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Abuse Potential of Lasmiditan: A Phase 1 Randomized, Placebo- and Alprazolam-Controlled Crossover Study

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Abstract

Lasmiditan is a centrally penetrant, highly selective 5-hydroxytryptamine (serotonin) receptor 1F ($5HT_{1F}$) agonist under development as a novel therapy for acute treatment of migraine. A phase 1 randomized, placebo- and positive-controlled crossover study assessed the abuse potential of lasmiditan in adult recreational polydrug users. Following a qualification phase, subjects were randomized into treatment sequences, each consisting of 5 study treatments: placebo, alprazolam 2 mg, lasmiditan 100, 200 (lasmiditan 100 and 200 mg are proposed therapeutic doses), and 400 mg (supratherapeutic). The abuse potential of lasmiditan was investigated and compared with alprazolam and with placebo using the maximal effect score (E_{max}) of the Drug-Liking Visual Analog Scale as the primary end point. Lasmiditan was not similar to placebo in drug-liking scores at all doses tested, with a maximum difference observed with the lasmiditan 400-mg dose (upper 90% confidence limit on difference in least-squares [LS] means > 14 for all lasmiditan doses). Drug-liking scores for lasmiditan 400 mg were not significantly different from alprazolam (lower 90% confidence limit on difference in LS means < 5), but drug-liking scores at lower doses (100 and 200 mg) were significantly different from alprazolam. During the treatment phase, the incidence of treatment-emergent adverse events (TEAEs) increased with increasing dose of lasmiditan; all TEAEs reported with lasmiditan treatment were mild. Subjective drug-liking effects for lasmiditan versus placebo and versus alprazolam, and the safety and tolerability profile of lasmiditan suggest that lasmiditan has a low potential for abuse.

Keywords

$5HT_{1F}$, abuse potential, lasmiditan, migraine, serotonin

Lasmiditan is a high-affinity, centrally penetrant, highly selective 5-hydroxytryptamine (serotonin) receptor 1F ($5HT_{1F}$) agonist under development as an orally available, novel therapy for the acute treatment of migraine, with a proposed maximum daily dose of no more than 200 mg. Lasmiditan has >440-fold selectivity for the human 5-HT_{1F} receptor relative to the 5-HT_{1B} and 5-HT_{1D} receptors and has a chemical structure and pharmacologic profile that is distinct from the triptans, the current standard of care for acute treatment of migraine. Lasmiditan targets 5-HT_{1F} receptors on neurons in the trigeminal system to alleviate migraine pain and lacks vasoconstrictor activity in nonclinical studies.[1,2] Because lasmiditan penetrates the central nervous system (CNS) and is associated with adverse events (AEs) consistent with central activity, the risk of abuse was evaluated in accordance with the United States Food and Drug Administration (FDA) Guidance for Assessment of Abuse Potential of Drugs.[3] The FDA considers information from a broad range of sources in assessing the abuse potential of a new drug in addition to human abuse potential studies, including the results of studies investigating chemistry, pharmacology, pharmacokinetics (PK), animal and human behavior, and abuse-related AEs in human studies.[3]

With the exception of the 5-HT_{1F} receptor subtype, receptor-binding studies have indicated that lasmiditan does not have an affinity for other 5-HT_1 receptor subtypes,[1] and its major metabolites (M7, M8, and M18) do not have an affinity for 5-HT_1 (including 5-HT_{1F}) serotonin receptor subtypes (unpublished data). Further, lasmiditan does not have an affinity for muscarinic, dopaminergic, adrenergic, or histamine receptors or γ-aminobutyric acid A ($GABA_A$) channels at concentrations <10 μM. The affinity of lasmiditan (1 μM) for 52 radioligand-binding sites, including G-protein-coupled receptors, ion channels, and transporters, was evaluated to provide a broad profile of

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selectivity. Lasmiditan at 1 μM produced < 50% inhibition of binding at 51 of the 52 binding sites examined. The only exception was the site of the benzodiazepine [^{3}H]-flunitrazepam on the $GABA_A$ channel, where the inhibition constant (K_i) was 0.29 μM, representing a >100-fold-lower affinity than for the 5-HT_{1F} receptor. Analysis of lasmiditan and its metabolites in different isoforms of $GABA_A$ α subunit suggests no agonist, antagonist, or positive allosteric modulator activity at concentrations up to 100 μM, indicating low selectivity at the $GABA_A$ benzodiazepine site (unpublished data).

Across phases 1, 2, and 3 clinical studies, doses of 0.1 to 400 mg of lasmiditan have been evaluated in healthy subjects or patients with migraine; methods of administration included intravenous, sublingual, and oral. As expected with a centrally penetrant drug, lasmiditan has been associated with CNS AEs in the clinical program, including somnolence, dizziness, fatigue, and paresthesia. In phase 1 single-dose lasmiditan studies in healthy subjects, the most commonly reported treatment-emergent adverse event (TEAE) terms that represent signs of abuse potential included euphoric mood (2.3%), feeling abnormal (1.4%), feeling drunk (0.7%), auditory hallucination (0.4%), and abnormal dreams (0.2%). In healthy subjects receiving multiple doses of lasmiditan, euphoric mood (7.0%) and feeling abnormal (2.3%) were the most commonly reported TEAE terms that may represent signs of abuse potential. Across all phase 2 and phase 3 oral lasmiditan studies in people with migraine, the most commonly reported TEAEs that may be related to abuse included feeling abnormal (0.9%), euphoric mood (0.6%), abnormal dreams (0.3%), and hallucination (0.2%).

Consistent with the United States Food and Drug Administration (FDA) Guidance for Assessment of Abuse Potential of Drugs,[3] a positive control was used in this study. Alprazolam, a short-acting benzodiazepine (schedule IV) shown to produce both sedative and euphoric symptom types,[4,5] was selected as the positive control. Both lasmiditan and alprazolam have rapid absorption with peak plasma concentrations occurring within 1 to 2 hours following administration. Similarities between both the PK and AE profiles of alprazolam and lasmiditan provide further rationale for the use of alprazolam as a positive control. Here, we report the results from a phase 1 randomized, subject- and investigator-blind, placebo- and positive-controlled crossover study to assess the abuse potential of lasmiditan in adult recreational polydrug users (ClinicalTrials.gov Identifier: NCT03286218).

Methods

This study was reviewed and approved by an independent ethics committee and independent review board (Midlands Independent Review Board) and conducted (Vince & Associates Clinical Research, Inc., Overland Park, Kansas) in accordance with consensus ethics principles derived from international ethics guidelines including the Declaration of Helsinki and the Council for International Organizations of Medical Sciences International Ethical Guidelines, as well as applicable International Council for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use. Written informed consent was provided by all subjects prior to starting any study procedure.

Study Participants

Healthy men and women aged 18 to 55 years with a body mass index of 18 to 32 kg/m^2, inclusive, were eligible for this study (Table 1). In addition, eligible subjects were required to be current recreational drug users, as defined by ≥10 lifetime nontherapeutic experiences (ie, for psychoactive effects) with CNS depressants (eg, benzodiazepines, barbiturates, zolpidem, eszopiclone, propofol/fospropofol, gamma-hydroxy-butyrate), ≥1 nontherapeutic use of a CNS depressant/sedative drug within the 12 weeks prior to screening, and ≥1 lifetime nontherapeutic use of another drug class of abuse (eg, opioids, stimulants, dissociatives, or hallucinogens), and agree not to consume any recreational drugs during the study. The selection of this population ensured that the subjects were familiar with the psychoactive effects of the positive control to improve the sensitivity for detecting any abuse potential for lasmiditan.

Subjects were excluded if there was evidence of drug or alcohol dependence (excluding nicotine and/or caffeine) within the past 1 year, as defined by the *Diagnostic and Statistical Manual of Mental Disorders*, 4th Edition, Text Revision, or the subject had a lifetime history of participation in a drug rehabilitation program, excluding past participation in tobacco smoking cessation programs or previous court-mandated treatment. Subjects were also excluded if currently seeking or participating in treatment for addiction or substance-related disorders, had recovered from substance abuse disorder, pr had a significant medical history capable of significantly altering the PK of drugs, constituting a risk while taking the investigational product or interfering with the interpretation of data.

Study Design and Treatment

This study included 4 phases — screening, qualification, treatment, and follow-up phases.

Screening Phase. Screening visits occurred within 28 days of dosing in the qualification phase. Subjects who failed screening were not rescreened.

Table 1. Demographics

	Qualification Phase (n = 96)	Treatment Phase (n = 58)	Did Not Complete Treatment Phase (n = 38)
Age (years), mean (SD)	31.4 (8.6)	31.4 (8.9)	31.5 (8.3)
Sex, M/F	77/19	48/10	29/9
Weight (kg), mean (SD)	74.83 (14.53)	73.73 (14.66)	76.50 (14.34)
BMI (kg/m^2), mean (SD)	24.83 (3.81)	24.41 (3.98)	25.46 (3.48)
Height (cm), mean (SD)	173.21 (7.69)	174.43 (7.19)	172.88 (8.49)
Race, n (%)			
African American	69 (71.9%)	43 (74.1%)	26 (68.4%)
White	24 (25.0%)	12 (20.7%)	12 (31.6%)
Other	3 (3.1%)	3 (5.2%)	0 (0.0%)

BMI, body mass index; F, female; M, male; n, number of subjects; SD, standard deviation.

Qualification Phase. Eligible subjects who met all inclusion criteria and none of the exclusion criteria entered a subject- and investigator-blind, placebo-controlled, 2-period crossover qualification phase. Subjects were randomized to a test dose of alprazolam 1 mg and placebo with a washout period of at least 72 hours between each dose. "Drug-liking" response was assessed before and after alprazolam and placebo administration using a 100-mm bipolar Drug-Liking Visual Analog Scale (VAS). Subjects whose maximal effect score (E_{max}) drug liking after placebo was between 40 and 60 (inclusive) on the 100-mm VAS and whose E_{max} drug liking after alprazolam was at least 15 mm higher than their placebo E_{max} drug liking were eligible to enter the treatment phase.

Treatment Phase. This was a subject- and investigator-blind, placebo- and positive-controlled, Williams square 5-period crossover design. Subjects were randomized to 1 of 10 dosing sequences. Dosing sequences consisted of 5 dosing periods that evaluated the abuse potential of each of the 5 study treatments: placebo, alprazolam 2 mg, and lasmiditan 100, 200, and 400 mg. The washout period between each dose was at least 72 hours. Eligible subjects were admitted on day -1 before receiving study drug in period 1 and remained in-house until completion of day 2 procedures for period 5. Blinded study drug was administered on day 1 of each period after an overnight fast.

The use of different doses of alprazolam between the qualification and treatment phases is consistent with precedent[6] and ensured that the subjects enrolled in the treatment phase could safely tolerate and were sensitive to the effects of the positive control. This helped to ensure that subjects could perform the tests and that significant liking was detectable in this study. Using the bipolar Drug-Liking VAS, the drug-liking effect difference between 1.5 and 3 mg alprazolam was modest (2 to 4 mm).[6] Therefore, only 1 dose of 2 mg alprazolam was evaluated in the treatment phase as a positive control.

Follow-up Phase. Subjects had a follow-up visit approximately 1 week after their last dose of study drug. Subjects who discontinued from the study before its completion were asked to attend an early-discontinuation visit approximately 1 week after the last dose of study drug.

Lasmiditan and Alprazolam Bioanalytical Method

Plasma samples obtained during this study were analyzed for lasmiditan and alprazolam. Analytes were extracted and analyzed using validated bioanalytical assays (liquid chromatography with tandem mass spectrometric detection) with adequate precision and accuracy (Covance Laboratories Inc., Madison, Wisconsin).

Pharmacodynamic Assessments

The primary objective of the study was to assess the abuse potential of lasmiditan compared with the positive control alprazolam and with placebo using the E_{max} of the at-the-moment 100-mm bipolar Drug-Liking VAS. The Drug Effects VAS Battery contains a series of measures that evaluate different subjective effects of the abuse potential of the study drug (Supplementary Table S1). The bipolar Drug-Liking VAS was consistent with FDA guidance,[3] such that in recreational polydrug users, placebo should produce a score between 40 and 60, representing neutral drug liking (ie, neither like nor dislike), with a score of 0 indicating strong disliking and a score of 100 indicating strong liking. According to abuse potential assessment principles, drug-liking measures tend to be some of the most sensitive and reliable measures of abuse potential and have been used widely in studies assessing abuse potential.[7] The remaining questions in the Drug Effects VAS Battery were assessed as secondary end points. An additional assessment, the Drug Similarity VAS Battery, was also evaluated as a secondary end point.

The Drug Similarity VAS provides an estimate of the drug class with which polydrug users most closely identify the novel drug.[7] FDA guidance suggests that data from secondary VAS measures including "drug similarity" should be considered along with the primary measures in determining whether a test drug carries the potential for abuse.[3] The secondary questions included in the Drug Similarity VAS Battery are listed in Supplementary Table S2. The "how familiar" questions were asked in the qualification phase only (baseline), whereas the "how similar" questions were asked in both the qualification and treatment phases.

The Cantab Connect electronic data capture system was used to present the VAS battery assessments, capture subject responses, and record data for transfer to a known company (Cambridge Cognition Limited, Cambridge, UK). Subjects were instructed to choose the point on a 100-mm horizontal line (presented on an electronic scale) that best represented their response to the given question. The end points of each electronic scale were marked with descriptive anchors.[8–11] In the "how familiar" questions, a score of 0 indicated definitely not familiar with, and a score of 100 indicated definitely familiar. In the "how similar" questions, a score of 0 indicated definitely not similar, and a score of 100 indicated definitely similar. During both the qualification and treatment phases, VAS measurements were assessed at baseline, 0.25 hours, and 0.5 hours and then every 30 minutes until 5 hours and at 6, 8, 12, and 24 hours for the Drug Effects VAS Battery for primary and secondary end points, except for overall drug liking and take drug again, which were assessed at 12 and 24 hours only. The Drug Similarity VAS Battery was assessed at 24 hours only.

Pharmacokinetic Assessments

During the treatment phase, serial blood samples were collected throughout 24 hours postdose to determine the plasma concentrations of lasmiditan and alprazolam. PK parameter estimates were determined using noncompartmental procedures in a validated software program (Phoenix WinNonlin version 6.4).

Safety Assessments

Safety was assessed through recording AEs, clinical laboratory tests, physical examinations, vital signs, electrocardiograms (ECGs), and the Columbia Suicide Severity Rating Scale (C-SSRS).

Statistical Analysis

Pharmacodynamic Analysis. The E_{max} was derived as the maximum VAS score among all the individual values that were collected for each subject at the scheduled postdose assessment times for each element of the Drug Effects VAS Battery. A linear mixed-effects model, including period, sequence, and treatment as fixed effects and subject as a random effect, was used to evaluate the E_{max} for each element by treatment. Least-squares (LS) mean estimates were reported for each treatment, and LS mean estimates and 90% confidence intervals (CIs) were reported for each paired difference among treatments for each element of the Drug Effects VAS Battery. To test the noninferiority hypotheses of primary interest, regarding at-the-moment drug liking at the E_{max}, the following pairwise comparisons were tested at a significance level of 0.05 (1-sided): alprazolam minus placebo, with null hypothesis that the difference is $\leq$15 mm, in which the null hypothesis was rejected if the lower limit of the 90%CI was $>$15 mm, showing assay sensitivity; alprazolam minus each dose of lasmiditan, with the null hypothesis that the difference was $\leq$5 mm. The null hypothesis was rejected if the lower limit of the 90%CI was greater than 5 mm, showing that alprazolam had a higher E_{max} of drug-liking score than lasmiditan, and each dose of lasmiditan minus placebo, with the null hypothesis that the difference was $\geq$14 mm. The null hypothesis was rejected if the upper limit of the 90%CI was lower than 14 mm, showing that lasmiditan did not have a clinically relevant higher drug-liking score than placebo.

After reviewing the data for the Alertness/Drowsiness and Agitation/Relaxation VAS scales, the minimal effect score (E_{min}) was derived for these 2 scales, and statistical analyses similar to those described above for E_{max} were performed for the E_{min} values. For variables that did not meet normality assumptions via Q-Q plot assessment, paired *t* test or Wilcoxon signed rank test was performed instead of the linear mixed-effects model.

Descriptive statistics for each element of the Drug Similarity VAS Battery were reported for each treatment.

Pharmacokinetic Analysis. The primary parameters for analysis were maximum observed drug concentration (C_{max}) and area under the concentration-versus-time curve (AUC) of lasmiditan and alprazolam. All PK parameters were listed and summarized by treatment using standard descriptive statistics (Table 2).

Pharmacokinetic/Pharmacodynamic Analysis. An analysis was performed to graphically explore the relationship between the individual E_{max} of the Drug-Liking VAS score and the C_{max} of lasmiditan following administration of placebo or lasmiditan 100, 200, or 400 mg.

Results

Demographics and Disposition

A total of 96 subjects, 77 male and 19 female, aged between 19 and 55 years participated in the

Table 2. Pharmacokinetic Parameters Following a Single Oral Dose of Lasmiditan 100, 200, or 400 mg or Alprazolam 2 mg

	Geometric Mean (Geometric CV%)			
Parameter	Lasmiditan 100 mg (n = 55)	Lasmiditan 200 mg (n = 55)	Lasmiditan 400 mg (n = 55)	Alprazolam 2 mg (n = 53)
C_{max} ng/mL	132 (37%)	299 (35%)	689 (34%)	34.3 (33%)
t_{max} (h)[a]	1.4 (0.6-2.9)	1.4 (0.4-2.9)	1.4 (0.9-2.9)	0.92 (0.40-2.92)
$AUC_{0-\infty}$ (ng·h/mL)	856 (32%)	1810 (35%)	3920 (28%)	554 (39%)
$t_{½}$ (h)[b]	4.6 (3.7-6.8)	4.4 (3.3-6.2)	4.3 (3.2-6.3)	15.0 (6.90-88.8)

$AUC_{0-\infty}$, area under the concentration-versus-time curve from time zero to infinity; C_{max}, maximum observed drug concentration; CV, coefficient of; n, number of subjects; $t_{½}$, half-life associated with the terminal rate constant in noncompartmental analysis; t_{max}, time of maximum observed drug concentration.
[a]Median (range).
[b]Geometric mean (range).

qualification phase. Of the 96 subjects who entered the qualification phase and received at least 1 dose of alprazolam 1 mg or placebo, 58 subjects qualified for the treatment phase (48 men and 10 women aged between 19 and 50 years). All 58 subjects who enrolled in the treatment phase received at least 1 dose of study drug (lasmiditan, alprazolam, or placebo). Of these, 53 subjects completed all 5 periods of the treatment phase, and 5 subjects withdrew before completing the study. All 5 withdrawals were because of subject decision; 1 subject withdrew from the study for personal issues, 3 subjects withdrew because of family emergencies, and 1 subject withdrew because of a sore throat. However, the investigator did not believe withdrawal from the study was medically necessary (Table 1 and Figure 1).

Pharmacodynamic Results

Drug-Liking Scores Over Time. Following oral administration of a single dose of lasmiditan, there was a dose-dependent increase in the LS mean drug-liking score during the first 1.5 hours postdose, which gradually returned to predose levels by approximately 8 hours postdose (Figure 2). There was separation of lasmiditan from placebo, for which the LS mean drug-liking score remained at approximately 50 (neither like nor dislike) at all assessment times (Figure 2). Following administration of the positive control, alprazolam 2 mg, the LS mean drug-liking score increased at a rate similar to that following the lasmiditan dose. However, (1) it reached a greater maximum than that seen by any lasmiditan dose, (2) it reached the maximum later (2 hours postdose) than observed at any dose of lasmiditan, and (3) it remained elevated for longer before returning to baseline by 24 hours postdose (Figure 2).

E_{max} Drug-Liking Scores. The results of the primary analysis confirmed assay sensitivity, with the lower limit of the 90%CI for the difference in LS means between alprazolam and placebo being greater than 15 (Figure 3, Supplementary Table S3).

Timilarity of lasmiditan to placebo in drug-liking scores was not demonstrated, with the upper limits of the 90%CIs for the differences in LS means between lasmiditan and placebo greater than 14 for all 3 doses of lasmiditan tested, with a maximum difference between drug-liking scores observed with the lasmiditan 400-mg dose (23.6; 90%CI, 19.6-27.6). Dissimilarity of lasmiditan to alprazolam was not demonstrated via the drug-liking scores, as the lower limit of the 90%CI for the difference in LS means between alprazolam and the supratherapeutic dose of lasmiditan (400 mg) was less than 5 (LS mean difference, 8.79; 90%CI, 4.80-12.80). Drug-liking scores for both lasmiditan 100-mg (LS mean difference, 16.8; 90%CI, 12.8-20.8) and 200-mg (LS mean difference, 12.1; 90%CI, 8.10-16.1) doses were significantly lower than those for alprazolam, with the lower limits of the 90%CIs for the difference in LS means between lasmiditan and alprazolam greater than 5 in both cases, suggesting dissimilarity between alprazolam 2 mg and doses of lasmiditan within the proposed therapeutic range (Supplementary Table S3).

Secondary Parameters

The primary statistical analysis, the mixed-effects model, was used to analyze the E_{max} or E_{min} of the following secondary parameters: Overall drug liking, take drug again, good effects, any effects, alertness/drowsiness, agitation/relaxation, and high. The E_{max} values of the secondary parameters bad effects and hallucinations were analyzed using the Wilcoxon signed rank test. The results of the statistical analyses of E_{max} or E_{min} of the secondary parameters of the Drug Effects VAS generally indicated that all doses of lasmiditan tested had a higher abuse potential than placebo but a lower abuse potential than alprazolam 2 mg (Supplementary Table S3). Notable exceptions were the mean E_{min} of agitation/relaxation, which was similar in alprazolam and the supratherapeutic dose of lasmiditan (Supplementary Table S3), and the median E_{max} of hallucinations, which differed from

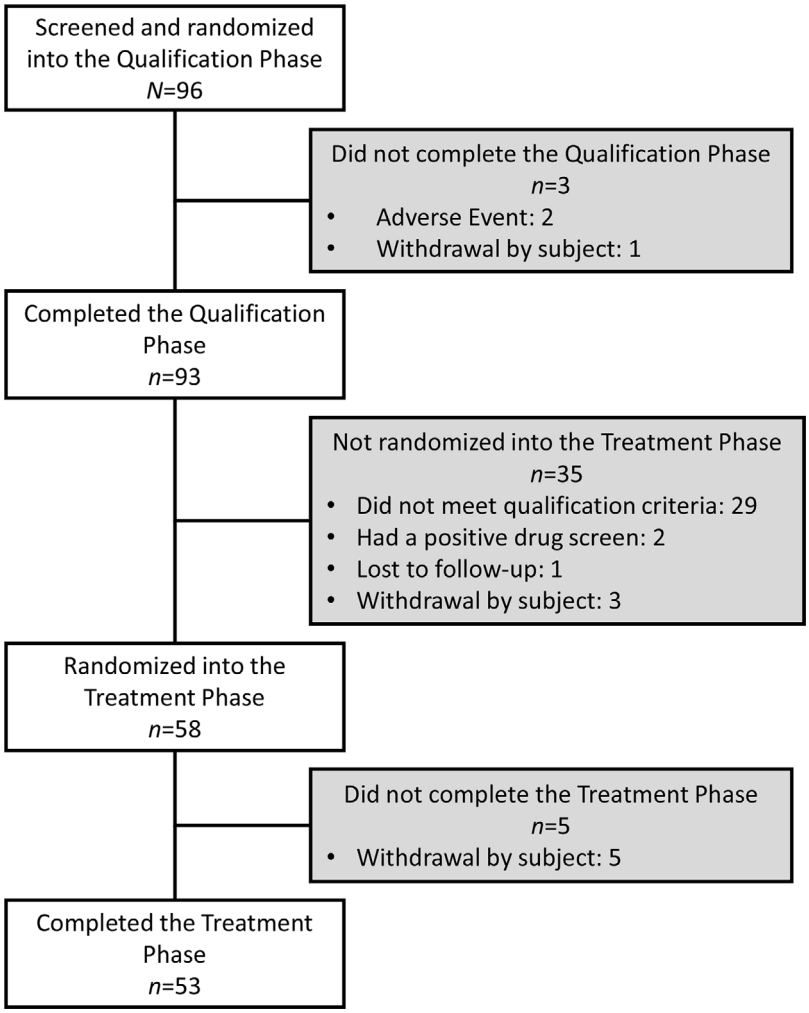

Figure 1. Subject disposition. A total of 96 subjects, 77 male and 19 female, aged between 19 and 55 years participated in the qualification phase. Of the 96 subjects who entered the qualification phase and received at least 1 dose of alprazolam 1 mg or placebo, 58 subjects qualified for the treatment phase (48 men and 10 women aged between 19 and 50 years). All of the 58 subjects who enrolled in the treatment phase received at least 1 dose of study drug (lasmiditan, alprazolam, or placebo). Of these, 53 subjects completed all 5 periods of the treatment phase, and 5 subjects withdrew before completing the study.

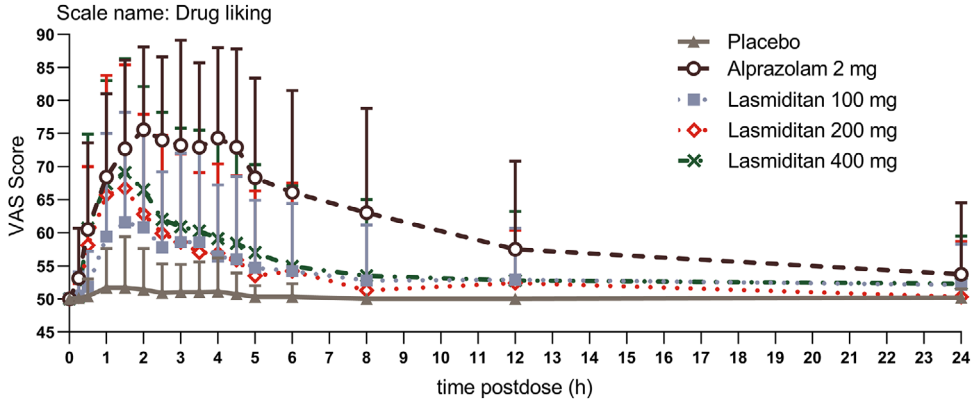

Figure 2. Mean (1-sided standard deviation) Drug-Liking VAS score profile following administration of lasmiditan 100, 200, and 400 mg, alprazolam 2 mg, and placebo. Subjects were instructed to choose the point on a 100-mm horizontal line (presented on an electronic scale) that best represented their response to the given question. The bipolar Drug-Liking VAS was consistent with FDA guidance[3] such that in recreational polydrug users, placebo should produce a score between 40 and 60, representing neutral drug liking (ie, neither like nor dislike), a score of 0 indicates strong disliking, and a score of 100 indicates strong liking. During the treatment phase, VAS Drug-Liking measurements were assessed at baseline, 0.25 hours, and 0.5 hours, and then every 30 minutes until 5 hours and at 6, 8, 12, and 24 hours. VAS, visual analog scale.

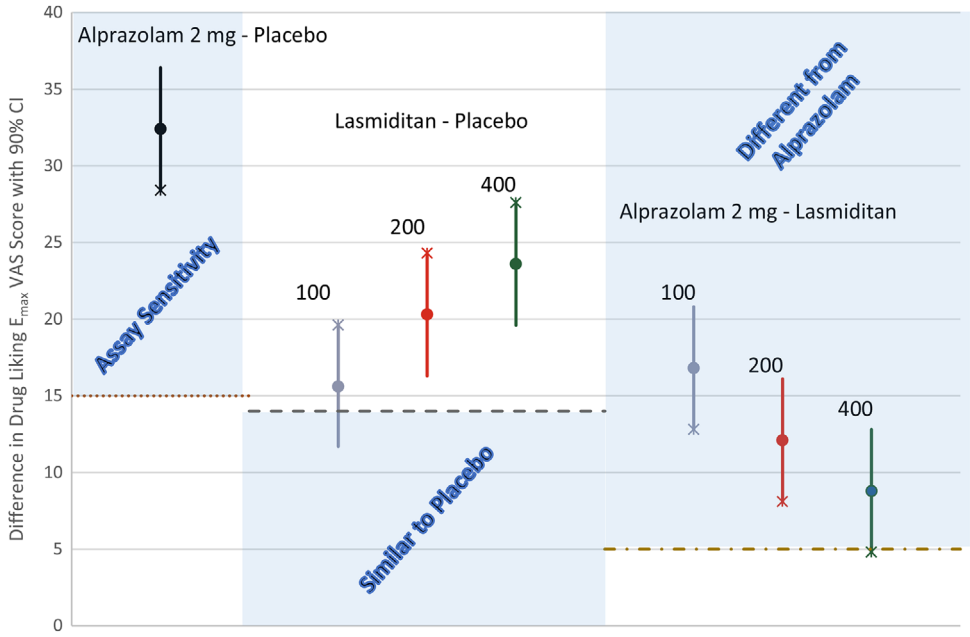

Figure 3. Mean differences between treatment groups in Drug-Liking E_{max} VAS scores. Subjects were instructed to choose the point on a 100-mm horizontal line (presented on an electronic scale) that best represented their response to the given question. During both the qualification and treatment phases, VAS drug-liking measurements were assessed at baseline, 0.25 hours, and 0.5 hours, and then every 30 minutes until 5 hours and at 6, 8, 12, and 24 hours. Asterisk indicates confidence limit tested in noninferiority hypothesis tests of primary interest; an asterisk outside the shaded area failed to demonstrate similarity to placebo or difference from alprazolam. CI, confidence interval; E_{max}, maximal effect score; VAS, visual analog scale.

that of placebo at only the supratherapeutic dose of lasmiditan (400 mg); see Supplementary Table S4.

Overall, subjects were reasonably familiar with the drug classes surveyed on the Drug Similarity VAS, with mean scores ranging from 44.3 to 85.3 on the "how familiar" questions (where 0 = definitely not familiar and 100 = definitely familiar); see Supplementary Table S5. The drug classes that were rated as most similar to lasmiditan were benzodiazepines (mean, 74.6 at the lasmiditan 400-mg dose; 57.2 and 66.9 at the 100- and 200-mg doses, respectively; compared with 88.1 for alprazolam), codeine, or morphine (mean, 45.9 at the lasmiditan 400-mg dose), cannabis (mean, 41.7 at the lasmiditan 400-mg dose), and phencyclidine (PCP; mean, 32.3 at the lasmiditan 400-mg dose); see Supplementary Table S6. Lasmiditan was rated as more similar to these drug classes (benzodiazepines, codeine or morphine, cannabis, and PCP) than placebo was rated to the same drug classes and less similar to these drug classes than alprazolam was, with the exception of PCP, for which the lasmiditan 400-mg dose was rated more similar than alprazolam (Supplementary Table S6).

Pharmacokinetics

Lasmiditan. The plasma concentration profiles of lasmiditan following a single oral dose of lasmiditan 100, 200, or 400 mg were characterized by a rapid absorption phase, with C_{max} reached approximately 1.5 hours postdose at all 3 doses (Table 2 and Supplementary Figure S1). Lasmiditan plasma concentrations then declined in a monophasic manner, with a similar half-life associated with the terminal rate constant in non-compartmental analysis ($t_{1/2}$, approximately 4.5 hours) observed at all doses (Table 2 and Supplementary Figure S1). There was a dose-dependent increase in systemic exposure (C_{max} and AUC from time zero to infinity [$AUC_{0-\infty}$]) to lasmiditan with increasing dose (Table 2 and Supplementary Figure S1).

Alprazolam. The plasma concentration profile of alprazolam following a single oral 2-mg dose was characterized by a rapid absorption phase, with C_{max} reached approximately 1 hour postdose (Table 2 and Supplementary Figure S2). Alprazolam plasma concentrations then declined in a biphasic manner, with a $t_{1/2}$ of 15.0 hours (Table 2 and Supplementary Figure S2). The PK for alprazolam was consistent with the literature.[4]

Pharmacokinetic/Pharmacodynamic Evaluations

The data (Figure 4) suggest that the E_{max} of the Drug-Liking VAS score may initially increase across lower lasmiditan concentrations (100 mg); at higher C_{max} concentrations (400 mg), no change in response was observed with increasing lasmiditan concentrations.

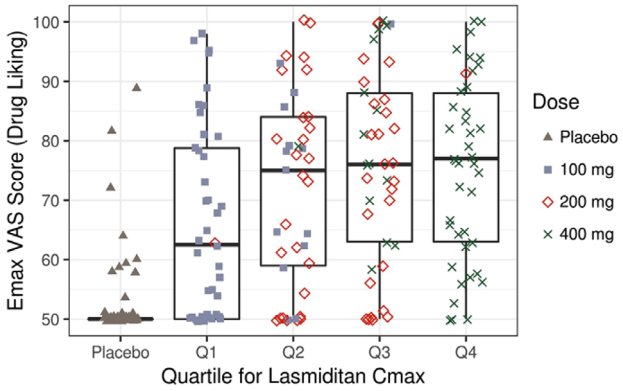

Figure 4. Plot of individual E_{max} of Drug-Liking VAS score versus C_{max} of lasmiditan following administration of placebo or lasmiditan 100, 200, or 400 mg. Boxplots are overlaid to illustrate trend. C_{max}, maximum observed drug concentration; E_{max}, maximal effect score; VAS, visual analog scale.

Safety and Tolerability

The safety analysis for the qualification phase included all 96 subjects entered in the study and for the treatment phase included all 58 subjects who qualified for the treatment phase. No deaths or other severe AEs occurred during this study.

Qualification Phase. More than 90% of all TEAEs reported in the qualification phase occurred following administration of alprazolam 1 mg. Most AEs reported in the qualification phase were of mild severity and occurred predominantly following alprazolam treatment.

Treatment Phase. Of the 58 subjects who received at least 1 dose of lasmiditan, alprazolam, or placebo during the treatment phase, 57 participants (98.3%) reported AEs. Most AEs that occurred in the treatment phase were of mild severity. Of the 7 moderate treatment-related AEs (TEAEs) reported, 6 were associated with alprazolam 2-mg treatment, and 1 was associated with placebo. There were no severe AEs reported. A higher percentage of subjects reported AEs following administration of each of the active treatments than following administration of placebo, with the highest incidence of TEAEs (94.3%) reported with alprazolam 2 mg. A dose-related increase in the incidence of TEAEs was observed with increasing doses of lasmiditan, with 85.5% of subjects reporting TEAEs at the 400-mg dose.

For subjects who received placebo, the most commonly reported TEAEs (reported by >5% of subjects) were euphoric mood (10.9%) and headache (5.5%). For subjects treated with alprazolam 2 mg, the most commonly reported TEAEs (>5%) were somnolence (84.9%), euphoric mood (43.4%), feeling of relaxation (22.6%), amnesia (18.9%), agitation (9.4%), and headache (7.5%). Of those treated with lasmiditan 100, 200, or 400 mg, the most commonly occurring TEAEs (>5%) included somnolence (32.7%, 40.0%, and 54.5%, respectively), euphoric mood (25.5%, 49.1%, and 45.5%, respectively), paresthesia (7.3%, 10.9%, and 9.1%, respectively), feeling of relaxation (10.9%, 7.3%, and 7.3%, respectively), dizziness (5.5%, 10.9%, and 3.6%, respectively), headache (5.5%, 5.5%, and 5.5%, respectively), and agitation (1.8%, 5.5%, and 3.6%, respectively); see Table 3.

Clinical Laboratory Evaluations

No clinically significant alterations in clinical laboratory values occurred following the lasmiditan dosing.

Vital Signs, Electrocardiograms, and Other Observations Related to Safety

Decreases from baseline in mean supine pulse rate and diastolic and systolic blood pressure were observed following administration of all study treatments, with maximum decreases observed between 2 and 6 hours postdose (Supplementary Figure S3). All vital signs returned to approximate baseline values by 24 hours postdose. Three subjects experienced AEs related to changes in vital signs during the treatment phase. Two subjects experienced a single AE of postural orthostatic tachycardia syndrome (following dosing with alprazolam 2 mg and lasmiditan 200 mg, respectively), whereas a single subject experienced an AE of presyncope following dosing with lasmiditan 200 mg. During the course of the study, there were no clinically meaningful changes in ECG parameters, and no subjects reported active suicidal ideation or suicidal behavior during the study, as indexed by the C-SSRS.

Discussion

This study compared the abuse potential of lasmiditan versus placebo and lasmiditan versus alprazolam in experienced recreational polydrug users. Assay sensitivity was confirmed with alprazolam in the primary analysis. Based on the primary statistical analysis of the E_{max} of drug-liking score, the possibility that lasmiditan had a higher abuse potential than placebo could not be ruled out, with the upper limits of the 90%CIs for the differences in LS means between lasmiditan and placebo greater than 14 for all 3 doses of lasmiditan tested. In assessing equivalence between placebo and a test drug, FDA guidance recommends that the test drug have a mean difference in the E_{max} of drug-liking scores greater than or equal to some prespecified threshold relative to placebo to be considered different from, or nonequivalent to placebo. Although the current study prespecified an E_{max} difference of 14 as the threshold, Chen and Bonson recommended this threshold be set at 11.[12] The interpretation of the current study's results,

Table 3. Frequency of Subjects With Treatment-Emergent Adverse Events (Related to Study Treatment): Treatment Phase

MedDRA Preferred Term	Placebo (n = 55)	Alprazolam 2 mg (n = 53)	Lasmiditan 100 mg (n = 55)	Lasmiditan 200 mg (n = 55)	Lasmiditan 400 mg (n = 55)
Somnolence	2 (3.6%)	45 (84.9%)	18 (32.7%)	22 (40.0%)	30 (54.5%)
Headache	3 (5.5%)	4 (7.5%)	3 (5.5%)	3 (5.5%)	3 (5.5%)
Paresthesia	0 (0.0%)	1 (1.9%)	4 (7.3%)	6 (10.9%)	5 (9.1%)
Dizziness	0 (0.0%)	2 (3.8%)	3 (5.5%)	6 (10.9%)	2 (3.6%)
Amnesia	0 (0.0%)	10 (18.9%)	0 (0.0%)	1 (1.8%)	0 (0.0%)
Euphoric mood	6 (10.9%)	23 (43.4%)	14 (25.5%)	27 (49.1%)	25 (45.5%)
Agitation	0 (0.0%)	5 (9.4%)	1 (1.8%)	3 (5.5%)	2 (3.6%)
Feeling of relaxation	1 (1.8%)	12 (22.6%)	6 (10.9%)	4 (7.3%)	4 (7.3%)

MedDRA, Medical Dictionary for Regulatory Activities; n, number of subjects studied.
Adverse events with a change in severity are only counted one time at the highest severity MedDRA version 20.0.

however, is the same whether 14 or 11 is used for this threshold.

Lasmiditan was not significantly different from alprazolam in drug-liking scores at the supratherapeutic dose of lasmiditan (400 mg), because the lower limit of the 90%CI for the difference in LS means between alprazolam and lasmiditan was less than 5. However, it was greater than 5 with the lasmiditan 100- and 200-mg doses, suggesting dissimilarity between alprazolam 2 mg and the proposed therapeutic doses of lasmiditan.

In addition to the primary parameter, 9 other scales of the Drug Effects VAS were statistically analyzed as secondary parameters. The mean or median E_{max} for each of these scales was higher (or the E_{min} was lower) for lasmiditan than for placebo, but not as high (or low) for lasmiditan as for alprazolam, with the exception of agitation/relaxation, for which the E_{min} was similar for alprazolam and the lasmiditan 400-mg dose. Generally, there was a tendency for the effects of the lasmiditan 400-mg dose to fall between the lasmiditan 200-mg and alprazolam 2-mg doses. For some secondary end points, the effects of the lasmiditan 200-mg dose more closely resembled those seen at the lasmiditan 1000mg dose than those seen at the 400-mg dose. For other secondary end points, the effects of the lasmiditan 200-mg dose more closely resembled those seen at the lasmiditan 400-mg dose than those seen at the 100-mg dose. The Drug Similarity VAS scores indicated that subjects considered the subjective effects of lasmiditan to be most similar to those of benzodiazepines (scores of 57.2 to 74.6 across the lasmiditan doses tested, compared with 88.1 for alprazolam); see Supplementary Table S6.

The 2 lower doses of lasmiditan used in this study (100 and 200 mg) were chosen to represent the likely commercial doses (proposed maximum daily dose of 200 mg) based on phases 2 and 3 data. The higher dose of 400 mg was selected because it represents 2 times the highest proposed commercial dose, which is consistent with FDA guidance for identifying a supratherapeutic dose for evaluation in a human abuse potential study; it is also the highest oral dose tested in the lasmiditan clinical program to date and has been tolerated by both healthy subjects and patients with migraine. As the pharmacodynamic (PD) effects of lasmiditan on Drug Effects and Drug Similarity VAS appeared to be dose dependent in the present study, and there was a dose-dependent increase in systemic exposure to lasmiditan across the dose range tested, it is possible that testing a higher dose of lasmiditan could have produced a greater PD effect. However, an exploratory PK/PD analysis did not show any evidence of an increase in the parameter E_{max} of the Drug-liking score (expressed as change from placebo) with increasing lasmiditan C_{max} within the range of the higher C_{max} values observed (Figure 4). This suggests that the dose dependency of the PD responses may not necessarily extend beyond the lasmiditan dose range tested in the study.

During the treatment phase, the incidence of TEAEs increased with increasing dose of lasmiditan; all TEAEs reported with lasmiditan treatment were mild. All doses of lasmiditan were associated with fewer TEAEs than alprazolam 2 mg. Most TEAEs were neurologic or psychiatric events. TEAEs that may represent a sign of abuse potential were reported in all treatment groups, although generally with higher frequency in the lasmiditan and alprazolam treatment groups. It is important to note that in the current study, subject reports of both "feeling high" and "high feeling" were coded to euphoric mood in the Medical Dictionary for Regulatory Activities and were reported at a similar frequency between the alprazolam 2-mg and the lasmiditan 200- and 400-mg dose groups (43.4%, 49.1%, and 45.5%, respectively). Accordingly, the incidence of the AE of euphoric mood is consistent with the VAS "high" results reported in this study. Further, although the current study reported results from healthy recreational drug users, in controlled phase 3 clinical studies in patients with migraine,[13,14] euphoric mood was reported in 0.4% of lasmiditan-treated patients (n = 3177) and in no placebo-treated patients (n = 1262). Vital signs revealed

no new safety findings, and assessment of clinical laboratory evaluations, ECGs, C-SSRS, and physical examination did not reveal any safety concerns.

Conclusions

The results of this study suggest that lasmiditan has higher abuse potential than placebo. Although lasmiditan at a supratherapeutic dose (400 mg) produced positive subjective effects that were not significantly different from those produced by a schedule IV benzodiazepine (alprazolam), lasmiditan doses within the proposed therapeutic range (100 and 200 mg) produced effects that suggest dissimilarity between alprazolam 2 mg and lasmiditan. The characterization of subjective drug-liking effects for lasmiditan was qualitatively different in terms of lower maximum values and shorter duration compared with those produced by alprazolam. Thus, lasmiditan is thought to have low potential for abuse. AEs that may represent signs of abuse potential were reported more frequently in alprazolam and lasmiditan treatment groups than in placebo. No safety concerns were noted in the clinical laboratory, physical examination, vital sign, or ECG data, and no reports of suicidal ideation or suicidal behavior were reported during the study.

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Conflicts of Interest

D.W., P.H.B., M.T., E.L., L.S.L., and E.G.D. are employees and minor shareholders of Eli Lilly and Company. E.S. received compensation from Eli Lilly for consulting work related to this project.

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Data-Sharing Statement

Lilly provides access to all individual participant data collected during the trial, after anonymization, with the exception of pharmacokinetic or genetic data. Data are available to request 6 months after the indication studied has been approved in the United States and European Union or after primary publication acceptance, whichever is later. No expiration date of data requests is currently set once data are made available. Access is provided after a proposal has been approved by an independent review committee identified for this purpose and after receipt of a signed data-sharing agreement. Data and documents, including the study protocol, statistical analysis plan, clinical study report, and blank or annotated case report forms, will be provided in a secure data-sharing environment. For details on submitting a request, see the instructions provided at www.vivli.org.

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Supplemental Information

Additional supplemental information can be found by clicking the Supplements link in the PDF toolbar or the Supplemental Information section at the end of web-based version of this article.