OPTIMIZING TOLERABILITY OF GANAXOLONE FOR THE TREATMENT OF RARE SEIZURE DISORDERS USING A MODIFIED TITRATION SCHEDULE

Kenneth Johnson[1], Michelle L. Shuffett[1], Christine Ochoa Escamilla*[1], Joe Hulihan[1], Rajsekar Rajaraman[2], Mary Kay Koenig[3]

[1]Immedica Pharma, North America. *Presenting author; [2]Department of Pediatrics and Psychiatry and Biobehavioral Sciences, University of California, Los Angeles, Los Angeles, CA, USA;
[3]Department of Pediatrics, McGovern Medical School at University of Texas Health Science Center at Houston and Children's Memorial Hermann Hospital, Houston, Tx, USA

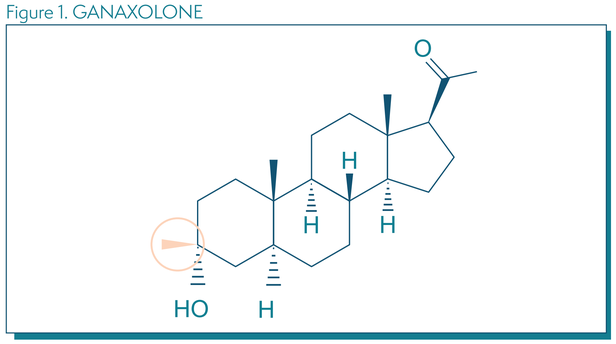
Immedica pharma

FPO

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] (**Figure 1**)
- Ganaxolone is approved in the US, Europe, and China for the treatment of seizures associated with CDKL Deficiency Disorder (CDD) in patients ≥2 years old.[4,5]

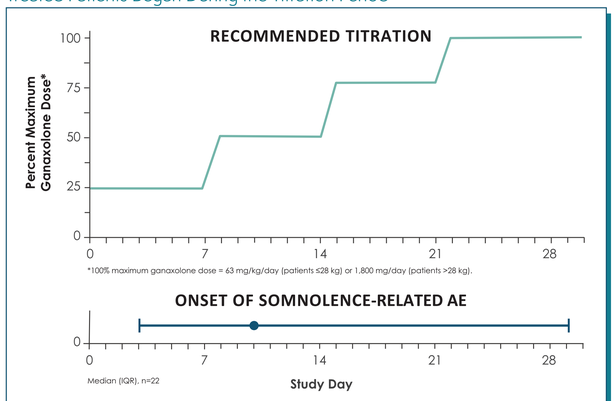
Figure 1. GANAXOLONE



Background

- The Phase 3, pivotal Marigold trial (NCT03572933) for ganaxolone in CDD established a 4-week titration schedule for ganaxolone to achieve individual clinical response and tolerability for CDD patients.[3]
- Within the Marigold Trial, somnolence-related adverse events (which include somnolence, sedation, fatigue, and lethargy) were commonly reported during the up-titration of ganaxolone.[3] (**Figure 2**)
- A separate Phase 2, open-label, proof-of concept study (TrustTSC: NCT04285346) conducted in Tuberous Sclerosis Complex (TSC) patients evaluated the safety and efficacy of ganaxolone on seizure frequency and also found that somnolence-related adverse events were commonly reported in TSC patients (60.8% (n=14/23).[6]
- To attempt to mitigate somnolence-related adverse events, the Phase 3 TrustTSC study progressed with a modified titration schedule.

Figure 2. The Majority of Somnolence-Related Adverse Events in Ganaxolone-Treated Patients Began During the Titration Period



Objective

- To attempt to mitigate somnolence-related adverse events, the Phase 3 TrustTSC study of Ganaxolone progressed with a modified titration schedule. A post hoc analysis was completed between each study to evaluate the adverse event profiles reported under the traditional and modified ganaxolone titration schedules.

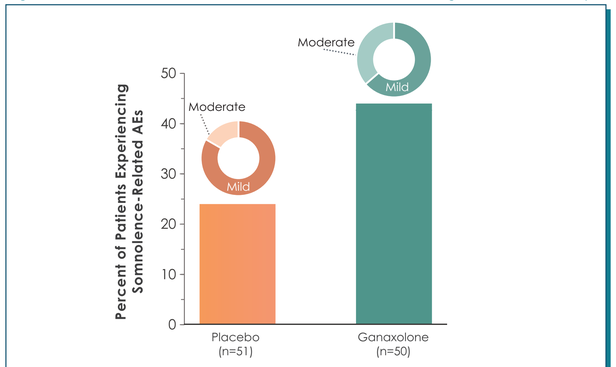
Methods

Somnolence-Related Adverse Events in the Marigold Study

Marigold Post-hoc Analysis:

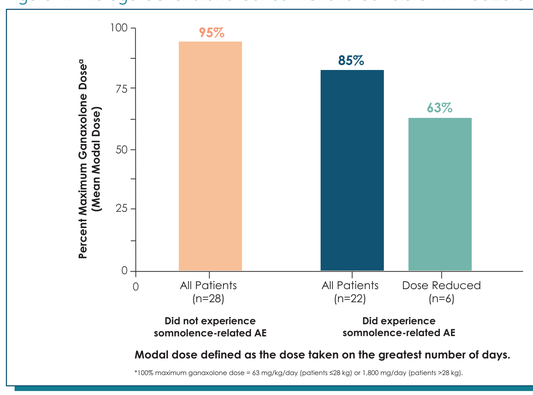
- A post-hoc analysis of somnolence-related adverse events (which included somnolence, sedation, hypersomnia, and lethargy) in the Marigold Phase 3 study was conducted.
- Somnolence-related adverse events were reported in 44% (22/50) of patients treated with ganaxolone and 24% (12/51) of patients on placebo. Most of the ganaxolone-treated patients reported mild somnolence-related adverse events (64%; 14/22); 36% (8/22) reported moderate and none reported severe. (**Figure 3**)
- The median onset of somnolence-related adverse events in patients treated with ganaxolone occurred at day 10 during the 4-week dose titration period.
- 75% of patients experiencing these adverse events did so within the first 29 days of receiving ganaxolone.
- 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.

Figure 3. Somnolence-Related Adverse Events in the Marigold Phase 3 Study



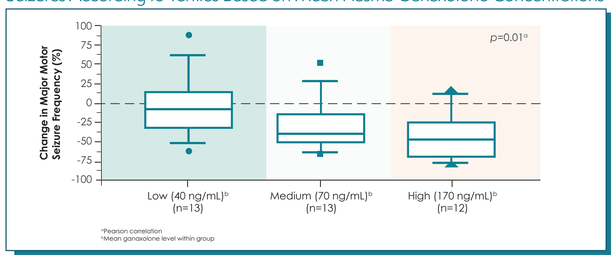
- The mean modal ganaxolone dose, defined as the dose taken the greatest number of days, was evaluated. In patients who reported somnolence-related AEs, the mean modal dose was 85% of maximal dose (63 mg/kg/day [patients ≤28 kg] or 1800 mg/day [patients >28 kg]) vs 95% in the 28 patients who did not 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 4**)

Figure 4. Average Ganaxolone Concentrations Correlate With Seizure Reduction



- In a separate pharmacokinetic-pharmacodynamic assessment, response relationships in ganaxolone-treated patients within the Marigold study were assessed.
- Mean and median percentage reductions in major motor seizures were calculated for low, medium, and high GNX concentration tertiles.
- There was a statistically significant difference between-groups 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 5. Comparision of Median Percentage Reduction in Major Motor Seizures According to Tertiles Based on Mean Plasma Ganaxolone Concentrations



Modified Titration Schedule Utilized in the TrustTSC Study

- The TrustTSC Phase 3 trial modified titration schedule included a lower initial dose of ganaxolone, implemented graded dose progression, and extended the up-titration time from 4 to 5 weeks to reach the same target dose as stated in the current prescribing information for ganaxolone. (**Figure 6** & **Table 1**)
- This revised titration schedule did not impact ganaxolone exposure levels and enabled patients to successfully titrate up to goal doses and achieve effective plasma concentrations.

Figure 6. Development of New Ganaxolone Titration Schedule

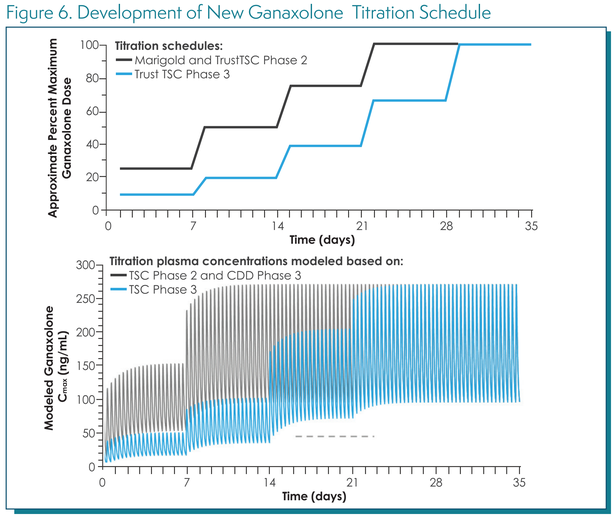


Table 1. Comparison of the Original (Orange) and Refined (Green) Dosing Titration for the Oral Ganaxolone Suspensions Studied in the Marigold and TrustTSC Clinical Trials

	Original Titration Schedule		Revised Titration Schedule	
	Dosage	Total Daily Dosage	Dosage	Total Daily Dosage
Patients Weighing 28 kgs 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 to ongoing	Continued Maintenance Dosing		21 mg/kg three times daily	63 mg/kg/day
Patients Weighing More than 28 kgs				
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 to ongoing	Continued Maintenance Dosing		600 mg/kg three times daily	1800 mg

Results

- A comparison of adverse events that occurred in ganaxolone-treated patients across the Marigold and TrustTSC Phase 2 & Phase 3 studies was completed. (**Table 2**)
- The onset of somnolence-related adverse events reported in the TrustTSC trial with the revised ganaxolone titration schedule was minimized when compared to the Marigold Trial.
- Therapy modifications due to somnolence-related adverse events were minimized between TrustTSC Phase 2 and Phase 3, and no patients discontinued the Phase 3 TrustTSC trial 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=30		TrustTSC Phase 2 N=23		TrustTSC Phase 3 N=64	
	Subjects n (%)	Events n	Subjects n (%)	Events n	Subjects n (%)	Events n
Somnolence-related TEAEs[a], n (%)	22 (44%)	27	14 (61%)	16	20 (31%)	27
TEAEs by severity[b]						
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
Onset of somnolence-related TEAEs, day – median [IQR]	8 [3, 15]	8 [4, 23]	7 [2, 13]	9 [3, 15]	24 [15, 43]	28 [20, 43]
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

[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.

Conclusions

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

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. Ztalymy Prescribing Information.
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

MKK was a consultant for Marinus. RR received funding from NIH, NINDS, and IFCR; served as a speaker and consultant for Marinus Pharmaceuticals; and consulted for UCB and Ultragenyx. KJ, MLS, and COE are employees of Immedica Pharma AB, and JH was employed at Marinus Pharmaceuticals.

Funding

Marinus Pharmaceuticals, Inc (now a wholly owned subsidiary of Immedica Pharma AB).

Poster presented at the 2025 CDKL5 Forum.