Effect of Ganaxolone on Seizure Frequency Across Subpopulations of Patients With CDKL5 Deficiency Disorder: Subgroup Analyses of the 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 phenotype of CDD is heterogenous but often includes early-onset refractory epilepsy, hypotonia, intellectual and gross motor impairment, and sleep disturbances
- The Marigold Study (NCT03572933) is the first phase 3, randomized, placebo-controlled trial to evaluate adjunctive investigational ganaxolone (GNX) in patients with refractory epilepsy associated with CDD
- Ganaxolone significantly reduced the frequency of major motor seizures in comparison with placebo in all enrolled patients with CDD (32.2% vs 4.0% reduction, respectively; $P = 0.002$)
- Additional subgroup analyses are needed to better understand the natural history of disease and the effect of GNX in subpopulations of patients with CDD

Objective

- To evaluate the efficacy of GNX in various subpopulations of patients enrolled in the Marigold Study
  - Subpopulations defined on the basis of patient demographics, baseline clinical characteristics, and geographic region

Methods

Study design

- Global, randomized, double-blind, placebo-controlled phase 3 clinical trial to assess the safety and efficacy of adjunctive ganaxolone for the treatment of seizures associated with CDD

Key eligibility criteria

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

Dosing

- Ganaxolone was taken 3 times per 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 17-week treatment phase in relation to the 6-week baseline
  - Differences between GNX and placebo are reported using the Hodges-Lehman estimate of median difference

Subgroup analyses conducted

- Change in major motor seizure frequency (MMSF) was assessed in patients stratified by:
  - Age
  - Gender
  - Baseline allopregnanolone-sulfate (Allo-S) concentration
  - Baseline MMSF
  - Number of concomitant antiepileptic drugs (AEDs)
  - Geographic region

Results

Patient enrollment

- 101 patients were randomized (n = 50 to GNX, n = 51 to placebo) at 36 clinical sites in 8 countries (**Table 1**)
  - One GNX patient did not record any seizure data during the prospective baseline and therefore is not included in seizure-related endpoints including percentage change in MMSF. All data presented herein will report on N = 100 patients with seizure data

Age

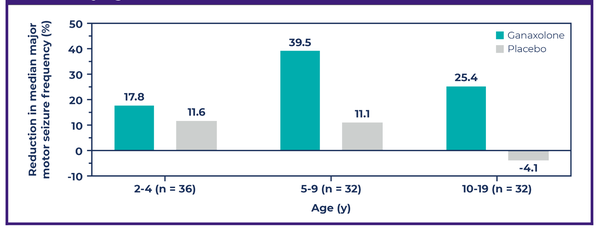
- Median age of patients enrolled in the study was 6.0 years old
- Ganaxolone demonstrated a numerical improvement in MMSF reduction in relation to placebo in all age cohorts (**Figure 1**)
  - Patients ages 2 to 4 years had the lowest baseline MMSF (median = 42.5 per 28 days) in comparison with other age cohorts potentially due to the natural history of epilepsy severity and seizure type evolution

Table 1. Patient Baseline Demographics, Clinical Characteristics, and Enrollment Location

	Placebo (n = 51)	Ganaxolone (n = 49)[a]
Age, n (%)		
2-4	15 (29.4)	21 (42.9)
5-9	17 (33.3)	15 (30.6)
10-19	19 (37.3)	13 (26.5)
Gender, n (%)		
Male	10 (19.6)	11 (22.5)
Female	41 (80.4)	38 (77.5)
Baseline Allo-S concentrate, n (%)[b]		
<2.5 ng/mL	37 (72.6)	39 (81.3)
2.5-6.0 ng/mL	12 (23.5)	5 (10.4)
>6.0 ng/mL	2 (3.9)	4 (8.3)
Baseline major motor seizure frequency, n (%)		
<35	19 (37.3)	13 (26.5)
35-93	19 (37.3)	15 (30.6)
>93	13 (25.4)	21 (42.9)
Concomitant AEDs, n (%)		
≤2	31 (60.8)	26 (53.1)
>2	20 (39.2)	23 (46.9)
Geographic region, n (%)		
United States	24 (47.1)	17 (34.7)
Australia, France, Israel, Italy, United Kingdom	15 (29.4)	20 (40.8)
Russia, Poland	12 (23.5)	12 (24.5)

AED, antiepileptic drug; Allo-S, allopregnanolone-sulfate; GNX, ganaxolone.
[a]One GNX patient did not record any baseline seizures and is not included in seizure-related endpoints.
[b]One GNX patient did not have baseline Allo-S concentrations measured.

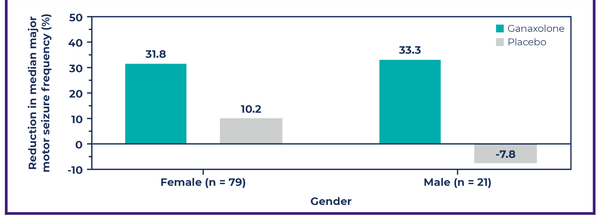
Figure 1. Percentage Reduction in 28-day Median Major Motor Seizure Frequency Stratified by Age Cohorts



Gender

- Gender distribution (79% female) aligned with published epidemiology of CDD[1]
  - Published literature suggests that males with CDD are more severely impacted than females[3,4]
- Ganaxolone demonstrated similar improvements in MMSF reduction in both females and males with CDD (**Figure 2**)
  - Female patients on GNX demonstrated a 26.3% difference from placebo in MMSF reduction (95% confidence interval [95% CI], 50.3-4.3)
  - Male patients on GNX demonstrated a 43.8% difference from placebo in MMSF reduction (95% CI, 94.0-11.0)

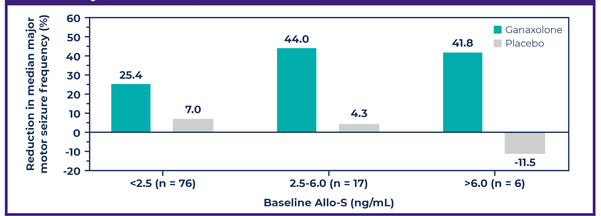
Figure 2. Percentage Reduction in 28-day Median Major Motor Seizure Frequency Stratified by Gender



Baseline allopregnanolone-sulfate (Allo-S) concentration

- Preliminary data from previous open-label clinical trials of GNX in genetic pediatric epilepsies suggest that lower plasma Allo-S concentrations may predict favorable antiseizure response
- No correlations between baseline Allo-S and response were observed in enrolled patients with CDD (**Figure 3**)
  - Future data from other clinical indications aim to provide further insights into the potential utility of plasma Allo-S levels to predict response

Figure 3. Percentage Reduction in 28-day Median Major Motor Seizure Frequency Stratified by Baseline Allo-S Concentrations

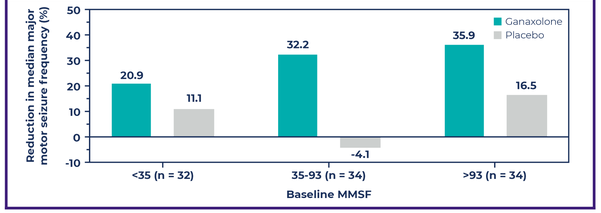


Allo-S, allopregnanolone-sulfate.

Baseline MMSF

- Baseline MMSF may be a marker for epilepsy phenotype severity
- Patients treated with ganaxolone experienced an increased numerical reduction in MMSF with increasing baseline MMSF. These differences were not significant (**Figure 4**)

Figure 4. Percentage Reduction in 28-day Median Major Motor Seizure Frequency Stratified by Baseline MMSF

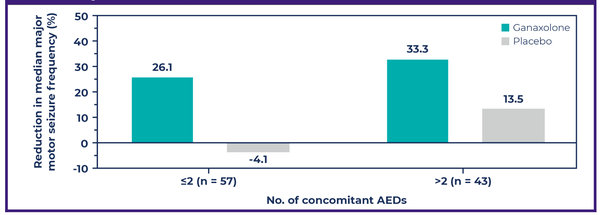


MMSF, major motor seizure frequency.

Number of concomitant AEDs

- Number of concomitant AEDs may also be a marker for epilepsy phenotype severity
- Patients tried and stopped a median of 7.0 prior AEDs. Patients were on a median of 2.0 concomitant AEDs during the study
  - The most common concomitant AEDs were valproate, levetiracetam, clobazam, and vigabatrin
- Ganaxolone demonstrated similar improvements in MMSF reduction in patients with CDD independent of the number of concomitant AEDs (**Figure 5**)

Figure 5. Percentage Reduction in 28-day Median Major Motor Seizure Frequency Stratified by Number of Concomitant AEDs

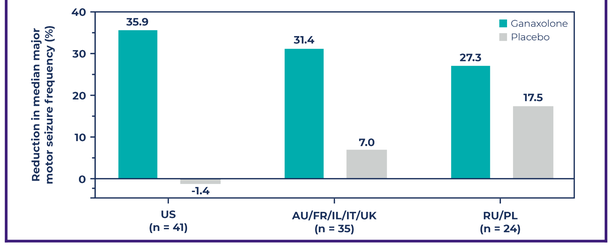


AEDs, antiepileptic drugs.

Geographic region

- Ganaxolone performed directionally better than placebo across geographic regions analyzed (**Figure 6**)
  - Ganaxolone demonstrated 36.7% MMSF difference in relation to placebo in the United States (95% CI, 62.8%-7.2%)
  - Ganaxolone demonstrated 29.9% MMSF difference in relation to placebo in Australia, France, Israel, Italy, and the United Kingdom (95% CI, 82.2% to −12.6%)
  - Ganaxolone demonstrated 16.9% MMSF difference in relation to placebo in Russia and Poland (95% CI, 63.1% to −15.9%)

Figure 6. Percentage Reduction in 28-day Median Major Motor Seizure Frequency Stratified by Geographic Region



AU, Australia; FR, France; IL, Israel; IT, Italy; PL, Poland; RU, Russia; UK, United Kingdom; US, United States.

Conclusions

- **CDD is a heterogenous disorder with variable baseline demographics and clinical severity measures**
- **Ganaxolone demonstrated directional improvements over placebo in MMSF reduction in every subgroup analyzed**
  - **These findings suggest that ganaxolone may have a beneficial effect on MMSF in a broad CDD patient population**
- **Future analyses are needed to evaluate safety findings within various subgroups**

References

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Acknowledgments

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Disclosures

Joseph Hulihan and Alex Aimetti are employees of Marinus Pharmaceuticals, Inc. No other disclosures were reported.

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