Pharmacokinetic-Pharmacodynamic Analysis of Oral Ganaxolone in Patients with CDKL5 Deficiency Disorder: Results From the Marigold Study

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Introduction

- Ganaxolone (GNX) is a synthetic neuroactive steroid that acts as a positive allosteric modulator of synaptic and extrasynaptic γ-aminobutyric acid type a ($GABA_A$) receptors (**Figure 1**)[1]
- The 3β-methyl group renders the molecule orally bioavailable in comparison with its analog, allopregnanolone
- Oral bioavailability of GNX is approximately 10% in the fed state with an approximate half-life ($t_{1/2}$) of 2 to 3 hours
- Past chronic epilepsy clinical trials with GNX studied twice daily (BID) dosing
- The Marigold Study (NCT03572933) in CDKL5 deficiency disorder (CDD) was the first phase 3 clinical trial with GNX to assess dosing 3 times a day (TID)
- Predicted pharmacokinetic (PK) curves for TID and BID dosing demonstrate that TID dosing maximizes GNX exposure greater than 100 ng/mL (**Figure 2**). It is hypothesized that TID dosing will result in better antiseizure activity because of increased plasma GNX exposure

Figure 1. Chemical Structure of Ganaxolone

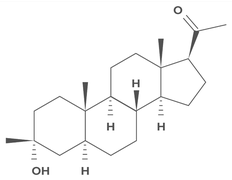
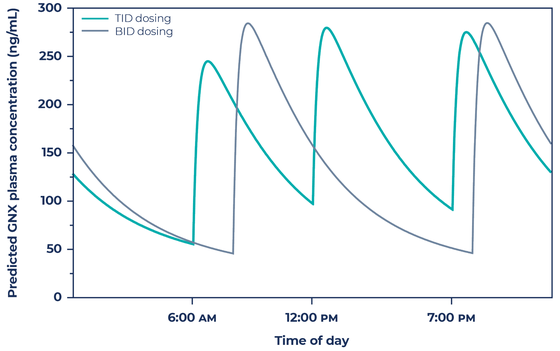


Figure 2. Predicted Plasma GNX Concentrations Following Oral BID Versus TID Dosing and Associated PK Parameters



Dose regimen	C_{max} (ng/mL)	$AUC_{0\text{-}24}$ (ng · h/mL)	% time (>100 ng/mL GNX)
TID	281	3763	78
BID	286	3135	53

AUC, area under the curve; BID, twice daily; GNX, ganaxolone; PK, pharmacokinetic; TID, 3 times a day.

Objectives

- To assess pharmacokinetic-pharmacodynamic (PK/PD) response relationships in GNX-treated patients enrolled in the double-blind portion of the Marigold Study in CDD
- Response relationships include change in frequency of major motor seizures (consisting of generalized tonic-clonic, focal to bilateral tonic-clonic, bilateral tonic, bilateral clonic, and atonic seizures) and the incidence of central nervous system (CNS) adverse events
  - The Marigold Study was not designed to provide a formal PK analysis. These analyses are intended to inform future clinical trial design and GNX formulation development

Methods

Study design

- Global, randomized, double-blind, placebo-controlled phase 3 clinical trial to assess the safety and efficacy of adjunctive ganaxolone for the treatment of seizures associated with CDD
- Patients aged 2 to 21 years with a pathogenic or likely pathogenic mutation of the *CDKL5* gene, neurodevelopmental impairment, and seizures refractory to treatment with at least 2 prior antiseizure medications who experienced at least 16 seizures per 28 days during the 2 months prior to screening were eligible to enroll
- Study consisted of a 6-week baseline followed by a 17-week double-blind phase (ganaxolone or placebo, 1:1)
- The dose of ganaxolone 50 mg/mL suspension was titrated over 4 weeks to 63 mg/kg/d (21 mg/kg TID), not to exceed 1800 mg/d (600 mg TID), or to the maximum tolerated dose
- Blood draws for PK analysis were scheduled to occur at visit 3 (week 5), visit 4 (week 9), and visit 5 (week 17)

PK/PD analysis

- Mean plasma ganaxolone levels were calculated for all GNX-treated participants who had at least one plasma level determination performed during the double-blind phase
- Mean plasma ganaxolone level and percentage reduction in major motor seizures were compared:
  - Linear regression was conducted using arithmetic- and natural logarithm-transformed percentage reduction in major motor seizures ($\log_e$ [percentage reduction + 100]) as the dependent variable and natural logarithm-transformed mean ganaxolone concentration as the predictor
  - Model performance was assessed using residual plots (scatterplot, histogram) and assessment of outliers and influential observations (Cook's distance, leverage values)
  - Observations with standardized residuals >2 or <−2 were excluded, and the regression was repeated
  - A robust regression was also performed including all observations
- Percentage seizure reductions in low-, medium-, and high-GNX exposure tertiles were compared using a Kruskal-Wallis test
- The number of patients who experienced CNS-related adverse events suggestive of potential dose-related toxicity (eg, somnolence, sedation, lethargy, drooling, and hypotonia) in ganaxolone-treated participants were tabulated
- Statistical calculations were performed using SPSS subscription version (IBM Corporation, Armonk, NY)

Results

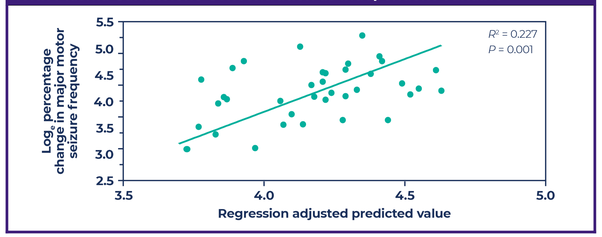
Patient enrollment and primary efficacy

- 101 patients were randomized (50 to GNX, 51 to placebo) at 36 clinical sites in 8 countries
- Median percentage of major motor seizure frequency reductions were 32.2% and 4.0% for ganaxolone and placebo, respectively (P = 0.002; Wilcoxon rank sum test)

PK/PD analysis: efficacy

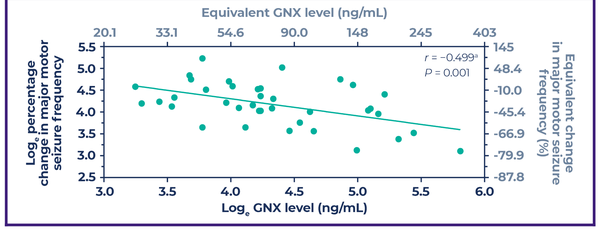
- Forty-four GNX-treated patients with seizure frequency change data had at least one plasma GNX level determination
- Average plasma GNX levels were calculated for each patient on the basis of available quantified GNX measurements (mean ± SD = 103.5 ± 79.2 ng/mL, n = 44)
- In linear regression with percentage seizure reduction as the dependent variable and mean plasma ganaxolone concentration as the independent variable, 6 observations were determined to be outliers because of standardized residuals >2 or ≤2 and review of Cook's distance and leverage values
- Repeat linear regression excluding those cases (n = 38) yielded an adjusted R^2 of 0.227 ($F(1,36)=11.89$), P = 0.001) (**Figure 3**)
  - Unstandardized coefficient for GNX level: B = −0.393, P = 0.001
- A robust regression was performed including all observations (n = 44) that replicated the findings of the primary analysis
- The correlation coefficient for mean plasma ganaxolone concentration and percentage reduction in major motor seizures using the same sample was −0.499 (P = 0.001) (**Figure 4**)
- Mean and median percentage reductions in major motor seizures were calculated for low, medium, and high GNX concentration tertiles (**Table 1**)
- There was a statistically significant between-groups difference in the percentage reduction of major motor seizure frequency (H(2) = 9.087, P = 0.011) (**Figure 5**). Post hoc pairwise comparisons of sample distributions for the 3 groups showed a statistically significant difference between low- and high-level GNX groups but not in other between-groups tests

Figure 3. Linear Regression of Percentage Change in Major Motor Seizures With Plasma Ganaxolone Concentration as Independent Variable



Values with standardized residual >2 or <−2 were excluded from analysis.

Figure 4. Bivariate Correlation of Percentage Change in Major Motor Seizures and Mean Plasma Ganaxolone Concentration



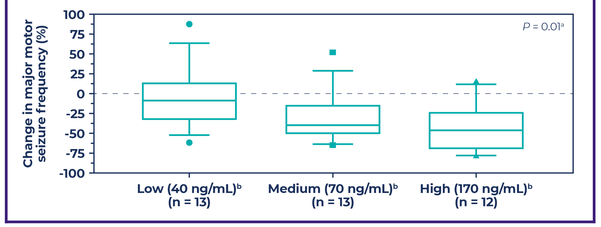
Analysis uses the same population (n = 38) as used for linear regression. $\log_e$ percentage change in major motor seizure frequency was calculated as $\log_e$ (percentage change + 100). Axes with equivalent GNX level and equivalent percentage change in major motor seizure frequency are displayed to approximate nontransformed values. GNX, ganaxolone.
[a]Pearson correlation.

Table 1. Tertiles Based on Mean Ganaxolone Plasma Concentration

GNX level groups	Mean GNX level (ng/mL)	Mean percentage change in major motor seizures (per 28 days)	Median percentage change in major motor seizures (per 28 days)
Low (n = 13)	40.2	−6.5	−8.4
Medium (n = 13)	72.3	−30.3	−39.5
High (n = 12)	172.6	−44.3	−46.0

GNX, ganaxolone.

Figure 5. Comparison of Median Percentage Reduction in Major Motor Seizures According to Tertiles Based on Mean Plasma Ganaxolone Concentrations

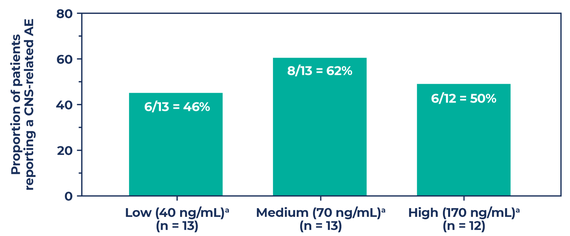


[a]Kruskal-Wallis test.
[b]Mean ganaxolone level within group.

PK/PD analysis: adverse events

- Similar incidence of CNS-related adverse events (AEs) across GNX plasma level groups (**Figure 6**)
- Of the 7 patients with the highest mean GNX plasma levels, only 1 experienced a CNS-related AE (somnolence, mild)

Figure 6. Proportion of Ganaxolone-treated Patients Who Experienced CNS-Related Adverse Events Across the 3 GNX Plasma Level Groups



AE, adverse event; CNS, central nervous system; GNX, ganaxolone.
[a]Mean GNX level within group.

Conclusions

- **Ganaxolone was generally well tolerated and demonstrated a significant reduction in major motor seizure frequency in comparison with placebo (32.2% vs 4.0%)**
- **Logarithms of plasma ganaxolone level and percentage change in major motor seizure frequency were negatively correlated**
  - **Back-transformation of log values indicates that a mean plasma ganaxolone level of approximately 148 ng/mL predicts a 50% seizure reduction in the participants in this study**
  - **Increases in plasma GNX concentration in the range of 27 to 333 ng/mL predict reductions in seizure frequency in patients with CDD**
- **The incidence of CNS-related AEs was similar across GNX dose level groups; therefore, unlike reduction in seizure frequency, these AEs may not demonstrate an exposure-response relationship**
- **These findings suggest that the transition from BID dosing to TID dosing has the potential to increase trough GNX levels and may provide improved seizure control**
- **This analysis also supports efforts to develop new oral GNX formulations that improve PK properties to achieve target GNX exposure levels**
- **Inclusion of additional factors in the regression model may improve its ability to predict treatment response**

Reference

1. Carter RB, et al. *J Pharmacol Exp Ther*. 1997;280(3):1284-1295.

Acknowledgments

This work was sponsored by Marinus Pharmaceuticals, Inc. (Radnor, Pennsylvania)

Disclosures

Joseph Hulihan, Dayong Li, and Alex Aimetti are employees of Marinus Pharmaceuticals, Inc.

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