A MODIFIED TITRATION REGIMEN OF GANAXOLONE IN THE TREATMENT OF RARE SEIZURE DISORDERS OPTIMIZES TOLERABILITY

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Introduction

- Cyclin-dependent kinase-like 5 (CDKL5) deficiency disorder (CDD) is a developmental and epileptic encephalopathy characterized by global developmental impairment and early-onset, refractory seizures.[1]
- Ganaxolone, a neuroactive steroid and positive allosteric modulator that acts on both synaptic and extrasynaptic $GABA_A$ receptors, was shown to significantly reduce seizures associated with CDD.[2,3]
- Ganaxolone is approved in the US, Europe, and China for the treatment of seizures associated with CDD in patients ≥ 2 years old.[4,5]

Background

- The Phase 3, pivotal Marigold trial (NCT03572933) for ganaxolone in CDD established a 21-day up titration schedule for ganaxolone, which was followed by maintenance dosing.[3]
- In Marigold, somnolence-related adverse events were commonly reported and typically occurred during the up-titration of ganaxolone.[3]

Somnolence-Related Adverse Events in Marigold

Marigold Post-hoc Analysis:

- A post-hoc analysis of somnolence-related adverse events (predefined as somnolence, sedation, hypersomnia, and lethargy) was conducted.
- Somnolence-related adverse events were reported in 44% (22/50) of patients treated with ganaxolone and 24% (12/51) of patients on placebo. Most of the ganaxolone-treated patients reported mild somnolence-related adverse events (64%; 14/22), whereas 36% (8/22) reported moderate, and none reported severe. (**Figure 1**)
- Somnolence-related adverse events resolved in 68% (15/22) of patients during the double-blind phase of the study, and the median duration of somnolence-related adverse events was 61 days for ganaxolone treated patients vs 58 days in placebo patients.

Percent Maximum Ganaxolone Dose Inversely Correlated with Somnolence-Related AEs

- The mean modal ganaxolone dose, defined as the dose taken the greatest number of days, was evaluated. In patients who reported somnolence-related adverse events, the mean modal dose was 85% of maximal dose (63 mg/kg/day [patients ≤28 kg] or 1800 mg/day [patients >28 kg]) vs 95% in the 28 patients who did not experience somnolence-related AEs.
- 27% (6/22) of patients in Marigold reduced their ganaxolone dose, and 5% (1/22) discontinued ganaxolone. Patients who reduced or temporarily stopped their ganaxolone dose due to somnolence-related adverse events (n=6) achieved a mean modal dose of 63% of maximum. Somnolence-related adverse events resolved in all patients following a dose reduction. (**Figure 2**)

Figure 1. Somnolence-Related Adverse Events in Marigold

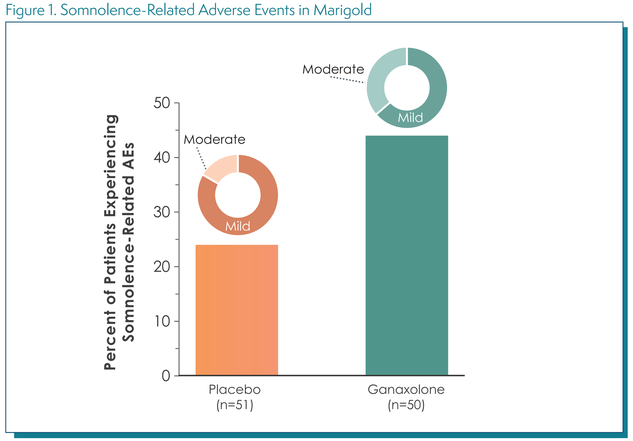
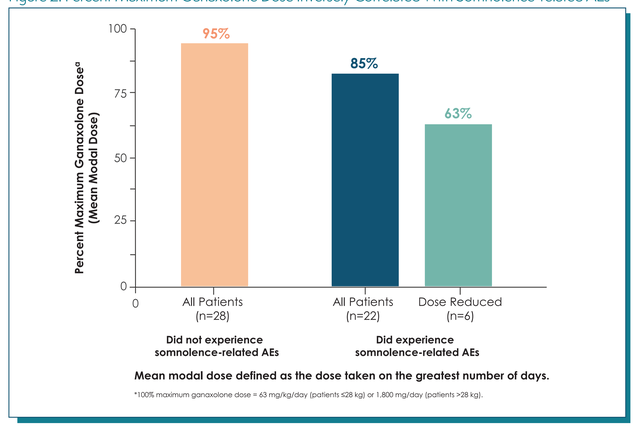


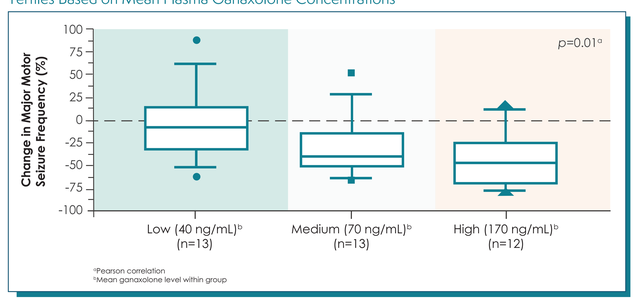
Figure 2. Percent Maximum Ganaxolone Dose Inversely Correlated With Somnolence-related AEs



Ganaxolone Pharmacokinetic/Pharmacodynamic (PK/PD) Assessments

- In a separate PK/PD assessment of Marigold, the reductions in major motor seizure frequency for patients with low (40 ng/mL), medium (70 ng/mL), or high (170 ng/mL) ganaxolone concentrations was analyzed.
- There was a statistically significant difference between-groups in the percentage reduction of major motor seizure frequency ($H(2) = 9.087$, $p=0.01$). (**Figure 3**) Post-hoc pairwise comparisons of sample distributions for the 3 groups showed a statistically significant difference in reduction of major motor seizure frequency between low- and high-level ganaxolone groups (with greater reductions in the high ganaxolone concentration group) but not in other between-groups tests.

Figure 3. Comparision of Median Percentage Reduction in Major Motor Seizures According to Tertiles Based on Mean Plasma Ganaxolone Concentrations



Phase 2 and Phase 3 TrustTSC Studies

- In a separate Phase 2, open-label, proof-of concept study (NCT04285346) conducted in Tuberous Sclerosis Complex (TSC) patients (Phase 2 TrustTSC), the safety and efficacy of ganaxolone on seizure frequency was evaluated and found that somnolence-related adverse events were commonly reported in TSC patients (60.8% (n=14/23).[6]
- To evaluate the impact on somnolence-related adverse events, the Phase 3 study evaluating ganaxolone in TSC patients (Phase 3 TrustTSC) adopted a modified titration schedule.

Objective

- To evaluate the impact of a modified titration schedule on plasma exposure and somnolence-related adverse events in TSC patients receiving ganaxolone in Phase 3 TrustTSC.

Methods

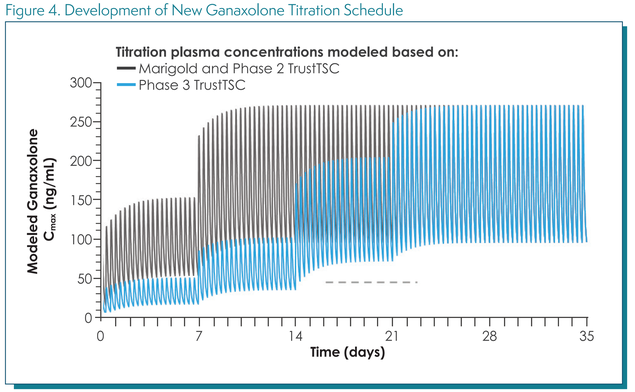
Modified Titration Schedule in Phase 3 TrustTSC

- Phase 3 TrustTSC modified titration schedule included a lower initial dose of ganaxolone, implemented graded dose progression, and extended the up-titration time from 21 to 28 days to reach the same target dose as stated in the current prescribing information for ganaxolone. (**Table 1** & **Figure 4**)
- This revised titration schedule did not impact final ganaxolone exposure levels and enabled patients to successfully titrate up to goal doses and achieve effective plasma concentrations. (**Figure 4**)
- A post hoc analysis was completed between Marigold, Phase 2 TrustTSC, and Phase 3 TrustTSC to evaluate the adverse event profiles reported under the traditional and modified ganaxolone titration schedules.

Table 1. Comparison of the Original (Orange) and Refined (Green) Dosing Titration Schedule for Ganaxolone

	Original Titration Schedule		Revised Titration Schedule	
	Dosage	Total Daily Dosage	Dosage	Total Daily Dosage
Patients Weighing 28 kg or Less				
Day 1 to 7	6 mg/kg three times daily	18 mg/kg/day	2 mg/kg three times daily	6 mg/kg/day
Day 8 to 14	11 mg/kg three times daily	33 mg/kg/day	4 mg/kg three times daily	12 mg/kg/day
Day 15 to 21	16 mg/kg three times daily	48 mg/kg/day	8 mg/kg three times daily	24 mg/kg/day
Day 22 to 28	21 mg/kg three times daily	63 mg/kg/day	14 mg/kg three times daily	42 mg/kg/day
Day 29 and thereafter	Continued Maintenance Dosing		21 mg/kg three times daily	63 mg/kg/day
Patients Weighing More than 28 kg				
Day 1 to 7	150 mg three times daily	450 mg	50 mg/kg three times daily	150 mg
Day 8 to 14	300 mg three times daily	900 mg	100 mg/kg three times daily	300 mg
Day 15 to 21	450 mg three times daily	1350 mg	200 mg/kg three times daily	600 mg
Day 22 to 28	600 mg three times daily	1800 mg	400 mg/kg three times daily	1200 mg
Day 29 and thereafter	Continued Maintenance Dosing		600 mg/kg three times daily	1800 mg

Figure 4. Development of New Ganaxolone Titration Schedule



Results

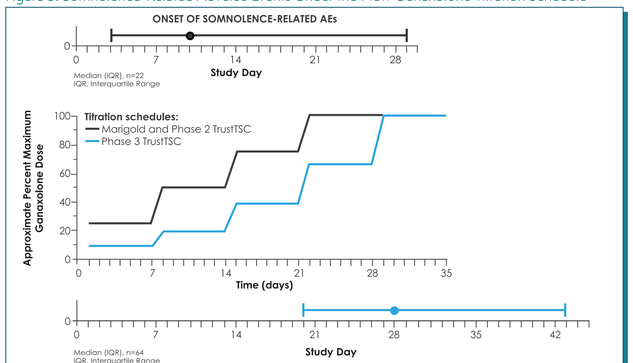
- A comparison of somnolence-related adverse events that occurred in ganaxolone-treated patients across Marigold, Phase 2 TrustTSC, and Phase 3 TrustTSC is presented in **Table 2** & **Figure 5**.
- Somnolence-related adverse events reported in Phase 3 TrustTSC, which utilized the revised ganaxolone titration schedule, were reduced when compared to Marigold (31% vs 44% respectively).
- Therapy modifications due to somnolence-related adverse events were reduced between Phase 2 TrustTSC and Phase 3 TrustTSC, and no patients discontinued Phase 3 TrustTSC due to somnolence-related adverse events.

Table 2. Adverse Events That Occurred in Ganaxolone-treated Patients at a Rate of at Least 3% (Marigold) or 5% (TrustTSC) and Greater Than in Placebo

	Marigold (n=50)		Phase 2 TrustTSC (n=23)		Phase 3 TrustTSC (n=64)	
	Subjects n (%)	Events n	Subjects n (%)	Events n	Subjects n (%)	Events n
Somnolence-related TEAEs[a]	22 (44%)	27	14 (61%)	16	20 (31%)	27
TEAEs by severity						
Mild	14 (28%)[c]	18	11 (48%)	13	14 (22%)	21
Moderate	8 (16%)	9	3 (13%)	3	6 (9%)	6
Severe	0	0	0	0	0	0
Therapy modification due to somnolence-related TEAE						
Study drug discontinuation	1 (2%)	2	2 (9%)	2	0	0
Dose reduction/interruption	6 (12%)	6	5 (22%)	5	7 (11%)	9
No therapy modification	15 (30%)	19	7 (30%)	9	13 (20%)	18
	Day [IQR]	Median [IQR]	Day [IQR]	Median [IQR]	Day [IQR]	Median [IQR]
Onset of somnolence-related TEAEs	8 [3, 15]	8 [4, 23]	7 [2, 13]	9 [3, 15]	24 [15, 43]	28 [20, 43]

IQR, interquartile range.
[a]Somnolence-related TEAEs includes: Somnolence, hypersomnia, lethargy sedation. [b]Worst severity of somnolence-related TEAEs reported per patient. [c]Percentage of all ganaxolone-treated subjects.

Figure 5. Somnolence-Related Adverse Events Under the New Ganaxolone Titration Schedule



Conclusions

- Modifying the titration schedule does not impact the final ganaxolone exposure levels that have demonstrated effectiveness in CDD patients.
- Somnolence-related adverse events were reduced under the modified ganaxolone titration schedule in patients with TSC.
- Therapy modifications due to somnolence-related adverse events were reduced under the modified titration schedule in patients with TSC.
- No TSC patients discontinued due to somnolence-related adverse events when following the modified titration schedule.
- Impact statement: Revising the ganaxolone titration schedule has the potential to improve ganaxolone tolerability during the up-titration period with respect to the somnolence-related adverse events that have been associated with therapy modifications.

References

1. Olson HE, *et al. Pediatr Neurol.* 2019;97:18-25. **2.** Reddy DS, *et al. Drugs Fut.* 2004;29(3):227-242. **3.** Pestana-Knight EM, *et al. Lancet Neurol.* 2022;21(5):417-427. **4.** ZTALMY [package insert]. Chicago, IL: Immedica Pharma US Inc.; Revised 8/2025. **5.** Olson HE, *et al. Epilepsia.* 2024; 65:37–45. **6.** "Phase 2 open label clinical study evaluating oral ganaxolone for the treatment of seizures associated with Tuberous Sclerosis Complex." Presented at the AES annual meeting, December 2021. Chicago, IL

Disclosures

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