A PHASE I, SINGLE DOSE STUDY OF GANAXOLONE PHARMACOKINETICS IN ADULT SUBJECTS WITH NORMAL AND IMPAIRED HEPATIC FUNCTION

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Introduction

- Ganaxolone is approved in the United States for the treatment of seizures associated with CDKL5 deficiency disorder in patients aged 2 years and older[1]
- Ganaxolone is available as a 50 mg/mL oral suspension, administered 3 times per day[1]

Patient Weight	Maximum Daily Dose
≤28 kg	63 mg/kg daily
>28 kg	1800 mg daily

- The current oral suspension formulation of ganaxolone demonstrates a variable dose-exposure profile
  - Bioavailability is low (~13%),[2] primarily due to extensive metabolism by CYP3A4/5, CYP2B6, CYP2C19, and CYP2D6[1]
  - Ganaxolone is ~99% protein-bound in serum[1]
  - Absorption is linear between 200 mg and 600 mg[2]
  - Exposure is higher when administered with a high-fat meal compared with fasted conditions[1]
- Given the important role of hepatic metabolism in the pharmacokinetic (PK) disposition of ganaxolone, it is important to understand the impact of hepatic impairment on exposure to ganaxolone

Objective

- Evaluate the PK and safety of ganaxolone in adult subjects with normal hepatic function versus impaired hepatic function

Methods

Study Design

- Phase 1, multicenter, open-label, non-randomized, parallel group, single-dose study
- Adaptive, step-wise design to compare subjects with varying levels of hepatic impairment versus subjects with normal hepatic function (**Figure 1**)

Figure 1. Adaptive Study Design

Step 1

Group 1, n=8	Subjects with moderate hepatic impairment[a]
Group 2a, n=8	Healthy adults with normal hepatic function matched to subjects with moderate hepatic impairment

Interim analysis: Safety and PK data

Step 2

Group 3, n=6	Subjects with severe hepatic impairment
Group 4, n=6	Subjects with mild hepatic impairment

[a]If results from Group 1 had indicated that the ganaxolone dose was to be lowered, a Group 2b of healthy adults (n=8) would have been enrolled to match the subjects with severe hepatic impairment using the reduced dose. However, Group 2b was not needed as the initial planned dose of ganaxolone was well tolerated.

Patients

- Key eligibility criteria:
  - Adult males and females 18-79 years old
  - Body mass index (BMI) ≥18.5 kg/m² to <42.0 kg/m²
  - Light, non-, or ex-smoker
- Subjects with normal hepatic function were matched 1:1 by sex, age (±10 years), smoking status, and BMI to subjects with moderate hepatic impairment
- Hepatic impairment was stable for ≥1 month prior to screening. Severity of hepatic impairment at screening was defined as:

Severity	Child-Pugh Class	Score
Mild	A	Between 5 and 6, inclusive
Moderate	B	Between 7 and 9, inclusive
Severe	C	Between 10 and 15, inclusive

Treatment

- Subjects received a single oral dose of ganaxolone 300 mg (6 mL of 50 mg/mL oral suspension) with 200 mL water on Day 1 under fed conditions (standardized breakfast 1 hour prior to dosing)

PK Analysis

- Blood samples were collected pre-dose and up to 48 hours post-dose
- Plasma ganaxolone concentrations were measured using a validated bioanalytical method
- PK parameters were calculated using non-compartmental methods (WinNonlin® software)
- The impact of hepatic impairment was analyzed using linear regression on individual Child-Pugh scores and log transformed PK parameters

Results

Patient Disposition, Demographics, and Baseline Characteristics

- A total of 28 subjects were enrolled; all subjects completed the study and were included in the analysis populations (**Table 1**)

Table 1. Summary of Subject Demographic and Baseline Characteristics

	Hepatic Function (N=28)				
	Normal (n=8)	Mild Impairment (n=6)	Moderate Impairment (n=8)	Severe Impairment (n=6)	Overall (N=28)
Mean (SD) age, years	61.0 (10.0)	58.8 (10.2)	60.9 (7.0)	55.3 (9.6)	59.3 (8.9)
Female, n (%)	3 (37.5)	4 (66.7)	3 (37.5)	3 (50.0)	13 (46.4)
Mean (SD) BMI, kg/m²	29.6 (3.5)	27.4 (3.5)	31.0 (4.6)	26.3 (2.5)	28.8 (3.9)

BMI, body mass index; SD, standard deviation.

PK Parameters

- Exposure to ganaxolone was higher in subjects with hepatic impairment compared with subjects with normal hepatic function (**Figure 2, Figure 3, Table 2**)
  - C_{max} was 38%, 45%, and 148% higher in the mild, moderate, and severe impairment groups, respectively
  - AUC_{0-t} was 8%, 50%, and 269% higher, respectively
  - The terminal half-life was at least 2-fold longer in the hepatic impairment groups (8.33 to 17.78 hours) relative to the normal hepatic function group (4.43 hours)
- The estimate of slope for the impact of Child-Pugh scores on C_{max}, AUC_{0-t}, and AUC_{0-inf} was 0.1, suggesting a potential correlation between hepatic impairment and PK parameters (**Table 3**)

Figure 2. Plasma Concentration-Time Profile of Ganaxolone Following a Single Oral Dose in Subjects With Normal Hepatic Function, and Subjects With Hepatic Impairment
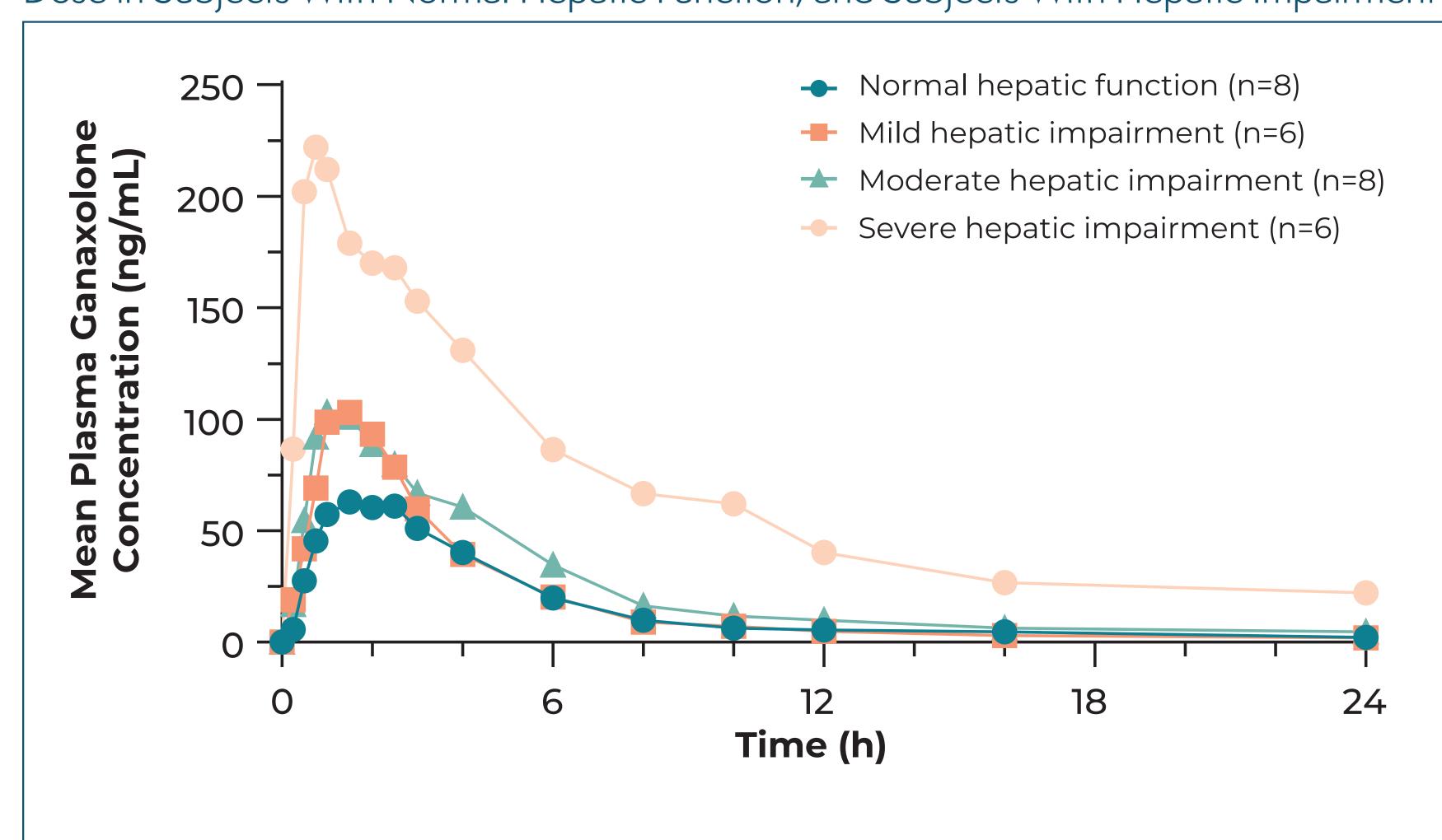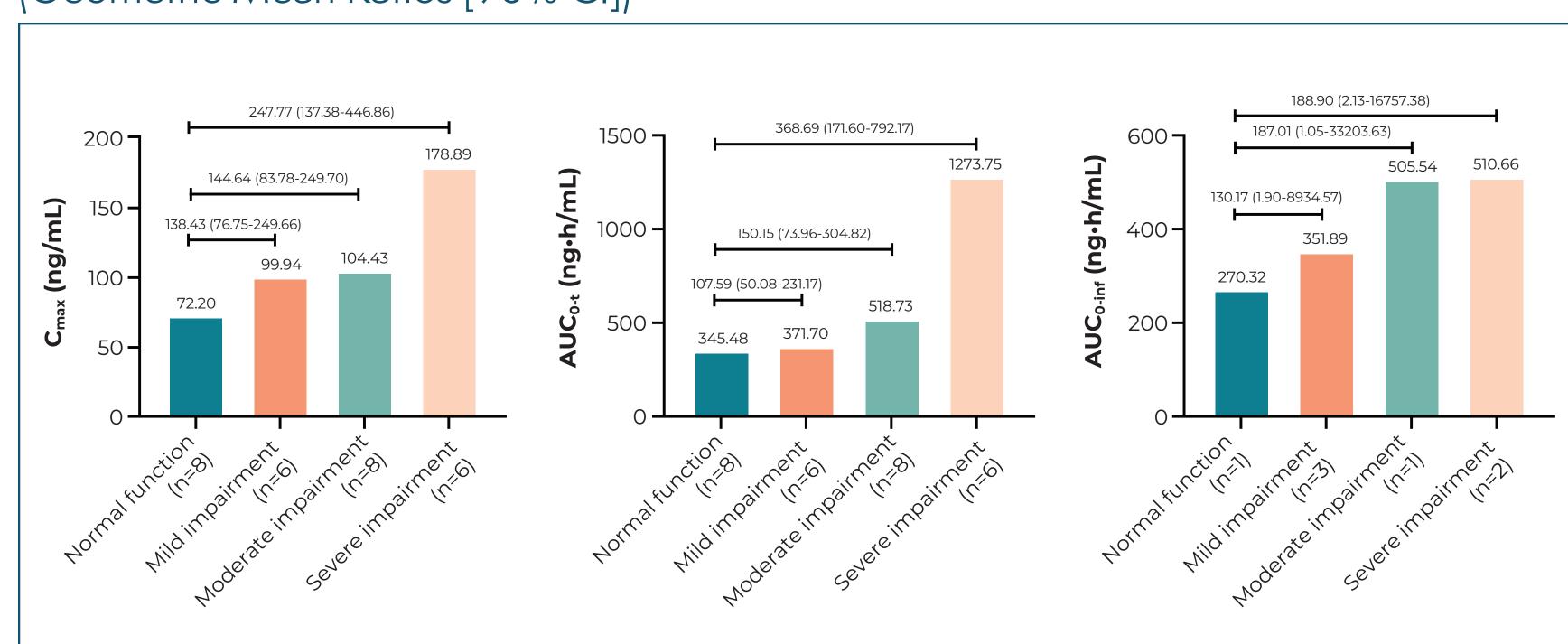

Figure 3. Comparison of Log Transformed PK Parameters by Hepatic Function Group (Geometric Mean Ratios [90% CI])

AUC_{0-inf}, area under the concentration-time curve extrapolated to infinity; AUC_{0-t}, area under the concentration-time curve from time 0 to the time of last quantifiable concentration; C_{max}, maximum observed concentration.

Table 2. Mean (%CV) PK Parameters of Ganaxolone

	Hepatic Function (N=28)			
	Normal (n=8)	Mild Impairment (n=6)	Moderate Impairment (n=8)	Severe Impairment (n=6)
T_{max}, h	2.00 (1.00-3.00)	1.50 (1.00-2.00)	1.50 (1.00-4.00)	0.88 (0.50-2.50)
C_{max}, ng/mL	76.6 (38.2)	114 (52.0)	115 (47.1)	252 (75.5)
AUC_{0-t}, ng•h/mL	371 (44.2)	448 (61.2)	628 (68.1)	1950 (55.3)
AUC_{0-inf}, ng•h/mL	270[a]	413 (72.4)[b]	506[a]	1570 (133.7)[c]
$t_{1/2}$, h	4.43[a]	8.78 (120.7)[b]	17.78[a]	8.33 (93.4)[c]
CL/F, L/h	1110[a]	1180[b]	593[a]	1800[c]
Vz/F, L	7090[a]	5310[b]	15200[a]	8130[c]

[a]n=1; [b]n=3; [c]n=2.
All parameters are reported as arithmetic mean (%CV), except T_{max}, which is reported as median (range) and CL/F and Vz/F, which are reported as median. AUC_{0-inf}, area under the concentration-time curve extrapolated to infinity; AUC_{0-t}, area under the concentration-time curve from time 0 to the time of last quantifiable concentration; CL/F, apparent total plasma clearance; C_{max}, maximum observed concentration; CV, coefficient of variation; $t_{1/2}$, apparent terminal elimination half-life; T_{max}, time of maximum observed concentration; Vz/F, apparent volume of distribution during the terminal phase.

Table 3. Impact of Hepatic Function (Child-Pugh Score) on Log Transformed PK Parameters

	Estimated Slope (95% CI)
C_{max}	0.1 (0, 0.1)
AUC_{0-t}	0.1 (0, 0.2)
AUC_{0-inf}	0.1 (-0.2, 0.4)

AUC_{0-inf}, area under the concentration-time curve extrapolated to infinity; AUC_{0-t}, area under the concentration-time curve from time 0 to the time of last quantifiable concentration; C_{max}, maximum observed concentration; CI, confidence interval.

Safety

- A total of 11 treatment-emergent adverse events (TEAEs) were reported by 8/28 (28.6%) subjects (**Table 4**). The most frequently reported TEAE was somnolence.
- 7 (25.0%) subjects reported treatment-related TEAEs, the most frequent of which was somnolence
- There were no treatment-related serious adverse events
- There were no clinically significant findings related to vital signs, laboratory parameters, ECGs, or physical examinations

Table 4. Summary of TEAEs

	Hepatic Function				
	Normal (n=8)	Mild Impairment (n=6)	Moderate Impairment (n=8)	Severe Impairment (n=6)	Overall (N=28)
Any TEAE	2 (25.0)	1 (16.7)	2 (25.0)	3 (50.0)	8 (28.6)
Somnolence	0	1 (16.7)	2 (25.0)	2 (33.3)	5 (17.9)
Headache	1 (12.5)	1 (16.7)	0	0	2 (7.1)
Hepatic encephalopathy	0	0	0	1 (16.7)	1 (3.6)
Lethargy	0	0	0	1 (16.7)	1 (3.6)
Muscle spasms	1 (12.5)	0	0	0	1 (3.6)
Mental status changes	0	0	0	1 (16.7)	1 (3.6)
Any treatment-related TEAE	1 (12.5)	1 (16.7)	2 (25.0)	3 (50.0)	7 (25.0)
Somnolence	0	1 (16.7)	2 (25.0)	2 (33.3)	5 (17.9)
Headache	1 (12.5)	1 (16.7)	0	0	2 (7.1)
Lethargy	0	0	0	1 (16.7)	1 (3.6)
Mental status changes	0	0	0	1 (16.7)	1 (3.6)

Data are given as n (%). TEAE, treatment-emergent adverse event.

Conclusions

- Exposure to ganaxolone increased with severity of hepatic impairment
- The safety profile in subjects with normal and impaired hepatic function was acceptable
- An adjustment of ganaxolone dose in patients with severe hepatic impairment is recommended[1]

Severe Hepatic Impairment, Patient Weight	Maximum Daily Dose
≤28 kg	21 mg/kg
>28 kg	600 mg

- No dosage adjustment is necessary in patients with mild or moderate hepatic impairment[1]

References

1. Marinus Pharmaceuticals, Inc. ZTALMY® (ganaxolone) oral suspension. CV [prescribing information]. Radnor, PA: Marinus Pharmaceuticals, Inc.; June 2023.
2. Marinus Pharmaceuticals Emerald Limited. ZTALMY 50 mg/mL oral suspension [summary of product characteristics]. Dublin, Ireland: Marinus Pharmaceuticals Emerald Limited; 2023.