DOSE PROPORTIONALITY AND THE EFFECT OF SPRINKLING ON THE BIOAVAILABILITY OF ONCE-DAILY EXTENDED-RELEASE LORAZEPAM

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BACKGROUND

- Anxiety is a very common disorder, affecting 32% of adults in the United States at some point during their lifetime[1,2]
- Anxiety disorders can cause substantial functional impairment and burden on both patients and their families, with an increase in healthcare utilization[1,3,4]
- Benzodiazepines are a class of small molecules that act as allosteric gamma-aminobutyric acid (GABA) receptor modulators, an important therapeutic target for anxiety.[5] One such drug, lorazepam, was approved by the US Food and Drug Administration in 1977 as an anti-anxiety medication[5,6]
- Traditionally lorazepam is administered as an immediate-release (IR) formulation that is divided in doses of 2 to 6 mg/day given two or three times daily, but doses can range from 1 to 10 mg/day[6,7]
- There is an unmet need for extended-release (ER) alternatives that deliver more consistent lorazepam levels for patients with anxiety, which may help reduce rebound anxiety and improve tolerability[8]
- A once-daily, ER formulation of lorazepam was approved in August 2021 for adults already receiving evenly divided doses of lorazepam IR three times a day, and was designed to deliver more stable drug levels[9,10]
- Four pharmacokinetic (PK) studies have been conducted evaluating the PK profile and safety of ER lorazepam as part of its clinical development
- Because some patients have difficulty swallowing solid oral dosage formulations, as part of this clinical program the impact on PK parameters of sprinkling once-daily ER lorazepam (4 mg) onto soft food was investigated compared to administration as an intact capsule
- Further, as ER lorazepam is available in doses ranging from 1 to 4 mg, the PK profiles of the lowest (1 mg) and highest (4 mg) doses were evaluated for dose proportionality
- Here we report the results of a Phase 1, randomized, open-label, three-period, six-sequence, three-treatment study in healthy adults evaluating the bioavailability and safety of once-daily ER lorazepam given as either a single 4 mg dose sprinkled on soft food, an intact 4 mg capsule, or as four 1 mg intact capsules

OBJECTIVES

- The primary objectives of this study were to:
  1) Evaluate the effect of ER lorazepam (4 mg) when sprinkled on soft food compared to intact capsules in healthy adult participants
  2) Evaluate the dose proportionality of four 1 mg (lowest dose form) ER lorazepam capsules to one 4 mg capsule (highest dose form)
- The secondary objective evaluated the safety and tolerability of ER lorazepam across treatments

METHODS

Study Design

- After a 28-day screening period, subjects fasted for 10 hours and were randomized to one of six dosing schedules; ABC, BCA, CAB, CBA, ACB, or BAC, separated by a 10-day washout between periods 1, 2, and 3:
  - Treatment A: once-daily ER lorazepam (1 x 4 mg) sprinkled on soft food (applesauce)
  - Treatment B: once-daily ER lorazepam (1 x 4 mg) given intact
  - Treatment C: once-daily ER lorazepam (4 x 1 mg) given intact
- Participants remained in the study clinic from Day 1 to 48 hours post-dose and returned to the clinic at 72, 96, and 120 hours post-dose for each period

Pharmacokinetic Measurements

- Blood samples for PK analysis were obtained after each administration for each treatment, for a total of 72 whole blood draws (**Table 1**)

Table 1. Schedule of Blood Draws to Assess Plasma Concentration of Lorazepam

Treatment Group	Timing of Blood Draws [hour(s)]
Treatment A, B, or C (Sprinkled, intact, or 4 x 1 mg dose)	0 (pre-dose) and at 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 18, 24, 36, 48, 72, 96, and 120 post-dose

Safety Assessments

- Safety assessments included monitoring of adverse events (AEs) as well as physical examinations, clinical laboratory tests, vital sign measurements, and electrocardiograms (ECGs)

Statistical Analyses

- Analysis Populations:
  - PK Population: All participants who completed at least one treatment period and provided sufficient PK data needed to calculate the planned parameters
  - Safety Population: All participants who received at least one dose of study medication and had at least one post-baseline safety evaluation

RESULTS

Demographics and Characteristics

- 30 participants were enrolled in the study, with 29 participants completing all study periods
- Subjects were healthy adults; 9 females and 21 males ranging from 26 to 55 years of age, with body mass index (BMI) between 22 and 30 kg/m^2, and weighing 61.5 to 100.2 kg (**Table 2**)
- Study population demographics were: 50% of Hispanic or Latino ethnicity, 30% black or African American, 67% white, and 3.3% American Indian or Alaskan Native (**Table 2**)

Table 2. Key Demographics and Characteristics of Subjects

Parameter	Overall[a] (N=30)
Age, mean (min, max), years	41.8 (26, 55)
Sex, n (%)	
Female	9 (30)
Male	21 (70)
Ethnicity, n (%)	
Hispanic or Latino	15 (50)
Not Hispanic or Latino	15 (50)
Race, n (%)	
American Indian or Alaskan Native	1 (3.3)
Asian	0
Black or African American	9 (30)
Native Hawaiian/Other Pacific Islander	0
White	20 (66.7)
Multiple races	0
Height, mean (SD), cm	171.04 (8.347)
Weight, mean (SD), kg	77.69 (9.709)
BMI, mean (SD), kg/m^2	26.49 (2.028)

[a]Once-daily ER lorazepam (4 mg) sprinkled on soft food, given as an intact capsule, or given as 4 x 1 mg capsules.
BMI=body mass index; ER=extended-release; max=maximum; min=minimum; SD=standard deviation.

Pharmacokinetic Results

- Overall, PK parameters including median T_{max}, mean C_{max}, AUC_{0-t}, AUC_{0-inf}, and $t_{1/2}$ were similar for once-daily 4 mg (total daily dose) ER lorazepam regardless of being sprinkled on food, given intact, or given as 4 x 1 mg capsules (**Figure 1 and Figure 2**, **Table 3**)
- The T_{max} was approximately 11 hours across treatments (**Table 3**)
- Mean plasma concentration-time profiles were similar when once-daily 4 mg ER lorazepam was administered intact versus sprinkled on soft food (**Figure 1**, **Table 3**), and the 90% confidence intervals (CIs) of the geometric mean ratios for C_{max}, AUC_{0-t}, and AUC_{0-inf} were within the bioequivalence limits of 80.00-125.00% (**Table 4**)
  - Administration of once-daily ER lorazepam sprinkled on food did not have a significant effect on bioavailability

Figure 1. Mean Lorazepam Plasma Concentration-Time Profiles Are Nearly Superimposable for Once-Daily ER Lorazepam (4 mg) Sprinkled on Soft Food or Given Intact, Plotted on Linear (A) and Semi-Logarithmic (B) Scales

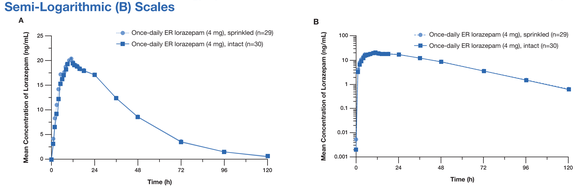

Table 3. Pharmacokinetic Parameters of Once-Daily ER Lorazepam Sprinkled on Soft Food, or Given Intact as Either 1 x 4 mg or 4 x 1 mg Capsules

Parameter, mean (SD) unless otherwise noted	Sprinkled (4 mg) (n=29)	Intact (1 x 4 mg) (n=30)	Intact (4 x 1 mg) (n=29)
T_{max}, median (range), h	11.00 (5.01-24.01)	11.01 (5.01-24.01)	11.01 (8.00-24.00)
T_{lag}, h	0.00 (0)	0.00 (0)	0.00 (0)
C_{max}, ng/mL	21.03 (4.40)	20.98 (4.06)	20.86 (5.03)
AUC_{0-t}, h*ng/mL	930.37 (311.86)	920.84 (309.35)	927.21 (333.32)
AUC_{0-inf}, h*ng/mL	949.52 (331.53)	939.13 (327.49)	948.65 (356.59)
K_{el}, L/h	0.04191 (0.01013)	0.04206 (0.008814)	0.04116 (0.01026)
$t_{1/2}$, h	17.41 (3.90)	17.19 (3.61)	17.83 (4.31)
CL/F, L/h	4.70 (1.54)	4.75 (1.55)	4.78 (1.70)
Vz/F, L	110.56 (18.13)	111.19 (20.41)	115.07 (27.01)

AUC=area under the concentration-time curve for time 0 to the last quantifiable concentration (AUC_{0-t}), 0 to infinity (AUC_{0-inf}), or AUC_{0-tau} based on extrapolation; C_{max}=maximum plasma concentration; CL/F=apparent total plasma clearance; ER=extended-release; K_{el}=terminal elimination rate constant; SD=standard deviation; $t_{1/2}$=terminal half-life; T_{lag}=time prior to the first measurable (non-zero) concentration; T_{max}=time to reach C_{max}; Vz/F=apparent volume of distribution.

- Likewise, virtually superimposable mean plasma concentration-time profiles were obtained for once-daily ER lorazepam administered as either 1 x 4 mg or 4 x 1 mg capsules (**Figure 2**), and the 90% CIs of the geometric mean ratios for C_{max}, AUC_{0-t}, and AUC_{0-inf} were also within the bioequivalence limits of 80.00-125.00% (98.89% [94.85-103.09%], 99.83% [96.63-103.13%], and 100.02% [96.83-103.32%], respectively) (**Table 4**)
  - Administration of once-daily ER lorazepam as either 1 x 4 mg or 4 x 1 mg capsules were found to be bioequivalent doses

Figure 2. Mean Plasma Concentration-Time Profiles Are Nearly Superimposable for Once-Daily ER Lorazepam Given 1 x 4 mg or 4 x 1 mg (Both Intact), Plotted on Linear (A) and Semi-Logarithmic (B) Scales

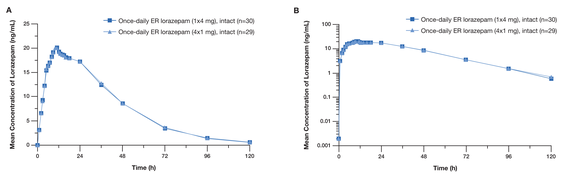

Table 4. Statistical Analysis of the Log-Transformed Systemic Exposure Parameters for Once-Daily ER Lorazepam Sprinkled on Soft Food, Given Intact (1 x 4 mg), or Given as 4 x 1 mg Intact Capsules

PK Parameter, Natural Log-transformed exposure	Geometric Mean: Sprinkled (4 mg) (n=29)	Intact (4 mg) (n=29)	Ratio (Sprinkled/Intact, %)	90% CI	ANOVA CV%
C_{max}	20.54	20.52	100.12	95.74 – 104.69	9.99
AUC_{last}	878.66	869.59	101.04	96.57 – 105.73	10.13
AUC_{inf}	893.16	883.75	101.06	96.53 – 105.81	10.26
	Intact (1 x 4 mg) (n=29)	**Intact (4 x 1 mg) (n=29)**	**Ratio (1 x 4 mg/4 x 1 mg, %)**	**90% CI**	**ANOVA CV%**
C_{max}	20.26	20.49	98.89	94.85 – 103.09	9.30
AUC_{last}	866.87	868.36	99.83	96.63 – 103.13	7.28
AUC_{inf}	882.70	882.51	100.02	96.83 – 103.32	7.24

ANOVA=analysis of variance; AUC=area under the concentration-time curve for last quantifiable concentration (AUC_{last}), 0-infinity (AUC_{inf}); CI=confidence interval; C_{max}=maximum plasma concentration; CV%=coefficient of variation; ER=extended-release; PK=pharmacokinetic.

Safety Results

- There were no serious AEs (SAEs) that led to death, although one reported AE (oral herpes, considered unlikely related to treatment) led to study withdrawal (**Table 5**)
- The most frequently reported AE was somnolence: n=5 (16.7%) overall subjects, with three following sprinkled dosing, one following intact 1 x 4 mg dosing, and one following 4 x 1 mg dosing
  - Additionally, two (6.7%) subjects reported dizziness and two (6.7%) subjects reported headache after intact 1 x 4 mg ER lorazepam, and two (6.9%) subjects experienced nausea after sprinkled ER lorazepam
- A total of 16 treatment-emergent AEs (TEAEs) were reported by 12 participants over the course of the study, all of which were mild in severity
  - 7 AEs were reported by 5 (17.2%) subjects following 4 mg ER lorazepam sprinkled on soft food, 7 AEs by 7 (23.3%) subjects following 4 mg ER intact capsules, and 2 AEs by 2 (6.9%) subjects following 4 x 1 mg ER intact capsules
- No clinically significant abnormalities in ECGs or vital signs were found, although there was one clinically significant physical examination finding (the case of oral herpes noted above, unrelated to treatment)

Table 5. Safety Overview: Safety Population

Adverse Events	Overall (N=30)	Sprinkled (4 mg) (n=29)	Intact (1 x 4 mg) (n=30)	Intact (4 x 1 mg) (n=29)
All TEAEs, n (%)	12 (40.0)	5 (17.2)	7 (23.3)	2 (6.9)
Most frequently reported TEAEs (n ≥2), n (%) m				
Somnolence	5 (16.7) 5	3 (10.3) 3	1 (3.3) 1	1 (3.4) 1
Dizziness	2 (6.7) 2	0	2 (6.7) 2	0
Headache	2 (6.7) 2	0	2 (6.7) 2	0
Nausea	2 (6.7) 2	2 (6.9) 2	0	0
TEAEs by severity, n (%)				
Mild	12 (40.0)	5 (17.2)	7 (23.3)	2 (6.9)
Moderate	0	0	0	0
Severe	0	0	0	0
TEAEs by relationship, n (%)				
Related to study drug	11 (36.7)	5 (17.2)	6 (20.0)	2 (6.9)
Not related	2 (6.7)	1 (3.4)	1 (3.3)	0
SAEs, n (%)	0	0	0	0
Related SAEs, n (%)	0	0	0	0
TEAEs leading to study withdrawal, n (%)	1 (3.3)	0	1 (3.3)	0

ER=extended-release; m=number of events; N/n=number of subjects; SAE=serious adverse event; TEAE=treatment-emergent adverse event.

CONCLUSIONS

- The PK profiles, including median T_{max} values, were similar across treatments in healthy adults
- Once-daily ER lorazepam (4 mg) sprinkled on soft food was found to be bioequivalent to the intact capsule
- ER lorazepam given as either one 4 mg or four 1 mg capsules showed dose proportionality and bioequivalence in healthy adults
- The most frequently reported AE across treatments overall was somnolence
- Once-daily ER lorazepam had a favorable safety profile across all treatments, suggesting that overall, ER lorazepam can provide well-tolerated flexible dosing options

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AUTHOR DISCLOSURES

S Jean-Lys, R Phull, and R Yarasani are employees of or associated with Alvogen PB Research & Development LLC. E Roers and PH Fackler are former employees of Alvogen PB Research & Development LLC.

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