Long-term Treatment with Ganaxolone for Seizures Associated with CDKL5 Deficiency Disorder: 1-year Minimum Open-label Extension Follow-up

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Introduction

- Cyclin-dependent kinase-like 5 (CDKL5) deficiency disorder (CDD) is a rare, X-linked, developmental, and epileptic encephalopathy characterized by early-onset, refractory seizures hypotonia, severe intellectual disability, and cortical visual impairment
- Ganaxolone is a 3ß-methylated, synthetic analog of the endogenous neurosteroid, allopregnanolone, and is thought to exert its anti-seizure effect via positive allosteric modulation of both synaptic and extrasynaptic $GABA_A$ receptors[1]
- The U.S. Food and Drug Administration has recently approved ganaxolone for the treatment of seizures associated with CDD in patients 2 years of age and older based, in part, on a Phase 3, double-blind, placebo-controlled study (Marigold Study, NCT03572933)[2]
- In this study, ganaxolone significantly reduced major motor seizure frequency (MMSF) over the 17-week treatment period (GNX 30.7% vs placebo 6.9%; p=0.0036) in patients with CDD
- Here we report on safety and seizure-related data in the open-label extension (OLE) of this study (1-year minimum)

Methods

Key Eligibility Criteria

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

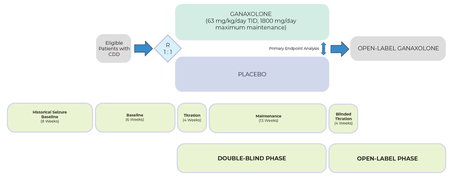
Double-blind Phase to Open Label Extension

- The Marigold Study design, including group assignment and dosing is illustrated in **Figure 1**
- Patients with CDD who completed the double-blind phase of the study were eligible to receive ganaxolone in the OLE
- The OLE began with a 4-week blinded cross-titration from double-blind treatment to open-label ganaxolone treatment
- Preliminary analysis includes all available data and does not account for missingness

Key Endpoints

- Long-term safety and tolerability of ganaxolone
- Median percent reduction in major motor seizure frequency (MMSF) from pre-randomization baseline to 3-month intervals in the OLE

Figure 1. MARIGOLD Study Design with Open Label Extension



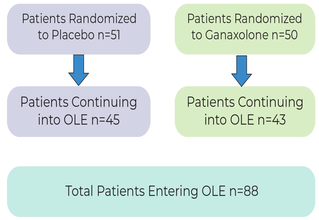
CDD, CDKL5 Deficiency Disorder; R, randomization; TID, three times daily

Results

Patient Disposition

- Of the 101 patients randomized in the double-blind phase, 88 (87.1%) continued into the OLE
  - Of the 88 patients, 43 were originally randomized to ganaxolone and 45 to placebo (**Figure 2**)
- At the time of this analysis (data cut: 22June2021), 34 had patients discontinued
  - Lack of efficacy (n=12); adverse event (n=10); or withdrawal by patient or parent/LAR (n=10), physician decision (n=1), sponsor decision (n=1)

Figure 2. Patient Disposition



OLE, open label extension

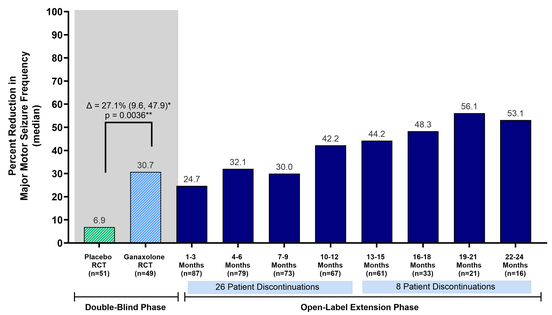
Table 1. Demographics and Baseline Characteristics (N=88)

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)
Non-United States	53 (60.2)

Baseline MMSF per 28 days[a]	
Median (IQR)	50.6 (26.0 – 146.7)
Most common ASMs[b], 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
[b]Used in ≥10% of patients

Figure 3. Percent Reduction in Major Motor Seizure Frequency



Preliminary analysis includes all available data and does not account for missingness. Decreasing patient numbers beyond 12-month assessments resulted primarily from staggered entry into the study.

Change in Major Motor Seizure Frequency

- Median baseline 28-day MMSF was 50.6
- During Months 1-3, 4-6, 7-9, and 10-12 in the OLE, patients experienced a median reduction in MMSF of 24.7% (n=87), 32.1% (n=79), 30.0% (n=73), and 42.2% (n=67), respectively (**Figure 3**)
  - When imputing missing data using Last Observation Carried Forward (LOCF), the median reduction in MMSF at 10-12 months was 30.0%
- During 3-month intervals of months 13-24, median MMSF reductions ranged from 44.2% to 56.1%

Table 2. Treatment-emergent Adverse Events (TEAEs) (N=88)

Any TEAE, n (%)	**78 (88.6)**
Serious TEAEs	22 (25.0)
Treatment-related[a] TEAE	41 (46.6)
Deaths[b]	1 (1.1)
TEAEs that occurred ≥10% of patients in the OLE phase, n (%)	
Seizure	20 (22.7)
Somnolence	18 (20.5)
Vomiting	16 (18.2)
Pyrexia	15 (17.0)
Nasopharyngitis	11 (12.5)
Upper Respiratory Tract Infection	10 (11.4)

TEAE, treatment-emergent adverse event
[a]AEs that were considered to be treatment-related by the investigator
[b]Death occurred in one patient due to sepsis that was deemed unrelated to study drug

Figure 4. 50% and 75% Response Rates in Major Motor Seizure Frequency During the OLE

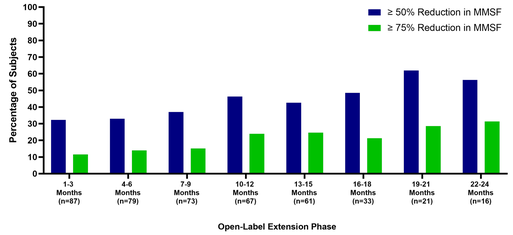
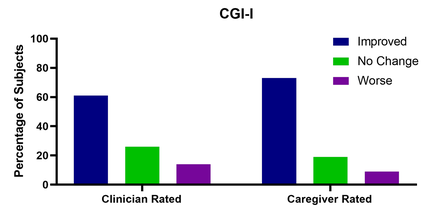


Figure 5. Clinician- and Caregiver-Rated CGI at 12 months in OLE



Conclusions

- **Ganaxolone was generally well-tolerated in the OLE, with safety findings consistent with those observed in the double-blind phase and the known safety profile of ganaxolone**
- **Reductions in median 28-day MMSF at 1 year and beyond provide supportive evidence for maintenance of ganaxolone efficacy in the CDD population**
- **Limitations of this preliminary OLE analysis include missing data due to patient discontinuations and active patients not yet contributing data to future time points**

Disclosures

EMPK has consulted for Marinus Pharmaceuticals, Inc., and participated in advisory boards for BioMarin, Inc. and Zogenix. STD has consulted for Taysha, Neurogene, Ovid, and Marinus Pharmaceuticals, Inc.; has received speaker honoraria from BioMarin and Marinus Pharmaceuticals, Inc.; has received funding from the National Institutes of Health, International Foundation for CDKL5 Research, and Mila's Miracle Foundation; and serves on advisory boards for the nonprofit foundations SLC6A1 Connect, FamilieSCN2A, and Ring 14 USA. OD receives grant support from the National Institute of Neurological Disorders and Stroke, National Institute of Mental Health, Multidisciplinary University Research Initiative, Centers for Disease Control and Prevention, and National Science Foundation. OD has equity, compensation, or both from the following companies: Tilray, Receptor Life Sciences, Q-State Biosciences, Tevard, Empatica, Papa & Barkley, Rettco, Silver Spike, and California Cannabis Enterprises, has received consulting fees from GW Pharmaceuticals, BridgeBio, Ultragenyx, Xenon, and Marinus Pharmaceuticals, Inc.; has received honoraria from Medscape; has multiple patents for use of cannabis but all financial benefits have been waived; has received royalties for the book Epilepsy in Children; and serves on the boards of FACES and Next for Autism.SA has received funding from GW Pharmaceuticals, Novartis, PTC Therapeutics, Boston Scientific, Nutricia, UCB, BioMarin, LivaNova, Medtronic, Desitin, Ipsen, CDKL5 UK, TSA, and the National Institute for Health Research. HEO has consulted for Takeda, Ovid, Zogenix, FOXG1 Research Foundation, and Marinus Pharmaceuticals, Inc.; has served as site Principal investigator for a trial with Ovid and for the currently reported trial with Marinus Pharmaceuticals, Inc. HEO has funding from National Institute of Neurological Disorders and Stroke, the Loulou Foundation, the Manton Center for Rare Disease Research, and the International Foundation for CDKL5 Research for research on CDKL5 deficiency disorder. AAA, ER, IM, JH are employees of Marinus Pharmaceuticals, Inc.

References

1. Lattanzi et al. Expert Rev Neurother 2021;21:1317-32
2. Pestana Knight et al. Lancet Neurol 2022;21:417-27

Acknowledgment

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