Ganaxolone Significantly Reduces Major Motor Seizures Associated with CDKL5 Deficiency Disorder and Demonstrates Sustained Seizure Control Over 2 Years

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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 ≥2 years old.[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 with CDD aged 2–19 years were randomized 1:1 to adjunctive ganaxolone oral suspension or placebo for 17 weeks. Patients who completed the 17-week double-blind study period were eligible to enroll in the long-term open-label extension phase.

Objectives

- Double-blind (DB) Phase:
  - To assess the efficacy of ganaxolone for the treatment of major motor seizures (MMS) in patients with genetically confirmed CDD.
  - To assess the safety and tolerability of ganaxolone.
- Open-Label Extension (OLE) Phase:
  - To assess the long-term safety, tolerability, and efficacy of ganaxolone for the treatment of seizures associated with CDD.

Methods

Study design

- The Marigold study was a double-blind, randomized, placebo-controlled, phase 3 clinical trial in patients with CDD **(Figure 1)**.
- Patients who completed the 17-week DB phase were eligible to continue into the OLE phase by undergoing a 4-week blinded titration to ganaxolone treatment.

Key eligibility criteria

- Ages 2-21 years old.
- 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 within 28 days prior to screening.

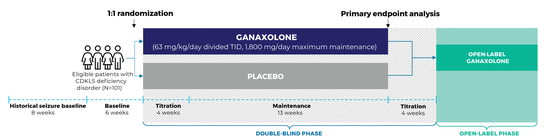
Treatment

- Ganaxolone was taken 3 times per day with food.
- Patients were titrated to a maintenance dose up to 63 mg/kg/day (for patients weighing ≤28 kg) or 1800 mg/day (for patients weighing >28 kg).

Analysis

- Double-Blind Phase:
  - Primary endpoint: percentage reduction in 28-day major motor seizure frequency (MMSF) during the 17-week treatment phase in relation to the 6-week baseline.
  - Safety and tolerability: assessments included treatment-emergent adverse events (TEAEs).
- Open-Label Extension:
  - Median percentage reduction in 28-day MMSF during each 3-month interval was analyzed using available data up to 24 months.
  - To impute missing values, both a multiple imputation mixed effects model and last observation carried forward (LOCF) method were employed.
- Safety and tolerability assessments.

Figure 1. Design of the Marigold Study: double-blind phase and open-label extension



CDKL5, cyclin-dependent kinase-like 5 deficiency; TID, 3 times daily

Results

Patient disposition and characteristics

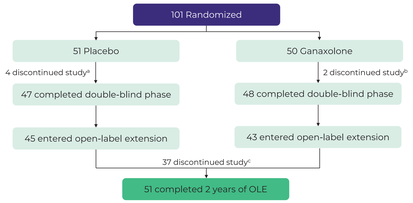
- In the DB phase, 101 patients were randomized at 39 clinical sites in 8 countries; 95 patients completed the DB phase **(Table 1)**.
- 88/101 (87.1%) patients continued into the OLE **(Figure 2)**.
  - n=1 completed 2 years in the OLE and transitioned to the expanded access program.
  - n=50 were ongoing at 2 years in the OLE.
  - n=37 discontinued.
- Patients experienced a median of 49.2 and 54.0 MMS per 28 days in the placebo and ganaxolone groups, respectively, during the 6-week baseline.
- Patients had previously tried a median of 7 ASMs and were on a median of 2 concomitant ASMs at randomization.
- For the 88 patients who continued into the OLE, the median baseline MMSF per 28 days was 50.6 with median of 2 concomitant ASMs.

Table 1. Patient demographics and baseline characteristics

	Double-blind phase		Open-label phase
	Ganaxolone (N=50)	Placebo (N=51)	Ganaxolone (N=88)
Age, median (range), years	5.0 (2.0-19.0)	7.0 (2.0-19.0)	5.0 (2.0-19.0)
Female sex, n (%)	39 (78.0)	41 (80.4)	70 (79.5)
Baseline MMSF/28 days, median (IQR)	54.0 (31.3-147.3)	49.2 (18.7-120.0)	50.6 (26.0-145.3)
No. of previously failed ASMs, median (range)	7 (2-16)	7 (1-14)	—
No. concomitant ASMs, median (range)	2 (0-6)	2 (0-5)	2 (0-4)
Concomitant ASMs, n (%)			
Valproate	18 (36)	16 (31)	32 (36)*
Levetiracetam	13 (26)	13 (25)	23 (26)*
Clobazam	12 (24)	13 (25)	26 (30)*
Vigabatrin	10 (20)	12 (24)	20 (23)*

*Administered on or after the first dosing day of the open-label extension phase.
ASM, anti-seizure medication; IQR, interquartile range; MMSF, major motor seizure frequency

Figure 2. Patient disposition through 2 years in the OLE



[a]Treatment-emergent adverse event, n=4.

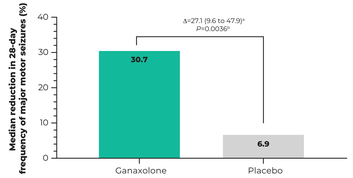
[b]Treatment-emergent adverse event, n=1; withdrawal of consent, n=1.

[c]Lack of efficacy, n=13; withdrawal by caregiver, n=12; adverse event, n=10; physician decision, n=1; death, n=1 (due to sepsis, not related to study drug).

Reduction in major motor seizure frequency

- Patients treated with ganaxolone experienced a median 30.7% reduction in MMSF from baseline in comparison with a 6.9% reduction for patients treated with placebo (P = 0.0036, Wilcoxon rank sum test) **(Figure 3)**.
- The Hodges–Lehmann estimate of median difference in responses to ganaxolone versus placebo was –27.1% (95% CI –47.9% to –9.6%).
- Median reduction from baseline in MMSF during months 22–24 of the OLE (n=50) was 48.2% (95% CI 27.4% to 56.1%) **(Figure 4)**.
- The median 28-day reduction in MMSF for months 22–24 was 43.8% (95% CI 28.5% to 53.9%) using the mixed effects model and 27.4% (95% CI 42.1% to –2.3%) using the LOCF method.
- The median 28-day reduction in MMSF cumulative from months 1–24 was 40.3% (n = 50, available data).
- Though no patients were seizure-free during the DB phase, 2–5 patients experienced MMS freedom within various 3-month intervals during the OLE.

Figure 3. Percentage reduction in 28-day MMSF in the double-blind phase

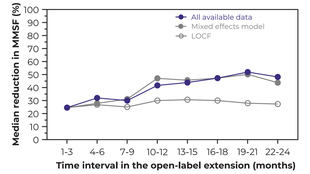


[a]Hodges-Lehman estimate of median difference (95% confidence interval).

[b]Wilcoxon rank sum test.

MMSF, major motor seizure frequency

Figure 4. Percentage reduction from baseline in 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

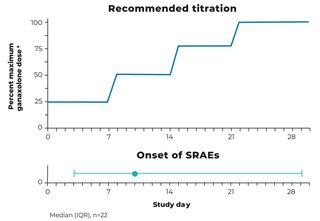
Baseline seizures for 1 patient were not recorded; that patient was excluded from the analysis of reduction in MMSF.

LOCF, last observation carried forward; MMSF, major motor seizure frequency; OLE, open-label extension

Safety

- Treatment-emergent adverse events (TEAEs) during the DB phase were reported in 86% and 88.2% of patients who received ganaxolone and placebo, respectively **(Table 2)**.
- The most frequent AEs reported by both groups (ganaxolone vs placebo) during the DB were somnolence (36% vs 16%), pyrexia (18% vs 8%), and upper respiratory tract infection (10% vs 6%).
  - Somnolence-related adverse events (SRAEs) which included somnolence, sedation, hypersomnia, or lethargy, occurred in 22 ganaxolone-treated patients with a median onset at day 10 (IQR 3 to 29) **(Figure 5)**.
  - SRAEs were classified as mild (64%) or moderate (36%) in severity with no impact on titration or dosing in 68% of patients.
- Serious treatment-emergent AEs (SAEs) were reported in 12% and 10% of ganaxolone- and placebo-treated patients, respectively, during the DB phase.
- The most commonly reported TEAEs during the OLE were seizure (24%), vomiting (23%), somnolence (22%), and pyrexia (17%).
- The most common AEs assessed as treatment-related in the OLE were somnolence (17%) and seizure (11.4%) **(Table 3)**.

Figure 5. Ganaxolone titration schedule and onset of somnolence-related adverse events



[a]100% maximum ganaxolone dose = 63 mg/kg/day (patients ≤28 kg) or 1800 mg/day (patients >28 kg).

SRAE, somnolence-related adverse event.

Table 2. Summary of TEAEs reported during the double-blind phase

	Ganaxolone (N=50)	Placebo (N=51)
Any TEAE,[a] n (%)	43 (86)	45 (88)
Somnolence	18 (36)	8 (16)
Pyrexia	9 (18)	4 (8)
Upper respiratory tract infection	5 (10)	3 (6)
Constipation	3 (6)	3 (6)
Salivary hypersecretion	3 (6)	1 (2)
Sedation	3 (6)	2 (4)
Any serious TEAE,[b] n (%)	6 (12)	5 (10)
TEAE leading to study drug discontinuation, n (%)	2 (4)[c]	4 (8)
TEAE leading to dose reduction or temporary treatment discontinuation, n (%)	11 (22)	8 (16)
TEAE leading to death	0	0

Patients could have reported more than 1 TEAE.
[a]Preferred terms from the Medical Dictionary for Regulatory activities Terminology reported in ≥5% of patients and at a higher percentage in the ganaxolone group.
[b]Serious TEAEs with ganaxolone use included (n=1 each): bronchitis, rhinovirus infection, urinary tract infection, oxygen saturation decreased, food refusal, aspiration pneumonia.
[c]One additional patient in the ganaxolone group discontinued the study drug due to a TEAE (somnolence) but remained in the study.
TEAE, treatment-emergent adverse event

Table 3. Summary of TEAEs reported during the OLE

	Total (N=88)
Treatment-related TEAE,[a] n (%)	41 (47)
Somnolence	15 (17)
Seizure	10 (11)
Decreased appetite	5 (6)
Weight decrease	4 (5)
Attention-seeking behavior	3 (3)
Gait disturbance	3 (3)
Any serious TEAE,[b] n (%)	28 (32)
TEAEs leading to study drug discontinuation,[c] n (%)	10 (11)
Seizure	3 (3)
Somnolence	2 (2)
Other[d]	1 (1)
TEAE leading to death, n (%)	1 (1)
Sepsis[e]	1 (1)

Patients could have reported more than 1 TEAE.
[a]Preferred terms from the Medical Dictionary for Regulatory activities Terminology reported in ≥2 patients within 24 months in the OLE are presented.
[b]Any serious TEAE that was reported in >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 that led to study drug discontinuation (n=1 each): aspiration, ataxia, dysphagia, hypersomnia, hypotonia, menorrhagia, renal failure, sopor, status epilepticus.
[e]Deemed unrelated to study drug.
OLE, open-label extension; TEAE, treatment-emergent adverse event

Conclusions

- **Enrolled patients with CDD experienced a high baseline seizure burden despite receiving treatment with multiple existing ASMs, reflecting the significant need for more effective treatments.**
- **A significant reduction in MMSF was demonstrated with ganaxolone therapy (30.7%) compared with placebo (6.9%) during the DB phase, and long-term treatment with ganaxolone for up to 24 months was associated with sustained reduction in frequency of MMS.**
- **Ganaxolone was generally well tolerated during both the DB phase and OLE. Somnolence was reported as the most common AE overall, with the onset noted most often during titration.**
- **These findings provide evidence that ganaxolone is effective and durable in the treatment of refractory epilepsy in patients with CDD and offers an acceptable safety profile.**

References

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