigational products is not permitted

Visit Schedule

Visit Schedule – Part A – Open Label Titration & Treatment

- **5 study visits* & 7 phone visits over 4 months**
  - **Screening visit will be in person**
    *This is when the patient will consent for the study and get the seizure diary
  - **Baseline visit occurs 4 weeks later, also in person**
    *This is when patient starts the ganaxolone
    *Study team will call the patient 1, 2, and 3 days after this visit to check-in
  - **3rd in person visit occurs 1 week later**
    *Study team will call 1, 2, and 3 weeks after this visit to check-in
  - **4th in person visit occurs 4 weeks after the 3rd visit**
    *Study team will call 1 month after this visit to check-in
  - **5th in person visit (and final visit for this part of the study) occurs 2 months later (4 months after enrolling in the study & 3 months after starting on the ganaxolone)**
    ***One of two things can happen at this visit:**
    - Final Visit – taper medication and complete study
    - Continue to Part B of the study (next slide)

* *Can be remote patient visits, if needed*

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Visit Schedule – Part B – Open-label Extension

- **5 study visits* & 3 phone visits over 7 months**

  - Patients in Part A who respond well to ganaxolone will be given an **option to stay on ganaxolone therapy**
  - While taking ganaxolone patients **will continue to be on the study** and will still need to have study visits.
  - These patients will have follow-up study visits in person every 2 months and the study team will check in on via telephone calls on the months they do not come to the study site.

** Can be remote patient visit, if needed*

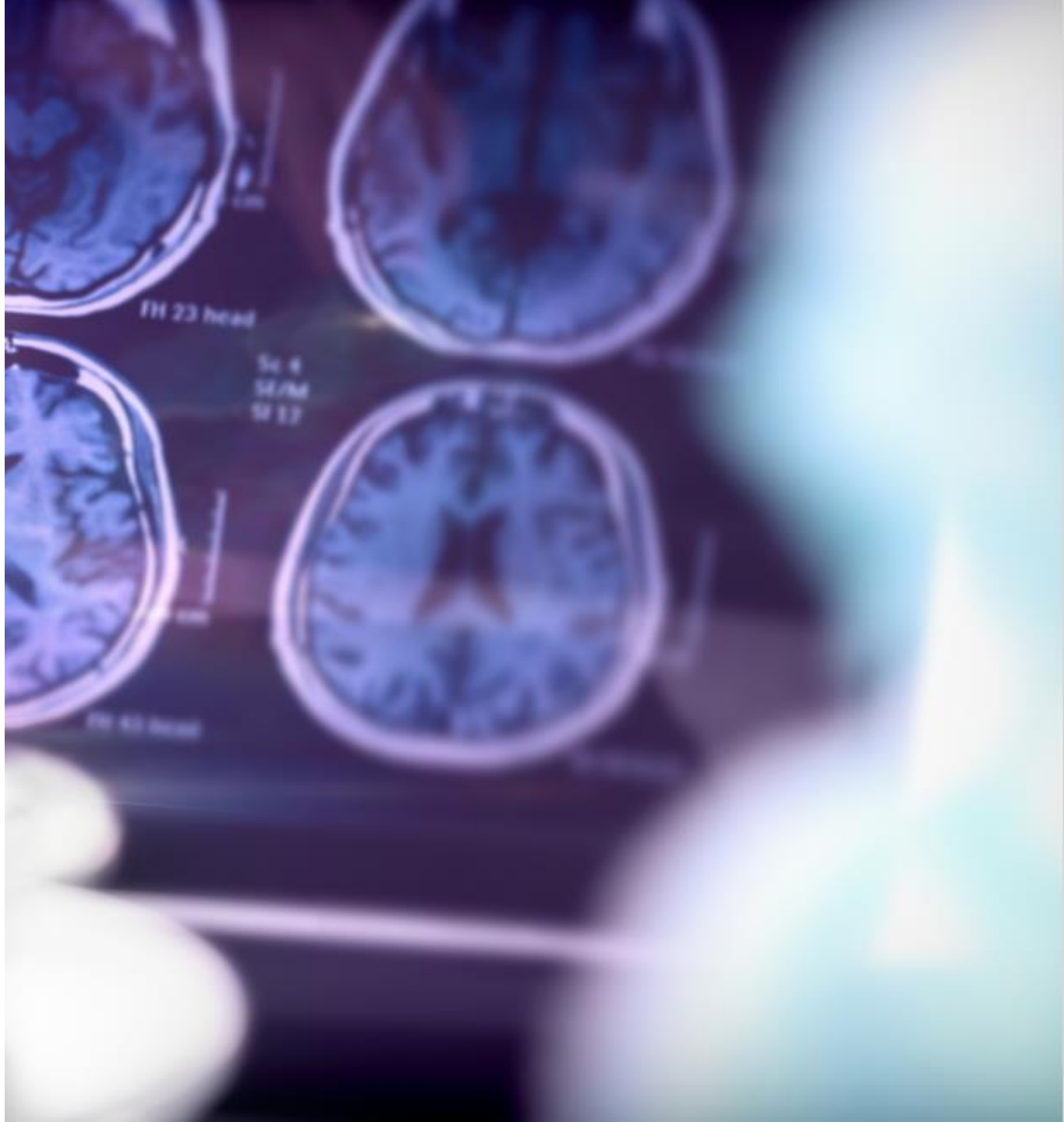
Study Assessments

Study Visits

During the Study Visits, Members of the Study Team will perform some of these procedures:

- Explain the study to the patient, how patient may qualify, and provide an Informed Consent document to review and sign
- Ask about the patient's health and medical history
- Ask patient to describe your seizures
- Measure patient's vital signs (pulse, blood pressure, height, weight)
- Conduct a physical exam (including neurological & developmental exams)
- Collect bloodwork (including drug and pregnancy screening)
- Conduct EEGs to measure brain activity and ECGs to check heart health

Study Medication

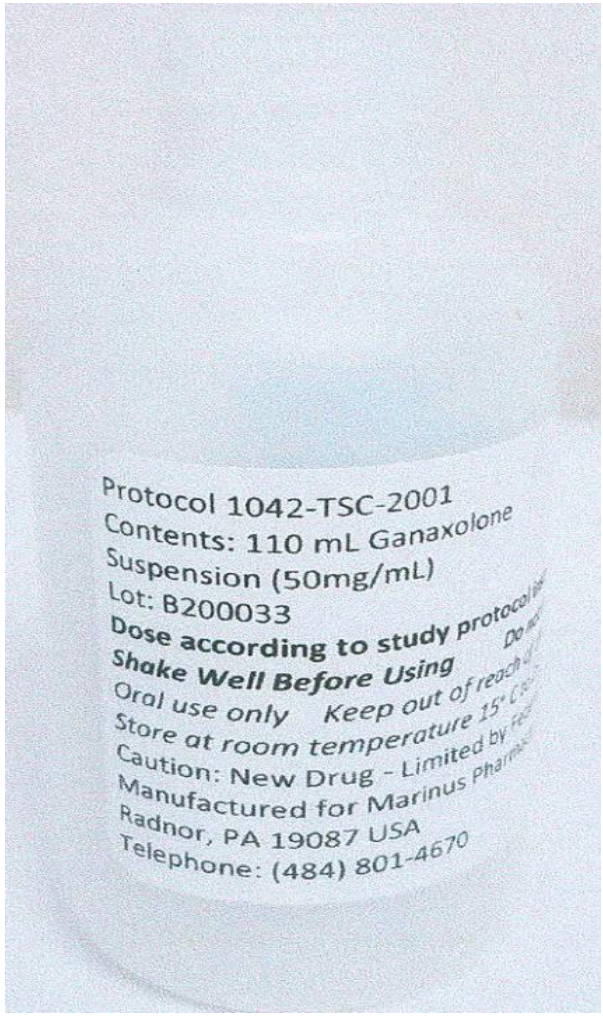


An Investigational Drug - Ganaxolone

Ganaxolone is:

- the name of the study drug
- a liquid suspension taken by mouth
- taken three times per day
- sweetened with sucralose and flavored with artificial cherry
- keto-friendly
- under investigation and is not yet approved by any regulatory authority for commercial sale

- Patients ≤ 28 kg will be dosed based on weight
- Must be taken with food



Expected Adverse Events

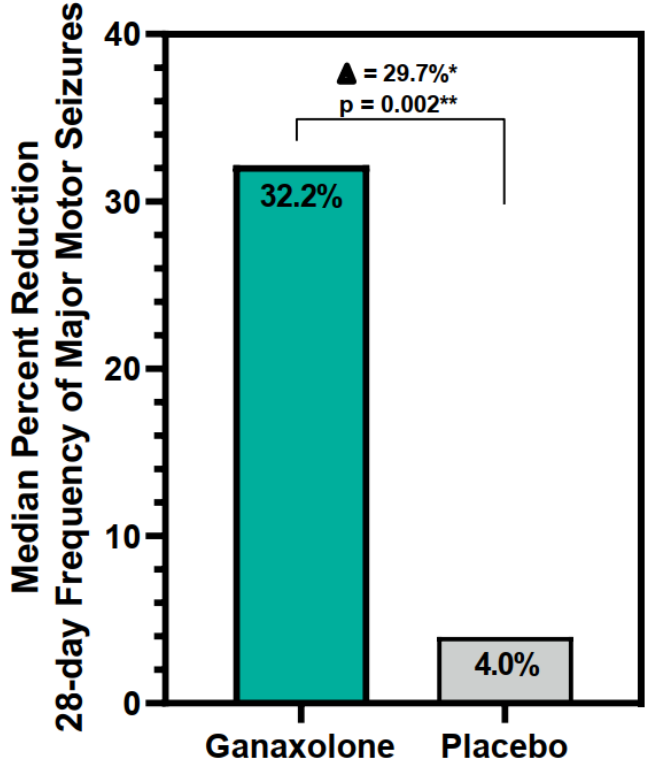
Expected Adverse Events

- Ganaxolone has generally been well tolerated in clinical studies to date
- Dosed in > 1,600 children and adults
- Most frequently reported adverse events related to taking ganaxolone:
  - Somnolence
  - Dizziness
  - Fatigue
  - Headache
  - Sedation

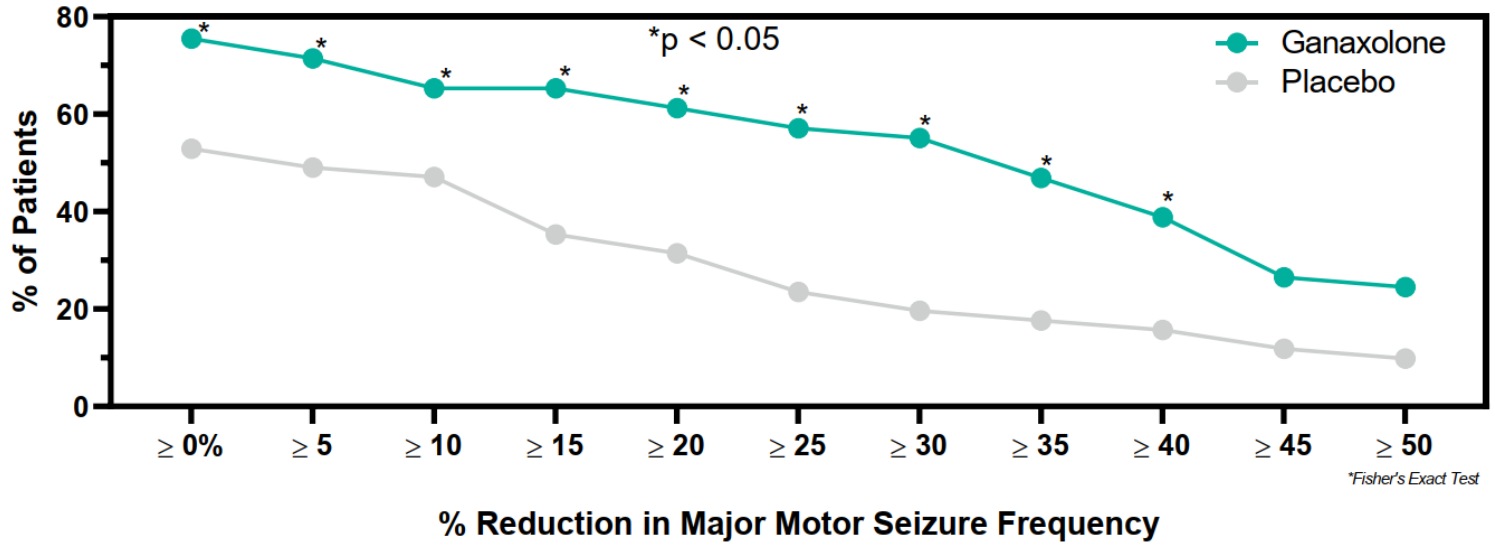
CDKL5 Study Results

Study Results CDKL5 Epilepsy Study – Released October 2020

- Evaluating ganaxolone for the treatment of seizures associated with CDKL5 Deficiency Disorder (CDD)
- ***Ganaxolone reduced seizures by 32.2% in the treated patients compared to only 4.0% in those on placebo***
- Good durability/duration of the response over 17-month treatment period



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



Study Contact

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