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

Rupinder Phull, PhD[1]; Shedly Jean-Lys, MS[1]; Erika Roers, BS[2]; Paul H. Fackler, PhD[2]; Rama Yarasani, PhD[1]

[1]Employee of Alvogen PB Research & Development LLC; [2]Former employee of Alvogen PB Research & Development LLC

BACKGROUND

- Anxiety disorders are the most common class of psychiatric disorders, with a lifetime prevalence of 32% in the United States[1,2]
- Patients with anxiety often experience a severe impact on their quality of life, functional impairment, patient and family burden, and increased utilization of healthcare services[2-4]
- Benzodiazepines are a class of small molecules that allosterically modulate the activity of the gamma-aminobutyric acid (GABA) receptor in the central nervous system, an important therapeutic target for anxiety disorders[5]
- One such benzodiazepine, lorazepam, first received US Food and Drug Administration approval in 1977 as an immediate-release (IR) formulation for the short-term treatment of anxiety[6]
- IR lorazepam provides short-term anxiety relief at doses usually ranging from 2 to 6 mg/day given in divided doses two to three times daily, but the daily dose can sometimes vary from 1 to 10 mg/day[6,7]
- There exists a need for an extended-release (ER) formulation of lorazepam that would deliver more consistent serum lorazepam concentrations throughout the day, thereby reducing rebound anxiety, adverse events, and pill burden on patients[8]
- ER lorazepam was approved in August 2021[9] for the treatment of anxiety disorders in adults who are receiving stable, evenly divided, thrice-daily dosing of lorazepam IR tablets[10]
- As part of the clinical development of ER lorazepam, four pharmacokinetic (PK) studies have been conducted evaluating the PK profile and safety of ER lorazepam
- Here we report findings from a Phase 1, randomized, open-label, two-period, two-sequence, two-treatment, multiple-dose crossover PK study assessing the steady-state safety and relative bioavailability of once-daily ER lorazepam (4 mg) compared to IR lorazepam (2 mg) administered twice daily every 12 hours (q12h) in healthy adults

OBJECTIVES

- The primary objective of this study was to compare the steady-state PK profile of once-daily (qd) 4 mg ER lorazepam to that of 2 mg IR lorazepam q12h
  - **Primary endpoints:**
    - Maximum and minimum observed steady-state plasma concentration of lorazepam on Day 7 (C_{maxSS}, C_{minSS})
    - Area under the concentration-time curve from time zero to tau (24 hours post-dose for qd dose, 12 hours post-dose for first and second bid doses) on Day 7 (AUC_{TAU})
- The secondary objective of this study was to evaluate the safety of once-daily ER lorazepam and IR lorazepam q12h

METHODS

Study Design

- Subjects received Treatment A (ER lorazepam, 4 mg) qd for 7 days and Treatment B (IR lorazepam, 2 mg) q12h for 7 days as 4 mg total daily dose
  - Subjects were randomized to one of the two treatment sequences, AB or BA (i.e., ER-IR or IR-ER)
  - Subjects followed assigned treatment for 7 days in Period 1 before switching overnight to their Period 2 alternate 4 mg total daily dose treatment without a washout or titration, and continued multiple dosing for 7 days
  - All subjects fasted overnight for at least 8 hours before each morning dose (0 hour). On Day 7, subjects fasted for at least 4 hours after the morning dose, on days 1-5 and 8-12, subjects received a light breakfast approximately 2 hours after the morning dose

Pharmacokinetic Measurements

- For each assigned treatment in periods 1 and 2, blood samples were obtained on days 5-7 (timing according to **Table 1**), with plasma lorazepam concentrations measured by a validated liquid chromatography with tandem mass spectrometry method (LC-MS/MS)

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

Treatment Group	Timing of Blood Draws [hour(s)]	
	Days 5 and 6	Day 7
Treatment A: ER lorazepam qd	24 post-dose	0 (pre-dose), and 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 18, and 24 post-dose
Treatment B: IR lorazepam q12h	24 post-AM dose	0 (pre-dose), and 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 10, 12, 12.5, 13, 13.5, 14, 15, 16, 17, 18, 20, 22, and 24 post-dose

Safety Assessments

- The safety population included all subjects who received at least one dose of study medication and had at least one post-baseline safety evaluation
- Safety assessments included monitoring of adverse events (AEs) as well as physical examinations, vital sign measurements, clinical laboratory evaluations, electrocardiograms (ECGs), and the Columbia-Suicide Severity Rating Scale (C-SSRS)

RESULTS

Demographics and Characteristics

- A total of 77 subjects participated in the study, with 68 subjects comprising the completer population
- Subjects were 38 healthy females and 39 healthy male adults, 19-59 years of age, ranging in body mass index (BMI) from 20.3-31.9 kg/m^2, and weighing between 60 and 103.5 kg (**Table 2**)
- Study population demographics were: 44% of Hispanic or Latino ethnicity, 38% black or African American, 57% white, 3% Asian, and 1% American Indian or Alaskan Native (**Table 2**)

Table 2. Key Demographics and Characteristics of Subjects

Demographics and Characteristics	Overall (N=77)	ER to IR[a] lorazepam (n=39)	IR to ER[a] lorazepam (n=38)
Age, mean (min, max), years	40.0 (19, 59)	40.1 (19, 59)	39.9 (19, 58)
Sex, n (%)			
Female	38 (49.4)	19 (48.7)	19 (50.0)
Male	39 (50.6)	20 (51.3)	19 (50.0)
Ethnicity, n (%)			
Hispanic or Latino	34 (44.2)	14 (35.9)	20 (52.6)
Not Hispanic or Latino	43 (55.8)	25 (64.1)	18 (47.4)
Race, n (%)			
American Indian or Alaskan Native	1 (1.3)	1 (2.6)	0
Asian	2 (2.6)	1 (2.6)	1 (2.6)
Black or African American	29 (37.7)	17 (43.6)	12 (31.6)
Native Hawaiian/Other Pacific Islander	0	0	0
White	44 (57.1)	19 (48.7)	25 (65.8)
Multiple races	1 (1.3)	1 (2.6)	0
Height, mean (SD), cm	168.71 (9.280)	169.77 (10.018)	167.62 (8.450)
Weight, mean (SD), kg	77.76 (10.828)	79.18 (12.068)	76.30 (9.324)
BMI, mean (SD), kg/m^2	27.28 (2.680)	27.38 (2.565)	27.17 (2.824)

[a]ER lorazepam administered as 4 mg dose qd, IR lorazepam as 2 mg dose q12h.

BMI=body mass index; ER=extended-release; IR=immediate-release; max=maximum; min=minimum; q12h=every 12 hours; qd=once daily; SD=standard deviation

Pharmacokinetic Results

- Maximum mean lorazepam plasma concentrations were lower following administration of once-daily ER lorazepam compared to IR lorazepam given q12h (**Figure 1 and Table 3**)
- C_{maxSS} of lorazepam was 27% lower after once-daily ER lorazepam compared to IR lorazepam given q12h, while C_{minSS} and AUC_{TAU} (AUC_{0-24}) were similar between groups
  - The geometric mean ratios (90% confidence interval [CI]) for C_{maxSS}, C_{minSS}, and AUC_{TAU} (AUC_{0-24}) were 72.97% (70.56-75.47%), 88.90% (85.53-92.42%), and 84.53% (81.93-87.22%), respectively
- Mean percent fluctuation and swing values were lower for once-daily ER lorazepam (38.6% and 0.491, respectively) compared to IR lorazepam given q12h (59.6% and 0.817, respectively) (**Table 4**)
- Average lorazepam concentrations at steady state and during the first 12 hours post-dose were similar between groups (**Table 4**)
  - Lorazepam exposure from 12-24 hours post-dose was 17% lower for those receiving ER lorazepam than for those on IR lorazepam (**Table 4**)
- Trough concentrations of lorazepam on days 5, 6, and 7 were not significantly different between ER lorazepam and IR lorazepam
- There was no significant effect of treatment sequence on lorazepam PK parameters (p >0.05)

Figure 1. Mean Plasma Concentration-Time Profiles of Lorazepam with ER Lorazepam Compared to IR Lorazepam on Day 7 on Linear (A) and Semi-Logarithmic (B) Scales

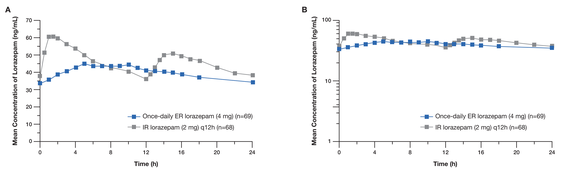

Table 3. Exploratory Analysis of AUC_{0-12} and AUC_{12-24} Showing Lower Lorazepam Concentration for Once-Daily ER Lorazepam Compared to IR Lorazepam q12h

PK Parameter, Natural log-transformed exposure	ER lorazepam[a] qd (n=68) Geometric Mean	IR lorazepam[a] q12h (n=68) Geometric Mean	Geometric Mean Ratio ER/IR (%)	90% CI
C_{avSS}	37.5	44.3	84.53	81.93-87.22
AUC_{0-12}	476	551	86.37	83.85-88.95
AUC_{12-24}	422	512	82.45	79.53-85.48

[a]ER lorazepam administered as 4 mg dose qd, IR lorazepam as 2 mg dose q12h.

AUC=area under the concentration-time curve from hours 0-12 or 12-24; C_{avSS}=average steady-state plasma concentration; CI=confidence interval; ER=extended-release; IR=immediate-release; PK=pharmacokinetic; q12h=every 12 hours; qd=once daily.

Table 4. Pharmacokinetic Parameters of Lorazepam After Multiple Doses of Once-Daily ER Lorazepam and IR Lorazepam q12h on Day 7

Parameter, mean (SD) unless otherwise noted	ER lorazepam[a] qd (n=69)	IR lorazepam[a] q12h (n=68)
T_{maxSS}, median (range), h	7.00 (3.06-13.0)	1.5 (0.5-6.0)
C_{maxSS}, ng/mL	47.2 (16.3)	63.5 (17.5)
AUC_{TAU}, h*ng/mL	956 (353)	576 (174)
AUC_{0-24}, h*ng/mL	956 (353)	1110 (334)
C_{avSS}, ng/mL	39.8 (14.7)	46.3 (13.9)
C_{minSS}, ng/mL	32.7 (13.5)	36.1 (12.5)
$C_{through,24}$, ng/mL[b]	34.4 (14.7)	38.5 (13.4)
Flu_t % [$(C_{maxSS} - C_{minSS})/C_{vSS}$][c]	38.6 (12.0)	59.6 (13.8)
Swing ($C_{maxSS} - C_{minSS}$)/C_{minSS}	0.491 (0.193)	0.817 (0.242)
CL_{ss}/F, L/h	4.77 (1.80)	3.94 (1.25)
Vz/F, L	299 (293)	109 (50.1)

[a]ER lorazepam administered as 4 mg dose qd, IR lorazepam as 2 mg dose q12h.

[b]$C_{through}$ on Day 7 at 24 hours post-dose.

[c]C_{maxSS} and C_{minSS} obtained between time 0 and tau, where tau=24 hours for qd dosing, and 12 hours for bid dosing.

AUC_{TAU}=area under the concentration-time curve from time zero to tau (24 hours post-dose for qd, 12 hours post-dose for first and second q12h dose); bid=twice-daily; C_{avSS}=average plasma concentration at steady state; C_{maxSS}=maximum plasma concentration at steady state; C_{minSS}=minimum plasma concentration at steady state; CL_{ss}/F=apparent total plasma clearance at steady state; C_{trough}=trough plasma concentration at the end of the dosing interval; ER=extended-release; Flu_t=fluctuation; IR=immediate-release; q12h=every 12 hours; qd=once-daily; SD=standard deviation; T_{maxSS}=time to maximum plasma concentration at steady state; Vz/F=apparent volume of distribution.

Safety Results

- No serious AEs (SAEs) or AEs that led to death occurred during the study. Four subjects withdrew due to vomiting (3 in the IR and 1 in the ER lorazepam treatment arms)
- 62 (80.5%) subjects reported treatment-emergent AEs (TEAEs): 36 and 48 subjects reported TEAEs on ER lorazepam and IR lorazepam q12h, respectively (**Table 5**)
- The most frequently reported TEAEs (>3 subjects overall) were: somnolence (75.3%), dizziness (16.9%), nausea (9.1%), gait disturbance (6.5%), and vomiting (5.2%); most were mild in severity
- No abnormal physical examinations, ECGs, or incidents of suicidality were reported

Table 5. Safety Overview: Safety Population

Adverse Events	Overall (N=77)	ER lorazepam[a] qd (n=72)	IR lorazepam[a] q12h (n=75)
All TEAEs, n (%)	62 (80.5)	36 (50.0)	48 (64.0)
Most frequently reported TEAEs (n >3), n (%) m			
Somnolence	58 (75.3) 137	27 (37.5) 45	42 (56.0) 92
Dizziness	13 (16.9) 25	2 (2.8) 4	11 (14.7) 21
Nausea	7 (9.1) 8	1 (1.4) 1	6 (8.0) 7
Vomiting	4 (5.2) 4	1 (1.4) 1	3 (4.0) 3
Gait disturbance	5 (6.5) 7	2 (2.8) 3	3 (4.0) 4
TEAEs by severity, n (%)			
Mild	60 (77.9)	35 (48.6)	47 (62.7)
Moderate	2 (2.6)	1 (1.4)	1 (1.3)
Severe	0	0	0
TEAEs by relationship, n (%)			
Related to study drug	62 (80.5)	35 (48.6)	46 (61.3)
Not related	0	1 (1.4)	2 (2.7)
SAEs, n (%)	0	0	0
Related SAEs, n (%)	0	0	0
TEAEs leading to study withdrawal, n (%)	4 (5.2)	1 (1.4)	3 (4.0)

[a]ER lorazepam administered as 4 mg dose qd, IR lorazepam as 2 mg dose q12h.

ER=extended-release; IR=immediate-release; m=number of events; n=number of subjects; q12h=every 12 hours; qd=once daily; SAE=serious adverse event; TEAE=treatment-emergent adverse event.

CONCLUSIONS

- This study compared the steady-state PK and safety profile of once-daily ER lorazepam (4 mg) to IR lorazepam (2 mg) q12h in healthy individuals
- Steady state was achieved for both treatments, and no significant differences in trough concentrations between ER and IR lorazepam were shown
- While lorazepam C_{maxSS} was lower after once-daily ER lorazepam, C_{minSS} and AUC_{TAU} were within bioequivalence limits (90% CI within 80.00-125.00%) of IR lorazepam q12h, with an overall similar PK profile
- As expected, once-daily ER lorazepam led to more consistent plasma lorazepam concentrations with less fluctuation observed throughout the day compared to IR lorazepam q12h
- Lorazepam was better tolerated when administered as once-daily ER lorazepam compared to IR lorazepam q12h, with fewer subjects reporting AEs on the ER formulation
  - The most frequently reported TEAEs were somnolence, dizziness, nausea, vomiting, and gait disturbance
- These data suggest that once-daily ER lorazepam can provide a more stable PK profile with improved tolerability compared to IR lorazepam q12h

REFERENCES

1. Kessler RC, et al. *Int J Methods Psychiatr Res.* 2012;21(3):169-184. 2. Murrough JW, et al. *Expert Opin Emerg Drugs.* 2015;20(3):393-406. 3. Mendlowicz MV, Stein MB. *Am J Psychiatry.* 2000;157(5):669-682. 4. Wilmer MT, et al. *Curr Psychiatry Rep.* 2021;23(11):77 5. Ghit A, et al. *J Genet Eng Biotechnol.* 2021;19(1):123. 6. Ativan (lorazepam product monograph). Kirkland, Quebec: Pfizer Canada ULC; 2021. 7. PDR, LLC. *Prescribers' Digital Reference.* 2022. Available at: https://www.pdr.net/drug-summary/Ativan-Tablets-lorazepam-2135.1869. Accessed August 16, 2022. 8. Kaplan EM, DuPont RL. *Curr Med Res Opin.* 2005;21(6):941-950. 9. New Drug Approval for Loreev XR. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2021/214826Orig1s000ltr.pdf. Accessed July 27, 2022. 10. Loreev XR. Prescribing information. Almatica Pharma LLC; 2021.

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.

ACKNOWLEDGMENTS

Editorial support was provided by IMPRINT Science, New York, NY, with funding from Almatica Pharma LLC.

This study was sponsored by Almatica Pharma LLC and managed by Alvogen PB Research & Development LLC; both companies are subsidiaries of Alvogen Pharma US, Inc.

For questions about the data presented above, contact the Clinical R & D department: Rupinder.Phull@alvogen.com and Shedly.Jean-Lys@alvogen.com

Presented at the Psych Congress Annual Meeting; September 17–20, 2022; New Orleans, LA.

Almatica Pharma