

PHARMACOTHERAPY

Flibanserin for Hypoactive Sexual Desire Disorder: An Open-Label Safety Study



James A. Simon, MD,¹ Leonard Derogatis, PhD,² David Portman, MD,³ Louise Brown, RPh,⁴
James Yuan, MD, PhD, MBA,⁴ and Robert Kissling, MD⁴

ABSTRACT

Background: To evaluate the safety of flibanserin in premenopausal and naturally postmenopausal women with hypoactive sexual desire disorder (HSDD) in an open-label extension (OLE) study.

Aim: To examine the safety and tolerability of flibanserin 100 mg once daily at bedtime in the treatment of premenopausal and naturally postmenopausal women with HSDD in a multicenter 28-week OLE study.

Methods: Patients entering this study received flibanserin or placebo in the double-blinded, placebo-controlled trials of premenopausal and postmenopausal women and in a pharmacokinetic study of postmenopausal women.

Outcomes: The primary end point of this OLE study was the incidence of adverse events (AEs). Secondary exploratory efficacy measures included the Female Sexual Distress Scale—Revised (FSDS-R) total score and FSDS-R item 13 (distress owing to low desire) score and the Female Sexual Function Index (FSFI) total score. Because the sponsor terminated the study early at discontinuation of the development of flibanserin, only descriptive statistics were calculated.

Results: Of the 595 patients receiving study medication, 346 and 249 patients were premenopausal and postmenopausal, respectively. The mean number of days of exposure to flibanserin was 72.8 (SD = 41.6). AEs were reported by 352 patients (59.2%), and most AEs (93.8%) were mild or moderate. The most common AEs ($\geq 5\%$) were dizziness (9.6%), somnolence (8.6%), insomnia (6.2%), and nausea (5.7%). There were no flibanserin-related serious AEs and no instances of suicidal ideation. The safety profile of flibanserin was similar for premenopausal and postmenopausal women. The FSDS-R total scores and FSDS-R item 13 scores were numerically lower at weeks 4, 12, and 20 than at baseline (decrease in distress owing to low desire) for premenopausal and postmenopausal women. Mean FSFI total scores were numerically higher at weeks 4, 12, and 20 than at baseline, irrespective of menopausal status of the patients.

Clinical Implications: The results of this study support the safety and tolerability of flibanserin for the treatment of HSDD in premenopausal and naturally postmenopausal women.

Strengths and Limitations: Although this open-label study was designed to be 28 weeks long, it was discontinued early by the sponsor, and patients' maximum duration of exposure to flibanserin was 23.9 weeks. The open-label design and lack of a placebo-controlled arm are other study limitations.

Conclusion: In this open-label study, flibanserin 100 mg once daily at bedtime was generally safe and well tolerated by premenopausal and naturally postmenopausal women with HSDD. **Simon JA, Derogatis L, Portman D, et al. Flibanserin for Hypoactive Sexual Desire Disorder: An Open-Label Safety Study. J Sex Med 2018;15:387–395.**

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¹George Washington University and Women's Health & Research Consultants, Washington, DC, USA;

²Johns Hopkins University School of Medicine, Baltimore, MD, USA;

³Columbus Center for Women's Health Research, Columbus, OH, USA;

⁴Valeant Pharmaceuticals North America, LLC, Bridgewater, NJ, USA

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INTRODUCTION

Hypoactive sexual desire disorder (HSDD) is a persistent or recurrent deficiency or absence of fantasies and desire for sexual activity that causes marked distress or interpersonal difficulty, as defined by the American Psychiatric Association's *Diagnostic and Statistical Manual of Mental Disorders, 4th Edition, Text Revision*.¹ The American Psychiatric Association further distinguishes between acquired and lifelong and between generalized and situational HSDD and specifies that the disorder must not be accounted for by another psychiatric condition, use of medication(s), or a medical condition. In addition, clinicians need to rule out relationship conflict as a primary causative factor before diagnosing HSDD.² Epidemiologic studies estimate the prevalence of HSDD at 7% to 14% of women, with higher rates among premenopausal vs late postmenopausal women and surgically vs naturally postmenopausal women and with a notable peak among perimenopausal or early postmenopausal women.^{3–5} Low sexual desire can negatively affect a woman's health and quality of life and increase relationship dissatisfaction.^{3,6}

Despite the prevalence of HSDD and the impact it has on an affected woman's life and that of her sexual partner, until 2015, no medication had received US Food and Drug Administration (FDA) approval for the treatment of HSDD.^{7,8} In August 2015, flibanserin, a multifunctional, serotonergic, postsynaptic 5-HT_{1A} agonist and 5-HT_{2A} antagonist,^{7–9} became the first drug to receive FDA approval for the treatment of premenopausal women with acquired, generalized HSDD.^{7,8} Randomized, placebo-controlled, 24-week studies have demonstrated the efficacy and safety of flibanserin 100 mg once daily at bedtime (qhs) in the treatment of HSDD in premenopausal and postmenopausal women.^{10–15} However, the FDA submission was only for premenopausal women, and flibanserin is not FDA approved for the treatment of postmenopausal women with HSDD.

The long-term safety and tolerability of flibanserin (flexible dose, 50 or 100 mg qhs or 25 or 50 mg twice daily) in premenopausal women with HSDD has been demonstrated in a 52-week open-label extension (OLE) study.¹⁶ However, the safety and tolerability of flibanserin have not been evaluated in postmenopausal women with HSDD in studies longer than 24 weeks.^{14,17} In addition, the safety of flibanserin in premenopausal and postmenopausal patients with HSDD has not been evaluated in the same study thus far. The present study is an OLE trial to further evaluate the safety and tolerability of flibanserin (100 mg fixed dose) in premenopausal and naturally postmenopausal women with HSDD.

METHODS

Study Design

The study was designed as a multicenter, 28-week, OLE trial to examine the safety and tolerability of flibanserin 100 mg qhs in the treatment of premenopausal and naturally postmenopausal

women with HSDD ([ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT01103362) identifier NCT01103362). The study was conducted from April 5, 2010 through February 28, 2011. The study protocol was approved by an institutional review board or independent ethics committee, and all participants provided written informed consent before the initiation of study procedures. Patients were drawn from previous 24-week, multicenter, randomized, double-blinded, placebo-controlled trials of flibanserin 100 mg qhs vs placebo for the treatment of acquired, generalized HSDD in premenopausal (study 147 [BEGONIA, [ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT00996164) identifier NCT00996164]) or naturally postmenopausal (studies 130 [SNOWDROP, [ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT00996372) identifier NCT00996372] and 156 [PLUMERIA, [ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT01057901) identifier NCT01057901]) women, and a pharmacokinetic study (study 146 [[ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT01188603) identifier NCT01188603]) of naturally postmenopausal women.^{12,14,17} Patients from a prior premenopausal parent study completed a 1-week follow-up period, and those from a postmenopausal parent study completed a 4-week follow-up period. Patients were enrolled in this OLE study within 7 days of completing the parent trial (on flibanserin or placebo). When enrolled, patients entered a screening period of up to 2 weeks. Patients enrolled in this OLE study were treated with flibanserin 100 mg qhs and attended follow-up clinic visits at baseline, weeks 4, 12, 20, and 28, and end of treatment. In addition, patients received follow-up phone calls at weeks 1, 8, 16, and 24. Because this extension study was stopped early at the determination of the sponsor at that time (Boehringer Ingelheim, Ingelheim, Germany) as a result of discontinuation of the clinical development of the product, the last clinic visit took place during a scheduled clinic visit or as soon as possible.

Patients

Premenopausal and naturally postmenopausal women with a primary diagnosis of acquired, generalized HSDD who had completed a previous parent trial of flibanserin were eligible to enter this OLE study. In the parent trials, women were required to be engaged in a monogamous heterosexual relationship of at least 1-year duration with a sexually functional partner who was expected to be physically present for at least 50% of every month of the study.^{12,14} Additional inclusion criteria for premenopausal women were the use of a medically acceptable method of contraception (double barrier method [diaphragm or condom and spermicide], hormonal contraceptive [subcutaneous, injectable, intravaginal, or oral], intrauterine device, tubal sterilization, or partner's surgical sterilization) for at least 2 months before baseline and continued use of that contraception during the trial; for postmenopausal women, inclusion criteria were the presence of at least 1 ovary and the onset of natural menopause (defined as >12 months of spontaneous amenorrhea). For the 2 groups, the ability and willingness to provide meaningful, written informed consent before study enrollment were required. Exclusion criteria included history of major depression disorder within 6 months

before the screening visit or a Beck Depression Inventory II score of at least 14; current suicidal ideation as measured by the suicidal ideation section of the Columbia-Suicide Severity Rating Scale; and suicidal behavior at the time of the screening visit or in the 30 days before the screening visit. Women also were excluded if they had predefined alterations in clinical laboratory test values; had symptoms of pelvic inflammatory disease, urinary tract infection, vaginal infection or vaginitis, cervicitis, interstitial cystitis, vulvodynia, or significant vaginal atrophy; had a history of cancer within the past 10 years; had sexual dysfunction deemed by the investigator as related to hysterectomy, oophorectomy, or any other pelvic or vaginal surgery; were taking medications known to cause sexual dysfunction or medication that might interact with flibanserin (ie, antidepressants, anxiolytics, antipsychotics, mood stabilizers, and anticonvulsants); or had experienced a major life stress or relationship discord (apart from HSDD) that interfered with sexual activity, as deemed by the investigator.

Outcome Measures

Adverse events (AEs) were monitored throughout the OLE study. At every clinic visit, vital signs and concomitant medication(s) were monitored and the Clinical Global Impression (CGI) of Efficacy Index (CGI-E; side effects component)¹⁸ question was asked. Clinical laboratory tests were performed at screening, week 12 visit, and end of treatment visit, and pelvic examinations were done at the end of treatment visit.

Secondary exploratory efficacy measures included the Female Sexual Distress Scale—Revised (FSDS-R) total score, a validated 13-item questionnaire rated on a 5-point scale from 0 (never) to 4 (always) designed to measure distress resulting from sexual dysfunction (total score range = 0–52)¹⁹; item 13 of the FSDS-R, a question designed to specifically assess distress related to low sexual desire (item 13 score range = 0–4; lower score indicates less distress); the Female Sexual Function Index (FSFI) total score, a validated, multidimensional, self-administered, 19-item questionnaire for assessing key dimensions of sexual function in women with HSDD (higher total scores are indicative of better sexual functioning)^{20,21}; a Patient Benefit Evaluation (PBE; yes or no response to the question, “Overall, do you believe that you have experienced a meaningful benefit from flibanserin?”); and the CGI of Severity (CGI-S) and CGI-E (therapeutic effect and side effects components), general tools that provide a global rating of a patient’s functional status in severity of impairment and perceived improvement after initiation of therapy.¹⁸

Statistical Analysis

The primary end point was the frequency of AEs. Because the study was discontinued early by the sponsor, no formal statistical tests were performed; instead, only descriptive statistics were calculated. Data from the safety population (ie, those patients who enrolled in the study and were documented

to have taken ≥ 1 dose of the study medication) were analyzed. Data from the premenopausal and postmenopausal patients were analyzed separately and combined. For safety and efficacy data, only observed cases were analyzed (ie, missing data were not imputed).

RESULTS

Of the 596 patients who entered the study, 595 patients (99.8%) received at least 1 dose of study medication and thus were included in the safety population (Figure 1). Of these 595 patients, 346 (58.2%) were premenopausal (entered from BEGONIA study) and 249 (41.8%) were postmenopausal (215, 22, and 12 patients entered from SNOWDROP study, PLUMERIA study, and a pharmacokinetic study, respectively). Of the patients who enrolled in this OLE study, 51.3% had received flibanserin and 48.7% had received placebo during the initial studies. None of the patients completed the present OLE study, largely as a result of early termination of the study when the previous sponsor discontinued development of flibanserin, which led to the discontinuation of 87.4% of patients.

Demographics and baseline characteristics for the treated population are presented in Table 1. Most patients (79.3%) were white. Mean age \pm SD was 37.6 ± 7.7 years for premenopausal women and 57.0 ± 5.8 years for postmenopausal women. Mean duration \pm SD of the patient’s current relationship was 11.5 ± 7.9 years for premenopausal women and 21.4 ± 12.9 years for postmenopausal women. Mean disease duration \pm SD was 56.5 ± 48.9 months for the overall treated population. Of premenopausal women, 38.7% of patients were on hormonal contraceptives before or during the study.

Baseline FSDS-R total scores, FSDS-R item 13 scores on desire, and CGI-S scores at the beginning of this study were similar for premenopausal and postmenopausal women; however, baseline FSFI total scores were higher for premenopausal than postmenopausal women, with 30.6% of premenopausal women and 7.2% of postmenopausal women reporting baseline FSFI total scores of at least 26.55. Based on a validation study in women 18 to 74 years old (mean age = 36.2 years), an FSFI total score lower than 26.55 was considered indicative of sexual dysfunction in premenopausal and postmenopausal women.²²

The mean number of days of exposure to flibanserin \pm SD was 72.8 ± 41.6 in the OLE trial and 155.4 ± 97.2 in the parent and OLE trials. The maximum duration of exposure to flibanserin was 167.0 days in the OLE trial and 325.0 days in the parent and OLE trials.

At the time of enrollment in this study, 136 patients (22.9%) reported unresolved AEs that they first experienced during a parent trial (Table 2), none of which worsened during the OLE period. During the OLE trial, 352 patients (59.2%) reported AEs, most of which (93.8%) were mild or moderate in intensity. The most common AEs affecting at least 5% of the safety population were dizziness (9.6%), somnolence (8.6%), insomnia

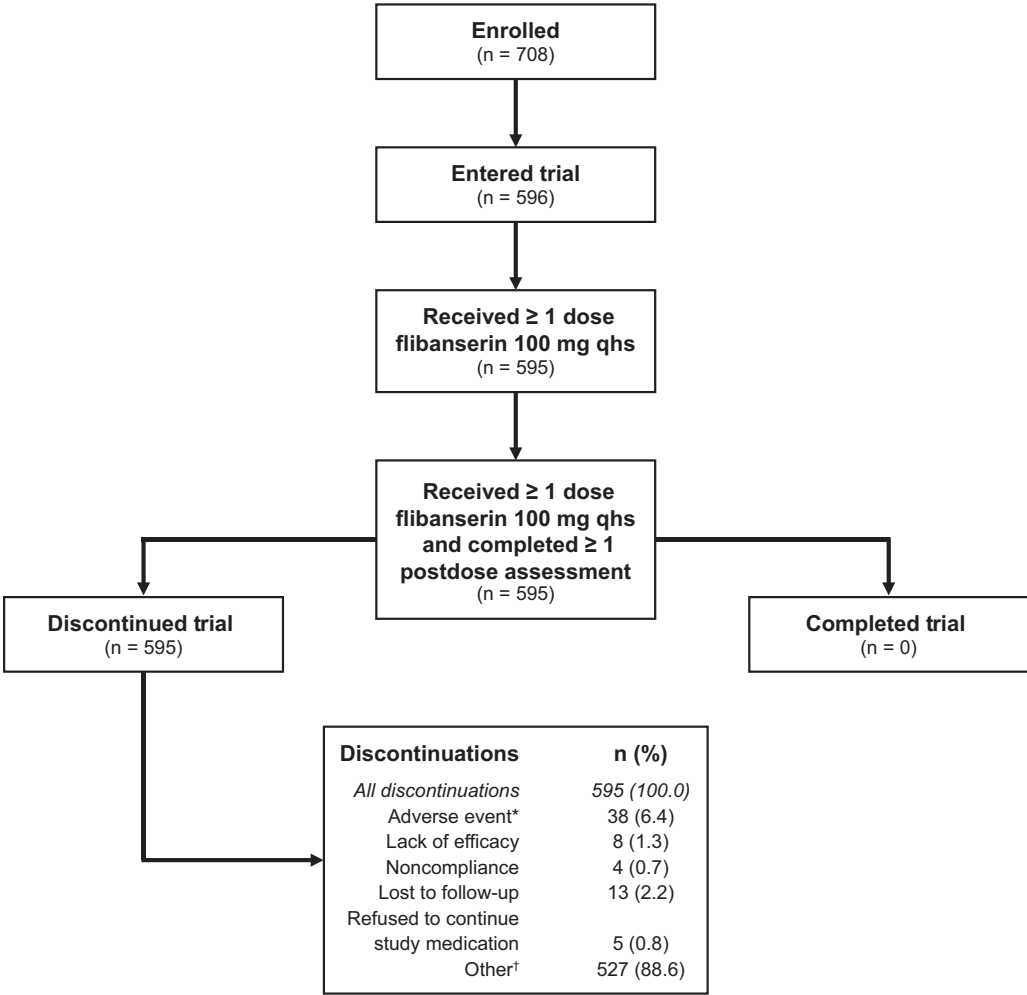


Figure 1. Patient disposition. *Adverse events that resulted in study discontinuation were worsening of other pre-existing disease (n = 1, 0.2%) and other adverse event (n = 37, 6.2%). †Of the 527 patients who discontinued for “other” reasons, 520 (98.7%) discontinued as a result of early study termination, 5 discontinued by withdrawing consent, 3 discontinued because of pregnancy, 1 discontinued to take a prohibited medication, and 1 discontinued because of relocation to another state. Figure 1 is available in color at www.jsm.jsexmed.org.

(6.2%), and nausea (5.7%). The safety profile of flibanserin was similar for premenopausal and postmenopausal women.

AEs that were deemed by the investigators to be related to the study medication occurred in 173 patients (29.1%). Of these, the most common (>2%) were dizziness (8.4%), somnolence (8.1%), nausea (4.5%), insomnia (4.5%), and fatigue (3.7%). 1 patient (0.3%) in the premenopausal group reported an AE of syncope that was moderate in intensity and deemed by the investigators to be related to study medication, and the patient was discontinued from the study. 3 patients (0.5%; 2 in the premenopausal group and 1 in the postmenopausal group) reported sedation during the study period that was deemed by the investigators to be related to the study medication. No other AEs of syncope, orthostatic hypotension, or sedation were reported during the study period. AEs leading to study discontinuation were reported for 38 patients (6.4%). Of these, the most common were dizziness (1.5%), insomnia (1.2%), and fatigue (0.8%).

Serious AEs occurred in 1 patient (0.3%) in the premenopausal group (cholelithiasis) and 3 patients (1.2%) in the postmenopausal group (basal cell carcinoma, animal bite and cellulitis, and irritable bowel syndrome); however, none of these were deemed by the investigators to be related to the study medication. No deaths occurred during the study period, and there were no instances of suicidal ideation. The results of other safety assessments, including clinical laboratory measures, blood pressure, and pelvic examinations, were unremarkable.

For efficacy, FSDS-R total scores were numerically lower at weeks 4, 12, and 20 than at baseline in premenopausal and postmenopausal women, indicating a decrease in distress during the follow-up period (Figure 2A). When stratified by baseline FSFI total score, women with baseline FSFI total scores of at least 26.55 had lower mean FSDS-R total scores than women with baseline FSFI total scores lower than 26.55, but FSDS-R total scores decreased from baseline during the follow-up period for all women (Table 3).

Table 1. Patient demographics and baseline characteristics for safety population*

Characteristic	Premenopausal (n = 346)	Postmenopausal (n = 249)	Overall (N = 595)
Age (y), mean \pm SD	37.6 \pm 7.7	57.0 \pm 5.8	45.7 \pm 11.9
Race and/or ethnicity, n (%)			
White	258 (74.6)	214 (85.9)	472 (79.3)
White Hispanic	38 (11.0)	15 (6.0)	53 (8.9)
Black or African American	38 (11.0)	15 (6.0)	53 (8.9)
Black or African American Hispanic	1 (0.3)	0	1 (0.2)
Asian	6 (1.7)	1 (0.4)	7 (1.2)
Other	5 (1.4)	4 (1.6)	9 (1.5)
Weight (kg), mean \pm SD	74.9 \pm 19.8	70.9 \pm 14.5	73.2 \pm 17.9
Body mass index (kg/m ²), mean \pm SD	27.7 \pm 6.9	26.8 \pm 5.3	27.4 \pm 6.3
Current relationship duration (y), mean \pm SD	11.5 \pm 7.9	21.4 \pm 12.9	15.5 \pm 11.3
Duration of HSDD (mo), mean \pm SD	52.5 \pm 45.9	62.3 \pm 52.5	56.5 \pm 48.9
Alcohol use, n (%)			
0 drink/d	238 (68.8)	141 (56.6)	379 (63.7)
1–3 drinks/d	108 (31.2)	106 (42.6)	214 (36.0)
> 3 drinks/d	0	2 (0.8)	2 (0.3)
FSDS-R total score, mean \pm SD	26.4 \pm 12.8	25.6 \pm 11.8	26.0 \pm 12.4
FSDS-R item 13 score, mean \pm SD [†]	2.8 \pm 1.2	2.9 \pm 1.0	2.8 \pm 1.1
FSFI total score, mean \pm SD	22.3 \pm 7.1	16.9 \pm 7.0	20.1 \pm 7.5
FSFI total score \geq 26.55, n (%)	106 (30.6)	18 (7.2)	124 (20.8)
CGI severity score, mean \pm SD	4.1 \pm 1.2	4.3 \pm 1.2	4.2 \pm 1.2

CGI = Clinical Global Impression; FSDS-R = Female Sexual Distress Scale—Revised; FSFI = Female Sexual Function Index; HSDD = hypoactive sexual desire disorder.

*Safety population was defined as those patients who enrolled in the study, received study medication, and were documented to have taken at least 1 dose.

[†]FSDS-R item 13 (desire) score and FSFI total score were missing for 1 premenopausal woman.

A similar effect was observed for FSDS-R item 13 on desire, with a decrease in desire-related distress during the follow-up period in premenopausal and postmenopausal women (Figure 2B). As with FSDS-R total scores, mean FSDS-R item 13 (desire) scores were lower for women with baseline FSFI total scores of at least 26.55 than for women with baseline FSFI total scores lower than 26.55, but FSDS-R item 13 (desire) scores decreased during the follow-up period for all women, regardless of baseline FSFI total score (Table 3).

Mean FSFI total scores were numerically higher at weeks 4, 12, and 20 than at baseline, indicating an improvement in sexual functioning during the follow-up period irrespective of

menopausal status or baseline FSFI total score (Figure 2C and Table 3).

Mean CGI-S scores decreased from baseline over the follow-up period, indicating a decrease in the severity of sexual dysfunction irrespective of menopausal status or baseline FSFI total score. Specifically, mean CGI-S scores \pm SD decreased from baseline scores of 4.1 \pm 1.2 and 4.3 \pm 1.2 to week 20 scores of 2.9 \pm 1.6 and 3.8 \pm 1.4 in premenopausal and postmenopausal women, respectively. For the CGI-E therapeutic effect component, mean scores improved slightly or remained unchanged during the follow-up period. The side effects component of the CGI-E score did not change during the follow-up period (mean

Table 2. Adverse events occurring in at least 5.0% of safety population*

AE, n (%)	Unresolved AE from parent trials [†] (n = 595)	Premenopausal (n = 346)	Postmenopausal (n = 249)	Overall (N = 595) [‡]
Any	136 (22.9)	165 (47.7)	123 (49.4)	352 (59.2)
Dizziness	0 (0.0)	30 (8.7)	27 (10.8)	57 (9.6)
Somnolence	4 (0.7)	31 (9.0)	16 (6.4)	51 (8.6)
Insomnia	6 (1.0)	18 (5.2)	13 (5.2)	37 (6.2)
Nausea	2 (0.3)	19 (5.5)	13 (5.2)	34 (5.7)

AE = adverse event.

*Safety population was defined as those patients who enrolled in the study, received study medication, and were documented to have taken at least 1 dose.

[†]Unresolved at time of enrollment in this study.

[‡]Overall includes patients with AEs occurring in this study and those with unresolved AEs from the parent trials; patients with an unresolved parent trial AE and an open-label extension study AE were counted only once.

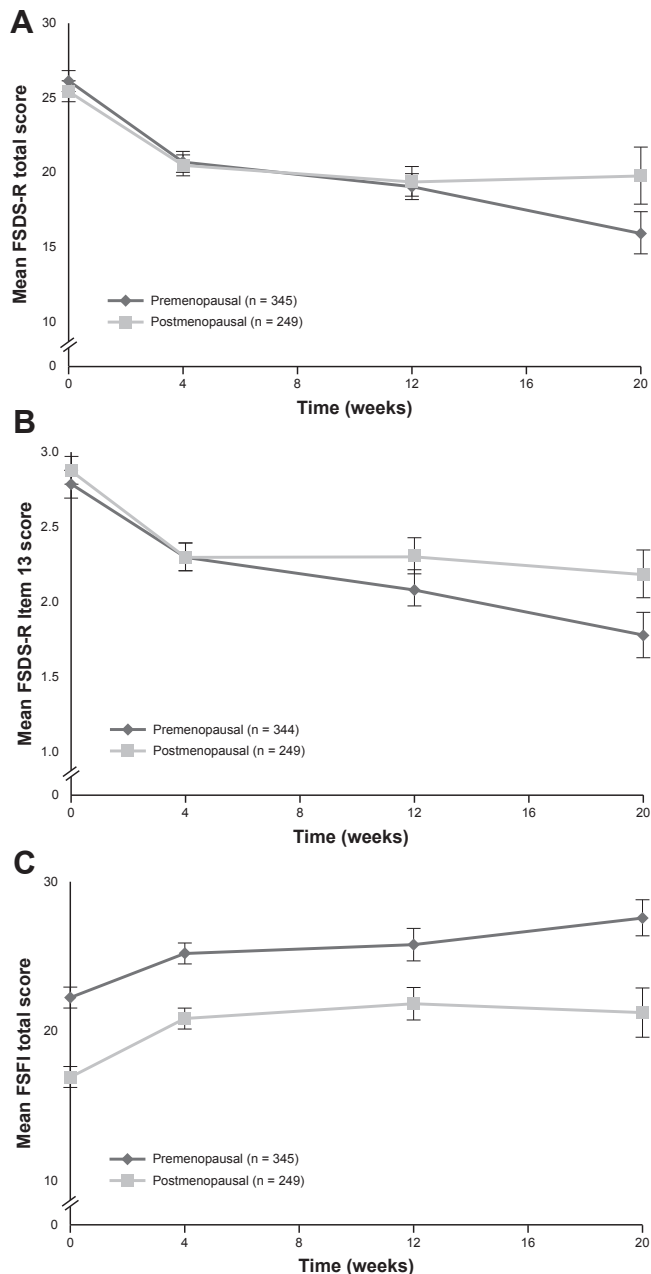


Figure 2. Panel A shows mean FSDS-R total scores. Panel B shows mean FSDS-R item 13 scores. Panel C shows mean FSFI total scores by menopausal status. Error bars represent standard error. FSDS-R = Female Sexual Distress Scale—Revised; FSFI = Female Sexual Function Index. Figure 2 is available in color at www.jsm.jsexmed.org.

score \pm SD = 3.6 ± 0.7 at baseline, 3.7 ± 0.6 at week 20), regardless of menopausal status or baseline FSFI total scores. Approximately half the patients (50.6%) answered “yes” at the end of the follow-up period when asked whether they had a meaningful benefit (PBE) from the study medication (Figure 3).

DISCUSSION

The results of this OLE trial support the safety and tolerability of flibanserin 100 mg qhs for the treatment of HSDD in

premenopausal women and naturally postmenopausal women. In contrast to the previous OLE study with flexible-dose flibanserin in premenopausal women with HSDD,¹⁶ this study evaluated fixed-dose flibanserin 100 mg qhs (the approved dose for premenopausal women with HSDD) and included premenopausal and naturally postmenopausal women with HSDD. Flibanserin 100 mg qhs has demonstrated safety and efficacy in 3 pivotal multicenter, randomized, double-blinded, placebo-controlled, 24-week trials in premenopausal women with a primary diagnosis of acquired, generalized HSDD.^{10–12} In addition, 2 phase 3 clinical trials of flibanserin 100 mg qhs in naturally postmenopausal women with a primary diagnosis of HSDD support the safety and efficacy of flibanserin.^{14,17}

The present study was designed as a 28-week OLE trial to further evaluate the safety and tolerability of flibanserin 100 mg qhs. Although designed as a 28-week trial, the sponsor discontinued the study early, and patients’ maximum duration of exposure to flibanserin was 23.9 weeks. The safety results of the present study were similar to those of the pivotal studies and the phase 3 study in postmenopausal women.^{10–12,14,23} Dizziness, somnolence, insomnia, and nausea were the most common AEs; there were no deaths in the present study. During the duration of this study, approximately 1 in 16 patients discontinued as a result of an AE. The safety profile of flibanserin was similar for premenopausal and postmenopausal women. As a point of comparison with other drugs that target the central nervous system, common AEs in this study were reported in studies of antidepressants frequently prescribed in women’s health care (ie, sertraline, bupropion, citalopram, escitalopram, fluoxetine),²⁴ with an incidence of 5% to 22% for dizziness, 6% to 20% for somnolence or sedation, 9% to 20% for insomnia, and 15% to 26% for nausea reported for these drugs.^{25–29}

An important consideration when using flibanserin is the potential for interaction with alcohol, which might increase the risk of severe hypotension, syncope, sedation, and somnolence.^{30,31} For this reason, the use of alcohol is contraindicated with flibanserin, and the drug is available only through a Risk Evaluation and Mitigation Strategy (REMS) program.^{7,32} The alcohol contraindication and REMS requirement are based on the results of a weight-based alcohol challenge study designed to elicit maximal effects of combined use of flibanserin and alcohol.^{7,30,32} In the present study, approximately 1/3 of patients reported alcohol use at baseline. During the study period, 51 patients (8.6%) reported somnolence, 1 patient (0.2%) reported moderate syncope, and 3 patients (0.5%) reported sedation; except for 3 patients with somnolence, each of these AEs was deemed by the investigators to be related to study medication. Whether these events were related to an interaction between the study medication and alcohol is unknown. No patients treated with flibanserin in the present study demonstrated any significant changes in blood pressure or any other clinical or laboratory measure that might be influenced by alcohol. 1 postmenopausal patient in 1 of the parent trials, the SNOWDROP study, died of

Table 3. FSDS-R total, FSDS-R item 13 (desire), and FSFI total scores by baseline FSFI total score (safety population)*

Efficacy measure at time point	FSFI total score < 26.55	FSFI total score \geq 26.55	Overall
FSDS-R total score, n	470	124	594
Baseline, mean (SEM)	28.5 (0.51)	16.5 (1.11)	26.0 (0.51)
Week 4, mean (SEM)	23.0 (0.58)	12.5 (1.09)	20.7 (0.54)
Week 12, mean (SEM)	22.0 (0.78)	10.2 (1.28)	19.5 (0.72)
Week 20, mean (SEM)	20.0 (1.29)	8.9 (2.25)	17.6 (1.20)
FSDS-R item 13 score, n	470	123	593
Baseline, mean (SEM)	3.1 (0.04)	1.9 (0.12)	2.8 (0.05)
Week 4, mean (SEM)	2.5 (0.06)	1.5 (0.12)	2.3 (0.05)
Week 12, mean (SEM)	2.4 (0.08)	1.2 (0.14)	2.2 (0.07)
Week 20, mean (SEM)	2.2 (0.14)	1.0 (0.24)	2.0 (0.13)
FSFI total score, n	470	124	594
Baseline, mean (SEM)	17.5 (0.28)	29.9 (0.22)	20.1 (0.31)
Week 4, mean (SEM)	21.6 (0.34)	30.4 (0.40)	23.5 (0.32)
Week 12, mean (SEM)	22.6 (0.45)	30.6 (0.65)	24.3 (0.42)
Week 20, mean (SEM)	23.3 (0.81)	32.3 (0.55)	25.2 (0.74)

FSDS-R = Female Sexual Distress Scale–Revised; FSFI = Female Sexual Function Index; SEM = standard error of the mean.

*The safety population was defined as those patients who enrolled in the study, received study medication, and were documented to have taken at least 1 dose.

acute alcohol intoxication 14 days after starting flibanserin.^{7,14} This patient had a history of hypertension and hypercholesterolemia. At study baseline, she reported alcohol consumption of 1 to 3 drinks daily. Blood alcohol level was 0.289 g/dL at autopsy examination; coronary artery disease also was noted in the autopsy report. The relation between this patient's death and the use of flibanserin is unknown.⁷

In this study, the efficacy assessments were exploratory, and no formal statistical tests were performed. In addition, this study did not evaluate some efficacy measures used as co-primary or secondary end points in the placebo-controlled trials with premenopausal and postmenopausal women with HSDD (eg, FSFI desire domain score and number of satisfying sexual events).^{10–12,14} However, the results with the efficacy end points evaluated in this study (FSDS-R total, FSDS-R item 13, and FSFI total scores) are similar to those of previous studies. For comparison, in the 4 previous phase 3 studies of flibanserin in

premenopausal and postmenopausal women, the mean change in FSDS-R total score from baseline to week 24 ranged from -7.8 to -9.4 for the flibanserin 100-mg group.^{10–12,14} Similarly, the mean change from baseline to week 24 ranged from -0.7 to -1.0 for the FSDS-R item 13 score (distress owing to low desire) and from 4.1 to 5.3 for the FSFI total score for the flibanserin 100-mg group in the previous studies.^{10–12,14}

The present study has several limitations that should be considered when interpreting the results. This extension study was designed as an open-label trial and lacked a placebo treatment arm. In addition, although this extension study was designed to be 28 weeks long, it was discontinued early by the sponsor at the time (Boehringer Ingelheim; because of a decision to end development of flibanserin); thus, no patients completed the study. Generalizability of the safety results in this study is limited to women who are free of psychiatric disease, not taking medication(s) that could affect sexual function, and are in a monogamous, heterosexual relationship with a sexually functional partner. Generalizability also is limited because the study excluded women who were menopausal because of surgery, chemotherapy, or any other method of induced menopause and those who had premature ovarian failure. Moreover, efficacy measures were exploratory, because the study was primarily designed to assess the safety and tolerability of flibanserin in premenopausal and naturally postmenopausal women.

The common AEs reported in the present study are consistent with the safety profile of flibanserin for the treatment of HSDD in premenopausal and naturally postmenopausal women. Although the efficacy data were descriptive in nature and available for only up to 20 weeks of the OLE, the efficacy results from this study were consistent with those of previous studies of flibanserin in the treatment of HSDD.

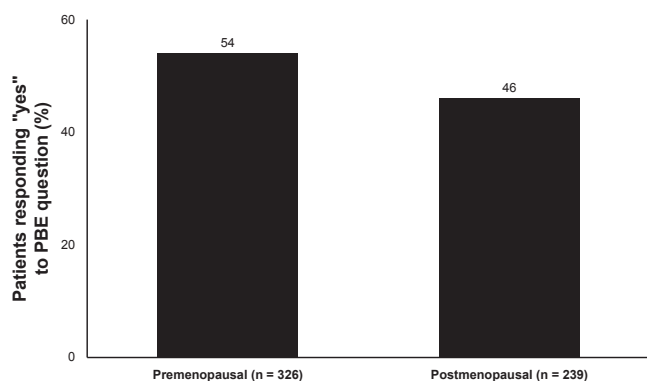


Figure 3. Perceived meaningful benefit of study medication by menopausal status based on PBE. PBE = patient benefit evaluation.

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Corresponding Author: James A. Simon, MD, Women's Health & Research Consultants, 1850 M Street, NW 450, Washington, DC 20036, USA; E-mail: jsimon@JamesASimonMD.com

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STATEMENT OF AUTHORSHIP

Category 1

(a) Conception and Design

James A. Simon; Leonard Derogatis; David Portman; Louise Brown; James Yuan

(b) Acquisition of Data

James A. Simon; Leonard Derogatis; David Portman

(c) Analysis and Interpretation of Data

James A. Simon; Leonard Derogatis; David Portman; Louise Brown; James Yuan; Robert Kissling

Category 2

(a) Drafting the Article

James A. Simon; Leonard Derogatis; David Portman; Louise Brown; James Yuan; Robert Kissling

(b) Revising It for Intellectual Content

James A. Simon; Leonard Derogatis; David Portman; Louise Brown; James Yuan; Robert Kissling

Category 3

(a) Final Approval of the Completed Article

James A. Simon; Leonard Derogatis; David Portman; Louise Brown; James Yuan; Robert Kissling

REFERENCES

1. American Psychiatric Association. Diagnostic and statistical manual of mental disorders. 4th ed, text rev. Washington, DC: American Psychiatric Publishing; 2000.
2. Goldstein I, Kim NN, Clayton AH, et al. Hypoactive sexual desire disorder: International Society for the Study of Women's Sexual Health (ISSWSH) expert consensus panel review. *Mayo Clin Proc* 2017;92:114-128.
3. Leiblum SR, Koochaki PE, Rodenberg CA, et al. Hypoactive sexual desire disorder in postmenopausal women: US results from the Women's International Study of Health and Sexuality (WISHeS). *Menopause* 2006;13:46-56.
4. Shifren JL, Monz BU, Russo PA, et al. Sexual problems and distress in United States women: prevalence and correlates. *Obstet Gynecol* 2008;112:970-978.
5. Rosen RC, Connor MK, Miyasato G, et al. Sexual desire problems in women seeking healthcare: a novel study design for ascertaining prevalence of hypoactive sexual desire disorder in clinic-based samples of U.S. women. *J Womens Health (Larchmt)* 2012;21:505-515.
6. Kingsberg SA. Attitudinal survey of women living with low sexual desire. *J Womens Health (Larchmt)* 2014; 23:817-823.
7. Addyi® (flibanserin) tablets, for oral use [package insert]. Bridgewater, NJ: Sprout Pharmaceuticals, a division of Valeant Pharmaceuticals North America LLC; 2016.
8. Kingsberg SA, Clayton AH, Pfaus JG. The female sexual response: current models, neurobiological underpinnings and agents currently approved or under investigation for the

- treatment of hypoactive sexual desire disorder. *CNS Drugs* 2015;29:915-933.
9. Lodise NM. Hypoactive sexual desire disorder in women: treatment options beyond testosterone and approaches to communicating with patients on sexual health. *Pharmacotherapy* 2013;33:411-421.
 10. DeRogatis LR, Komer L, Katz M, et al. Treatment of hypoactive sexual desire disorder in premenopausal women: efficacy of flibanserin in the VIOLET Study. *J Sex Med* 2012;9:1074-1085.
 11. Thorp J, Simon J, Dattani D, et al. Treatment of hypoactive sexual desire disorder in premenopausal women: efficacy of flibanserin in the DAISY study. *J Sex Med* 2012;9:793-804.
 12. Katz M, DeRogatis LR, Ackerman R, et al. Efficacy of flibanserin in women with hypoactive sexual desire disorder: results from the BEGONIA trial. *J Sex Med* 2013;10:1807-1815.
 13. Goldfischer ER, Breaux J, Katz M, et al. Continued efficacy and safety of flibanserin in premenopausal women with hypoactive sexual desire disorder (HSDD): results from a randomized withdrawal trial. *J Sex Med* 2011;8:3160-3172.
 14. Simon JA, Kingsberg SA, Shumel B, et al. Efficacy and safety of flibanserin in postmenopausal women with hypoactive sexual desire disorder: results of the SNOWDROP trial. *Menopause* 2014;21:633-640.
 15. Gao Z, Yang D, Yu L, et al. Efficacy and safety of flibanserin in women with hypoactive sexual desire disorder: a systematic review and meta-analysis. *J Sex Med* 2015;12:2095-2104.
 16. Jayne C, Simon JA, Taylor LV, et al. Open-label extension study of flibanserin in women with hypoactive sexual desire disorder. *J Sex Med* 2012;9:3180-3188.
 17. Portman DJ, Brown L, Yuan J, et al. Flibanserin in postmenopausal women with hypoactive sexual desire disorder: results of the PLUMERIA study. *J Sex Med* 2017;14:834-842.
 18. Busner J, Targum SD. The Clinical Global Impressions Scale: applying a research tool in clinical practice. *Psychiatry (Edgmont)* 2007;4:28-37.
 19. DeRogatis L, Clayton A, Lewis-D'Agostino D, et al. Validation of the Female Sexual Distress Scale—Revised for assessing distress in women with hypoactive sexual desire disorder. *J Sex Med* 2008;5:357-364.
 20. Revicki DA, Margolis MK, Bush EN, et al. Content validity of the Female Sexual Function Index (FSFI) in pre- and postmenopausal women with hypoactive sexual desire disorder. *J Sex Med* 2011;8:2237-2245.
 21. Rosen R, Brown C, Heiman J, et al. The Female Sexual Function Index (FSFI): a multidimensional self-report instrument for the assessment of female sexual function. *J Sex Marital Ther* 2000;26:191-208.
 22. Wiegel M, Meston C, Rosen R. The Female Sexual Function Index (FSFI): cross-validation and development of clinical cutoff scores. *J Sex Marital Ther* 2005;31:1-20.
 23. Jaspers L, Feys F, Bramer WM, et al. Efficacy and safety of flibanserin for the treatment of hypoactive sexual desire disorder in women: a systematic review and meta-analysis. *JAMA Intern Med* 2016;176:453-462.
 24. Dawson AL, Ailes EC, Gilboa SM, et al. Antidepressant prescription claims among reproductive-aged women with private employer-sponsored insurance—United States 2008–2013. *MMWR Morb Mortal Wkly Rep* 2016;65:41-46.
 25. Zoloft® (sertraline hydrochloride) tablets, for oral use; Zoloft® (sertraline hydrochloride) oral concentrate; Zoloft® (sertraline hydrochloride) oral solution [package insert]. New York: Roerig, Division of Pfizer; 2017.
 26. Wellbutrin® (bupropion hydrochloride) tablets, for oral use [package insert]. Research Triangle Park, NC: GlaxoSmithKline; 2017.
 27. Celexa® (citalopram hydrobromide) tablets/oral solution [package insert]. St Louis, MO: Forest Laboratories; 2011.
 28. Lexapro® (escitalopram oxalate) tablets Lexapro® (escitalopram oxalate) oral solution [package insert]. Irvine, CA: Allergan USA; 2017.
 29. Prozac® (fluoxetine hydrochloride) for oral use Prozac (fluoxetine hydrochloride) delayed-release capsules for oral use [package insert]. Indianapolis, IN: Lilly USA, LLC; 2017.
 30. Stevens DM, Weems JM, Brown L, et al. The pharmacodynamic effects of combined administration of flibanserin and alcohol. *J Clin Pharm Ther* 2017;42:598-606.
 31. Sicard E, Raimondo D, Vittitow J, et al. Effect of alcohol administered with flibanserin on dizziness, syncope, and hypotension in healthy, premenopausal women. Presented at: 23rd Congress of World Association for Sexual Health; May 28–31, 2017; Prague, Czech Republic.
 32. Joffe HV, Chang C, Sewell C, et al. FDA approval of flibanserin—treating hypoactive sexual desire disorder. *N Engl J Med* 2016;374:101-104.