

# Efficacy of Flibanserin in Women with Hypoactive Sexual Desire Disorder: Results from the BEGONIA Trial

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## ABSTRACT

**Introduction.** Hypoactive Sexual Desire Disorder (HSDD) is characterized by low sexual desire that causes marked distress or interpersonal difficulty.

**Aim.** The aim of this study was to assess the efficacy and safety of the 5-HT<sub>1A</sub> agonist/5-HT<sub>2A</sub> antagonist flibanserin in premenopausal women with HSDD.

**Methods.** This was a randomized, placebo-controlled trial in which premenopausal women with HSDD (mean age: 36.6 years) were treated with flibanserin 100 mg once daily at bedtime (qhs) (n = 542) or placebo (n = 545) for 24 weeks.

**Main Outcome Measures.** Coprimary end points were the change from baseline to study end in Female Sexual Function Index (FSFI) desire domain score and in number of satisfying sexual events (SSE) over 28 days. Secondary end points included the change from baseline in FSFI total score, Female Sexual Distress Scale-Revised (FSDS-R) total score, and FSDS-R Item 13 score.

**Results.** Compared with placebo, flibanserin led to increases in mean (standard deviation) SSE of 2.5 (4.6) vs. 1.5 (4.5), mean (standard error [SE]) FSFI desire domain score of 1.0 (0.1) vs. 0.7 (0.1), and mean (SE) FSFI total score of 5.3 (0.3) vs. 3.5 (0.3); and decreases in mean (SE) FSDS-R Item 13 score of -1.0 (0.1) vs. -0.7 (0.1) and mean (SE) FSDS-R total score of -9.4 (0.6) vs. -6.1 (0.6); all  $P \leq 0.0001$ . The most frequently reported adverse events in the flibanserin group were somnolence, dizziness, and nausea, with adverse events leading to discontinuation in 9.6% of women receiving flibanserin vs. 3.7% on placebo.

**Conclusion.** In premenopausal women with HSDD, flibanserin 100 mg qhs resulted in significant improvements in the number of SSE and sexual desire (FSFI desire domain score) vs. placebo. Flibanserin was associated with significant reductions in distress associated with sexual dysfunction (FSDS-R total score) and distress associated with low sexual desire (FSDS-R Item 13) vs. placebo. There were no significant safety concerns associated with the use of flibanserin for 24 weeks. **Katz M, DeRogatis LR, Ackerman R, Hedges P, Lesko L, Garcia M, and Sand M. Efficacy of flibanserin in women with Hypoactive Sexual Desire Disorder: Results from the BEGONIA trial. J Sex Med \*\*;\*\*:\*\*\_\*\*.**

**Key Words.** Hypoactive Sexual Desire Disorder; Flibanserin; HSDD; Premenopausal Women; Patient-Reported Outcomes; Distress

## Introduction

Hypoactive Sexual Desire Disorder (HSDD) is defined by the American Psychiatric Association as a persistent or recurrent deficiency or absence of sexual fantasies and desire for sexual activity that causes marked distress or interper-

sonal difficulty. For a diagnosis of HSDD to be given, the desire problem must not be better accounted for by another psychiatric disorder (e.g., depression), substance (e.g., a medication), or medical condition [1]. Female sexual dysfunction must be diagnosed by a clinician taking into account the woman's sexual, medical, and

psychosocial history [2]. This means that the prevalence of HSDD is hard to determine in population studies. However, a large demographically representative survey found that about 10% of premenopausal women in the United States reported low sexual desire with associated distress [3,4].

HSDD is hypothesized to be caused by an imbalance in the excitatory and inhibitory activity that regulates the sexual response in the central nervous system [5,6]. Dopamine and norepinephrine have been identified as excitatory factors, whereas serotonin (5-HT) has inhibitory effects. Flibanserin is a postsynaptic 5-HT<sub>1A</sub> receptor agonist and 5-HT<sub>2A</sub> receptor antagonist [7] that has been shown to regulate levels of dopamine and norepinephrine and induce transient decreases in serotonin in specific regions of the brain [8–10].

The efficacy of flibanserin 100 mg once daily at bedtime (qhs) as a treatment for HSDD is supported by results from two randomized placebo-controlled trials in North American premenopausal women with HSDD (VIOLET and DAISY) [11,12]. In these trials, flibanserin 100 mg qhs was associated with an increase in satisfying sexual events (SSE), an improvement in sexual desire (measured using the Female Sexual Function Index [FSFI]), and a decrease in sexual distress. However, the coprimary end point of change in desire score measured using a daily electronic diary (eDiary) did not reach statistical significance in either trial. An increasing body of data and expert opinion suggest that the FSFI desire domain score is a more appropriate measure of sexual desire in women with HSDD than a daily measure of the intensity of desire such as the eDiary desire score [13,14]; thus, a new randomized placebo-controlled trial was designed in which the primary desire end point was changed to FSFI desire domain score.

This trial, named BEGONIA, investigated the efficacy and safety of 24 weeks' treatment with flibanserin 100 mg qhs in premenopausal women with HSDD.

## Methods

### Study Design and Participants

BEGONIA was a multicenter, randomized, double-blind, placebo-controlled trial, which included a 4-week baseline period (week -4 to week 0) followed by a 24-week treatment period, and a 1-week post-treatment period. Women were randomized to receive flibanserin 100 mg qhs

(n = 543) or placebo (n = 547) using an interactive voice (or internet) response system.

The trial was carried out in compliance with the protocol, the principles laid down in the Declaration of Helsinki (1996 Version), 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.

To be eligible to enter the trial, women had to be aged  $\geq 18$  years, premenopausal according to Stages of Reproductive Aging Workshop criteria [15] and diagnosed with generalized acquired HSDD (i.e., 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 American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders, 4<sup>th</sup> edition, text revision (DSM-IV-TR) criteria [1] of  $\geq 24$  weeks' duration. The diagnosis of HSDD was made by a clinician who was experienced and trained in the diagnosis of female sexual disorders using a structured clinical interview for FSD, a sexual symptom checklist and the Beck Depression Inventory II [16] to rule out depression. Participants had to be in a monogamous heterosexual relationship of  $\geq 1$  year's duration and to have a sexually functional partner who was expected to be physically present for  $\geq 50\%$  of every month during the trial. Women with significant relationship discord in the opinion of the investigator (who conducted an extensive diagnostic interview with the woman as part of the screening process) were excluded from the trial. To be eligible to participate in this trial, women had to be willing to engage in sexual activity (which included sexual intercourse, oral sex, masturbation, or genital stimulation by the partner) at least once monthly.

Women with secondary arousal and/or orgasmic disorder were eligible to enter the study if the arousal or orgasmic disorder was deemed to be of lesser concern to the woman than her HSDD and to have developed after her HSDD. Women with any other form of sexual dysfunction, or with any other psychiatric disorder that could impact sexual function, were excluded. Women were excluded if they had a score of  $\geq 14$  on the Beck Depression Inventory II [16], suicide ideation according to the Columbia Suicide Severity Rating Scale (C-SSRS) [17], or a history of suicidal behavior. Women were excluded if they were using any medication that, in

the investigator's opinion, may affect sexual function or any of the following medications: antiepileptics; CYP3A4 inducers; dopamine agonists and other antiparkinsonian drugs; metoclopramide; androgens and antiandrogens; antiestrogens (estrogens and progestins were permitted if the dose had been stable for 6 months prior to screening, unless prescribed for low sexual desire); fluoxetine or any long-acting hormonal implant in the 30 days prior to screening (unless used for contraception); gonadotrophin-releasing hormone analogues and other hormones and inhibitors; benzodiazepines; non-benzodiazepine prescription sleep aids; sedatives and hypnotics; antidepressants; antipsychotics; mood stabilizers; St. John's wort; narcotics (unless used for short-term pain relief); and vaginal lubricants/moisturizers containing warming and/or enhancing agents. Women with gynecological disorders such as endometriosis were excluded. Women were required to use a medically acceptable method of contraception for  $\geq 6$  months prior to and during the study. Investigators were asked to exclude women from the trial if they believed that the woman's contraceptive was contributing to her HSDD. To be eligible to enter the treatment phase of the trial, women were required to have completed the eDiary for  $\geq 80\%$  of days during the 4-week baseline period.

### Assessments

There were two coprimary end points: change from baseline (week 0) to week 24 in FSFI desire domain score and in number of SSE standardized to a 28-day period. The desire domain of the FSFI [18] comprises two questions: (i) "Over the past 4 weeks, how often did you feel sexual desire or interest?" and (ii) "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, with the weighted (factor 0.6) domain score ranging from 1.2 to 6 [18].

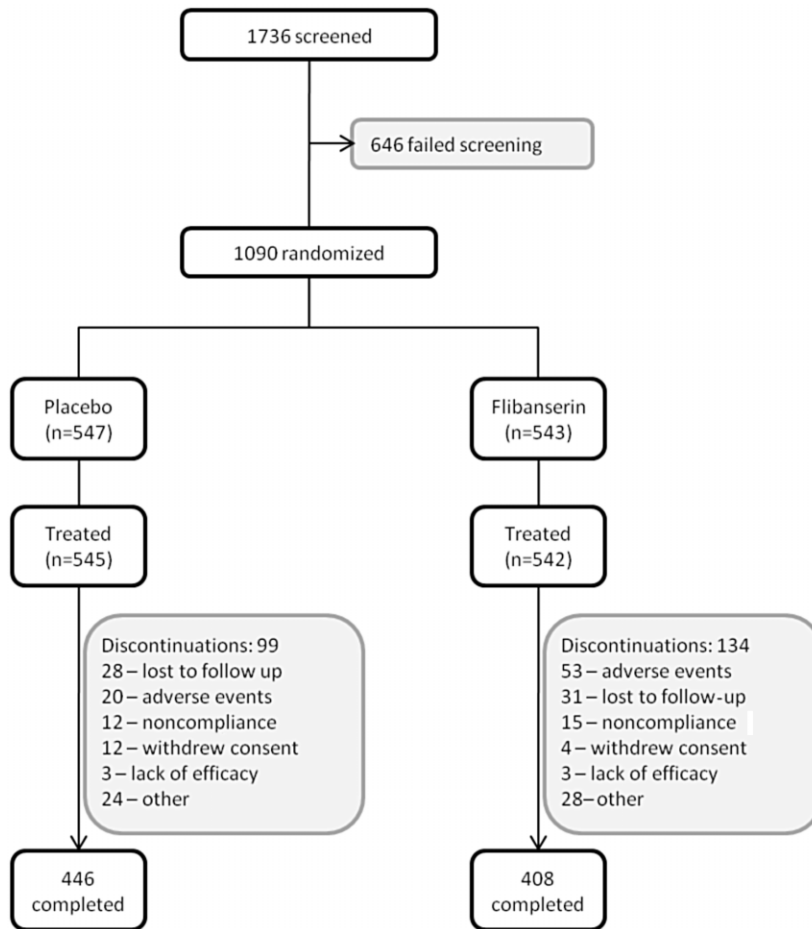
The number of SSE was measured using an eDiary (Invivodata, Inc., Pittsburgh, PA, USA) that prompted women to record, on a daily basis, the number of sexual events that she had experienced, and for every event, whether it was satisfying for her (yes or no). A sexual event was defined for the participants as sexual intercourse, oral sex, masturbation, or genital stimulation by a partner. Data could be entered for 7 days after the day in question. To standardize to a 28-day period, the sum of SSE was divided by number of eDiary entries and multiplied by 28.

Secondary end points included: change from baseline to week 24 in the Female Sexual Distress Scale-Revised (FSDS-R) Item 13 and total scores [19] and FSFI total score [18]; and Patient's Global Impression of Improvement (PGI-I) score and Patient Benefit Evaluation (PBE) at week 24. The FSDS-R is a self-administered questionnaire that assesses the frequency of sexual distress or bother over the past 7 days. Its 13 items are rated from 0 to 4, so the total score can range from 0 to 52, with lower scores indicating less distress. Item 13 specifically assesses distress due to low sexual desire. The FSFI is a measure of sexual function over the past 28 days that includes six domains (desire, arousal, lubrication, orgasm, satisfaction, and pain). The domain scores are weighted so that every domain contributes a maximum of six points to the total score, where higher scores indicate better sexual function. The PGI-I consisted of a single question: "How is your condition (i.e., decreased sexual desire and feeling bothered by it) today compared with when you started study medication?" and was rated by the women on a seven-point scale from 1 (very much improved) through 4 (no change) to 7 (very much worse). The FSFI, FSDS-R, and PGI-I were assessed at weeks 0, 4, 8, 16, and 24. The PBE was a single yes/no question asked 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), clinical laboratory parameters (testosterone, prolactin, hematology, biochemistry, and urinalysis), vital signs (blood pressure and pulse rate), suicide ideation (C-SSRS), and physical examinations. Data on AEs, vital signs, and weight were collected at every visit; physical examination was performed at screening and end of study, and the C-SSRS was administered at screening (week -4), baseline, and end of treatment.

### Statistical Analysis

Sample size calculations were performed using a Wilcoxon two-sided test at level  $\alpha = 0.05$ . Based on the coprimary end point of standardized SSE as a continuous outcome, 420 subjects per treatment arm at week 0 were required to achieve  $\geq 90\%$  power to detect a difference between treatments, allowing for a drop-out rate of 7% before the first complete month of SSE data collection (baseline period). The expected effect size (estimated from previous North American randomized placebo-controlled trials of flibanserin) was estimated as 1.



**Figure 1** Disposition of participants

Efficacy analyses were based on the full analysis set, which included all women who had  $\geq 1$  on-treatment efficacy assessment. An intention-to-treat last observation carried forward methodology was used for all efficacy analyses. No data were carried forward from predrug to postdrug assessments. For SSE, treatments were compared using a stratified Wilcoxon rank sum test, where strata were the pooled centers. Analysis of covariance was used to analyze FSFI desire domain and total scores, FSDS-R Item 13 and total scores and PGI-I scores, with treatment and study center as fixed effects, and baseline score and hormonal contraceptive use as covariates. Mixed Model Repeated Measures (MMRM) was used as a sensitivity analysis for the coprimary end points. The proportions of patients who responded to treatment according to PGI-I and PBE were analyzed using the Cochran–Mantel–Haenszel test. Safety analyses were based on the treated set, which included all women who received  $\geq 1$  dose of study medication.

## Results

### Participants

A total of 1,736 women were screened, and 646 women were excluded. The remaining 1,090 women were randomized to receive flibanserin ( $n = 543$ ) or placebo ( $n = 547$ ). Three women were not treated, and 233 women discontinued the trial prematurely (134 [24.7%] on flibanserin and 99 [18.2%] on placebo) (Figure 1). Baseline characteristics were similar between groups (Table 1).

### Coprimary End points

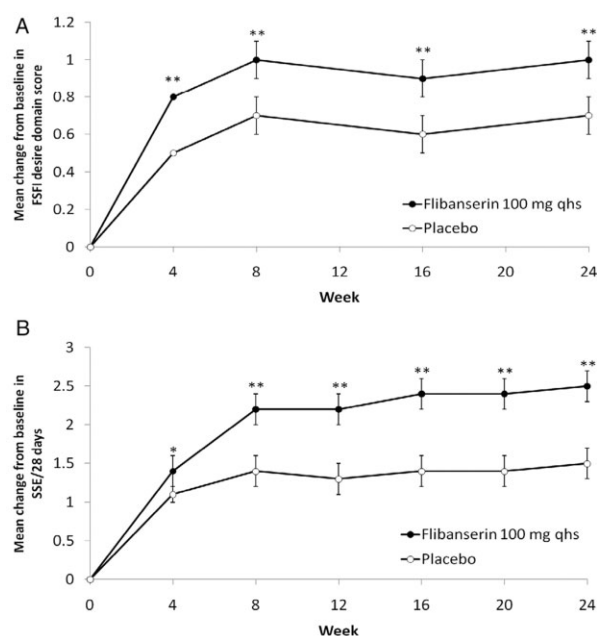
At week 24, change in adjusted (least squares) mean (standard error [SE]) FSFI desire domain score from baseline was 1.0 (0.1) with flibanserin vs. 0.7 (0.1) with placebo ( $P < 0.001$ ; Table 2 and Figure 2A). Similar results were observed using an MMRM analysis (1.0 [0.1] vs. 0.7 [0.1];  $P < 0.001$ ). Mean (standard deviation) standardized SSE increased by 2.5 (4.6) with flibanserin vs. 1.5 (4.5) with placebo ( $P < 0.001$ ; Table 2 and Figure 2B),

with similar results observed using an MMRM analysis (mean [SE]: 2.3 [0.2] vs. 1.4 [0.2];  $P = 0.001$ ). The difference between the flibanserin and placebo groups was significant at all time-points for both coprimary end points (Figure 2).

### Secondary End points

Improvements in sexual distress and distress associated with low sexual desire were observed with flibanserin vs. placebo. Adjusted mean (SE) change from baseline in FSDS-R Item 13 score was  $-1.0$  (0.1) with flibanserin vs.  $-0.7$  (0.1) with placebo ( $P < 0.001$ ; Table 2 and Figure 3A), and adjusted mean (SE) change from baseline in FSDS-R total score was  $-9.4$  (0.6) with flibanserin vs.  $-6.1$  (0.6) with placebo ( $P < 0.001$ ; Table 2 and Figure 3B).

An increase in FSFI total score was observed with flibanserin vs. placebo. Adjusted mean (SE) increase from baseline was 5.3 (0.3) with fi-



**Figure 2** Coprimary end points. (A) Change from baseline to week 24 in Female Sexual Function Index (FSFI) desire domain score. Last observation carried forward analyses on the full analysis set; data plotted are adjusted (least squares) mean; error bars denote standard error. \*\* $P < 0.001$  vs. placebo. (B) Change from baseline to week 24 in satisfying sexual event(s) (SSE). Last observation carried forward analyses on the full analysis set; data plotted are adjusted (least squares) mean; error bars denote standard error. SSE were standardized to a 28-day period. \* $P < 0.05$ , \*\* $P < 0.001$  vs. placebo

**Table 1** Baseline characteristics

|  | Placebo     | Flibanserin 100 mg qhs |
|--|-------------|------------------------|
| Age, years*                                    | 36.6 (7.8)  | 36.5 (8.0)             |
| Race/ethnicity, n (%)*                         |             |                        |
| White  | 407 (74.7)  | 397 (73.2)             |
| White Hispanic                                 | 56 (10.3)   | 69 (12.7)              |
| Black/African American                         | 60 (11.0)   | 63 (11.6)              |
| Asian  | 9 (1.7)     | 7 (1.3)                |
| Other  | 13 (2.4)    | 6 (1.2)                |
| Weight, kg*                                    | 75.0 (19.0) | 74.4 (18.3)            |
| BMI, kg/m <sup>2</sup> *                       | 27.3 (7.0)  | 27.3 (6.3)             |
| Duration of present relationship, years*       | 10.9 (7.2)  | 11.1 (7.5)             |
| Duration of HSDD, months*                      | 49.5 (44.7) | 49.2 (40.3)            |
| FSFI desire domain score <sup>†</sup>          | 1.9 (0.7)   | 1.9 (0.7)              |
| FSFI total score <sup>†</sup>                  | 19.0 (6.1)  | 19.0 (6.0)             |
| FSDS-R Item 13 score <sup>†</sup>              | 3.4 (0.7)   | 3.4 (0.7)              |
| FSDS-R total score <sup>†</sup>                | 32.5 (8.7)  | 32.8 (9.0)             |
| SSE standardized to 28-day period <sup>‡</sup> | 2.7 (2.9)   | 2.5 (2.5)              |

\*Treated set: n = 545 and n = 542

<sup>†</sup>Full analysis set: n = 536 and n = 532

<sup>‡</sup>Full analysis set: n = 532 and n = 528 for placebo and flibanserin, respectively

Data are mean (SD) unless otherwise specified

HSDD = Hypoactive Sexual Desire Disorder; FSFI = Female Sexual Function Index; FSDS-R = Female Sexual Distress Scale-Revised; SSE = satisfying sexual event(s)

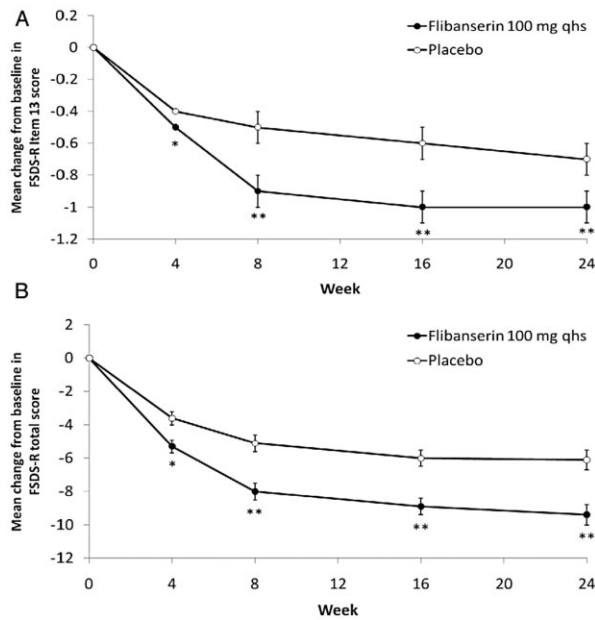
**Table 2** Efficacy end points: change from baseline to week 24

|   | Placebo (n = 525) | Flibanserin 100 mg qhs (n = 506) | Cohen's D | P value |
|---|-------------------|----------------------------------|-----------|---------|
| SSE standardized to 28-day period, mean (SD)* | 1.5 (4.5)         | 2.5 (4.6)                        | 0.39      | <0.001  |
| FSFI desire domain score                      | 0.7 (0.1)         | 1.0 (0.1)                        | 0.43      | <0.001  |
| FSFI total score                              | 3.5 (0.3)         | 5.3 (0.3)                        | 0.30      | <0.001  |
| FSDS-R Item 13 score                          | -0.7 (0.1)        | -1.0 (0.1)                       | 0.46      | <0.001  |
| FSDS-R total score                            | -6.1 (0.6)        | -9.4 (0.6)                       | 0.39      | <0.001  |

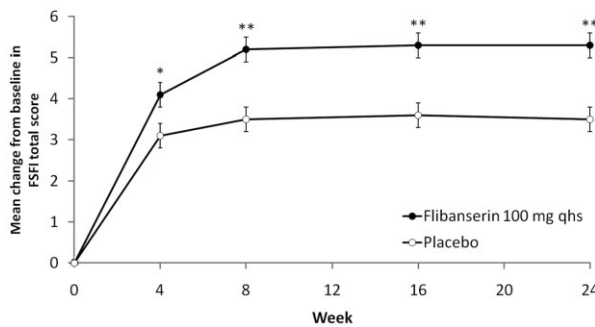
\*n = 521 and 500 for placebo and flibanserin, respectively

Data are adjusted (least squares) mean (SE) unless otherwise specified. Last observation carried forward analyses on the full analysis set. FSFI = Female Sexual Function Index; FSDS-R = Female Sexual Distress Scale-Revised; SSE = satisfying sexual event(s)

banserin vs. 3.5 (0.3) with placebo ( $P < 0.001$ ; Table 2 and Figure 4). At week 24, adjusted mean PGI-I scores were lower in the flibanserin group than placebo (3.2 vs. 3.5;  $P < 0.001$ ), indicating greater improvement. A PGI-I score of 1 or 2 (“very much” or “much” improved) was given by 119 (23.5%) women taking flibanserin vs. 85 (16.2%) women taking placebo ( $P = 0.003$ ), whereas a PGI-I score of 1, 2, or 3 (“very much,” “much,” or “minimally” improved) was given by



**Figure 3** Improvements in sexual distress and distress associated with low sexual desire. (A) Change from baseline to week 24 in Female Sexual Distress Scale-Revised (FSDS-R) Item 13 score. \* $P < 0.01$ , \*\* $P < 0.001$  vs. placebo. Last observation carried forward analyses on the full analysis set; data plotted are least squares mean; error bars denote standard error. (B) Change from baseline to week 24 in FSDS-R total score. \* $P < 0.01$ , \*\* $P < 0.001$  vs. placebo. Last observation carried forward analyses on the full analysis set; data plotted are least squares mean; error bars denote standard error.



**Figure 4** Change from baseline to week 24 in Female Sexual Function Index (FSFI) total score. Last observation carried forward analyses on the full analysis set; data plotted are least squares mean; error bars denote standard error. \* $P < 0.01$ , \*\* $P < 0.001$  vs. placebo

262 (51.8%) women taking flibanserin and 198 (37.7%) on placebo ( $P < 0.001$ ). The number of women who responded “yes” when asked whether they had experienced meaningful benefit from study medication (PBE) was higher in the

flibanserin group (219 [44.7%]) than placebo (174 [34.8%];  $P = 0.001$ ).

### Adverse Events

The most frequently reported AEs in the flibanserin group were somnolence, dizziness, and nausea (Table 3). Six women experienced  $\geq 1$  serious AE: two (0.4%) women on placebo (two events) and four (0.7%) women on flibanserin (six events), none of which was considered by the investigator to be related to study medication. No deaths occurred. There were two cases of suicide ideation, one in each group. There were no clinically significant differences in laboratory parameters, vital signs, or physical examinations between treatment groups. The number of women who reported AEs during the 1-week posttreatment period was similar in the flibanserin (2.8%) and placebo (2.6%) groups. Eight pregnancies were reported: seven resulted in normal delivery at full term and one woman had a therapeutic abortion.

### Discussion

In this randomized placebo-controlled trial, 24 weeks’ treatment with flibanserin 100 mg qhs was associated with significant improvements in sexual desire and number of SSE. Significant improvements in overall sexual function, sexual distress, and distress associated with low sexual desire were also observed. At the end of the study, more women receiving flibanserin considered their condition to have improved, and to have experienced a meaningful benefit from study medication, than

**Table 3** Adverse events (AEs)

|                                       | Placebo<br>(n = 545) | Flibanserin<br>100 mg qhs<br>(n = 542) |
|---------------------------------------|----------------------|--|
| Women with any AE                     | 275 (50.5)           | 337 (62.2)                             |
| Investigator-defined drug-related AEs | 86 (15.8)            | 198 (36.5)                             |
| AEs leading to discontinuation        | 20 (3.7)             | 52 (9.6) <sup>§</sup>                  |
| Serious AEs*                          | 2 (0.4)              | 4 (0.7)                                |
| Severe AEs <sup>†</sup>               | 19 (3.5)             | 23 (4.2)                               |
| Most frequent AEs <sup>‡</sup>        |                      |  |
| Somnolence                            | 19 (3.5)             | 78 (14.4)                              |
| Dizziness                             | 6 (1.1)              | 56 (10.3)                              |
| Nausea                                | 12 (2.2)             | 41 (7.6)                               |
| Fatigue                               | 18 (3.3)             | 31 (5.7)                               |
| Upper respiratory tract infection     | 13 (2.4)             | 28 (5.2)                               |

\*Serious AEs were defined as AEs that resulted in death, were immediately life threatening, resulted in persistent or significant disability, required or prolonged hospitalization, or were deemed serious for any other reason

<sup>†</sup>Severe AEs were defined as AEs that were incapacitating or caused inability to work or undertake usual activity

<sup>‡</sup>Reported by  $\geq 5\%$  of patients in either treatment group. Data are n (%).

<sup>§</sup>Treated set

<sup>§</sup>Does not include one AE reported on trial termination

those who had received placebo. These results support the findings of previous placebo-controlled trials of flibanserin 100 mg qhs in North American premenopausal women with HSDD, in which similar improvements in the number of SSE, FSFI total and desire domain scores, and FSDS-R total and Item 13 scores were observed [11,12,20].

Sexual dysfunctions are complex disorders and, as such, multiple end points are required to assess changes in symptomatology related to treatment. Change in the frequency of SSE was required by the FDA as a primary end point in this trial. Frequency of SSE does not necessarily correlate with sexual desire, nor with the distress associated with HSDD [13], and there are many factors that may affect the frequency of SSE other than a woman's sexual desire. Nonetheless, a significant increase in SSE was observed in the flibanserin group compared with placebo.

Low sexual desire is a defining characteristic of HSDD [1], and the FSFI desire domain score is regarded as an appropriate end point for detection of treatment-induced changes [13]. The FSFI has been validated as a measure of sexual function in women with HSDD [14,21]. Data from two recent studies confirmed that both questions in the FSFI desire domain were understood and of relevance to women with HSDD and that recall periods of 1–4 weeks were more meaningful than daily retrospection for assessment of sexual desire [14]. A substantial substudy within the current trial showed that scores associated with a 1-week recall period were equivalent to scores associated with a 4-week recall period for measurement of desire via the FSFI desire domain [22].

For a sexual problem to be diagnosed as a sexual dysfunction, it must be associated with distress or interpersonal difficulty [1]. Relief of distress is recognized as a key aim of the treatment of FSD. Indeed, it has been argued that a validated measure of distress should be a primary end point in trials in FSD [13]. In this trial, reductions in scores obtained using the FSDS-R and its Item 13 [23] showed a significant reduction in sexual distress in women who received flibanserin. This likely contributed to the fact that more women receiving flibanserin than placebo considered their condition to have improved during the study and suggests that the effects of flibanserin are meaningful to women with HSDD.

Flibanserin was well tolerated, with AEs that were consistent with those observed in previous

randomized placebo-controlled trials [11,12] as well as a 12-month open-label extension study [24] and a randomized withdrawal study [25]. Consistent with the results of the latter study, no withdrawal effects were evident in this study following discontinuation of flibanserin. AEs were reported by more women in the flibanserin group than in the placebo group (62% vs. 51%), and there were more dropouts due to AEs in the flibanserin group than in the placebo group (10% vs. 4% of women treated). The AEs reported most frequently by women taking flibanserin were somnolence, dizziness, and nausea. These are consistent with AEs associated with other 5-HT<sub>2A</sub> receptor antagonists [26,27].

In response to regulatory agency feedback regarding generalizability of the study findings, the inclusion/exclusion criteria used for this trial were less restrictive than those used in previous phase III trials of flibanserin; for example, the list of prohibited medications was greatly reduced. The demographics and baseline characteristics of the women in this trial were similar to those of the premenopausal cohort of women who participated in a recent HSDD registry [28]. This supports the generalizability of the study sample to the population of premenopausal women with HSDD. However, a limitation of this study was its restriction to women in stable heterosexual relationships with a sexually functional partner to minimize the chance that loss of sexual desire was due to relationship problems or sexual problems experienced by the partner. Women in non-heterosexual relationships were excluded to increase the uniformity of the study population. Women who had psychiatric disorders including depression, which is often comorbid with HSDD [28,29], or who were taking certain medications, including SSRIs, which may affect sexual function [30], were excluded from the study. As a result, approximately one-third of the women screened were not eligible to participate.

## Conclusion

The results of this randomized placebo-controlled trial indicate that flibanserin 100 mg qhs has the potential to improve sexual desire and sexual function and reduce distress related to loss of sexual desire in premenopausal women with HSDD. There were no significant safety concerns associated with 24 weeks of flibanserin treatment.

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### Conflict of Interest:

Molly Katz

- Investigator in BEGONIA trial and investigator for Proctor and Gamble.

Leonard R. DeRogatis

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## References

- 1 American Psychiatric Association. Diagnostic and statistical manual of mental disorders. 4th edition, text revision. Washington, DC: American Psychiatric Press; 2000.
- 2 Hatzichristou D, Rosen RC, DeRogatis LR, Low WY, Meuleman EJ, Sadowsky R, Symonds T. Recommendations for the clinical evaluation of men and women with sexual dysfunction. *J Sex Med* 2010;7:337–48.
- 3 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;6:1549–60.
- 4 Shifren JL, Monz BU, Russo PA, Segreti A, Johannes CB. Sexual problems and distress in United States women: Prevalence and correlates. *Obstet Gynecol* 2008;112:970–8.
- 5 Bancroft J, Graham CA, Janssen E, Sanders SA. The dual control model: Current status and future directions. *J Sex Res* 2009;46:121–42.
- 6 Pfaus JG. Pathways of sexual desire. *J Sex Med* 2009;6:1506–33.
- 7 Borsini F, Evans K, Jason K, Rohde F, Alexander B, Pollentier S. Pharmacology of flibanserin. *CNS Drug Rev* 2002;8:117–42.
- 8 Allers KA, Dremencov E, Ceci A, Flik G, Ferger B, Cremers TI, Ittrich C, Sommer B. Acute and repeated flibanserin administration in female rats modulates monoamines differentially across brain areas: A microdialysis study. *J Sex Med* 2010;7:1757–67.
- 9 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.
- 10 Marazziti D, Palego L, Giromella A, Mazzoni MR, Borsini F, Mayer N, Naccarato AG, Lucacchini A, Cassano GB. Region-dependent effects of flibanserin and bupropion on adenylyl cyclase activity in the human brain. *Int J Neuropsychopharmacol* 2002;5:131–40.
- 11 Thorp J, Simon J, Dattani D, Taylor L, Kimura T, Garcia M Jr, Lesko L, Pyke R. Treatment of hypoactive sexual desire disorder in premenopausal women: Efficacy of flibanserin in the DAISY study. *J Sex Med* 2012;9:793–804.



- 12 DeRogatis LR, Komer L, Katz M, Moreau M, Kimura T, Garcia M Jr, Wunderlich G, Pyke R. Treatment of hypoactive sexual desire disorder in premenopausal women: Efficacy of flibanserin in the VIOLET study. *J Sex Med* 2012;9:1074–85.
- 13 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;7:541–60.
- 14 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;8:2237–45.
- 15 Soules MR, Sherman S, Parrott E, Rebar R, Santoro N, Utian W, Woods N. Executive summary: Stages of Reproductive Aging Workshop (STRAW). *Climacteric* 2001;4:267–72.
- 16 Beck AT, Steer RA, Brown GK. Beck depression inventory: Manual. 2nd edition. San Antonio, TX: The Psychological Corporation; 1996:1–38.
- 17 Posner K. State of the science: measurement of suicidal adverse events and the Columbia Suicide Severity Rating Scale. Abstract presented at the 47th New Clinical Drugs Evaluation Unit (NCDEU) Annual Meeting, Boca Raton, Florida, June 11–14, 2007.
- 18 Rosen R, Brown C, Heiman J, Leiblum S, Meston C, Shabsigh R, Ferguson D, D'Agostino R Jr. 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.
- 19 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;5:357–64.
- 20 Clayton AH, Dennerstein L, Pyke R, Sand M. Flibanserin: A potential treatment for hypoactive sexual desire disorder in premenopausal women. *Womens Health (Lond Engl)* 2010;6:639–53.
- 21 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.
- 22 Katz M, DeRogatis L, Rosen RC, Fisher WA, Garcia M, Lesko L, Pyke R, Sand M. Do shorter recall periods provide better assessment of desire in women with hypoactive sexual desire disorder? *J Sex Med* 2011;8:153.
- 23 DeRogatis L, 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;8:2810–5.
- 24 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;9:3180–8.
- 25 Goldfischer ER, Breaux J, Katz M, Kaufman J, Smith WB, Kimura T, Sand M, Pyke R. 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;8:3160–72.
- 26 Watanabe N, Omori IM, Nakagawa A, Cipriani A, Barbui C, McGuire H, Churchill R, Furukawa TA. 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.
- 27 Kent JM. SNaRIs, NaSSAs, and NaRIs: New agents for the treatment of depression. *Lancet* 2000;355:911–8.
- 28 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.
- 29 Johannes C, Clayton AH, Odom DM, Rosen RC, Russo PA, Shifren JL, Monz BU. Distressing sexual problems in United States women revisited: Prevalence after accounting for depression. *J Clin Psychiatry* 2009;70:1698–706.
- 30 Clayton AH, Montejo AL. Major depressive disorder, antidepressants, and sexual dysfunction. *J Clin Psychiatry* 2006;67(suppl 6):33–7.