3.279

Effect of Ganaxolone on Quality of Life in Children with the CDKL5 Deficiency Disorder

Scott Demarest, MD[1]; Alex Aimetti, PhD[2]; Eva Rybak, PharmD[2]; Dayong Li, PhD[2]; Joseph Hulihan, MD[2]; Peter Jacoby, MSc[3]; Helen Leonard, MBChB, MPH[3]; Jenny Downs, PhD[3]

[1]University of Colorado at Denver, Aurora, CO, USA; [2]Marinus Pharmaceuticals, Inc., Radnor, PA, USA; [3]Telethon Kids Institute, The University of Western Australia, Perth, WA, Australia

Background

- Ganaxolone is an investigational neuroactive steroid that acts as a positive allosteric modulator of synaptic and extrasynaptic $GABA_A$ receptors to enhance GABAergic tone[1,2]
- Cyclin-dependent kinase-like 5 (CDKL5) deficiency disorder (CDD) is a rare, X-linked, developmental epileptic encephalopathy associated with early-onset, refractory seizures, and severe global developmental impairment[3]
- In the international, Phase 3, randomized, double-blind, placebo-controlled Marigold study, patients with CDD treated with adjunctive ganaxolone experienced a median 30.7% (vs 6.9% placebo, *P*=0.0036) reduction in 28-day major motor seizure (MMS) frequency[4]
  - In general, treatment-emergent adverse events (TEAEs) were similar between groups, were mostly mild to moderate in severity, and led to ganaxolone discontinuation in <5% of patients
  - In addition to efficacy and safety outcomes, quality of life (QOL) was assessed by the parents/caregivers during the 17-week double-blind phase
- Recent data suggest that functional impairment is the most likely factor leading to poor QOL for patients with CDD[5]
- The objective of this analysis was to determine whether treatment with ganaxolone was associated with improvements in QOL compared to placebo in children with CDD in the Marigold study

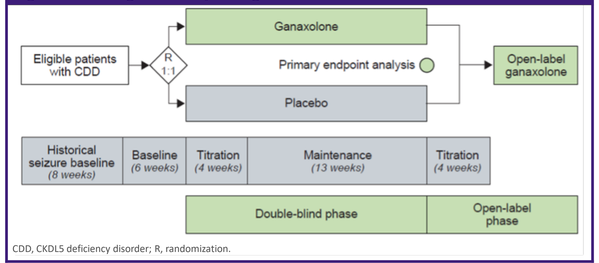
Design/Methods

Marigold study

Trial design and eligibility criteria

- Global, randomized, double-blind, placebo-controlled, Phase 3 clinical trial with a 17-week double-blind phase followed by an open-label phase (**Figure 1**)
- Inclusion criteria:
  - Patients 2-21 years old, inclusive, with a molecularly confirmed pathogenic or likely pathogenic *CDKL5* variant, including mosaic variants
  - >16 MMS per month in an 8-week retrospective baseline
    - MMS consisted of the following seizure types: atonic/drop, bilateral tonic (with sustained motor activity > 3 seconds), bilateral clonic, focal to bilateral tonic-clonic, and generalized tonic-clonic seizures

Figure 1. Marigold Study Design



CDD, CKDL5 deficiency disorder; R, randomization.

Study dosing

- Patients received either ganaxolone or placebo as an oral suspension 3 times daily with food during the 17-week double-blind phase
- Ganaxolone was titrated for 4 weeks up to a maximum dose of 63 mg/kg/day (≤28 kg) or 1800 mg/day (>28 kg) followed by maintenance dosing for 13 weeks

QOL measurement

- The Quality of Life Inventory-Disability (QI-Disability) scale was used to assess patient's QOL
  - The QI-Disability scale is a 32-item parent/caregiver/legally authorized representative (LAR) reported measure developed for and validated in children with intellectual disabilities, including CDD[5-7]
  - There are 6 domains: social interaction (7 items), positive emotions (4 items), negative emotions (7 items), physical health (4 items), leisure and the outdoors (5 items), and independence (5 items)
  - Each item is rated on a 5-point Likert scale considering the patient's behaviors over the past month
  - Items are then transformed linearly to a scale of 0 to 100; higher scores indicate better QOL
- QI-Disability scores were measured at baseline and Week 5, 9, and 17 of the double-blind phase of the trial

Analyses

- Total and domain QI-Disability scores were calculated
  - Following reverse coding for set items, scores were transformed to a 100-point scale
  - Domain scores were calculated by adding up each item score within the domain and dividing the sum by the number of items in the domain
  - Total scores were determined by adding up each domain score and dividing the sum by 6 (the number of domains)
- Analysis of variance (ANOVA) testing was used to determine the effect of ganaxolone on total and domain QI-Disability scores from baseline to Week 17 of the double-blind phase
  - The model was adjusted for potential predictive factors of age, sex, number of concomitant antiseizure medications (ASMs), baseline 28-day frequency of MMS, developmental skills at baseline, and QOL at baseline
- The effect of percentage change in MMS frequency on change in total and domain QI-Disability scores from baseline to Week 17 of the double-blind phase was also analyzed using ANOVA testing
  - The model was adjusted for potential predictive factors of age, sex, number of concomitant ASMs, and baseline QOL score

Results

Marigold patient enrollment, baseline clinical characteristics, and exposure

- 101 patients from 39 clinical sites in 8 countries were randomized (**Table 1**)
- Most patients (79.2%) were female with a median age of 6.0 years

Table 1. Baseline Clinical Characteristics

Characteristic	Ganaxolone (n=50)	Placebo (n=51)	Total (N=101)
Median age, years (IQR)	5.0 (3.0-10.0)	7.0 (4.0-11.0)	6.0 (3.0-10.0)
Gender, n (%)			
Male	11 (22.0)	10 (19.6)	21 (20.8)
Female	39 (78.0)	41 (80.4)	80 (79.2)
Ethnicity, n (%)			
Hispanic or Latino	4 (8.0)	6 (11.8)	10 (9.9)
Non-Hispanic or Latino	44 (88.0)	43 (84.3)	87 (86.1)
Unknown	1 (2.0)	1 (2.0)	2 (2.0)
Not reported	1 (2.0)	1 (2.0)	2 (2.0)
Race, n (%)			
White	46 (92.0)	47 (92.2)	93 (92.1)
Asian	2 (4.0)	3 (5.9)	5 (5.0)
Other	2 (4.0)	1 (2.0)	3 (3.0)
MMS types during the study, n (%)[a]			
Bilateral tonic	35 (71.4)	39 (76.5)	-
Generalized tonic-clonic	24 (49.0)	20 (39.2)	-
Atonic/drop	9 (18.4)	12 (23.5)	-
Bilateral clonic	6 (12.2)	3 (5.9)	-
Focal to bilateral tonic-clonic	7 (14.3)	6 (11.8)	-
Median 28-day MMS frequency, n (IQR)[a,b]	54.0 (31.3-147.3)	49.2 (18.7-120.0)	-
Median number of prior ASMs used, n (IQR)	7 (5-10)	7 (4-9)	7 (5-10)
Median number of concomitant ASMs, n (IQR)	2 (2-4)	2 (1-3)	2 (1-3)
Concomitant ASMs, n (%)			
Valproate	18 (36.0)	16 (31.4)	34 (33.7)
Levetiracetam	13 (26.0)	13 (25.5)	26 (25.7)
Clobazam	12 (24.0)	13 (25.5)	25 (24.8)
Vigabatrin	10 (20.0)	12 (23.5)	22 (21.8)

[a]One patient randomized to ganaxolone experienced seizures during the 6-week baseline period (seizure frequency not recorded).
[b]Determined during the 6-week baseline period.
ASM, antiseizure medication; IQR, interquartile range; MMS, major motor seizure.

- Median 28-day MMS frequency during the baseline was 54.0 and 49.2 in the ganaxolone and placebo groups, respectively
- A total of 95 (94.1%) patients completed the 17-week double-blind phase

Post-hoc QOL patient population

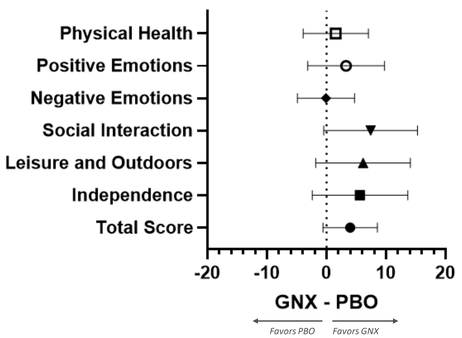
- Of the 101 patients, 80 (79.2%) were analyzed for improvements in QOL on QI-disability scale (All Items)

Post-hoc QOL analyses

QI-Disability: total and individual domains

- Change from baseline in total QI-Disability score was 4.0 points greater for patients in the ganaxolone group vs placebo (95% CI -0.60, 8.55; *P*=0.087) (**Figure 2**)
- Change from baseline in Social Interaction score was 7.4 points greater for patients in the ganaxolone group vs placebo (95% CI -0.45, 15.27; *P*=0.064)
  - Mean changes in score for the 5 other domains were similar between groups

Figure 2. QI-Disability Scores Adjusted for Treatment Group



GNX, ganaxolone; PBO, placebo.

Conclusions

- In addition to a reduction in MMS frequency, children in the Marigold trial who received ganaxolone had higher total QOL scores than those who received placebo when controlling for potential confounding factors, though the estimates lacked precision
- Though confidence intervals were wide, ganaxolone-treated children had greater improvements in the social interaction QI-Disability domain compared to placebo, but changes were similar between groups across the other domains
- Improvements in QOL observed in ganaxolone-treated children were unrelated to reduction in MMS frequency; future analyses will investigate the reasons for improved QOL following administration of ganaxolone

References

1. Carter RB, et al. *J Pharmacol Exp Ther*. 1997;280:1284-95.
2. Reddy DS, et al. *Epilepsy Res*. 2010;89:254-60.
3. Olson HE, et al. *Pediatr Neurol*. 2019;97:18-25.
4. Specchio N, et al. Presented at International Epilepsy Congress, August 28 – September 1, 2021, Virtual.
5. Leonard H, et al. *Epilepsy Res*. 2021;169:doi: 10.1016/j.eplepsyres.2020.106521.
6. Downs J, et al. *Qual Life Res*. 2019;28:783-94.
7. Epstein A, et al. *Child Care Health Dev*. 2019;45:654-59.

Acknowledgments

This study was supported by Marinus Pharmaceuticals, Inc. (Radnor, PA). Medical writing and editorial assistance were provided by MedVal Scientific Information Services, LLC (Princeton, NJ) and was funded by Marinus Pharmaceuticals, Inc.

Disclosures

SD: has consulted for Upsher-Smith, BioMarin, Neurogene, Ovid, 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 board for the nonprofit foundations SLC6A1 Connect and Families SCN2A.
AA: salaried employee of Marinus Pharmaceuticals, Inc., and owns stock in the company.
ER: salaried employee of Marinus Pharmaceuticals, Inc., and owns stock in the company.
DL: salaried employee of Marinus Pharmaceuticals, Inc., and owns stock in the company.
JH: salaried employee of Marinus Pharmaceuticals, Inc., and owns stock in the company.
PJ: No conflicts to disclose.
HL: Consultancy for Marinus, Newron, Ultragenyx, and GW; Clinical Trials with Newron and Anavex; All remuneration has been made to her department.
JD: Consultancy for Marinus, Newron, Ultragenyx, and Taysha; Clinical Trials with Newron and Anavex; All remuneration has been made to her department.

Presented at the American Epilepsy Society Annual Meeting, December 3-7, 2021, Chicago, IL.