**ABSTRACT**

**Background:** The efficacy of flibanserin in treating hypoactive sexual desire disorder (HSDD) is based upon statistically significant improvements in sexual desire, satisfying sexual events, and distress. However, clinically meaningful benefit has not been well characterized.

**Aim:** Evaluate clinically meaningful benefit of flibanserin.

**Methods:** Data were pooled from 3 pivotal trials evaluating flibanserin 100 mg qhs in premenopausal women (flibanserin, n = 1192; placebo, n = 1215). Flibanserin trial data in postmenopausal women (flibanserin, n = 450; placebo, n = 476) were analyzed separately. Clinically meaningful benefit was evaluated by the Patient Global Impression of Improvement (PGI-I). Responders were determined through anchor-based analyses that used the PGI-I for key efficacy endpoints: satisfying sexual events (SSE), desire domain of the Female Sexual Function Index (FSFI-d), and distress associated with decreased sexual desire (FSDS-R13). Odds ratios were calculated to assess effect size and Kaplan-Meier analyses were performed to estimate onset time for treatment benefit.

**Outcomes:** PGI-I, anchor-based analyses for key efficacy endpoints (SSE, FSFI-d, FSDS-R13), odds ratios, onset time for treatment benefit.

**Results:** Based on the PGI-I, more patients reported clinically meaningful benefit with flibanserin treatment versus placebo (49.8% vs 33.6%, premenopausal cohort; 40.3% vs 28.7%, postmenopausal cohort). In anchor-based analyses, responder rates were significantly higher for premenopausal women on flibanserin (46.1%–55.2%) than placebo (34.1%–44.2%) for all 3 key efficacy endpoints ($P < .0001$). Responder rates for postmenopausal women on flibanserin were higher compared to placebo for SSE (29.8% vs 22.9%; $P = .015$) and FSFI-d (38.9% vs 26.3%; $P = .0001$). Odds ratios for key endpoints indicated that premenopausal women were 2.0–2.4 times as likely to be responders with flibanserin treatment compared to placebo. Postmenopausal women were 1.6 times as likely to be responders with flibanserin for FSFI-d. Kaplan-Meier analyses indicated significant separation between flibanserin and placebo for the key endpoints in both premenopausal and postmenopausal cohorts (log-rank tests $P < .01$) with earlier median response times among patients receiving flibanserin.

**Clinical Implications:** Patient-reported benefit assessments such as the PGI-I capture the patient’s perspective and may be a useful approach in assessing overall clinical meaningfulness for sexual dysfunction therapies.

**Strengths and Limitations:** Strengths include a well-powered study with large enrollment, use of validated instruments, and self-assessment of treatment benefit. Limitations include pooling of trial data in premenopausal women with slightly different study designs and use of an endpoint (SSE) indirectly related to HSDD.
INTRODUCTION

Hypoactive sexual desire disorder (HSDD) is characterized by decreased desire to participate in sexual activity accompanied by clinically significant personal distress.1-3 Flibanserin, a 5-HT1A receptor agonist and 5-HT2A receptor antagonist, is an oral therapy for the indication of acquired, generalized HSDD, and is approved in the US for premenopausal women and in Canada for premenopausal women and naturally postmenopausal women, 60 years of age or younger.2,4,5 The efficacy of flibanserin in premenopausal women is primarily based upon the results of three randomized, double-blind, placebo-controlled trials that demonstrated significant increases in sexual desire and number of satisfying sexual events, and significantly decreased distress.6-8 These efficacy findings remained consistent in a pooled post-hoc analysis of the pivotal phase 3 trials in premenopausal women.9 In a separate randomized, placebo-controlled trial, flibanserin has also been shown to significantly improve sexual desire, increase the number of satisfying sexual events, and decrease distress in naturally postmenopausal women with HSDD and is approved for use in this population in Canada.5,10 Adverse event data have previously been published6-8,10 and the safety profile of flibanserin has been summarized with updated information in a recent comprehensive review.11

Despite its approval by regulatory agencies in North America, the efficacy of flibanserin remains incompletely understood. The response to flibanserin has been characterized as “small” based on comparisons of efficacy endpoints between flibanserin and placebo treatment groups in randomized, controlled trials.12 The high placebo response rates observed in these studies and a significant number of flibanserin-treated women who did not report improvements in HSDD symptoms that were greater than placebo contributed to the perception of this small treatment effect. However, such high placebo rates are not unusual and have also been reported in studies for therapeutic agents treating other conditions such as depression, anxiety, urinary urge incontinence, rheumatoid arthritis, irritable bowel, and menopausal hot flashes.13-24 In addition, the results of clinical trials may differ from real-world clinical outcomes, partly because of the wide variability of patient characteristics in everyday practice.25-27

The objective of this set of analyses of clinical trial data was to more extensively characterize the efficacy of flibanserin in premenopausal and postmenopausal women with HSDD. While patient ratings of improvement have been previously reported in aggregate in a cursory fashion, we determined clinically meaningful treatment benefit by evaluating the distribution of patient-reported global ratings of overall change and performed additional responder analyses that included determining the percentage of responders for each key efficacy endpoint, calculation of odds ratios, and time-to-onset of treatment response.

METHODS

Study Design and Participants

In this analysis, data were pooled from 3 similarly designed, 24-week, randomized, double-blind, placebo-controlled studies (VIOLET, DAISY, BEGONIA) of flibanserin in premenopausal women with HSDD.6-8 Data from a 24-week, double-blind, placebo-controlled study of flibanserin in naturally postmenopausal women with HSDD (SNOWDROP) were analyzed separately.10 Conduct of each of these studies was consistent with the principles of the Declaration of Helsinki (1996) and the International Conference on Harmonisation Good Clinical Practice Guidelines. All studies were approved by an institutional review board or independent ethics committee at each investigative site, and all participants provided written informed consent before the initiation of study procedures. Clinical trials were funded by Boehringer Ingelheim while post-hoc analyses were funded by Valeant Pharmaceuticals and Sprout Pharmaceuticals.

Study methodology and primary results for each study included in these analyses have been published elsewhere.6-10 Briefly, premenopausal or naturally postmenopausal women with a diagnosis of acquired, generalized HSDD, as determined by criteria in the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR), for ≥24 weeks and in a stable, monogamous, heterosexual relationship for ≥1 year were randomly assigned to receive flibanserin (dose groups varied by study) or placebo for up to 24 weeks. Exclusion criteria included sexual dysfunctions other than acquired, generalized HSDD, dyspareunia (not caused by inadequate foreplay stimulation or alleviated by lubricants), arousal disorder, or orgasm disorder (only allowed if deemed to be lesser concern to the woman than HSDD); major depressive disorder within the past 6 months; substance abuse in the past year; or any ongoing serious clinical disorder.

Conclusion: Assessment of clinically meaningful benefit and additional responder analyses provide further support for flibanserin’s efficacy beyond numerical improvements in endpoint measures. Simon JA, Clayton AH, Kim NN, et al. Clinically Meaningful Benefit in Women with Hypoactive Sexual Desire Disorder Treated with Flibanserin. Sex Med 2022;10:100476.
Measures of Efficacy

Key measures of efficacy were patient-reported outcomes and included changes from baseline to end of study at week 24 in the frequency of satisfying sexual events (SSEs), least square mean change from baseline for Female Sexual Function Index desire domain (FSFI-d) scores, and Female Sexual Distress Scale-Revised, Item 13 (FSDS-R13) scores. SSE frequency (a coprimary endpoint in the trials) were entered by patients in electronic diaries. The FSFI is a self-report measure consisting of 19 items across 6 domains (desire, arousal, lubrication, orgasm, satisfaction, pain).28,29 The FSFI-d score is reported on an adjusted scale of 1.2 to 6.0 and was a coprimary endpoint in the most recent premenopausal study (BEGONIA) and the postmenopausal study (SNOWDROP), and a key secondary endpoint in the first two clinical trials (VIOLET and DAISY) in premenopausal women.6,8,10 The FSDS-R (a key secondary endpoint in the flibanserin trials) is a 13-item self-report questionnaire that assesses sexually related personal distress, with higher scores indicating greater distress.30 Item 13 of the FSDS-R asks how frequently the respondent is bothered by low sexual desire; the score ranges from 0 (never) to 4 (always).30

The Patient Global Impression of Improvement (PGI-I) was included as a secondary endpoint in the flibanserin trials to capture women’s self-report of clinically meaningful treatment benefit during the studies.31 The PGI-I consisted of a single question: “How is your condition [ie, decreased sexual desire and feeling bothered by it] today compared with when you started study medication?” Possible responses were: 1 = “very much improved”, 2 = “much improved”, 3 = “minimally improved”, 4 = “no change”, 5 = “minimally worse”, 6 = “much worse”, and 7 = “very much worse”. Patients reporting any kind of improvement (1, 2, or 3) were considered responders.

Data Analyses

The full dataset from the clinical trials was made available to the authors and data were analyzed using SAS version 9.4 (SAS Institute Inc., Cary, NC, USA). For the studies of premenopausal women, individual patient data were pooled for flibanserin 100 mg qhs (the FDA-approved dose) or placebo. The flibanserin group included patients uptitrated from 50 mg qhs to 100 mg qhs at week 2, as well as those who received 100 mg qhs for the entire study (24 weeks). Patients randomly assigned to non-approved, subtherapeutic flibanserin doses (25 mg twice daily, 50 mg qhs) or doses associated with higher rates of adverse events due to morning dosing (50 mg twice daily) were excluded from this analysis. In the study of postmenopausal women, all patients were randomly assigned to receive placebo or flibanserin 100 mg qhs for the entire study (24 weeks) with no uptitration.

The treated set, primarily used for safety analyses, consisted of those patients who were randomized to a treatment group and received at least one dose of study medication, and had at least one on-treatment efficacy assessment. Sample sizes varied among measures of efficacy based on the number of patients with both baseline and post-dose assessments for a given endpoint. Missing data were handled by using the method of last observation carried forward (LOCF). In sensitivity analyses, alternative missing data imputation methods (ie, baseline observation carried forward and mixed model repeated measures) yielded differences between flibanserin and placebo treatment groups that were consistent with LOCF.

Based upon guidance from the US Food and Drug Administration (FDA), additional assessments of clinically meaningful benefit (beyond the PGI-I) were performed through anchor-based analyses32 in which PGI-I scores were used to determine threshold values for key measures of efficacy (Figure 1). Thus, assessments of efficacy outcomes were “anchored” to the global ratings of overall change reported in the PGI-I. These analyses were prespecified during the design of the flibanserin trials. Similar anchor-based analyses were performed post-hoc for the premenopausal cohort pooled from the 3 pivotal trials. For each efficacy endpoint (FSFI-d, SSE, FSDS-R13), the mean change-from-baseline to week 24 in patients with a PGI-I response of “minimally improved” (score of 3) was used to calculate a threshold value. Threshold values in each trial are shown in Table 1. Women with efficacy measures at week 24 that met or exceeded these threshold values were considered to be responders. As shown in Figure 1, this analysis enabled the determination of the percentage of HSDD patients who were defined as responders for each endpoint. The percentage of responders for each of the three key endpoints among the pooled premenopausal women and the postmenopausal women were compared between treatment groups using the Cochran-Mantel-Haenszel test.

In post-hoc exploratory analyses, odds ratios33 of being a responder were also calculated for each key efficacy endpoint to provide a quantitative estimate of the likelihood of flibanserin treatment resulting in clinically significant benefit. For each efficacy endpoint, odds ratios were calculated by dividing the odds of being a responder in the flibanserin group by the odds of being a responder in the placebo group. Associated 95% confidence intervals for each odds ratio were also calculated. In addition, Kaplan-Meier analyses with log-rank tests were used to evaluate the time to benefit for flibanserin 100 mg qhs compared with placebo.

RESULTS

Patient Demographics

The pooled premenopausal analysis cohort consisted of 2,407 patients: 1,192 were treated with flibanserin 100 mg qhs and 1,215 were treated with placebo (Figure 2). The postmenopausal analysis cohort consisted of 926 patients; 450 were treated with flibanserin 100 mg qhs and 476 were treated with placebo (Figure 2). Demographic characteristics and baseline scores were similar between the flibanserin and placebo groups except for
duration of relationship, where postmenopausal women were in a relationship with the same partner for twice as long as premenopausal women (Table 2). Duration of HSDD was similar between cohorts and treatment groups, ranging from 4.5 – 5.1 years. Mean total FSFI scores at baseline ranged from 15.9 – 19.3 and mean FSFI-d scores ranged from 1.8 – 1.9. The average frequency of SSEs at baseline was 2.7 per month in premenopausal women and 2.0 per month in postmenopausal women, while the mean FSDS-R13 score was 3.3 for both premenopausal and postmenopausal women.

**Responder Analyses**

In premenopausal women, clinically meaningful benefit was reported by 49.8% of patients in the flibanserin group versus 33.6% of patients in the placebo group, based upon responses to the PGI-I (“minimally improved” or greater). The distribution of responses for each treatment group is shown in Figure 3A. Similarly, in postmenopausal women, clinically meaningful benefit was reported by 40.5% of patients in the flibanserin group versus 28.7% of patients in the placebo group (Figure 3B). In both premenopausal and postmenopausal cohorts, fewer patients in the flibanserin groups reported either “no change” or “worsening” compared to those in the placebo groups.

In anchor-based analyses of key efficacy endpoints, 46 – 55% of premenopausal women receiving flibanserin were responders, while 34 – 44% of those receiving placebo were responders (Figure 4A). In postmenopausal women, 30 – 54% in the flibanserin group were responders, while 23 – 48% in the placebo group were responders (Figure 4B). In both premenopausal and postmenopausal women, the percentage of responders for each efficacy endpoint (based on PGI-I anchor analysis) was greater after treatment with flibanserin compared to placebo. All comparisons between flibanserin and placebo in anchor-based analyses were statistically significant except FSDS-R Item 13 in postmenopausal women.

Another evaluation method of efficacy is the estimation of effect size through the calculation of odds ratios. Depending on the assessment endpoint, premenopausal women were 2.3 – 2.4 times more likely to be responders when treated with flibanserin compared to placebo (Table 3). These odds ratios were statistically significant, as noted by the lower confidence intervals that were all greater than 1.0. Postmenopausal women treated with flibanserin were 1.6 times more likely to be responders compared to placebo treatment when assessed by FSFI-d (sexual desire). Odds ratios for SSE or FSDS-R13 did not reach statistical significance in postmenopausal women.

When time to benefit was analyzed using Kaplan-Meier analyses, there was significant separation between flibanserin and placebo for each efficacy endpoint for both premenopausal and postmenopausal women, as indicated by the log rank P values (Figure 5). For premenopausal women, the median times to benefit for patients receiving flibanserin were consistently shorter

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**Table 1.** Threshold values for responders, as defined by the PGI-I, are expressed as change from baseline.

| Clinical Trial | Study Cohort | SSE  | FSFI-d | FSDS-R13 |
|---------------|-------------|------|--------|----------|
| VIOLET        | Premenopausal | 1.22 | 0.83   | -0.44    |
| DAISY         | Premenopausal | 1.25 | 0.74   | -0.41    |
| BEGONIA       | Premenopausal | 1.70 | 0.90   | -0.50    |
| SNOWDROP      | Postmenopausal| 1.30 | 0.90   | -0.50    |

FSDS-R13 = Female Sexual Distress Scale-Revised, item 13 (distress); FSFI-d = Female Sexual Function Index, desire domain; PGI-I = Patient Global Impression of Improvement; SSE = satisfying sexual events. Increased scores for SSE and FSFI-d indicate greater numbers of satisfying sexual events and increased sexual desire, whereas decreased scores for item 13 of the FSDS-R indicates decreased distress.
than the median times for patients receiving placebo (Table 4). Similarly, postmenopausal women receiving flibanserin had shorter median times to benefit for SSE and FSFI-d when compared to those receiving placebo. While median times to benefit for FSDS-R13 were similar between treatment groups in postmenopausal women, the overall difference between the Kaplan-Meier curves was statistically significant, as noted by the log-rank P value (Figure 5).

**DISCUSSION**

These analyses provide additional parameters of efficacy based upon patients’ self-report of benefit. The Patient Global Impression of Improvement was used to identify women who experienced clinically meaningful treatment benefit through improvements in their HSDD symptoms. In both premenopausal and postmenopausal cohorts, a greater percentage of patients treated with flibanserin reported benefit compared to...
those treated with placebo. In anchor-based analyses, the percentage of responders in the 
flibanserin group ranged from 46−55% in premenopausal women and 30−54% in postmeno-
pausal women, depending upon the endpoint. The number of responders who reported clinically meaningful improvements in their HSDD symptoms was higher in the 
flibanserin group and comparisons to the placebo group were statistically signi-
ficant with the exception of FSDS-R Item 13 in postmenopausal women. Self-reports of improvement in HSDD symptoms during flibanserin therapy were further supported by odds ratios that suggested that premenopausal women were more than twice as likely to report improvement in their HSDD with flibanserin treatment compared to placebo, while postmenopausal women were 60% more likely to report increased sexual desire. Postmenopausal women did not exhibit a statistically significant decrease in distress that was clinically meaningful despite the fact that they did experience a statistically significant decrease in FSDS-R13 score, as previously reported by Simon et al.10

The rates of women reporting meaningful treatment benefit with flibanserin, ranging from 30−55%, are not unexpected. Similar or lower rates are reported for many approved medica-
tions, indicating that a substantial proportion of patients do not report a meaningful benefit to treatment or do not demonstrate a therapeutic response based on a clinical endpoint independent of patients’ impression of improvement. For example, approximately 50% of patients with major depressive disorder fail to respond to first-line antidepressant medication.34 High non-
responder rates (≥47%) have also been observed with non-CNS-
active drugs such as treatments for cancer, rheumatoid arthritis, and dry eye disease.\textsuperscript{35-37}

For additional perspective, an examination of existing meta-analyses for the most common pharmacological therapies in the US noted that 11 out of 17 medications or medication categories (eg, aspirin for vascular disease, statins for cholesterol lowering, anticholinergics for overactive bladder, angiotensin-converting enzyme inhibitors for hypertension, bisphosphonates for osteoporosis, metformin for type II diabetes) achieved minimal clinically important difference with small to moderate effect sizes (Cohen’s $d < 0.8$) and 4 of the 17 medication categories used surrogate outcomes such as blood pressure or plasma glucose instead of patient-oriented outcomes of benefit assessment.\textsuperscript{38}

As noted previously, large placebo effects were noted in the flibanserin trials. High response to placebo is a common observation in studies of sexual dysfunction.\textsuperscript{13,39,40} In randomized placebo-controlled studies, significant improvement after receiving placebo has been observed in 40% or more of women with HSDD or female sexual arousal disorder.\textsuperscript{13} Yet, it should be emphasized that this is not unique to treatments for female sexual dysfunction. High placebo responses (more than half that of active comparator in the primary endpoints) are also seen in recent publications reporting efficacy in vasomotor symptoms,\textsuperscript{16,17} urinary incontinence,\textsuperscript{18-20} and rheumatoid arthritis.\textsuperscript{21} A high placebo effect certainly increases the difficulty of demonstrating significant efficacy of a pharmaceutical treatment.\textsuperscript{13} However, the current analyses focused on self-reports of treatment benefits for flibanserin in both premenopausal and postmenopausal women with HSDD. These data strongly suggest that the efficacy of flibanserin is both meaningful to women and clinically relevant, and are in agreement with previous analyses of flibanserin’s efficacy.\textsuperscript{41}

**Table 3.** Odds ratios of responders (flibanserin/placebo) for efficacy assessments

| Endpoint | Odds Ratio (95% CI) |
|----------|---------------------|
|          | Premenopausal       | Postmenopausal     |
| SSE      | 2.4 (1.9 - 2.9)     | 1.3 (1.0 - 1.8)    |
| FSFI-d   | 2.4 (2.0 - 2.9)     | 1.6 (1.2 - 2.2)    |
| FSDS-R13 | 2.3 (1.9 - 2.9)     | 1.2 (0.9 - 1.5)    |

**Figure 5.** Kaplan-Meier curves for time to response on key outcome measures. Probability of response at the end of the study for each treatment group is shown in parentheses. (FSDS-R13 = Female Sexual Distress Scale-Revised, item 13; FSFI-d = Female Sexual Function Index, desire domain; SSE = satisfying sexual events).
In our Kaplan-Meier analyses, the quantitative separation of curves between treatment groups was not necessarily represented by the median times. Nevertheless, the median time to benefit was consistently shorter with flibanserin than placebo on the SSE, FSFI-d, and FSDS-R13. The median time to benefit (approximately 2 months) and the total probability of experiencing a meaningful benefit by 24 weeks (66%–82%) in the flibanserin treatment group suggests that a substantial proportion of patients may require treatment with flibanserin for longer than 2 months before clinically meaningful HSDD symptom improvement is experienced. However, according to the prescribing information, flibanserin is to be discontinued if the patient reports no improvement in symptoms after 8 weeks of therapy.\(^4,5\) Ultimately, the decision to discontinue treatment for patients not experiencing sufficient benefit should be a decision that each patient makes with their clinical care provider.

**Strengths and Limitations**

The strengths of these analyses include a large dataset from multiple randomized, placebo-controlled studies (2,465 premenopausal women and 947 postmenopausal women). Further, two of the three endpoints that were examined are validated instruments (FSFI and FSDS). Lastly, the use of patient-reported benefit data in these analyses directly assesses clinical meaningfulness of flibanserin therapy and supports statistically significant improvements in clinical trial endpoints that have been reported previously.

Our study has several limitations. The studies of flibanserin in premenopausal women were similar in many respects but did differ in their inclusion criteria (less restrictive in the third study in premenopausal women\(^6\)) and coprimary endpoints (changing from SSE plus sexual desire score measured using an electronic diary\(^6,7\) to number of SSEs and the FSFI-d score\(^8\)). Also, SSE, which was used as a primary endpoint based on FDA recommendations for studies of female sexual dysfunction,\(^9\) has come under criticism for its lack of relevance and validity in the assessment of HSDD.\(^9\) In addition, anchor-based analyses using the PGI-I are not widely published for drug efficacy studies and represent only one of several ways in which treatment benefit may be defined. Lastly, the analysis of the data in postmenopausal women did not include a second 24 week, placebo-controlled trial (PLUMERIA)\(^44\) because this trial was discontinued early by the sponsor (Boehringer Ingelheim) when less than half of the participants had completed week 16. Early discontinuation of this trial was not due to any safety concern and occurred after the sponsor ended the development program.

**CONCLUSIONS**

In studies of premenopausal and postmenopausal women with acquired, generalized HSDD, significant self-reported treatment benefits with flibanserin, relative to placebo, were observed. Our analyses demonstrated both a significantly higher probability of women experiencing a meaningful treatment benefit and a significantly shorter time to treatment benefit with flibanserin compared with placebo. The use of the PGI-I to determine treatment benefit from the patient’s perspective may be a useful approach in assessing overall clinical meaningfulness for sexual dysfunction therapies in addition to validated instruments assessing specific parameters of sexual function. This approach enables the examination of efficacy data that incorporates clinical meaningfulness and goes beyond mere statistical changes in the magnitude of endpoint scales.

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STATEMENT OF AUTHORSHIP
Conceptualization, S.P., J.A.S., A.H.C., N.N.K; Investigation, J.A.S. and A.H.C.; Resources, S.P.; Writing - Original Draft, N.N.K. and J.A.S.; Writing - Review & Editing, N.N.K., S.P., J.A.S., A.H.C.; Visualization, N.N.K.

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