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Effects of Lasmiditan on Cardiovascular Parameters and Pharmacokinetics in Healthy Subjects Receiving Oral Doses of Propranolol

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Abstract

Lasmiditan (LY573144/COL-144) is a high-affinity, centrally penetrant, selective 5-HT_{1F} receptor agonist currently under investigation for acute treatment of migraine. Although lasmiditan is not known to induce vasoconstriction, it remains important to understand its effect on cardiovascular parameters because it is likely to be coadministered with β-adrenergic receptor antagonists used for migraine prophylaxis, such as propranolol. This phase 1, single-center, open-label, fixed-sequence study evaluated the cardiovascular and pharmacokinetic effects of 200 mg lasmiditan in 44 healthy subjects receiving repeated oral doses of twice-daily 80 mg propranolol under fasting conditions. Coadministration caused statistically significant decreases in mean hourly heart rate relative to propranolol alone, but the maximum magnitude of this effect was –6.5 bpm and recovered to predose levels by 3 to 4 hours before stabilizing. Additionally, short-lived ($\leq$2.5 hours) statistically significant increases in systolic blood pressure (8.3 mm Hg) and diastolic blood pressure (6.4 mm Hg) were observed following coadministration. Consistent with the largely nonoverlapping metabolic pathways of lasmiditan and propranolol, exposure to either drug was not affected by coadministration. Overall, compared with administration of either drug alone, coadministration was generally well tolerated.

Keywords

lasmiditan, propranolol, migraine, vasoconstriction, pharmacokinetics, cardiovascular effects, drug-drug interaction

Lasmiditan (LY573144/COL-144) is a high-affinity, centrally penetrant, selective 5-HT_{1F} receptor agonist that exerts therapeutic effects in the acute treatment of migraine by decreasing neuropeptide release and inhibiting pain pathways.[1–4] Lasmiditan has demonstrated efficacy in acute treatment of migraine in phase 3 studies.[5–8]

Data from nonclinical studies[9] suggest that lasmiditan does not induce vasoconstriction, unlike triptans which are commonly prescribed for migraine.[1–3,10–14] Inconsistent changes in blood pressure were observed following lasmiditan dosing across the individual studies in the clinical pharmacology program, with increases in systolic blood pressure (SBP) and diastolic blood pressure (DBP) observed in some but not all studies (data on file).

Completed clinical pharmacology studies have shown that oral lasmiditan 200 mg, the highest potential recommended dose, is associated with maximum mean decreases in heart rate of 10 beats per minute (bpm) compared with 5 bpm for placebo and an increased incidence of bradycardia (<50 bpm with a decrease from baseline of $\geq$15 bpm) of 4.1% compared with 1.1% for placebo (data on file).

It is important to understand how these cardiovascular changes may interact with drugs such as propranolol that are commonly prescribed in this patient population.[7,15] Propranolol is a β-adrenergic receptor antagonist, commonly prescribed for migraine prophylaxis, that is known to decrease heart rate by approximately 17% to 18%.[16] Therefore, understanding the cardiovascular impact of lasmiditan and propranolol coadministration is of particular clinical relevance.

Understanding how exposure of each drug is influenced by the other is also important to assess given

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the likelihood of coadministration in clinical practice. Based on the results from nonclinical in vitro studies that measured the disappearance of lasmiditan and formation of metabolites using liquid chromatography with tandem mass spectrometry (LC-MS/MS) in human liver microsomes and recombinant human cytochrome P450 (CYP) enzymes, lasmiditan undergoes extensive hepatic and extrahepatic metabolism in humans primarily through non–CYP-mediated ketone reduction (data on file). Therefore, inducers and inhibitors of CYP enzymes are unlikely to affect lasmiditan pharmacokinetics (PK). Although in vitro data indicate that lasmiditan may be a weak CYP2D6 inhibitor, propranolol metabolism involves multiple CYP pathways including CYP1A2, CYP2C19, and CYP2D6.[17–19] In view of these findings, an interaction between lasmiditan and propranolol due to overlapping metabolic pathways is not expected. PK analyses in this study were, therefore, secondary outcomes.

The primary objective of the current study was to evaluate heart rate following coadministration of lasmiditan and propranolol at steady-state levels of propranolol in healthy adults under fasting conditions, compared with propranolol alone. Secondary and exploratory objectives included assessments of tolerability, blood pressure, and pulse rate. The PK following coadministration of lasmiditan and propranolol compared with those with lasmiditan alone or propranolol alone were also evaluated.

Methods

Subjects

The study included 44 healthy male and female subjects, 18 to 65 years of age, who were nonsmokers for at least 3 months with a body mass index of 19 to 35 kg/m^2 and clinical laboratory test (hematology, clinical chemistry, and urinalysis) results within normal reference ranges. Pregnant subjects and those with reproductive potential but no adequate contraception were excluded. Also excluded were subjects with a significant medical history (including cardiovascular and neurological disorders), known allergies to the study drugs or any components therein, or clinically significant ECG abnormalities at screening. Subjects were also excluded if they had a baseline supine pulse rate of <50 or >90 bpm or abnormal blood pressure, defined as an SBP <95 or >140 mm Hg or a DBP <65 or >90 mm Hg.

The present study was approved by the Ethics Committee of the Midlands Independent Review Board (Overland Park, Florida) and conducted in accordance with the Declaration of Helsinki, the International Conference for Harmonisation, and Good Clinical Practice guidelines. Written informed consent was provided by all subjects before starting any study procedure. The study was conducted at a single Covance clinical research unit, located in the United States (Daytona Beach, Florida).

Study Design

This phase 1, single-center, open-label, fixed-sequence study in healthy subjects was designed to evaluate the cardiovascular and PK effects of oral coadministration of 200 mg lasmiditan with 80 mg twice daily (bid) propranolol, under fasting conditions (ClinicalTrials.gov identifier: NCT03270644). The dose of lasmiditan (200 mg once daily) was selected because it is the highest potential recommended dose and was well tolerated in previous studies of healthy subjects.[20–22] The dose of propranolol (80 mg bid) was selected because it is within the recommended dose for migraine and has been shown to be tolerated by healthy subjects in previous PK and pharmacodynamic (PD) studies.[20–25]

As shown in Figure 1, screening occurred up to 28 days before enrollment, and subjects were admitted to the clinical research unit on day -2, 2 days prior to their first dose of study drug. On day 1 subjects received a single dose of 200 mg lasmiditan. From day 4 through day 10 subjects received doses of 80 mg bid propranolol in the morning and evening, approximately 12 hours apart, to achieve steady-state concentrations, given the half-life of 3 to 6 hours with oral administration.[18] On the morning of day 9 propranolol and lasmiditan were coadministered, with the second daily dose of propranolol administered at the usual evening time. This intermittent lasmiditan dosing schedule aligns with the intended use of lasmiditan for acute treatment of migraine. Subjects were discharged from the clinical research unit on day 11 on completion of all study procedures. A follow-up visit occurred approximately 7 days after the last dose.

The 8-day washout period between lasmiditan doses on days 1 and 9 and the 7-day washout at the end were considered sufficient based on its half-life.

Treatments were given at approximately the same time for all subjects, with propranolol administered immediately before lasmiditan on the morning of day 9. All morning doses were administered after an overnight fast of at least 8 hours. Subjects were to remain fasting for 3 hours postdose on days 1, 8, and 9. On all other days, a light breakfast was allowed at the discretion of the investigator. As specified in the Study Assessments section, on intensive PK sampling days (days 1, 8, and 9), subjects abstained from water 1 hour before and after dosing (except for the 240 mL of room-temperature water given with each oral dose). Subjects were to refrain from caffeine and alcohol 48 hours before the study and during the inpatient stay.

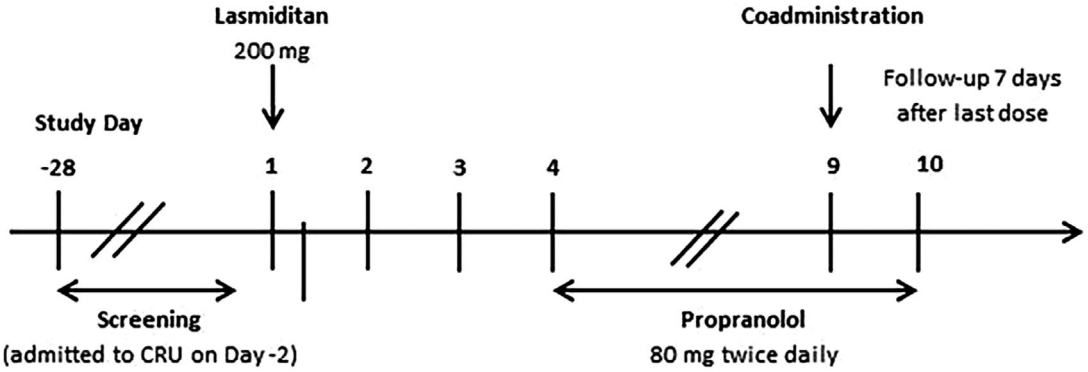

Figure 1. Study design. CRU indicates clinical research unit.

Both study drugs were stored in an environmentally controlled, monitored area in accordance with the labeled storage conditions, and access to this area was limited to the investigator and authorized site staff. Propranolol was administered as an 80-mg film-coated, immediate-release tablet (half-life approximately 3 to 6 hours) and was supplied by the investigative site. Lasmiditan was administered as a 200-mg film-coated tablet and was supplied by Eli Lilly and Company in bulk supply bottles.

Study Assessments

Continuous 12-lead Holter ambulatory monitoring was conducted through the 12-hour postdose time point on days –1, 1, 8, and 9. Monitoring on day –1 started approximately 1 hour before the anticipated daily dosing time, whereas monitoring on days 1, 8, and 9 started approximately 1 hour predose. Mean hourly heart rate was calculated from 1 hour predose to 12 hours postdose, and nadir (defined as the lowest mean hourly heart rate) was calculated from 0 to 6 hours postdose, >6 to 12 hours postdose, and 0 to 12 hours postdose. Triplicate ECG data extraction was performed at frequent intervals during the recording period.

During the continuous 12-lead Holter ambulatory monitoring procedure, subjects were in a quiet atmosphere without significant external stimulation (television, Internet, etc), in a supine position for at least 5 to 10 minutes before the specified ECG collection times. They remained supine but awake during ECG collection and for at least 10 minutes afterward and were encouraged to remain still, if possible.

Blood pressure and pulse rate were evaluated as part of standard vital sign assessments at screening and day –1 and predose on study days when lasmiditan and propranolol were administered. These measures were also obtained at 1, 1.5, 2, 2.5, 3, 4, 6, 8, and 12 hours postdose on days 1, 8, and 9. Blood pressure and pulse rate were measured after at least 5 minutes supine. All supine blood pressure and pulse rate measurements (except for screening) were done in triplicate at approximately 1-minute intervals. For each individual subject, the same cuff size was used throughout the study for measurements of blood pressure. Orthostatic assessments were obtained at screening and were conducted predose and at 1 and 2 hours postdose on days –1, 1, 8, and 9. For these orthostatic assessments, subjects were in a supine position for at least 5 minutes before the supine measurement was taken and standing for 2 minutes (but no longer than 3 minutes) before the standing measurement was done.

Venous blood samples of approximately 2 mL each were collected to determine the plasma concentrations of lasmiditan and propranolol. For lasmiditan, PK samples were collected predose and 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, 24, 36, and 48 hours following dosing on days 1 and 9. For propranolol, PK samples were collected predose and 0.5, 1, 1.5, 2, 3, 4, 6, 8, and 12 hours following dosing on days 8 and 9.

Lasmiditan was extracted from plasma by supported-liquid extraction and analyzed using LC-MS/MS at Covance Laboratories Inc (Madison, Wisconsin). Plasma samples for propranolol (human tripotassium EDTA with sodium metabisulfite) were analyzed at PPD (Middleton, Wisconsin) using a validated LC-MS/MS method. Full details of the analytic methods are provided in the online Supplementary File.

Safety Analyses

All safety parameters including adverse events (AEs), clinical laboratory parameters, vital sign measurements, and 12-lead ECG parameters were listed and summarized using standard descriptive statistics. A treatment-emergent AE (TEAE) was defined as an AE that occurred postdose or was present before dosing and became more severe postdose. Each symptom was classified by the most suitable term from *MedDRA* (*Medical Dictionary for Regulatory Activities*), version 20.0.

Table 1. Subject Demographics (N = 44)

Age, y	Mean	41.1
	SD	12.8
	Median	43.0
	Minimum	21
	Maximum	63
Sex, n (%)	Male	32 (72.7%)
	Female	12 (27.3%)
Ethnicity, n (%)	Hispanic or Latino	20 (45.5%)
	Not Hispanic or Latino	24 (54.5%)
Race, n (%)	American Indian or Alaska Native	0 (0.0%)
	Asian	0 (0.0%)
	Black or African American	15 (34.1%)
	Native Hawaiian or Other Pacific Islander	0 (0.0%)
	White	28 (63.6%)
	Unknown	1 (2.3%)
Weight, kg	Mean	77.91
	SD	13.34
	Median	75.25
	Minimum	55.8
	Maximum	105.6
Body mass index (kg/m^2)	Mean	26.82
	SD	3.41
	Median	27.20
	Minimum	19.8
	Maximum	33.1

Statistical Analyses

Sample size determination was based on a heart rate standard deviation (SD) of 10.9 bpm, approximated from observations in previous lasmiditan clinical pharmacology studies in healthy volunteers (data on file). Based on the approximated SD, a sample size of 36 subjects was calculated to have a 90% probability that the half-width of the 90%CI about the mean within-subject change would be no larger than 5 bpm. Forty-four subjects were enrolled to ensure that the minimum requirement of 36 subjects would complete the study.

The impact of coadministration of propranolol with lasmiditan on blood pressure and heart rate compared with propranolol alone was determined as follows. Primary cardiovascular parameters were evaluated in a linear mixed-effects model with a fixed effect for treatment (lasmiditan coadministered with propranolol [day 9; test treatment] versus propranolol alone [day 8; steady-state reference treatment]), and a random effect for subject. Least squares (LS) means were calculated for the test and reference treatments. Mean treatment differences were presented, along with the corresponding 90%CIs.

The impact of coadministration of propranolol with lasmiditan on pulse rate was evaluated using descriptive statistics.

PK parameter estimates for lasmiditan and propranolol were calculated by standard noncompartmental methods of analysis. The primary parameters for analysis were peak concentration (C_{max}), time from dose to C_{max} (t_{max}), and area under the concentration-time curve ($AUC_{0-\infty}$) of lasmiditan on days 1 and 9; and C_{max}, t_{max}, and AUC_{τ} of propranolol on days 8 and 9.

PK parameters were evaluated to determine the impact of propranolol coadministration on the PK of a single dose of lasmiditan. Log-transformed C_{max} and AUC parameters were evaluated in a linear mixed-effects model with a fixed effect for treatment (lasmiditan coadministered with propranolol [day 9; test treatment] versus lasmiditan alone [day 1; reference treatment]), and a random effect for subject. The treatment differences were back-transformed to present the ratios of geometric means and the corresponding 90%CIs.

The t_{max} was analyzed using a Wilcoxon signed-rank test. Estimates of the median difference based on the observed medians, 90%CIs, and *P*-values from the Wilcoxon test were calculated.

A similar analysis was performed to determine the impact of coadministration of a single dose of lasmiditan on the steady-state PK of propranolol. The model included the following treatments: propranolol coadministered with lasmiditan (day 9; test treatment) versus propranolol alone (day 8; reference treatment).

Results

Subjects

A total of 44 healthy subjects, including 32 men (72.7%) and 12 women (27.3%), participated in this study and received at least 1 dose of 200 mg lasmiditan (Table 1).

Two subjects did not complete the study for reasons that were unrelated to study treatment. One subject, who had not disclosed an ongoing medical history of migraine at screening, was withdrawn from the study after experiencing a migraine on day 4 because he no longer met the eligibility criteria. Another subject was withdrawn for unacceptable behavioral issues. There were no major deviations from the study protocol.

Cardiovascular Assessments

Mean hourly heart rate using Holter ambulatory monitoring decreased following coadministration of lasmiditan in the presence of propranolol from 62.4 bpm predose to the lowest value of 54.2 bpm at 1 to 2 hours postdose (Figure 2). Mean hourly heart rate then showed an increasing trend towards predose levels, rising from 54.5 bpm at 2 to 3 hours postdose

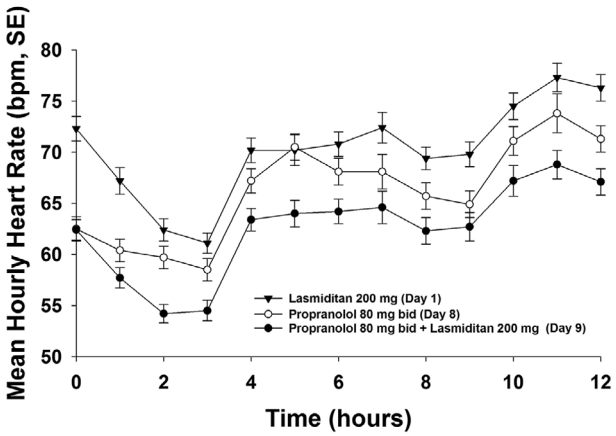

Figure 2. Hourly mean heart rate following lasmiditan, propranolol, and their coadministration. bid indicates twice daily; bpm, beats per minute; SE, standard error.

to 63.4 bpm at 3 to 4 hours postdose, before remaining relatively stable up through 12 hours postdose (range 62.3 to 68.8 bpm).

Relative to propranolol alone, mean hourly heart rate following coadministration was statistically lower at all postdose time points up through 12 hours (Supplementary Table 1). The maximum difference between coadministration and propranolol alone was between 4 and 5 hours postdose (–6.5 bpm; 90% CI –8.3 to –4.7). A similar effect was seen with heart rate obtained from triplicate ECG data extraction (Supplementary Table 2).

Mean hourly heart rate nadir was also significantly decreased following coadministration relative to propranolol alone at 0 to 6 hours postdose (–4.7 bpm; 90%CI –5.4 to –4.0) and >6 to 12 hours postdose (–3.2 bpm; 90%CI –4.4 to –2.0) (Supplementary Table 3).

Mean pulse rate decreased following coadministration of lasmiditan in the presence of propranolol from 56.2 bpm predose to the lowest value of 47.5 bpm at 1.5 hours postdose (Figure 3A). Mean pulse rate then remained depressed from 2 to 3 hours postdose (range of 49.1 to 50.2 bpm) before increasing at 4 hours postdose to 58.6 bpm and remaining relatively stable through 12 hours postdose (range of 55.1 to 60.2 bpm).

Pulse rate decreased following repeated dosing with propranolol, with a maximum decrease of 14.2 bpm

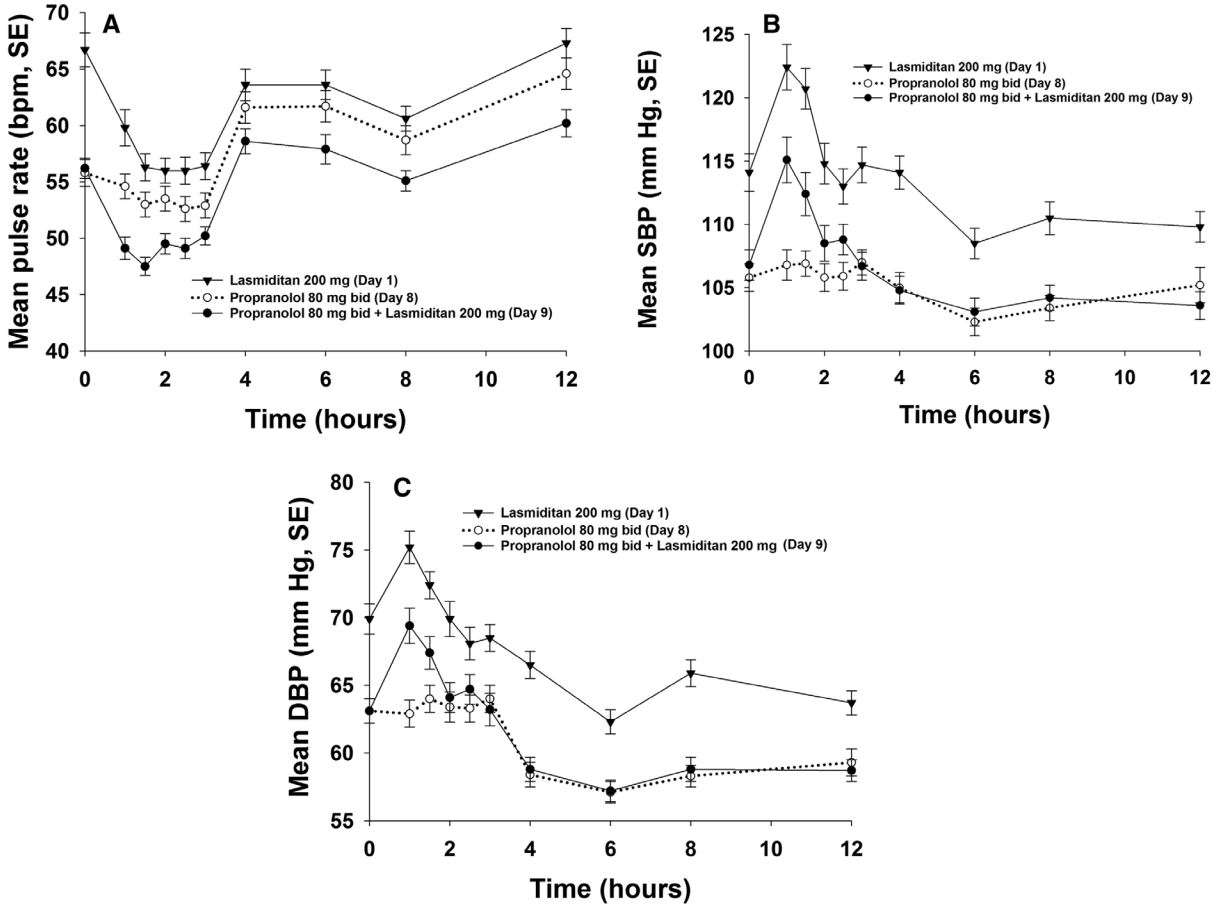

Figure 3. Mean pulse rate and blood pressure following propranolol, lasmiditan, and their coadministration. A, Pulse rate. B, Systolic blood pressure. C, Diastolic blood pressure. bid indicates twice daily; bpm, beats per minute; DBP, diastolic blood pressure; SBP, systolic blood pressure; SE, standard error.

relative to baseline (day 1 predose) at 2.5 hours postdose. Following coadministration of lasmiditan in the presence of steady-state propranolol, pulse rate decreased by 19.3 bpm relative to baseline at 1.5 hours postdose. Therefore, although pulse rate decreased on administration of propranolol alone and on coadministration, the maximal decrease in pulse rate relative to baseline was 5.1 bpm greater on coadministration compared with propranolol alone.

Mean SBP increased following coadministration of lasmiditan in the presence of propranolol from 106.8 mm Hg predose to the highest value of 115.1 mm Hg at 1 hour postdose (Figure 3B). Between 1.5 hours postdose and 3 hours postdose mean SBP gradually declined to predose levels from 112.4 to 106.7 mm Hg before remaining relatively stable through 12 hours postdose (range of 103.1 to 104.8 mm Hg).

Relative to propranolol alone, mean SBP following coadministration was statistically higher up through 2.5 hours postdose before becoming similar and relatively stable for both treatments from 3 to 12 hours postdose (Supplementary Table 4). The maximum difference between coadministration and propranolol alone was at 1 hour postdose (8.3 mm Hg; 90%CI 6.33-10.33).

Mean DBP increased following coadministration of lasmiditan in the presence of propranolol from 63.1 mm Hg predose to the highest value of 69.4 mm Hg at 1 hour postdose (Figure 3C). Between 1.5 hours postdose and 3 hours postdose, mean DBP gradually declined to predose levels from 67.4 to 63.2 mm Hg, before remaining relatively stable through 12 hours postdose (range of 57.2 to 58.8 mm Hg).

Relative to propranolol alone, mean DBP following coadministration was statistically higher through 1.5 hours postdose before becoming similar and relatively stable for both treatments from 2 to 12 hours postdose (Supplementary Table 4). The maximum difference between coadministration and propranolol alone was at 1 hour postdose (6.4 mm Hg; 90%CI 4.96-7.91).

When mean orthostatic SBP, DBP, and pulse rate were normalized relative to baseline on day 1, all were found to decrease following coadministration through 2 hours postdose with no notable differences between treatment regimens.

Pharmacokinetics

At steady state following twice-daily dosing, the plasma concentration profiles for propranolol were characterized by an absorption phase with a median t_{max} value of approximately 2.05 hours (range of 1.50 to 4.02) and 3.00 hours (range of 1.50 to 4.02) following dosing with propranolol alone and in combination with lasmiditan, respectively (Figure 4B). Plasma concentrations of propranolol appeared to decline in a monophasic manner after t_{max}.

There were no significant differences observed in exposure to propranolol based on C_{max} and AUC_{τ} following coadministration of propranolol and lasmiditan relative to propranolol alone, with the 90%CIs for the ratios of geometric LS means spanning unity for all parameters (Supplementary Table 5). The difference in propranolol t_{max} was statistically significant between treatments, but the 90%CI of the median difference in t_{max} values contained 0.

Following single oral dosing, the plasma concentration profile for lasmiditan alone and in the presence of propranolol was characterized by an absorption phase with a median t_{max} value of approximately 2.50 hours for both treatments (range of 1.50 to 4.00 hours [alone] and 1.50 to 4.02 hours [with propranolol]) (Figure 4A). Plasma concentrations of lasmiditan appeared to decline in a monophasic manner after t_{max}, and the resulting geometric mean elimination half-life values following dosing with lasmiditan alone or lasmiditan with propranolol were 4.39 and 4.65 hours, respectively.

Following coadministration of lasmiditan and propranolol (day 9), the overall exposure (AUC) to lasmiditan did not change, and C_{max} decreased by approximately 12%, relative to lasmiditan alone (day 1). The ratios of geometric LS means were 0.884 (90%CI 0.832-0.939), 1.01 (90%CI 0.967-1.04), and 1.00 (90%CI 0.966-1.04) for C_{max}, $AUC_{0\text{-tlast}}$, and $AUC_{0\text{-}\infty}$, respectively (Table 2).

Adverse Events

No serious adverse events related to the study drugs were reported. Of the 44 subjects who received 1 or more doses of the study drug (ie, 200 mg lasmiditan on day 1), 18 reported TEAEs that were related to study treatments (either lasmiditan or propranolol) as judged by the investigator (Table 3). When lasmiditan alone is compared with coadministration, similar numbers of subjects experienced similar numbers of TEAEs (11 subjects [21 events] versus 10 subjects [16 events], respectively). The most commonly occurring (frequency $\geq$3% with any treatment) TEAEs deemed related to study treatment by the investigator were dizziness, fatigue, paresthesia, somnolence, discomfort, and nausea. All were mild in severity, and no cardiovascular TEAEs were reported.

Discussion

Short-lived decreases in heart and pulse rate were observed following coadministration of lasmiditan in the presence of steady-state levels of propranolol. Coadministration caused statistically significant decreases in

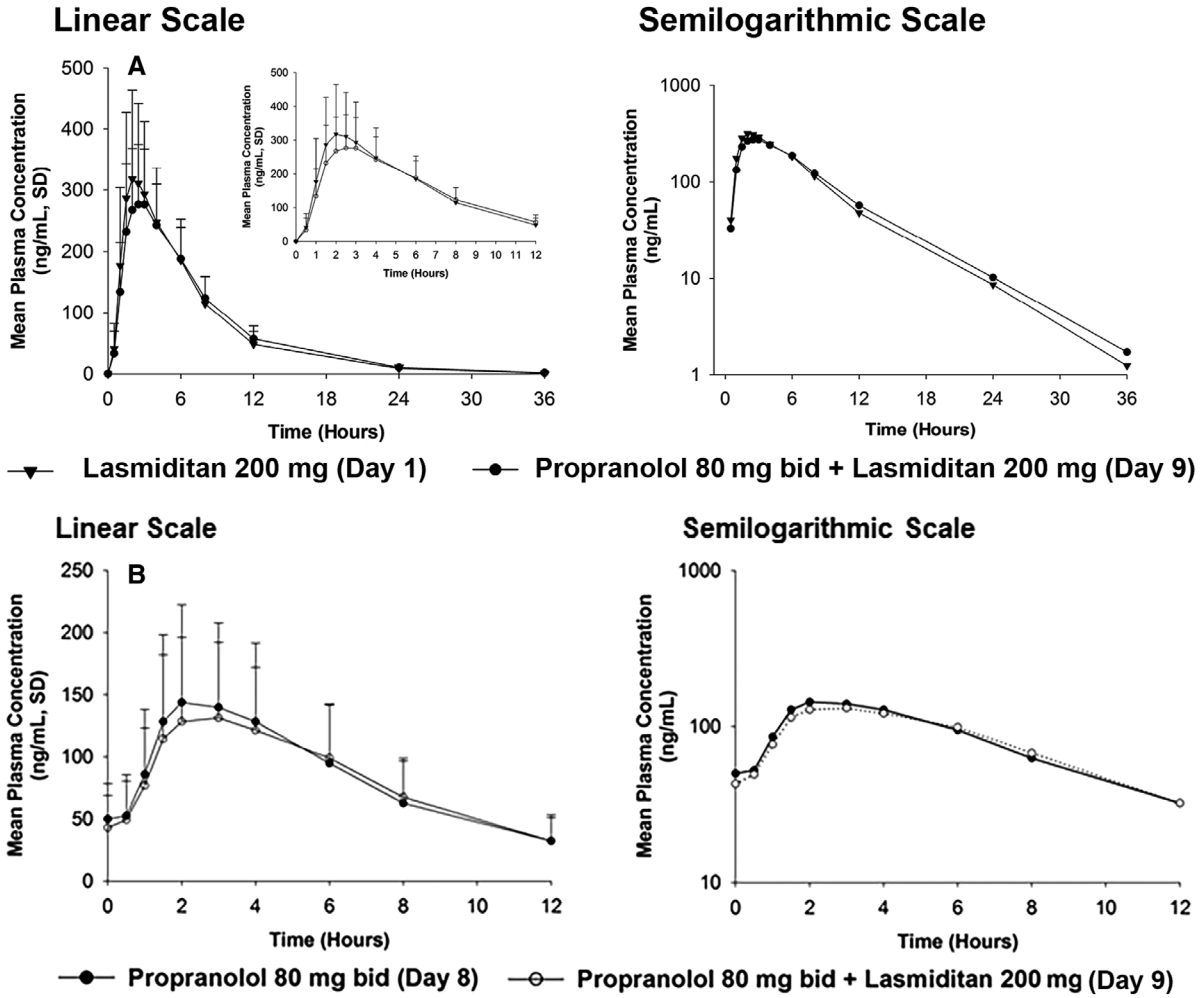

Figure 4. Mean plasma concentration-vs-time profiles following lasmiditan and propranolol compared with their coadministration. A, Lasmiditan. B, Propranolol. bid indicates twice daily.

mean hourly heart rate relative to propranolol alone at all postdose time points: the maximum magnitude of this effect was –6.5 bpm and recovered to predose levels by 3 to 4 hours before stabilizing. A similar decrease in pulse rate was also observed following coadministration.

These heart- and pulse-rate findings were not associated with an increased incidence of drug-related AEs relative to lasmiditan alone, nor were they associated with higher rates of dizziness compared with other lasmiditan studies.[5,26] Although decreased heart rate has been observed across lasmiditan studies that have collected postdose assessments, the potential mechanism of action is currently unknown.[27]

Statistically significant increases in blood pressure were also observed immediately following coadministration with blood pressure values returning to predose levels by 3 hours postdose. The maximal difference in blood pressure was observed 1 hour following coadministration and was 8.3 mm Hg for SBP and 6.4 mm Hg for DBP. The mechanism of this immediate, short-lived effect on blood pressure is not currently understood, as nonclinical studies have shown that lasmiditan does not induce vasoconstriction. No cardiovascular adverse events were reported during the period of BP elevation in this study. The clinical implications of the mild, nonsustained elevations in BP observed in this study remain to be determined, given inconsistent findings across the clinical program.

Little to no change in exposure to propranolol or lasmiditan was observed following coadministration of lasmiditan in the presence of steady-state levels of propranolol, relative to administration of either drug alone. This was not unexpected because the metabolism of lasmiditan and propranolol have been shown to occur through largely nonoverlapping pathways. The 90%CIs for C_{max} and AUC ratios were all entirely contained within 80% to 125% for lasmiditan and propranolol, indicating that the changes in exposure were not considered to be clinically relevant. In addition,

Table 2. Statistical Analysis of PK Parameters of Lasmiditan Following a Single Oral Dose of 200 mg Lasmiditan Alone and in the Presence of 80 mg bid Propranolol

Parameter	Treatment	N	Arithmetic Mean (SD)	Geometric LS Means	Ratio of Geometric LS Means (Test:Reference)	90%CI for the Ratio (Lower, Upper)
C_{max} (ng/mL)	**Reference**: Lasmiditan alone	44	350 (147)	323	n/a	n/a
	Test: Lasmiditan + Propranolol	42	303 (93.8)	285	0.884	(0.832-0.939)
$AUC_{0\text{-}tlast}$ (ng.h/mL)	**Reference**: Lasmiditan alone	44	2250 (874)	2103	n/a	n/a
	Test: Lasmiditan + Propranolol	42	2250 (660)	2114	1.01	(0.967-1.04)
$AUC_{0\text{-}\infty}$ (ng.h/mL)	**Reference**: Lasmiditan alone	44	2270 (872)	2122	n/a	n/a
	Test: Lasmiditan + Propranolol	42	2270 (658)	2128	1.00	(0.966-1.04)
$t_{½}$ (h)	**Reference**: Lasmiditan alone	44	4.45 (0.801)	4.39	n/a	n/a
	Test: Lasmiditan + Propranolol	42	4.71 (0.760)	4.65	n/a	n/a

$AUC_{0\text{-}\infty}$ indicates area under the concentration-vs-time curve from time 0 to infinity; $AUC0\text{-}_{tlast}$, area under the concentration-vs-time curve from time 0 to time t_{last}, which is the last time point with a measurable concentration; bid, twice daily; C_{max}, maximum observed drug concentration; LS, least square; n/a, not applicable; PK, pharmacokinetic; $t_{½}$, elimination half-life.
Model: Log(PK) = SUBJECT + TREATMENT + RANDOM ERROR.

Table 3. Frequency of Subjects With TEAEs on Either Treatment Regimen

	Treatment			
System Organ Class Preferred Term	200 mg Lasmiditan	80 mg Propranolol (bid)	80 mg Propranolol (bid) + 200 mg Lasmiditan	Overall
Number of events [number of subjects] (%)	N = 44	N = 43	N = 42	N = 44
Overall	21 [11] (25.0)	2 [2] (4.7)	16 [10] (23.8)	39 [18] (40.9)
Nervous system disorders	14 [9] (20.5)	1 [1] (2.3)	7 [6] (14.3)	22 [13] (29.5)
Dizziness	8 [6] (13.6)	1 [1] (2.3)	4 [4] (9.5)	13 [9] (20.5)
Paraesthesia	3 [3] (6.8)	0	0	3 [3] (6.8)
Somnolence	1 [1] (2.3)	0	2 [2] (4.8)	3 [3] (6.8)
Headache	1 [1] (2.3)	0	1 [1] (2.4)	2 [2] (4.5)
General disorders and administration site conditions	4 [4] (9.1)	0	4 [4] (9.5)	8 [7] (15.9)
Fatigue	2 [2] (4.5)	0	3 [3] (7.1)	5 [4] (9.1)
Discomfort	2 [2] (4.5)	0	1 [1] (2.4)	3 [3] (6.8)
Gastrointestinal disorders	0	0	4 [3] (7.1)	4 [3] (6.8)
Nausea	0	0	3 [3] (7.1)	3 [3] (6.8)
Paraesthesia oral	0	0	1 [1] (2.4)	1 [1] (2.3)

bid indicates twice daily; TEAEs, treatment-emergent adverse events.

the PK of propranolol was consistent with previous reports in the literature.[11,14]

All related TEAEs were mild in severity, and the TEAE profile was consistent with previous studies of lasmiditan in healthy subjects.[7] There was no marked difference in the frequency, severity, or nature of AEs reported following coadministration of lasmiditan in the presence of propranolol compared with propranolol alone. Importantly, no cardiovascular TEAEs were reported during the study.

Conclusions

Coadministration of lasmiditan in the presence of propranolol decreased heart and pulse rate shortly after dosing while increasing blood pressure relative to propranolol alone. These cardiovascular parameters returned to predose levels within 3 hours, whereas heart and pulse rates remained significantly lower following coadministration over the entire 12-hour postdose period compared with propranolol alone. However, compared with administration of either drug alone, coadministration was generally well tolerated and did not appreciably change the exposure of either drug.

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Conflicts of Interest

All authors are employees and stockholders of Eli Lilly and Company and/or a wholly owned subsidiary.

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