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RESEARCH ARTICLE

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# Effects of lasmiditan on simulated driving performance: Results of two randomized, blinded, crossover studies with placebo and active controls

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## Abstract

**Objective:** To evaluate the impact of lasmiditan, an oral, centrally-penetrant, selective serotonin 1F (5-$HT_{1F}$) receptor agonist developed for the acute treatment of migraine, on simulated driving.

**Methods:** Healthy adult volunteers enrolled in two randomized, placebo and active comparator-controlled, crossover studies. Study 1 (*N* = 90) tested lasmiditan (50-, 100-, 200-mg), alprazolam (1-mg), and placebo at 1.5 hr post-dose. Study 2 (*N* = 68) tested lasmiditan (100-, 200-mg), diphenhydramine (50-mg, administered 2 hr pre-assessments), and placebo at 8, 12 and 24 hr post-dose. Driving performance was assessed using a validated driving simulator employing a 100 km driving scenario. Standard deviation of lateral position (SDLP), a measure of lane position control, was the primary endpoint.

**Results:** Assay sensitivity was confirmed by increased SDLP for active comparators at 1.5- and 8-hr time points. Lasmiditan doses showed significant driving impairment versus placebo at 1.5 hr post-dose. Lasmiditan doses were non-inferior to placebo at 8 hr. Driving impairment was concentration-dependent at 1.5 hr but not at 8 hr. Common adverse events were central nervous system-related and mild-to-moderate in severity.

**Conclusions:** Lasmiditan was associated with impaired simulated driving performance at 1.5 hr post-dose, but showed no clinically meaningful impairment at 8 hr post-dose.

KEYWORDS

lasmiditan, migraine, selective serotonin receptor agonist

## 1 | INTRODUCTION

Lasmiditan is a high-affinity, centrally-penetrant, selective human serotonin 1F (5-$HT_{1F}$) receptor agonist developed for the acute treatment of migraine. Lasmiditan is structurally and mechanistically distinct from other acute migraine therapies, lacking the vasoconstrictive effects that may be associated with the 5-$HT_{1B}$ activity of triptans. Lasmiditan exerts its therapeutic effects by decreasing

neuropeptide release and inhibiting pain pathways that are implicated in migraine, including the trigeminal nerve (Nelson et al., 2010; Vila-Pueyo, 2018). Lasmiditan (50-, 100- and 200-mg) has demonstrated clinical efficacy in randomized, controlled studies assessing pain and associated symptoms in adults with migraine (Kuca et al., 2018; Wietecha, Kuca, Asafu-Adjei, & Aurora, 2018). Identified adverse drug reactions include dizziness, paraesthesia, somnolence, nausea, fatigue, muscle weakness and hypoesthesia, which were mostly mild to moderate in severity.

A Food and Drug Administration (FDA) guidance issued in 2017 (FDA, 2017) outlines the circumstances under which sponsors need to assess drug effects on driving ability in development programs, including when central nervous system (CNS) effects of the agent are known. Since lasmiditan is centrally-penetrant and the common adverse effects were primarily CNS-related events including dizziness, somnolence and fatigue, driving studies were required to evaluate any potential driving impairment. The FDA guidance supports the use of simulated driving studies, in combination with other assessments, to assess drug-related driving impairment. Lasmiditan was studied using the Cognitive Research Corporation Driving Simulator (CRCDS), mini-Sim, to conduct driving assessments following study drug administration.

A randomized, blinded, placebo- and active-controlled crossover study was conducted to assess lasmiditan effects on simulated driving performance at the time of peak lasmiditan plasma concentration, approximately 1.5 hr post-dose. A second randomized, blinded, placebo- and active-controlled crossover study was conducted to assess lasmiditan effects on simulated driving at 8, 12 and 24 hr post-dose.

**TABLE 1** Study designs and assessments

| | Study 1 | Study 2 |
|---|---|---|
| Study design | Phase 1, single-centre, randomized, subject- and investigator-blind, placebo- and active-controlled, five-period crossover study in healthy adult volunteers | Phase 1, multi-centre, randomized, subject- and investigator-blind, placebo- and active-controlled, four-period crossover study in healthy adult volunteers |
| Study treatments | **Lasmiditan**: Single oral dose of 50, 100 or 200 mg | **Lasmiditan**: Single oral dose of 100 or 200 mg (dosed once at start of each period) |
| | **Alprazolam**: Single oral dose of 1 mg | **Diphenhydramine**: Oral doses of 50 mg (dosed 2 hr before each driving test time point) |
| | **Placebo**: Single oral dose | **Placebo**: Oral doses (given when active drug not dosed, to maintain blind) |
| Assessment time points | **Driving assessments**: 1.5 hr post-dose (relative to all study drug administration) | **Driving assessments**: 8, 12, 24 hr post-dose (relative to lasmiditan administration) |
| | **Lasmiditan pharmacokinetic sampling**: Pre-dose and following conclusion of driving test (2.58 hr post-dose) | **Lasmiditan pharmacokinetic sampling**: Pre-dose and up to 48 hr post-dose |

## 2 | METHODS

### 2.1 | Study design and population

Both studies had randomized, double-blind, placebo-controlled, Williams-square crossover designs. Subjects were randomized to treatment sequences and were to complete all treatment periods within the assigned sequence (Table 1). Each study included an active control to establish the sensitivity of the study endpoints to detect residual sedation and resulting driving impairment, per FDA guidelines (FDA, 2017). In Study 1, alprazolam was chosen based on impairment described in epidemiological research, as well as its performance in prior driving research (Dassanayake, Michie, Carter, & Jones, 2011; Leufkens, Vermeeren, Smink, van Ruitenbeek, & Ramaekers, 2017; Rapoport et al., 2009; Verster, Volkerts, & Verbaten, 2002). As Study 2 required evidence of assay sensitivity at multiple timepoints over a 24-hr period, diphenhydramine was selected as the positive control and administered 2 hr prior to the three scheduled driving assessments, due its moderately sedating properties, lack of cumulative sedating effect, and prior performance in driving research (Kay et al., 1997; Kay, Schwartz, Wingertzahn, Jayawardena, & Rosenberg, 2016).

Study 1 (LAHG; NCT03012334) was a single-centre, five-period study to test single oral doses of lasmiditan 50-, 100- and 200-mg; alprazolam 1-mg; and placebo, with pharmacodynamic assessments initiated at 1.5 hr post-dose in each of the five periods to correspond with the time of peak lasmiditan plasma concentration (Figure 1a).

Study 2 (LAIF; NCT03459612) was a multi-centre, four-period study to test single oral doses of lasmiditan 100 and 200-mg administered once at the start of each period; diphenhydramine 50-mg administered 2 hr prior to driving assessments; and placebo administered during treatment periods as necessary to maintain the blind, with pharmacodynamic assessments conducted at 8, 12 and 24 hr in each of the four periods (Figure 1(b)).

Both studies enrolled subjects who were active drivers with no history of sleep disorder, substance abuse, or concomitant stimulant or sleep aid use. Key eligibility criteria were men and women aged 21 to 50 years with a body mass index of 18 to 35 $kg/m^2$, active drivers who were defined as subjects with a valid driver's license who had driven at least 10,000 miles per year for the previous

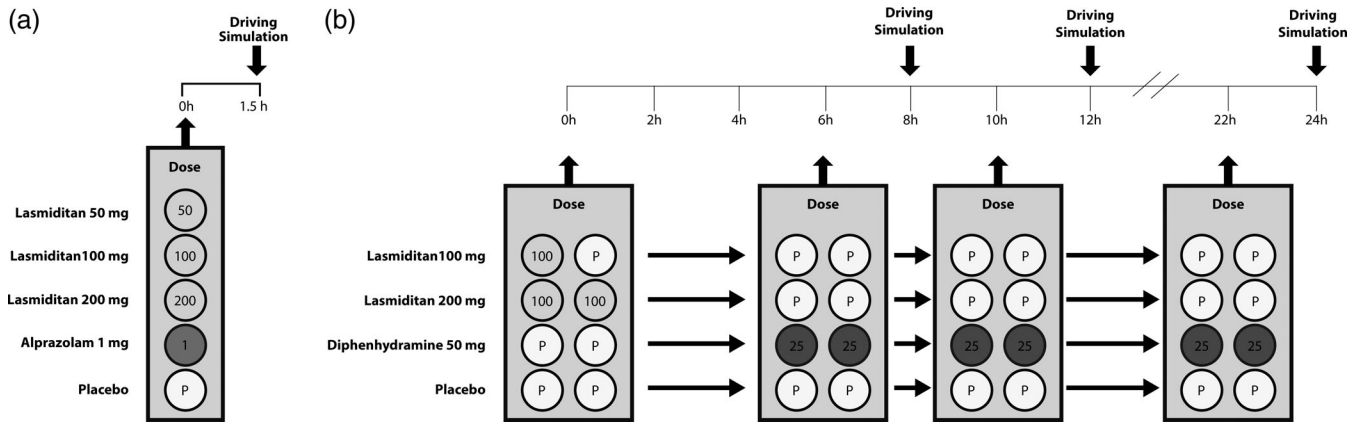


**FIGURE 1** Study schedules. (a) Study 1 tested single oral doses of lasmiditan (50-, 100-, 200-mg), alprazolam (1-mg), and placebo with driving assessments at 1.5 hr post-dose. (b) Study 2 tested lasmiditan (100-, 200-mg) taken once at the start of the dosing period; diphenhydramine (50-mg) taken 2 hr before each driving assessment; and placebo taken at other dosing times to maintain the blind, with driving assessments at 8, 12 and 24 hr

3 years, a regular sleep pattern, and a score of <10 on the Epworth Sleepiness Scale. After screening, subjects were admitted to the clinic on Day −1 to confirm eligibility and receive simulator practice. Subjects in both studies were monitored in the clinical research unit for up to 3 days for each treatment period. Standard meals were provided while subjects were resident at the clinical research unit. Both studies had a minimum of 2 days between study drug dosing in each period. Advarra, Inc. (Aurora, Ontario, Canada) and Midlands Independent Review Board (Overland Park, Kansas) approved the study protocols at participating sites for Study 1 and Study 2, respectively, and subjects' consent was obtained in accordance with the Declaration of Helsinki. Both studies were conducted in accordance with Good Clinical Practice guidelines and applicable local regulations.

## 2.2 | Primary endpoint variable

The primary endpoint for both studies was standard deviation of lateral position (SDLP), a measure of lane position control (i.e., weaving). The simulation was conducted using the CRCDS miniSim driving simulator and employed the Country Vigilance-Divided Attention (CVDA) driving scenario (Video S1). The CVDA is a 62.1-mile (100-km), monotonous, 2-lane highway driving task lasting about 1 hr. This scenario has been shown to be sensitive to the effects on driving performance of fatigue, sleepiness and CNS depressants including alcohol and sedating antihistamines, and to have comparable results to over-the-road driving tests (Cognitive Research Corporation, 2019; Rudisill, Zhu, Kelley, Pilkerton, & Rudisill, 2016; Simen et al., 2015). Increase in placebo-corrected SDLP is consistent with decrease in vehicle control presumed to be related to drug effects. Validation of the CRCDS-miniSim included establishing an a priori SDLP threshold of +4.4-cm for placebo-subtracted differences, which represents the average impairment in simulated driving observed in individuals with a blood alcohol concentration (BAC) of 0.05% (Cognitive Research Corporation, data on file). A BAC of 0.05% or greater is associated with an increased relative risk of motor vehicle accidents (Owens & Ramaekers, 2009).

## 2.3 | Secondary endpoint variables

Secondary endpoints were the same in both studies. Secondary driving and information processing endpoints presented in this report were selected with consideration of prior evidence of relative sensitivity to sedation effects, potential relevance to on-road crash risk, or both (Simen et al., 2015; Kay, Hochadel, Sicard, Natarajan, & Kim, 2017). Additional driving-related parameters obtained during the simulation included measures of lane exceedance, or the ability to stay in the lane as assessed by the number of times the vehicle's front left or right tire crosses over the lane boundary (number, maximum, duration and exceedance area); speed (average speed, speed deviation and excessive speed count); exceedance of cornering speed threshold (excessive Ay); and total number of collisions (assessed as the sum of collisions with other vehicles, off-road crashes and number of lane deviations exceeding 4 ft, viewed as a crash-likely event).

Additional endpoints were obtained from the divided attention (DA) task: accuracy (correct responses, omission errors, commission errors and percent accuracy) and response speed (reaction time and reaction time variability). The DA task involved periodic presentation of targets located in the periphery. When an arrow pointing left appeared on the left mirror, or an arrow pointing right appeared on the column to the right of the windshield, the subject was to press a corresponding button on the left or right side of the steering wheel as quickly as possible. The subject was to ignore arrows pointing up that appeared on either side. The arrow stimuli appeared for 5 s, or disappeared when the subject responded.

The CogScreen Symbol Digit Coding (SDC) test is a computer analogue of the conventional digit symbol-substitution task included in the Wechsler Adult Intelligence Scale Revised. This task evaluates aspects of attention, including visual scanning, working memory, and speed of information processing (Wechsler, 1981). Subjects use a stylus to tap the associated digit for each symbol on a touchscreen. The CogScreen SDC subtest was administered post-dose, within 30 min before the driving simulation. Measures obtained from the SDC include: number of correct responses, response accuracy and standard deviation of reaction time.

Subject self-appraisal endpoints are presented in this report for descriptive purposes and to accompany objective driving and information processing assessments, as self-perception of impairment is recognized as an inadequate measure of the presence or degree of impaired driving performance or risk mitigation (FDA, 2017). Subjects provided self-evaluations of their level of sleepiness via the Karolinska Sleepiness Scale (KSS), a Likert scale ranging from 1 (maximal alertness) to 9 (maximal sleepiness). Subjects were instructed to "indicate your sleepiness during the 5 min before this rating" (Akerstedt & Gillberg, 1990). The KSS was administered post-dose, within 30 min of beginning the driving simulation. Prior to the driving simulation, subjects were also asked to report their self-perceived safety to drive based on a yes/no response to the question "Right now do you feel safe to drive?" A visual analogue scale (VAS) evaluation of subject self-motivation and driving performance was administered immediately after each driving simulation. Subjects were instructed to indicate: "How motivated did you feel to drive at your best during the last 60 min of driving?" and "How well you think you drove for the last 60 min?" Subjects recorded responses by drawing a vertical line on a 100-mm horizontal line. Scores were measured to the nearest millimetre from the left.

Blood samples were obtained pre- and post-dose to measure lasmiditan plasma concentrations in both studies, assayed by validated supported liquid extraction method. Serial blood draws were performed post-dose in Study 2, whereas only a single post-dose blood draw was performed at the end of the driving simulation in Study 1. The relationship between lasmiditan concentrations and driving performance (SDLP) was evaluated in a pharmacokinetic/pharmacodynamic (PK/PD) model.

Safety evaluations included physical examinations, medical history, prior and concomitant medication usage, clinical laboratory tests, electrocardiograms (ECGs), vital signs and adverse events categorized by seriousness, severity and relationship to study drug.

## 2.4 | Statistical methods

For primary and secondary endpoints (except as noted), pairwise comparisons of differences in least square (LS) means and corresponding 95% confidence intervals (CIs) of the differences were provided by time point for each lasmiditan dose versus placebo and for the active control versus placebo.

The primary endpoint of placebo-subtracted SDLP was analysed in a mixed effects model with fixed effects for sequence, period, and treatment and either random effect for subject within sequence using variance component covariance structure (Study 1) or repeated observations for subjects for each time point using unstructured covariance structure (Study 2), with Kenward-Roger degrees of freedom. Within-subject differences in SDLP were tested for symmetry about zero using the maximally-selected McNemar's test. Additionally, within-subject differences in SDLP >4.4 cm (the a priori threshold defined for the CRCDS-miniSim) in absolute values were compared using McNemar's test.

Secondary endpoints (excluding total collisions and self-reported safety to drive) were analysed by time point using a mixed repeated-measures model similar to the SDLP analysis. Separate models were used for each time point. Lane exceedance was log-transformed as ln [x + 1] prior to analyses. Pairwise comparisons for self-reported safety to drive were analysed using McNemar's test (Laska, Meisner, & Wanderling, 2012). The total number of collisions by time point and treatment group was summarized with descriptive statistics. Differences in number of collisions for each pairwise comparison were evaluated with their corresponding Wilcoxon Signed Rank *p*-value and pooled total number of collisions (0, 1, 2 or ≥3) by treatment group.

To address multiplicity of testing, ascending doses of lasmiditan were interpreted in a sequential manner in both studies, and additionally by descending time points for Study 2 (starting with the lowest dose at 24 hr, proceeding to the highest dose and earlier time points via a multiple comparisons procedure). In both studies, lasmiditan doses were non-inferior to placebo if the upper limit of the 95% CI for the mean placebo-subtracted SDLP difference was <4.4 cm. No adjustments were made to alpha-levels for comparison of active control to placebo or lasmiditan, or for secondary endpoints or analyses. Control of type I error for non-inferiority for the primary endpoint was at a 1-sided alpha = 0.025.

The PK/PD relationship to SDLP was described by $SDLP=BASE \cdot (1 + SLP(t) \cdot CONC^{\gamma})$, where BASE is placebo baseline SDLP, $\gamma$ is the exponent on lasmiditan plasma concentrations (CONC), and SLP(t) is a proportionality factor with exponential decrease over time.

Data were collected by Algorithme Pharma, Inc. (Laval, Quebec, Canada) for Study 1 and Covance Clinical Research Units (Dallas, Texas; Daytona Beach, Florida; and Madison, Wisconsin) for Study 2. Subject disposition and characteristics, PK, and safety endpoints were summarized using descriptive statistics. Adverse events were coded by system organ class and preferred term per Medical Dictionary for Regulatory Activities version 16.1 (Study 1) or 20.1 (Study 2).

# 3 | RESULTS

## 3.1 | Subject population

Study 1 enrolled 90 healthy subjects, of whom 84 subjects (93.3%) completed the study. Reasons for discontinuation included protocol deviations in 2 subjects who had positive urine screens for prohibited drugs, elective withdrawal by 2 subjects, an adverse event (dislocated shoulder) unrelated to study treatment for 1 subject, and an unspecified reason for 1 subject. All 90 enrolled subjects received at least one dose of study drug and were included in all analyses.

Study 2 enrolled 68 healthy subjects, of whom 67 subjects (98.5%) completed the study. One subject electively withdrew due to a family emergency. All 68 enrolled subjects received at least one dose of study drug and were included in all analyses.

Overall subject demographics and baseline characteristics were similar in both studies (Table 2). Mean age was 33 to 35 years, and sex was relatively equally distributed in each study (48.9% male in Study 1, 58.5% male in Study 2). Study 2 enrolled a more racially diverse population than Study 1 (Table 2). Review of subjects' medical history and prior and concomitant medication usage were deemed to have no important impact on study assessments or outcomes.

## 3.2 | Standard deviation of lateral position

Sensitivity of the simulator and analysis models were supported by significant SDLP findings on the driving endpoints for the active control in each study compared with placebo (Figure 2).

In Study 1, dose-related driving impairment was observed for lasmiditan 50-, 100- and 200-mg versus placebo in the simulator driving assessment that commenced at 1.5 hr post-dose (Figure 2a; Table S1). For each dose of lasmiditan, the upper limit of the 95% CI exceeded the 4.4-cm non-inferiority margin. These results were confirmed by symmetry analysis.

In Study 2, lasmiditan 100 and 200-mg were non-inferior to placebo at the 8-hr primary analysis time point (non-inferiority $p \leq .0002$) (Figure 2b; Table S2). There was a small impairment of simulated driving performance observed at 8 hr after lasmiditan dosing. However, since the upper limit of the 95% confidence interval did not exceed the 4.4-cm non-inferiority margin, the magnitude of impairment was not considered to be clinically meaningful. There was no observed impairment on simulated driving performance for lasmiditan as measured by SDLP at 12 or 24 hr post-dose (Tables S3 and S4). These outcomes were supported by symmetry analyses at all time points.

**TABLE 2** Subject demographics at baseline

| | Study 1 (*N* = 90) | Study 2 (*N* = 68) |
|---|---|---|
| **Age, years** | | |
| Mean (*SD*) | 34.9 (8.1) | 32.8 (7.1) |
| Median (range) | 34 (22–49) | 32 (20–48) |
| **Gender, *n* (%)** | | |
| Female | 46 (51.1) | 28 (41.2) |
| Male | 44 (48.9) | 40 (58.8) |
| **Ethnicity, *n* (%)** | | |
| Hispanic or Latino | 15 (16.7) | 12 (17.6) |
| Not Hispanic or Latino | 75 (83.3) | 56 (82.4) |
| **Race, *n* (%)** | | |
| Asian | 2 (2.2) | 5 (7.4) |
| Black or African American | 4 (4.4) | 19 (27.9) |
| White | 84 (93.3) | 41 (60.3) |
| Multiple | 0 | 3 (4.4) |
| **Body mass index, kg/m$^2$** | | |
| Mean (*SD*) | 25.2 (3.6) | 25.9 (4.1) |
| Median (range) | 25 (18.9–32.0) | 26.1 (18.2–34.6) |

## 3.3 | Secondary outcomes

Secondary driving and information processing test outcomes were generally consistent with the primary outcome (SDLP) in both studies, reflecting impairment at 1.5 hr post-dose that was not apparent at 8 hr post-dose for lasmiditan versus placebo (Figure 3). The absence of clinically meaningful impairment at 8 hr following lasmiditan dosing in Study 2 remained generally consistent at 12 and 24 hr. Selected driving and information processing measures presented include representative outcomes for domains of driving impairment believed to be most sensitive to sedation effects, relevant to crash risk or both. Additionally, results for lane exceedance, total collisions and subject self-appraisals are detailed below.

### 3.3.1 | Lane exceedance

In Study 1, the number of lane exceedances was significantly higher for all doses of lasmiditan compared with placebo at 1.5 hr post-dose (Figure 3a). The maximum lane exceedance was significantly greater, and the duration of lane exceedance was significantly longer, for all doses of lasmiditan versus placebo ($p < .001$).

In Study 2, there was no statistically significant effect of lasmiditan 100-mg on the number of lane exceedances at 8 hr, but a statistically significant increase in the number of lane exceedances was observed for lasmiditan 200-mg (Figure 3b). At 12 hr there was a small but statistically significant increase in the number of lane exceedances for lasmiditan 100-mg compared with placebo ($p = .0267$), and a similar, but statistically non-significant, increase in the number of lane exceedances for lasmiditan 200-mg versus placebo. At 24 hr there was no statistically significant effect of either dose of lasmiditan, and the number of lane exceedances was lower than for placebo. There was no statistically significant increase in lane exceedance maximum or duration for either dose of lasmiditan compared with placebo at any time point.

### 3.3.2 | Collisions

In Study 1, lasmiditan administration was associated with a significantly greater number of total collisions compared with placebo at 1.5 hr post-dose, which increased with higher lasmiditan dose, although most subjects overall had no collisions (Figure 3a).

In Study 2, collisions were infrequent for all treatments at 8 hr post-dose (Figure 3b). This was also the case at 12 and 24 hr post-dose.

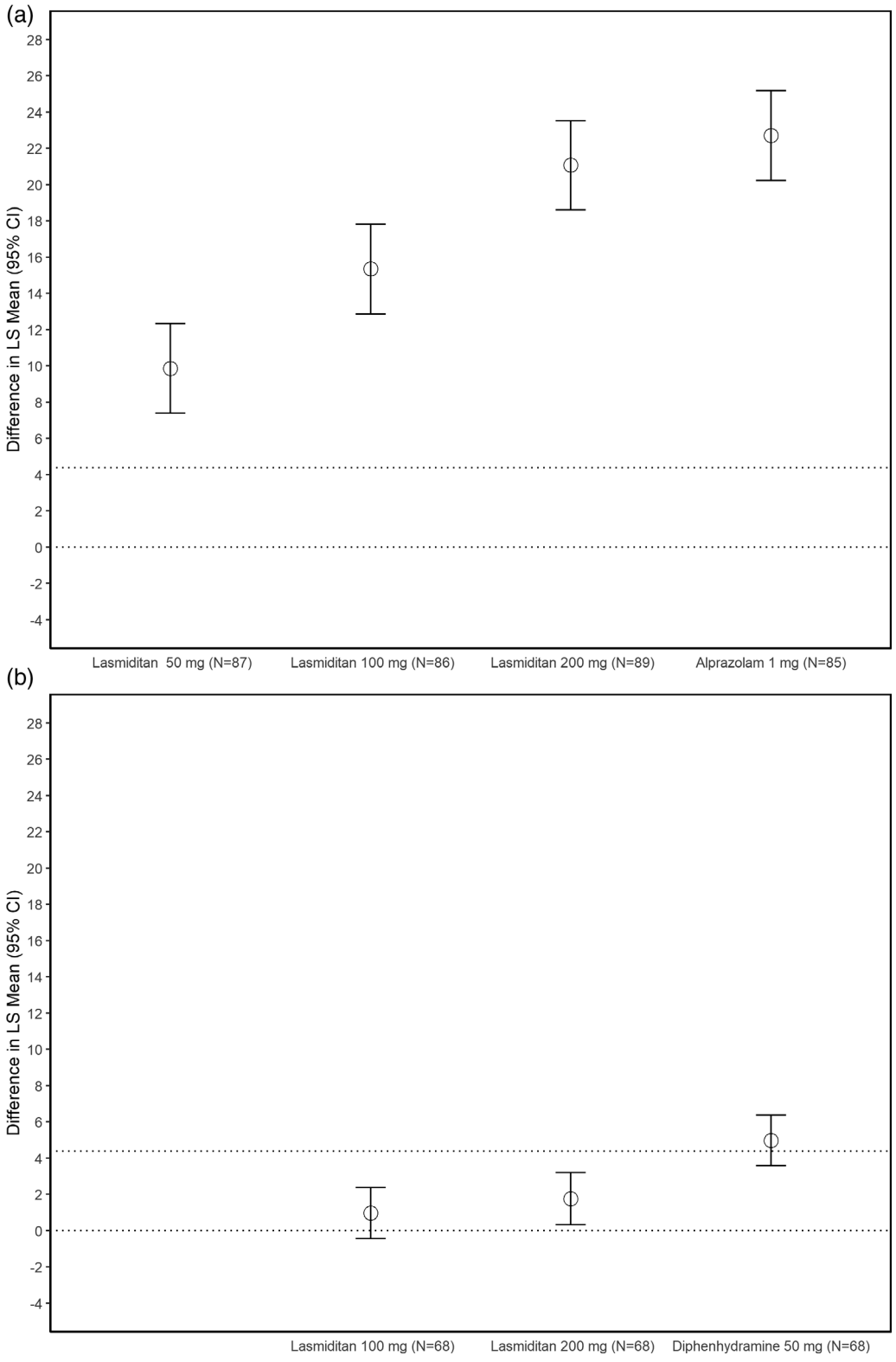


**FIGURE 2** Standard Deviation of Lateral Position (SDLP). The primary endpoint of SDLP was assessed on the driving simulator at (a) 1.5 hr post-dose in Study 1 and (b) 8 hr post-dose in Study 2 (with active control diphenhydramine administered 2 hr prior to driving assessments), and compared to a 4.4-cm placebo-subtracted non-inferiority margin associated with impairment. Data represent differences from placebo in least squares (LS) means with 95% confidence intervals

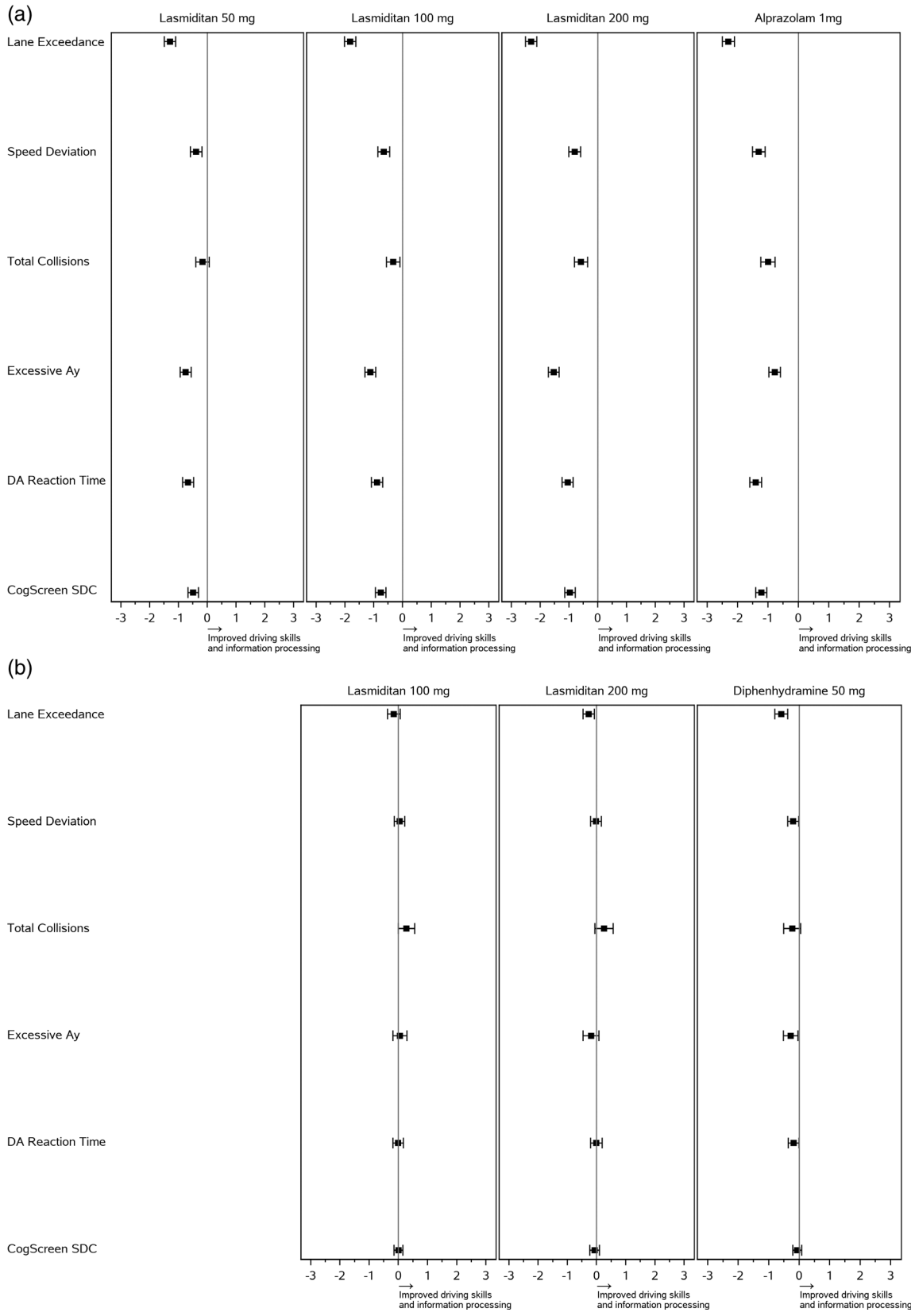


**FIGURE 3** Secondary assessments. Driving simulation assessments of lane exceedance, speed deviation, total collisions, excessive Ay, divided attention (DA) reaction time, and CogScreen Symbol Digit Coding (SDC) were evaluated (a) 1.5 hr post-dose in Study 1 and (b) 8 hr post-dose in Study 2 (with active control diphenhydramine administered 2 hr prior to driving assessments). Data represent differences from placebo in least squares (LS) means with 95% confidence intervals (CIs). Results were standardized by dividing each LS mean difference and upper and lower 95% CI by the *SD*

### 3.3.3 | Self-appraisals

In Study 1, subjects reported significantly more sleepiness on the KSS just prior to driving simulation at approximately 1.5 hr following administration of all lasmiditan doses and alprazolam 1-mg compared with placebo ($p < .0001$). Placebo was associated with an LS mean KSS score of 2.8 compared with 4.4, 5.1 and 5.7 for lasmiditan 50, 100 and 200-mg doses and 6.2 for alprazolam 1-mg. Subjects rated themselves on the VAS as significantly less motivated to drive at the best of their ability and had poorer self-evaluated driving performance after all doses of lasmiditan versus placebo ($p < .0001$). In contrast, most subjects indicated they felt safe to drive at approximately 1.5 hr after administration of lasmiditan 50-mg (80.0%), 100-mg (67.9%) and 200-mg (55.3%) compared with fewer than half of subjects following dosing with alprazolam 1-mg (43.5%).

In Study 2, there were no clinically meaningful differences in subjective sleepiness on the KSS between either lasmiditan dose and placebo at 8, 12 or 24 hr. There were no significant differences in VAS self-reported motivation or performance for either dose of lasmiditan versus placebo at any time point. All subjects indicated they were safe to drive following administration of all study drugs at 8 hr. Only 1 subject at 12 hr and 2 subjects at 24 hr indicated that they did not feel safe to drive, all following dosing with diphenhydramine 50-mg (administered 2 hr prior to each time point).

## 3.4 | Lasmiditan pharmacokinetics

Lasmiditan PK appeared to be consistent between the two studies. Single oral doses of lasmiditan were rapidly absorbed and eliminated, with median time to maximum concentration of about 2 hr and mean elimination half-life of about 4.25 hr post-dose. Exposure to lasmiditan was approximately dose proportional over the evaluated dose range.

The estimate for the model parameters, BASE and $\gamma$, were 29.3 cm and 0.51, respectively. SLP(t) was defined by the function $SLP(t) = 0.0628\ [cm/ng/mL] \cdot e^{-\log(2)/1.76 \cdot time}$. Based on the PK/PD model, the predicted placebo-subtracted SDLP increased in a concentration-dependent manner at 1.5 hr post-dose, whereas it did not appear to increase with increasing lasmiditan concentrations at 8, 12 and 24 hr post-dose (Figure 4).

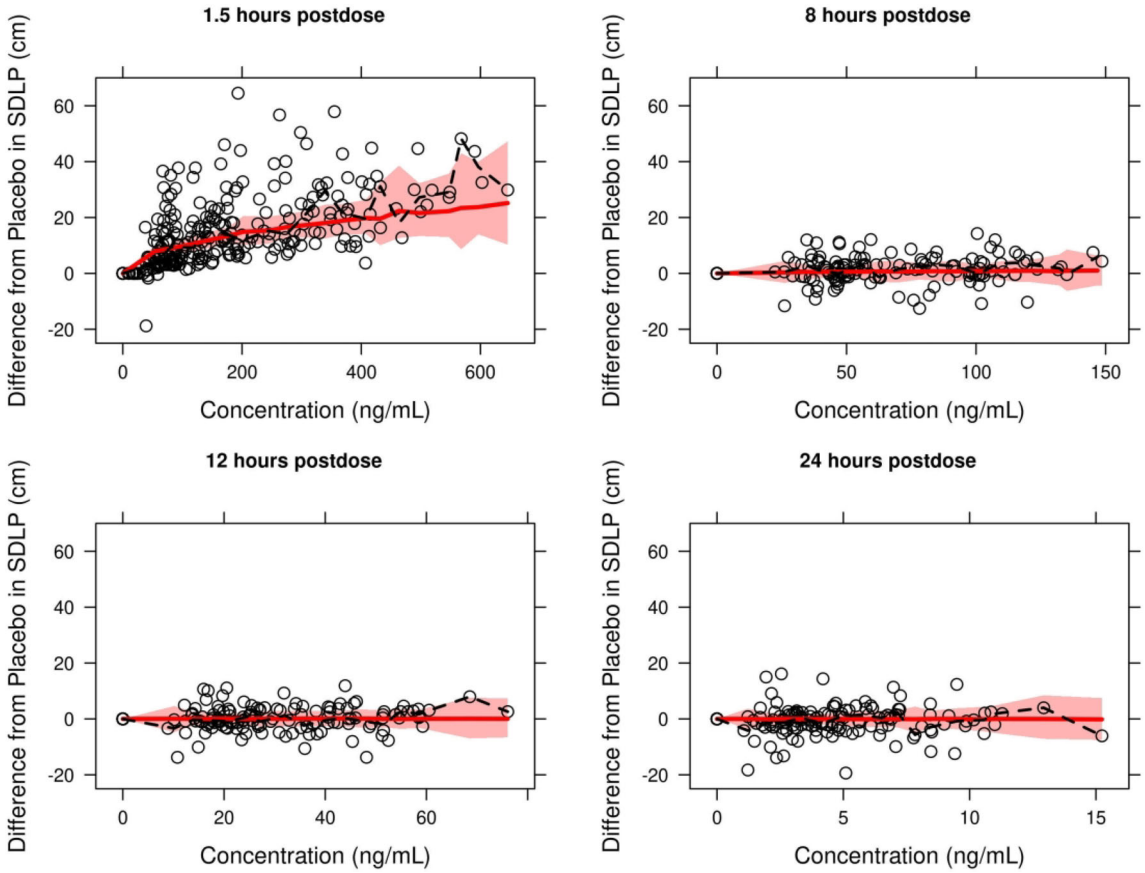


**FIGURE 4** Standard Deviation of Lateral Position (SDLP) versus lasmiditan concentration. Data represent the relationship between placebo-subtracted SDLP and lasmiditan concentrations at 1.5 hr (Study 1) and at 8, 12 and 24 hr (Study 2) as evaluated in a pharmacokinetic/pharmacodynamic (PK/PD) model. Black points and dashed lines represent the observed individual and median data, respectively. Red lines and shaded area represent the model-predicted median and 95% confidence interval, respectively. Note that the *x*-axis for each panel is scaled to the lasmiditan concentration range at the respective time point to facilitate visualization of the PK/PD relationship

### 3.5 | Safety findings

In Study 1, the highest overall incidence of treatment-emergent adverse events was reported after dosing with alprazolam 1-mg, followed by lasmiditan 200-mg, with incidences decreasing with decreasing lasmiditan dose (Table 3). Most adverse events were mild or moderate in severity, and most were considered related to study treatment. The most common adverse events were somnolence, dizziness and fatigue. After dosing with alprazolam 1-mg, the most common adverse event was somnolence. Few adverse events were reported for placebo with the most common being headache. One subject had a severe, serious adverse event of cerebellar hematoma in the final treatment period after receiving placebo, considered unrelated to study treatment; this subject had received all doses of lasmiditan and alprazolam. Another subject had a severe adverse event of bladder pain after dosing with alprazolam; this subject had previously received all doses of lasmiditan and placebo and no clinical concerns were identified regarding treatment sequence.

In Study 2, higher overall incidences of treatment-emergent adverse events were reported after administration of lasmiditan compared with placebo or diphenhydramine 50-mg (Table 3). All adverse events were mild in severity, and most were considered related to study treatment. The most common adverse events were dizziness, somnolence and fatigue, reported at similar frequencies across lasmiditan doses. The most common adverse event after dosing with diphenhydramine 50-mg was somnolence and after placebo administration was nausea. The majority of adverse events were resolved prior to the 8-hr driving assessment.

In both studies, safety assessments of vital signs, ECGs, and clinical laboratory tests suggested no new safety signals or notable findings related to study treatment or to lasmiditan.

## 4 | DISCUSSION

Driving performance on a validated measure of driving impairment (SDLP) was shown to be significantly impaired on simulator

**TABLE 3** Treatment-emergent adverse events reported in five or more subjects in either study

| | Study 1 | | | | | Study 2 | | | |
|---|---|---|---|---|---|---|---|---|---|
| | Placebo *N* = 85 | Lasmiditan 50 mg *N* = 87 | Lasmiditan 100 mg *N* = 86 | Lasmiditan 200 mg *N* = 89 | Alprazolam 1 mg *N* = 85 | Placebo *N* = 67 | Lasmiditan 100 mg *N* = 68 | Lasmiditan 200 mg *N* = 68 | Diphenhydramine 50 mg *N* = 68 |
| **Any event, *n* (%)** | **18 (21.2)** | **39 (44.8)** | **56 (65.1)** | **67 (75.3)** | **76 (89.4)** | **11 (16.4)** | **29 (42.6)** | **30 (44.1)** | **12 (17.6)** |
| Somnolence | 2 (2.4) | 10 (11.5) | 23 (26.7) | 38 (42.7) | 45 (52.9) | 0 | 6 (8.8) | 7 (10.3) | 5 (5.9) |
| Dizziness | 1 (1.2) | 14 (16.1) | 17 (19.8) | 36 (40.4) | 26 (30.6) | 1 (1.5) | 11 (16.2) | 12 (17.6) | 1 (1.5) |
| Fatigue | 2 (2.4) | 15 (17.2) | 10 (11.6) | 7 (7.9) | 14 (16.5) | 1 (1.5) | 7 (10.3) | 4 (5.9) | 1 (1.5) |
| Headache | 3 (3.5) | 8 (9.2) | 3 (3.5) | 6 (6.7) | 6 (7.1) | 0 | 3 (4.4) | 6 (8.8) | 1 (1.5) |
| Nausea | 0 | 3 (3.4) | 5 (5.8) | 6 (6.7) | 3 (3.5) | 4 (6.0) | 2 (2.9) | 2 (2.9) | 1 (1.5) |
| Lethargy | 0 | 3 (3.4) | 4 (4.7) | 7 (7.9) | 3 (3.5) | 0 | 0 | 0 | 0 |
| Paraesthesia | 0 | 1 (1.1) | 0 | 2 (2.2) | 0 | 1 (1.5) | 4 (5.9) | 6 (8.8) | 0 |
| Vision blurred | 0 | 3 (3.4) | 3 (3.5) | 3 (3.4) | 3 (3.5) | 0 | 1 (1.5) | 1 (1.5) | 0 |
| Feeling abnormal | 1 (1.2) | 2 (2.3) | 2 (2.3) | 3 (3.4) | 3 (3.5) | 0 | 1 (1.5) | 2 (2.9) | 0 |
| Hypoesthesia | 0 | 1 (1.1) | 4 (4.7) | 5 (5.6) | 0 | 0 | 1 (1.5) | 2 (2.9) | 0 |
| Feeling cold | 1 (1.2) | 0 | 4 (4.7) | 0 | 3 (3.5) | 0 | 1 (1.5) | 0 | 0 |
| Chills | 0 | 1 (1.1) | 4 (4.7) | 1 (1.1) | 1 (1.2) | 0 | 1 (1.5) | 0 | 0 |
| Disturbance in attention | 0 | 0 | 3 (3.5) | 1 (1.1) | 1 (1.2) | 0 | 2 (2.9) | 1 (1.5) | 0 |
| Asthenia | 0 | 1 (1.1) | 0 | 2 (2.2) | 3 (3.5) | 0 | 1 (1.5) | 0 | 0 |
| Oropharyngeal pain | 1 (1.2) | 1 (1.1) | 3 (3.5) | 1 (1.1) | 0 | 0 | 1 (1.5) | 0 | 0 |
| Diarrhoea | 0 | 1 (1.1) | 0 | 0 | 0 | 1 (1.5) | 1 (1.5) | 3 (4.4) | 1 (1.5) |
| Rhinorrhoea | 1 (1.2) | 1 (1.1) | 1 (1.2) | 0 | 2 (2.4) | 0 | 1 (1.5) | 0 | 0 |
| Bradyphrenia | 0 | 1 (1.1) | 2 (2.3) | 1 (1.1) | 2 (2.4) | 0 | 0 | 0 | 0 |
| Hiccups | 0 | 0 | 0 | 0 | 5 (5.9) | 0 | 0 | 0 | 0 |

assessments that commenced at 1.5 hr after dosing with 50-, 100- and 200-mg lasmiditan, compared with placebo. The SDLP increases following lasmiditan administration at all doses suggested more vehicle weaving and therefore decreased vehicle control. These SDLP increases exceeded the a priori non-inferiority margin of 4.4-cm, a placebo-subtracted threshold established for the CRCDS-miniSim that represents the impairment noted in subjects with a BAC of 0.05%. A consistent lasmiditan dose-related impairment was also evident on secondary driving measures including lane exceedance, speed control, and other safety-related measures. Similarly, compared with placebo, lasmiditan at 1.5 hr post-dose showed a dose-related impact on self-reported alertness and information processing speed.

The active control alprazolam 1-mg confirmed assay sensitivity for the primary endpoint in Study 1 as well as demonstrated statistically significant differences versus placebo on secondary endpoints. As Study 1 identified significant driving impairment around the time of peak lasmiditan concentration, Study 2 was conducted to identify the duration of that effect and to help inform patients and health care providers regarding administration of lasmiditan.

Study 2 showed no clinically meaningful impairment on simulated driving performance for lasmiditan 100- or 200-mg at 8, 12 or 24 hr post-dose. In the primary analysis of SDLP, performance was non-inferior to placebo for both doses of lasmiditan at all time points tested. A small but not clinically meaningful decrease in lane position control was observed at 8 hr post-dose following dosing with lasmiditan 200-mg. There was no evidence of any impairing effect for either dose of lasmiditan at 12 or 24 hr post-dose. Secondary measures supported the SDLP results, generally showing no significant or clinically meaningful effects of lasmiditan at either dose at 8, 12 or 24 hr post-dose.

Consistent with other driving studies, diphenhydramine 50-mg served as the active control for Study 2, administered 2 hr prior to simulated driving assessments to ensure maximum cognitive and sedative effects (Kay et al., 1997; Kay et al., 2016; Ramaekers & O'Hanlon, 1994). Diphenhydramine demonstrated assay sensitivity for the primary endpoint and showed statistically significant differences versus placebo for most secondary endpoints at each time point.

Following treatment with lasmiditan, placebo-subtracted SDLP increased in a lasmiditan concentration-dependent manner at 1.5 hr but not at 8, 12 and 24 hr post-dose, despite some overlapping concentration ranges. The mechanism by which the dissipation of simulated driving impairment occurs more rapidly than the associated decline in lasmiditan plasma concentrations is unknown, but acute tolerance of benzodiazepines such as alprazolam on psychomotor effects has been previously reported (Barbanoj, Urbano, Antonijoan, Ballester, & Valle, 2007). One potential explanation for the effects on simulated driving is somnolence, which was among the most common treatment-emergent adverse events in both studies. Somnolence was reported for lasmiditan in a dose-dependent manner (up to 42.7%) at the 1.5-hr time point in Study 1, and was generally resolved by the 8-hr time point in Study 2. Importantly, not all participants in Study 1 reported somnolence, though almost all participants showed significant driving impairment at the 1.5-hr time point.

One possible limitation in interpreting the lasmiditan simulated driving results is the enrolment of only healthy volunteers. It is not known whether these effects would be similar in a population of patients with migraine, either during migraine-free periods or during treatment of a migraine attack. This limitation is balanced by the similarity in PK and safety profiles between healthy adult subjects and patients with migraine when compared collectively across prior clinical trials.

Relatively high proportions of subjects reported they felt safe to drive just prior to assessments commencing at 1.5 hr after lasmiditan administration in Study 1, despite simulated driving test parameters demonstrating significant impairment. The lack of association between subjective assessments and driving performance has been well-documented (Verster & Roth, 2012). The FDA guidance notes that subjects' perception of driving ability is inadequate to evaluate driving impairment, and emphasizes the need for objective assessment of driving performance (FDA, 2017).

## 5 | CONCLUSION

Lasmiditan was associated with impaired simulated driving performance at 1.5 hr post-dose, which corresponds to the approximate time of peak plasma concentration. Clinically meaningful driving impairment was not observed at 8, 12 or 24 hr after lasmiditan administration. Patients taking lasmiditan are cautioned not to engage in potentially hazardous activities requiring complete mental alertness, such as driving a motor vehicle or operating machinery, for at least 8 hr after each dose of lasmiditan. Patients and prescribers should be aware that patients may not be able to assess their own driving competence and the degree of impairment caused by lasmiditan.

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### CONFLICT OF INTEREST

E. M. P., D. W., E. B. D., P. H. B., M. T. and E. G. D. are full-time employees and shareholders of Eli Lilly & Company (Indianapolis, IN, USA). GGK is an executive of Cognitive Research Corporation (St. Petersburg, FL, USA) which provided paid consulting services to Eli Lilly & Company (Indianapolis, IN, USA).

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## SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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