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Extended Duration Safety and Efficacy of Adjunctive Ganaxolone Treatment in Patients with CDKL5 Deficiency Disorder: 8-Month Minimum Open-Label Extension Follow-Up

Marigold Study
CDKL5 Deficiency Disorder

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Introduction

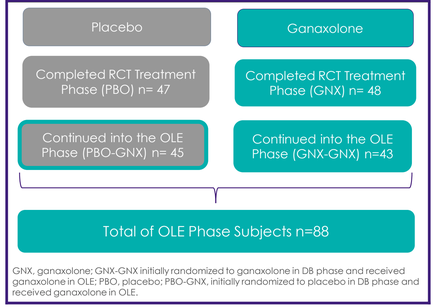
- CDKL5 deficiency disorder (CDD) is a rare X-linked epileptic encephalopathy resulting from pathogenic, loss-of-function variant(s) in the *CDKL5* gene[1-2]
- Clinical presentations include early-onset refractory epilepsy and developmental and intellectual impairment, along with disorders related to sleep, respiration, gastrointestinal function, and cortical vision[1-3]
- Despite treatment with multiple current anti-seizure medications (ASMs), many patients with CDD-associated epilepsy are highly refractory and continue to experience seizures[1-4-6]
  - Improvements have been reported to often be short-lived (median, 6 months)[4]
  - The chronic refractory nature of seizures combined with severe comorbidities results in a heavy burden of care and diminished quality of life for patients and their caregivers[1,7]
- In a recent placebo-controlled Phase 3 clinical study (Marigold Study, NCT03572933), ganaxolone, a neuroactive steroid, significantly reduced major motor seizure frequency (MMSF) over the 17-week treatment period (ganaxolone 30.7% vs placebo 6.9%; p=0.0036) in patients with CDD when added to the standard of care
- Here, we present an update from the open-label extension (OLE) (data cutoff, February 24, 2021), reporting safety and efficacy in patients with a minimum 8-month follow-up on ganaxolone for treatment of CDD-associated seizures

Methods

- Patients who completed the 17-week double-blind phase of the Marigold study were eligible to enroll in the OLE
- Key eligibility criteria:
  - Pathogenic or likely pathogenic CDKL5 variant
  - Aged 2-21 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 8-week historical baseline period
  - The blinding of the original treatment assignment was maintained during the transition to the open-label phase
- In the OLE, the maximum daily dose of ganaxolone allowed was 63 mg/kg/day up to 1,800 mg/day taken in three divided doses
- Key endpoints:
  - Long-term tolerability and safety of adjunctive ganaxolone
  - MMSF reduction evaluated at 2-month intervals
  - Clinical Global Impression—Improvement (CGI-I) assessments by clinicians and caregivers
- There was no imputation of missing data for patients who discontinued before 8 months
- Results presented here represent a preliminary analysis of the OLE data as of February 24, 2021, with a minimum 8-month follow up in the OLE phase. Data shown include all available data except efficacy data, which are presented out to 12 months to minimize data missingness.

Results

Figure 1. Patient Disposition



GNX, ganaxolone; GNX-GNX initially randomized to ganaxolone in DB phase and received ganaxolone in OLE; PBO, placebo; PBO-GNX, initially randomized to placebo in DB phase and received ganaxolone in OLE.

Patient Disposition

- Of the 101 patients entering the double-blind phase, 88 (87.1%) continued into the OLE (43 were initially randomized to ganaxolone [GNX-GNX] and 45 to placebo [PBO-GNX]; **Figure 1**)
- At the time of this analysis, 57 patients were remaining in the OLE study
  - 31 (35.2%) patients dropped out of the OLE due to lack of efficacy (n=12), adverse events (n=9), withdrawal by subject or parent/LAR (n=8), sponsor decision (n=1), or physician decision (n=1)

Patient Exposure to Ganaxolone

- Patients assigned placebo that transitioned into the OLE (PBO-GNX) were exposed to ganaxolone for a median of 256 days, whereas patients assigned ganaxolone that transitioned into the OLE (GNX-GNX) remained on it for a median of 263 days

Baseline Characteristics

- Patients who transitioned to the OLE had overall similar baseline clinical characteristics and demographics to the double-blind intent-to-treat population (N=101) (**Table 2**)
- The OLE group experienced a median 28-day MMSF 6-week prospective baseline of 50.6 (**Table 3**)
- GNX-GNX and PBO-GNX patients experienced 62.9 and 46.7 baseline median 28-day MMSF values, respectively

Table 2. Demographics

	Total (N=88)
Age, years[a]	
Mean (SD)	7.3 (4.6)
Median (min, max)	5.0 (2.0, 19.0)
Sex, n (%)	
Male	18 (20.5)
Female	70 (79.5)
Region, n (%)	
United States	35 (39.8)
Australia/France/Israel/Italy/United Kingdom	33 (37.5)
Poland/Russia	20 (22.7)

Table 3. Baseline Characteristics

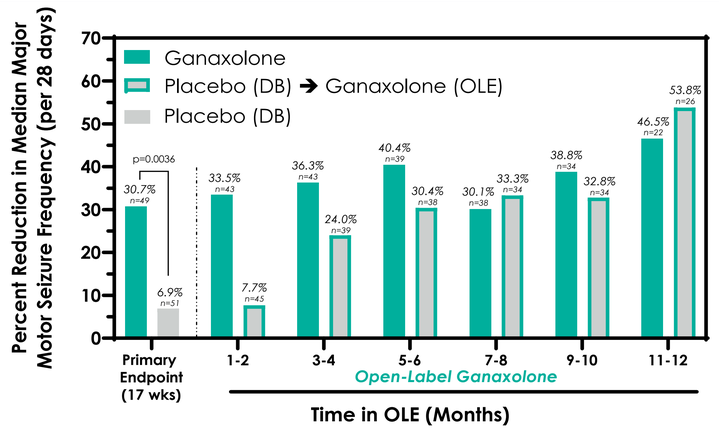
	Total (N=88)
Baseline MMSF per 28 days[a]	
Median (IQR)	50.6 (26.0 – 146.7)
Concomitant ASMs in Open-Label	
Median (IQR)	3.0 (2.0 – 4.5)
Most common ASMs used in ≥10% of patients, n (%)	
Valproic acid	32 (36.4)
Clobazam	26 (29.5)
Levetiracetam	23 (26.1)
Vigabatrin	20 (22.7)

ASM, antiseizure medication; IQR, interquartile range; max, maximum; min, minimum; MMSF, major motor seizure frequency; OLE, open-label extension.
[a]During the 6-week prospective baseline.

Change in Major Motor Seizure Frequency

- MMSF was significantly reduced in patients treated with ganaxolone compared to placebo at the end of the double-blind phase (30.7% vs. 6.9% reduction, respectively; p=0.0036; **Figure 2**)
- The median MMSF reduction from baseline in the OLE was 30.1% in the GNX-GNX arm (n=38) and 33.3% in the PBO-GNX arm (n=34) at 8 months and 46.5% (n=22) and 53.8% (n=26), respectively, at 12 months (**Figure 2**)

Figure 2. Percent Reduction in 28-Day Median Major Motor Seizure Frequency at Various Time Points Within the OLE

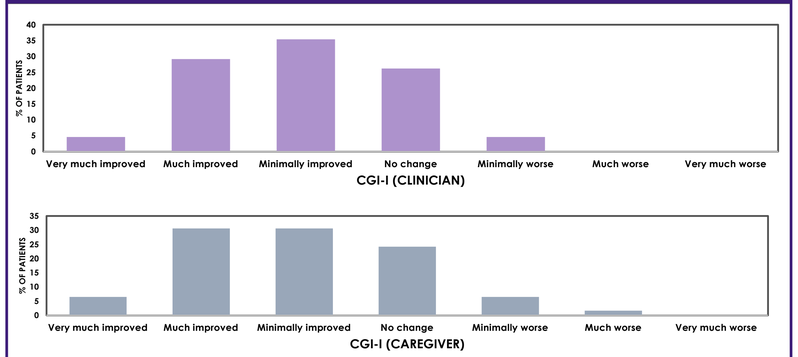


Sample size varies due to patient discontinuation and due to patients still ongoing within the OLE. Dashed line represents transition from double-blind (left) to OLE (right).
DB: Double-blind, OLE: open-label extension. [a]Includes all patients randomized (N=101).

Clinical Global Impression—Improvement

- Improvements in CGI-I assessments (minimally improved or better) were similar between GNX-GNX and PBO-GNX groups, ranging from 66.6% to 82.1% for the caregiver and from 68.9% to 76.9% for the clinician observations at 34 weeks follow-up (**Figure 3**)

Figure 4. Clinical Global Impression—Improvement Assessment by Clinicians and Caregivers at 34 Weeks



All patients in the open-label that reached Week 34 in the OLE (n=80) are presented here in aggregate and are not separated by their double-blind treatment assignment.
CGI-I: Clinical Global Impression—Improvement.

Safety and Tolerability

Table 3. Treatment-emergent Adverse Events (TEAEs)

	Open-Label (N=88)
Any TEAE, n (%)	73 (83.0)
Serious TEAEs, n (%)	22 (25.0)
Treatment-related* TEAE, n (%)	39 (44.3)
TEAE leading to discontinuation	11 (12.5)
Deaths	1 (1.1)
TEAEs that occurred ≥10% of patients in the OLE phase, n (%)	
Seizure	17 (19.3)
Somnolence	16 (18.2)
Pyrexia	12 (13.6)
Vomiting	11 (12.5)
Nasopharyngitis	9 (10.2)
Upper respiratory tract infection	9 (10.2)

* AEs that were considered treatment-related by the investigator.

- No new safety signals were observed in the OLE at the time of this analysis (**Table 3**)
- 73 patients (83.0%) reported at least one treatment-emergent adverse event (TEAE)
  - 25 (28.4%), 30 (34.1%), and 18 (20.5%) patients in the OLE reported mild, moderate, and severe TEAEs, respectively
- The most frequently reported AEs leading to ganaxolone discontinuation were seizures (3.4%) and somnolence (2.3%)
- The most common TEAEs in the OLE (≥10% of patients) were seizures, somnolence, pyrexia, vomiting, nasopharyngitis, and upper respiratory tract infections

Conclusions

- Adverse events in the OLE are consistent with those observed in the double-blind phase as well as the known safety profile of ganaxolone
- Data from the OLE provide supportive evidence for maintenance of effect on reducing major motor seizures associated with CDD at approximately 8 months and up to 12 months in patients who continue ganaxolone treatment
- Limitations of this preliminary OLE analysis include missing data due to patient dropouts, the open-label nature of the OLE, and the lack of a control arm
- These preliminary OLE findings indicate that ganaxolone has the potential to provide sustained seizure improvements in patients with CDD

References

1. Olson HE, et al. *Pediatr Neurol*. 2019;97:18-25.
2. Tao J, et al. *Am J Hum Genet*. 2004;75(6):1149-54.
3. Mangatt M, et al. *Orphanet J Rare Dis*. 2016;11:39.
4. Müller A, et al. *Eur J Paediatr Neurol*. 2016;20(1):147-51.
5. Demarest ST, et al. *Epilepsia*. 2019;60(8):1733-42.
6. Olson HE, et al. *J Neurodev Disord*. 2021;13:40.
7. Leonard H, et al. *Epilepsy Res*. 2021;169:106521.

Disclosures

HEO: consulting with Marinus Pharmaceuticals, Inc., and site PI for the ganaxolone trial; consulting with Zogenix and Ovid.
EPK: consulting with Marinus Pharmaceuticals, Inc., and participated in advisory boards for BioMarin.
ANM: nothing to disclose
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MARINUS PHARMACEUTICALS

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