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Phase 2, Placebo-Controlled Clinical Study of Oral Ganaxolone in PCDH19-Clustering Epilepsy

Joseph Sullivan, MD[1]; Boudewijn Gunning, MD[2]; Muhammad Zafar, MD[3]; Renzo Guerrini, MD[4];
Marta Zolnowska, MD[5]; Jozef Gecz, PhD[6]; Debopam Samanta, MD[7]

[1]University of California San Francisco Weill Institute for Neurosciences, Benioff Children's Hospital, San Francisco, CA, USA; [2]Stichting Epilepsie Instellingen Nederland, Zwolle, The Netherlands; [3]Duke University School of Medicine, Durham, North Carolina, USA; [4]Meyer Children Hospital, Florence, Italy; [5]Medical Center Pleiades, Krakow, Poland; [6]University of Adelaide, Adelaide, South Australia, Australia; [7]University of Arkansas for Medical Sciences, Little Rock, Arkansas, USA

Background

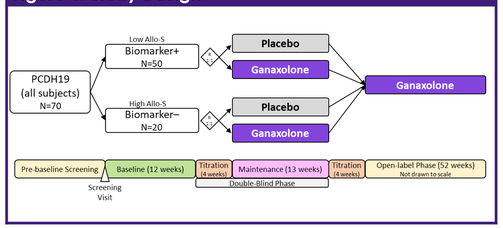
- PCDH19-clustering epilepsy (PCDH19-CE) is a distinct developmental and epileptic encephalopathy characterized by early-onset refractory seizures often occurring in clusters, intellectual disability, autism spectrum disorder, and behavioral disorders[1]
- Previous research has linked pathogenic *PCDH19* variants to reduced neurosteroidogenesis, including allopregnanolone[2,3]
- Ganaxolone is a synthetic analog of allopregnanolone that acts as a positive allosteric modulator of synaptic and extrasynaptic $GABA_A$ receptors[4]
- Ganaxolone is an investigational drug that was evaluated in a Phase 2, double-blind, placebo-controlled study (Violet Study, NCT03865732) to assess its efficacy and safety in PCDH19-CE
  - The primary study objective was to assess the efficacy of ganaxolone compared with placebo as adjunctive therapy for the treatment of primary endpoint seizures (included seizure types were countable focal or generalized seizures with a clear motor component) in children with genetically confirmed PCDH19-CE during the 17-week double-blind phase
  - The secondary objective was to assess safety and tolerability in patients receiving ganaxolone compared with patients receiving placebo (PBO) as adjunctive therapy during the 17-week double-blind phase

Design/Methods

Study Design

- This randomized, double-blind, placebo-controlled trial was conducted at 20 sites in 7 countries
  - During screening visit, the patient's blood biomarker level was assessed; patients were assigned to biomarker + or – groups based on allopregnanolone-sulfate-S (Allo-S) level. Those classified as biomarker + had baseline levels ≤2500 pg/mL.
  - Enrolled patients prospectively tracked seizure frequency during a 12-week baseline period and were then randomized (1:1) to receive ganaxolone or placebo added to standard of care for the 17-week treatment period (**Figure 1**)

Figure 1. Study Design



Endpoints

- The primary endpoint was the percentage change in seizure frequency from baseline during the 17-week double-blind treatment period
- A secondary endpoint was the percentage of patients experiencing ≥50% reduction in 28-day seizure frequency compared to baseline

Endpoints (cont.)

- Additional endpoints included ≥50% responder rate and clinical global impression of improvement (CGI-I)
- Adverse events (AEs) were tabulated by overall, system organ class, Preferred Term using the Medical Dictionary for Regulatory Activities (MedDRA) coding system and classified by severity

Patients

- Key inclusion criteria
  - Eligible patients were females, 1-17 years old with a pathogenic *PCDH19* variant, and uncontrolled seizures (≥12 seizures during a 12-week period prior to screening)
  - Seizure types included were countable focal or generalized seizures with a clear motor component
- Key exclusion criteria
  - Patients with >8 consecutive weeks (56 consecutive days) of primary seizure freedom during the 12-week pre-baseline screening period

Dosing

- Patients received ganaxolone three times daily at a maintenance dose of up to 63 mg/kg/day or 1,800 mg/day maximum

Analyses

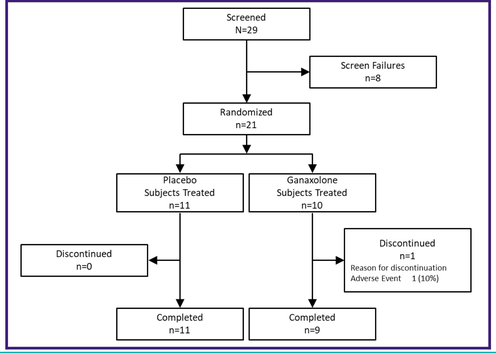
- The intent-to-treat (ITT) population was comprised of all randomized patients who received ≥1 dose of study drug and had ≥1 post-baseline efficacy assessment
- The safety population included all randomized patients who received ≥1 dose of study drug
- The data cut-off of for this analysis was January 19, 2021
- Data were summarized with descriptive statistics

Results

Baseline Demographics and Clinical Characteristics

- Twenty-one patients were randomized (**Figure 2**); median age was 7.0 years (**Table 1**)
- Patients in the ganaxolone (n=10) and placebo (n=11) groups experienced a median 28-day baseline seizure frequency of 14.5 and 17.7, respectively (**Table 1**)

Figure 2. Patient Disposition



- Baseline demographics were generally similar between patients who received ganaxolone and placebo (**Table 1**)

Table 1. Baseline Demographics and Clinical Characteristics

	Ganaxolone (n=10)	Placebo (n=11)
Age (years)		
Median	6.5	8.0
Sex, n (%)		
Female	10 (100)	11 (100)
Race, n (%)		
White	7 (70.0)	10 (90.9)
Black or African American	0	1 (9.1)
Asian	0	0
American Indian or Alaska Native	1 (10.0)	0
Other	1 (10.0)	0
Multiple races	1 (10.0)	0
Concomitant ASM, n (%)	10 (100.0)	10 (90.9)
28-day baseline seizure frequency		
Median	14.5	17.7

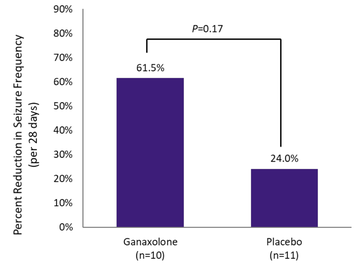
ASM, antiseizure medication, SD, standard deviation.

Efficacy

Reduction in seizure frequency

- Following the 17-week treatment period, patients on ganaxolone had a median 61.5% reduction in PCDH19-associated seizures compared to a 24.0% reduction in the placebo group (*P*=0.17) (**Figure 3**)

Figure 3. Primary Efficacy Endpoint of Percent Reduction in PCDH19-associated Seizure Frequency

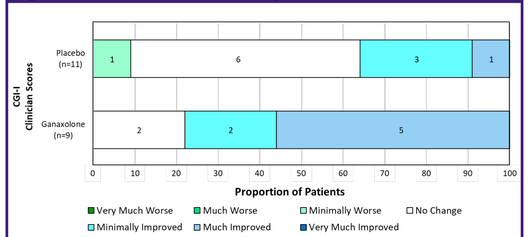


- The proportion of patients achieving a ≥50% reduction in seizure frequency in the ganaxolone and placebo groups was 50% and 36%, respectively, compared to the 8-week baseline period
- Results between biomarker + and biomarker – patients were similar to results between the ganaxolone and placebo groups

Clinical Global Impression of Improvement

- CGI-I Clinician scores, recorded by clinicians and patients/caregivers at Weeks 5, 9, and 17, were compared to baseline
  - At Week 17, clinicians rated 78% (n=7/9) of patients on ganaxolone as minimally improved or better compared to 36% (n=4/11) of patients on placebo (**Figure 4**)
- A larger proportion of patients in the ganaxolone group had 'Much Improved' CGI-I clinician scores at Week 17, compared with those in the placebo group (55.6% [n=5/9] patients vs 9.1% [n=1/11] patients, respectively)
- The CGI-I clinician scores demonstrated a mean 1.0 (95% CI, -1.8, -0.2) improvement in the ganaxolone group compared to placebo (**Figure 4**)

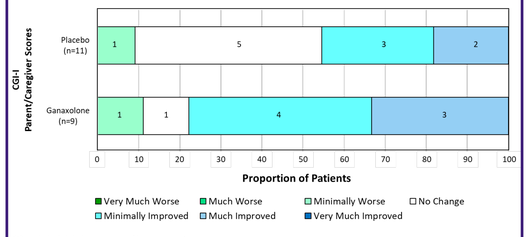
Figure 4. CGI-I Documented by the Clinician



CGI-I, clinical global impression of improvement.

- At Week 17, CGI-I Parent/Caregiver scores in all response categories were similar in both treatment groups
  - Parents and caregivers rated 78% (n=7/9) of patients receiving ganaxolone as 'Minimally Improved' or better compared to 46% (n=5/11) of patients receiving placebo (**Figure 5**)

Figure 5. CGI-I Documented by Parent/Caregiver



CGI-I, clinical global impression of improvement.

Safety

- During the 17-week double-blind phase, treatment-emergent adverse events (TEAEs) occurred in 70% of ganaxolone and 100% of placebo patients, with somnolence being the most common (40% in the ganaxolone group compared to 27% in the placebo group)
- One patient in the ganaxolone group discontinued the study due to a serious TEAE (psychogenic nonepileptic seizure), which the investigator assessed as related to treatment (**Table 2**)

Table 2. Summary of Treatment-emergent Adverse Events

Category	Ganaxolone (n=10) n (%)	Placebo (n=11) n (%)
Patients with TEAEs[a]	7 (70.0)	11 (100)
TEAE by severity[b]		
Mild	0	3 (27.3)
Moderate	7 (70.0)	8 (72.7)
Severe	0	0
Serious TEAEs	1 (10.0)	5 (45.5)
Treatment-related TEAE	6 (60.0)	6 (54.5)
Patients with TEAEs leading to discontinuation	1 (10.0)	0
AE of special interest[c]	0	2 (18.2)
TEAE resulting in death	0	0
TEAEs >1 patient by preferred term		
Somnolence	4 (40.0)	3 (27.3)
Seizure	0	4 (36.4)
Seizure cluster	0	2 (18.2)
Diarrhea	1 (10.0)	2 (18.2)
Vomiting	0	2 (18.2)
Rash		2 (18.2)
Aggression	2 (20.0)	1 (9.1)
Agitation	2 (20.0)	0
Fatigue	2 (20.0)	2 (18.2)
Alanine aminotransferase increased	2 (20.0)	0

AE, adverse event; TEAEs, treatment-emergent adverse events; SOC, system organ class.
If a patient experienced more than 1 AE in a category, the patient was counted only once in that category.
[a]TEAE defined as an AE that occurred or worsened on the day of or after the first dose of study drug and, for patients who entered the open-label extension phase, before the first dosing day of that phase.
[b]Highest severity for patients.
[c]Includes rash and AEs classified under Reproductive System and Breast Disorders SOC.

Discontinuations and dose reductions

- Overall, 1 (10.0%) patient in the ganaxolone group had any TEAE leading to study drug discontinuation (2 events; 1 event of aggression and 1 event of psychogenic seizure). No other TEAEs leading to study drug discontinuation were reported.
- All TEAEs leading to dose reduction or temporary study drug discontinuation were in the SOC of Nervous System Disorders and in the Preferred Term of somnolence and dizziness

Serious AEs and deaths

- Overall, 1 (10.0%) patient in the ganaxolone group and 5 (45.5%) patients in the placebo group reported at treatment-emergent serious AE
- No TEAEs resulting in death were reported in either treatment group

Conclusions

- Despite the limited sample size, patients treated with ganaxolone experienced directional improvements in seizure frequency compared to those on placebo
- Ganaxolone was generally well-tolerated with no new safety findings
- Due to seizure cluster fluctuation in PCDH19-CE, novel epilepsy clinical trial designs may be needed for future studies

References

1. Smith L, et al. *Epilepsia.* 2018;59(3):679-89.
2. Trivisano M, et al. *Epilepsia.* 2017;58(6):e91-e95.
3. Tan C, et al. *Hum Mol Genet.* 2015;24(18):5250-9.
4. Carter RB, et al. *J Pharmacol Exp Ther.* 1997;280(3):1284-95.

Disclosures

JS: Nothing to disclose.
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