Ganaxolone is approved in the United States for the treatment of seizures associated with CDKL5 deficiency disorder (CDD) in patients ≥2 years of age. In the phase 3 Marigold study (NCT03572933), 101 patients aged 2–19 years were randomized 1:1 to ganaxolone or placebo for 8 weeks to evaluate effectiveness and safety. The primary endpoint was the median reduction in major motor seizure frequency (MMSF) from baseline to Week 8. Patients treated with ganaxolone experienced a median 30.7% reduction in MMSF from baseline in comparison with placebo (P = 0.0036, Wilcoxon rank sum test). The Hodges–Lehmann estimate of median difference in responses to ganaxolone versus placebo was –27.1% (95% CI: –41.9% to –14.3%). The median 28-day reduction in MMSF cumulative from months 1–24 was 40.3% (n = 50, available data). Patients treated with ganaxolone experienced a median 30.7% reduction in MMSF from baseline in comparison with placebo (P = 0.0036, Wilcoxon rank sum test). The Hodges–Lehmann estimate of median difference in responses to ganaxolone versus placebo was –27.1% (95% CI: –41.9% to –14.3%).

Background

- CDKL5 deficiency disorder (CDD) is a rare and fatal developmental and synaptic neurodegenerative disorder, characterized by global developmental impairment and early-onset refractory seizures.
- Antiseizure medications (ASMs) are ineffective for most patients due to the high expression of the glycine transporter (GlyT1), which limits the efficacy of drugs that target GABAergic pathways.

Objectives

- To evaluate the efﬁcacy and safety of ganaxolone in the treatment of major motor seizures in patients with CDD aged 2–19 years.
- To assess the safety and tolerability of ganaxolone.

Methods

- Study design: Enrolled patients were randomized 1:1 to ganaxolone or placebo in a double-blind phase lasting 8 weeks followed by an open-label extension phase (OLE) of up to 2 years. Eligible patients were aged 2–19 years and had a pathogenic or likely pathogenic CDKL5 gene variant.
- Double-blind (DB) Phase: Patients were randomized to ganaxolone or placebo at a dose of 2 mg/kg twice daily or 100% of the maximum dosing interval for the patient, whichever was smaller, for 8 weeks. Any serious or life-threatening adverse events (SAEs) were reported to the sponsor. Patients returning for the 6-week baseline were required to have an MMSF of ≥30%.
- OLE Phase: Patients could have reported more than 1 TEAE. Any serious TEAE, treatment-emergent SAE, or unexpected SAE was reported to the sponsor. The OLE phase was only available for patients who completed the DB phase and had an available MMSF.

Results

Patient disposition and characteristics

- Of the 101 patients enrolled, 88/101 (87.1%) continued into the OLE. The most common AEs assessed as treatment-related in the OLE were somnolence (17%) and seizure (11.4%).

Safety

- The most common AEs reported by both groups were headache (56.1%) and vomiting (54.0%). AEs reported in >2 patients throughout the OLE until the data cutoff (June 30, 2022) included: somnolence (17%), headache (16%), and vomiting (11.4%).

Conclusions

- Ganaxolone significantly reduces major motor seizures associated with CDKL5 deficiency disorder and demonstrates sustained seizure control over 2 years in patients with CDD.
- Ganaxolone was generally well tolerated, 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.