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Ganaxolone Significantly Reduces Major Motor Seizures Associated With CDKL5 Deficiency Disorder: A Randomized, Double-Blind, Placebo-Controlled Phase 3 Study (Marigold Study)

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Introduction

- CDKL5 deficiency disorder (CDD) is a rare, X-linked, epileptic encephalopathy with an estimated incidence of 1:40,000 to 1:60,000 live births[1-2]
- Clinical characteristics commonly include early-onset refractory epilepsy, hypotonia, intellectual and gross motor impairment, and sleep disturbances
- Seizures associated with CDD are often refractory to treatment with existing antiepileptic drugs (AEDs), and improvements may be short-lived[3]
- The Marigold Study (NCT03572933) is the first phase 3, randomized, placebo-controlled trial to evaluate adjunctive investigational ganaxolone in patients with refractory epilepsy associated with CDD

Objectives

Primary

- To assess the efficacy of ganaxolone in comparison with placebo as an adjunctive therapy for the treatment of major motor seizures in children and young adults with genetically confirmed CDD at the end of the 17-week double-blind phase

Secondary

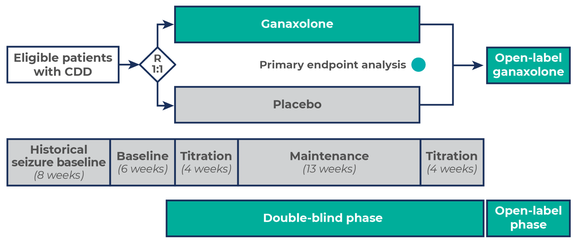
- To assess the safety and tolerability of ganaxolone in comparison with placebo as an adjunctive therapy at the end of the 17-week double-blind phase
- To assess the long-term safety and efficacy of ganaxolone when administered as an adjunctive therapy throughout the open-label phase

Methods

Study design

- Global, randomized, double-blind, placebo-controlled phase 3 clinical trial (**Figure 1**)
- Designed to evaluate safety and efficacy of adjunctive ganaxolone or placebo

Figure 1. Marigold Study Design



CDD, *CDKL5* deficiency disorder; R, randomization to ganaxolone or placebo.

Key eligibility criteria

- Pathogenic or likely pathogenic *CDKL5* variant
- Ages 2 to 21 years, inclusive
- >16 major motor seizures (defined as bilateral tonic, generalized tonic-clonic, atonic/drop, bilateral clonic, or focal to bilateral tonic-clonic) per month in the historical seizure baseline

Dosing

- Ganaxolone was taken 3 times a day at a maintenance dose of up to 63 mg/kg/d or 1800 mg/d maximum

Primary endpoint

- Percentage change in 28-day major motor seizure frequency during the 17-week treatment phase in relation to the 6-week baseline

Key secondary endpoints

- ≥50% major motor seizure frequency reduction responder rate
- Clinical Global Impressions Scale—Improvement (CGI-I): clinician and caregiver

Results

Patient enrollment

- 101 patients were randomized at 36 clinical sites in 8 countries (**Table 1**)

Table 1. Patient Baseline Demographics

Demographic	Placebo (n = 51)	Ganaxolone (n = 50)	Total (n = 101)
Age, median (IQR)	7.0 (4.0-11.0)	5.0 (3.0-10.0)	6.0 (3.0-10.0)
Gender, n (%)			
Male	10 (19.6)	11 (22.0)	21 (20.8)
Female	41 (80.4)	39 (78.0)	80 (79.2)
Ethnicity, n (%)			
Hispanic or Latino	6 (11.8)	4 (8.0)	10 (9.9)
Not Hispanic or Latino	43 (84.3)	44 (88.0)	87 (86.1)
Unknown	1 (2.0)	1 (2.0)	2 (2.0)
Not reported	1 (2.0)	1 (2.0)	2 (2.0)
Race, n (%)			
White	47 (92.2)	46 (92.0)	93 (92.1)
Asian	3 (5.9)	2 (4.0)	5 (5.0)
Other	1 (2.0)	2 (4.0)	3 (3.0)

IQR, interquartile range.

Patient baseline clinical characteristics

- Patients experienced a median of 50.0 and 57.3 major motor seizures per 28 days in the placebo and ganaxolone groups, respectively, during the 6-week baseline (**Table 2**)
- Patients tried and stopped a median of 7 AEDs and were on a median of 2 concomitant AEDs during the study

Table 2. Patient Baseline Seizure Frequency and Prior/Concomitant AEDs

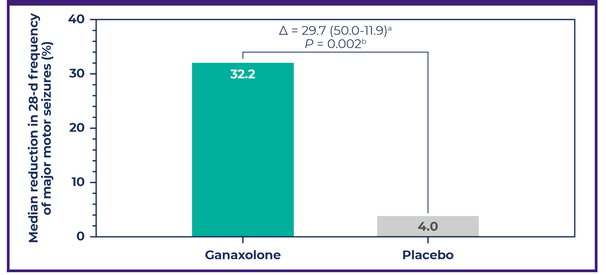
Characteristic	Placebo	Ganaxolone	Total
Baseline primary seizure frequency per 28 days, median (IQR)	50.0 (18.7-120.0)	57.3 (32.8-156.0)	—
Median no. of AED medications taken prior (min-max)	7 (1-14)	7 (2-16)	7
Median no. of AED medications taken concomitantly (min-max)	2 (1-5)	2 (1-6)	2
Concomitant AED medications, n (%)			
Valproate	16 (31.4)	18 (36.0)	34 (33.7)
Levetiracetam	13 (25.5)	13 (26.0)	26 (25.7)
Clobazam	13 (25.5)	12 (24.0)	25 (24.8)
Vigabatrin	12 (23.5)	10 (20.0)	22 (21.8)

AED, antiepileptic drug; max, maximum; min, minimum; IQR, interquartile range.

Efficacy outcomes

- Primary endpoint
  - Patients treated with ganaxolone experienced a median 32.2% reduction in major motor seizure frequency in comparison with a 4.0% reduction for patients treated with placebo (P = 0.002, Wilcoxon rank sum test) (**Figure 2**)

Figure 2. Percentage Change in 28-Day Major Motor Seizure Frequency

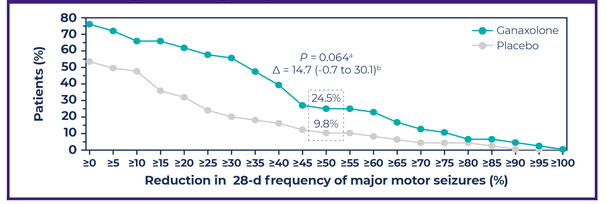


[a]Hodges-Lehman estimate of median difference (95% confidence interval).
[b]Wilcoxon rank sum test.

Key secondary endpoints

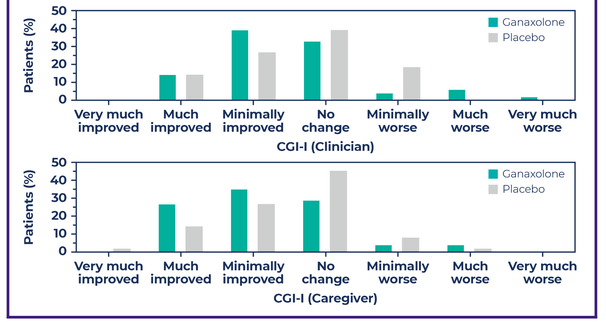
- Ganaxolone demonstrated a directional improvement in the proportion of patients with ≥50% reduction in major motor seizure frequency but did not achieve statistical significance (P = 0.064) (**Figure 3**)
- Ganaxolone demonstrated directional improvements in both the clinician's and caregiver's CGI-I scores (**Figure 4**)

Figure 3. Cumulative Response Curve Highlighting the ≥50% Reduction—Key Secondary Endpoint



[a]Determined by Fisher's exact test.
[b]Difference (95% confidence interval).

Figure 4. Changes Noted on the Clinical Global Impressions Scale—Improvement by the Clinician and the Caregiver



Determined by logistic regression.
CGI-I, Clinical Global Impressions Scale—Improvement.

Safety

- Adverse events (AEs) occurred in 86% and 88% of ganaxolone patients and placebo patients, respectively. Most frequent AEs reported by both groups were somnolence, pyrexia, and upper respiratory tract infection (**Table 3**)
- Serious treatment-emergent AEs occurred in 12.0% and 9.8% of ganaxolone- and placebo-treated patients, respectively. The 5 placebo patients and 6 ganaxolone patients who experienced ≥1 SAE collectively experienced 8 SAEs and 6 SAEs, respectively. No SAE occurred more than once in either group

Table 3. Treatment-Emergent Adverse Events Experienced in the Marigold Study

Preferred term, n (%)	Placebo (n = 51)	Ganaxolone (n = 50)
Any TEAE	45 (88.2)	43 (86.0)
Somnolence	8 (15.7)	18 (36.0)
Pyrexia	4 (7.8)	9 (18.0)
Upper respiratory tract infection	3 (5.9)	5 (10.0)
Constipation	3 (5.9)	3 (6.0)
Salivary hypersecretion	1 (2.0)	3 (6.0)
Sedation	2 (3.9)	3 (6.0)

Includes TEAEs that occurred in >5% of patients in the ganaxolone arm and more frequently than in the placebo arm.
TEAE, treatment-emergent adverse event.

Conclusions

- **Enrolled patients experienced a high baseline seizure burden despite the trial of multiple existing AEDs, reflecting their significant need for effective treatments for seizures associated with CDD**
- **Ganaxolone demonstrated a significant reduction in major motor seizure frequency in comparison with placebo (32.2% vs 4.0%)**
- **Ganaxolone was generally well tolerated. Patients experienced a <5% discontinuation rate in the ganaxolone arm, with somnolence being the most common AE**
- **These findings provide strong evidence that ganaxolone is effective and generally well tolerated in the treatment of refractory epilepsy in patients with CDD**

References

1. Olson HE, et al. *Pediatr Neurol*. 2019;97:18-25.
2. Symonds JD, et al. *Brain*. 2019;142(8):2303-2318.
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JH Cross has acted as an investigator for studies with GW Pharmaceuticals, Zogenix, Vitaflo, and Marinus Pharmaceuticals; has been a speaker and on advisory boards for GW Pharmaceuticals, Zogenix, and Nutricia; all remuneration has been paid to her department.

N Specchio reported consultancy for Marinus Pharmaceuticals, GW Pharmaceuticals, Zogenix, LivaNova, and BioMarin (speaker honoraria).

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Marigold Study
CDKL5 Deficiency Disorder

MARINUS PHARMACEUTICALS