Ganaxolone Treatment in Patients with CDKL5 Deficiency Disorder with Comorbid Lennox-Gastaut Syndrome: A Post-hoc Analysis from the Marigold Study

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Introduction

- Cyclin-dependent kinase-like 5 (CDKL5) deficiency disorder (CDD) is a rare X-linked developmental epileptic encephalopathy (DEE) resulting from pathogenic loss-of-function mutation(s) in the *CDKL5* gene[1,2]
- CDD presents with treatment-refractory seizures, severe global developmental impairment, and multiple comorbidities[3]
- Lennox-Gastaut syndrome (LGS) is also a severe age-dependent DEE with onset between 1 and 8 years of age[4] and may result from a number of underlying structural or genetic neurologic disorders
- The clinical presentation of LGS includes multiple drug-resistant seizure types, a slow spike-and-wave EEG pattern, and serious neurodevelopmental disability[4]
- Despite treatment with numerous antiseizure medications (ASMs), less than 10% of patients with LGS become seizure-free,[5] indicating a significant unmet treatment gap
- Within the CDD population, patients with a genetic diagnosis of CDD may also have a phenotypic diagnosis of LGS

Ganaxolone

- Ganaxolone is an investigational neuroactive steroid and a synthetic analog of allopregnanolone[6]
  - Ganaxolone is a positive allosteric modulator of $GABA_A$ receptors[6,7]
  - GNX exhibited broad-spectrum antiseizure activity in preclinical models, including when benzodiazepine resistance developed[6]

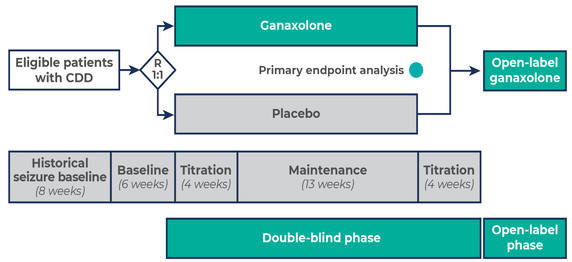
➢ The aim of this post-hoc subgroup analysis was to gain preliminary insights into the effects of ganaxolone in CDD patients who also met diagnostic criteria for LGS

Methods

Study Design

- Global, randomized, double-blind (DB), placebo-controlled phase 3 clinical trial
- 6-week prospective baseline (BL) period followed by 17-week DB treatment phase (**Figure 1**)
- Following the DB phase, patients were eligible to enter an open-label extension (OLE)
- Seizure data were collected at 17 weeks of ganaxolone treatment in both the DB and open-label phases

Figure 1. Marigold Study Design



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

Primary Endpoint

- Percent change in 28-day major motor seizure frequency (MMSF) during the 17-week treatment phase in relation to the 6-week BL

Key Inclusion Criteria

- Pathogenic or likely pathogenic CDKL5 variant
- Aged 2-21 years, inclusive
- >16 major motor seizures (MMS, defined as bilateral tonic, generalized tonic-clonic, atonic/drop, bilateral clonic, or focal to bilateral tonic-clonic) per month at BL

Dosing

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

Results

Patient Enrollment

- Patients (N=101, 79% female) were randomized at 36 clinical sites in 8 countries to either ganaxolone (n=50) or placebo (n=51) (**Figure 2**)
- Patients had a median age of 6 years and had failed a median of 7 ASMs
- For patients originally randomized to placebo, seizure data were collected after 17 weeks of ganaxolone treatment in the OLE

LGS Patient Demographics and Clinical Characteristics

- Of the 101 patients randomized, 7 (6.9%) had a co-diagnosis of LGS
- Patients ranged in age from 3-19 years (median, 11 years)
- Two patients were randomized to ganaxolone and received treatment through the DB phase (**GNX DB**)
- Five patients were randomized to placebo; four continued into the OLE and received ganaxolone treatment for 17 weeks (**GNX OLE**)
- One placebo patient did not enter the OLE; therefore, 6 patients were evaluable for this analysis (**Table 1**)
- Patients were taking a median 3 ASMs at BL
- Median MMSF per 28 days at BL was 88.7

Table 1. LGS Patient Baseline Demographics and Clinical Characteristics

Subject	Sex	Age at Enrollment	Median BL MMSF	Number of Concomitant ASMs
1	F	12	15.3	3
2	F	12	190	2
3	F	19	49.2	3
4	F	11	116	4
5	F	3	132	1
6	M	5	88.7	3
All Patients with LGS (n=6)				
Median Concomitant ASMs				3
Median MMS per 28 days at BL				88.7

ASM, antiseizure medication; BL, baseline; LGS, Lennox-Gastaut syndrome; MMS, major motor seizures; MMSF, major motor seizure frequency.

Efficacy Outcomes

- 4 of the 6 evaluable LGS patients (2 GNX DB, 2 GNX OLE) demonstrated improvements in seizure frequency after 17 weeks of ganaxolone treatment compared to BL (**Table 2**)
  - The 2 GNX DB patients experienced percent changes in MMSF of -25.4% and -43.5%
  - The 2 GNX OLE patients experienced percent changes in MMSF of -21.0% and -36.3%
- The other 2 GNX OLE patients did not show improvement with ganaxolone treatment (4.6% and 27.1% change in MMSF)

Table 2. Percent Change in MMSF at 17 Weeks of Ganaxolone Treatment

Subject	Group	% Change MMSF at 17 Weeks GNX Treatment
1	GNX DB	-25.7
2	GNX OLE	27.1
3	GNX OLE	-21
4	GNX DB	-43.5
5	GNX OLE	-36.3
6	GNX OLE	4.6

GNX, ganaxolone; GNX DB, patients randomized to ganaxolone and treated through the double-blind phase; GNX OLE, patients randomized to placebo and treated through the open-label extension; MMSF, major motor seizure frequency.

Safety and Tolerability

- All patients with LGS (n=7) were included in the safety analysis
- Treatment-emergent adverse events (TEAEs) were reported by 4 (80%) GNX OLE patients and 2 (100%) GNX DB patients
- Seizures were the most common TEAE reported in the GNX DB group (n=2)
- Among patients in the GNX OLE group, infections were the most common TEAE (n=2)

Conclusions

- The high seizure burden and refractory nature of LGS-related seizures indicates a significant need for new and effective treatments
- This post-hoc analysis found that treatment with ganaxolone three times daily was associated with decreases in MMSF in 4 of 6 patients with both CDD and LGS
- Ganaxolone was generally well-tolerated, and no new safety signals emerged in the LGS subgroup
- These findings provide preliminary evidence that treatment with ganaxolone may reduce seizure frequency in some patients with co-diagnoses of LGS and CDD
- Larger studies are needed to further elucidate the potential of ganaxolone as treatment for seizures associated with LGS

References

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Disclosures

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