Sustained Seizure Control With 2 Years of Ganaxolone Treatment for Cyclin-dependent Kinase-like 5 (CDKL5) Deficiency Disorder (CDD) in the Marigold Study Open-Label Extension

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BACKGROUND

- Cyclin-dependent kinase-like 5 (CDKL5) deficiency disorder (CDD) is a rare X-linked developmental and epileptic encephalopathy characterized by global developmental impairment and early-onset, refractory seizures[1]
- Achieving durable seizure control is problematic, with up to 84% of patients developing refractoriness to antiseizure medications (ASMs) within weeks to months of treatment initiation[2-4]
- Ganaxolone is a neuroactive steroid that enhances GABAergic inhibitory tone via positive allosteric modulation of synaptic and extrasynaptic $GABA_A$ receptors[5]
  - Ganaxolone is approved in the United States for the treatment of seizures associated with CDD in patients aged ≥2 years[6]
  - In Europe, ganaxolone is indicated for the adjunctive treatment of seizures associated with CDD in patients 2-17 years old, and may be continued in patients ≥18 years old[7]
- In the phase 3 Marigold Study (NCT03572933), patients aged 2-19 years with CDD were treated with adjunctive ganaxolone oral suspension for 17 weeks
  - Median 28-day major motor seizure frequency (MMSF) was significantly reduced from baseline with ganaxolone (30.7% reduction [IQR 1.9-4.5]) versus placebo (6.9% reduction [-39.7-24.1]; p=0.0036)[8]

OBJECTIVE

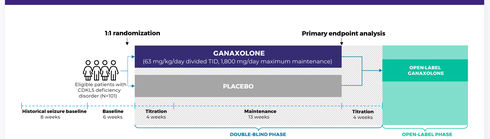
- To evaluate the long-term safety, tolerability, and effectiveness of oral ganaxolone in the treatment of seizures associated with CDD

METHODS

Study Design

- Marigold was a randomized, placebo-controlled, double-blind, phase 3 study in patients with CDD (**Figure 1**)
- Patients who completed the 17-week double-blind phase were eligible to undergo a 4-week blinded cross-titration to open-label ganaxolone treatment

Figure 1. Design of the Marigold Study and Open-Label Extension



CDKL5, cyclin-dependent kinase-like 5 deficiency; TID, three times daily.

Key Eligibility Criteria

- Pathogenic or likely pathogenic *CDKL5* gene variant
- ≥16 major motor seizures per 28 days in each of the 4-week periods in an 8-week historical control period. Motor seizures were defined as bilateral tonic, generalized tonic-clonic, bilateral clonic, atonic, or focal to bilateral tonic-clonic
- No history of West Syndrome with hypsarrhythmia or predominantly infantile spasms
- No use of adrenocorticotropic hormone, prednisone, or other non-inhaled steroids
- 2-21 years old

Treatment

- Ganaxolone 63 mg/kg/day (for patients weighing ≤28 kg) or 1800 mg/day maximum (for patients weighing >28 kg)

Analysis

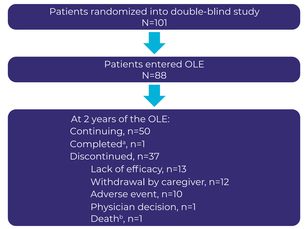
- Data were collected up to June 30, 2022
- Assessments:
  - Percent change in MMSF from baseline to 3-month intervals up to 24 months
  - Caregiver Global Impression of Change–Improvement (CGI-I), and CGI–Seizure Intensity and Duration (CGI-CSID) score
  - Safety and tolerability
- Median percent reduction in 28-day MMSF during each 3-month interval was analyzed using available data
  - To impute missing values, both a multiple imputation mixed effects model and last observation carried forward (LOCF) method were employed

RESULTS

Patient Disposition and Characteristics

- Of 101 patients randomized in Marigold, 88 (87.1%) continued into the OLE (**Figure 2, Table 1**)
  - n=1 completed 2 years in the OLE and transitioned to the expanded access program
  - n=50 were ongoing at 2 years in the OLE
  - n=37 discontinued

Figure 2. Patient Disposition at 2 Years in the OLE



OLE, open-label extension.
[1]Patient completed 2 years in the OLE and transitioned to the expanded access program.
[2]Death occurred due to sepsis and was not related to study drug.

Table 1. Patient Demographics and Baseline Characteristics

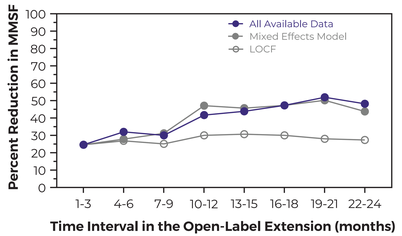
	Total (N=88)
Age, years[a]	
Mean (SD)	7.3 (4.6)
Median (minimum, maximum)	5.0 (2.0, 19.0)
Female, n (%)	70 (79.5)
Region, n (%)	
United States	35 (39.8)
Outside United States	53 (60.2)
Baseline MMSF per 28 days[a]	
Median (IQR)	50.6 (26.0-145.3)
Achieved target ganaxolone dose, n (%)	83 (94.3)
Number of concomitant ASMs at the start of the OLE	
Median (range)	2.0 (0-4.0)

IQR, interquartile range; MMSF, major motor seizure frequency; OLE, open-label extension; SD, standard deviation.
[a]During the 6-week prospective baseline.

Reduction in Major Motor Seizure Frequency

- Median reduction from baseline in MMSF during Months 22–24 (n=50) was 48.2% (95% CI 27.4, 56.1) (**Figure 3**)
- During Months 22-24, 23/50 (46.0%), 12/50 (24.0%), and 3/50 (6.0%) patients had a response of ≥50%, ≥75%, and 100%, respectively (**Figure 4**)
- Seizures occurred on a median of 73.5% of days during baseline
  - During Months 22-24, the number of days with seizures was reduced by a median of 20.0%, equivalent to ~4 fewer days with seizures per month (**Figure 5**)

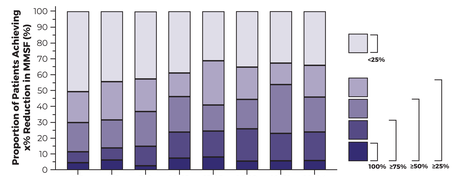
Figure 3. Percent Reduction From Baseline in Median 28-day MMSF Through 2 Years of the OLE



All Available Data	n=87	n=79	n=73	n=67	n=61	n=54	n=52	n=50
Mixed Effects Model	n=87	n=87	n=87	n=87	n=87	n=87	n=87	n=87
LOCF	n=87	n=87	n=87	n=87	n=87	n=87	n=87	n=87

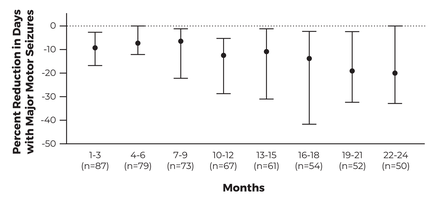
LOCF, last observation carried forward; MMSF, major motor seizure frequency; OLE, open-label extension.
Baseline seizures for 1 patient were not recorded; that patient was excluded from the analysis of reduction in MMSF.

Figure 4. Response Categories by 3-month Intervals During the OLE



MMSF, major motor seizure frequency; OLE, open-label extension.
Response rate is defined as the percent change from baseline in 28-day MMSF within the specified ranges. The percentages are based on the number of patients who contributed data within each 3-month interval.

Figure 5. Median (95% CI) Reduction From Baseline in the Percentage of Days with Major Motor Seizures in the OLE

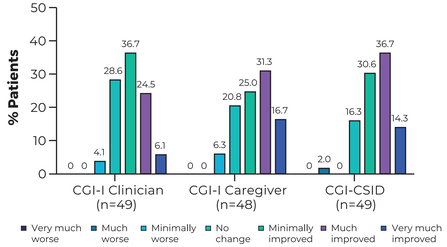


CI, confidence interval; OLE, open-label extension.

Improvement in CGI-I and CGI-CSID Score

- At Week 116 (~2 years), 15/49 (30.6%) and 23/48 (47.9%) patients were rated on the CGI-I by clinicians and caregivers, respectively, as "much improved" or "very much improved" (**Figure 6**)
- CGI-CSID scores also indicated "much" and "very much" improvement for 25/49 (51.0%) patients

Figure 6. CGI-I Scores at Week 116 of the OLE



CGI-I Clinician, Clinical Global Impression of Improvement (Clinician Rated); CGI-I Caregiver, Clinical Global Impression of Improvement (Caregiver Rated); CGI-CSID, Clinical Global Impression – Change in Seizure Intensity and Duration (Caregiver Rated); OLE, open-label extension.
CGs are rated on a 7-point Likert scale, with 1 point = very much improved, 2 points = much improved, 3 points = minimally improved, 4 points = no change, 5 points = minimally worse, 6 points = much worse, and 7 points = very much worse.

Safety

- The most commonly reported treatment-emergent adverse events (TEAEs) during the OLE were seizure (23.9%), vomiting (22.7%), somnolence (21.6%), and pyrexia (17.0%)
- Somnolence and seizure were the most frequent treatment-related TEAEs (**Table 2**)

Table 2. Summary of TEAEs Reported During the OLE

	Total (N=88)
Treatment-related TEAE[b], n (%)	41 (46.6)
Somnolence	15 (17.0)
Seizure	10 (11.4)
Decreased appetite	5 (5.7)
Weight decrease	4 (4.5)
Attention-seeking behavior	3 (3.4)
Gait disturbance	3 (3.4)
Any serious TEAE[b], n (%)	28 (31.8)
Seizure	6 (6.8)
Pneumonia	5 (5.7)
Acute Respiratory Failure	3 (3.4)
Pneumonia aspiration	3 (3.4)
Dehydration	3 (3.4)
TEAEs leading to study drug discontinuation, n (%)[c]	10 (11.4)
Seizure	3 (3.4)
Somnolence	2 (2.3)
Other[d]	1 (1.1)
TEAE leading to death n (%)	1 (1.1)
Sepsis[e]	1 (1.1)

OLE, open-label extension; TEAE, treatment-emergent adverse event.
Patients could have more than one TEAE.
[a]Preferred terms from the Medical Dictionary for Regulatory Activities Terminology (version 16.0 or higher) reported in more than 2 patients within 24 months of the OLE are presented.
[b]TEAEs that occurring in more than 2 patients throughout the OLE until the data cutoff (June 30, 2022).
[c]TEAEs leading to study drug discontinuation within 24 months in the OLE are presented.
[d]Other TEAEs leading to study drug discontinuation (n=1 each) were: aspiration, ataxia, dysphagia, hypersomnia, hypotonia, menorrhagia, renal failure, sepsis, status epilepticus.
[e]Deemed unrelated to study drug.

Conclusions

- **Long-term treatment with ganaxolone for up to 24 months was associated with continued reduction in frequency of major motor seizures and the number of days on which they occurred**
- **Global improvement and improvement in seizure intensity and duration were reported by approximately half of caregivers**
- **Safety findings were consistent with the double-blind phase of the study**
- **These results support the durability of ganaxolone effectiveness for the treatment of seizures in CDD**

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MARINUS SCIENTIFIC AFFAIRS

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