Pharmacokinetics of Co-administered Ganaxolone and Cannabidiol in Healthy Adults

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Introduction

- Ganaxolone is a 3ß-methylated, synthetic analog of the endogenous neurosteroid, allopregnanolone[1], that has recently been FDA-approved for the treatment of seizures associated with CDKL5 Deficiency Disorder (CDD) in patients 2 years of age and older
- Ganaxolone is thought to exert its anti-seizure effect via positive allosteric modulation of both synaptic and extrasynaptic $GABA_A$ receptors[1]
- Ganaxolone is also being developed for other chronic epilepsies, including Tuberous Sclerosis Complex (TSC)
- Seizure treatment in TSC often includes polypharmacy with antiseizure medications (ASMs), including approved medications such as cannabidiol (Epidiolex®), highlighting the need to understand potential drug-drug interactions

Objective

- To evaluate the pharmacokinetic effects of co-administration of ganaxolone with cannabidiol in healthy adult volunteers

Methods

- This was a Phase 1, open-label, fixed-sequence, 2-treatment drug-drug interaction (DDI) study

Dosing

- Each participant was administered the following study treatments under fed conditions:
  - Day 1: A single 600 mg (12 mL of 50 mg/mL) oral dose of ganaxolone
  - Days 4 to 15: 12.5 mg/kg oral doses of cannabidiol (Epidiolex®) administered BID in the morning and evening approximately 12 hours apart (total daily dose: 25 mg/kg/day) for 12 consecutive days
  - Day 13: A single 600 mg (12 mL of 50 mg/mL) oral dose of ganaxolone co-administered with the 12.5 mg/kg cannabidiol morning dose
- The morning doses were administered 30 minutes following a standardized breakfast, and the evening doses were administered 30 minutes following an evening meal

Clinical Endpoints

Primary endpoints included the following plasma PK parameters for ganaxolone:

- C_{max}
- AUC_{0-t}
- AUC_{0-inf}

Secondary endpoints included:

- Incidence rate of treatment-emergent adverse events (TEAEs) and serious adverse events (SAEs)
- Clinical laboratory tests
- Physical examination
- Vital signs
- 12 lead electrocardiogram (EEG)
- The Columbia Suicide Severity Rating Scale (C-SSRS)

Exploratory endpoints included the following plasma concentrations for cannabidiol:

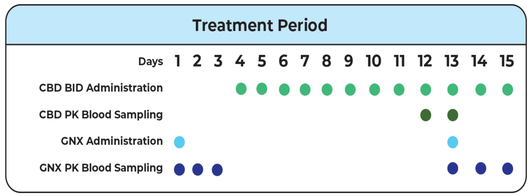
- C_{max}
- T_{max}
- AUC_{0-12}

PK Sampling

- Ganaxolone and cannabidiol plasma concentrations were obtained through bioanalysis of the plasma derived from the blood samples drawn during this study using validated bioanalytical methods
  - Blood samples for PK analysis of ganaxolone were collected prior to and until 72 hours following each ganaxolone administration
  - Blood samples for PK analysis of cannabidiol were collected prior to and until 12 hours following the morning cannabidiol administration on Days 12 and 13

Trial Design

Figure 1. Trial Design



Day 1: A single 600 mg (12 mL of 50 mg/mL) oral dose of ganaxolone
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Day 13: A single 600 mg (12 mL of 50 mg/mL) oral dose of ganaxolone co-administered with the 12.5 mg/kg cannabidiol morning dose
BID, Twice Daily; CBD, Cannabidiol; GNX, Ganaxolone; PK, Pharmacokinetic

Results

- Twenty healthy adults completed the study

Baseline Characteristics

- Mean age of participants was 42.4 years (range: 25 to 59 years)
- Participants were primarily male (57.1%), white (47.6%), and not Hispanic/Latino (71.4%).
- Participants mean BMI was 27.1 kg/m^2 (range: 21.3 to 31.6 kg/m^2)

Ganaxolone PK

- Plasma levels of ganaxolone were slightly lower when co-administered with cannabidiol **(Figure 1, Table 1)**
  - Ganaxolone C_{max} was 10% lower when co-administered cannabidiol
  - Ganaxolone AUC_{0-t} was 19% lower when co-administered with cannabidiol
  - Only differences in AUC, not C_{max}, were statistically significant

Figure 1: Mean Plasma Concentration-Time Profiles of Ganaxolone Following a Single Oral Dose Administration in Healthy Subjects on Day 1 and Day 13

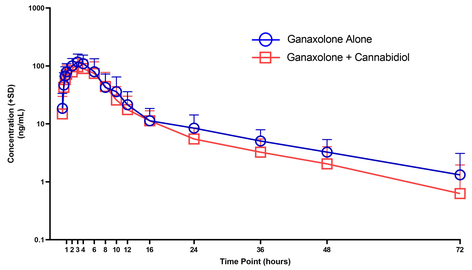

Table 1. Comparison of Results with Standard for Drug-Drug interaction for Ganaxloxone

Parameter	Intra-Subject C.V. (%)	Geometric LSmeans[a] GNX alone (n=20)	GNX + CBD (n=20)	Ratio (%)	90% Confidence Limits (%) Lower	Upper
C_{max}	21.7	119.2	107.6	90.3	80.3	101.6
AUC_{0-T}	18.2	1010.5	813.7	80.5	73.0	88.9
$AUC_{0-\infty}$	17.0	1100.1	902.8	82.1	74.8	90.0

[a]units are ng/mL for C_{max} and ng·h/mL for AUC_{0-t} and $AUC_{0-\infty}$
CBD, Cannabidiol; GNX, Ganaxolone

Cannabidiol PK

- Plasma levels of cannabidiol were slightly lower when co-administered with ganaxolone **(Figure 2, Table 2)**
  - Cannabidiol C_{max} was 10% lower when co-administered ganaxolone
  - AUC_{0-12} was similar between cannabidiol alone and cannabidiol co-administered with ganaxolone
  - There were no statistically significant differences on cannabidiol PK parameters

Figure 2: Mean Plasma Concentration-Time Profiles of Cannabidiol Following a Multiple Oral Dose Administration in Healthy Subjects on Day 12 and Day 13

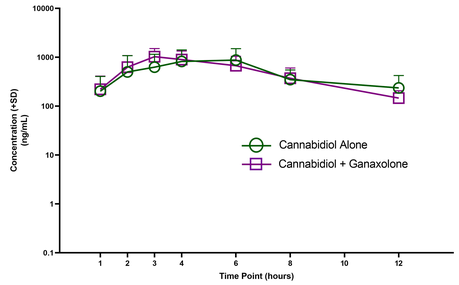

Table 2. Comparison of Results with Standard for Drug-Drug Interaction for Cannabidiol

Parameter	Intra-Subject C.V. (%)	Geometric LSmeans[a] CBD alone (n=20)	CBD + GNX (n=20)	Ratio (%)	90% Confidence Limits (%) Lower	Upper
C_{max}	23.2	1248.0	1145.5	91.8	81.0	104.0
AUC_{0-12}	14.8	5624.5	5840.3	103.8	95.8	112.5

[a]units are ng/mL for C_{max} and ng·h/mL for AUC_{0-12}
CBD, Cannabidiol; GNX, Ganaxolone

Table 3. Summary of Safety Findings

	Treatment at Onset of AE GNX Alone (N=21) n (%) [E]	CBD Alone (N=20) n (%) [E]	GNX + CBD (N=20) n (%) [E]	Overall (N=21) n (%) [E]
Subjects with any TEAE[a]	6 (28.6) [12]	7 (35.0) [10]	6 (30.0) [15]	11 (52.4) [37]
Subjects discontinued due to TEAE	1 (4.8) [1]	1 (5.0) [1]	0	2 (9.5) [2]
Subjects with severe TEAE[b]	0	0	0	0
Subjects with any related TEAE[c]	4 (19.0) [10]	7 (35.0) [9]	3 (15.0) [8]	10 (47.6) [27]
Subjects with any serious TEAE	0	0	0	0
Subjects with any serious TEAEs resulting in death	0	0	0	0

Notes: For each row category, a subject with 2 or more AEs in that category was counted only once
Summaries are presented as: number of subjects (percentage of subjects per treatment and overall) [number of events]
[a]A TEAE was an AE which starts or worsens after use of study treatment
[b]A severe TEAE was an AE where the severity is severe or missing.
[c]A related TEAE is defined as related to study drug
AE, adverse event; CBD, cannabidiol; E, number of events; GNX, ganaxolone; TEAE, treatment-emergent adverse event

Safety and Laboratory Findings

- Eleven participants experienced at least 1 TEAE **(Table 3)**
- The most commonly experienced TEAEs in the study were nausea (4 events experienced by 3 (14.3%) participants), followed by diarrhea and headache (each with 3 events experienced by 3 (14.3%) participants)
- No clinically significant laboratory findings were found related to ganaxolone or the combination of ganaxolone and cannabidiol. One participant receiving cannabidiol alone had abnormanal laboratory findings (increased alanine aminotransferase, aspartate aminotransferase, and gamma glutamyl transferase).
- No clinicaly signficant abnormal findings in ECGs or the C-SSRS were noted during the study

Conclusion

- **No clinically meaningful interactions between a single dose of ganaxolone and cannabidiol at steady state were observed in this study**
- **The administration of ganxolone alone and in combination with cannabidiol was well tolerated in healthy subjects**

References

1.Lattanzi et al. Expert Rev Neurother 2021;21:1317-32

Disclosures

IM, RB, AA, and JH are employees of Marinus Pharmaceuticals, Inc.

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