

RESEARCH ARTICLE

Next-day residual effects of flibanserin on simulated driving performance in premenopausal women

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Abstract

Objective: The objective of this study was to determine the next-day residual effects of acute and steady-state nighttime dosing of flibanserin on simulated driving performance and cognitive function in healthy premenopausal women.

Methods: In this randomized, double-blind, placebo-controlled, four-way crossover study, 72 subjects were treated with either acute oral doses of placebo, zopiclone 7.5 mg (positive control) or flibanserin 100 mg at bedtime (indicated therapeutic dose), or after chronic nightly oral doses of flibanserin 100 mg for 1 week followed by a single bedtime dose of flibanserin 200 mg (supratherapeutic dose). Simulated driving assessments were conducted 9 hr after dosing and cognitive function tests were administered immediately before or during the driving assessment.

Results: Zopiclone increased standard deviation of lateral position (≥ 3.1 cm; $p < .0001$) relative to placebo and impaired other parameters previously shown to be sensitive to sedation. No impairment was detected for flibanserin at either dose relative to placebo. Flibanserin 200 mg was similar to the 100-mg dose on cognitive testing and driving performance even though commonly reported adverse events for flibanserin were predictably increased at the higher dose.

Conclusions: At both therapeutic and supratherapeutic doses, flibanserin did not impair next-day driving performance and cognitive function compared to placebo.

KEYWORDS

Addyi, hypoactive sexual desire disorder, multifunctional serotonin agonist and antagonist

1 | INTRODUCTION

Flibanserin (FLI; Addyi) is a multifunctional serotonin agonist and antagonist that has recently been approved by the U.S. Food and Drug Administration (FDA) for the treatment of acquired, generalized hypoactive sexual desire disorder (HSDD) in premenopausal women (Addyi Package Insert, 2016; Joffe et al., 2016; Stahl, 2015). HSDD is defined as the persistent lack of sexual desire that causes marked distress or interpersonal difficulty and is not due to (a) a coexisting medical or psychiatric condition, (b) problems within the relationship, or (c) the effects of medication or other drug substance (American Psychiatric Association, 2000). HSDD in women has an estimated overall prevalence of 7.4% in the United States with a significant negative impact on health-related quality of life and has been associated with higher healthcare expenditure (16.8% greater than a control group with no sexual dysfunction) and a health-related quality of life similar to diabetes and chronic back pain (Biddle et al., 2009; Foley, Foley, & Johnson,

2010; Leiblum, Koochaki, Rodenberg, Barton, & Rosen, 2006; Maserejian et al., 2010; Rosen et al., 2012).

FLI's mechanism of action has not been fully characterized, but its primary pharmacological activity involves the activation of post-synaptic 5-HT_{1A} receptors and inhibition of post-synaptic 5-HT_{2A} receptors (Stahl, 2015; Stahl, Sommer, & Allers, 2011). FLI also acts as an antagonist on 5-HT_{2B} and 5-HT_{2C} receptors and has been shown to have either antagonistic or weak agonist activity on dopamine D₄ receptors (Stahl et al., 2011). While its clinical usefulness in treating HSDD has been controversial (Goldstein, Simon, & Parish, 2016; Jaspers et al., 2016; Joffe et al., 2016), consistent efficacy has been demonstrated in three pivotal phase III trials in premenopausal women (Derogatis et al., 2012; Katz et al., 2013; Thorp et al., 2012). In these trials, FLI 100 mg once daily significantly increased sexual desire and function while decreasing distress relative to placebo (PBO). These findings were further confirmed by a recent meta-analysis (Gao, Yang, Yu, & Cui, 2015), and similar findings were

reported in a phase III trial in naturally postmenopausal women with HSDD (Simon et al., 2013).

Clinically, the most common adverse events in premenopausal women included somnolence, dizziness, nausea, and fatigue (Derogatis et al., 2012; Katz et al., 2013; Thorp et al., 2012). While the recommended oral dosing for FLI is 100 mg, once daily at bedtime, the degree to which sedative effects might persist and influence cognitive function remained uncertain. Thus, a randomized, multiple-dose, double-blind, PBO-controlled, four-way, four-period crossover phase I study was conducted to determine the next-day residual effects of FLI in healthy premenopausal female subjects. This study was designed in accordance with the recommendations of the FDA prior to approval of Addyi and before the FDA's draft guidance document for evaluating drug effects on the ability to operate a motor vehicle became available in January 2015 (Food and Drug Administration, Center for Drug Evaluation and Research, 2015). Using well-established simulated driving and cognitive performance assessments, both acute and steady-state nighttime doses of FLI 100 mg and the acute effect of a suprathreshold dose of FLI (200 mg) were compared to PBO and zopiclone (ZOP) 7.5 mg as a positive control. The effect of ZOP on driving has been well established in the epidemiology and toxicology literature, as well as in prior over-the-road and simulated driving research (Leufkens, Lund, & Vermeeren, 2009; Leufkens & Vermeeren, 2014; Mets et al., 2011; Verster, Spence, Shahid, Pandi-Perumal, & Roth, 2011).

2 | MATERIAL AND METHODS

2.1 | Study participants

Subjects were premenopausal healthy women between the ages of 18 and 50 years old with a valid driver's license and who were active drivers for 3 years prior to study start. Two hundred fifty-seven women were screened, 83 subjects were randomized to treatment sequence, and 72 completed all four treatment periods of the study. All study participants provided informed consent, and procedures were in accordance with the ethical standards of the overseeing human subjects research committee (Institutional Review Board Services, Aurora, Ontario, Canada) and with the Helsinki Declaration, the International Conference on Harmonization, Good Clinical Practice guidance, and applicable Health Canada requirements.

Subjects were required to have a regular sleep pattern (with normal bedtime between 21:00 and 24:00 hr) and a score <10 on the Epworth Sleepiness Scale with no recent history of sleep disorder. With the exception of hormonal birth control, subjects were to abstain from using prescription or nonprescription drugs, vitamins, dietary supplements, herbal supplements, grapefruit-containing foods and beverages, or Seville orange-containing foods and beverages from 14 days before first admission to the clinical research unit until discharge from the study. Acetaminophen (paracetamol) could be used intermittently throughout the study, but the dose was not to exceed 1 g/day.

Subjects were not allowed to consume alcoholic beverages from 48 hr prior to admission to the clinical research unit before simulated driving and cognitive function assessments and until after completion

of all assessments for each period. At all other times, alcohol consumption was limited to no more than three alcoholic beverages or equivalent (284 ml of beer or 125 ml of wine or 25 ml of distilled spirits per day). Subjects were also not allowed to consume caffeine-containing products from approximately 1 pm on the days of admission to the clinical research unit and until after completion of all assessments for each period. At all other times, caffeinated beverages were permitted to no more than 4 units per day (1 unit = 120 mg caffeine). Lastly, subjects were instructed to avoid vigorous physical activity at least 24 hr prior to admission to the clinical research unit and until after completion of all assessments for each period. At all other times, there were no limitations to physical activity.

2.2 | Study design

This was a randomized, multiple-dose, double-blind, PBO-controlled, Latin-square design with four-way, four-period (full) crossover study. Subjects were randomized to treatment sequences (one treatment group per period for four periods) and completed all four treatment periods within the treatment group to which they were randomized. All dosing occurred in the evenings at bedtime.

Treatment groups:

- Treatment A (FLI 100 mg acute and steady-state dosing): FLI 100 mg + ZOP PBO on Night 1, FLI only on Nights 2–6, and FLI 100 mg + FLI PBO + ZOP PBO on Night 7.
- Treatment B (ZOP acute dosing): ZOP 7.5 mg + FLI PBO on Night 1, FLI PBO only on Nights 2–6, and FLI PBO (2) + ZOP 7.5 mg on Night 7.
- Treatment C (PBO): ZOP PBO + FLI PBO on Night 1, FLI PBO only on Nights 2–6, and FLI PBO (2) + ZOP PBO on Night 7.
- Treatment D (FLI 100 mg steady-state dosing with 200 mg suprathreshold Day 7 dose): FLI 100 mg + ZOP PBO on Night 1, FLI 100 mg only on Nights 2–6, and FLI 100 mg (×2) + ZOP PBO on Night 7.

Subjects were randomized equally (1:1:1:1) into one of four treatment sequences, as shown in Table 1. Each treatment period was approximately 1 week in duration ±2 days. The washout between treatment periods was approximately 5–7 days (minimum 5 days to a

TABLE 1 Treatment sequences for crossover study

Treatment sequence	Period 1	Period 2	Period 3	Period 4
1	A	D	B	C
2	B	A	C	D
3	C	B	D	A
4	D	C	A	B

Note. Treatment A = flibanserin 100 mg on Nights 1–7; Treatment B = zopiclone 7.5 mg on Night 1, flibanserin placebo only on Nights 2–6, and zopiclone 7.5 mg on Night 7; Treatment C = placebo on Nights 1–7; Treatment D = flibanserin 100 mg on Nights 1–6 and flibanserin 100 mg × 2 on Night 7. Each treatment arm included coadministration of placebo pills identical in appearance to flibanserin or zopiclone to equalize the number and type of pills dosed.

maximum 14 days). All active drug and PBO tablets were over-encapsulated to maintain study blind for both subjects and site staff. Subjects were admitted to the clinical research unit 1 day before simulated driving and cognitive assessments and discharged after all assessments were completed. Prior to discharge, subjects were provided instructions on bedtime dosing and provided sufficient medication or PBO for the week.

Subjects were evaluated following a single dose and at steady-state (7 ± 1 days) dosing. Testing was conducted in the morning (on Days 2 and 8) following bedtime doses administered by site staff on the previous evening (Days 1 and 7). Subjects went to bed 30 min after dosing (lights out) and were awakened (lights on) approximately 8 hr (± 5 min) after dosing. After a low-fat breakfast of non-caffeinated foods and beverages and within approximately 60 min of waking, subjects performed the CogScreen symbol digit coding (SDC) test, a sensitive measure of information processing speed (Kane & Kay, 1992; Kay & Horst, 1988; Kay et al., 1997), and the Karolinska Sleepiness Scale (KSS) (Kaida et al., 2006), and indicated their self-perceived safety to drive by answering the question "Right now do you feel safe to drive?" This is a non-validated assessment used for exploratory purposes and was included at the request of the FDA.

Subjects then performed the Country Vigilance Divided Attention driving scenario on the CRCDS-MiniSim driving simulator (Cognitive Research Corp., St. Petersburg, FL; Simen et al., 2015), commencing 9 hr post-dosing. The Country Vigilance Divided Attention required the subject to drive 100 km at 95 kph on a monotonous, simulated two-lane highway that included a secondary visual vigilance task (divided attention). The divided attention assessments included evaluations of accuracy (correct responses) and response speed (reaction time). To familiarize subjects with the driving simulator, subjects were required to perform a practice drive that was approximately 20 min in duration on the driving simulator prior to each in-clinic dose.

Upon completion of the driving scenario, subjects were administered a Visual Analog Scale (VAS) to assess the subject's motivation and self-appraisal of their driving performance. Subjects responded to two separate questions with the VAS: (a) "How well do you think you drove for the last 60 minutes?"; (b) "How motivated did you feel to drive at your best during the last 60 minutes of driving?" Blood samples for the measurement of plasma FLI concentrations were drawn within 10 min before each dosing and at 8 hr (-15 to $+30$ min) after dosing of FLI or PBO to determine systemic FLI concentration immediately prior to simulated driving and cognitive assessments. The total duration of subject participation was approximately 11 weeks (range 11–14 weeks). Sequencing and approximate timing of assessments after dosing are shown in Table 2.

2.3 | Endpoints

The primary endpoint was standard deviation of lateral position (SDLP). Secondary endpoints were assessments of sleepiness (KSS and self-reported readiness to drive) and next-day performance. Performance assessments included CogScreen SDC, lane exceedance, ratio above speed limit, excessive speed count, excessive speed ratio, average speed, speed deviation, speeding count, speeding ratio, excessive A_y (cornering speed threshold), collision count, off-road crashes,

TABLE 2 Schedule of assessments following in-clinic dosing

Assessment	Hours post-dose					
	8.50	8.75	8.83	9.00	10.17	10.25
CogScreen SDC	X					
KSS		X			X	
Self-perceived safety to drive question			X			
CRCDS-MiniSim				X		
VAS of motivation and driving performance						X

Note. SDC = symbol digit coding; KSS = Karolinska Sleepiness Scale; CRCDS = Cognitive Research Corporation Driving Simulator; VAS = Visual Analog Scale.

total collisions, and divided attention parameters (correct responses, omission errors, commission errors, reaction time, and standard deviation [SD] of reaction times). We also administered a single question on the subjects' self-perceived safety to drive and a VAS to assess the subject's motivation and a self-appraisal of driving performance.

2.4 | Data collection and analysis

Data for cognitive and performance assessments were autonomously collected in real time during assessments at the clinical trial site. Responses to questionnaires were manually entered into an electronic database. All data were analyzed by Cognitive Research Corp. SDLP results were analyzed using a mixed model with fixed effects for sequence, period, and treatment, and a random effect for subject within sequence. An unstructured covariance structure and Kenward–Roger degrees of freedom were used. Lane exceedance data were log transformed [$\ln(x + 1)$] prior to analyses. Differences in means and 95% confidence intervals on differences for treatment groups were compared in a pairwise fashion. For the KSS and self-perceived safety to drive question, responses were analyzed using McNemar's test.

3 | RESULTS

3.1 | Demographics, treatment compliance, and pharmacokinetics

Study subjects had a mean (\pm SD) age of 32.4 ± 7.5 and were 92.8% White, 4.8% Black, and 2.4% Asian with 14.5% self-identifying as Latino. Mean body mass index (\pm SD) was 23.9 ± 3.1 . The overall compliance rate of drug dosing was $>99\%$. Out of 1,522 doses, 11 subjects reported 14 missed doses while at home. Nine of these missed doses were with FLI, and the five missed doses were with PBO. In-clinic dosing had 100% compliance.

At steady state, the geometric mean (gMean) plasma concentrations of FLI at ~ 8.25 hr after the last dose (chronic dosing regimen) were 95.3 and 190 ng/ml for the 100- and 200-mg doses, respectively. These data were consistent with previous pharmacokinetic studies (unpublished results) and indicate that proportionality in dosing was achieved.

3.2 | Standard deviation of lateral position (SDLP)

The least squares (LS) mean for SDLP was significantly higher after ZOP administration compared to PBO by 3.107 cm on Day 2 ($p < .0001$) and 3.518 cm on Day 8 ($p < .0001$) (Figure 1 and Table 3). These changes indicate worsening of driving performance with ZOP and confirmed the sensitivity of the test paradigm. The ZOP versus PBO treatment difference approached the increase in SDLP seen with a blood alcohol level of 0.05% using the same driving simulator and driving scenario (i.e., 4.4 cm, data on file at Cognitive Research Corporation).

Compared to PBO, the LS mean for SDLP was significantly lower after acute administration (difference = -2.465 cm; $p = .0009$) or steady-state dosing (difference = -1.788 cm; $p = .0126$) of FLI 100 mg (Figure 1 and Table 3). Compared to PBO, SDLP for the supratherapeutic 200-mg dose of FLI was also lower with an LS mean difference of -1.399 cm, approaching statistical significance ($p = .0502$). When FLI 200 mg was compared to FLI 100 mg at

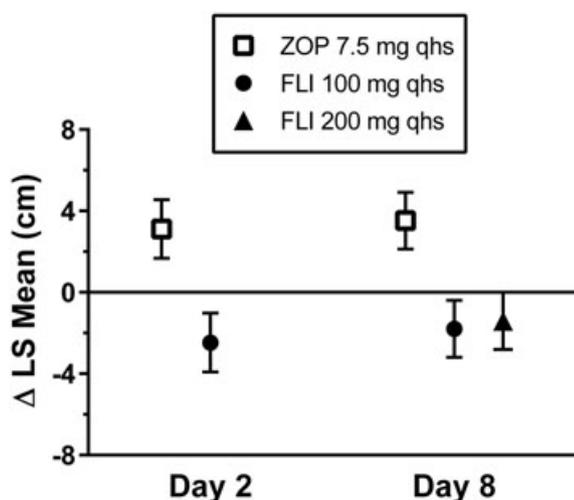


FIGURE 1 Effect of evening dosing of zopiclone (ZOP) and flibanserin (FLI) on standard deviation of lateral position during next-day simulated driving. Healthy female volunteers were administered a single dose of ZOP 7.5 mg or FLI 100 mg in the evening at bedtime and evaluated in a driving simulator approximately 9 hr after dosing (Day 2). The simulated driving assessment was also performed 9 hr after a single evening bedtime dose of FLI 100 mg or 200 mg, preceded by 7 days of evening bedtime dosing with FLI 100 mg (Day 8). For each treatment, the change in least squares (LS) mean and 95% confidence interval for SDLP between active drug and placebo is shown. qhs = once daily at bedtime

steady-state dosing, there was no significant difference between the SDLP results (LS mean difference = -0.390 ; $p = .5818$). This finding was further supported by an analysis designed to detect asymmetry in the distribution (about zero) of within-subject differences between 100 and 200 mg, which failed to achieve statistical significance.

3.3 | SDLP in hormonal contraceptive users

In a subanalysis of hormonal contraceptive users (43% of study subjects), changes in SDLP between treatment groups were consistent with the overall population and similar to nonusers of hormonal contraception. Compared to PBO, ZOP 7.5 mg increased SDLP (LS mean difference was 3.63 cm on Day 2 and 2.85 on Day 8; $p < .025$ for both days), while FLI 100 mg decreased SDLP at both acute (-4.01 cm on Day 2; $p = .005$) and steady state (-2.58 cm on Day 8; $p = .038$) dosing (Figure 2). In hormonal contraceptive users, FLI 200 mg also decreased SDLP relative to PBO by 1.69 cm, but this difference was not statistically significant ($p = .18$). Nevertheless, there was no indication of increased next-day impairment with the supratherapeutic dose of FLI, and there was no difference between the 100- and 200-mg doses of FLI ($p = .47$).

3.4 | Lane exceedances and total collisions

ZOP increased the frequency of lane exceedances relative to PBO on Day 2 (LS mean difference = 0.431 ; $p = .0004$) and Day 8 (LS mean difference = 0.595 ; $p < .0001$). In contrast, FLI 100 mg decreased the frequency of lane exceedance compared to PBO on Day 2 (LS mean difference = -0.28 ; $p = .0213$) and Day 8 (LS mean difference = -0.203 ; $p = .0963$), although this decrease was statistically significant only on Day 2. There was no significant difference between PBO and FLI 200 mg or between FLI 100 mg and FLI 200 mg with respect to lane exceedance. Standardized differences (with 95% confidence intervals) between active drug treatment and PBO for lane exceedances and other secondary endpoints are summarized in the forest plot in Figure 3. Secondary endpoints known to be sensitive to sedation are noted with an arrow.

Most subjects had no collisions while completing the monotonous driving task. However, the maximum number of collisions was higher after ZOP administration, relative to PBO (9 vs. 3 on Day 2 and 13 vs. 5 on Day 8). The difference in mean number of collisions between ZOP and PBO was 0.30 ± 1.45 on Day 2 and 0.30 ± 2.10 on Day 8. These differences were not statistically significant on either day ($p = .108$ for Day 2; $p = .3868$ for Day 8). Compared to PBO, the mean

TABLE 3 Mean and LS mean values for standard deviation of lateral position (units = cm)

Assessment day		PBO (N = 75)	FLI 100 mg (N = 77)	FLI 200 mg (N = 78)	ZOP 7.5 mg (N = 78)
Day 2	Mean (SD)	31.212 (6.269)	28.903 (5.572)	-	34.409 (8.862)
	LS mean	31.446	28.981**	-	34.553***
Day 8	Mean (SD)	30.877 (8.116)	29.201 (5.773)	29.503 (6.090)	34.548 (8.580)
	LS mean	31.050	29.262*	29.651	34.568***

Note. SD = standard deviation; PBO = placebo; FLI = flibanserin; ZOP = zopiclone; LS = least squares.

* $p < .05$ compared to PBO.

** $p < .001$ compared to PBO.

*** $p < .0001$ compared to PBO.

FIGURE 2 Effect of evening dosing of zopiclone (ZOP) and flibanserin (FLI) on next-day simulated driving in nonusers versus users of hormonal contraception (HC). Healthy female volunteers were administered ZOP, FLI, or placebo in the evening at bedtime and evaluated in a driving simulator approximately 9 hr after dosing, as described in Figure 1. For each treatment, the change in least squares (LS) mean and 95% confidence interval for standard deviation of lateral position between active drug and placebo is shown. qhs = once daily at bedtime

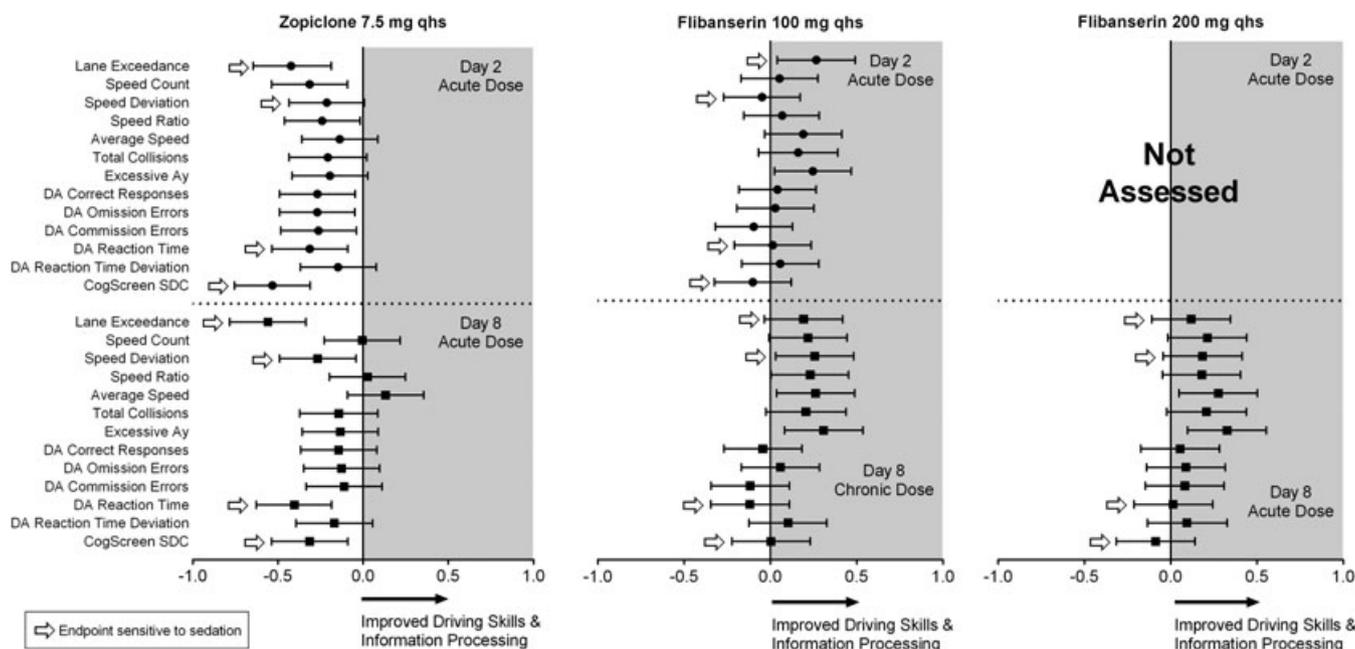
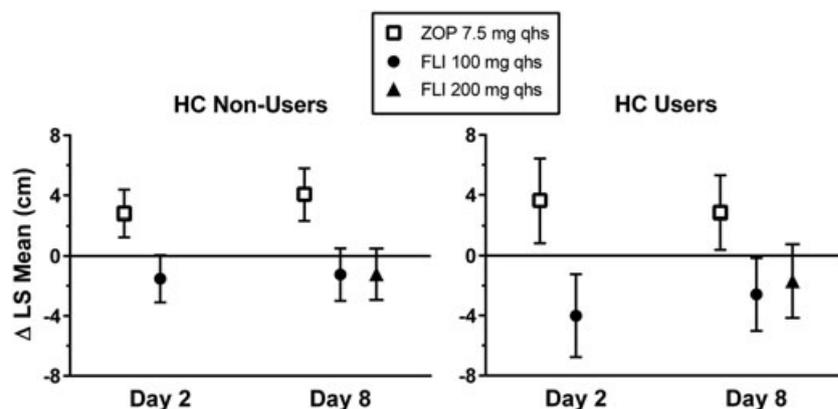


FIGURE 3 Standardized forest plot of secondary assessments for simulated driving and cognitive function. For each parameter, the standardized mean difference between active drug and placebo treatment is shown with the 95% confidence interval. Due to the differences in scale of the various measures, all data were standardized by dividing each of the mean differences and upper and lower limits by the standard deviation. For overall consistency in presentation, the direction of change (negative or positive) and upper and lower limit values were reversed for parameters with negative correlations to driving ability or cognitive function such that an increase to the right of the zero line on the forest plot represents better driving ability and cognitive function, while a decrease to the left of the zero line represents worsening driving ability and cognitive function. Parameters known to be sensitive to sedation are indicated by arrows. DA = divided attention; SDC = symbol digit coding; qhs = once daily at bedtime

number of collisions after administration of FLI 100 mg was slightly smaller on both Day 2 (difference = -0.1 ± 0.62 ; $p = .3125$) and Day 8 (difference = -0.2 ± 0.94 ; $p = .0938$), but these differences were not statistically significant. Further, there was no difference between PBO and FLI 200 mg or between the 100- and 200-mg doses of FLI with regard to the number of collisions.

3.5 | Divided attention tasks and symbol digit coding (SDC) test

Divided attention assessments during simulated driving indicated decreased accuracy and slower reaction time after ZOP treatment compared to PBO. In general, after ZOP treatment, divided attention

assessments were statistically significant on Day 2 but not on Day 8 (Figure 3). The exception was reaction time on the divided attention test, which was statistically significant on both Day 2 ($p = .0061$) and Day 8 ($p = .0004$) when comparing ZOP to PBO. There were no significant differences between PBO and acute or steady-state dosing with FLI 100 mg or with the 200-mg dose of FLI for any of these measures (Figure 3).

Performance on the CogScreen® SDC test (number of correct responses) was significantly poorer following treatment with ZOP than following PBO on Day 2 (LS mean difference = -2.78 ; $p < .0001$) and on Day 8 (LS mean difference = -2.00 ; $p = .0062$). There was no evidence of a worsening of performance on this measure following treatment with FLI 100 mg compared to PBO on Day 2 (LS mean

difference = -0.53 ; $p = .3728$) and on Day 8 (LS mean difference = 0.02 ; $p = .9750$). In addition, there was no significant difference between PBO and FLI 200 mg (LS mean difference = -0.55 ; $p = .45$) or between the 100- and 200-mg doses of FLI with respect to SDC performance on Day 8 (LS mean difference = 0.57 ; $p = .43$).

Reaction time was also measured during the SDC test and analyzed as the SD of reaction time. Compared to PBO, SD of reaction times were significantly increased by 44 ms on Day 2 after ZOP administration ($p = .0028$), but not significantly different on Day 8 after ZOP administration (LS mean difference = 19 ms; $p = .2476$). SDs of reaction times were also not significantly different between PBO and FLI 100 mg on Day 2 (LS mean difference = 23 ms; $p = .11$) or on Day 8 (LS mean difference = 1 ms; $p = .96$). Also, FLI 200 mg was not significantly different from PBO (LS mean difference = -11 ms; $p = .52$) or FLI 100 mg (LS mean difference = -12 ms; $p = .48$).

3.6 | Self-reported measures of sleepiness, safety, motivation, and performance

Comparisons of self-reported alertness on the KSS demonstrated a trend ($p = .1083$) for increased sleepiness on Day 2 for ZOP relative to PBO. On Day 8, ZOP was significantly different from PBO ($p = .0045$), suggesting that subjects were more aware of their sedation. Approximately 30–32% of women reported feeling alert, and 68–70% of women reported feeling not alert on ZOP, irrespective of how they felt on PBO.

There was no significant difference in self-reported alertness on the KSS for FLI 100 mg compared to PBO on Day 2 ($p = .8084$) and on Day 8 ($p = .7963$). Approximately 42–47% of women reported feeling alert on FLI on Day 2 or 8, irrespective of how they felt on PBO, while 54–58% of women reported not feeling alert for FLI on Day 2 or 8, irrespective of how they felt on PBO. FLI 200 mg was not significantly different from FLI 100 mg with 48% of women feeling alert and 52% of women feeling not alert on FLI 200 mg.

When asked to evaluate their ability to drive safely immediately before the driving simulator test, almost all subjects reported feeling safe to drive. On Day 2, only one subject receiving PBO, one subject receiving FLI 100 mg, and two subjects receiving ZOP reported that they did not feel safe to drive. On Day 8, one subject who had taken PBO, four subjects who had taken FLI 100 mg, three who had taken FLI 200 mg, and two who had taken ZOP reported not feeling safe to drive. None of the pairwise group comparisons on either Day 2 or 8 were statistically significant.

Administration of VAS assessments after the driving simulator test indicated that subjects described themselves as less motivated to perform at the best of their ability after ZOP treatment compared to FLI 100 mg on both Day 2 (LS mean difference = 6.11 ; $p = .023$) and on Day 8 (LS mean difference = 8.11 ; $p = .003$). However, statistically significant differences were not found between active drug and PBO. For VAS related to driving performance, subjects rated their performance to be generally poorer after ZOP treatment compared to PBO, and this was statistically significant on Day 8 (LS mean difference = -9.04 ; $p = .004$) but not on Day 2 (LS mean difference = -4.55 ; $p = .156$). In contrast, subjects rated their driving performance as better following treatment with FLI 100 mg compared to PBO ($p = .043$) or ZOP ($p = .0006$) on Day 2. Similarly, subjects also rated their driving performance to be better following treatment with FLI 100 mg compared to ZOP on Day 8 (LS mean difference = 9.97 ; $p = .002$). No differences were observed in self-assessment of driving performance between FLI 200 mg and PBO.

3.7 | Adverse events and study discontinuations

The overall rate of adverse events for FLI 100 mg (70%) was similar to PBO, with the rate of adverse events predictably higher for the 200-mg dose (80%) compared to the 100-mg dose of FLI (Table 4). The total rate of adverse events after ZOP administration was 78% and similar

TABLE 4 Treatment-emergent adverse events occurring in $\geq 5\%$ of subjects (safety population^a)

Adverse events	Subjects with adverse events by treatment, N (%)			
	PBO (N = 75)	FLI 100 mg (N = 77)	FLI 200 mg (N = 78)	ZOP 7.5 mg (N = 78)
Total	52 (69.3)	54 (70.1)	62 (79.5)	61 (78.2)
Somnolence	37 (49.3)	37 (48.1)	37 (47.4)	53 (67.9)
Nausea	2 (2.7)	12 (15.6)	22 (28.2)	7 (9.0)
Headache	8 (10.7)	19 (24.7)	21 (26.9)	9 (11.5)
Dizziness	1 (1.3)	5 (6.5)	9 (11.5)	16 (20.5)
Dysgeusia	1 (1.3)	3 (3.9)	1 (1.3)	15 (19.2)
Insomnia	8 (10.7)	8 (10.4)	8 (10.3)	5 (6.4)
Fatigue	4 (5.3)	7 (9.1)	7 (9.0)	7 (9.0)
Disturbance in attention	1 (1.3)	0 (0.0)	2 (2.6)	5 (6.4)
Palpitations	0 (0.0)	1 (1.3)	5 (6.4)	0 (0.0)
Abdominal pain	1 (1.3)	2 (2.6)	3 (3.8)	4 (5.1)
Dry mouth	2 (2.7)	4 (5.2)	3 (3.8)	1 (1.3)
Oropharyngeal pain	1 (1.3)	3 (3.9)	2 (2.6)	4 (5.1)
Hypoaesthesia	0 (0.0)	2 (2.6)	4 (5.1)	0 (0.0)

Note. PBO = placebo; FLI = flibanserin; ZOP = zopiclone.

^aSafety population is defined as subjects who received at least one dose of study medication.

to the FLI 200 mg group. For either dose of FLI, most adverse events (>96%) were mild to moderate in severity.

There were no serious adverse events reported during the study. All adverse events were intermittent or episodic in nature. The rate of somnolence was high in the entire study population, with 49% of women experiencing somnolence while in the PBO treatment arm. Somnolence associated with either dose of FLI administration (47–48%) was similar to PBO. As expected, the rate of somnolence was higher for ZOP (68%). Other prevalent adverse events were nausea, headache, dizziness, and fatigue, consistent with the FLI phase 3 program (Derogatis et al., 2012; Katz et al., 2013; Thorp et al., 2012).

Six women experienced severe adverse events consisting of somnolence, fatigue, fever, apathy, and migraine. One woman suffered a foot fracture while in the clinic prior to the normal dosing time of 23:00 hr. In the FLI treatment arms, two women had severe adverse events associated with the 100-mg dose, and two other women had severe adverse events associated with the 200-mg dose. Three women had severe adverse events with ZOP, including one woman who also experienced a severe adverse event after FLI 200 mg.

Four subjects discontinued the study due to adverse events after experiencing multiple symptoms that were mild to moderate in severity. All women experiencing adverse events recovered or had resolution of their symptoms. Two women discontinued while in the FLI 200-mg treatment arm, and two women discontinued while in the ZOP treatment arm.

4 | DISCUSSION

Our data demonstrate that FLI 100 mg, taken orally in the evening at bedtime, significantly decreases SDLP in a simulated driving test performed 9 hr after dosing in healthy premenopausal women. SDLP, the primary endpoint in this study, is a measure of a driver's ability to maintain consistency of lane position and is a sensitive measure of driving performance. Decreased SDLP is consistent with better driving performance. Other measures of driving performance, cognitive function (CogScreen and divided attention tasks), and self-reported alertness after FLI treatment either improved or remained unchanged compared to PBO. However, because this study was designed to test the non-inferiority of FLI relative to PBO, we can only conclude that acute or chronic dosing of FLI does not cause impairment above and beyond PBO treatment.

Surprisingly, the suprathreshold dose of FLI 200 mg after steady-state dosing of FLI 100 mg was similar to PBO and similar to acute dosing with FLI 100 mg on driving performance, assessments of cognitive function, and self-reported alertness. Direct measurements of FLI confirmed that the suprathreshold dose of 200 mg did indeed achieve twice the plasma concentration of the normal indicated dose of 100 mg. Further, subjects experienced a greater number of adverse events during the suprathreshold dosing arm. Thus, the lack of impairment of the suprathreshold dose provides a measure of reassurance concerning the safety profile of FLI with respect to its sedating effects.

The sensitivity of the driving simulator and the CogScreen SDC test to detect impairment was demonstrated by the decrease in next-

day simulated driving performance and cognitive function after ZOP treatment. ZOP is known to have prolonged residual sedative effects and has been shown to impair driving performance (Leufkens & Vermeeren, 2014; Leufkens et al., 2009; Mets et al., 2011; Verster et al., 2011). Thus, the lack of impairment observed after FLI administration is not an anomalous finding inherent to the specific assessments and testing paradigms used in this study.

The subanalysis of SDLP between users and nonusers of hormonal contraceptives provides important information for the indicated population of premenopausal women, because the use of hormonal contraceptives is widespread. After oral dosing, FLI reaches maximum plasma concentration after 45–60 min with a terminal half-life of 11 hr at steady state (Addyi Package Insert, 2016). FLI is metabolized primarily by cytochrome P450 (CYP) 3A4. Hormonal contraceptives that contain ethinyl estradiol are considered weak CYP3A4 inhibitors and can moderately increase FLI concentrations, increasing or prolonging adverse events (Addyi Package Insert, 2016). The lack of any difference in SDLP between users and nonusers of hormonal contraceptives suggests that concomitant use of FLI with weak CYP3A4 inhibitors does not cause additional impairment. This is consistent with the lack of impairment observed with twice the indicated dose of FLI (200 mg), because hormonal contraceptives have been shown to increase FLI's C_{max} by 30% and area under the curve by 40% (Addyi Package Insert, 2016). These increases are clearly below the range of the supraphysiological dose used in this study.

This study has several limitations that include the non-inferiority design and the assessment of only a single time period after dosing with a single time period of sleep. Thus, the statistically significant improvement in SDLP after FLI treatment does not allow us to conclude that FLI actually improves driving performance. Furthermore, our findings are limited to the time of assessments after dosing that were initiated approximately 8.5–9 hr after drug administration (CogScreen, driving simulator, KSS, and self-perceived safety to drive). Performing assessments at earlier timepoints with less sleep may have helped to identify a critical window of residual sedation. Nevertheless, the long terminal half-life of FLI (11 hr) and the results with the suprathreshold dose lend further assurance that any residual effects of sedation after FLI administration are not functionally impairing in an individual with normal sleep hygiene. The lack of impairment for FLI on driving performance is even more remarkable when taking into consideration that across all four treatment arms of the study, subjects completed a cumulative total of 57,600 km of simulated driving.

5 | CONCLUSION

Using sensitive and objective measures of driving performance, alertness, and attention, our findings suggest that FLI 100 mg, taken orally at bedtime, does not exhibit residual effects of sedation 8.5 to 9 hr after dosing. While actual sleep was not documented, it should be emphasized that all assessments were performed the next morning after a “lights-out” period of 7.5 hr to allow for sleep. Surprisingly, the suprathreshold dose of FLI 200 mg did not exhibit any impairment on measures of driving performance or cognitive function. Our data also suggest that concomitant use of hormonal contraceptives

with FLI does not exacerbate or prolong symptoms of sedation the next day. Thus, these findings characterize the residual impact of FLI on alertness and provide corroborative evidence for the safe use of this new therapy for HSDD in premenopausal women.

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CONFLICT OF INTEREST

Gary Kay and Thomas Hochadel are former consultants to Sprout Pharmaceuticals (Raleigh, NC) and executives of Cognitive Research Corp. (Saint Petersburg, FL), the contract research organization that conducted the trial. Eric Sicard was the site investigator and has received research funding from Sprout Pharmaceuticals. Karthi Natarajan is a former employee and stockholder of Sprout Pharmaceuticals and a current consultant to Valeant Pharmaceuticals North America LLC (Bridgewater, NJ). Noel N. Kim is a former consultant and stockholder of Sprout Pharmaceuticals, former consultant to Valeant Pharmaceuticals North America LLC, and has received research funding from Valeant Pharmaceuticals North America LLC.

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