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Phase 2 Open-label Clinical Study Evaluating Oral Ganaxolone for the Treatment of Seizures Associated with Tuberous Sclerosis Complex

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Background

- Tuberous sclerosis complex (TSC), caused by pathogenic variants in *TSC1* or *TSC2* genes, is associated with malformations and benign tumors in the brain and other organs[1]
  - Over 80% of patients with TSC have epilepsy (mostly focal onset seizures with some secondary generalized) and are often refractory to existing antiseizure medications (ASMs)[1-3]
- Despite current treatments, many patients with TSC continue to have seizures, which highlights the unmet need for new treatment options in this patient population
- Ganaxolone is an investigational neuroactive steroid with a differentiated mechanism of action that acts as a positive allosteric modulator of both synaptic and extrasynaptic $GABA_A$-receptors, aimed to increase both phasic and tonic inhibitory signaling[4]

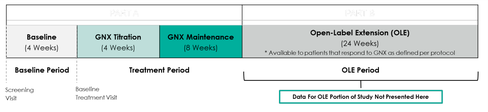
Here we report results from an open-label, proof-of-concept study of adjunctive ganaxolone in patients with TSC-associated refractory epilepsy

Design/Methods

Study design

- Open-label, phase 2, proof-of-concept study conducted at 7 sites in the United States (NCT04285346) (**Figure 1**)
- After a 4-week titration period, patients underwent 8 weeks of maintenance treatment with ganaxolone, up to 63 mg/kg/day or 1,800 mg/day maximum dosage (**Figure 1**)
- Patients/caregivers tracked seizure frequency using diaries during a 4-week baseline period; this was followed by a 12-week treatment period consisting of 4 weeks of ganaxolone titration

Figure 1. Study Design: Effects of Ganaxolone in TSC-Associated Seizures



GNX, ganaxolone; TSC, tuberous sclerosis complex.

Endpoints

- The primary endpoint was the median percent change from baseline in the frequency of TSC-associated seizures during the 12-week treatment period
- Primary TSC-associated seizure types were defined as:
  - Focal motor seizures without impairment of consciousness or awareness
  - Focal seizures with impairment of consciousness or awareness
  - Focal seizures evolving to bilateral tonic-clonic convulsive seizures
  - Generalized motor seizures including tonic-clonic, bilateral tonic, bilateral clonic, or atonic/drop seizures
- A secondary endpoint was the percentage of patients who achieved ≥50% responder rates (ie, ≥50% reduction in seizure frequency) after 12 weeks of treatment
- Safety was assessed via treatment-emergent adverse events (TEAEs), defined as any AEs that occurred or worsened at the time of or following the administration of the first dose of study drug

Endpoints (cont.)

- Post-hoc analyses included percent change from baseline in focal seizure frequency, the percentages of patients who achieved a ≥50% reduction in TSC-associated seizure frequency in the intent-to-treat (ITT) population as well as in concomitant cannabidiol and everolimus subgroups, and percent changes from baseline in TSC-associated seizure frequency in patients who did and did not report somnolence-related AEs (includes somnolence, sedation, fatigue, and lethargy)

Patients

- Key inclusion criteria:
  - Patients aged 2-65 years
  - Clinical diagnosis of TSC or mutation in either *TSC1* or *TSC2* genes
  - Failure to control seizures despite appropriate trial of ≥2 ASMs at therapeutic doses
  - Experienced ≥8 TSC-associated seizures during 4-week baseline period with ≥1 TSC-associated seizure occurring in at least 3 of the 4 weeks of baseline
- Key exclusion criteria:
  - Previous exposure to ganaxolone
  - Other than approved concomitant ASMs, concurrent use of any strong inducers or inhibitors of CYP3A4, CYP3A5, or CYP3A7 were not allowed—any use of these were to be discontinued ≥28 days prior to study drug initiation

Statistical analysis

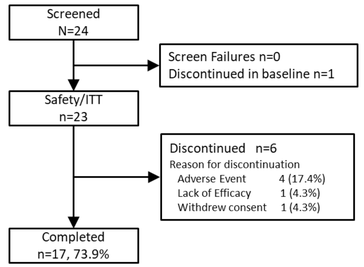
- The ITT population included all subjects who received at least one dose of study drug and had at least one post-baseline efficacy assessment
- The safety population included all subjects who received at least one dose of study drug
- All outcomes were assessed descriptively with efficacy outcomes including point estimates and 95% confidence intervals (CIs)

Results

Baseline demographics and clinical characteristics

- Among a total of N=24 patients screened, 1 patient discontinued during baseline, and n=23 were enrolled and included in the safety and ITT populations (**Figure 2**)

Figure 2. Patient Disposition



ITT, intention to treat.

- Demographics and clinical characteristics of the ITT/safety populations are outlined in **Table 1**
- Most patients (83%) were receiving concomitant newer generation ASMs, including cannabidiol, everolimus, or both

Table 1. Patient Demographics and Clinical Characteristics (ITT/Safety Population)

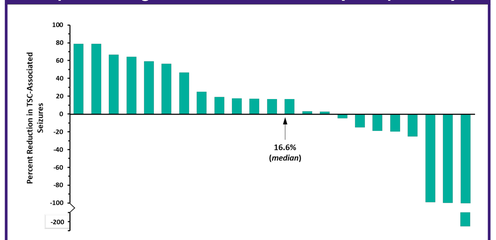
Characteristic	Ganaxolone (n=23)
Age (years) at informed consent	
Mean (SD)	13.7 (8.7)
Median	11.0
Min, max	2, 32
Sex (n, %)	
Male	14 (60.9)
Female	9 (39.1)
Race (n, %)	
Asian	3 (13.0)
White	17 (73.9)
Declined to answer	1 (4.3)
Other	2 (8.7)
Weight category, n (%)	
>28 kg	16 (69.6)
≤28 kg	7 (30.4)
Prior ASMs	
Mean	3.7
Median	3.0
TSC-associated seizure frequency/28 days at baseline	
Mean (SD)	77.2 (123.2)
Median (min, max)	36.6 (6.4, 569.7)

ASMs, antiseizure medications; BMI, body mass index; SD, standard deviation; TSC, tuberous sclerosis complex.

Efficacy

- Median (95% CI) reduction in TSC-associated seizures per 28 days was 16.6% (56.4%, 14.9%) compared with baseline following the 12-week treatment period with ganaxolone (**Figure 3**)

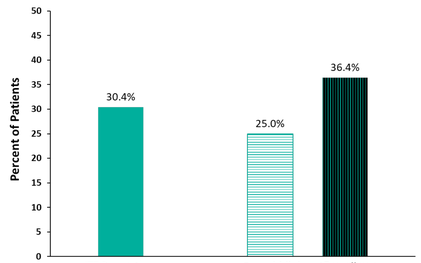
Figure 3. Percent Reduction in TSC-Associated Seizures Per 28 Days Following Ganaxolone Treatment (ITT Population)



ITT, intention to treat; TSC, tuberous sclerosis complex.

- The proportion of patients in the ITT population achieving a ≥50% reduction in TSC-associated seizure frequency (responder rate) was 30.4% (**Figure 4**)
  - The percentages of patients taking concomitant cannabidiol (n=12) or everolimus (n=11) who experienced a ≥50% reduction in TSC-associated seizure frequency were 25.0% and 36.4%, respectively

Figure 4. Percent of Patients Treated with Ganaxolone Achieving ≥50% Responder Rates (ITT Population and Concomitant ASM Subgroups)



ASM, antiseizure medication; ITT, intention to treat.

- Focal seizure types are the most common seizure presentation in patients with TSC
- Enrolled patients who experienced focal seizures (n=19) demonstrated a median 25.2% reduction in focal seizure frequency

Safety

- A total of 20 (87.0%) patients experienced TEAEs, most of which (82.6%) were mild or moderate in severity (**Table 2**)
  - The most-commonly reported TEAEs were somnolence, fatigue, and sedation
  - 3 serious TEAEs (SAEs) of seizure, aspiration, and angioedema occurred in n=1 patient each
  - TEAEs leading to discontinuation were seizure (n=2), somnolence (n=2), sedation (n=1), diarrhea (n=1), and angioedema (n=1)
  - No deaths occurred throughout the study

Table 2. Overall Summary of Safety and TEAEs Occurring in ≥2 Patients by Preferred Term (Safety Population)

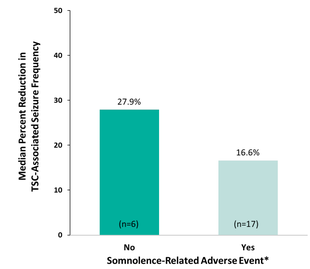
Category, n (%) [events]	Ganaxolone (n=23)
Any TEAEs	20 (87.0) [58]
TEAE by severity	
Mild	10 (43.5) [42]
Moderate	9 (39.1) [15]
Severe	1 (4.3) [1]
Serious TEAEs	3 (13.0) [3]
Treatment-related TEAEs	19 (82.6) [34]
TEAEs leading to discontinuation	7 (30.4) [7]
TEAEs resulting in death	0 (0.0) [0]
Preferred term, n (%) [events]	
Somnolence	10 (43.5) [13]
Fatigue	3 (13.0) [3]
Sedation	3 (13.0) [3]
Asthenia	2 (8.7) [3]
Dizziness	2 (8.7) [2]
Hyponatraemia	2 (8.7) [2]
Seizure	2 (8.7) [2]

TEAE, treatment-emergent adverse events.

Potential connection between tolerability and efficacy

- Patients who did not experience somnolence-related AEs (n=6) demonstrated a median 27.9% reduction in TSC-associated seizure frequency compared to a 16.6% median reduction observed in those who did report somnolence-related AEs (n=17) (**Figure 5**)

Figure 5. Percent Reduction in TSC-Associated Seizure Frequency in Patients Who Did and Did Not Experience Somnolence-Related Adverse Events



*Somnolence-related adverse events include somnolence, sedation, fatigue, and lethargy.
TSC, tuberous sclerosis complex.

Conclusions

- In this highly refractory TSC-associated epilepsy patient population, in which most patients were taking newer generation concomitant ASMs, adjunctive ganaxolone treatment resulted in a modest median percent reduction in seizure frequency
- Approximately 1/3 of patients in the study experienced ≥50% seizure reduction with 12 weeks of adjunctive ganaxolone
- Ganaxolone was generally well-tolerated; somnolence was the most commonly reported TEAE
  - Limited data suggest a possible connection between safety and efficacy, as evidenced by the differences in rates of reduction in seizure frequency in patients who did versus did not experience somnolence-related AEs
- Based on the results of this proof-of-concept study, a phase 3 study of ganaxolone in refractory TSC-associated seizures is planned
  - The design for the phase 3 study includes titration and dosing schedule modifications from the phase 2 study to improve tolerability and efficacy

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BEP: Nothing to disclose.
RRR: Consultant for Marinus Pharmaceuticals.
MZ: Reported outside activities with LivaNova, Inc.
AA: Employee of Marinus Pharmaceuticals, Inc.
IM: Employee of Marinus Pharmaceuticals, Inc.
JH: Employee of Marinus Pharmaceuticals, Inc.
DAK: personal fees from Novartis Pharmaceuticals, and RenGenXBio; grants and personal fees from Greenwich Biosciences, and Marinus Pharmaceuticals; grants and nonfinancial support from Tuberous Sclerosis Alliance; nonfinancial support from Italpharma; and serves on the Board of Directors of the Tuberous Sclerosis Alliance.

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