Ganaxolone Administration Via G-tube: Subgroup Analysis of the Phase 3 Marigold Study in CDKL5 Deficiency Disorder (CDD)

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Background

- Ganaxolone is a neuroactive steroid and positive allosteric modulator that targets both synaptic and extrasynaptic $GABA_A$ receptors
- Ganaxolone is approved in the United States for the treatment of seizures associated with CDKL5 Deficiency Disorder (CDD) in patients ≥2 years old
- CDD presents with treatment-refractory seizures, severe global developmental impairment, and multiple comorbidities[1]
- Ganaxolone is administered as an oral suspension, however ~20% of patients with CDD are fed exclusively by gastrostomy (g-tube) or nasogastric tubes[2]
- The Marigold study was a global, phase 3, randomized, double-blind, placebo-controlled study of patients with CDD treated with adjunctive ganaxolone

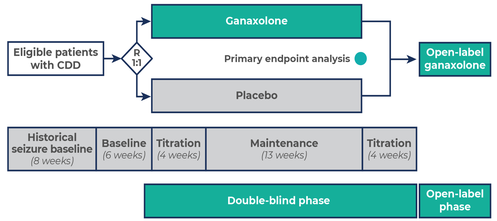
Objective

- Analyze the safety and efficacy of the subgroup of patients with feeding tubes in the Marigold study

Methods

- Marigold Study Design
  - A total of 101 patients with CDD aged 2-19 years were enrolled in the study
  - 6-week prospective baseline period followed by a 17-week double-blind treatment phase (**Figure 1**)
  - Seizure data were collected at baseline and at 17 weeks of ganaxolone treatment
  - Primary endpoint was percent change in 28-day major motor seizure frequency (MMSF) during the 17-week treatment phase in relation to the 6-week baseline
    - Major motor seizures were defined as bilateral tonic, bilateral clonic, generalized tonic-clonic, atonic/drop, focal to bilateral tonic-clonic
- 17 patients had a g-tube in place prior to enrollment
  - 10 were randomized to the ganaxolone group
  - 7 were randomized to the placebo group
- Ganaxolone was taken 3 times a day at a maintenance dose of up to 63 mg/kg/day or 1800 mg/day

Figure 1. Marigold Study Design



CDKL5, cyclin-dependent kinase-like 5; CDD, CDKL5 deficiency disorder; R, randomization.

- Outcomes
  - Percent change in 28-day MMSF
  - Plasma ganaxolone concentrations
  - Treatment-emergent adverse events (TEAEs)
  - TEAE severity

Results

Table 1. Enrollment and Baseline Demographics of Entire Marigold Population by Route of Administration

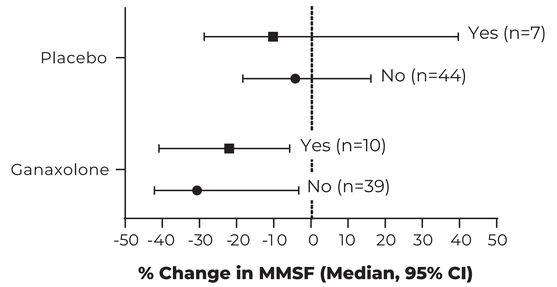
	G-tube			No G-tube		
	Ganaxolone (n=10)	Placebo (n=7)	Total (n=17)	Ganaxolone (n=40)	Placebo (n=44)	Total (n=84)
Age, yr, median (Q1-Q3)	8 (5, 13)	10 (5-15)	10 (5-13)	4 (3-9)	7 (3.5-10.5)	5 (3-10)
Sex, n (%)						
Male	4 (40)	1 (14)	5 (29)	7 (18)	9 (21)	16 (19)
Female	6 (60)	6 (86)	12 (71)	33 (83)	35 (80)	68 (81)
Ethnicity, n (%)						
Hispanic or Latino	1 (10)	0	1 (6)	3 (8)	6 (14)	9 (11)
Not Hispanic or Latino	9 (90)	7 (100)	16 (94)	35 (88)	36 (83)	71 (85)
Unknown	0	0	0	1 (3)	1 (2)	2 (2)
Not reported	0	0	0	1 (3)	1 (2)	2 (2)
Race, n (%)						
White	9 (90)	7 (100)	16 (94)	37 (93)	40 (91)	77 (92)
Asian	0	0	0	2 (5)	3 (7)	5 (6)
Other	1 (10)	0	1 (6)	1 (3)	1 (2)	2 (2)

Table 2. Baseline Clinical Characteristics of Entire Marigold Population by Route of Administration

	G-tube			No G-tube		
	Ganaxolone (n=10)	Placebo (n=7)	Total (n=17)	Ganaxolone (n=40)	Placebo (n=44)	Total (n=84)
Baseline MMSF per 28 days, median (IQR)	133.3 (48.5-279.1)	60.0 (49.2-84.0)	60.7 (49.2-253.3)	45.5 (30.7-141.3)[a]	43.8 (17.7-125.9)	45.3 (35.3-63.9)[b]
Number of ASMs taken prior to the study, median (IQR)	10 (8-13)[c]	7 (3-11)	9 (5.5-11.5)[d]	7 (5-10)[e]	7 (4-9)[f]	7 (5-9)[g]
Number of concomitant ASMs, median (IQR)	2 (1-3)	3 (2-4)	2 (2-3)	3 (2-4)	2 (1-3)	2 (1.5-3)
Concomitant ASMs[h], n (%)						
Valproate	2 (20)	4 (6)	6 (35)	16 (40)	12 (27)	28 (33)
Levetiracetam	2 (20)	0	2 (12)	11 (28)	13 (30)	24 (29)
Clobazam	4 (40)	4 (6)	8 (47)	8 (20)	10 (23)	18 (21)
Vigabatrin	1 (10)	0	1 (6)	9 (23)	12 (27)	21 (25)

ASM, antiseizure medication. [a]n=39; [b]n=83; [c]n=9; [d]n=16; [e]n=39; [f]n=43; [g]n=82; [h]The 4 most common concomitant ASMs.

Figure 2. Median (95% CI) % Change in MMSF Shows No Difference Between the G-tube and No G-tube Groups



- Percent change in MMSF was consistent between patients with (yes) and without (no) drug administered via g-tube

Table 3. Summary of Ganaxolone Concentration Level (ng/mL) for Patients With or Without Drug Administered via G-tube, 17-week, Double-Blind Phase, Intent-to-Treat Population

Time Point	Drug via G-tube (number of patients)	Mean (SD)	Median (min, max)
Pre-dose[a]	No (29)	85.93 (75.55)	61.7 (13.2, 348)
	Yes (5)	92.34 (65.22)	64.2 (44.5, 204)
0-4 hr post-dose	No (25)	106.54 (71.68)	82.8 (21.2, 336)
	Yes (6)	92.35 (51.15)	89.4 (34, 181)
1-5 hr post-dose	No (11)	119.7 (107.55)	94.7 (24.7, 325)
	Yes (2)	46.4 (31.67)	46.4 (24, 68.8)
4-8 hr post-dose	No (25)	103.04 (83.99)	61.4 (28.1, 341)
	Yes (7)	90.31 (73.54)	70 (29.9, 246)

[a]Pre-dose concentration levels taken at end of Week 17.

- Trough ganaxolone levels were comparable in patients with and without g-tubes, indicating little potential for compromised efficacy in patients receiving ganaxolone via g-tube. Likewise post-dose plasma ganaxolone levels showed no clinically meaningful differences in the two groups.

Safety

- Adverse events occurred in 80% of patients with g-tubes and 87.5% of patients without g-tubes who received ganaxolone
- Two patients taking ganaxolone were hospitalized due to TEAEs: urinary tract infection of moderate severity and decreased oxygen saturation. The latter was considered related to study drug.
- With or without a g-tube, the type, frequency, and severity of TEAEs were similar
- TEAEs were mild or moderate; there were no severe events

Table 4. Treatment-Emergent Adverse Events in Both G-tube and Non–G-tube Populations Are Similar

	G-tube Number of Events		No G-tube Number of Events	
TEAE, n (%)	Ganaxolone (n=28)	Placebo (n=19)	Ganaxolone (n=125)	Placebo (n=156)
Infections and infestations	9 (32)	5 (26)	22 (18)	33 (21)
Nervous system disorders	5 (18)	4 (21)	36 (29)	31 (20)
Somnolence/sedation/lethargy	4 (14)	2 (11)	21 (17)	10 (6)
General disorders and administration site conditions	1 (4)	1 (5)	14 (11)	17 (11)
Gastrointestinal disorders	3 (11)	4 (21)	13 (10)	29 (19)
Psychiatric disorders	0	0	9 (7)	12 (8)
Respiratory, thoracic, and mediastinal disorders	5 (18)	0	8 (6)	13 (8)
Metabolism and nutritional disorders	0	0	5 (4)	4 (3)
Eye disorders	0	0	2 (2)	0
Immune system disorders	1 (4)	0	2 (2)	0
Injury and procedural complications	0	0	5 (4)	4 (3)
Investigations	3 (11)	1 (5)	3 (2)	4 (3)
Skin and subcutaneous tissue disorders	1 (4)	3 (16)	2 (2)	5 (3)
Severity				
Mild	17	16	85	118
Moderate	11	3	39	34
Severe	0	0	1	4

All events are reported by system organ class except for somnolence/sedation/lethargy, which are included as preferred terms. Events that were reported more than once in at least 1 group are presented.

Conclusions

- **Based on data from the phase 3 study, efficacy, safety, and drug exposure appear similar between patients administered ganaxolone orally and via g-tube**

References

1. Jakemiec M, et al. *Brain Sci.* 2020;10:107.
2. Olson HE, et al. *Pediatr Neurol.* 2019;97:18-25.

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