

Efficacy and safety of flibanserin in postmenopausal women with hypoactive sexual desire disorder: results of the SNOWDROP trial

James A. Simon, MD,¹ Sheryl A. Kingsberg, PhD,² Brad Shumel, MD,³ Vladimir Hanes, MD,⁴ Miguel Garcia Jr, MS,³ and Michael Sand, PhD, MPH³

Abstract

Objective: This study aimed to assess the efficacy and safety of flibanserin, a serotonin receptor 1A agonist/serotonin receptor 2A antagonist, in postmenopausal women with hypoactive sexual desire disorder (HSDD).

Methods: Naturally postmenopausal women with HSDD received flibanserin 100 mg once daily at bedtime (n = 468) or placebo (n = 481) for 24 weeks. Co-primary endpoints were changes from baseline to week 24 in the number of satisfying sexual events (SSEs) across 28 days and in the Female Sexual Function Index (FSFI) desire domain score. Secondary endpoints included change from baseline in Female Sexual Distress Scale—Revised (FSDS-R) Item 13 score (which assesses distress due to low sexual desire), FSDS-R total score, and FSFI total score. The Patient Benefit Evaluation was asked on treatment discontinuation.

Results: There were significant improvements with flibanserin versus placebo in the mean (SE) changes in the number of SSEs (1.0 [0.1] vs 0.6 [0.1]), FSFI desire domain score (0.7 [0.1] vs 0.4 [0.1]), FSDS-R Item 13 score (−0.8 [0.1] vs −0.6 [0.1]), FSDS-R total score (−8.3 [0.6] vs −6.3 [0.6]), and FSFI total score (4.2 [0.4] vs 2.7 [0.4]); all $P < 0.01$. More women on flibanserin (37.6%) than women on placebo (28.0%) reported experiencing meaningful benefits from the study medication on treatment discontinuation. The most frequent adverse events associated with flibanserin were dizziness, somnolence, nausea, and headache.

Conclusions: In naturally postmenopausal women with HSDD, flibanserin, compared with placebo, has been associated with improvement in sexual desire, improvement in the number of SSEs, and reduced distress associated with low sexual desire, and is well tolerated.

Key Words: Flibanserin – Hypoactive sexual desire disorder – Female sexual dysfunction – Menopausal – Low desire.

Hypoactive sexual desire disorder (HSDD) is defined by the American Psychiatric Association as a persistent or recurrent deficiency in or absence of sexual fantasies and desire for sexual activity that causes marked distress or interpersonal difficulty. For a diagnosis of HSDD to be assigned, the desire problem must not be better accounted

for by another psychiatric disorder (eg, depression), substance (eg, a medication), or medical condition.¹

Although the most commonly reported sexual problem among older women is loss of desire,^{2–4} estimates of the prevalence of HSDD vary depending on the methodology used and the population studied.⁵ The prevalence of low sexual desire

Received December 24, 2012; revised and accepted September 19, 2013.

From the ¹Women's Health and Research Consultants, George Washington University School of Medicine, Washington, DC; ²University Hospitals Case Medical Center, Cleveland, OH; ³Boehringer Ingelheim Pharmaceuticals Inc, Ridgefield, CT; and ⁴Boehringer Ingelheim Pharma GmbH and Co KG, Ingelheim, Germany.

The authors were responsible for all content and editorial decisions, were involved at all stages of manuscript development, and approved the final version.

Funding/support: The study reported in this article was funded by the previous owner of the flibanserin program and initiator of the study, Boehringer Ingelheim (ClinicalTrials.gov registry number: NCT00996372). Medical writing assistance, supported financially by Boehringer Ingelheim, was provided by Isobel Lever, PhD, and Wendy Morris, MSc, of Fleishman-Hillard Group Limited (London, UK) during the preparation of this manuscript. Sprout Pharmaceuticals Inc has acquired flibanserin and is now fully responsible for future development.

Financial disclosure/conflicts of interest: In the 12 months before the final submission of this article, J.A.S. has served as a consultant to or on the advisory boards of Abbott Laboratories/AbbVie Inc, Agile Therapeutics Inc, Amgen Inc, Apotex Inc, Ascend Therapeutics, BioSante, Depomed Inc, Everett Laboratories Inc, Intimina by Lelo Inc, Lupin Pharmaceuticals, TherapeuticsMD, Meda Pharmaceuticals Inc, Merck and Co Inc,

Novartis Pharmaceuticals Corp, Noven Pharmaceuticals Inc, Novo Nordisk, Novogyne, Shionogi Inc, Shippin Point Advisors LLC, Slate Pharmaceuticals Inc, Sprout Pharmaceuticals, Teva Pharmaceutical Industries Ltd, Warner Chilcott, and Watson Pharmaceutical Inc. He has received or is currently receiving grant/research support from Abbott Laboratories/AbbVie Inc, BioSante, EndoCeutics Inc, Novo Nordisk, Novogyn, Palatin Technologies, Teva Pharmaceutical Industries Ltd, and Warner Chilcott. He has served or is currently serving on the speaker's bureaus of Amgen Inc, Eisai Inc, Merck and Co Inc, Novartis, Noven Pharmaceuticals Inc, Novo Nordisk, Novogyne, Shionogi Inc, Teva Pharmaceutical Industries Ltd, and Warner Chilcott. J.A.S. was the chief medical officer for Sprout Pharmaceuticals and holds stock options in the company. S.A.K. has served as a consultant to and/or advisory board member for Boehringer Ingelheim, The North American Menopause Society, Society for Assisted Reproductive Technologies, Sprout, Palatin, Emotional Brain, Trimel, Pfizer, Shionogi, BioSante, Apricus, and Novo Nordisk. She has been paid to give educational presentations by Boehringer Ingelheim, Medscape/WebMD, and Haymarket. She also holds stock/stock options in Viveve. V.H., M.G. Jr., and M.S. are employees of Boehringer Ingelheim. B.S. is a former employee of Boehringer Ingelheim.

Address correspondence to: James A. Simon, MD, George Washington University School of Medicine, Women's Health & Research Consultants, 1850 M Street, NW, Washington, DC 20036. E-mail: jsimon@jamesasimonmd.com

associated with distress among naturally postmenopausal women was 6.6% in a US survey of 541 naturally postmenopausal women conducted in 2004-2005⁶ and 9.3% in a US survey of 10,429 women conducted in 2006.⁷

HSDD is a multifactorial condition.⁸ It has been hypothesized that HSDD is caused by dysregulation of the excitatory and inhibitory signals in the central nervous system that regulate sexual response.^{9,10} Dopamine, norepinephrine, and testosterone seem to play roles in the stimulation of sexual desire, whereas serotonin inhibits sexual desire.^{9,11} Treatment with testosterone has been shown to improve sexual desire in both naturally and surgically postmenopausal women with HSDD¹²⁻¹⁴; however, that women with HSDD are, in general, deficient in testosterone has not been established.¹⁵

Currently, there are no Food and Drug Administration (FDA)-approved pharmacological treatments for HSDD. In 2004, a testosterone patch (Intrinsa; Procter and Gamble Pharmaceuticals, Cincinnati, OH) was reviewed by an FDA advisory committee, which, based on safety concerns, recommended against approval. The application for FDA approval was subsequently withdrawn, but the patch was approved in Europe in 2006 for the treatment of HSDD in surgically postmenopausal women who are receiving estrogen therapy.¹⁶ Few agents are undergoing clinical development for the treatment of HSDD. Although draft guidance on the development of drugs for female sexual dysfunction was issued by the FDA in 2000,¹⁷ it was never finalized and has now been withdrawn.

Flibanserin is a postsynaptic agonist of serotonin (5-HT) receptor 1A and an antagonist of serotonin receptor 2A¹⁸ that has been shown to induce transient decreases in serotonin and increases in dopamine and norepinephrine in certain regions of the brain.¹⁹⁻²¹ By modulating these neurotransmitters in specific brain areas, flibanserin is believed to improve the balance of systems that regulate sexual desire in women with HSDD.²⁰ The efficacy and safety of flibanserin 100 mg once daily at bedtime (qhs) as HSDD treatment are supported by results from three randomized placebo-controlled trials in North American premenopausal women with HSDD (BEGONIA, DAISY, and VIOLET) and an extension trial.²²⁻²⁵ In these studies, flibanserin was associated with an increase in satisfying sexual events (SSEs), an improvement in sexual desire (measured using the Female Sexual Function Index desire domain [FSFI-d]²⁶), and a decrease in sexual distress, and was well tolerated.

The SNOWDROP trial was designed to investigate the efficacy and safety of flibanserin 100 mg qhs across 24 weeks of treatment in naturally postmenopausal women with HSDD. This was the first clinical trial to investigate flibanserin as a treatment for HSDD in postmenopausal women.

METHODS

Study design

The SNOWDROP trial was a multicenter, randomized, double-blind, placebo-controlled trial, which included a 4-week screening period, followed by a 24-week treatment period, and a 4-week follow-up period. Women were randomized to

receive flibanserin 100 mg qhs or placebo using an interactive voice (or Internet) response system.

The trial was carried out in compliance with the protocol and the principles laid down in the Declaration of Helsinki (1996), in accordance with the International Conference on Harmonization Harmonized Tripartite Guideline for Good Clinical Practice and applicable regulatory requirements. The protocol was approved by the Institutional Review Board and the Independent Ethics Committee. All participants provided written informed consent.

Participants

Naturally postmenopausal women of any age with at least one ovary and a diagnosis of generalized acquired HSDD (ie, HSDD that is not limited to certain types of stimulation, situation, or partner, and that developed after a period of normal sexual functioning)—according to the *Diagnostic and Statistical Manual of Mental Disorders, 4th Edition, Text Revision*¹—lasting 6 months or more were eligible to enter the trial. The diagnosis of HSDD was made by a clinician who was experienced and trained in diagnosing female sexual disorders following a structured clinical interview. A woman was allowed to enter the trial if she had an arousal or orgasmic dysfunction that was deemed to be of lesser concern to her than her HSDD and to have developed after her HSDD. Women with any other form of sexual dysfunction or any other psychiatric disorder that could impact sexual function were excluded. Participants had to be engaged in a monogamous heterosexual relationship lasting 1 year or longer with a sexually functional partner who was expected to be available for sexual activity at some point during a 24-hour day for 50% or more of every month during the trial. They had to have a score of 15 or more on the Female Sexual Distress Scale—Revised (FSDS-R),²⁷ indicating distress due to sexual dysfunction, and a score of 1 or 0 on the receptivity item of the Sexual Interest and Desire Inventory—Female, indicating little or no receptivity to a partner's sexual approaches.²⁸ At baseline, women were required to have completed entries in an electronic diary (eDiary; Invivodata Inc, Pittsburgh, PA) for recording of SSEs for 80% or more of days during a screening period of 28 ± 7 days.

Exclusion criteria included a score of 14 or more on the Beck Depression Inventory-II,²⁹ suicide ideation according to the Columbia Suicide Severity Rating Scale,³⁰ or a history of suicidal behavior. Women with a history of a serious clinical disorder, gynecological disorder, bilateral oophorectomy, or unexplained vaginal bleeding within the past 12 months, or with a double-walled endometrial thickness of 6 mm or more (as measured by transvaginal ultrasound at screening or within ≤ 6 mo of screening) were excluded, as were those who had undergone abdominal or vaginal hysterectomy, oophorectomy, or any other pelvic, vaginal, or urologic surgical operation that may impair sexual function. Women with pelvic pain, pelvic inflammatory disease, endometriosis, urinary tract or vaginal infection/vaginitis, cervicitis, interstitial cystitis, vulvodynia, or symptomatic vaginal atrophy, or any

other gynecological pathology identified at screening and requiring further evaluation were not permitted to enter the trial. Women were excluded if they were using any of the following medications or had used them in the past 4 weeks: hormone agonists/antagonists; CYP3A inducers; dopamine receptor agonists and other antiparkinsonian drugs; benzodiazepines; prescription sleep aids, sedatives, and hypnotics; antidepressants; antipsychotics; mood stabilizers/antiepileptics; St John's wort; metoclopramide; chronically used narcotics; or any medication that, in the investigator's opinion, may affect the woman's sexual function. Women on systemic hormone therapy were permitted to enter the study provided the hormone therapy had not been prescribed for the treatment of low sexual desire and the dose had remained stable for 6 months or more before screening and would remain unchanged during the trial.

Assessments

There were two co-primary endpoints: change from baseline (week 0) to week 24 in the number of SSEs over the previous 28-day period and change from baseline to week 24 in FSFI-d score.

An eDiary was used to record the number of SSEs. Every participant was prompted to enter, on a daily basis, the number of sexual events that she had experienced and, for every event, whether it was satisfying for her (yes or no). For the women in the trial, a sexual event was defined as sexual intercourse, oral sex, masturbation, or genital stimulation by a partner. Information could be retrospectively entered in the eDiary for up to 7 days.

The Female Sexual Function Index (FSFI) is a 19-item measure of overall sexual function and includes six domains (desire, arousal, lubrication, orgasm, satisfaction, and pain).²⁶ Every domain contributes a maximum of six points to the total score; thus, the maximal score is 36. Higher scores indicate better sexual function. The FSFI-d comprises two questions: (1) "Over the past 4 weeks, how often did you feel sexual desire or interest?" and (2) "Over the past 4 weeks, how would you rate your level (degree) of sexual desire or interest?" Both questions are rated on a scale from 1 to 5; their sum is multiplied by 0.6 to give the domain score, which ranges from 1.2 to 6.²⁶

The FSDS-R assesses the frequency of sexual distress or bother during the past 7 days.^{27,31} Its 13 items are rated on a 5-point scale from 0 (never) to 4 (always); thus, the total score ranges from 0 to 52, with lower scores indicating less distress. Item 13 specifically assesses distress due to low sexual desire. The Patient's Global Impression of Improvement (PGI-I) was used to assess women's evaluation of the overall change in their HSDD. It comprised one question, "How is your condition (ie, decreased sexual desire and feeling bothered by it) today compared with when you started study medication?", and was rated on a 7-point scale from 1 (very much improved) through 4 (no change) to 7 (very much worse). The Patient Benefit Evaluation (PBE) was assessed with a single yes/no question on treatment discontinuation: "Overall, do you believe that

you have experienced a meaningful benefit from the study medication?"

Safety assessments included evaluation of adverse events (AEs), laboratory tests (hematology, biochemistry, urinalysis, and hormone assays), vital signs (blood pressure and pulse rate), physical examinations, and suicide ideation. Data on AEs and vital signs were collected at every visit. Physical examinations and laboratory tests were performed at screening and at the end of treatment. The Columbia Suicide Severity Rating Scale was administered at screening, at baseline, and at the end of treatment. Vital signs and AEs were evaluated at the end of the posttreatment period.

Statistical analyses

A nonparametric method was used to calculate sample size for the FSFI, as it has discontinuous variables. A parametric test was used to calculate sample size for the SSE endpoint. The final determination of sample size used the method that generated the larger of these two samples. Thus, sample size was based on the requirement to detect a difference in the SSE endpoint between treatment groups with a power of 90% or more. The sample size calculation was performed with a Wilcoxon two-sided test at an α of 0.05 (assuming SSEs to be a continuous outcome) and indicated that 420 participants per treatment arm were needed to have a power of 90% or more. A sample size of 450 women per arm was selected to allow for a dropout rate of 7% before the first complete month of SSE data collection (ie, during the baseline period).

Efficacy analyses were based on the full analysis set, which included all women who had at least one on-treatment efficacy assessment. Last-observation-carried-forward (LOCF) analysis was used in the case of missing data. No data were carried forward from predrug to postdrug assessments. To control for type I error, we used an a priori ordered hierarchical model for the primary analyses. The order was SSEs \rightarrow FSFI-d \rightarrow FSDS-R Item 13. For these endpoints, the numbers of women were 462 for placebo and 429 for flibanserin, 463 for placebo and 432 for flibanserin, and 462 for placebo and 432 for flibanserin, respectively. These represent the number of women in the analyses comparing change from baseline to week 24. As a sensitivity analysis, a mixed-model repeated-measures test was used for the co-primary endpoints. Change from baseline in the number of SSEs was analyzed using the stratified Wilcoxon rank sum test. Data for a visit (ie, from the 28-d period before a visit) were only evaluated if 14 days or more of data were available; otherwise, the most recent period for which 14 days of data were available was used for LOCF analysis. Analysis of covariance was used to analyze FSFI and FSDS-R scores, with treatment and center as fixed effects and with the baseline value as covariate. PGI-I and PBE responses were analyzed using the Cochran-Mantel-Haenszel test. The FDA-approved protocol listed all of the secondary endpoints as "a priori." Safety analyses were based on the treated set, which included all women who received one or more doses of study medication.

The analysis approach used is standard and consistent with other investigational therapies in this therapeutic class. The analysis plan was mandated by the FDA in accordance with its then draft “guidance for industry” for the approval of therapies for HSDD.¹⁷ As per protocol, a separate analysis was performed using an intent-to-treat approach with LOCF, which may be a more conservative approach. This analysis demonstrated identical results with a greater treatment effect (data not shown). Only prespecified analyses are reported. A separate analysis of the minimally clinically important difference was completed and is planned to be the subject of a separate article.

RESULTS

Participants

A total of 1,997 women were screened, and 949 women were randomized to receive flibanserin ($n = 468$) or placebo ($n = 481$; Fig. 1). The most frequent reasons for screen failure were as follows: endometrial thickness of more than 4 mm, depression (history of major depressive disorder within 6 mo before screening or a score of ≥ 14 on the Beck Depression Inventory-II),²⁹ and use of medication prohibited by the study protocol. Among the randomized women, 2 were not treated,

and 185 (19.5%) discontinued the trial prematurely (102 [21.8%] in the flibanserin group and 83 [17.3%] in the placebo group). Baseline characteristics were similar between groups (Table 1). At baseline, there were 2.0 SSEs in the placebo group and 2.1 SSEs in the flibanserin group (standardized to 28 d).

Co-primary endpoints

At week 24, improvements in both co-primary endpoints were observed with flibanserin versus placebo. Mean (SE) SSEs increased by 1.0 (0.1) with flibanserin versus 0.6 (0.1) with placebo ($P = 0.004$; Fig. 2, Table 2). Adjusted mean (SE) FSFI-d score increased by 0.7 (0.1) with flibanserin versus 0.4 (0.1) with placebo ($P < 0.001$; Fig. 3, Table 2). Similar results were achieved using mixed-model repeated-measures analyses: the adjusted mean (SE) change in SSEs was 1.1 (0.2) with flibanserin versus 0.5 (0.2) with placebo ($P = 0.002$), and the adjusted mean (SE) change in FSFI-d score was 0.7 (0.1) with flibanserin versus 0.4 (0.1) with placebo ($P < 0.001$).

Secondary endpoints

Improvements in sexual distress (FSDS-R total score) and distress associated with low sexual desire (FSDS-R Item

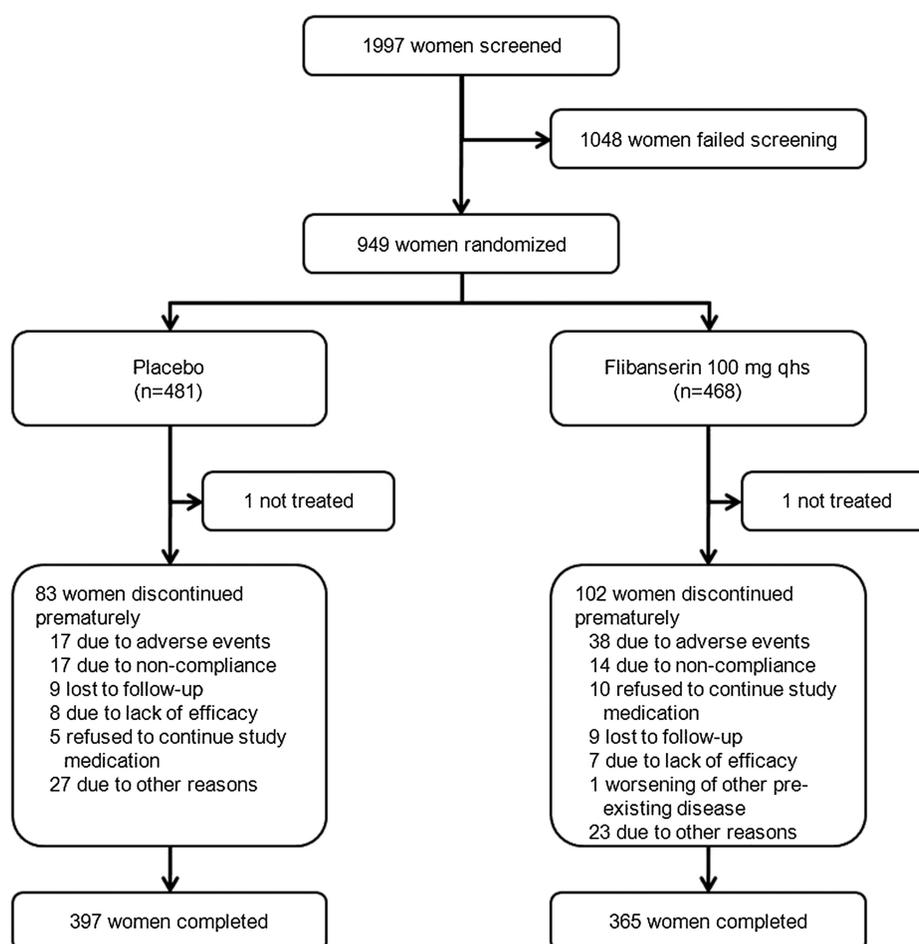


FIG. 1. Disposition of trial participants. Three hundred ninety-seven of 481 women randomized to placebo (82.5%), and 365 of 468 women randomized to flibanserin (78%) completed the trial. qhs, at bedtime.

TABLE 1. Baseline characteristics

	Placebo	Flibanserin 100 mg qhs
Age, y ^a	55.5 (5.3)	55.4 (5.4)
Age group, n (%) ^a		
<45 y	6 (1.3)	8 (1.7)
45-54 y	212 (44.2)	192 (41.1)
55-64 y	237 (49.4)	247 (52.9)
≥65 y	25 (5.2)	20 (4.3)
Race/ethnicity, n (%) ^a		
White	421 (87.7)	397 (85.0)
Black/African American	27 (5.6)	35 (7.5)
White Hispanic	23 (4.8)	28 (6.0)
Asian	4 (0.8)	4 (0.9)
Other	5 (1.0)	3 (0.6)
Weight, kg ^a	73.2 (15.1)	74.3 (15.4)
BMI, kg/m ^{2a}	27.3 (5.4)	27.7 (5.7)
Free testosterone, pg/mL	1.5 (1.0)	1.4 (1.0)
Duration of present relationship, y ^a	20.6 (12.6)	21.6 (12.3)
Duration of HSDD, mo ^a	61.6 (51.3)	59.5 (46.0)
SSEs across the 28-d period (count) ^b	2.0 (2.4)	2.0 (2.2)
FSFI-d score ^b	1.8 (0.7)	1.8 (0.7)
FSDS-R Item 13 score ^b	3.3 (0.7)	3.3 (0.8)
FSDS-R total score ^b	31.2 (9.1)	30.5 (9.3)
FSFI total score ^b	15.9 (6.4)	15.9 (6.6)

Data are presented as mean (SD), unless otherwise indicated. qhs, at bedtime; BMI, body mass index; HSDD, hypoactive sexual desire disorder; SSE, satisfying sexual event; FSFI-d, Female Sexual Function Index desire domain; FSDS-R, Female Sexual Distress Scale—Revised; FSFI, Female Sexual Function Index.

^aTreated set (n = 480 and n = 467 for placebo and flibanserin, respectively; n = 479 for the duration of HSDD and placebo).

^bFull analysis set (n = 476 and n = 450 for placebo and flibanserin, respectively).

13 score) were observed with flibanserin versus placebo. The adjusted mean (SE) change in FSDS-R Item 13 score was -0.8 (0.1) with flibanserin versus -0.6 (0.1) with placebo ($P = 0.008$; Fig. 4, Table 2), whereas the adjusted mean (SE) change in FSDS-R total score was -8.3 (0.6) with flibanserin versus -6.3 (0.6) with placebo ($P = 0.006$; Fig. 5, Table 2). The adjusted mean (SE) FSFI total score increased by 4.2 (0.4) with flibanserin versus 2.7 (0.4) with placebo ($P = 0.003$; Fig. 6, Table 2).

At week 24, the adjusted mean (SE) PGI-I score was lower with flibanserin (3.4 [0.1]) than with placebo (3.7 [0.1]; $P < 0.001$), indicating greater improvement. The number of

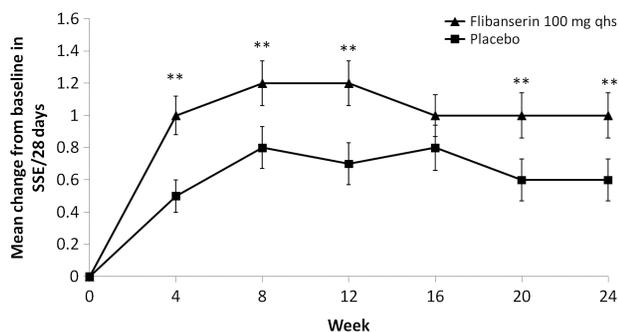


FIG. 2. Change in the number of satisfying sexual events (SSEs) from baseline to week 24. Last-observation-carried-forward analysis on the full analysis set. Data are presented as means; error bars denote SE. ** $P < 0.01$ for flibanserin 100 mg at bedtime (qhs) versus placebo.

TABLE 2. Efficacy endpoints: change from baseline to week 24

	Placebo	Flibanserin 100 mg qhs	P
SSE (count) ^{a,b}	0.6 (0.1)	1.0 (0.1)	0.004
FSFI-d score	0.4 (0.1)	0.7 (0.1)	<0.001
FSDS-R item 13 score ^a	-0.6 (0.1)	-0.8 (0.1)	0.008
FSDS-R total score ^a	-6.3 (0.6)	-8.3 (0.6)	0.006
FSFI total score	2.7 (0.4)	4.2 (0.4)	0.003

Data are presented as least squares mean.

Last-observation-carried-forward analyses on the full analysis set (n = 463 and n = 432 for placebo and flibanserin, respectively).

qhs, at bedtime; SSE, satisfying sexual event; FSFI-d, Female Sexual Function Index desire domain; FSDS-R, Female Sexual Distress Scale—Revised; FSFI, Female Sexual Function Index.

^an equals 462 for placebo.

^bn equals 429 for flibanserin.

women who responded “yes” when asked whether they had experienced a meaningful benefit from the study medication (PBE) was higher in the flibanserin group (163 [37.6%]) than in the placebo group (127 [28.0%]; $P = 0.003$).

Safety and tolerability

AEs were experienced by 296 (63.4%) women in the flibanserin group versus 248 (51.7%) women in the placebo group (Table 3). Almost all AEs reported were mild or moderate in intensity (96.5% in the placebo group and 94.0% in the flibanserin group). The most frequently reported AEs were dizziness, somnolence, nausea, and headache (Table 3). AEs were considered by the investigator to be drug-related in 139 (29.8%) women on flibanserin versus 61 (12.7%) women on placebo. Thirty-eight (8.1%) women on flibanserin and 17 (3.5%) women on placebo discontinued treatment because of an AE. The most common AEs leading to discontinuation of flibanserin were dizziness (1.3%) and insomnia (0.9%).

Twelve women experienced one or more serious AEs: four (0.8%) women on placebo (5 events) and eight (1.7%) women on flibanserin (12 events). Two AEs in the flibanserin group were considered life-threatening, and one AE (alcohol poisoning) was fatal. No serious AEs were considered by the investigator to be related to treatment. There was no evidence of increased suicide ideation in the flibanserin group. The

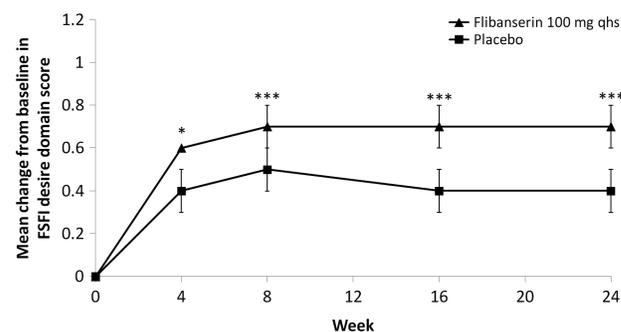


FIG. 3. Change in Female Sexual Function Index desire domain (FSFI-d) score from baseline to week 24. Last-observation-carried-forward analyses on the full analysis set. Data are presented as adjusted (least squares) means; error bars denote SE. * $P < 0.05$, *** $P < 0.001$ for flibanserin 100 mg at bedtime (qhs) versus placebo.

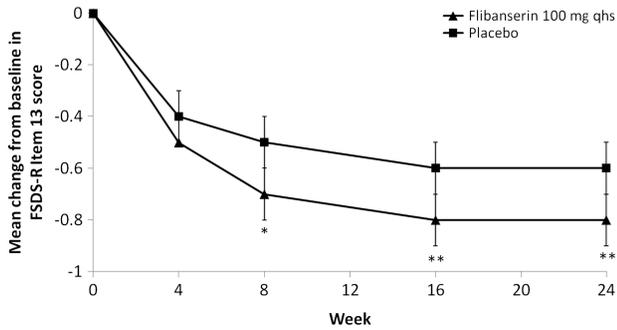


FIG. 4. Change in Female Sexual Distress Scale—Revised (FSDS-R) item 13 score from baseline to week 24. Data are presented as adjusted (least squares) means; error bars denote SE. Last-observation-carried-forward analysis on the full analysis set. * $P < 0.05$, ** $P < 0.01$ for flibanserin 100 mg at bedtime (qhs) versus placebo.

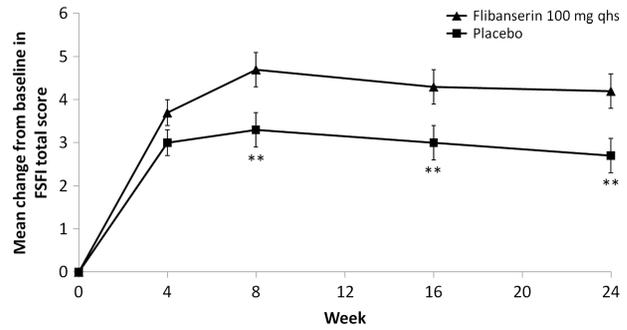


FIG. 6. Change in Female Sexual Function Index (FSFI) total score from baseline to week 24. Data are presented as adjusted (least squares) means; error bars denote SE. Last-observation-carried-forward analysis on the full analysis set. *** $P < 0.01$ for flibanserin 100 mg at bedtime (qhs) versus placebo.

incidence of AEs in the posttreatment period was similar in the placebo (8.3%) and flibanserin (11.1%) groups.

Increases in prolactin, progesterone, and sex hormone-binding globulin that were of possible clinical significance (cutoff: prolactin, >30 ng/dL; progesterone, $\geq 3,750$ ng/mL; sex hormone-binding globulin, >120 nmol/L) were reported in 5 (1.4%), 14 (3.8%), and 12 (3.3%) women on flibanserin versus 2 (0.5%), 10 (2.5%), and 15 (3.8%) women on placebo, respectively. Clinically relevant changes in blood pressure (defined as outside the reference range and ± 15 mm Hg [diastolic] or ± 20 mm Hg [systolic]) were observed in three (0.6%) women on flibanserin and four (0.8%) women on placebo. Clinically relevant decreases in pulse (by ≥ 15 bpm and reaching below 50 bpm) were observed in three (0.6%) women on flibanserin and one (0.2%) woman on placebo.

DISCUSSION

In this randomized, placebo-controlled trial, 24-week treatment with flibanserin 100 mg qhs was associated with significant improvements in sexual desire and distress associated with low sexual desire in postmenopausal women with HSDD. This is the first time that a nonhormone pharmacological treatment has been shown to be effective for treating HSDD in postmenopausal women.

The FSFI-d score, chosen as a co-primary endpoint in this study, has been used extensively as a measure of sexual desire in women and has been validated in both premenopausal and postmenopausal women with HSDD.^{32,33} Change in SSEs was required by the FDA as a primary endpoint in this trial and has been shown to be responsive to treatment in previous trials on premenopausal women with HSDD.²²⁻²⁵ However, the frequency of SSEs is influenced by multiple factors and does not necessarily correlate with sexual desire or with the distress associated with low sexual desire.³⁴ Distress associated with low sexual desire is a defining feature of HSDD, and relief of distress is recognized as a key aim of its treatment. The FSDS-R and its item 13 (distress due to low desire) have been validated to be of relevance to women with HSDD.^{27,31}

The baseline characteristics of the women in this trial were broadly similar to those of the postmenopausal cohort of women who participated in a recent HSDD registry. The mean baseline FSFI total score in this trial population was 15.9 compared with 14.0 in postmenopausal women in the registry.³⁵ Baseline measures of SSEs and FSFI total score were lower in postmenopausal women in this trial (2.0 and 15.9, respectively) than in studies of flibanserin in North American premenopausal women (2.5-2.8 and 19.0-20.1,

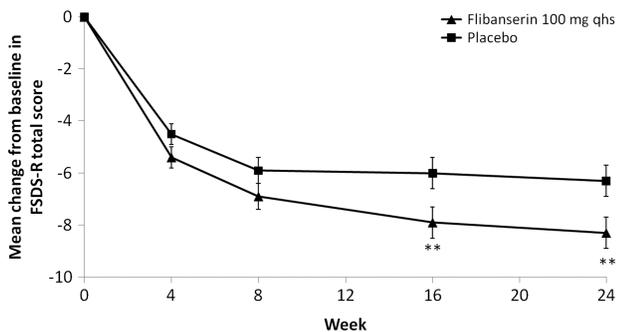


FIG. 5. Change in Female Sexual Distress Scale—Revised (FSDS-R) total score from baseline to week 24. Data are presented as adjusted (least squares) means; error bars denote SE. Last-observation-carried-forward analysis on the full analysis set. ** $P < 0.01$ for flibanserin 100 mg at bedtime (qhs) versus placebo.

TABLE 3. Adverse events

	Placebo (n = 480)	Flibanserin 100 mg qhs (n = 467)
Women with any adverse events	248 (51.7)	296 (63.4)
Investigator-defined drug-related adverse events	61 (12.7)	139 (29.8)
Adverse events leading to discontinuation	17 (3.5)	38 (8.1)
Severe adverse events	17 (3.5)	28 (6.0)
Serious adverse events	4 (0.8)	8 (1.7)
Most frequent adverse events ^a		
Dizziness	15 (3.1)	46 (9.9)
Somnolence	7 (1.5)	41 (8.8)
Nausea	17 (3.5)	35 (7.5)
Headache	23 (4.8)	28 (6.0)

Data are presented as n (%). qhs, at bedtime.

^aReported by 5% or more of women in either group (treated set).

respectively).²²⁻²⁵ However, baseline FSFI-d scores were similar in postmenopausal women in this trial (1.8) and in premenopausal women in similar trials (1.8-1.9).²²⁻²⁴ The magnitude of improvement in FSFI-d and total scores with flibanserin was similar in the trials in premenopausal and postmenopausal women, with FSFI-d score improvements of 0.9 to 1.0 point in the DAISY, VIOLET, and BEGONIA trials versus 0.7 point in this trial, and with FSFI total score improvements of 4.1 to 5.3 points in the DAISY, VIOLET, and BEGONIA trials versus 4.2 points in this trial. However, the increase in SSEs seemed to be somewhat smaller in this trial than in the trials of flibanserin conducted in premenopausal women (1.0 vs 1.6-2.5). This may have been because postmenopausal women with HSDD have a greater prevalence of arousal and sexual pain problems than premenopausal women with HSDD,³⁵ partner issues, or other reasons.

Flibanserin was well tolerated by the postmenopausal women in this study, with the observed AEs being consistent with those reported in trials of flibanserin in premenopausal women^{22-25,36} and with those associated with other serotonin receptor 2A antagonists.^{37,38} Nearly all AEs were mild or moderate, and only about 8% of women in the flibanserin group (vs 3.5% in the placebo group) discontinued from the investigation prematurely because of AEs. Although the active treatment group had double the number of discontinuations due to AEs as the placebo group, the percentage of women discontinuing from the trial overall was quite low and consistent with other trials of this type and duration.³⁹⁻⁴¹ The AEs that most frequently resulted in discontinuation were dizziness (1.3%) and insomnia (0.9%) in the flibanserin group, and anxiety (0.8%) and fatigue (0.8%) in the placebo group.

The inclusion and exclusion criteria for this trial were less constrained than those used in previous phase III trials of flibanserin (eg, the list of prohibited medications was greatly reduced). However, a limitation of this study was its restriction to women in stable heterosexual relationships with a sexually functional partner, who, except for their sexual dysfunction, were not experiencing any other psychiatric disorder (including depression, which often occurs concomitantly with HSDD)⁴² and were not taking concomitant medications that could affect sexual function. Also excluded from this study population were women with induced menopause (ie, caused by radiation, chemotherapy, or surgical operation). Thus, the study population was not entirely reflective of women seeking treatment for distressing low sexual desire in clinical practice.

CONCLUSIONS

These results demonstrate that flibanserin 100 mg qhs improves sexual desire, improves sexual function, and reduces distress related to loss of desire in naturally postmenopausal women with HSDD, and is well tolerated.

Acknowledgments: We wish to thank Drs. Krista A. Barbour and James P. Symons for their critical comments and generous editorial assistance in the final preparation of this manuscript.

REFERENCES

1. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders, 4th Edition, Text Revision*. Washington, DC: American Psychiatric Press, 2000:1-943.
2. Shifren JL, Monz BU, Russo PA, Segreti A, Johannes CB. Sexual problems and distress in United States women: prevalence and correlates. *Obstet Gynecol* 2008;112:970-978.
3. Laumann EO, Waite LJ. Sexual dysfunction among older adults: prevalence and risk factors from a nationally representative U.S. probability sample of men and women 57-85 years of age. *J Sex Med* 2008;5:2300-2311.
4. Lindau ST, Schumm LP, Laumann EO, Levinson W, O'Muirheartaigh CA, Waite LJ. A study of sexuality and health among older adults in the United States. *N Engl J Med* 2007;357:762-774.
5. Hayes RD, Dennerstein L, Bennett CM, Fairley CK. What is the "true" prevalence of female sexual dysfunctions and does the way we assess these conditions have an impact? *J Sex Med* 2008;5:777-787.
6. West SL, D'Aloisio AA, Agans RP, Kalsbeek WD, Borisov NN, Thorp JM. Prevalence of low sexual desire and hypoactive sexual desire disorder in a nationally representative sample of US women. *Arch Intern Med* 2008;168:1441-1449.
7. Rosen RC, Shifren JL, Monz BU, Odom DM, Russo PA, Johannes CB. Correlates of sexually related personal distress in women with low sexual desire. *J Sex Med* 2009;6:1549-1560.
8. Simon JA. Low sexual desire—is it all in her head? Pathophysiology, diagnosis, and treatment of hypoactive sexual desire disorder. *Postgrad Med* 2010;122:128-136.
9. Pfaus JG. Pathways of sexual desire. *J Sex Med* 2009;6:1506-1533.
10. Bancroft J, Graham CA, Janssen E, Sanders SA. The dual control model: current status and future directions. *J Sex Res* 2009;46:121-142.
11. Clayton AH. The pathophysiology of hypoactive sexual desire disorder in women. *Int J Gynaecol Obstet* 2010;110:7-11.
12. Panay N, Al-Azzawi F, Bouchard C, et al. Testosterone treatment of HSDD in naturally menopausal women: the ADORE study. *Climacteric* 2010;13:121-131.
13. Davis SR, Braunstein GD. Efficacy and safety of testosterone in the management of hypoactive sexual desire disorder in postmenopausal women. *J Sex Med* 2012;9:1134-1148.
14. Shifren JL, Braunstein GD, Simon JA, et al. Transdermal testosterone treatment in women with impaired sexual function after oophorectomy. *N Engl J Med* 2000;343:682-688.
15. Basson R, Brotto LA, Petkau AJ, Labrie F. Role of androgens in women's sexual dysfunction. *Menopause* 2010;17:962-971.
16. European Medicines Agency (EMA). Intrinsic summary of product characteristics. Available at: http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/000634/human_med_000845.jsp&mid=WC0b01ac058001d124. Accessed February 27, 2012.
17. US Food and Drug Administration. Draft guidance for industry—female sexual dysfunction: clinical development of drug products for treatment. Available at: <http://www.fda.gov/ScienceResearch/SpecialTopics/WomensHealthResearch/ucm133202.htm>. Accessed February 27, 2012.
18. Borsini F, Evans K, Jason K, Rohde F, Alexander B, Pollentier S. Pharmacology of flibanserin. *CNS Drug Rev* 2002;8:117-142.
19. Allers KA, Dremencov E, Ceci A, et al. Acute and repeated flibanserin administration in female rats modulates monoamines differentially across brain areas: a microdialysis study. *J Sex Med* 2010;7:1757-1767.
20. Stahl SM, Sommer B, Allers KA. Multifunctional pharmacology of flibanserin: possible mechanism of therapeutic action in hypoactive sexual desire disorder. *J Sex Med* 2011;8:15-27.
21. Marazziti D, Palego L, Giromella A, et al. Region-dependent effects of flibanserin and buspirone on adenylyl cyclase activity in the human brain. *Int J Neuropsychopharmacol* 2002;5:131-140.
22. 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.
23. 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.
24. 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.

25. Jayne C, Simon JA, Taylor LV, Kimura T, Lesko LM. Open-label extension study of flibanserin in women with hypoactive sexual desire disorder. *J Sex Med* 2012;9:3180-3188.
26. 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.
27. DeRogatis LR, Clayton A, Lewis-D'Agostino D, Wunderlich G, Fu Y. 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.
28. Clayton AH, Goldmeier D, Nappi RE, Wunderlich G, Lewis-D'Agostino DJ, Pyke R. Validation of the Sexual Interest and Desire Inventory—Female in hypoactive sexual desire disorder. *J Sex Med* 2010;7:3918-3928.
29. Beck AT, Steer RA, Brown GK. *Beck Depression Inventory: Manual*, 2nd ed. San Antonio, TX: The Psychological Corporation, 1996:1-38.
30. Posner K. State of the science: measurement of suicidal adverse events and the Columbia Suicide Severity Rating Scale. Paper presented at: 47th New Clinical Drugs Evaluation Unit (NCDEU) Annual Meeting; June 11-14, 2007; Boca Raton, FL.
31. DeRogatis LR, Pyke R, McCormack J, Hunter A, Harding G. Does the Female Sexual Distress Scale—Revised cover the feelings of women with HSDD? *J Sex Med* 2011;8:2810-2815.
32. Meston CM. Validation of the Female Sexual Function Index (FSFI) in women with female orgasmic disorder and in women with hypoactive sexual desire disorder. *J Sex Marital Ther* 2003;29:39-46.
33. Revicki DA, Margolis MK, Bush EN, DeRogatis LR, Hanes V. 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.
34. Clayton AH, Dennerstein L, Fisher WA, Kingsberg SA, Perelman MA, Pyke RE. Standards for clinical trials in sexual dysfunction in women: research designs and outcomes assessment. *J Sex Med* 2010;7:541-560.
35. Rosen RC, Maserejian NN, Connor MK, Krychman ML, Brown CS, Goldstein I. Characteristics of premenopausal and postmenopausal women with acquired, generalized hypoactive sexual desire disorder: the Hypoactive Sexual Desire Disorder Registry for women. *Menopause* 2012;19:396-405.
36. 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.
37. Watanabe N, Omori IM, Nakagawa A, et al. Safety reporting and adverse-event profile of mirtazapine described in randomized controlled trials in comparison with other classes of antidepressants in the acute-phase treatment of adults with depression: systematic review and meta-analysis. *CNS Drugs* 2010;24:35-53.
38. Kent JM. SNaRIs, NaSSAs, and NaRIs: new agents for the treatment of depression. *Lancet* 2000;355:911-918.
39. Braunstein GD, Sundwall DA, Katz M, et al. Safety and efficacy of a testosterone patch for the treatment of hypoactive sexual desire disorder in surgically menopausal women: a randomized, placebo-controlled trial. *Arch Intern Med* 2005;165:1582-1589.
40. Simon J, Braunstein G, Nachtigall L, et al. Testosterone patch increases sexual activity and desire in surgically menopausal women with hypoactive sexual desire disorder. *J Clin Endocrinol Metab* 2005;90:5226-5233.
41. Buster JE, Kingsberg SA, Aguirre O, et al. Testosterone patch for low sexual desire in surgically menopausal women: a randomized trial. *Obstet Gynecol* 2005;105(pt 1):944-952.
42. Johannes C, Clayton AH, Odom DM, et al. Distressing sexual problems in United States women revisited: prevalence after accounting for depression. *J Clin Psychiatry* 2009;70:1698-1706.