Introduction

- Cyclin-dependent kinase-5 (CDKL5) deficiency disorder (CDD) is a rare X-linked developmental epileptic encephalopathy (DEE) resulting from pathogenic loss-of-function mutation(s) in the CDKL5 gene.
- CDD presents with treatment-refractory seizures, severe global developmental impairment, and multiple comorbidities.
- Lennox-Gastaut syndrome (LGS) is also a severe age-dependent DEE with onset between 1 and 8 years of age and may result from a number of underlying structural or genetic neurological disorders.
- The clinical presentation of LGS includes multiple drug-resistant seizure types, a slow spike-and-wave EEG pattern, and serious neurodevelopmental disability.
- Despite treatment with numerous antiepileptic medications (ASMs), less than 10% of patients with LGS become seizure-free, indicating a significant unmet treatment gap.

Methods

- Within the CDD population, patients with a genetic diagnosis of CDD may also have a phenotypic diagnosis of LGS.
- Ganaxolone is a synthetic analog of allopregnanolone.
- Ganaxolone is an investigational neuroactive steroid and a selective positive allosteric modulator of GABAA receptors.
- Ganaxolone was taken 3 times a day at a maintenance dose of 2 mg/kg/day.

Study Design

- Global, randomized, double-blind (DB), placebo-controlled study.
- Patient Enrollment:
  - Aged 2-21 years, inclusive
  - Pathogenic or likely pathogenic CDKL5 variant
  - CDD presents with treatment-refractory seizures, severe drug dependence or DEE with onset between 1 and 8 years of age
  - Five patients were randomized to placebo; four continued into the OLE.
  - One placebo patient did not enter the OLE.

Primary Endpoint

- Percent change in 28-day major motor seizure frequency (MMSF) during the 17-week DB treatment phase in relation to the 6-week BL.

Key Inclusion Criteria

- Pathogenic or likely pathogenic CDKL5 variant
- Aged 2-21 years, inclusive
- >16 major motor seizures (MMS, defined as bilateral tonic, generalized tonic-clonic, atonic/drop, bilateral clonic, or focal to bilateral tonic-clonic) per month at BL

Dosing

- Ganaxolone was taken 3 times a day at a maintenance dose of up to 63 mg/kg/day or 1800 mg/day maximum

Efficacy Outcomes

- Of the 6 evaluable LGS patients (2 GNX DB, 2 GNX OLE) demonstrated improvements in seizure frequency after 17 weeks of ganaxolone treatment compared to BL.
- The 2 GNX DB patients experienced percent changes in MMSF of -25.4% and -43.5%.
- The other 2 GNX OLE patients did not show improvement with ganaxolone treatment (4.6% and 27.1% change in MMSF).

LGS Patient Demographics and Clinical Characteristics

- Of the 101 patients randomized, 7 (6.9%) had a co-diagnosis of LGS.
- Patients randomized in age from 3-19 years (median, 11 years).
- Two patients were randomized to ganaxolone and received treatment through the DB phase (GNX DB).
- Five patients were randomized to placebo; four continued into the OLE.
- One placebo patient did not enter the OLE; therefore, 6 patients were evaluable for this analysis.

Results

- Patients were taking a median 3 ASMs at BL.
- Median MMSF per 28 days at BL was 88.7.

Safety and Tolerability

- All patients with LGS (n=7) were included in the safety analysis.

Conclusions

- The high seizure burden and refractory nature of LGS-related seizures indicates a significant need for new and effective treatments.
- This post-hoc analysis found that treatment with ganaxolone three times daily was associated with decreases in MMSF in 4 of 6 patients with both CDD and LGS.
- Ganaxolone was generally well-tolerated, and no new safety signals emerged in the LGS subgroup.
- Further studies are needed to elucidate the potential of ganaxolone as treatment for seizures associated with LGS.

Acknowledgments

- This study was sponsored by Marinus Pharmaceuticals, Inc. (Baddo, Pennsylvania).

Disclosures

- All authors are employed by Marinus Pharmaceuticals, Inc.