A Phase 1 Single Ascending Dose, Open-Label Crossover Comparative Bioavailability Study of a Second-Generation Ganaxolone Oral Formulation

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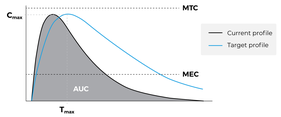
Background

- Ganaxolone is a neuroactive steroid anticonvulsant that acts as a positive allosteric modulator of both synaptic and extrasynaptic $GABA_A$ receptors[1]
- Ganaxolone is approved in the United States for the treatment of seizures associated with cyclin-dependent kinase-like 5 (CDKL5) deficiency disorder (CDD) in patients ≥2 years old[2] and in the European Union for treatment of seizures associated with CDD in patients 2-17 years old, which may be continued in patients 18 years of age or older[3]
- The current oral suspension formulation of ganaxolone (GNX REF, 50 mg/mL suspension):
  - Has bioavailability of ~13%[1]
  - Demonstrates a variable dose-exposure profile[1]
  - Has non-linear kinetics with reduced exposure at higher doses[1]
  - Has higher exposure when administered with a high-fat meal compared with fasted conditions[1]
- A second-generation oral ganaxolone formulation (GNX TEST, powder [300 mg GNX/1000 mg product]) was developed with the goal of optimizing the PK profile to:
  - Decrease the C_{max}/AUC ratio to allow increased GNX exposure without a concomitant increase in C_{max}-related adverse effects
  - Reduce dosing frequency while maintaining sustained ganaxolone exposure within the therapeutic range (**Figure 1**)

Figure 1. Target Pharmacokinetic Profile for Second-Generation Oral Ganaxolone Formulation



AUC, area under the curve; C_{max}, maximum concentration; MEC, minimum effective concentration; MTC, minimum toxic concentration; T_{max}, time to peak drug concentration.

OBJECTIVE

- To evaluate the PK and safety characteristics of GNX TEST versus GNX REF in healthy volunteers enrolled in a phase 1 single ascending dose study

METHODS

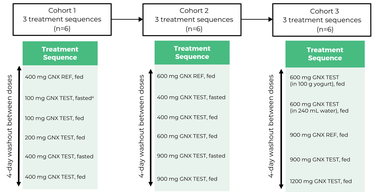
Subjects

- Healthy non-smoking adult male or female volunteers age 18-55 years (inclusive) with body mass index of 18-32 kg/m^2 and body weight ≥50 kg at screening

Study Design

- Phase 1, single-center, open-label, 3-cohort, 6-period, 3- or 6-sequence crossover single ascending dose study (**Figure 2**)
  - Administration of successive cohorts depended on the PK, safety, and tolerability observed for previous cohorts

Figure 2. Study Design and Treatments



GNX REF, ganaxolone reference formulation (50 mg/mL oral suspension); GNX TEST, second-generation ganaxolone powder formulation.
[a]GNX TEST powder was administered as a sprinkle in 240 mL water under fasted (no food for at least 10 hours prior to dosing) or fed (high-fat, high-calorie meal 30 minutes before dosing) conditions, or as a sprinkle in 100 g of yogurt under fed conditions.

Pharmacokinetic Analyses

- Blood samples for measurement of plasma ganaxolone concentrations were collected up to 96 hours post-dose
- The PK population consisted of subjects who received ≥1 dose of ganaxolone and had sufficient data to derive ≥1 PK parameter
- Non-compartmental analysis of plasma PK parameters was conducted using Phoenix® WinNonlin®
  - PK parameters that were dependent on the elimination rate constant (ie, $T_{1/2}$, $AUC_{0\text{-}inf}$, Vz, CL) were excluded if adjusted r^2 <0.8
- Dose proportionality was evaluated using a power model that compared treatments of interest in each cohort
  - Point estimates and 90% confidence intervals were derived for the slope; dose proportionality was suggested if the 90% confidence interval for the slope coefficient included "1"

Safety & Tolerability Assessments

- Safety was monitored at screening and/or check-in, and after dosing
  - Safety and tolerability were assessed by adverse events, physical exams, changes in vital signs, clinical laboratory tests, ECG
  - Suicidality assessment using the Columbia Suicide Severity Rating Scale (C-SSRS) was performed at baseline and end of study

RESULTS

Subject Disposition and Characteristics

- All subjects (N=18; **Table 1**) completed the study and were included in the PK and safety datasets

Table 1. Demographic and Baseline Characteristics

Demographic Variable	Cohort 1 (n=6)	Cohort 2 (n=6)	Cohort 3 (n=6)
Age (years), mean (SD)	34.5 (10.6)	35.5 (9.9)	40.8 (6.0)
Female sex, n (%)	3 (50.0)	1 (16.7)	2 (33.3)
BMI (kg/m^2), mean (SD)	27.6 (3.4)	25.8 (2.9)	28.1 (2.5)

BMI, body mass index; SD, standard deviation.

Pharmacokinetic Analyses

Table 2. PK Parameters Following Single Dosing in Healthy Subjects for Cohorts 1, 2, and 3

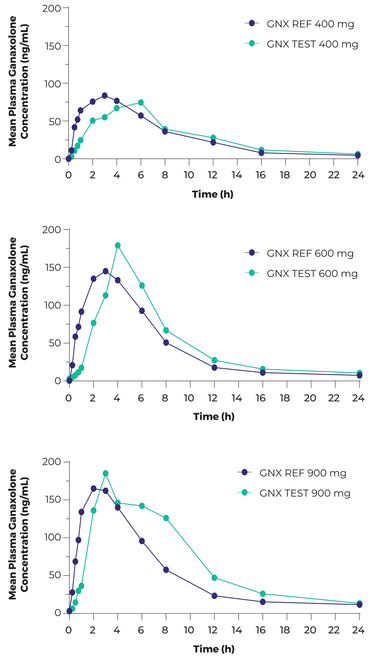
Treatment Sequence	T_{max} (h)	C_{max} (ng/mL)	$AUC_{0\text{-}t}$ (ng-h/mL)	$AUC_{0\text{-}inf}$ (ng-h/mL)	$T_{1/2}$ (h)	CL/F (L/h)	Vz/F (L)
Cohort 1							
400 mg GNX REF, fed	3.50 (2.00-6.00)	99.4 (29)	823 (38)	897 (41)	21.4 (93)	509 (38)	11,600 (66)
100 mg GNX TEST,[a] fasted	6.00 (1.00-6.10)	4.31 (22)	26.6 (52)	NC	NC	NC	NC
400 mg GNX TEST, fasted	5.00 (2.00-6.00)	11.5 (37)	231 (66)	373 (92)[b]	29.5 (101)[b]	2060 (82)[b]	39,400 (35)[b]
100 mg GNX TEST, fed	4.00 (3.00-8.00)	21.4 (25)	145 (46)	194 (57)[b]	9.6 (131)[b]	613 (38)[b]	5450 (77)[b]
200 mg GNX TEST, fed	3.50 (2.00-6.00)	57.5 (34)	463 (47)	547 (55)	23.4 (97)	453 (47)	10,300 (59)
400 mg GNX TEST, fed	6.00 (2.00-6.00)	87.5 (34)	870 (36)	996 (40)	29.6 (79)	460 (48)	15,200 (48)
Cohort 2							
600 mg GNX REF, fed	3.00 (2.00-4.00)	163 (23)	1290 (30)	1410 (28)	31.7 (34)	452 (27)	21,400 (58)
400 mg GNX TEST,[a] fasted	6.00 (3.00-6.00)	9.86 (21)	262 (49)	425 (54)[c]	46.9 (65)[c]	1310 (78)[c]	60,000 (24)[c]
900 mg GNX TEST, fasted	3.00 (2.00-6.00)	25.0 (31)	599 (26)	956 (59)[b]	85.3 (102)[c]	1170 (46)[b]	100,000 (44)[b]
400 mg GNX TEST, fed	4.00 (3.00-8.00)	113 (38)	989 (34)	1090 (33)	24.8 (49)	415 (43)	12,500 (32)
600 mg GNX TEST, fed	4.00 (2.00-8.00)	189 (46)	1580 (33)	1870 (39)	51.8 (45)	357 (32)	24,600 (31)
900 mg GNX TEST, fed	4.00 (3.00-12.00)	224 (52)	2170 (29)	2700 (23)[d]	49.7 (34)[d]	351 (27)[d]	23,700 (19)[d]
Cohort 3							
900 mg GNX REF, fed	3.00 (1.00-6.00)	191 (31)	1780 (29)	2080 (24)	49.3 (49)	450 (19)	32,100 (56)
600 mg GNX TEST,[a] with yogurt	2.00 (1.00-4.00)	233 (49)	1270 (7)	1400 (11)	33.3 (46)	431 (11)	20,000 (39)
600 mg GNX TEST, with water	4.00 (3.00-6.00)	115 (43)	1370 (49)	1490 (41)	34.1 (54)	453 (42)	25,600 (88)
900 mg GNX TEST, fed	3.50 (2.00-6.02)	204 (33)	1930 (41)	2570 (31)[d]	50.1 (36)[d]	380 (34)[d]	25,400 (26)[d]
1200 mg GNX TEST, fed	4.00 (2.00-6.00)	244 (27)	2690 (29)	3250 (31)	53.0 (40)	397 (28)	2930 (46)

[a]GNX TEST powder was administered as a sprinkle in 240 mL water under fasted (no food for at least 10 hours prior to dosing) or fed (high-fat, high-calorie meal 30 minutes before dosing) conditions, or as a sprinkle in 100 g of yogurt under fed conditions. [b]n=4. [c]n=3. [d]n=5. All parameters are reported as arithmetic mean (CV%), except T_{max}, which is reported as median (range).
$AUC_{0\text{-}t}$, area under the concentration-time curve from time zero to infinity; $AUC_{0\text{-}t}$, area under the concentration-time curve from time zero to t hours; CL/F, total body clearance; C_{max}, maximum plasma concentration; GNX, ganaxolone; GNX REF, ganaxolone reference formulation (50 mg/mL oral suspension); GNX TEST, second-generation ganaxolone powder formulation; NC, not calculated; $T_{1/2}$, terminal elimination half-life; T_{max}, time to reach maximum concentration; Vz/F, volume of distribution.

Relative Bioavailability

- Compared to GNX REF (**Figure 3**):
  - T_{max} for GNX TEST under fed conditions occurred later for the 400-mg, 600-mg, and 900-mg doses
  - C_{max} and AUC for GNX TEST were similar for the 400-mg dose, but were slightly higher for the 600-mg and 900-mg doses

Figure 3. GNX TEST and GNX REF Mean Plasma Concentration-Time Profiles Following Single Doses of 400 mg, 600 mg, and 900 mg Under Fed Conditions in Healthy Subjects

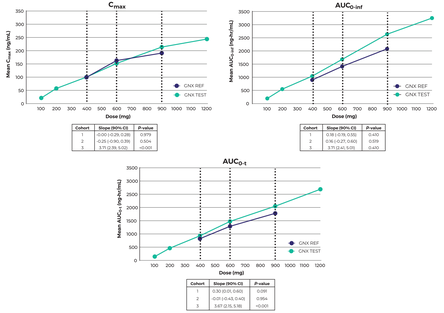


Samples were collected up to 96-h post-dose; however, plasma concentrations up to 24 hours are depicted.
GNX REF, ganaxolone reference formulation (50 mg/mL oral suspension); GNX TEST, second-generation ganaxolone powder formulation.

Dose Proportionality

- GNX TEST demonstrated generally linear PK over the dose range studied (100-1200 mg; **Figure 4**)
- Following administration of GNX TEST under fed conditions, plasma concentrations increased with dose (C_{max} of 21.4-244 ng/mL and $AUC_{0\text{-}t}$ of 145-2690 ng-h/mL)
- At doses of 600, 900, and 1200 mg GNX TEST under fed conditions, the change in AUC was greater than the change for C_{max} with increasing dose

Figure 4. Dose Proportionality Curves for GNX TEST at Single Doses of 100-1200 mg and Comparison to GNX REF at 400-, 600-, and 900-mg Doses With Assessment of PK Parameters by Cohort



Cohort	Slope (90% CI)	P-value
1	-0.001 (-0.29, 0.28)	0.979
2	-0.25 (-0.90, 0.39)	0.504
3	3.71 (2.78, 5.02)	<0.001

Cohort	Slope (90% CI)	P-value
1	0.18 (-0.19, 0.55)	0.410
2	0.16 (-0.27, 0.60)	0.519
3	3.71 (2.47, 5.11)	0.410

Cohort	Slope (90% CI)	P-value
1	0.30 (0.01, 0.60)	0.091
2	0.01 (-0.43, 0.47)	0.964
3	3.67 (2.15, 5.18)	<0.001

For Cohort 1, treatments of comparison include GNX TEST fed 100, 200, and 400 mg. For Cohort 2, treatments of comparison include GNX TEST fed 400, 600, and 900 mg. For Cohort 3, treatments of comparison include GNX TEST 600 mg with water fed, GNX TEST 900 mg fed, and GNX TEST 1200 mg fed. Where doses were administered in more than one cohort, averages are graphed.
$AUC_{0\text{-}t}$, area under the concentration-time curve from time zero to infinity; $AUC_{0\text{-}t}$, area under the concentration-time curve from time zero to t hours; CI, confidence interval; C_{max}, maximum plasma concentration; GNX REF, ganaxolone reference formulation (50 mg/mL oral suspension); GNX TEST, second-generation ganaxolone powder formulation.

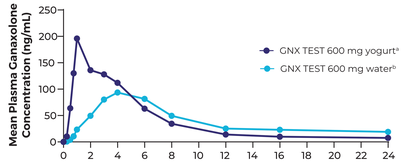
Effect of Food

- Exposure following administration of GNX TEST (100, 400, 900 mg) was significantly higher in the fed state compared to fasted (**Table 2**)
- Median T_{max} was slightly delayed in the fed state compared to fasted

Effect of Yogurt

- When GNX TEST was administered with yogurt, C_{max} doubled compared to administration with water; $AUC_{0\text{-}t}$ and $AUC_{0\text{-}inf}$ remained consistent whether administered with yogurt or water (**Figure 5**)

Figure 5. Mean Plasma Concentration-Time Profile Following Single Dosing of GNX TEST in Healthy Subjects, Yogurt Versus Water



GNX REF, ganaxolone reference formulation (50 mg/mL oral suspension); GNX TEST, second-generation ganaxolone powder formulation.
[a]Administered as a sprinkle in 100 g of yogurt under fed conditions.
[b]Administered as a sprinkle in 240 mL water under fed conditions.

Safety

- 13 of 18 subjects (72.2%) reported a total of 70 TEAEs
  - 61/70 TEAEs were deemed related to study treatment
- The most common TEAEs were somnolence, headache, dizziness, and nausea (**Table 3**)
  - Most TEAEs were mild in severity; 5 moderate TEAEs were reported in 2 subjects
    - 1 subject in Cohort 2 reported 1 moderate TEAE (presyncope)
    - 1 subject in Cohort 3 reported 4 moderate TEAEs (headache, dizziness, euphoric mood, and gait disturbance)
  - There were no severe TEAEs
- No serious adverse events or deaths occurred and no subjects withdrew
- No clinically significant abnormalities or TEAEs related to vital signs, laboratory assessments, ECG, or C-SSRS were reported

Table 3. Summary of Treatment-Emergent Adverse Events Reported Overall by ≥2 Subjects

MedDRA Preferred Term	Subjects Reporting TEAE, n (%)	Subjects With TEAE Deemed Treatment-Related, n (%)
Somnolence	9 (50.0)	9 (100)
Headache	8 (44.4)	6 (75.0)
Dizziness	5 (27.7)	4 (80.0)
Nausea	5 (27.7)	4 (80.0)
Fatigue	3 (16.6)	3 (100)
Feeling abnormal	3 (16.6)	2 (66.6)
Gait disturbance	2 (11.1)	2 (100)
Paraesthesia	2 (11.1)	2 (100)
Dyspepsia	2 (11.1)	2 (100)
Rash	2 (11.1)	2 (100)

MedDRA, Medical Dictionary for Regulatory Activities.
Note: A TEAE that occurred 2 or more times for a subject is counted only once.

Conclusions

- **The second-generation oral formulation of ganaxolone, GNX TEST, has a predictable PK profile and demonstrates generally linear PK after single dosing over the range of 100-1200 mg**
- **The increase in AUC with higher doses was greater than the increase in C_{max}**
  - **This may indicate the potential for improvements in efficacy with increasing dose without a proportional increase in C_{max}-related adverse effects**
- **Exposure was significantly higher in the fed state compared to fasted**
- **When administered with yogurt, C_{max} doubled compared to administration with water under fed conditions; $AUC_{0\text{-}t}$ and $AUC_{0\text{-}inf}$ remained consistent whether administered with yogurt or water**
- **In healthy volunteers, administration of 100- to 1200-mg doses of GNX TEST demonstrated a safety profile consistent with the reference formulation**
- **These findings have been used to inform the design of an ongoing multiple ascending dose study in adult volunteers**

References

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Disclosures

JH, MG, IA, HW: Employee: Marinus Pharmaceuticals, Inc.

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MARINUS SCIENTIFIC AFFAIRS

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