Ganaxolone as a Treatment for Drug-Resistant Epilepsy in Children

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Safe Harbor Statement

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Overview of Marinus Pharmaceuticals Inc.

- Dedicated to the formulation, development and commercialization of ganaxolone to treat serious neurologic disorders
- Capsule, oral suspension and IV formulations
Diversified Clinical Stage Opportunities
Large and Pediatric Orphan Indications

<table>
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<tr>
<th>Ganaxolone (formulation)</th>
<th>Preclinical</th>
<th>Phase 1</th>
<th>Phase 2</th>
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<td>Epilepsy - Adults (Oral Capsules)</td>
<td>Adjunctive Treatment of Focal Onset Epileptic Seizures</td>
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<td>Epilepsy - Pediatrics (Oral Liquid &amp; Capsule)</td>
<td>PCDH19 Female Pediatric Epilepsy (orphan)</td>
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<td>Epilepsy - Hospitalized Patients (Intravenous)</td>
<td>Acute Seizure Treatment</td>
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<td>Developmental Disorders (Oral Liquid)</td>
<td>Behaviors in Fragile X Syndrome (orphan, grant funded)</td>
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Ganaxolone, with its validated GABA$_A$ mechanism, has opportunities in both large and pediatric orphan indications and in chronic and acute care settings.
Ganaxolone is Designed to Modulate GABA through Synaptic and Extrasynaptic Receptors

- Ganaxolone is a synthetic analog of natural allopregnanolone
  - -CH₃ on 3- C prevents conversion to an active steroid while maintaining affinity at GABA A receptors
- Ganaxolone is designed to provide allosteric modulation of GABAergic signaling via extrasynaptic and synaptic GABA A receptors
- Anticonvulsant mechanism has been validated in adult refractory POS, pediatric partial and generalized seizures, and status epilepticus
### Completed Trials in Pediatric Seizure Disorders

<table>
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<th>Study</th>
<th>Description</th>
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<td>Study 9408.01 Stage 1</td>
<td>Open-label POC in pediatric epilepsy</td>
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<td>Study 9408.01 Stage 2</td>
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<td>Study 101</td>
<td>Open-label, pediatric epilepsy, history infantile spasm</td>
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<td>Study 500</td>
<td>DB, PBO-controlled infantile spasm (West syndrome)</td>
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<tr>
<td>Study 501</td>
<td>Open extension, infantile spasm (West syndrome)</td>
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Five investigations have been conducted with Ganaxolone in Pediatric Epilepsy

- **Open-label Pediatric Refractory Epilepsy Stages 1 (N=15) and 2 (N=45)**
  - Subjects (2-15 yo) who were highly refractory, having failed on average 7 AEDs including ACTH, vigabatrin, valproate and benzodiazepines
  - Mean time since diagnosis was 8.0 and 5.5 yrs for Stages 1 and 2, respectively
  - >93% of subjects diagnosed with moderate to severe mental retardation

- **Pediatric Epilepsy w/ History of West Syndrome (N=20)**
  - US Study of pediatric subjects aged 6 mo to 7 yrs with treatment refractory epilepsy (mostly West Syndrome) diagnosed by 1st birthday
  - West Syndrome is characterized by seizures with 2-100 spasms. Onset at 6 mo; 95% mental retardation; 5-20% mortality

- **Double-Blind, PBO-controlled West Syndrome with OLE (N=57), New GNX Formulation**
  - Multinational study of infants aged 4-24 mo; 54% had failed ACTH or vigabatrin
  - Comorbidities included metabolic disorders, developmental delays, and brain abnormalities (eg aicardi syndrome, cerebral dysgensis, tuberous sclerosis)
Study 9408.01 Stage 2 (N=45), up to 36 mg/kg/d
- All seizures: 27% (12/45) ITT and 44% (12/27) completers met 50% Responder criteria
- 33% d/c for AE. Common AEs: agitation (38%), change in seizures (36%), infections (36%), somnolence (24%)

Study 101 (N=20), Pediatric w/ History of West Syndrome, up to 36 mg/kg/d
- 33% (5/15) completers met 50% Responder criteria; another 5 subjects had response of 25% to <50%
- AEs: somnolence (25%), diarrhea (20%), nervousness, vomiting (15% each), convulsion (10%)

Study 500, West Syndrome (N=57) up to 54 mg/kg/day using New Formulation, with 96 Week OLE (Study 501)
- Study 500: Crossover study with two 8-day treatment periods, vEEG, trend towards improvement
- Study 501: 13% spasm-free at endpoint; 40% achieved spasm freedom during study
- Safety and tolerability consistent w ganaxolone profile
## Ongoing Pediatric Trials

<table>
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<tr>
<th>Study 900</th>
<th>Open-label Proof-of-Concept Study of Ganaxolone in Girls with PCDH19 Female Pediatric Epilepsy</th>
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<td>Study 800</td>
<td>Double-Blind, Pbo-Controlled Crossover in Children and Adolescents with Fragile X Syndrome</td>
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PCDH19 Female Epilepsy
Orphan indication, early childhood onset

- Rare, serious epileptic syndrome - affects ~15-30K in US
  - No approved therapies
  - Orphan designation granted

- Inherited mutation of protocadherin 19 (PCDH19) gene
  - Located on X chromosome; related to disturbances in allopregnanolone signaling

- Initial presentation: female < 2yrs, cluster seizures temporally associated with fever or vaccination, phenotypic overlap with Dravet’s Syndrome
  - Characterized by early-onset seizures, cognitive and sensory impairment, and psychiatric and behavioral disorders
  - Seizure clusters last from one day to weeks, often requiring hospitalization, sensitive to fever and illness

- Open-label, Phase 2 clinical trial of approx 10 pediatric subjects underway
Behaviors in Fragile X Syndrome
Orphan indication linked to GABA dysfunction

- Mutation of fmr1 gene causes syndrome of intellectual disability, cognitive impairment, anxiety, seizures, hypersensitivity to stimuli

- Studies using the fmr1 knock-out mouse model confirm:
  - Deficit in extrasynaptic GABA\(_A\) receptors
  - Decrease in GABAergic enzymes and proteins

- Fragile X Syndrome (FXS) estimated to affect 100,000 children and adults in the U.S.

- Randomized, placebo-controlled, crossover, Phase 2 grant funded study: n=60; children & adolescents 6-17 years; doses up to 1800 mg/day

Wild-type | Fragile X Knockout
---|---
![Image of Wild-type](image1.png) | ![Image of Fragile X Knockout](image2.png)

*Fewer cortical GABAergic interneurons which are larger*

Populations in POC pediatric epilepsy studies are complex, refractory cases

135 unique pediatric treated in completed studies
- Various severe epileptic syndromes in childhood including West Syndrome, and treatment-resistant partial and/or generalized epilepsies
- Additional data from ongoing Fragile X and PCHD19 studies

New patented ganaxolone oral suspension allows dosing to 54 mg/kg/day and above

Studies in pediatric populations support safety
- In populations ranging from <1 to 15 yrs
- At doses ranging up to 54 mg/kg/day or 1500 mg/day
- Some patients treated for >2 yrs

No changes in safety parameters noted in pediatric studies
Marinus Pharmaceuticals

www.marinuspharma.com