BIOEQUIVALENCE OF ONCE-DAILY EXTENDED-RELEASE LORAZEPAM COMPARED TO THRICE-DAILY IMMEDIATE-RELEASE LORAZEPAM

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BACKGROUND

- Anxiety disorders are among the most frequently occurring psychiatric disorders, with ~8% of adults in the United States being diagnosed with generalized anxiety disorder in their lifetime and a cumulative 20-30% prevalence of anxiety disorders among older adolescents/young adults[1-3]
- Anxiety can significantly affect a patient's quality of life and can contribute to functional impairment, patient and family burden, and increased utilization of healthcare services[3-5]
- Lorazepam is a member of the benzodiazepine class of allosteric gamma-aminobutyric acid (GABA)-receptor modulators, a key therapeutic target in anxiety disorders,[6,7] and it first received US Food and Drug Administration (FDA) approval in 1977 as an immediate-release (IR) formulation for the short-term treatment of anxiety[7]
- IR lorazepam is usually prescribed at doses ranging from 1 to 6 mg/day administered two to three times daily for anxiety, with a total daily dose of up to 10 mg[7-9]
- There is a need for an extended-release (ER) formulation of lorazepam to deliver improved, consistent serum concentrations throughout the day, leading to a reduction in rebound anxiety, adverse events, and treatment burden for patients[10]
- ER lorazepam received FDA approval in August 2021[11] for the treatment of anxiety disorders in adults who are currently taking evenly divided IR lorazepam three times daily[12]
- Here we report results of a Phase 1, randomized, open-label, two-treatment, multiple-dose crossover PK study comparing the steady-state bioavailability and safety of once-daily ER lorazepam (3 mg) to that of IR lorazepam (1 mg) administered thrice daily every 8 hours (q8h) in healthy adults for 8 consecutive days

OBJECTIVES

- The primary objective of this study was to compare the steady-state PK profile of once-daily (qd) 3 mg ER lorazepam to that of 1 mg IR lorazepam given q8h
- The secondary objective of this study was to evaluate the safety of once-daily ER lorazepam and IR lorazepam q8h

METHODS

Study Design

- Subjects received two separate multiple-dose administrations of Treatment A (ER lorazepam, 3 mg) qd or Treatment B (IR lorazepam, 1 mg) q8h
  - Subjects were randomized to one of the two treatment sequences, AB or BA (i.e., ER-IR or IR-ER)
  - Subjects switched to the next treatment period following a washout of at least 10 days and continued on that treatment for another 8 days
  - All subjects fasted overnight for at least 8 hours before each morning (0 hour) dose. On days 1-7, subjects received a light breakfast approximately 2 hours after the morning dose. On Day 8, subjects fasted for at least 4 hours after the morning dose
  - Subjects receiving Treatment B (q8h) received the evening meal at least 2 hours after the second (8-hour) dose and a snack at least 2.5 hours before the third (16-hour) dose

Pharmacokinetic Measurements

- For each assigned treatment in periods 1 and 2, blood samples were obtained on days 5-8 according to the schedule in **Table 1**, with plasma lorazepam concentrations measured by a validated liquid chromatography with tandem mass spectrometry method (LC-MS/MS)

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

Treatment Group	Timing of Blood Draws [hour(s)]	
	Day 5, 6, and 7	Day 8
Treatment A: ER lorazepam qd	0 (pre-dose)	0 (pre-dose), 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
Treatment B: IR lorazepam q8h	0 (pre-dose 1)	0 (pre-dose 1), 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8 (pre-dose 2), 8.5, 9, 9.5, 10, 11, 12, 14, 16 (pre-dose 3), 16.5, 17, 17.5, 18, 19, 20, 22, 24, 30, 36, 48, 72, 96, and 120 post-dose

ER=extended-release; IR=immediate-release; q8h=every 8 hours; qd=once daily.

Safety Assessments

- Safety assessments included monitoring of adverse events (AEs) as well as physical examinations, vital sign measurements, clinical laboratory evaluations, electrocardiograms, and the Columbia-Suicide Severity Rating Scale

RESULTS

Demographics and Characteristics

- A total of 46 subjects participated in the study; 43 completed both study periods (3 withdrew early in the study for reasons unrelated to AEs)
- The study population included healthy female (12) and male (34) adults, 22 to 55 years of age, ranging in body mass index (BMI) from 20.3 to 29.9 kg/m^2, and weighing between 61.1 and 97.2 kg (**Table 2**)
- Of the study population, 46% were of Hispanic or Latino ethnicity, 37% were Black or African American, 57% were White, and 4% were Asian (**Table 2**)

Table 2. Key Demographics and Characteristics of Subjects

Demographics and Characteristics	Overall (N=46)	ER to IR[a] lorazepam (n=23)	IR to ER[a] lorazepam (n=23)
Age, mean (min, max), years	38.4 (22, 55)	38.7 (28, 54)	38.1 (22, 55)
Sex, n (%)			
Female	12 (26.1)	6 (26.1)	6 (26.1)
Male	34 (73.9)	17 (73.9)	17 (73.9)
Ethnicity, n (%)			
Hispanic or Latino	21 (45.7)	10 (43.5)	11 (47.8)
Not Hispanic or Latino	25 (54.3)	13 (56.5)	12 (52.2)
Race, n (%)			
American Indian or Alaskan Native	1 (2.2)	0	1 (4.3)
Asian	2 (4.3)	1 (4.3)	1 (4.3)
Black or African American	17 (37.0)	8 (34.8)	9 (39.1)
Native Hawaiian/Other Pacific Islander	0	0	0
White	26 (56.5)	14 (60.9)	12 (52.2)
Multiple races	0	0	0
Height, mean (SD), cm	169.34 (8.731)	168.89 (9.539)	169.79 (8.031)
Weight, mean (SD), kg	75.11 (9.481)	76.64 (10.218)	73.58 (8.634)
BMI, mean (SD), kg/m^2	26.16 (2.343)	26.80 (2.251)	25.52 (2.301)

[a]ER lorazepam administered as 3 mg dose qd, IR lorazepam as 1 mg dose q8h.

BMI=body mass index; ER=extended-release; IR=immediate-release; max=maximum; min=minimum; q8h=every 8 hours; qd=once daily; SD=standard deviation.

Pharmacokinetic Results

- Mean lorazepam plasma concentrations were similar throughout the 24-hour sampling window on Day 8 for subjects treated with once-daily ER lorazepam and IR lorazepam q8h, and 90% confidence intervals for lorazepam $C_{max,SS}$, C_{min}, and $AUC_{TAU,SS}$ were within 80.00-125.00% (**Figure 1, Table 3**)
- Maximum mean (± standard deviation) concentrations were achieved at 11 hours post-dose for the ER formulation (33.02 ± 9.83 ng/mL) compared to 1 hour post-dose for the IR formulation (39.30 ± 12.69 ng/mL)
  - Subjects treated with IR lorazepam q8h showed three peaks in lorazepam concentrations, corresponding to the timing of each of the thrice-daily doses (**Figure 1**)
- Mean trough lorazepam concentrations were similar across days 5, 6, 7, and 8 for both treatments, but were slightly higher following IR lorazepam than with ER lorazepam (**Figure 2**)

Figure 1. Mean Plasma Concentration-Time Profiles of Once-Daily ER Lorazepam Compared to IR Lorazepam q8h on Day 8 on Linear Scale

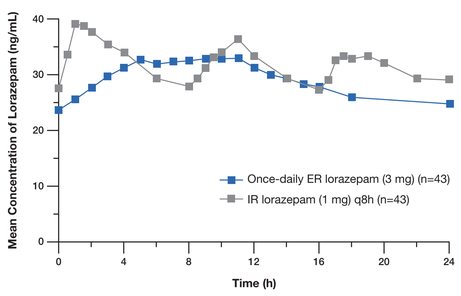
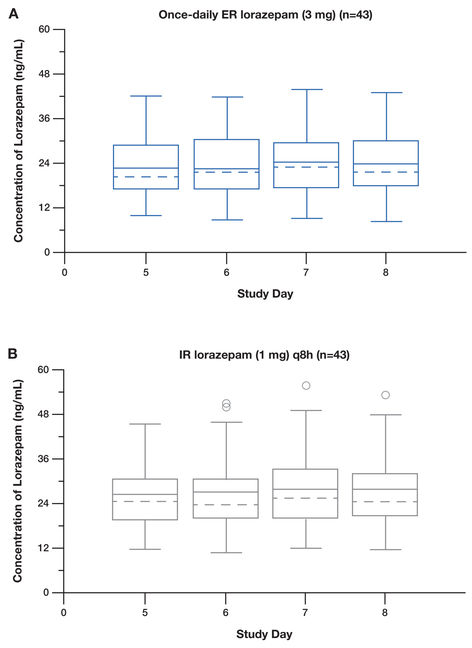


Figure 2. Box Plots of Pre-dose Plasma Lorazepam Concentrations on Days 5, 6, 7, and 8 Showing Similar Levels for Both ER Lorazepam and IR Lorazepam



Dashed line=Mean; Solid line=Average; Box=Upper and Lower Quartiles; Whiskers=5% and 95% percentiles; Circle=Outlier.

Table 3. Pharmacokinetic Parameters of Lorazepam After Multiple Doses of Once-Daily ER Lorazepam and IR Lorazepam q8h on Day 8

Parameter, mean (SD) unless otherwise noted	ER lorazepam[a] qd (n=43)	IR lorazepam[a] q8h (n=43)
$T_{max,SS}$, median (range), h	9.00 (4.00-14.0)	1.5 (0.770-3.01)
$C_{max,SS}$, ng/mL	35.26 (10.0)	40.70 (12.91)
C_{min}, ng/mL	24.75 (8.82)	29.11 (11.17)
C_{av}, ng/mL	28.92 (9.12)	31.87 (10.18)
$AUC_{TAU,SS}$, h*ng/mL	694.17 (218.91)	264.30 (85.05)
AUC_{0-24}, h*ng/mL	694.17 (218.91)	764.96 (244.44)
K_{el}, 1/h	0.0405 (0.00831)	0.0414 (0.00898)
$t_{1/2}$, h	17.81 (3.63)	17.61 (4.33)
Flu, % [($C_{max,SS}$ - C_{min})/C_{av}][b]	38.12 (12.93)	38.30 (11.97)
Swing, % ($C_{max,SS}$ - $C_{min,SS}$)/$C_{min,SS}$)	47.0 (21.0)	44.0 (16.0)
CL_{SS}/F, L/h	4.75 (1.51)	4.28 (1.24)
Vz/F, L	115.95 (21.62)	102.57 (14.60)

[a]ER lorazepam administered as 3 mg dose qd, IR lorazepam as 1 mg dose q8h. [b]$C_{max,SS}$ and C_{min} obtained between time 0 and tau, where tau=24 hours on Day 8.

AUC_{0-24}=area under the concentration-time curve from time 0 to 24; $AUC_{TAU,SS}$=area under the concentration-time curve from time zero to tau (24-hours post-dose); C_{av}=average plasma concentration; $C_{max,SS}$=maximum plasma concentration at steady state; $C_{min,SS}$=minimum plasma concentration at steady state; CL_{SS}/F=apparent total plasma clearance at steady state; ER=extended-release; Flu=fluctuation; IR=immediate-release; K_{el}=terminal elimination rate constant; q8h=every 8 hours; qd=once daily; SD=standard deviation; $t_{1/2}$=terminal half-life; $T_{max,SS}$=time to reach C_{max} at steady state; Vz/F=apparent volume of distribution.

Safety Results

- There were no reported serious AEs (SAEs) or AEs that led to death or withdrawal from the study
- 26 subjects reported 74 treatment-emergent AEs (TEAEs) during the study: 36 TEAEs were reported by 19 subjects on ER lorazepam qd and 38 TEAEs were reported by 20 subjects on IR lorazepam q8h (**Table 4**)
- The most frequently reported TEAEs (n ≥5 subjects overall) were constipation (26.1%), headache (15.2%), dizziness (10.9%), and insomnia (10.9%), with most TEAEs being mild in severity
- No clinically significant abnormalities in physical examinations or ECGs, or incidents of suicidality were reported

Table 4. Safety Overview: Safety Population

Adverse Events	Overall[a] (N=46)	ER lorazepam[b] qd (n=46)	IR lorazepam[b] q8h (n=46)
All AEs	26 (56.5)	19 (41.3)	20 (43.5)
All TEAEs, n (%)	26 (56.5)	19 (41.3)	20 (43.5)
Most frequently reported TEAEs (n ≥5), n (%) m			
Constipation	12 (26.1) 19	6 (13.0) 6	10 (21.7) 13
Headache	7 (15.2) 9	3 (6.5) 3	4 (8.7) 6
Dizziness	5 (10.9) 5	4 (8.7) 4	1 (2.2) 1
Insomnia	5 (10.9) 6	3 (6.5) 4	2 (4.3) 2
TEAEs by severity, n (%)			
Mild	15 (32.6)	15 (32.6)	12 (26.1)
Moderate	11 (23.9)	4 (8.7)	8 (17.4)
Severe	0	0	0
TEAEs by relationship, n (%)[c]			
Related to study drug	21 (45.7)	14 (30.4)	16 (34.8)
Not related	15 (32.6)	9 (19.6)	10 (21.7)
SAEs, n (%)	0	0	0
TEAEs leading to study withdrawal, n (%)	0	0	0

[a]Overall values reported for individual subjects experiencing an AE during either or both treatment periods. [b]ER lorazepam administered as 3 mg dose qd, IR lorazepam as 1 mg dose q8h. [c]Subjects were counted twice if they experienced both a related and an unrelated TEAE.

AE=adverse event; ER=extended-release; IR=immediate-release; m=number of events; n=number of subjects; q8h=every 8 hours; qd=once daily; SAE=serious adverse event; TEAE=treatment-emergent adverse event.

CONCLUSIONS

- Steady state was achieved for both treatments on Day 5, and the 90% confidence intervals for lorazepam $C_{max,SS}$, C_{min}, and $AUC_{TAU,SS}$ were within the 80.00%-125.00% limits for evaluating steady-state bioequivalence
  - These results show that once-daily ER lorazepam is bioequivalent to IR lorazepam q8h
- ER lorazepam administered once daily demonstrated a favorable safety profile in this population of healthy adults
  - The most frequently reported TEAEs were constipation, headache, dizziness, and insomnia
- These data suggest that once-daily ER lorazepam is well tolerated and can provide a more stable PK profile with less fluctuation compared to IR lorazepam q8h

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AUTHOR DISCLOSURES

R Phull, S Jean-Lys, 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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