EFFECT OF FOOD, DOSE PROPORTIONALITY, AND PRODUCT SPRINKLING ON THE PHARMACOKINETICS OF ONCE-DAILY EXTENDED-RELEASE LORAZEPAM

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BACKGROUND

- Anxiety is a highly prevalent disorder associated with significant functional impairment, family and patient burden, and increased utilization of healthcare services[1-4]
- Lorazepam is an allosteric gamma-aminobutyric acid (GABA) receptor modulator (part of the benzodiazepine class) and is traditionally administered as an immediate-release (IR) formulation two or three times daily for the short-term treatment of anxiety, with doses ranging from 1 to 10 mg/day[5-7]
- There is a need for an extended-release (ER) option providing more consistent lorazepam levels throughout the day, in order to reduce rebound anxiety and potentially improve tolerability[8]
- Further, an important characteristic of an anxiolytic is the ability to be administered with or without food for both flexibility of dosing and tolerability.[9,10] Some patients, particularly the elderly, also have difficulty swallowing solid oral dosage formulations and may require their medication sprinkled on food[11-13]
- ER lorazepam is a once-daily formulation developed to administer more consistent lorazepam levels that was approved by the US Food and Drug Administration (FDA) in August 2021 for the treatment of anxiety in adults already receiving evenly divided, thrice-daily dosing of lorazepam IR tablets[14,15]
- Here we report the results of two Phase 1, randomized, open-label, crossover PK studies evaluating the effect of (Study 1) food; and (Study 2) administration as a single 4 mg dose sprinkled onto soft food, an intact 4 mg capsule, or as four 1 mg intact capsules on the bioavailability of once-daily ER lorazepam in healthy adults

OBJECTIVES

- The primary objective of Study 1 compared the PK profile of once-daily ER lorazepam (4 mg) under both fasted and fed conditions in healthy adults
- The primary objective of Study 2 evaluated the PK profile of ER lorazepam (4 mg) when sprinkled on soft food compared to intact capsules, as well as the dose proportionality of one 4 mg capsule vs four 1 mg capsules in healthy adults
- Secondary objectives across both studies evaluated the safety and tolerability of ER lorazepam

METHODS

Study Design

- After a 28-day screening period, healthy subjects fasted for 10 hours and were randomized to their treatment sequence (**Table 1**), with each dosing period separated by a 10-day washout

Table 1. ER Lorazepam Treatment Sequences for Studies 1 and 2

Study 1: AB or BA	Study 2: ABC, BCA, CAB, CBA, ACB, or BAC
Treatment A: 4 mg, fasted condition	**Treatment A:** 4 mg sprinkled on soft food (applesauce)
Treatment B: 4 mg, fed condition: FDA-standard high-fat, high-calorie breakfast 30 minutes prior to dose	**Treatment B:** 1 x 4 mg given intact
	Treatment C: 4 x 1 mg given intact

Pharmacokinetic Measurements

- Plasma PK parameters were assessed after each dose, with blood samples taken according to **Table 2** and plasma lorazepam concentrations measured by liquid chromatography with tandem mass spectrometry (LC-MS/MS)

Table 2. Schedule of Blood Draws to Assess Plasma Concentration of Lorazepam

Treatment Group	Timing of Blood Draws [hour(s)]
Study 1 and Study 2 (All treatments)	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, vital sign measurements, clinical laboratory evaluations, and electrocardiograms (ECGs) for both studies

RESULTS

Demographics and Characteristics

- Twenty-eight (28) subjects were enrolled in Study 1, with 27 subjects completing both study periods. One subject withdrew consent for reasons unrelated to AEs
- Thirty (30) subjects were enrolled in Study 2, with 29 completing all study periods (**Table 3**)

Table 3. Key Demographics and Characteristics of Subjects in Studies 1 and 2

Parameter	Study 1 Overall[a] (N=28)	Study 2 Overall[b] (N=30)
Age, mean (min, max), years	35.5 (18, 54)	41.8 (26, 55)
Sex, n (%)		
Female	9 (32.1)	9 (30)
Male	19 (67.9)	21 (70)
Ethnicity, n (%)		
Hispanic or Latino	15 (53.6)	15 (50)
Not Hispanic or Latino	13 (46.4)	15 (50)
Race, n (%)		
American Indian or Alaskan Native	0 (0)	1 (3.3)
Asian	0 (0)	0
Black or African American	9 (32.1)	9 (30)
Native Hawaiian/Other Pacific Islander	0 (0)	0
White	19 (67.9)	20 (66.7)
Multiple races	0 (0)	0
Height, mean (SD), cm	169.58 (9.333)	171.04 (8.347)
Weight, mean (SD), kg	77.58 (11.262)	77.69 (9.709)
BMI, mean (SD), kg/m^2	26.88 (2.170)	26.49 (2.028)

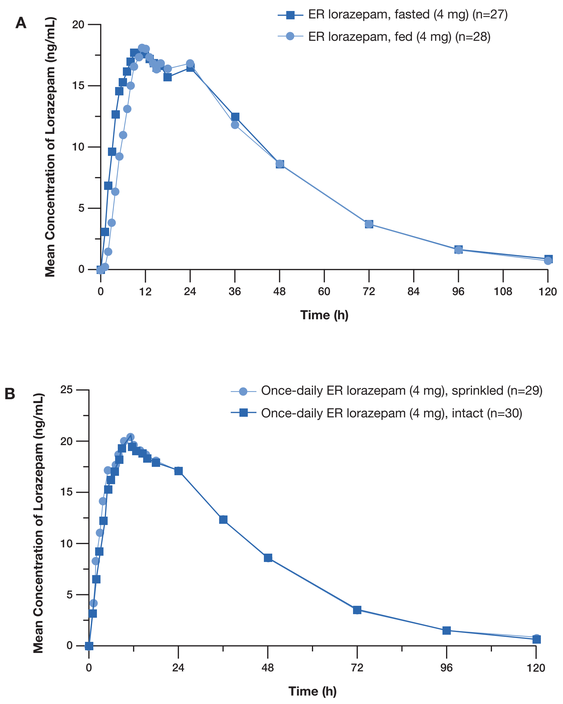
[a]ER lorazepam 4 mg once daily under fasted and fed conditions.

[b]ER lorazepam 4 mg once daily 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

Figure 1. Mean Plasma Concentration-Time Profiles of Once-Daily ER Lorazepam 4 mg (A) Under Fasted and Fed Conditions, (B) Sprinkled Over Food or Taken as an Intact Capsule, and (C) Given as 1 x 4 mg or 4 x 1 mg Capsules



- Mean PK parameters were similar across all treatment conditions in both Study 1 and Study 2 with once-daily ER lorazepam, although administration with food delayed the median T_{max} by ~2 hours (**Figure 1, Table 4**)
  - The geometric mean ratios [90% CI] for C_{max}, AUC_{inf} or $AUC_{0\text{-}inf}$, and AUC_{last} or $AUC_{0\text{-}t}$ between each condition were within bioequivalence limits of 80.00-125.00% in both studies
- Food or sprinkle administration did not have a significant effect on the bioavailability of ER lorazepam, and 1 x 4 mg and 4 x 1 mg dose forms were found to be bioequivalent

Table 4. PK Parameters of Once-Daily ER Lorazepam (4 mg) Across Studies 1 and 2

Parameter, mean (SD) unless otherwise noted	Study 1		Study 2		
	Fasted (n=27)	Fed (n=28)	Sprinkled (4 mg) (n=29)	Intact (1 x 4 mg) (n=30)	Intact (4 x 1 mg) (n=29)
T_{max}, median (range), h	10.00 (6.00-24.20)	11.99 (8.00-24.00)	11.00 (5.01-24.01)	11.01 (5.01-24.01)	11.01 (8.00-24.00)
T_{lag}, h	0.00 (0.00)	0.14 (0.45)	0.00 (0)	0.00 (0)	0.00 (0)
C_{max}, ng/mL	19.20 (5.11)	19.58 (3.24)	21.03 (4.40)	20.98 (4.06)	20.86 (5.03)
$AUC_{0\text{-}24}$, h*ng/mL	353.50 (92.50)	323.99 (53.96)	930.37 (311.86)[a]	920.84 (309.35)[a]	927.21 (333.32)[a]
AUC_{inf}, h*ng/mL[b]	936.89 (386.66)	895.25 (329.57)	949.52 (331.53)[a]	939.13 (327.49)[a]	948.65 (356.59)[a]
K_{el}, 1/h[b]	0.0442 (0.0142)	0.0443 (0.0131)	0.04191 (0.01013)	0.04206 (0.008814)	0.04116 (0.01026)
$t_{1/2}$, h[b]	17.59 (6.68)	17.38 (6.64)	17.41 (3.90)	17.19 (3.61)	17.83 (4.31)
CL/F, L/h[b]	5.04 (2.16)	5.09 (1.90)	4.70 (1.54)	4.75 (1.55)	4.78 (1.70)
Vz/F, L[b]	112.93 (23.65)	114.38 (18.80)	110.56 (18.13)	111.19 (20.41)	115.07 (27.01)

[a]$AUC_{0\text{-}t}$, and $AUC_{0\text{-}inf}$, respectively.

[b]n for these values was 26.

AUC=area under the concentration-time curve for 0-24 ($AUC_{0\text{-}24}$), 0-infinity (AUC_{inf}); C_{max}=maximum plasma concentration; CL/F=apparent total plasma clearance; ER=extended-release; K_{el}=terminal elimination rate constant; PK=pharmacokinetic; SD=standard deviation; $t_{1/2}$=terminal half-life; T_{max}=time to reach C_{max}; T_{lag}=time prior to the first measurable (non-zero) concentration; Vz/F=apparent volume of distribution.

Safety Results

- In Study 1, there were no serious AEs (SAEs) or AEs that led to study withdrawal or death (**Table 5**)
  - ER lorazepam given with food was well tolerated, with the most frequently reported TEAEs being headache (3.7% fasted and 3.6% fed) and somnolence (7.4% fasted, 0 fed)
- In Study 2, there were no SAEs that led to death, although one AE led to study withdrawal (oral herpes, considered unlikely related to treatment) (**Table 5**)
  - The most frequently reported TEAEs included somnolence (10.3%, 3.3%, 3.4%), dizziness (0%, 6.7%, 0%), headache (0%, 6.7%, 0%), and nausea (6.9%, 0%, 0%) across sprinkled, intact, and 4 x 1 mg doses, respectively
- No clinically significant abnormalities in ECGs or vital signs were reported in either Study 1 or Study 2, although there was one clinically significant physical examination finding in Study 2 (the noted case of oral herpes)

Table 5. Safety Overview for Studies 1 and 2, Safety Populations

Adverse Events	Study 1		Study 2		
	Fasted (4 mg) (n=27)	Fed (4 mg) (n=28)	Sprinkled (4 mg) (n=29)	Intact (1 x 4 mg) (n=30)	Intact (4 x 1 mg) (n=30)
All TEAEs, n (%)	4 (14.8)	4 (14.3)	5 (17.2)	7 (23.3)	2 (6.9)
TEAEs by severity, n (%)					
Mild	3 (11.1)	3 (10.7)	5 (17.2)	7 (23.3)	2 (6.9)
Moderate	1 (3.7)	1 (3.6)	0	0	0
Severe	0	0	0	0	0
TEAEs by relationship, n (%)[a]					
Related to study drug	3 (11.1)	3 (10.7)	5 (17.2)	6 (20.0)	2 (6.9)
Not related	1 (3.7)	1 (3.6)	1 (3.4)	1 (3.3)	0
SAEs, n (%)	0	0	0	0	0
TEAEs leading to study withdrawal, n (%)	0	0	0	1 (3.3)	0

[a]Subjects were counted twice if they experienced both a related and an unrelated TEAE.
n=number of subjects; SAE=serious adverse event; TEAE=treatment-emergent adverse event.

CONCLUSIONS

- Once-daily ER lorazepam achieved a similar PK profile regardless of dosing modality, although food delayed median T_{max} by approximately 2 hours in Study 1
- PK parameters (C_{max}, AUC_{last}, and AUC_{inf}) of once-daily ER lorazepam were within bioequivalence limits of 80.00-125.00% under fasted or fed conditions, given sprinkled or intact, or as 1 x 4 mg vs 4 x 1 mg doses
  - This suggests there is no impact of food or sprinkling administration on the bioavailability of ER lorazepam
- Overall, once-daily ER lorazepam (4 mg) was well tolerated in healthy adults, whether it was given with or without food, sprinkled or intact, or as four 1 mg capsules

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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. SJ Mathew has served as a consultant to Allergan, Alkermes, Almatica Pharma, Axsome Therapeutics, Biohaven Pharmaceuticals, BioXcel Therapeutics, Clexio Biosciences, COMPASS Pathways, Eleusis, EMA Wellness, Engrail Therapeutics, Greenwich Biosciences, Intra-Cellular Therapies, Janssen, Levo Therapeutics, Neumora, Neurocrine, Perception Neuroscience, Praxis Precision Medicines, Relmada Therapeutics, Sage Therapeutics, Seelos Therapeutics, Signant Health, and Sunovion. He has received research support from Biohaven Pharmaceuticals, Boehringer Ingelheim, Janssen, Merck, Sage Therapeutics, and VistaGen Therapeutics.

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