Extended Duration Safety and Efficacy of Ganaxolone for the Treatment of CDKL5 Deficiency Disorder: Preliminary Open-Label Extension Analysis (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 antiseizure medications (ASMs), and improvements may be short-lived (≤3 months)[3]
  - Effective ASMs that provide a meaningful and durable reduction in seizures are needed for patients with CDD
- The Marigold Study (NCT03572933) of adjunctive ganaxolone (GNX) in CDD is the first randomized, placebo-controlled trial of an investigational medication in this disorder
- The open-label extension (OLE) of the study will provide long-term safety data and allows a preliminary analysis on durability of effect for ganaxolone in the treatment of CDD

Objective

- To evaluate preliminary long-term efficacy and safety of ganaxolone in patients with CDD beyond the 17-week double-blind phase

Methods

Double-blind phase

- 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 2-21 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 in 17-week treatment phase in relation to the 6-week baseline

Open-label extension

- At the end of the 17-week double-blind phase, all patients who elected to enter the OLE were provided open-label GNX. The blinding of the original treatment assignment was maintained during the transition to the OLE
- Safety data include events that occurred during the OLE
- Patients assigned to ganaxolone and placebo in the double-blind phase are presented separately when describing seizure frequency efficacy
  - Patients assigned to active treatment (GNX) in the double-blind phase were exposed to ganaxolone for the 17 weeks during the double-blind phase plus the duration in the OLE at the time of this analysis
- The results represent observed-case data for each assessment at the reported time point
- **Data presented here represent a *preliminary* analysis of the OLE data as of September 1, 2020**

Results

Transition to open-label extension

- 88 patients completed the double-blind phase and entered the OLE (n = 43 assigned to the GNX group during the double-blind phase [GNX-GNX]; n = 45 assigned to the placebo (PBO) group during the double-blind phase [PBO-GNX]) (**Table 1**)
- Patients in the OLE had overall similar demographics and baseline clinical characteristics to the intent-to-treat population (N = 101) during the double-blind phase
  - Approximately 80% were female with a median age of 5.0 years old
  - The OLE cohort experienced a median 28-day major motor seizure frequency of 50.6 during the 6-week prospective baseline
    - GNX-GNX and PBO-GNX patients experienced a baseline median 28-day major motor seizure frequency of 62.9 and 46.7, respectively

Table 1. OLE Patient Demographics

Baseline attribute	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)
Baseline major motor seizure frequency, per 28 days[a]	
Median (IQR)	50.6 (26.7-141.3)
Concomitant ASMs in open label	
Median (IQR)	3.0 (2.0-4.0)

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

Patient disposition

- Data cut-off as of September 1, 2020
- 88 patients entered the OLE (**Table 2**)
  - No patients have completed the OLE
  - Fifteen patients have discontinued the OLE
    - The most common reasons for discontinuation were lack of efficacy (n = 7) and adverse event (n = 6)
  - 73 patients remain in the OLE
- Patients assigned to placebo in the double-blind phase who transitioned into the OLE (PBO-GNX) were exposed to ganaxolone an average of 205 days. Patients assigned to ganaxolone in the double-blind phase who transitioned into the OLE (GNX-GNX) were exposed to ganaxolone an average of 335 days

Table 2. Patient Disposition in OLE and Patient Exposure to Ganaxolone

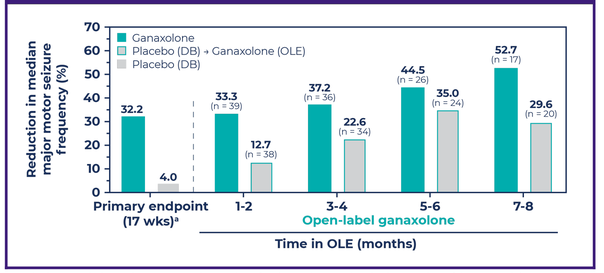
Patient disposition	n
Entering the OLE	**88**
Completing the OLE	**0**
Discontinuing the OLE	**15**
Lack of efficacy	7
Adverse event	6
Physician decision	1
Withdrawal by parent/LAR	1
Exposed to ganaxolone	**Days**
PBO-GNX	
Mean	205
Median (IQR)	144 (119-281)
GNX-GNX	
Mean	335
Median (IQR)	322 (243-407)

Data as of September 1, 2020. GNX, ganaxolone; IQR, interquartile range; LAR, legally authorized representative; OLE, open-label extension; PBO, placebo; SD, standard deviation.

Change in major motor seizure frequency

- Ganaxolone significantly reduced the frequency of major motor seizures in comparison with placebo at the end of the double-blind phase (32.2% vs 4.0% reduction, respectively; $P = 0.002$)
- Patients assigned to ganaxolone in the double-blind phase continued to experience a marked reduction in major motor seizure frequency in the OLE, ranging from 33.3% to 52.7% (median) (**Figure 1**)
  - Of these patients, 17 experienced a 52.7% median reduction in major motor seizure frequency at months 7-8 in the OLE, representing ≈11-12 months exposed to ganaxolone inclusive of the double-blind phase
- Patients assigned to placebo in the double-blind phase began experiencing a reduction in major motor seizure frequency within the first 2-month period of the OLE and demonstrated improvement out to 8 months

Figure 1. Percentage Reduction in 28-Day Median Major Motor Seizure Frequency at the End of the Double-Blind Phase (Primary Endpoint) and at Various Time Points Within the OLE



Sample size at each time point represents the number of patients who completed at least 28 days of that 2-month interval. Sample size varies because of patient discontinuation and because of patients still ongoing within the OLE. The dashed vertical line represents transition from the double-blind phase (left) to the OLE (right). DB, double blind; OLE, open-label extension; wks, weeks.
[a]Includes all patients randomized (N = 101).

- Patients who remained in the OLE for 6 months (n = 41) had a median 34.3% major motor seizure frequency reduction over that time in relation to baseline
- In contrast, patients who discontinued from the OLE prior to 6 months (n = 10) had a median 0.3% major motor seizure frequency increase during their variable time in the OLE (<6 months) in relation to baseline

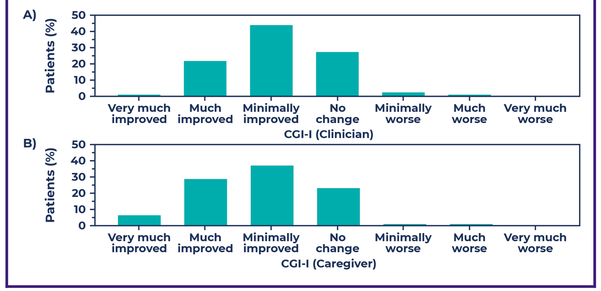
Clinical Global Impressions—Improvement scale

- Response was reported as minimally improved or better by 68.0% and 73.6% of clinicians and caregivers, respectively, at week 17 in the OLE (N = 72) (**Figure 2**)
  - 26 patients (36.1%) and 17 patients (23.6%) were reported as much improved or very much improved by the caregiver and clinician, respectively

Safety

- At least 1 treatment-emergent adverse event (TEAE) was reported in 63 patients (71.6%) (**Table 3**)
  - Of the patients in whom TEAEs were reported, 36.5% and 42.9% of the patients' adverse events were of mild or moderate severity, respectively
  - Somnolence remains the most commonly reported TEAE, occurring in 15 patients (17.0%)
- Serious adverse events were reported in 17 patients
- No new safety signals have been observed in the OLE at the time of this analysis

Figure 2. Clinical Global Impressions—Improvement Assessment at Week 17 in the OLE (Week 34 Overall)



Clinical Global Impressions—Improvement assessment by A) clinician and B) caregiver at week 17 in the OLE (week 34 overall). All patients in the open-label phase who reached week 17 in the OLE (n = 72) are presented here in aggregate and are not separated by their double-blind phase treatment assignment. CGI-I, Clinical Global Impressions—Improvement scale; OLE, open-label extension.

Table 3. Most Common Treatment-Emergent Adverse Events in the OLE

Preferred term	Open label (n = 88)
Any TEAE, n (%)	63 (71.6)
Somnolence	15 (17.0)
Seizure	13 (14.8)
Pyrexia	10 (11.4)
Vomiting	9 (10.2)

Includes TEAEs that occurred in ≥10% of patients and began in the OLE. OLE, open-label extension; TEAE, treatment-emergent adverse event.

Conclusions

- **Ganaxolone provided a clinically meaningful and significant reduction in major motor seizure frequency in comparison with placebo during the double-blind phase ($P = 0.002$)**
- **Patients taking ganaxolone for 12 months maintained a durable seizure reduction (median, 52.7%)**
  - **The median 28-day reduction in major motor seizure frequency in all patients who have completed 7-8 months in the OLE is 33.0% (n = 37)**
- **Clinical improvements in the OLE were documented on the Clinical Global Impressions—Improvement scale by clinicians and caregivers**
- **Ganaxolone was generally well tolerated in the OLE with no new safety signals observed**
- **Limitations of this preliminary OLE analysis include missing data, the open-label nature of the OLE, and the lack of a control arm**
- **These preliminary findings indicate that ganaxolone has the potential to provide clinically meaningful, durable seizure improvements in patients with CDD**

References

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3. Müller A, et al. *Eur J Paediatr Neurol*. 2016;20(1):147-151.

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