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**FLIBANSERIN**

**FOR THE TREATMENT OF HYPOACTIVE SEXUAL DESIRE  
DISORDER IN PREMENOPAUSAL WOMEN**

**NDA 022526**

**ADVISORY COMMITTEE BRIEFING DOCUMENT**

**4 JUNE 2015**

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## EXECUTIVE SUMMARY

### Background

Flibanserin is a postsynaptic 5-HT<sub>1A</sub> agonist 5-HT<sub>2A</sub> antagonist developed as a novel, non-hormonal treatment for hypoactive sexual desire disorder (HSDD) in premenopausal women.

HSDD is characterized by a deficiency or absence of sexual fantasies and desire for sexual activity which causes marked distress or interpersonal difficulty, and is not better accounted for by another psychiatric disorder or due exclusively to the direct physiological effects of a substance or to the direct physiological effects of another medical condition. HSDD does not encompass normal (e.g., daily or weekly) fluctuations in levels of desire.

These definitional criteria lend themselves to a straightforward and reliable diagnosis of HSDD. Assessment of a patient presenting for possible treatment involves readily discernable factors including:

- Degree of satisfaction with her current level of sexual desire or interest
- Change from her previous level of sexual desire or interest
- Whether that change is causing her distress, and
- Whether there are alternative explanations for the lack of desire such as dissatisfaction with relationship or partner, concomitant medication or medical condition causing sexual dysfunction, pregnancy, recent childbirth, or other pre-existing sexual dysfunction

HSDD is a serious and long-recognized disorder with impacts far beyond the bedroom affecting relationships, self-confidence and self-image. Women suffering from distressing low desire are eight to ten times more likely than women with normal desire/distress to report often, very often or always feeling unhappy, disappointed, upset, frustrated, sad, ashamed and bitter, as well as feeling low self-esteem [Leiblum et al., 2006].

The impact of HSDD is exacerbated by the lack of proven therapies. While HSDD has been recognized in the medical literature for 40 years, the development, validation, and acceptance of survey instruments necessary for assessment of HSDD symptoms has only occurred more recently. Endpoints assessing sexual function, sexual distress, sexual desire, sexual activity and overall patient benefit are now in place and permit regulatory evaluation of the efficacy of drug candidates intended to treat HSDD.

The impact and seriousness of HSDD, the lack of approved therapies and the common use of untested products making misleading claims combine to expose patients to unnecessary risks.

There is great need for a proven, safe, and properly labeled medication that provides meaningful and quantifiable benefits to HSDD patients.

### **Flibanserin Efficacy Studies - Design**

Efficacy of flibanserin 100 mg qhs has been demonstrated across three pivotal randomized, double-blind, placebo-controlled 24-week studies (Studies 147, 71 and 75) conducted in North America. Studies 71 and 75 were previously presented to an FDA advisory committee in 2010. Study 147 was completed more recently in response to recommendations from FDA and the advisory committee. Over 2,700 patients received the recommended flibanserin dose (100 mg qd) with 1,658 of those receiving the recommended dosing regimen (100 mg qhs). Over 1,700 placebo and flibanserin patients from these studies rolled over into a one-year single-arm, open-label extension study of flibanserin.

Each pivotal study enrolled premenopausal women, per the STRAW criteria, who met the DSM-IV-TR criteria for diagnosis of HSDD for at least 6 months. Inclusion criteria were designed to identify patients who met the HSDD definition of low sexual desire with associated distress while maintaining some degree of sexual activity in order to permit assessment of drug effects. All subjects were required to be in a stable, monogamous relationship, with a sexually functional partner, for at least one year.

Each pivotal study measured sexual activity, sexual desire and distress associated with low desire using various validated patient reported outcome (PRO) instruments. Use of these endpoints as co-primary or secondary measures in the pivotal studies is discussed in the context of each study in the following section.

- Sexual Activity was measured as mean change from baseline to Week 24 in the number of satisfying sexual events (SSEs), recorded via a daily electronic diary (eDiary) and standardized to a 28-day period. Range of values for this variable is 0 to no upper limit. Change in SSEs was a primary endpoint in all three pivotal studies.
- Across all studies, sexual desire was measured as mean change from baseline to Week 24 in FSFI-Desire, the desire domain of the Female Sexual Function Index (FSFI) which is the most frequently used tool for measuring female sexual dysfunction. The weighted score of FSFI-Desire ranges from 1.2 to 6.0. Consistent with the time period embedded in the FSFI questions, FSFI-Desire was collected using a 28-day recall period. Change in FSFI-Desire was a primary endpoint in the more recently completed Study 147 and a secondary endpoint in Studies 71 and 75.
- In the two early studies sexual desire was also measured as mean change from baseline to Week 24 in the monthly sum of responses to an eDiary daily desire question (eDiary Desire) regarding the patient's most intense level of desire that day. Reporting of sexual desire information was limited to a 24-hour retrospective period. Change in eDiary

Desire was the primary endpoint measure of desire in Studies 71 and 75 – the two early studies.

- Distress related to low sexual desire was measured as mean change from baseline to Week 24 in Female Sexual Distress Scale-Revised Item 13 (FSDS-R13 (Distress)) which asks how often the patient was bothered by her low desire and is scored from 0 to 4. FSDS-R13 (Distress) was collected using a 7-day recall period. Change in FSDS-R13 (Distress) was an important secondary endpoint in all three pivotal studies.

### **Flibanserin Efficacy Studies - Results**

A total sample of 1,227 patients received flibanserin 100 mg qhs and 1,238 received placebo in the three pivotal studies. Premenopausal women with a primary diagnosis of HSDD enrolled in the pivotal Phase 3 program were primarily white, in a stable relationship, and, on average 36 years of age - sample characteristics that are representative of the population of premenopausal women suffering from HSDD.

The populations from the three pivotal efficacy studies demonstrated clinically relevant symptoms of HSDD at baseline, had been in their current relationship for a mean of 10.9 (placebo) and 10.7 (flibanserin 100 mg qhs) years and had experienced HSDD symptoms for a mean of 56.9 (placebo) and 54.3 (flibanserin 100 mg qhs) months.

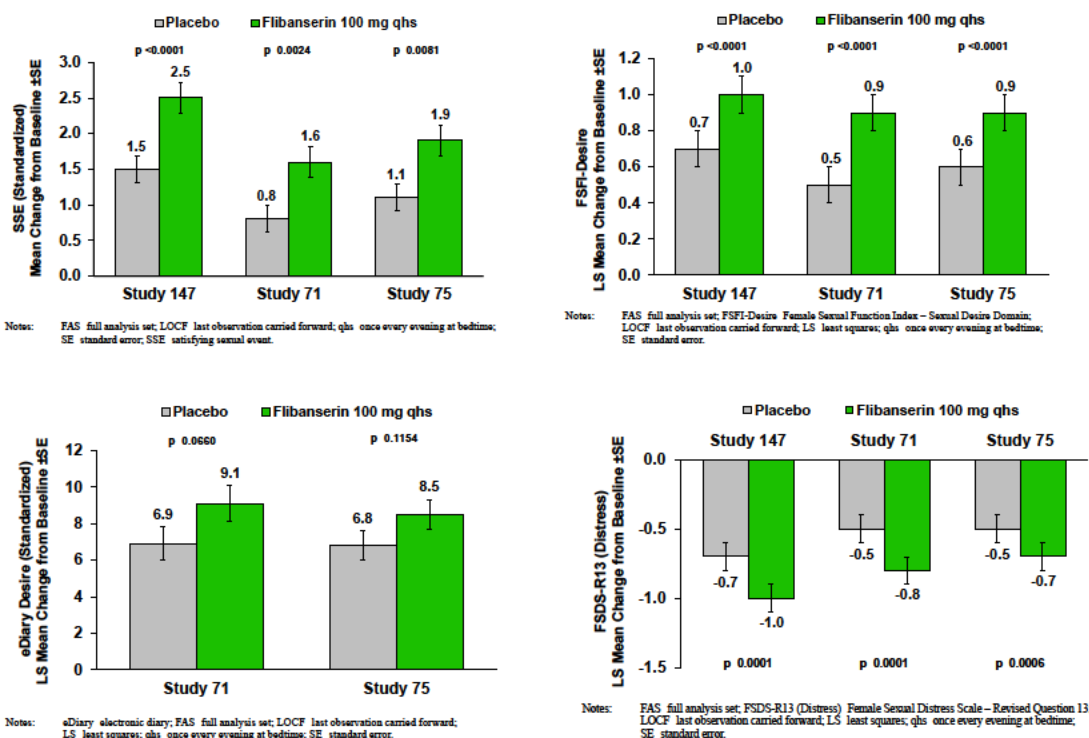
Results are presented for the Full Analysis Set (FAS) populations consisting of those patients who were randomized to a treatment group, received at least one dose of study medication, and had at least one on-treatment efficacy assessment. The FAS was analyzed for efficacy using the pre-specified last observation carried forward (LOCF) method of handling missing data. Because the LOCF assumption that data are missing completely at random is seldom true, sensitivity analyses using mixed model repeated measures (MMRM) and missing at random (MAR) were also conducted. Additional more conservative sensitivity analyses using methods which impute missing data assuming no treatment benefit (i.e., baseline observation carried forward (BOCF), control-based imputation (CBI) and jump to reference (J2R)) were also conducted.

In the initial pivotal program (Studies 71 and 75) flibanserin demonstrated statistically significant superiority to placebo on only one of two co-primary endpoints, change in SSEs. Regarding improvements in desire, flibanserin showed separation from placebo on both eDiary Desire (primary) and FSFI-Desire (secondary) but that difference reached statistical significance only for the secondary endpoint. Consistent with the recommendations of FDA and its advisory committee, the Sponsor completed an additional pivotal study (Study 147), using a validated instrument for measuring desire (FSFI-Desire) as the primary measure of change in sexual desire. This study demonstrated statistically significant improvement on both that endpoint and the co-primary endpoint, change in SSEs. Results across key efficacy endpoints in the three



pivotal studies are shown in Figure 1. Results showing numbers of subjects per arm are presented in corresponding tables in the main body of this briefing document.

**Figure 1 Change from Baseline at Week 24 in Key Efficacy Endpoints – Pivotal Phase 3 Studies in Premenopausal Women (FAS, LOCF)**



Statistical separation (i.e. 2-sided  $p < 0.05$ ) between flibanserin and placebo was maintained across SSEs, FSFI-Desire and FSDDS-R13 (Distress) in Studies 147, 71 and 75 in all cases with the exception of SSEs when analyzed via J2R in Study 75 ( $p = 0.08$ ). Sensitivity analyses were not conducted for eDiary Desire because it did not reach significance via the primary analysis.

Mean Change from Baseline in SSEs at Week 24 was a co-primary endpoint in all three pivotal studies. The flibanserin 100 mg qhs arm in each study experienced a statistically significant increase in SSEs (standardized) compared with the placebo arm at Week 24. In terms of absolute numbers, mean SSEs per month in the flibanserin arm increased to between 4.5 and 5 at the end of the 24-week study period so that patients were experiencing approximately one satisfying sexual event per week.

Low desire is one of the two hallmark features of HSDD and the 4.8-point FSFI-Desire scale (scale range: 1.2 – 6.0) is the validated standard instrument for measuring female sexual desire. Mean Change from Baseline in FSFI-Desire at Week 24 was a co-primary endpoint in Study 147. It was also a secondary endpoint in Studies 71 and 75. The flibanserin 100 mg qhs treatment group in each study experienced a statistically significant mean increase in

FSFI-Desire compared with the placebo group at Week 24. In terms of absolute numbers, mean FSFI-Desire scores in the flibanserin group improved from a baseline of 1.8 to 1.9, well below the clinical cut point of 3 for classifying women with and without HSDD, to between 2.7 and 2.9 at the end of the 24-week study period. This near restoration of normal sexual desire in the span of a 24-week study is notable in a population of women who have suffered from distressing low desire for a mean of over 4 years.

Mean Change from Baseline in eDiary Desire at Week 24 was not measured in Study 147. It was, however, a co-primary endpoint in the early studies, Studies 71 and 75, and is reported here for completeness. Of the patients who were active at the end of Studies 71 and 75, only 44.4% of placebo patients and 43.6% of flibanserin patients had eDiary entries on 26 or more days of the 28-day period demonstrating poor compliance with completion of the daily assessments. The flibanserin 100 mg qhs treatment group in Studies 71 and 75 experienced a numerically but not statistically significant mean increase in eDiary Desire compared with the placebo group at Week 24.

Mean Change from Baseline in FSDS-R13 (Distress) at Week 24 was a secondary endpoint in all three pivotal studies. Distress associated with low desire is one of the two hallmark features of HSDD. The 5-point FSDS-R13 (Distress) is a validated widely-recognized PRO question for measuring that distress associated with sexual desire. The flibanserin 100 mg qhs treatment group in each study experienced a statistically significant decrease in FSDS-R13 (Distress) as compared with placebo. In terms of absolute numbers, mean FSDS-R13 (Distress) scores in the flibanserin group at baseline ranged from 3.2 to 3.4, indicating that patients were frequently (score = 3) or always (score = 4) bothered by their low desire. At the end of the 24-week study, mean FSDS-R13 (Distress) scores decreased to between 2.4 and 2.6 indicating that they were occasionally (score = 2) to frequently (score = 3) bothered by their low desire.

The totality of the patient improvement in her condition is what ultimately determines treatment success. Because HSDD is a multifaceted disorder, predominantly, but not exclusively impacting sexual desire, other domains of sexual response such as arousal and orgasm also play a part in measuring overall satisfying and healthy sexuality. An assessment of the effect of flibanserin through instruments that take a broader view of sexual function permits a broader understanding of the overall benefit to women with HSDD.

The FSFI Total Score, a 52-point scale, is the most frequently used and widely accepted instrument for understanding sexual function. It includes domains assessing sexual desire, sexual arousal, lubrication, orgasm, sexual satisfaction and pain. Across all pivotal studies, at Week 24, mean change from baseline for flibanserin 100 mg qhs was statistically superior to placebo for this secondary endpoint. In terms of absolute numbers, mean FSFI Total Scores in the flibanserin group at baseline ranged from 19.0 to 19.8, below the clinical cut-off of 26.5 distinguishing dysfunctional from normal sexual functioning in women. After 24 weeks of

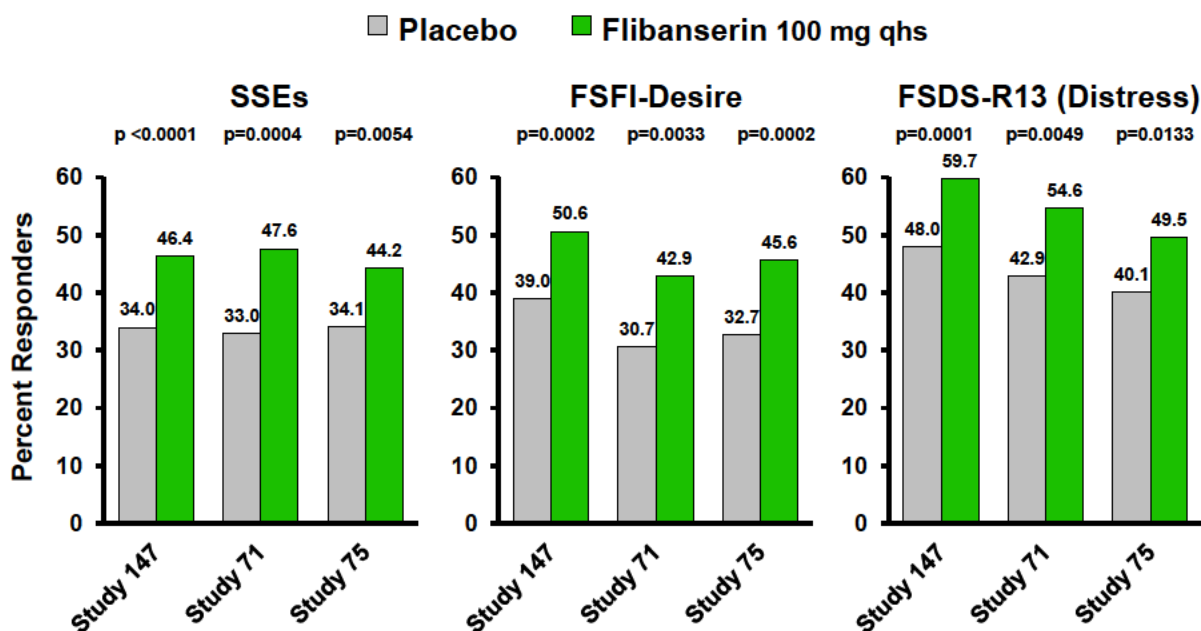
flibanserin therapy FSFI Total Scores improved to between 23.2 and 24.5. This mirrors the pronounced effect on the desire domain alone.

FSDS-R (Distress) Total Score provides a complementary broad view of sexually-related personal distress as it integrates changes in feelings of guilt, frustration, inferiority, inadequacy, embarrassment and dissatisfaction. As with FSFI Total Score, this secondary endpoint was consistent across all studies, showing statistical superiority over placebo for flibanserin 100 mg qhs in mean change from baseline at Week 24. In terms of absolute numbers, mean FSDS-R (Distress) Total Scores in the flibanserin group at baseline ranged from 30.2 to 32.8, well over the cut-off score of 15 for categorizing sexual distress. FSDS-R (Distress) Total Score decreased to between 21.2 and 23.4 at the end of the 24-week study.

Since even consistent, robust statistically significant efficacy may not adequately capture the treatment experienced by a woman suffering from HSDD, a pre-specified analysis method (i.e., the Patient Global Impression of Improvement (PGI-I) or PGI-I-anchored responder analysis) was designed to assess the clinical meaningfulness of flibanserin effects. The pre-specified PGI-I responder analysis allows patients with HSDD to evaluate the personal benefit of flibanserin's treatment effect.

Using this analysis, between 43% and 60% of flibanserin-treated patients were responders on three important endpoints (SSEs, FSFI-Desire and FSDS-R13) across all three pivotal studies with margins of responder superiority of 9.4% to 14.6% over placebo across endpoints (Figure 2). Flibanserin responders reported mean changes in key symptoms that often more than doubled the effect in the overall flibanserin population with an approximately two point increase on the 4.8-point desire scale and an approximately 1.8 point improvement on the 5-point distress scale.

**Figure 2 Number (%) of Responders (PGI-I Anchor Criteria) across Efficacy Endpoints – Pivotal Phase 3 Studies in Premenopausal Women**



Endpoint		SSE			FSFI-Desire			FSDS-R13 (Distress)		
Study		147	71	75	147	71	75	147	71	75
Placebo	FAS (N)	521	285	381	525	290	388	525	289	389
	Completers (N)	361	219	278	380	236	290	426	235	290
	Responders (n)	177	94	134	205	89	127	252	124	156
Flibanserin	FAS (N)	500	275	371	506	280	379	506	280	380
	Completers (N)	329	196	245	343	208	261	391	208	261
	Responders (n)	232	131	165	256	120	173	302	153	188

Notes: FSFI-Desire = Female Sexual Function Index – Sexual Desire Domain; FSDS-R13 (Distress) = Female Sexual Distress Scale – Revised Question 13; SSE = satisfying sexual event; FAS = full analysis set.

## Flibanserin Safety

Overall, 17,940 subjects/patients have participated in the flibanserin development programs, including studies of healthy normal volunteers (1,427), patients with major depressive disorder (2,439) and patients with HSDD (14,074). In these studies, 10,713 individuals have been exposed to flibanserin (1,122 healthy volunteers, 1,366 patients with major depressive disorder and 8,225 patients with HSDD). Of these, 7,922 patients took 100 mg qd with 5,636 patients taking the recommended dosing regimen of 100 mg qhs. This substantial database considerably exceeds the 1,500 subject minimum threshold required by FDA and other regulatory agencies for premarket assessment of novel drug therapies intended for chronic administration, and establishes a well-characterized safety profile for flibanserin.

Experience with longer-term flibanserin exposure is also fairly extensive. In open-label studies, 2,521 patients have been exposed to flibanserin for at least six months (1,819 at flibanserin 100 mg qhs) and 1,096 patients have been exposed to flibanserin for at least one year (852 at flibanserin 100 mg qhs). These exposure levels, also significantly exceeding the established FDA minimum threshold for new chronic use drugs (i.e., 300 - 600 subjects exposed for 6 months and 100 subjects exposed for a year), serve to provide further information regarding long term effects.

The overall safety review in this briefing document focuses primarily on the 5 double-blind, randomized, placebo-controlled Phase 3 studies in the intended population: premenopausal women with HSDD (the Target Population Set). Across these studies, a total of 3,973 women received flibanserin, 1,543 of these at the 100 mg qhs dose. Safety data from Phase 1 studies in special populations or circumstances (e.g., drug-drug interaction studies) address specific safety questions. Included among these studies is the recently completed Next-Day Driving and Cognition Study requested by the FDA.

For the Phase 3 double-blind, placebo-controlled studies in premenopausal women, 55.7% of placebo subjects had at least 1 AE compared with 66.9% of subjects who received flibanserin 100 mg qhs and 65.6% of subjects who received any dose of flibanserin. The greatest frequency of AEs was reported for the flibanserin 50 mg bid dose, suggesting that bedtime dosing may have a beneficial effect on safety. Both the proportion of subjects experiencing any AE and the proportion of subjects with AEs leading to discontinuation increased slightly with increasing dose and with morning dosing.

For subjects who received placebo, 24.7% of subjects had mild AEs, 26.3% had moderate AEs, and 4.7% had severe AEs. For subjects who received any dose of flibanserin, 26.6% of subjects had mild AEs, 32.7% had moderate AEs, and 6.3% had severe AEs. For subjects receiving flibanserin 100 mg qhs, 26.8% of subjects had mild AEs, 33.2% had moderate AEs, and 6.9% had severe AEs.

Dizziness was the most common AE occurring in Phase 3 double-blind studies in premenopausal women for the placebo group and the flibanserin 100 mg qhs treatment group. The number of premenopausal subjects with AEs that occurred in  $\geq 2\%$  of subjects and at a frequency twice that in subjects receiving placebo are listed in descending order of frequency for Phase 3 double-blind, placebo-controlled studies in premenopausal women in [Table 1](#). Dose dependence and the benefit of bedtime dosing are apparent across several AEs (e.g., dizziness, somnolence, nausea, fatigue).

**Table 1**      **Number (%) of Subjects with Adverse Events Occurring at  $\geq 2.0\%$  and Twice that of Placebo by Treatment - Phase 3 Studies in Premenopausal Women (Target Population Set)**

Preferred Term	Placebo, n (%) N = 1905	Flibanserin, n (%)			
		25 mg bid N = 733	50 mg qhs N = 969	50 mg bid N = 728	100 mg qhs N = 1543
Dizziness	41 (2.2)	31 (4.2)	61 (6.3)	111 (15.2)	176 (11.4)
Somnolence	59 (3.1)	51 (7.0)	55 (5.7)	122 (16.8)	173 (11.2)
Nausea	71 (3.7)	41 (5.6)	68 (7.0)	90 (12.4)	161 (10.4)
Fatigue	95 (5.0)	35 (4.8)	59 (6.1)	101 (13.9)	142 (9.2)
Insomnia	46 (2.4)	14 (1.9)	19 (2.0)	20 (2.7)	75 (4.9)
Dry mouth	17 (0.9)	6 (0.8)	12 (1.2)	10 (1.4)	37 (2.4)
Anxiety	17 (0.9)	5 (0.7)	19 (2.0)	10 (1.4)	28 (1.8)
Metrorrhagia	24 (1.3)	10 (1.4)	25 (2.6)	13 (1.8)	22 (1.4)

Notes: bid = Twice daily; n = Total population size; N = Number of subjects; qhs = Once every evening at bedtime.

MedDRA version used for reporting: 11.1.

Includes Studies 511.70, 511.71, 511.75, 511.77 and 511.147.

Source: ISS Table 2.3.10.

### Sedation-related AEs

CNS depression, presenting as sedation-related AEs (i.e., dizziness, somnolence, fatigue), is the hallmark adverse effect of flibanserin and has been uniformly reported across the flibanserin clinical development program. Bedtime dosing appears to markedly decrease the incidence of these events as demonstrated by a comparison of AEs in the 50 mg bid versus 100 mg qhs flibanserin groups.

Onset for sedation-related AEs occurred most often during the first week of treatment with the incidence of new events decreasing over time. Median time to first onset was 5.5 days for dizziness, 2 days for somnolence, and 4 days for fatigue. Median duration of dizziness of any intensity was 10 days for placebo and 11 days for flibanserin 100 mg qhs. Median duration of somnolence of any intensity was 35 days for placebo and 37 days for flibanserin 100 mg qhs. Median duration of fatigue of any intensity was 26 days for placebo and 29 days for flibanserin 100 mg qhs.

No sedation-related serious adverse events (SAEs) were reported during the Phase 3 double-blind studies in premenopausal women. Reported AEs were largely mild to moderate. Severe sedation-related AEs occurred in 0.1 to 0.6% of subjects taking placebo or flibanserin 100 mg qhs, respectively, with a tendency for greater frequency of severe events at higher dose or with morning dosing.

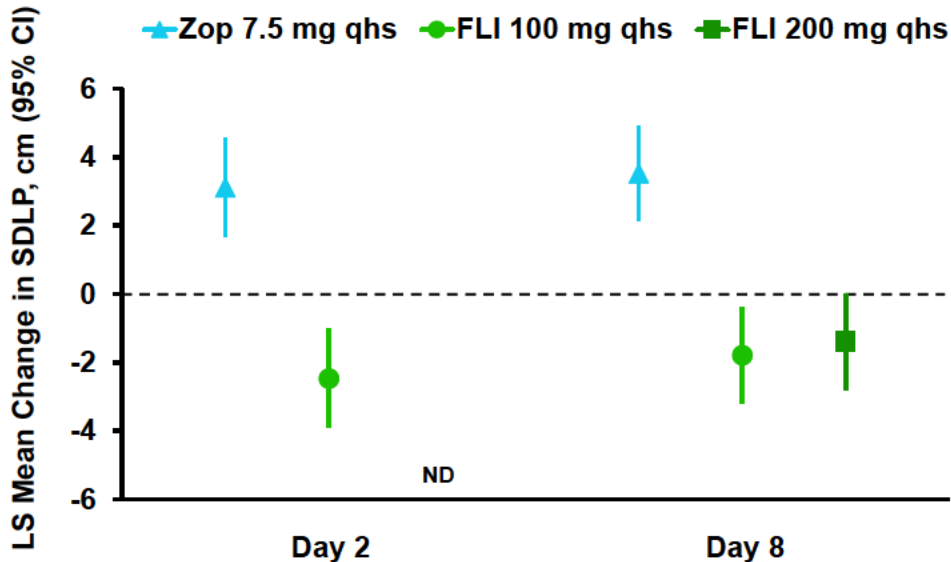
Less than 2% of subjects randomized to flibanserin 100 mg qhs discontinued from the Phase 3 double-blind studies due to any individual sedation-related AE. The apparent benefit of bedtime

dosing is again notable in the difference in discontinuation rates between the 50 mg bid (20.3%) and 100 mg qhs (12.8%) flibanserin groups.

The potential for bedtime dosing of flibanserin to lead to next day sedation and impairment was studied in a simulated driving impairment and cognition study. Designed with substantial input from FDA, this study evaluated next-day residual effects after acute (single bedtime dose) and steady state (7 nightly doses) exposure to flibanserin at the recommended 100 mg dose and acute exposure to a supratherapeutic dose (single bedtime dose at 200 mg after 6 nightly doses at 100 mg). The primary endpoint assessment was standard deviation of lateral position (SDLP) which measures lane position control and has been shown to be highly predictive of driving safety and impairment. A higher score on SDLP compared to placebo indicates poorer driving performance.

SDLP was significantly higher after bedtime dosing with the active hypnotic zopiclone, which served as a positive control, than placebo. For subjects dosed with flibanserin 100 mg qhs, SDLP values were significantly lower at both acute and steady state dosing when compared to placebo. Further, there was no significant difference between acute dosing at bedtime of 100 and 200 mg flibanserin (Figure 3).

**Figure 3 Mean Change (95% CI) in Standard Deviation of Lateral Position Difference from Placebo – Driving and Cognition Study**



Notes: CI=confidence interval; FLI=flibanserin; LS=least squares; ND=not done; qhs=once every evening at bedtime; SDLP=standard deviation of lateral position; Zop=zopiclone.

Multiple secondary sedation-sensitive driving endpoints and non-driving assessments of cognition were consistent with results on SDLP: the positive control showed deterioration in



performance on each of these endpoints while all flibanserin arms performed similar to or better than placebo arms.

The positive outcome of the Driving and Cognition Study results is consistent with results of early Phase 1 and 2 cognition studies which showed sedation peaking at one to three hours post-dose and largely resolving by 6 hours post-dose, and provides assurance that flibanserin use, even at elevated acute exposure levels up to twice the recommended dose, has effects no worse than placebo on next-day driving performance and cognitive assessments after 7 hours of sleep.

CNS depression was more pronounced in Phase 1 studies in which flibanserin was co-administered with moderate to strong CYP3A4 inhibitors which inhibit flibanserin metabolism or with substantial concentrations of alcohol, a CNS depressant. In each of these studies flibanserin was administered during the daytime rather than at bedtime as recommended in the proposed labeling – a potentially significant departure from dosing in the Phase 3 studies. These studies provide evidence for potential increases in rates of certain sedation-related AEs with high flibanserin exposure or concomitant significant alcohol use in the morning. Sedation-related severe AEs were reported in the Alcohol Study but not in the CYP3A4 inhibitor studies. The degree of additive CNS inhibition with alcohol use would likely be proportional to the amount of ethanol ingested, its rate of ingestion and any delay between alcohol and flibanserin ingestion. There is no evidence to suggest that premenopausal women seeking treatment for their HSDD would exhibit the excessive alcohol consumption patterns tested in the Alcohol Study. Similar to other drugs with CNS depressant activity, flibanserin when used as directed in the proposed labeling and as it was in Phase 3 studies (subjects were instructed to take flibanserin at bedtime and were not prohibited from consuming alcohol per their usual habits), presents a manageable risk of sedation-related AEs.

While the risk of sedation-related AEs with flibanserin may increase with daytime dosing, in the presence of strong or moderate concomitant CYP3A4 inhibitor use or use with alcohol, the risk is still readily manageable. Sedation-related risks will be minimized in clinical practice through patient and prescriber understanding of the flibanserin safety profile and the importance of bedtime dosing, skipping any missed dose, avoidance of concomitant strong or moderate CYP3A4 inhibitors and a warning that the patient should avoid alcohol consumption until she knows how flibanserin affects her.

### **Hypotension and Syncope AEs**

No signal for syncope or hypotension-related AEs was noted during conduct of the Phase 3 studies in premenopausal women. Clinically significant AEs of hypotension and syncope were observed in three Phase 1 studies of flibanserin that involved daytime dosing and either high exposure due to coadministration of a CYP3A4 inhibitor, direct administration of a supratherapeutic dose of flibanserin, or concomitant and significant alcohol use. No hypotension or syncope AEs were noted in other studies that involved high flibanserin exposure



(e.g., supratherapeutic dose study, QT study, driving impairment study, hepatic impairment study). The proposed flibanserin package insert and Risk Evaluation and Mitigation Strategy (REMS) are designed to mitigate the risk of both CYP3A4 inhibition and excessive alcohol consumption.

Flibanserin combined with high dose fluconazole, a moderate CYP3A4 inhibitor, resulted in large flibanserin exposure increases (AUC 7-fold;  $C_{max}$  2.24-fold). The Fluconazole Study was discontinued due to hypotension-related AEs seen in three subjects following dosing with flibanserin 100 mg and fluconazole 200 mg. One of these events was clinically significant with the subject becoming unresponsive with a blood pressure of 64/41 mm Hg and recovered fully in approximately 3 hours. Each of these events occurred approximately 1 hour after dosing when serum levels of flibanserin were near their maximum. Pharmacokinetic data collected near the time of these events indicates that these three subjects had the three highest  $C_{max}$  values of subjects dosed with flibanserin while at steady-state on fluconazole. These values were 3 - 4 times in excess of the mean for subjects taking flibanserin alone in the study (e.g., 1,290 - 1,530 ng/mL versus 405 ng/mL mean for flibanserin alone). AUC values were 6 - 9 times in excess of the mean for subjects taking flibanserin alone in the study (e.g., 11,611 - 16,547 h\*ng/mL versus 1869 h\*ng/mL mean for flibanserin alone). This would support the conclusion that hypotension is more likely with excessive levels of flibanserin than with therapeutic levels. No subjects in the other treatment groups had hypotensive events.

Flibanserin combined with itraconazole, a strong CYP3A4 inhibitor, resulted in no syncope or hypotension AEs despite mean exposure increases (AUC 2.57-fold;  $C_{max}$  1.69-fold) over flibanserin alone. Flibanserin combined with ketoconazole resulted in higher mean flibanserin exposure increases (AUC 4.50-fold;  $C_{max}$  1.84-fold) compared with flibanserin alone. Orthostatic hypotension (2 episodes) and syncope (2 episodes) were reported in a single subject receiving flibanserin plus ketoconazole (the second episode occurring 17 days after treatment). The events resolved without treatment but led to her discontinuation from the study. An additional report of moderate syncope, and moderate circulatory collapse, both of which resolved without treatment, occurred in a subject dosed with flibanserin alone. Because both subjects vomited after flibanserin administration,  $C_{max}$  and AUC values recorded for these subjects are minimally informative.

In addition, AEs of severe syncope, dizziness and/or hypotension requiring medical intervention were reported in three subjects receiving 0.4 g/kg ethanol plus flibanserin and one event of severe dizziness was reported in a subject receiving 0.8 g/kg ethanol plus flibanserin in the Alcohol Study.

The High Dose Study was specifically conducted to understand the risk of syncope in the setting of supratherapeutic flibanserin exposure in the morning hours. No trends were noted in the mean changes from sitting to standing blood pressure during the study across the flibanserin and placebo treatment groups. During the first four hours of the treatment phase, clinically

significant decreases in blood pressure ( $\geq 20$  mm Hg) occurred in three of the eight subjects after dosing with flibanserin 100 mg and one of the eight subjects after dosing with flibanserin 200 mg. In each of the flibanserin 100 mg and flibanserin 250 mg (N = 6) groups, one additional clinically significant decrease in Systolic Blood Pressure (SBP) was noted in the post-treatment period (48 h after dosing). Higher doses showed no tendency for greater effects.

A total of 41 clinically significant changes in sitting to standing pulse rate ( $\geq 20$  bpm) were observed during periods when subjects received flibanserin, compared to 8 clinically significant changes in sitting to standing pulse rate during periods when subjects received placebo. During the first four hours after dosing, the greatest number of events (16) occurred at the flibanserin 100 mg dose, with fewer events at 150 mg (11), 200 mg (12), 250 mg (10) doses and with placebo (5). One additional clinically significant increase in pulse rate was reported for each of the flibanserin 100 mg, 150 mg and 250 mg groups in the post-treatment period while 4 such events were reported for placebo. While flibanserin appears to have some effect on pulse rate, higher doses show no tendency for greater effects.

The most commonly reported AE during the study was dizziness, the frequency of which generally increased with higher doses. Dizziness was reported in 12.5% (1/8) of subjects when receiving 100 mg of flibanserin, 37.5% (3/8) of subjects receiving 150 mg of flibanserin, 85.7% (6/7) of subjects receiving 200 mg of flibanserin, 83.3% (5/6) of subjects in the 250 mg flibanserin group, and 7.1% (1/14) of subjects receiving placebo.

In general, flibanserin does not appear to have a significant pharmacological effect on blood pressure when used as directed. Isolated instances of both hypotension and syncope have been reported in the Phase 3 program and were largely characterized as mild or moderate in severity. While patients may experience hypotension and/or syncope with therapeutic doses of flibanserin, the risk is low.

The most prominent effects of flibanserin treatment on blood pressure were seen in the Phase 1 program. Individual subjects exposed to high doses of flibanserin, flibanserin and fluconazole, or flibanserin with very high concentrations of ethanol, all dosed in the morning, had episodes of clinically significant hypotension or syncope.

The proposed flibanserin package insert warns that taking flibanserin in the morning, taking doses higher than recommended, or taking flibanserin with moderate to strong CYP3A4 inhibitors or with CNS depressants such as ethanol can result in potentially dangerous incidents of hypotension or syncope. Moderate to strong CYP3A4 use is contraindicated. Alcohol use is to be avoided until the patient knows how flibanserin affects her. Numerous statements reinforce the need to take flibanserin only at bedtime and to skip any missed bedtime dose. These messages are repeatedly reinforced through a Medication Guide and a REMS (discussed below) that serves to buttress physician, provider and patient understandings of flibanserin safe use.

## **Risk Management**

The Sponsor has developed a comprehensive risk management program to ensure safe use of flibanserin. The safety of flibanserin is optimized when it is taken at bedtime by patients who understand that flibanserin can cause dizziness, syncope or hypotension in addition to sedation. Appropriate patients are those who are premenopausal, have been diagnosed with HSDD, are not taking moderate or strong CYP3A4 inhibitors, and have been cautioned about the risks of concomitant alcohol use. These considerations form the basis of the flibanserin package insert, REMS, and voluntary risk mitigation activities.

The proposed flibanserin package insert is intended to prominently put forth responsible messaging and includes, among other things:

- Instructions to stop treatment if adequate clinical response is not achieved by 12 weeks
- Explicit instruction to avoid daytime dosing or double dosing
- A contraindication for use with moderate to strong CYP3A4 inhibitors
- A warning regarding alcohol use
- Clear language about the potential risks of sedation, dizziness, hypotension and syncope
- An indication statement also reinforces that flibanserin should not be used for any sexual dysfunction other than HSDD

A Medication Guide presents the key risks, necessary precautions and mitigation activities in non-professional language designed for patient comprehension. Clear, patient-friendly language is included regarding bedtime dosing, avoidance of driving until the next morning, discontinuation of therapy if an adequate response is not achieved, avoidance of alcohol until flibanserin's effects are understood and the importance of disclosing other medication use.

A Communication Plan REMS, consisting of communication plan letters to prescribers, pharmacist and medical societies, a REMS website, and tools for diagnosing HSDD and determining whether flibanserin use is appropriate for a specific patient, has been included as part of flibanserin's risk management program in an effort to assure enhanced awareness of safe use and appropriate prescribing. The Sponsor believes this REMS will improve patient safety without creating healthcare burdens that might reduce drug access and so cause HSDD patients to experience an ongoing unmet need.

Recognizing that specific patient requests for a new drug may put pressure on prescribers, upon approval of flibanserin the Sponsor plans a focused product launch, without use of direct to consumer television and radio advertising of flibanserin for at least 18 months, with a concerted

educational effort for prescribers in order to ensure a clear understanding of the appropriate population for flibanserin treatment.

The Sponsor is also preparing a physician training slide deck to further reinforce key messages regarding safe use of flibanserin. Health care professional (HCP) training will focus on flibanserin's safety profile and appropriate patient selection. Training will be distributed by the Sponsor's field personnel and Medical Information Department, and will be available on the flibanserin brand website. By presenting appropriate use and safety messages through a different vehicle, physician training provides an additional avenue for reinforcement of those messages.

The effect of the REMS and other risk management tools on HCP and patient knowledge, attitudes and behaviors will be regularly assessed through multiple measurement tools. Prescribing information will also be mined to assess prescribing and dispensing behaviors related to age (as a rough indicator of menopausal status), bedtime dosing instructions, and drug-drug interaction information. Patient focused assessment tools will be designed to obtain demographic information for patients who receive a flibanserin prescription and also to assess patient awareness and understanding of common flibanserin AEs and safe use conditions. Results of these assessment tools will provide critical information regarding the impact of the flibanserin risk management program and any need to change or refine messages or delivery tools.

### **Flibanserin Benefits and Risks**

HSDD is a significant condition for which proven medical therapies are needed. It has been recognized by the FDA as a key area of unmet medical need. Flibanserin has demonstrated consistent and meaningful efficacy in the treatment of HSDD. That efficacy is evident across all measured symptoms, on validated instruments across multiple time points, and in a pre-specified responder analysis. The treatment effect has been deemed meaningful by patients. In the arena of female sexual disorders, FDA has repeatedly called for development of the lowest effective dose – that is, drugs that provide a meaningful benefit but that are administered at a dose that may sacrifice additional benefit in favor of maintaining a more favorable side effect profile. Flibanserin was the subject of numerous studies examining different doses and dosing regimens which resulted in the selection of the 100 mg qhs dose as optimal because it has an effect that is clinically and statistically significant and it demonstrated a favorable AE profile when compared with higher doses and different dosing regimens.

At 100 mg qhs, 43%-60% of flibanserin patients in the pivotal program (patients who had been in their current relationships for over 10 years on average and had suffered HSDD symptoms for nearly half that time) exceeded the patient-anchored criteria for improvement for the three important endpoints, and those patients reported mean changes in important symptoms that often more than doubled the effect in the overall population. The proposed package insert language instructing that patients should discontinue therapy if improvement is not seen within 12 weeks

is designed to increase the likelihood that women who take flibanserin chronically will experience this magnitude of effect.

The large flibanserin Phase 1, Phase 2 and Phase 3 programs have allowed for extensive characterization of drug-related adverse effects, including effects in specific unintended situations. Serious risks are, for the most part, theoretical and can be managed through labeling and other risk management tools as they are for other drugs. The concern for side effects is somewhat ameliorated in the setting of a symptomatic disease like HSDD in which patients are otherwise generally healthy and will stop taking medication if not receiving benefit or if they experience unacceptable side effects.

The Sponsor has sought to develop draft labeling and risk management measures that adequately instruct physicians and patients on the appropriate use of flibanserin and looks forward to working with FDA to refine these tools. Patients at the 27 October 2014 patient-focused drug development meeting reported a willingness to risk serious (and often unknown) adverse effects and even to undergo periodic minor surgery with its related risk of serious infection in order to obtain HSDD relief.

In summary, flibanserin has shown statistically significant, rapid, consistent, sustained, clinically meaningful improvements in HSDD symptoms in premenopausal women. Its known common safety risks are recognizable and manageable. Less common events which are potentially clinically relevant and drug-drug interactions are well-characterized and are readily avoided through appropriate prescribing information and a REMS. The benefit-risk profile of flibanserin for the treatment of premenopausal women with HSDD is highly positive and warrants approval.

## TABLE OF CONTENTS

	Page
<b>EXECUTIVE SUMMARY .....</b>	<b>I</b>
<b>TABLE OF CONTENTS .....</b>	<b>1</b>
<b>LIST OF APPENDICES .....</b>	<b>3</b>
<b>LIST OF TABLES .....</b>	<b>4</b>
<b>LIST OF FIGURES .....</b>	<b>7</b>
<b>LIST OF ABBREVIATIONS .....</b>	<b>9</b>
<b>1 OVERVIEW OF HSDD .....</b>	<b>11</b>
<b>2 FLIBANSERIN PROPOSED INDICATION AND MECHANISM .....</b>	<b>14</b>
2.1 Product Characteristics .....	15
2.2 Regulatory History .....	16
2.3 Clinical Development Program .....	17
<b>3 EFFICACY .....</b>	<b>20</b>
3.1 Efficacy Endpoints .....	20
3.2 Phase 3 Program - Overview .....	22
3.3 Study Design - Pivotal Studies .....	23
3.4 Demographics and Baseline Characteristics - Pivotal Studies .....	27
3.4.1 Demographics .....	27
3.4.2 Baseline Characteristics .....	28
3.5 Principal Efficacy Data - Pivotal Studies .....	29
3.5.1 Satisfying Sexual Events .....	30
3.5.2 Sexual Desire .....	32
3.5.2.1 FSFI-Desire .....	32
3.5.2.2 eDiary Desire .....	34
3.5.3 FSDS-R13 (Distress) .....	36
3.6 Results Across all Efficacy Measures .....	38
3.7 Clinically Meaningful Benefit in HSDD .....	41
3.7.1 Benefit across Sexual Function Domains .....	41
3.7.2 Pre-specified Responder Analysis .....	42
3.7.3 Consistent Effect Across Symptoms .....	47
3.7.4 Other Indicators of Meaningfulness .....	48
<b>4 SAFETY .....</b>	<b>49</b>
4.1 Datasets .....	49
4.2 Overall Exposure .....	50
4.3 Demographics .....	51

4.4	Concomitant Baseline Diagnoses .....	53
4.5	Safety in Premenopausal Women with HSDD .....	55
4.5.1	Overall AEs .....	55
4.5.2	Common AEs .....	56
4.5.2.1	Sedation-related AEs .....	58
4.5.3	Hypotension and Syncope (AEs of Special Interest) .....	73
4.5.3.1	CYP3A4 Inhibition .....	73
4.5.3.2	Dedicated High Dose Study .....	74
4.5.3.3	Concomitant Use with Alcohol .....	75
4.5.3.4	Phase 3 Studies in Premenopausal Women .....	77
4.5.3.5	Assessment of Overall Risk of Hypotension and Syncope .....	79
4.5.4	SAEs .....	80
4.5.5	Other AEs of Special Interest .....	82
4.5.5.1	Suicidal Ideation .....	82
4.5.5.2	Neoplasms .....	83
4.5.5.3	Appendicitis .....	84
4.6	Risk Management .....	84
4.6.1	Safety Messages .....	84
4.6.1.1	Risks of Flibanserin .....	85
4.6.1.2	Importance of Bedtime Dosing .....	85
4.6.1.3	Avoidance of Moderate to Strong CYP3A4 inhibitors .....	85
4.6.1.4	Caution When Used with Alcohol .....	85
4.6.1.5	Appropriate Patient Selection .....	85
4.6.2	Tools .....	86
4.6.2.1	Package Insert .....	86
4.6.2.2	Medication Guide .....	86
4.6.2.3	Communication Plan REMS .....	87
4.6.2.4	Non-REMS tools .....	88
4.6.2.5	Phase 4 Studies .....	89
4.6.2.6	Enhanced Pharmacovigilance .....	90
4.6.3	Assessments .....	90
<b>5</b>	<b>BENEFIT RISK PROFILE.....</b>	<b>91</b>
5.1	Benefits .....	91
5.2	Risks .....	92
5.3	Risk Benefit Considerations .....	93
5.4	Balance of Flibanserin Benefit and Risk for Premenopausal Women with HSDD .....	94
	<b>REFERENCES.....</b>	<b>96</b>

## LIST OF APPENDICES

	Page
APPENDIX A	FDA MINUTES OF FLIBANSERIN 2010 ADVISORY COMMITTEE ....101
APPENDIX B	FLIBANSERIN REGULATORY HISTORY .....110
APPENDIX C	SUMMARY OF 27 OCTOBER 2014 PATIENT FOCUSED DRUG DEVELOPMENT MEETING .....112
APPENDIX D	SUMMARY EFFICACY DATA FROM NON PIVOTAL PHASE 3 STUDIES IN PREMENOPAUSAL WOMEN WITH HSDD .....117
APPENDIX E	SUMMARY OF PHASE 3 SAFETY STUDY OF CONCOMITANT SSRI/SNRI USE .....128
APPENDIX F	SUMMARY SAFETY DATA FROM PHASE 3 STUDIES IN PREMENOPAUSAL AND POSTMENOPAUSAL WOMEN WITH HSDD .....131
APPENDIX G	QUICK REFERENCE GUIDE FOR EFFICACY INSTRUMENTS .....144
APPENDIX H	FEMALE SEXUAL FUNCTION INDEX (FSFI) VALIDATION STUDIES .....146
APPENDIX I	EDIARY DESIRE VALIDATION AND IMPLEMENTATION LIMITATIONS.....160
APPENDIX J	FEMALE SEXUAL DISTRESS SCALE – REVISED (FSDS-R (DISTRESS)) VALIDATION STUDIES.....163
APPENDIX K	OVERVIEW OF PHASE 3 STUDY STATISTICAL PRINCIPLES AND ANALYSES .....189
APPENDIX L	STUDY 75 EFFICACY RESULTS EXCLUDING 2 STUDY SITES .....219
APPENDIX M	NUMBER (%) OF SUBJECTS WITH ADVERSE EVENTS OCCURRING IN $\geq 1.0\%$ IN PHASE 3 DOUBLE BLIND STUDIES IN PREMENOPAUSAL WOMEN .....238
APPENDIX N	CENTRAL NERVOUS SYSTEM EFFECTS OF FLIBANSERIN.....241
APPENDIX O	PROPOSED FLIBANSERIN PACKAGE INSERT .....273
APPENDIX P	DECREASED SEXUAL DESIRE SCREENER (DSDS).....287
APPENDIX Q	FLIBANSERIN APPROPRIATE USE CHECKLIST .....289



## LIST OF TABLES

	Page
Table 1 Number (%) of Subjects with Adverse Events Occurring at $\geq 2.0\%$ and Twice that of Placebo by Treatment - Phase 3 Studies in Premenopausal Women (Target Population Set).....	ix
Table 2 Summary of Phase 3 Efficacy Studies in Premenopausal Women with HSDD.....	19
Table 3 Summary of Pre-specified Outcome Measures - Pivotal Phase 3 Studies in Premenopausal Women .....	20
Table 4 Exposure by Dose and Dose Regimen - Phase 3 Studies in Premenopausal Women.....	23
Table 5 Summary of Pre-specified Outcome Measures - Pivotal Phase 3 Studies in Premenopausal Women .....	25
Table 6 Patient Disposition - Pivotal Phase 3 Studies in Premenopausal Women (Efficacy Treated Set).....	27
Table 7 Demographic Characteristics of Patients - Pivotal Phase 3 Studies in Premenopausal Women (Efficacy Treated Set).....	28
Table 8 Baseline Characteristics for Efficacy Endpoints - Pivotal Phase 3 Studies in Premenopausal Women (FAS) .....	29
Table 9 SSEs (Standardized) Change from Baseline at Week 24 – Pivotal Phase 3 Studies in Premenopausal Women (FAS, LOCF) .....	30
Table 10 FSFI-Desire Change from Baseline at Week 24 – Pivotal Phase 3 Studies in Premenopausal Women (FAS, LOCF) .....	33
Table 11 eDiary Desire (Total Monthly Score) Change from Baseline at Week 24 – Studies 71 and 75 (FAS, LOCF).....	35
Table 12 FSDS-R13 (Distress) Change from Baseline at Week 24 – Pivotal Phase 3 Studies in Premenopausal Women (FAS, LOCF) .....	37
Table 13 Mean Change from Baseline to Week 24 in Primary and Secondary Endpoints – Pivotal Phase 3 Studies in Premenopausal Women.....	39
Table 14 Response Thresholds Established via PGI-I Anchoring – Pivotal Phase 3 Studies in Premenopausal Women.....	44
Table 15 Number (%) of Responders (PGI-I Anchor Criteria) and Percent Differences across Efficacy Endpoints at Week 24 – Pivotal Phase 3 Studies in Premenopausal Women (FAS, LOCF) .....	44
Table 16 Mean Change from Baseline at Week 24 on Primary and Secondary Endpoints – Flibanserin Group Pivotal Phase 3 Studies in Premenopausal Women (FAS and Responder Populations) .....	47
Table 17 Overall Exposure to Flibanserin – Phase 3 Studies in Premenopausal Women (Target Population Set) and Open Label Safety Studies .....	49
Table 18 Exposure by Non-overlapping Intervals - Phase 3 Studies in Premenopausal Women (Target Population Set) and Open Label Safety Studies.....	50

Table 19	Overall Exposure to Flibanserin – Phase 3 Studies in Premenopausal Women (Target Population Set) and Open Label Safety Studies .....	51
Table 20	Demographic and Other Baseline Characteristics by Treatment - Phase 3 Studies in Premenopausal Women (Target Population Set).....	51
Table 21	Number (%) of Subjects with Concomitant Baseline Diagnoses/Diseases ( $\geq 5\%$ of Subjects) - Phase 3 Studies in Premenopausal Women (Target Population Set).....	54
Table 22	Number (%) of Subjects using Expected Concomitant Medications - Phase 3 Studies in Premenopausal Women (Target Population Set).....	55
Table 23	Overall Summary of Adverse Events – Phase 3 Studies in Premenopausal Women (Target Population Set) .....	56
Table 24	Number (%) of Subjects with Adverse Events Occurring at $\geq 2.0\%$ and Twice that of Placebo by Treatment - Phase 3 Studies in Premenopausal Women (Target Population Set).....	57
Table 25	Number (%) of Subjects with Adverse Events Leading to Discontinuation in $\geq 1.0\%$ of Subjects by Treatment - Phase 3 Studies in Premenopausal Women (Target Population Set).....	58
Table 26	Number (%) of Subjects with Sedation-Related Adverse Events – Phase 3 Studies in Premenopausal Women (Target Population Set).....	59
Table 27	Number (%) of Subjects with Severe Sedation-Related Adverse Events – Phase 3 Studies in Premenopausal Women (Target Population Set).....	60
Table 28	Number (%) of Subjects Who Discontinued Due to Sedation-related Adverse Events of Interest – Phase 3 Studies in Premenopausal Women (Target Population Set).....	60
Table 29	Mean and LS Mean Change (SD) in Standard Deviation of Lateral Position Difference from Placebo (ITT Population) – Driving and Cognition Study .....	64
Table 30	Summary of Sedation-Related AE Impact with Concomitant CYP3A4 Inhibitor Exposure or Hepatic Impairment.....	67
Table 31	Number (%) of Subjects with Adverse Events and Sedation-Related Adverse Events by Alcohol Use and Treatment – Phase 3 Studies in Premenopausal Women (Target Population Set) .....	69
Table 32	Number (%) of Subjects with Sedation-Related Adverse Events – Alcohol Study .....	70
Table 33	Summary of Hypotension and Syncope AEs with Concomitant CYP3A4 Inhibitor Exposure or Hepatic Impairment.....	74
Table 34	Number (%) of Subjects with Adverse Events of Interest by Treatment Group and Preferred Term – Alcohol Study .....	77
Table 35	Individual Hypotension, Syncope or Possible Hypotension-related Adverse Events - Phase 3 Studies in Premenopausal Women (Target Population Set) .....	79
Table 36	Overall Summary of Adverse Events - Phase 3 Studies in Premenopausal Women (Target Population Set) .....	80

Table 37	Number (%) of Subjects with Treatment-Emergent Serious Adverse Events - Phase 3 Studies in Premenopausal Women (Target Population Set).....	81
Table 38	Number (%) of Subjects with Adverse Events of Suicide/Self-Injury by Treatment and Preferred Term - Phase 3 Studies in Premenopausal Women (Treated Set) .....	82
Table 39	Individual Subjects with Breast Cancer Adverse Events – Flibanserin HSDD Development Program .....	83

## LIST OF FIGURES

	Page
Figure 1 Change from Baseline at Week 24 in Key Efficacy Endpoints – Pivotal Phase 3 Studies in Premenopausal Women (FAS, LOCF) .....	iv
Figure 2 Number (%) of Responders (PGI-I Anchor Criteria) across Efficacy Endpoints – Pivotal Phase 3 Studies in Premenopausal Women.....	vii
Figure 3 Mean Change (95% CI) in Standard Deviation of Lateral Position Difference from Placebo – Driving and Cognition Study.....	x
Figure 4 Representation of Population of Premenopausal Women with HSDD .....	12
Figure 5 Flibanserin Chemical Structure.....	14
Figure 6 Mechanism of Action.....	15
Figure 7 Flibanserin Development Program .....	18
Figure 8 SSEs (Standardized) Change from Baseline at Week 24 – Pivotal Phase 3 Studies in Premenopausal Women (FAS, LOCF) .....	31
Figure 9 SSEs (Standardized) Change from Baseline by Visit – Pivotal Phase 3 Studies in Premenopausal Women (FAS, LOCF) .....	32
Figure 10 FSFI-Desire Change from Baseline at Week 24 – Pivotal Phase 3 Studies in Premenopausal Women (FAS, LOCF) .....	33
Figure 11 FSFI-Desire Change from Baseline by Visit – Pivotal Phase 3 Studies in Premenopausal Women (FAS, LOCF) .....	34
Figure 12 eDiary Desire (Standardized) Change from Baseline at Week 24 – Studies 71 and 75 (FAS, LOCF).....	35
Figure 13 eDiary Desire (Standardized) Change from Baseline by Visit – Studies 71 and 75 (FAS, LOCF) .....	36
Figure 14 FSDS-R13 (Distress) Change from Baseline at Week 24 – Pivotal Phase 3 Studies in Premenopausal Women (FAS, LOCF) .....	37
Figure 15 FSDS-R13 (Distress) Change from Baseline by Visit – Pivotal Phase 3 Studies in Premenopausal Women (FAS, LOCF) .....	38
Figure 16 Differences from Placebo (95% CI) for Primary and Secondary Efficacy Endpoints (Standardized) – Pooled Pivotal Phase 3 Studies in Premenopausal Women (FAS, LOCF).....	40
Figure 17 Forest Plot of Difference from Placebo in Mean Change (95% CI) from Baseline in SSEs, FSFI-Desire and FSDS-R13 (Distress) at Week 24 – Pooled Pivotal Phase 3 Studies in Premenopausal Women (FAS, LOCF).....	41
Figure 18 Percent of Patients by Patient Global Impression of Improvement (PGI-I) Score at Week 24 – Pivotal Phase 3 Studies in Premenopausal Women (FAS, LOCF) .....	43
Figure 19 Number (%) of Responders (PGI-I Anchor Criteria) across Efficacy Endpoints – Pivotal Phase 3 Studies in Premenopausal Women.....	45
Figure 20 Number (%) of Responders Using Various PGI-I Anchor Criteria across Efficacy Endpoints – Study 147 .....	46

Figure 21	Correlation between Key Efficacy Endpoints – Pooled Pivotal Phase 3 Studies in Premenopausal Women (FAS, LOCF) .....	47
Figure 22	Time to Onset of First Event of Sedation-related AEs with Severity – Phase 3 Studies in Premenopausal Women (Target Population Set) .....	59
Figure 23	Driving and Cognition Study Design.....	63
Figure 24	Mean Change (95% CI) in Standard Deviation of Lateral Position Difference from Placebo – Driving and Cognition Study.....	64
Figure 25	Mean (95% CI) Difference from Placebo on Selected Secondary Driving Endpoints – Driving and Cognition Study.....	65
Figure 26	Mean Pulse Rate, Diastolic and Systolic Blood Pressure by Study Visit - Phase 3 Studies in Premenopausal Women (Target Population Set) .....	78

## LIST OF ABBREVIATIONS

AE	Adverse Event
AESI	Adverse Events of Special Interest
ANCOVA	Analysis of Covariance
AR(1)	First Order Autoregressive Covariance Structure
AUC	Area Under the Plasma Concentration Time Curve
BAC	Blood Alcohol Content
bid	Twice Daily
BMI	Body Mass Index
BOCF	Baseline Observation Carried Forward
BPH	Benign Prostatic Hyperplasia
BSS	Beck Scale for Suicide Ideation
CBI	Control-based Imputation
C <sub>max</sub>	Maximum Plasma Concentrations
CYP	Cytochrome P450
DSDS	Decreased Sexual Desire Screener
DSM-IV-TR	Diagnostic and Statistical Manual of Mental Disorders IV Text Revision
eDiary Desire	Daily Electronic Desire Measure
ETASU	Elements to Assure Safe Use
EU	European Union
FAS	Full Analysis Set
FOD	Female Orgasmic Disorder
FSAD	Female Sexual Arousal Disorder
FSD	Female Sexual Dysfunction
FSDS-R (Distress)	Female Sexual Distress Scale – Revised
FSDS-R13 (Distress)	Female Sexual Distress Scale – Revised Question 13
FSFI	Female Sexual Function Index
FSFI-Desire	Female Sexual Function Index – Sexual Desire Domain
HCP	Healthcare Professional
HSDD	Hypoactive Sexual Desire Disorder
ICSR	Individual Case Safety Report
J2R	Jump to Reference
LOCF	Last Observation Carried Forward
MAR	Missing at Random

MedDRA	Medical Dictionary for Regulatory Activities
MMRM	Mixed Model Repeated Measures
NDA	New Drug Application
OTC	Over the Counter
PDE-5	Phosphodiesterase-5
PFDD	Patient Focused Drug Development
PGI-I	Patient Global Impression of Improvement
PRO	Patient Reported Outcome
qd	Once Daily
qhs	Once Daily at Bedtime
REM	Rapid Eye Movement
REMS	Risk Evaluation and Mitigation Strategy
RHDAC	Reproductive Health Drugs Advisory Committee
SAE	Serious Adverse Event
SBP	Systolic Blood Pressure
SDLP	Standard Deviation of Lateral Position
SMQ	Standard Medical Query
SNRI	Serotonin Norepinephrine Reuptake Inhibitor
SOC	System Organ Class
SSE	Satisfying Sexual Event
SSRI	Selective Serotonin Reuptake Inhibitor
STRAW	Stages of Reproductive Aging Workshop
$t_{1/2}$	Half-life
$T_{max}$	time of maximum analyte plasma concentration after administration
VAS	Visual Analog Scale

## 1 OVERVIEW OF HSDD

Hypoactive sexual desire disorder (HSDD) is a type of sexual dysfunction characterized by 3 criteria:

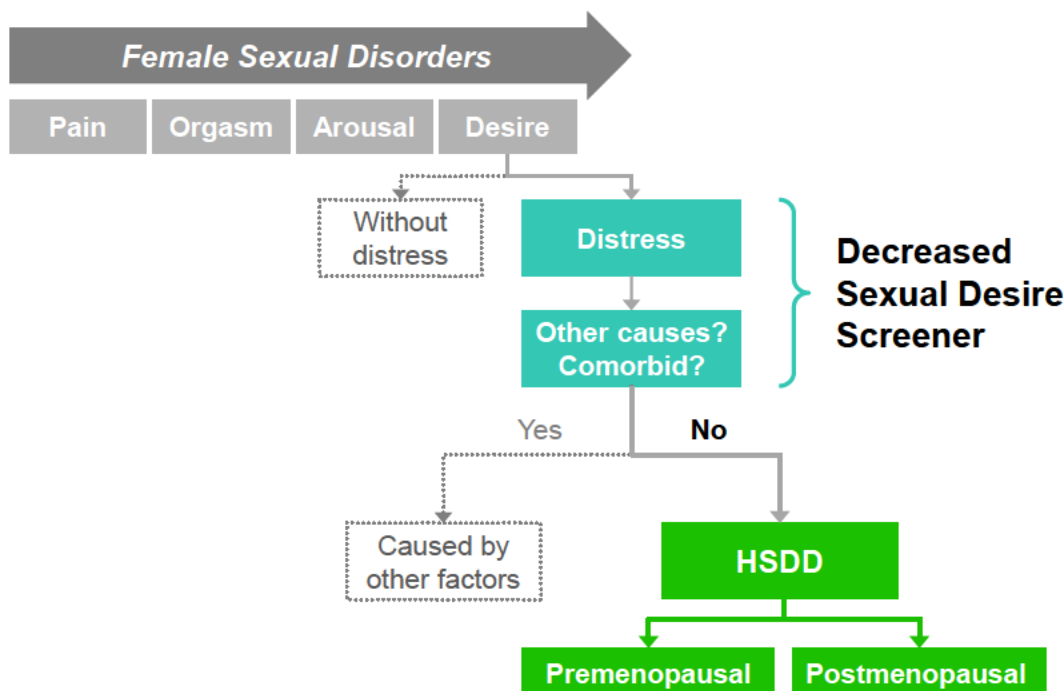
1. A persistent or recurrent deficiency or absence of sexual fantasies and desire for sexual activity,
2. The disturbance causes marked distress or interpersonal difficulty, and
3. The dysfunction is not
  - better accounted for by another psychiatric disorder (e.g., major depressive disorder, anxiety disorders, mood disorders, eating disorders)
  - due exclusively to the direct physiological effects of a substance
  - due exclusively to the direct physiological effects of another medical condition

[Diagnostic and Statistical Manual of Mental Disorders, 4th Edition, Text Revision, 2000 (DSM-IV-TR)]. In addition, the subtype of HSDD being discussed in this briefing document is both acquired and generalized. “Acquired” refers to the onset of the dysfunction beginning after a period of normal function. “Generalized” indicates that the dysfunction is not limited to certain types of stimulation, situations or partners.

It is important to consider that not all low sexual desire results from HSDD. First, HSDD does not encompass normal (e.g., daily or weekly) fluctuations in levels of desire, but rather includes only patients with a persistent or recurrent deficiency or absence of desire. Second, some women do not find their level of sexual desire to be distressing and therefore do not have HSDD. Finally, among those women who do find their low desire to be distressing, the HSDD definition and diagnosis excludes the subset for which distressing low desire may be attributable to another cause. [Figure 4](#) depicts the narrowing of the population of women with low desire to premenopausal women with HSDD, the population of interest for this application. Less than 25% of women with distressing low desire have generalized acquired HSDD likely attributable to biological rather than psychological etiology [Rosen, 2012]. In total, approximately 4.8 million premenopausal American women suffer with HSDD.



**Figure 4 Representation of Population of Premenopausal Women with HSDD**



Notes: HSDD=hypoactive sexual desire disorder.

These definitional criteria lend themselves to a straightforward and reliable diagnosis of HSDD. Assessment of a patient presenting for possible treatment involves readily discernible factors including degree of satisfaction with her current level of sexual desire or interest, change from her previous level of sexual desire or interest, whether that change is causing her distress, and whether there are alternative explanations for the lack of desire such as dissatisfaction with relationship or partner, concomitant medication or medical condition causing sexual dysfunction, pregnancy, recent childbirth, difficult life circumstances, partner dysfunction or other pre-existing sexual dysfunction.

DSM-IV-TR listed HSDD and Female Sexual Arousal Disorder (FSAD) separately. More recently, DSM-5 has grouped problems in women with low desire under the umbrella term Female Sexual Interest-Arousal Disorder in light of research suggesting that complete distinction between certain phases of sexual response may be unwarranted. This labeling change does not fundamentally alter the symptoms of HSDD or the ability of health care professionals (HCPs) to diagnose HSDD, and is consistent with DSM-IV-TR's recognition that "low sexual interest is frequently associated with problems of sexual arousal." Retaining the separation between desire and arousal diagnostic categories in women was supported by expert panelists at FDA's 28 October 2014 Scientific Workshop on female sexual dysfunction (FSD) who recommended that FDA maintain separation of arousal and desire disorders for clinical drug development and

noted that the combination of the two could be problematic for clarity of both diagnostic and outcome definitions/measurements.

HSDD is a serious and long-recognized disorder with impacts far beyond the bedroom affecting relationships, self-confidence and self-image. HSDD was first recognized in the medical literature in 1977 [Singer Kaplan, 1977]. Additional research over the past 40 years has led to a common understanding of the disorder and its impacts. Several more recent brain imaging studies have shown differences between normal women and women suffering from HSDD when exposed to erotic stimuli, which suggest a neurobiological component of HSDD [Woodward et al., 2013; Arnov et al., 2009; Huynh et al., 2012]. Women suffering from distressing low desire are eight to ten times more likely than women with normal desire/distress to report often, very often or always feeling unhappy, disappointed, upset, frustrated, sad, ashamed and bitter, as well as feeling low self-esteem [Leiblum et al., 2006].

FDA has identified FSD, a diagnosis that includes HSDD, as a priority condition under the Prescription Drug User Fee Act V, Patient Focused Drug Development (PFDD) Initiative [79 Federal Register 57942; 2014]. FDA held a public meeting in October 2014 to obtain patient perspectives on disease severity and unmet need for FSD. HSDD patients consistently described the significant impact of HSDD on their quality of life, including impacts on self-esteem, marital dissatisfaction, marital and family disruption, and non-sexual relationships. HSDD can significantly impact quality of life and result in major disturbances in family circumstance.

The impact of HSDD is exacerbated by the lack of proven therapies. While some studies suggest that psychotherapy may produce benefits in HSDD, this has not been demonstrated in randomized, controlled studies. In addition, there is a complete lack of pharmacologic therapies for HSDD in women [PFDD Meeting Transcript]. Testosterone is commonly prescribed off-label for HSDD in postmenopausal women despite safety concerns associated with hormonal therapy and contrary recommendations of the American Endocrine Society and FDA. Bupropion, approved for the treatment of major depressive disorder and as an aid to smoking cessation has also been used off-label for the treatment of HSDD despite a lack of evidence of efficacy or safety in this condition. Patients report being treated with muscle relaxants, analgesics, nerve injections and anti-depressants, which can exacerbate the cycle of adverse sexual consequences [PFDD Meeting Transcript]. In the absence of proven and approved therapies, HSDD patients are often victims of unscrupulous and fraudulent internet advertisements for pills, patches, creams and even chewing gum claiming to have natural, hormonal or other active ingredients and promising dramatic improvement in such areas as blood flow, virility, sex drive, and zest. These products are largely untested, apparently seeking more to prey on an unmet patient need than to provide appropriate treatment.

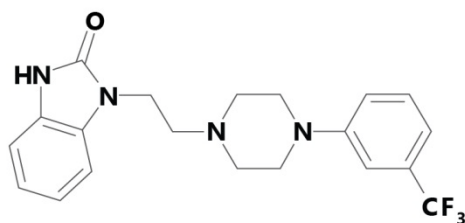
The impact and seriousness of HSDD, the lack of approved therapies and the common use of untested products making misleading claims combine to expose patients to unnecessary risks.

There is great need for a proven, safe, properly dosed and labeled medication that provides meaningful and quantifiable benefits to HSDD patients.

## 2 FLIBANSERIN PROPOSED INDICATION AND MECHANISM

Flibanserin (Figure 5) is a non-hormonal therapy developed for the treatment of HSDD in premenopausal women. Flibanserin will be made available as a 100 mg tablet intended to be taken orally once daily at bedtime (qhs).

**Figure 5 Flibanserin Chemical Structure**



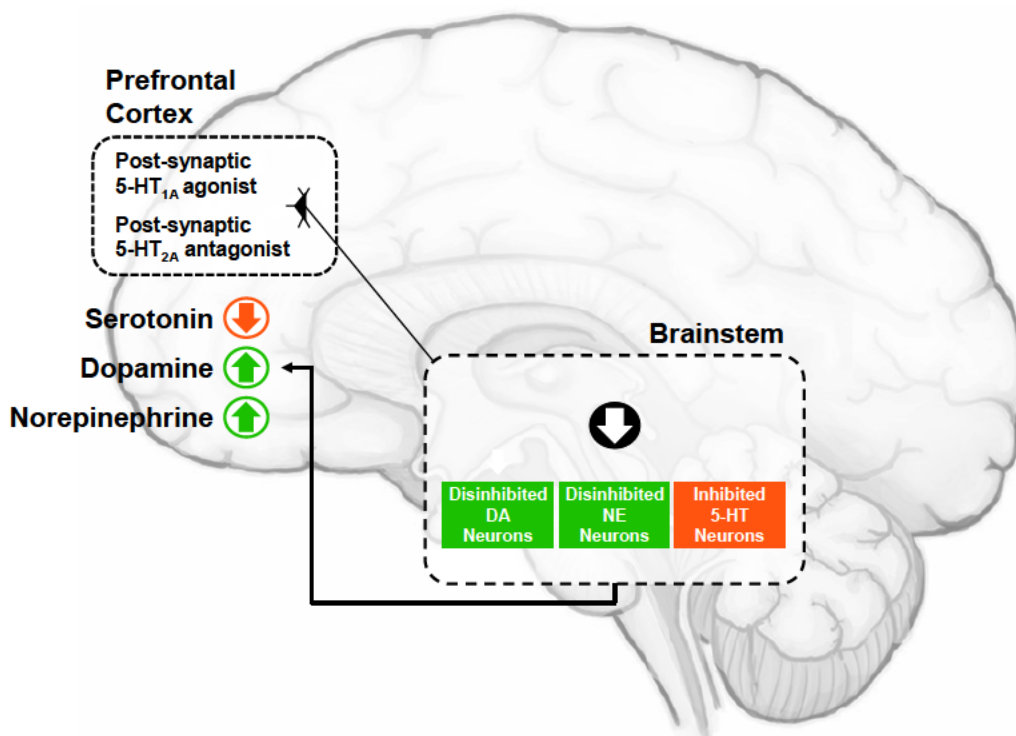
Flibanserin is centrally acting and, while the exact mechanism of action is not known, the molecule is thought to improve sexual desire by increasing dopamine and norepinephrine activity and reducing serotonin activity in the central nervous system. This is achieved by activating 5-HT<sub>1A</sub> receptors and blocking 5-HT<sub>2A</sub> receptors [Stahl, 2015].

Although the underlying pathophysiology of HSDD is not well defined, functional MRI studies comparing women with HSDD to healthy controls, offer insight into some of the neurophysiological abnormalities that might be responsible. These studies suggest that excessive neuronal activity in portions of the prefrontal cortex, an area of the brain that exercises executive inhibitory control over reward seeking behaviors, may play an important role in the pathophysiology of HSDD.

Pyramidal neurons in the prefrontal cortex project to three important nuclei in the brainstem: the serotonergic dorsal raphe nucleus which serves to inhibit activity in a variety of brain areas, the dopaminergic ventral tegmental area which plays an important excitatory role in reward circuits in the brain, and the noradrenergic locus coeruleus, which plays a central role in optimizing conscious arousal. Under normal conditions, there is a healthy balance between the inhibitory activity of the serotonergic neurons and the excitatory activity of dopaminergic and noradrenergic neurons that allows the generation of sexual desire.

The pyramidal cells in the prefrontal cortex express 5-HT<sub>1A</sub> and 5-HT<sub>2A</sub> serotonin receptors which have opposing effects. 5-HT<sub>1A</sub> receptors in the prefrontal cortex are largely inhibitory while 5-HT<sub>2A</sub> receptors are excitatory. Excessive excitatory signaling from the prefrontal cortex causes dysregulation of the neurotransmitters dopamine, norepinephrine and serotonin (Figure 6).

**Figure 6 Mechanism of Action**



Notes: 5-HT=5-hydroxytryptamine receptor; DA=dopamine; NE=noradrenergic.

The precise mechanism of action by which flibanserin enhances sexual desire in patients with HSDD is not known. What is known is that flibanserin is a highly selective post-synaptic 5-HT<sub>1A</sub> agonist and 5-HT<sub>2A</sub> antagonist. By activating 5-HT<sub>1A</sub> and blocking 5-HT<sub>2A</sub> receptors on pyramidal neurons, flibanserin reduces glutamate transmission to the brainstem resulting in:

1. Disinhibition of ascending dopamine and norepinephrine neurons and
2. Inhibition of ascending serotonin neurons.

Together these actions serve to regulate dopamine, norepinephrine and serotonin thereby restoring appropriate balance of excitatory and inhibitory activity of reward structures to the prefrontal cortex. The net result is a greater ability for premenopausal women with HSDD to feel sexual desire when appropriate.

## 2.1 Product Characteristics

Flibanserin is available as a 100 mg tablet intended to be taken orally once daily at bedtime (qhs). After oral administration, flibanserin absorption from the intestine is rapid and nearly complete. Maximum plasma concentrations ( $C_{max}$ ) occur 45 to 60 minutes after oral dosing with a half-life ( $t_{1/2}$ ) of approximately 10 hours. Steady state is achieved within three days. Food

moderately affects the rate and extent of flibanserin absorption. Peak plasma concentrations of flibanserin occur at 1.75 to 4 hours post-dosing with food, and the extent of exposure is increased up to 56% after a high-fat, high-caloric meal. Grapefruit juice increases flibanserin exposure approximately 38% and  $C_{\max}$  by 10%. Cytochrome P450 (CYP)3A4-mediated biotransformation is responsible for most of flibanserin elimination, with negligible or minimal (<10%) contributions from CYP2C9, CYP2C19 and/or CYP2D6.

## 2.2 Regulatory History

The flibanserin NDA for the treatment of HSDD in premenopausal women was originally submitted by the previous sponsor on 27 October 2009 and presented to the Bone, Reproductive and Urologic Drugs Advisory Committee on 18 June 2010. FDA's minutes of that committee meeting are provided in [Appendix A](#). A summary of important flibanserin regulatory history predating that 2010 meeting is provided in [Appendix B](#). At that 2010 meeting, the committee voted 11 to 0 that the overall benefit-risk balance had not been sufficiently established due in large part to failure to reach statistical significance on the pre-specified co-primary endpoint of sexual desire (measured by eDiary Desire) in the two pivotal studies available at that time (Study 71 and Study 75). While statistically significant differences in favor of flibanserin were seen on a validated secondary measure of desire (Female Sexual Function Index – Sexual Desire Domain (FSFI-Desire)), the committee found that altering the pre-specified method of assessing sexual desire during the clinical study did not maintain the integrity of the study. The committee was not asked any question specific to safety, but members raised concern regarding potential drug interactions with flibanserin and the need for long-term data. Consistent with the committee's recommendation, FDA denied approval of the application in 2010.

The committee also specifically recognized a significant need for women to have a treatment for HSDD and recommended that efforts be put forth to develop therapy to treat this disorder. Regarding efficacy of flibanserin, the committee suggested that further documentation of improved sexual desire be established for reconsideration of flibanserin for treatment of HSDD.

In the years that followed, the Sponsor met with FDA several times and, consistent with FDA guidance at those meetings, completed an additional pivotal study (Study 147) using the validated FSFI-Desire instrument as the primary measure of desire. Study 147 also permitted enrollment of patients taking a broader array of concomitant medications. Study 147 was successful on all primary and secondary endpoints. In addition, the Sponsor collected data from long-term Phase 3 open-label extension studies and conducted a 12-week Phase 3 double-blind safety study of flibanserin and concomitant Selective Serotonin Reuptake Inhibitor (SSRI) or Serotonin Norepinephrine Reuptake Inhibitor (SNRI) used in premenopausal women with HSDD and mild or remitted depressive disorder. The Sponsor also conducted dedicated Phase 1 studies intended to address various interactions (i.e., ethanol, fluconazole, grapefruit juice) and exposure to unintended high doses of flibanserin.

These additional data were submitted in 2013 and FDA again did not approve the NDA. The Division concluded that although efficacy had been established, specific safety questions would need to be addressed to permit a positive risk-benefit balance in light of what were seen as modest benefits. The Sponsor gained further clarity on the amount and type of further information that would be needed through FDA's dispute resolution process. Through these various reviews, communications and meetings, FDA recommended that the Sponsor provide additional support for the clinical meaningfulness of the efficacy data. FDA also recommended that the Sponsor conduct a next-day driving impairment study and assess whether cytochrome P450 enzymes CYP2C9 or CYP2C19 are involved in flibanserin metabolism but did not require that an additional pivotal efficacy study be completed for approval. The Sponsor has since provided additional analyses of clinical meaningfulness and conducted both requested safety studies. These studies demonstrate a lack of next-day impairment effects for flibanserin, and rule out substantial involvement of CYP2C9 and CYP2C19 in the metabolism of flibanserin. FDA also recommended that the application be presented to this advisory committee for expert input and recommendations.

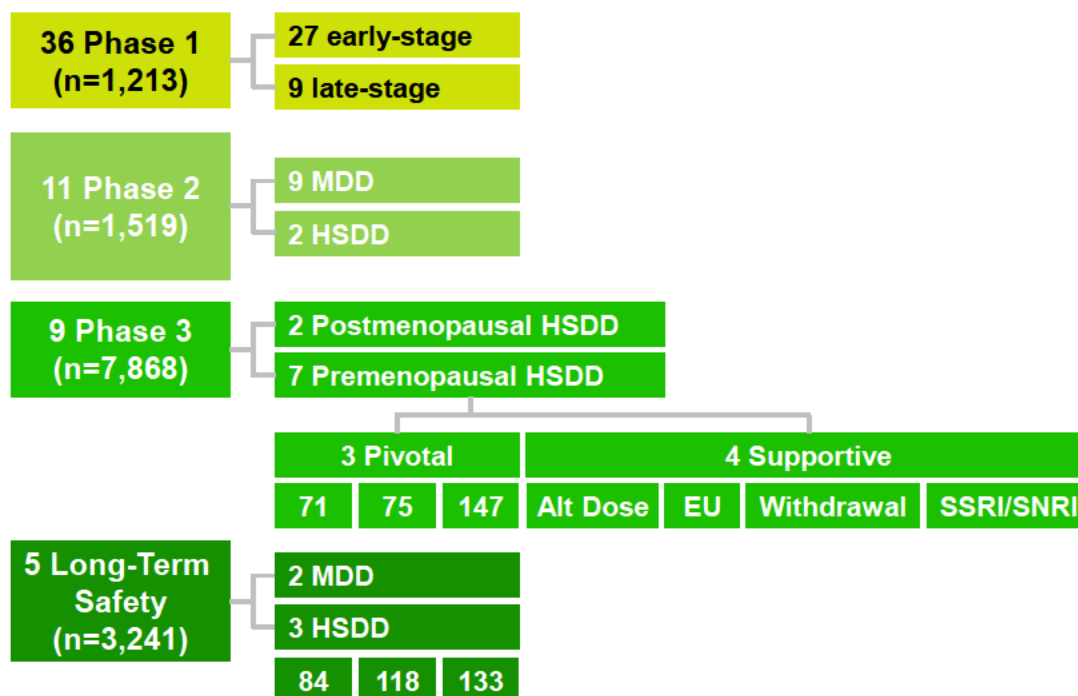
In addition to providing valuable feedback on flibanserin's development, since 2013 FDA has also held a broader 2-day public workshop to obtain patient and expert views relevant to drug development in FSD. FDA's summary comments from the patient-portion of the Patient-focused Drug Development Meeting are provided in [Appendix C](#). The scientific workshop portion of the meeting provided additional insights into HSDD drug development (e.g., appropriate endpoints and patient reported outcomes (PROs) to measure those endpoints, acceptable recall period for assessing desire, ability of healthcare providers to reliably diagnose HSDD) that are consistent with the design of the flibanserin clinical program.

## 2.3 Clinical Development Program

The flibanserin clinical development program is depicted in [Figure 7](#). Flibanserin was initially studied by the previous sponsor to assess its possible utility in patients suffering from major depressive disorder. After initial signals of improvement were noted on the sex drive question of the Arizona Sexual Experiences Scale in patients with major depressive disorder treated with flibanserin, development focus for the product shifted to HSDD. Two randomized, controlled 12-week Phase 2 studies were conducted in the US and Canada to assess flibanserin's effect in premenopausal women with HSDD. Positive effects on multiple measures of efficacy in these studies provided sufficient proof of concept to initiate a Phase 3 development program with 24-week studies as recommended by FDA. Data from the Phase 2 studies, which tested two twice daily (bid) doses (50 mg bid and 100 mg bid), led to selection of 50 mg and 100 mg total daily doses for Phase 3 testing. In addition to the bid dosing regimen utilized in Phase 2, both doses were tested as a single bedtime (qhs) dose in Phase 3 in an attempt to limit sedation-related AEs.



**Figure 7 Flibanserin Development Program**



Notes: Alt=alternate; EU=European; HSDD=hypoactive sexual desire disorder; MDD=major depressive disorder; SNRI=Serotonin-norepinephrine reuptake inhibitor; SSRI=Selective serotonin reuptake inhibitor.

In [Figure 7](#), the pivotal Phase 3 studies in premenopausal women are denoted by study number while the supportive studies are noted by abbreviated study name. The Phase 3 efficacy database includes data on a pproximately 6,200 pr emenopausal women with HSDD treated with flibanserin (4,136) or placebo (2,075) in five Phase 3, 24 -week, randomized, double-blind, placebo-controlled studies and one Phase 3, 48-week, randomized withdrawal study. Across these six studies, over 2,700 patients received the recommended flibanserin dose (100 mg qd) with 1,658 of those receiving the recommended dosing regimen (100 mg qhs). Three of the 24-week studies (Studies 147, 71 a nd 75) were conducted in North America, and included the recommended dosing regimen of 100 mg qhs and therefore serve as the pivotal studies for establishing the efficacy of flibanserin ([Table 2](#)). Of these, Studies 71 and 75 were previously presented to an FDA advisory committee in 2010 while Study 147 was completed more recently in response to recommendations from FDA and the committee. Efficacy across these three studies is presented in this briefing document. Three additional non-pivotal Phase 3 safety and efficacy studies were conducted. Key efficacy outcomes in these three non-pivotal studies, one of which did not include the to-be-marketed dosing regimen, one of which was not conducted in US patients and one of which followed a randomized withdrawal design, are presented in [Appendix D](#).

**Table 2 Summary of Phase 3 Efficacy Studies in Premenopausal Women with HSDD**

Study	Design/Control	No. of Patients Treated Study & Control Drugs	Planned Duration	Study Start/Stop Dates
<b>Pivotal Phase 3 Studies</b>				
Study 147	Randomized, double-blind, placebo-controlled	1087 545 placebo 542 flibanserin	24 weeks	15 Oct 2009- 01 Feb 2011
Study 71	Randomized, double-blind, placebo-controlled	880 295 placebo 585 flibanserin <sup>a</sup>	24 weeks	28 Jul 2006- 28 Apr 2008
Study 75	Randomized, double-blind, placebo-controlled	1581 398 placebo 1183 flibanserin <sup>a</sup>	24 weeks	25 Jul 2006- 31 Mar 2008
<b>Non-pivotal Phase 3 Studies</b>				
Alternate Dose Study	Randomized, double-blind, placebo-controlled	1385 349 placebo 1036 flibanserin <sup>a</sup>	24 weeks	02 Aug 2006- 02 May 2008
EU Study	Randomized, double-blind, placebo-controlled	945 318 placebo 627 flibanserin <sup>a</sup>	24 weeks	26 Jun 2007- 16 Mar 2009
Withdrawal Study	Open-label, flexible dose regimen, followed by randomized, double-blind, placebo-controlled fixed dose	738 flibanserin open-label, 333 <sup>b</sup> randomized 170 placebo 163 flibanserin	48 weeks (24 weeks open label period + 24 weeks randomized, double- blind)	25 Jan 2006- 13 Jul 2007

<sup>a</sup> Multiple doses tested.

<sup>b</sup> Double-blind; stable regimen from last 8 weeks of open-label period.

Notes: EU = European Union.

Source: 511.70 CTR, Section 11.2; 511.71 CTR, Section 11.2; 511.74 CTR, Section 11.2; 511.75 CTR, Section 11.2; 511.77 CTR, Section 11.2; 511.147 CTR, Section 11.2, Module 5.3.5.1.

The seventh Phase 3 study in premenopausal women was a safety study of flibanserin in combination with SSRI/SNRI therapy in women with HSDD and mild or remitted depressive disorder ([Appendix E](#)).

In addition to these seven Phase 3 and two Phase 2 studies in premenopausal patients with HSDD, the overall flibanserin program also included two additional Phase 3 studies in postmenopausal women suffering from HSDD, three open-label Phase 3 extension studies, nine Phase 2 studies in major depressive disorder, two open-label Phase 2 extension studies in major depressive disorder and 36 Phase 1 studies, several conducted in parallel with Phase 3 to better characterize the emerging flibanserin safety profile. Reports from all Phase 1, Phase 2 and Phase 3 studies in HSDD were provided in the new drug application (NDA) to allow a comprehensive review of the safety of flibanserin. In the interests of brevity, this briefing document focuses largely on the premenopausal Phase 3 population with summary data for safety in the overall (pre- and postmenopausal) Phase 3 HSDD population provided in [Appendix F](#).



## 3 EFFICACY

### 3.1 Efficacy Endpoints

While HSDD has been recognized in the medical literature for 40 years, the development, validation and acceptance of survey instruments necessary for assessment of HSDD symptoms has occurred more recently. Endpoints assessing sexual function, sexual distress, sexual desire, sexual activity and overall patient benefit are now in place and permit regulatory evaluation of the efficacy of drug candidates intended to treat HSDD. A quick reference chart including important characteristics of each instrument is provided in [Appendix G](#) for ease of reference during review of this briefing document.

There were four principal efficacy measures, all based on PRO instruments, variably used as primary or secondary tools to evaluate efficacy in the pivotal Phase 3 studies ([Table 3](#)).

**Table 3 Summary of Pre-specified Outcome Measures - Pivotal Phase 3 Studies in Premenopausal Women**

Efficacy Endpoint	No. of Items	Response Range	Clinical Cut Point	Recall Period (Days)
SSEs (Standardized)	1	0 – NUL	-	3
FSFI-Desire	2	1.2 – 6 <sup>a</sup>	3.0	28/7
FSDS-R13 (Distress)	1	0 - 4	-	28/7
eDiary Desire (Standardized)	1	0 - NUL	-	1

<sup>a</sup> Standardized domain score derived from total raw score of two items (score range of each item is 1 to 5) and then multiplied by 0.6.  
Notes: FSDS-R13 = Female sexual distress scale-revised Question 13; FSFI-Desire = Female sexual function index – desire domain;  
NUL = No upper limit; SSE = Satisfying sexual event.

Each of these endpoints and instruments is discussed below in connection with the symptom it is intended to measure.

Sexual Activity was measured as mean change from baseline to Week 24 in the number of satisfying sexual events (SSEs), recorded via a daily electronic diary (eDiary) and standardized to a 28-day period.

An SSE was recorded when a patient reported a sexual event or encounter (i.e., sexual intercourse, oral sex, masturbation, or genital stimulation by the partner) and answered “yes” to the eDiary question: “Was the event satisfying for you?”

Patients were to report on a daily basis whether they had engaged in sexual activity and, if so, whether it was satisfying. The patient was prompted to enter information on sexual activity retrospectively for up to 72 hours (3 days). If a patient failed to enter information for more than three consecutive days, sexual activity data beyond the last 72 hours was considered missing. Range of values for this variable is 0 to no upper limit.

SSEs are a measure of sexual activity rather than desire. Sexual event frequency and satisfaction are not parts of the diagnosis or definition of HSDD largely because the frequency of sexual experiences is affected by confounding factors such as pressure from a partner or nonsexual needs for physical comfort or intimacy. In light of these considerations, FDA's 28 October 2014 expert panel on development of drugs for FSD recommended repositioning SSEs from a primary to a secondary endpoint in future studies of HSDD drugs.

Desire was measured by two different instruments: FSFI-Desire (the sexual desire domain of the Female Sexual Function Index) and eDiary Desire.

Sexual desire was measured as mean change from baseline to Week 24 in *FSFI-Desire* score which is a single domain of the larger FSFI PRO. The two items in the FSFI-Desire are:

1. Over the past 4 weeks, how often did you feel sexual desire or interest? – answers range from “almost never or never” to “almost always or always”
2. Over the past 4 weeks, how would you rate your level (degree) of sexual desire or interest? – answers range from “very low or none at all” to “very high”

The weighted score of FSFI-Desire ranges from 1.2 to 6.0 with lower scores indicating less desire. Consistent with the time period embedded in the FSFI questions, FSFI-Desire was collected using a 28-day recall period. FSFI is the most frequently used tool for measuring FSD, has been extensively validated and was endorsed by FDA's 28 October 2014 expert panel on development of drugs for FSD. Specific studies have been conducted to validate FSFI-Desire in the premenopausal HSDD population. A comprehensive review of FSFI-Desire validation is provided in the [Appendix H](#).

In the two early studies sexual desire was also measured as mean change from baseline to Week 24 in monthly sum of responses to an eDiary daily desire question (*eDiary Desire*), standardized to a 28-day period.

The eDiary Desire asks a patient to “Indicate your most intense level of sexual desire in the last 24 hours [or] since your last visit”. Possible responses were “strong”, “moderate”, “low” or “none.” A measure of sexual desire was recorded by eDiary on a daily basis. Reporting of sexual desire information was limited to a 24-hour retrospective period.

The eDiary Desire assessment has since been shown to be associated with poor compliance and to lack adequate sensitivity. It is unclear whether these issues are due to the dulling effect of repetitive daily questioning about desire or the lack of consistency between the instrument's recording period and the experience of desire (i.e., as a state rather than an event). A discussion of eDiary Desire limitations is included in [Appendix H](#).

Distress related to low sexual desire was measured as mean change from baseline to Week 24 in Female Sexual Distress Scale-Revised Item 13 (FSDS-R13 (Distress)). FSDS-R13 (Distress) is a single question from the larger Female Sexual Distress Scale – Revised (FSDS-R (Distress)) instrument which asks “How often did you feel bothered by low sexual desire?” Response choices are “Never, Rarely, Occasionally, Frequently or Always”, scored from 0 to 4. FSDS-R13 (Distress) was collected using a 7-day recall period. Like the FSFI, the FSDS-R (Distress), including Item 13 has been extensively validated. Copies of the key validation publications for FSDS-R (Distress) are provided in [Appendix J](#).

FDA’s October 2014 expert panel on development of drugs for FSD endorsed use of the FSDS-R13 (Distress) and elevation of distress to a primary measure of efficacy in future studies for HSDD drugs.

Other Measures of Overall Sexual Function. In addition to the measures discussed above, the following more global measures of sexual function or overall improvement were evaluated across the pivotal program:

- FSFI Total Score, a 52-point scale measures overall female sexual function via domains assessing sexual desire, sexual arousal, lubrication, orgasm, sexual satisfaction and pain;
- FSDS-R (Distress) Total Score, a 13-question measure of distress associated with female sexual function including feelings of guilt, frustration, inferiority, inadequacy, embarrassment and dissatisfaction;
- Patient Global Impression of Improvement (PGI-I), a recognized tool for evaluating the patient’s impression of overall improvement of her HSDD condition on a 7-point scale.

The quick reference chart provided in [Appendix G](#) provides additional details regarding these three instruments.

### **3.2 Phase 3 Program - Overview**

The Phase 3 efficacy program for premenopausal women with HSDD included six Phase 3 efficacy studies:

- Three 24-week, randomized, double-blind, placebo-controlled studies conducted in North America using the recommended dose and dosing regimen (the pivotal studies: Studies 147, 71, and 75)
- One 24-week, randomized, double-blind, placebo-controlled study conducted in North America using exploratory doses and dosing regimens (the Alternate Dose Study)

- One 24-week, randomized, double-blind, placebo-controlled study conducted in Europe (the EU Study)
- One 48-week, randomized withdrawal study (the Withdrawal Study)

Numbers of patients randomized to each flibanserin dose group for each Phase 3 study are shown in [Table 4](#). Over 2,700 patients received the recommended flibanserin dose with 1,658 of those receiving the recommended dosing regimen (100 mg qhs). Over 1,700 placebo and flibanserin patients from these studies rolled over into a one-year single-arm, open-label extension study of flibanserin.

**Table 4 Exposure by Dose and Dose Regimen - Phase 3 Studies in Premenopausal Women**

Study No.	Placebo (N - Treated)	Flibanserin (N - Treated)			
		25 mg bid	50 mg qhs	50 mg bid	100 mg qhs
Pivotal Phase 3 Studies					
147	N=545	-	-	-	N=542
71	N=295	-	N=295	-	N=290
75	N=398	N=396	-	N=392 <sup>a</sup>	N=395 <sup>a</sup>
Non-pivotal Phase 3 Studies					
Alternate Dose Study	N=349	N=337	N=363	N=336	-
EU Study	N=318	-	N=311	-	N=316 <sup>a</sup>
Withdrawal Study					
Open-label	-	-	N=738 <sup>b</sup>	-	-
Double-blind	N=170	-	N=35	N=13	N=115

<sup>a</sup> Up-titration from FLI 50 mg qhs after the first 2 weeks of treatment as part of the dosing regimen.

<sup>b</sup> 738 patients started on FLI 50 mg qhs and could return to FLI 50 mg qhs as optional down-titration from FLI 50 mg bid or FLI 100 mg qhs.

Notes: bid = Twice daily; EU = European Union; qhs = Once every evening at bedtime.

Source: 511.70 CTR, Section 10.1; 511.71 CTR, Section 10.1; 511.74 CTR, Section 10.1 and Table 12.1.2; 511.75 CTR, Section 10.1; 511.77 CTR, Section 10.1; 511.147 CTR, Section 10.1, Module 5.3.5.1.

Efficacy discussion in this briefing document will focus on a comparison of flibanserin 100 mg qhs with placebo in each of the three pivotal studies. A summary of key efficacy endpoint data for the three non-pivotal Phase 3 trials in premenopausal women is provided in [Appendix D](#).

### 3.3 Study Design - Pivotal Studies

Each of the three pivotal Phase 3 studies was a 24-week randomized, double-blind, placebo-controlled, parallel-group study in premenopausal women with HSDD.

Each used the DSM-IV-TR criteria for diagnosis of HSDD and also required that the patient be diagnosed with HSDD for at least 6 months. This latter criterion has been added to DSM-5.

Inclusion criteria were designed to identify patients who met the HSDD definition of low sexual desire with associated distress while maintaining some degree of sexual activity in order to permit assessment of drug effects.

Across all three studies, key eligibility criteria to establish the population and the diagnosis of HSDD included:

- Pre-menopausal women per the Stages of Reproductive Aging Workshop (STRAW) criteria who had a primary diagnosis of HSDD, generalized acquired type, according to DSM-IV-TR criteria
- Current HSDD episode of at least 24 weeks duration
- Co-morbid Secondary FSAD and/or Female Orgasmic Disorder (FOD) permitted only if HSDD commenced prior to FSAD and/or FOD and the HSDD was of more importance to the patient
- A score of 15 or higher on the FSDS-R (Distress) Total Score
- Score of 0 or 1 out of 5 on item number 2 of the Sexual Interest and Desire Inventory-Female which measures both frequency and intensity of receptivity
- Willingness to try to engage in sexual activity at least once per month
- In a stable, monogamous relationship with a sexually functional partner, for at least one year

Eligibility criteria further served to exclude patients who:

- Were taking medications which could confound the results
- Had other DSM-IV-TR disorders such as Sexual Aversion Disorder, Substance-Induced Sexual Dysfunction, Dyspareunia (not caused by inadequate foreplay stimulation or alleviated by lubricants), Vaginismus, Gender Identity Disorder, Paraphilia or Sexual Dysfunction Due to a General Medical Condition
- Had a history of major depressive disorder, or evidence of depression or suicidal ideation or
- Started non-drug psychotherapeutic treatment within 12 weeks of study start

Based on recommendations from FDA and the 2010 advisory committee to broaden the list of permitted concomitant medications after review of the first two pivotal studies, Study 147 was

expanded to permit the inclusion of patients taking triptans, antiarrhythmics, anticoagulants, beta blockers, muscle relaxants, benzodiazepines, mood stabilizers (e.g., lithium, carbamazepine, valproic acid), or respiratory agents.

Consistent efficacy endpoints (discussed in detail above) were used across studies with variations in whether they were considered primary or secondary. The positioning of each of these endpoints is summarized in [Table 5](#).

**Table 5 Summary of Pre-specified Outcome Measures - Pivotal Phase 3 Studies in Premenopausal Women**

Efficacy Endpoint	Study 147	Study 71	Study 75
SSEs (Standardized)	Co-Primary	Co-Primary	Co-Primary
FSFI-Desire	Co-Primary	Secondary	Secondary
eDiary Desire (Standardized)	Not Done	Co-Primary	Co-Primary
FSDS-R13 (Distress)	Secondary	Secondary	Secondary

Notes: FSDS-R13 = Female sexual distress scale-revised Question 13; FSFI-Desire = Female sexual function index – desire domain;  
SSE = Satisfying sexual event.

Source: 511.71 CTR, Section 8.0; 511.75 CTR, Section 8.0; 511.147 CTR, Section 9.5.

Results are presented for the Full Analysis Set (FAS) populations. The FAS consisted of those patients who were randomized to a treatment group, received at least one dose of study medication, and had at least one on-treatment efficacy assessment. The FAS was analyzed for efficacy using the last observation carried forward (LOCF) method of handling missing data. Recognizing that the LOCF assumption that data are missing completely at random is seldom true, sensitivity analyses using mixed model repeated measures (MMRM) and missing at random (MAR) were conducted. Additional more conservative sensitivity analyses using methods which impute missing data assuming no treatment benefit (i.e., baseline observation carried forward (BOCF), control-based imputation (CBI) and jump to reference (J2R)) were also conducted. Statistical separation (i.e. 2-sided  $p < 0.05$ ) between flibanserin and placebo was maintained across SSEs, FSFI-Desire and FSDS-R13 (Distress) in Studies 147, 71 and 75 in all cases with the exception of SSEs when analyzed via J2R in Study 75 ( $p = 0.08$ ). Sensitivity analyses were not conducted for eDiary Desire because it did not reach significance via the primary analysis.

The Efficacy Treated Set (all patients randomized to a treatment group who received at least one dose of study medication) is used only to analyze demographic data and baseline characteristics and will be more fully assessed in the discussion of safety. Fifty eight (23 placebo and 35 flibanserin) additional subjects not included in the FAS are included in the Efficacy Treated Set.

The statistical design and analyses were similar for the three pivotal efficacy studies and are detailed in [Appendix K](#).

- Patients were randomized to either flibanserin or placebo, stratified by center.
- Efficacy comparisons were made between the 4-week screening period and Week 21 to 24, except for PGI-I which, based on the nature of the endpoint, was assessed only at Week 24.
- The null hypothesis was that the mean change from baseline was equal for patients treated with flibanserin and placebo. The alternative hypothesis was that the mean change from baseline was not equal for patients treated with flibanserin and placebo.
- All hypothesis tests were 2-sided with an overall study Type I error of 0.05. In each study, both co-primary endpoints were required to be statistically significant at a level of  $\alpha = 0.05$  in order for the study to be deemed positive.
- For SSEs (standardized), mean change from baseline to Week 24 was compared using a stratified Wilcoxon rank sum test where strata were the pooled centers. The adjustment for baseline SSEs was taken into account by using mean change from baseline in the number of SSEs in the test.
- For FSFI-Desire, FSDS-R13 (Distress), eDiary Desire, FSFI Total Score, and FSDS-R (Distress) Total Score, mean change from baseline to Week 24 was compared using analysis of covariance (ANCOVA) with treatment and pooled center as fixed effects and baseline score as a covariate.
- A responder analysis, anchored to the responses of the patients on the PGI-I instrument, was pre-specified in each study as the method for determination of clinically meaningful benefit. The percentages of responders in the placebo and flibanserin treatment groups were compared using Chi-square test for the SSE endpoint (no adjustment for center) and the Cochran-Mantel-Haenszel test adjusting for center for all other endpoints. This analysis was based on defining a responder as a patient with a change from baseline in an endpoint value greater than the minimal response threshold observed in the PGI-I assessment i.e., between “minimally improved” (score of 3) and “no change” (score of 4) on the PGI-I.
- The primary method for handling missing data in the FAS was the LOCF method. Sensitivity analyses using BOCF and MMRM were conducted to assess the impact of alternate missing data imputation methods. The MMRM analyses were performed without any data imputation using only the observed cases. The MMRM analyses were performed to mirror the ANCOVA analysis (except for repeated measures aspect); therefore, these analyses used baseline as a covariate with study and pooled center nested in study. The model included the treatment-by-visit interaction term from which the treatment versus placebo contrast at a given visit was reported. The first order

autoregressive [AR(1)] covariance structure was used. If AR(1) did not converge, the unstructured and compound symmetry covariance structures were examined.

### 3.4 Demographics and Baseline Characteristics - Pivotal Studies

#### 3.4.1 Demographics

A total of 1,227 patients received flibanserin 100 mg qhs and 1,238 received placebo in the three pivotal studies. The overall completion rates for flibanserin 100 mg qhs and placebo treatment groups were 70% and 78%, respectively. Discontinuations were attributed primarily to AEs with more discontinuations on drug than placebo (Table 6).

**Table 6 Patient Disposition - Pivotal Phase 3 Studies in Premenopausal Women (Efficacy Treated Set)**

	Placebo N (%)	Flibanserin 100 mg qhs N (%)
Randomized	1241	1229
Treated	1238 (100.0)	1227 (100.0)
Discontinued	271 (21.9)	369 (30.1)
Adverse Event	73 (5.9)	148 (12.1)
Lost to Follow-up	55 (4.4)	68 (5.5)
Consent Withdraw	67 (5.4)	53 (4.3)
Noncompliance	22 (1.8)	33 (2.7)
Lack of Efficacy	22 (1.8)	21 (1.7)
Other <sup>a</sup>	32 (2.6)	46 (3.7)
Completed	967 (78.1)	858 (69.9)

<sup>a</sup> Other includes pregnancy, personal reasons, moving away, etc.

Notes: qhs = Once every evening at bedtime.

Includes Studies 511.71, 511.75, and 511.147.

Source: ISE Appendix 6 Table 3.1.1.5, 3.1.1.6; 511.147 CTR Table 15.1.1:1.

Premenopausal women with a primary diagnosis of HSDD enrolled in the pivotal Phase 3 program were primarily white, married, and, on average 36 years of age – population characteristics that are representative of the population of premenopausal women suffering from HSDD [Shifren et al., 2008; Rosen et al., 2012; Connor et al., 2011]. Demographic data for the flibanserin and placebo groups were similar for all variables (Table 7).



**Table 7 Demographic Characteristics of Patients - Pivotal Phase 3 Studies in Premenopausal Women (Efficacy Treated Set)**

	<b>Placebo N = 1238</b>	<b>Flibanserin 100 mg qhs N = 1227</b>
Age, Years		
Mean	36.2	35.9
Min, Max	19, 54	19, 55
Race, n (%)		
White	1089 (88.0)	1073 (87.4)
Black or African American	119 (9.6)	131 (10.7)
Asian	21 (1.7)	20 (1.6)
Other	9 (0.8)	3 (0.3)
Body Mass Index, kg/m <sup>2</sup> , n (%)		
Underweight (<18.5)	19 (1.5)	20 (1.6)
Normal (18.5 - <25)	571 (46.1)	559 (45.6)
Overweight/Obese (≥25)	644 (52.0)	644 (52.5)
Missing	4 (0.3)	4 (0.3)

Notes: qhs = Once every evening at bedtime.  
Includes Studies 511.71, 511.75, and 511.147.  
Source: ISS Post Hoc Table 1.3.1a.

### 3.4.2 Baseline Characteristics

At baseline, patients in the Phase 3 pivotal studies had been in their current relationship for a mean of 10.9 (placebo) and 10.7 (flibanserin 100 mg qhs) years and had been symptomatic with HSDD for a mean of 56.9 (placebo) and 54.3 (flibanserin 100 mg qhs) months.

The populations from the three pivotal efficacy studies demonstrated clinically relevant symptoms of HSDD. For FSFI-Desire, baseline scores ranged from 1.8 to 1.9, below the validated cut-off score of 3.0 for classifying women with and without HSDD [Gerstenberger, 2010]. FSFI Total Score at baseline ranged from 19.0 to 19.8, also below the clinical cut-off of 26.5 distinguishing dysfunctional from normal sexual functioning in women [Rosen, 2000]. Baseline scores for FSDS-R13 (Distress), in which a score of 4 represents the upper limit of distress (score range 0 - 4), ranged from 3.2 to 3.4, indicating a significant level of distress associated with lack of sexual desire. FSDS-R (Distress) Total Score at baseline ranged from 30.2 to 32.8, well over the cut-off score of 15 for categorizing sexual distress [Derogatis, 2002] (Table 8).

**Table 8 Baseline Characteristics for Efficacy Endpoints - Pivotal Phase 3 Studies in Premenopausal Women (FAS)**

	147		71		75	
	Placebo	FLI 100 mg qhs	Placebo	FLI 100 mg qhs	Placebo	FLI 100 mg qhs
<b>Number of Patients</b>	<b>536</b>	<b>532</b>	<b>290</b>	<b>280</b>	<b>389</b>	<b>380</b>
<b>Baseline SSE (Standardized)</b>						
N	532	528	288	280	388	377
Mean (SD)	2.7 (2.9)	2.5 (2.5)	2.7 (2.8)	3.0 (2.8)	2.7 (2.8)	2.6 (2.9)
<b>Baseline FSFI-Desire</b>						
N	536	532	290	280	388	380
Mean (SD)	1.9 (0.7)	1.9 (0.7)	1.9 (0.7)	1.9 (0.7)	1.8 (0.7)	1.8 (0.7)
<b>Baseline FSDS-R13 (Distress)</b>						
N	536	532	290	280	389	380
Mean (SD)	3.4 (0.7)	3.4 (0.7)	3.2 (0.8)	3.2 (0.9)	3.2 (0.8)	3.3 (0.7)
<b>Baseline FSDS-R (Distress) Total Score</b>						
N	536	532	290	280	389	380
Mean (SD)	32.5 (8.7)	32.8 (9.0)	30.1 (9.9)	30.7 (10.0)	30.2 (9.9)	30.6 (9.3)
<b>Baseline FSFI Total Score</b>						
N	536	532	290	280	388	380
Mean (SD)	19.0 (6.1)	19.0 (6.0)	19.8 (7.0)	19.5 (6.6)	19.5 (6.3)	19.1 (6.0)

Notes: FAS = Full analysis set; FLI = Flibanserin; FSDS-R (Distress) = Female sexual distress scale-revised (score range 0 – 52; clinical cut point >15); FSDS-R13 = Female sexual distress scale-revised Question 13 (score range 0 – 4); FSFI = Female sexual function index (score range 2 – 36; clinical cut point >26.6); FSFI-Desire = Female sexual function index- desire domain (score range 1.2 – 6; clinical cut point 3); N = Number of subjects; qhs = Once every evening at bedtime; SD = Standard deviation; SE = Standard error; SSE = Satisfying sexual event.

Source: 511.147, 511.71 and 511.75 CTRs, Tables 15.1.4: 4.

### 3.5 Principal Efficacy Data - Pivotal Studies

In the initial pivotal program (Studies 71 and 75) flibanserin demonstrated statistically significant superiority to placebo on only one of two co-primary endpoints, change in SSEs. Regarding improvements in desire, flibanserin showed separation from placebo on eDiary Desire but that difference did not reach statistical significance. Consistent with the recommendations of FDA and its advisory committee, the Sponsor completed an additional pivotal study (Study 147) with the goal of demonstrating statistically significant improvements over placebo on two co-primary measures, SSEs and a validated and consistent instrument for measuring desire (FSFI-Desire), and on a key secondary measure of distress associated with low desire (FSDS-R13 (Distress)). Study 147 was successful on each of these required endpoints, as well as all other secondary measures of efficacy. Secondary endpoints for Studies 71 and 75, including results on the FSFI-Desire instrument, are also presented below, along with nominal p-values, to provide a sense of the consistency of the results across studies.

The data presentations in this section are based on the FAS population using LOCF. Numbers of subjects who completed therapy are provided in each figure with data from only those subjects who completed the study provided in [Appendix K](#). In addition, due to data integrity issues detected and reported by the Sponsor at two study sites that participated in Study 75, sensitivity analyses showing results from Study 75 excluding subjects enrolled at these two sites were included in the original 2009 NDA and are presented in [Appendix L](#).

### 3.5.1 Satisfying Sexual Events

Mean Change from Baseline in SSEs at Week 24 was a co-primary endpoint in all three pivotal studies. The flibanserin 100 mg qhs treatment group in each study experienced a statistically significant increase in SSEs (standardized) compared with the placebo group at Week 24 ([Table 9](#); [Figure 8](#)). In terms of absolute numbers, mean SSEs per month in the flibanserin group increased to 5 in Study 147, 4.6 in Study 71, and 4.5 in Study 75 at the end of the 24-week study period so that patients were experiencing a doubling of their baseline number of SSEs and a total of approximately one SSE per week.

**Table 9**      **SSEs (Standardized) Change from Baseline at Week 24 – Pivotal Phase 3 Studies in Premenopausal Women (FAS, LOCF)**

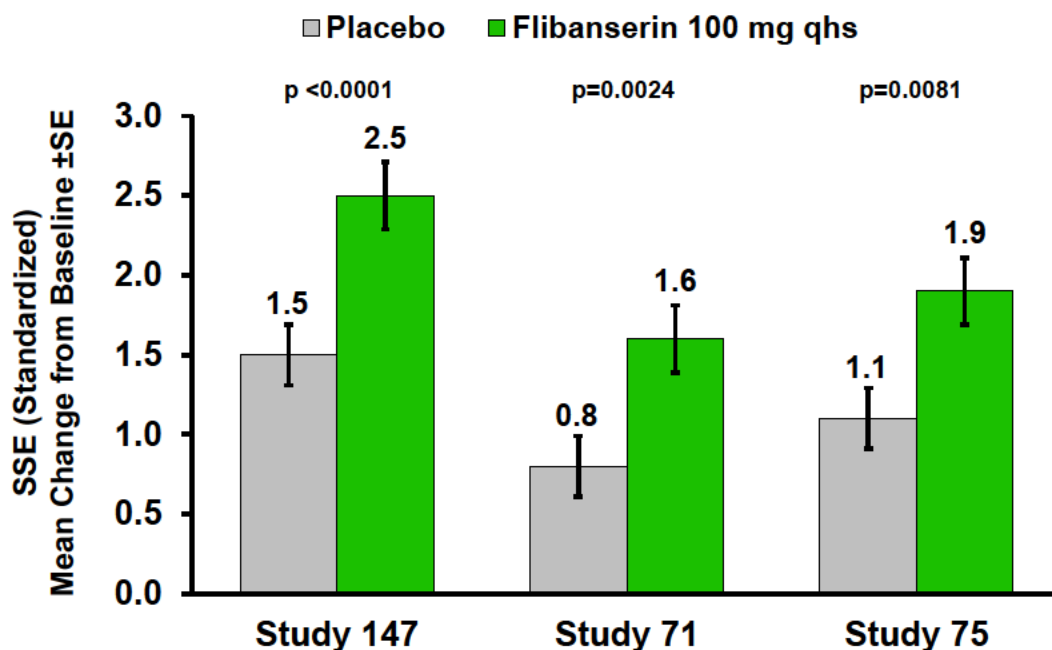
Endpoint SSEs (Standardized)	Treatment	N	Change from Baseline	
			Mean (SD)	P-value <sup>a</sup>
Study 147	Placebo	521	1.5 (4.5)	<0.0001
	Flibanserin 100 mg qhs	500	2.5 (4.6)	
Study 71	Placebo	285	0.8 (3.4)	0.0024
	Flibanserin 100 mg qhs	275	1.6 (3.8)	
Study 75	Placebo	381	1.1 (3.4)	0.0081
	Flibanserin 100 mg qhs	371	1.9 (5.3)	

<sup>a</sup> P-value based on Wilcoxon rank sum test.

Notes: FAS = Full analysis set; LOCF = Last observation carried forward; qhs = Once every evening at bedtime; SD = Standard deviation; SSE = Satisfying sexual event.

Source: 511.71 CTR Table 15.2.1: 2, Module 5.3.5.1; 511.75 CTR Table 15.2.1: 2, Module 5.3.5.1; 511.147 CTR Table 15.2.1: 4, Module 5.3.5.1.

**Figure 8**      **SSEs (Standardized) Change from Baseline at Week 24 – Pivotal Phase 3 Studies in Premenopausal Women (FAS, LOCF)**

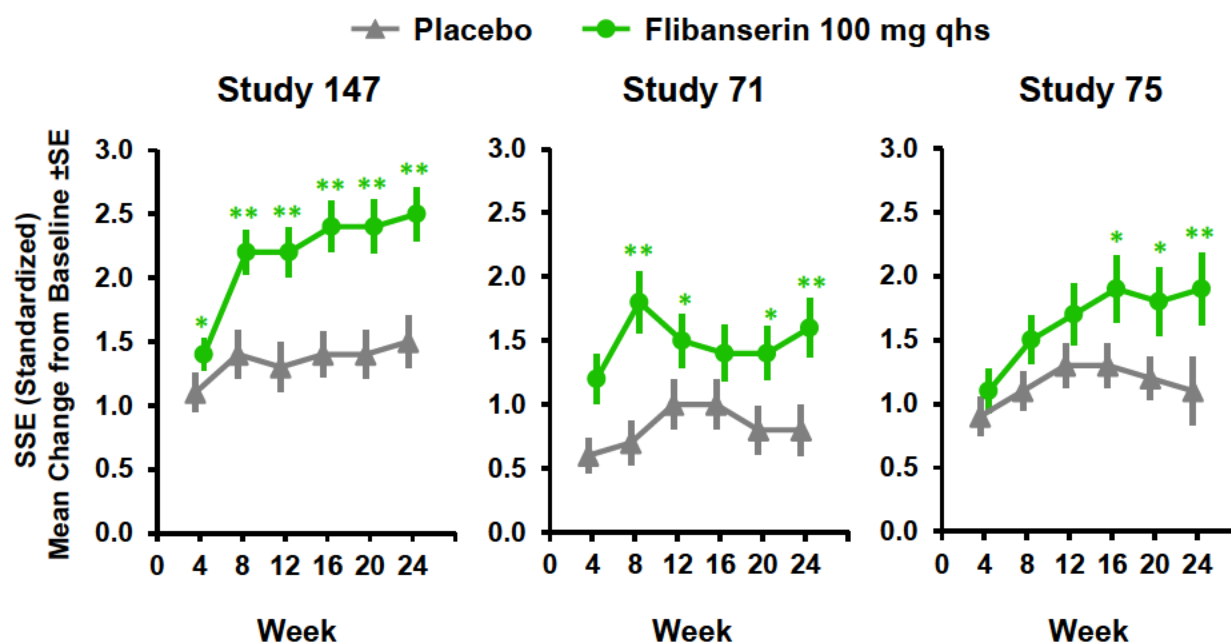


		Study 147	Study 71	Study 75
Placebo	FAS (N)	521	285	381
	Completers (N)	361	219	278
Flibanserin	FAS (N)	500	275	371
	Completers (N)	329	196	245

Notes: FAS = Full analysis set; LOCF = Last observation carried forward; qhs = Once every evening at bedtime; SE = Standard error; SSE = Satisfying sexual event.

Early separation from placebo on mean change from baseline in SSEs was evident in all three studies, and reached nominal statistical significance by Week 4 in Study 147 (Figure 9).

**Figure 9** SSEs (Standardized) Change from Baseline by Visit – Pivotal Phase 3 Studies in Premenopausal Women (FAS, LOCF)



Notes: \* $p < 0.05$ , \*\* $p < 0.01$ .

FAS = Full analysis set; LOCF = Last observation carried forward; qhs = Once every evening at bedtime; SE = Standard error; SSE = Satisfying Sexual event.

Source: Summary of Clinical Efficacy, Figure 1; Figure 10; Figure 20.

### 3.5.2 Sexual Desire

#### 3.5.2.1 FSFI-Desire

Low desire is one of the two hallmark features of HSDD and the 4.8-point FSFI-Desire domain which queries frequency and intensity of desire (scale range: 1.2 – 6.0) is the validated standard instrument for measuring female sexual desire. Mean Change from Baseline in FSFI-Desire at Week 24 was a co-primary endpoint in Study 147. It was also a secondary endpoint in Studies 71 and 75. The flibanserin 100 mg qhs treatment group in each study experienced a statistically significant mean increase in FSFI-Desire compared with the placebo group at Week 24 (Table 10; Figure 10). In terms of absolute numbers, mean FSFI-Desire scores in the flibanserin group improved from a baseline of 1.8 to 1.9, well below the clinical cut point of 3 for classifying women with and without HSDD, to between 2.7 and 2.9 at the end of the 24-week study period.

**Table 10 FSFI-Desire Change from Baseline at Week 24 – Pivotal Phase 3 Studies in Premenopausal Women (FAS, LOCF)**

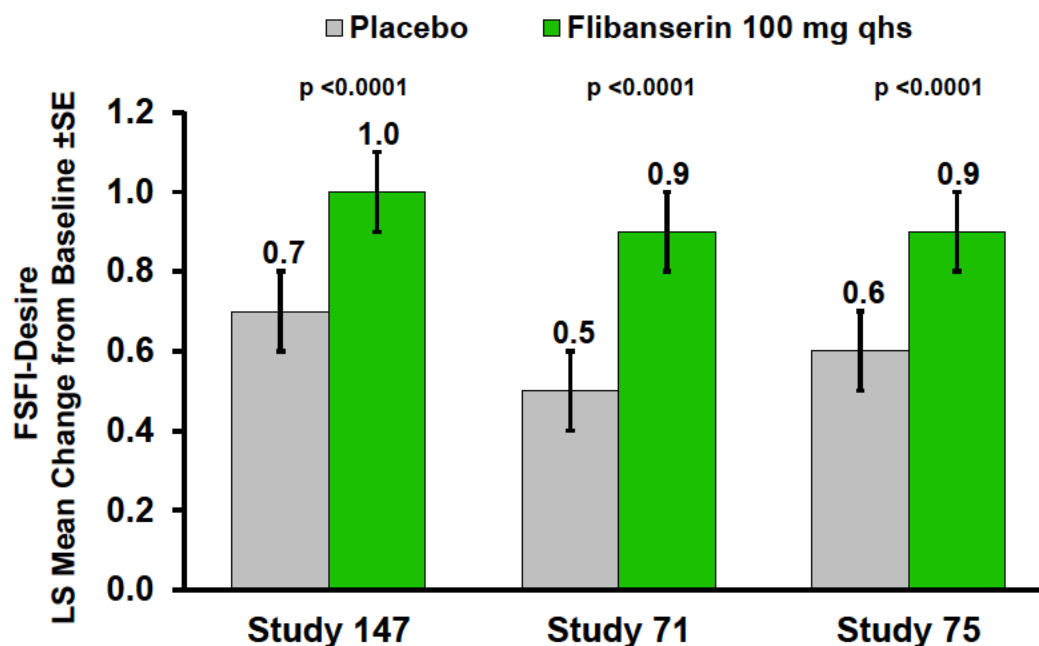
Endpoint FSFI-Desire	Treatment	N	Change from Baseline		
			LS Mean (SE)	LS Diff (SE)	P-value <sup>a</sup>
Study 147	Placebo	525	0.7 (0.1)		
	Flibanserin 100 mg qhs	506	1.0 (0.1)	0.3 (0.1)	<0.0001
Study 71	Placebo	290	0.5 (0.1)		
	Flibanserin 100 mg qhs	280	0.9 (0.1)	0.4 (0.1)	<0.0001
Study 75	Placebo	388	0.6 (0.1)		
	Flibanserin 100 mg qhs	379	0.9 (0.1)	0.3 (0.1)	<0.0001

<sup>a</sup> P-value based on ANCOVA model with main effect terms treatment and pooled center and using baseline as a covariate.

Notes: FAS = Full analysis set; FSFI-Desire = Female sexual function index – desire domain (score range 1.2 – 6); LOCF = Last observation carried forward; LS = Least square; N = Number of subjects; qhs = Once every evening at bedtime; SE = Standard error.

Source: 511.71 CTR Table 15.2.1: 11, Module 5.3.5.1; 511.75 CTR Table 15.2.2.3: 5, Module 5.3.5.1; 511.147 CTR Table 15.2.1: 2, Module 5.3.5.1.

**Figure 10 FSFI-Desire Change from Baseline at Week 24 – Pivotal Phase 3 Studies in Premenopausal Women (FAS, LOCF)**

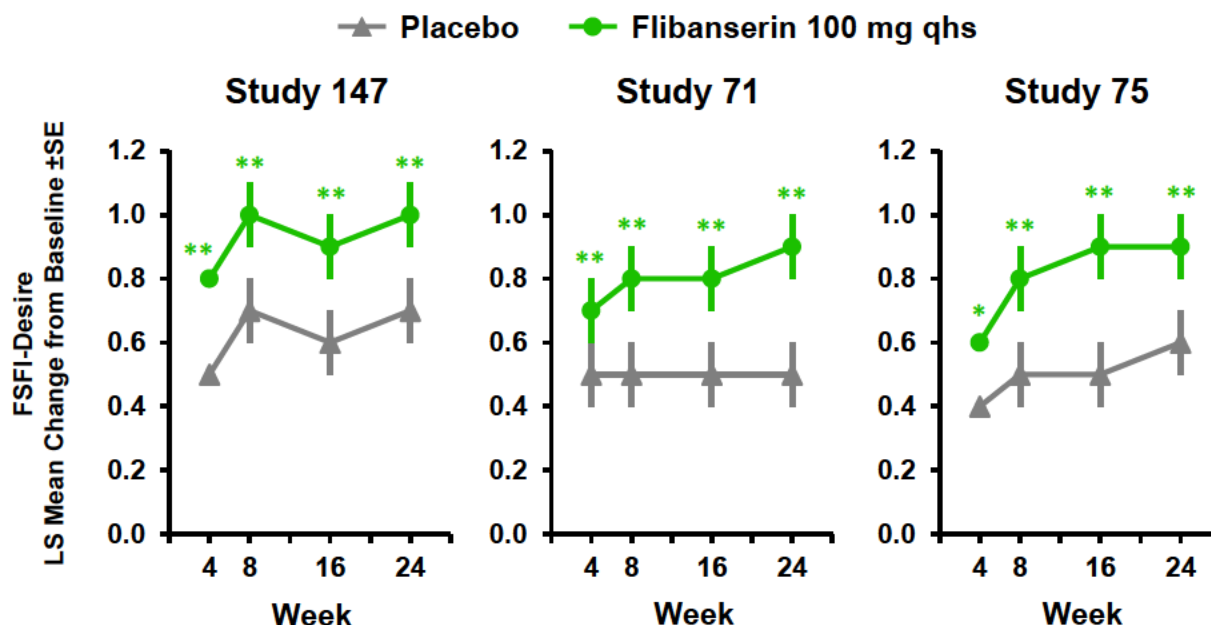


		Study 147	Study 71	Study 75
Placebo	FAS (N)	525	290	388
	Completers (N)	380	236	290
Flibanserin	FAS (N)	506	280	379
	Completers (N)	343	208	261

Notes: FAS = Full analysis set; FSFI-Desire = Female Sexual Function Index – Sexual Desire Domain; LOCF = Last observation carried forward; LS = Least squares; qhs = Once every evening at bedtime; SE = Standard error.

Separation from placebo on mean change from baseline in FSFI-Desire was evident and reached statistical significance by Week 4 in all three pivotal studies (Figure 11).

**Figure 11 FSFI-Desire Change from Baseline by Visit – Pivotal Phase 3 Studies in Premenopausal Women (FAS, LOCF)**



Notes: \*p<0.05, \*\*p<0.01.

FAS = Full analysis set; FSFI-Desire = Female Sexual Function Index – Sexual Desire Domain; LOCF = Last observation carried forward; LS = Least squares; qhs = Once every evening at bedtime; SE = Standard error.

Source: Summary of Clinical Efficacy, Figures 2, 12 and 24.

### 3.5.2.2 eDiary Desire

Mean Change from Baseline in eDiary Desire at Week 24 was not measured in Study 147. It was, however, a co-primary endpoint in the early studies, Studies 71 and 75, and is reported here for completeness. Poor compliance with this instrument was a consistent issue. Of the patients who were active at the end of Studies 71 and 75, only 44.4% of placebo patients and 43.6% of flibanserin patients had eDiary entries on 26 or more days of the 28-day period. Daily recording is inconsistent with the symptom of low desire in HSDD and has repeatedly failed to correlate with other validated instruments in flibanserin clinical studies when all other endpoints showed efficacy. The flibanserin 100 mg qhs treatment group in Studies 71 and 75 experienced a numerically but not statistically significant mean increase in eDiary Desire compared with the placebo group at Week 24 (Table 11, Figure 12).

**Table 11 eDiary Desire (Total Monthly Score) Change from Baseline at Week 24 – Studies 71 and 75 (FAS, LOCF)**

Endpoint eDiary Desire	Treatment	N	Change from Baseline		
			LS Mean (SE)	LS Diff (SE)	P-value <sup>a</sup>
Study 71	Placebo	285	6.9 (0.9)		
	Flibanserin 100 mg qhs	275	9.1 (1.0)	2.2 (1.2)	0.0660
Study 75	Placebo	381	6.8 (0.8)		
	Flibanserin 100 mg qhs	371	8.5 (0.8)	1.7 (1.1)	0.1154

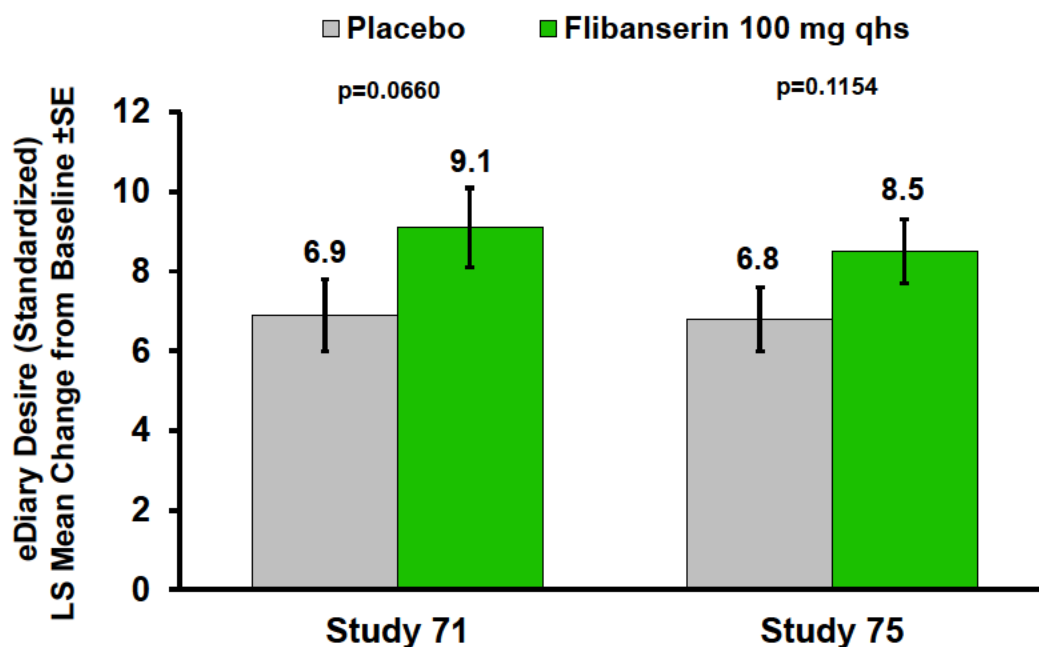
<sup>a</sup> P-value based on ANCOVA model with main effect terms treatment and pooled center and using baseline as a covariate.

Notes: FAS = Full analysis set; LS = Least squares; LOCF = Last observation carried forward; SE = Standard error.

N = Number of subjects; qhs = Once every evening at bedtime; SE = Standard error.

Source: 511.71 CTR, Table 15.2.1: 5, Module 5.3.5.1; 511.75 CTR Table 15.2.1: 5, Module 5.3.5.1.

**Figure 12 eDiary Desire (Standardized) Change from Baseline at Week 24 – Studies 71 and 75 (FAS, LOCF)**



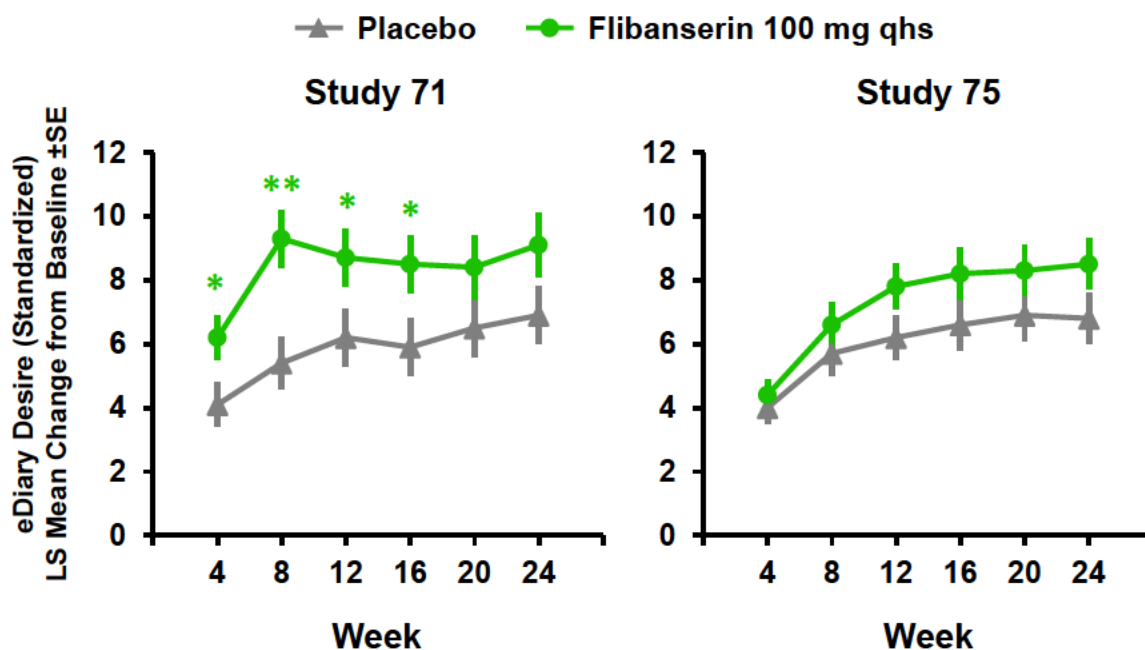
		Study 71	Study 75
Placebo	FAS (N)	285	381
	Completers (N)	219	278
Flibanserin	FAS (N)	275	371
	Completers (N)	196	245

Notes: eDiary = Electronic diary; FAS = Full analysis set; LOCF = Last observation carried forward; LS = Least squares; qhs = Once every evening at bedtime; SE = Standard error.

Separation from placebo on mean change from baseline in eDiary Desire was evident in both studies and reached nominal statistical significance at early time points in Study 71 (Figure 13).



**Figure 13 eDiary Desire (Standardized) Change from Baseline by Visit – Studies 71 and 75 (FAS, LOCF)**



Notes: \* $p < 0.05$ , \*\* $p < 0.01$ .

FAS = Full analysis set; LOCF = Last observation carried forward; LS = Least squares; qhs = Once every evening at bedtime; SE = Standard error.

Source: Summary of Clinical Efficacy Figures 11 and 21.

### 3.5.3 FSDS-R13 (Distress)

Mean Change from Baseline in FSDS-R13 (Distress) at Week 24 was a secondary endpoint in all three pivotal studies. Distress associated with low desire is one of the two hallmark symptoms of HSDD and FSDS-R13 (Distress) is the validated PRO question for measuring that distress. The flibanserin 100 mg qhs treatment group in each study experienced a statistically significant decrease in FSDS-R13 (Distress) as compared with placebo (Table 12, Figure 14). In terms of absolute numbers, mean FSDS-R13 (Distress) scores in the flibanserin group at baseline scores ranged from 3.2 to 3.4, indicating that patients were frequently or always bothered by their low desire. At the end of the 24-week study, mean FSDS-R13 (Distress) scores decreased to between 2.4 and 2.6 indicating that they were occasionally to frequently bothered by their low desire.

**Table 12 FSDS-R13 (Distress) Change from Baseline at Week 24 – Pivotal Phase 3 Studies in Premenopausal Women (FAS, LOCF)**

Endpoint FSDS-R13 (Distress)	Treatment	N	Change from Baseline		
			LS Mean (SE)	LS Diff (SE)	P-value <sup>a</sup>
Study 147	Placebo	525	-0.7 (0.1)		
	Flibanserin 100 mg qhs	506	-1.0 (0.1)	-0.3 (0.1)	0.0001
Study 71	Placebo	289	-0.5 (0.1)		
	Flibanserin 100 mg qhs	280	-0.8 (0.1)	-0.4 (0.1)	0.0001
Study 75	Placebo	389	-0.5 (0.1)		
	Flibanserin 100 mg qhs	380	-0.7 (0.1)	-0.3 (0.1)	0.0006

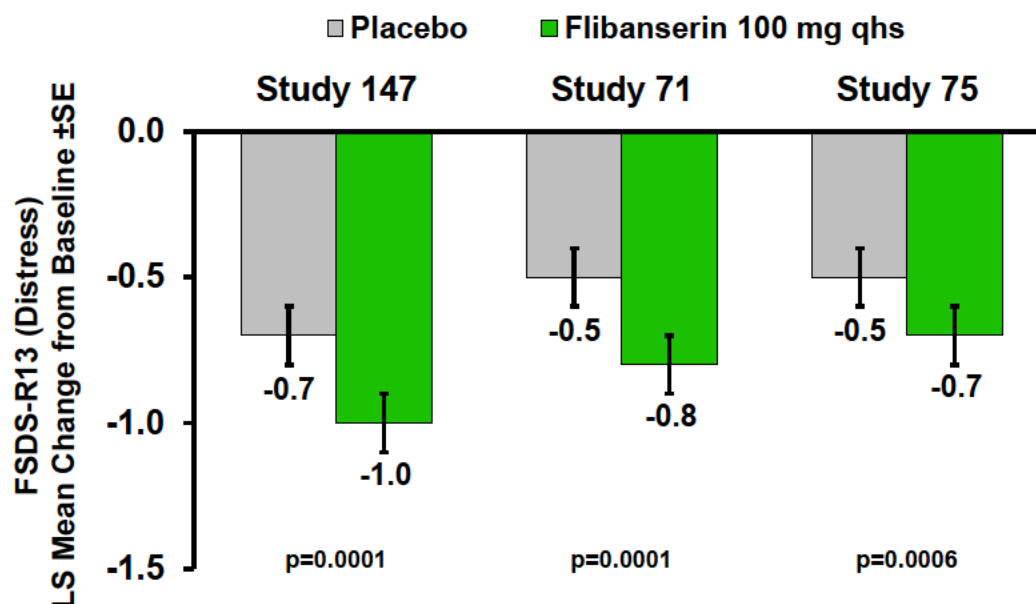
<sup>a</sup> P-value based on ANCOVA model with main effect terms treatment and pooled center and using baseline as a covariate.

Notes: FAS = Full analysis set; FSDS-R13 = Female sexual distress scale-revised Question 13 (range 0 - 4);

LOCF = Last observation carried forward; LS = Least squares; N = Number of subjects; qhs = Once every evening at bedtime; SE = Standard error.

Source: 511.71 CTR Table 15.2.2.2: 4, Module 5.3.5.1; 511.75 CTR Table 15.2.2.2: 4, Module 5.3.5.1.; 511.147 CTR Table 15.2.1: 6, Module 5.3.5.1.

**Figure 14 FSDS-R13 (Distress) Change from Baseline at Week 24 – Pivotal Phase 3 Studies in Premenopausal Women (FAS, LOCF)**

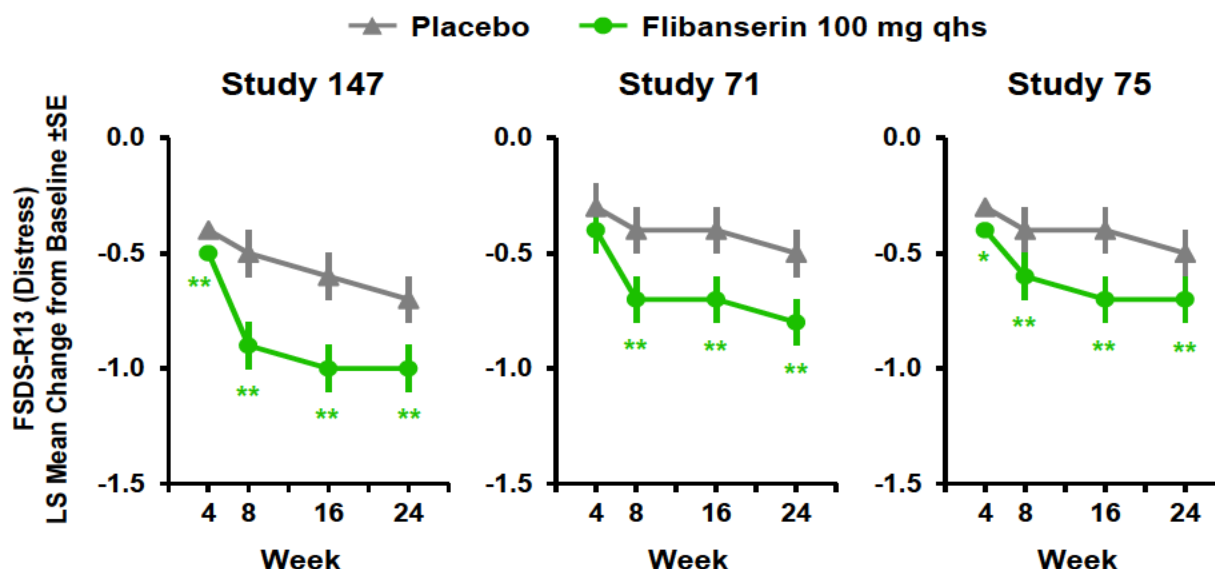


		Study 147	Study 71	Study 75
Placebo	FAS (N)	525	289	389
	Completers (N)	426	235	290
Flibanserin	FAS (N)	506	280	380
	Completers (N)	391	208	261

Notes: FSDS-R13 (Distress) = Female Sexual Distress Scale – Revised Question 13; FAS = Full analysis set; LOCF = Last observation carried forward; LS = Least squares; qhs = Once every evening at bedtime; SE = Standard error.

Separation from placebo on mean change from baseline in FSDS-R13 (Distress) was evident and reached nominal statistical significance by Week 4 in Studies 75 and 147 and by Week 8 in Study 71 (Figure 15).

**Figure 15 FSDS-R13 (Distress) Change from Baseline by Visit – Pivotal Phase 3 Studies in Premenopausal Women (FAS, LOCF)**



Notes: \* $p < 0.05$ , \*\* $p < 0.01$ .

FAS = Full analysis set; FSDS-R13 (Distress) = Female sexual distress scale – revised question 13; LOCF = Last observation carried forward; LS = Least squares; qhs = Once every evening at bedtime; SE = Standard error.

Source: Summary of Clinical Efficacy, Figures 3, 14 and 23.

### 3.6 Results Across all Efficacy Measures

In the initial pivotal program (Studies 71 and 75) flibanserin demonstrated statistically significant superiority to placebo on only one of two co-primary endpoints, change in SSEs. Regarding improvements in desire, flibanserin showed separation from placebo on eDiary Desire (primary) but that difference did not reach statistical significance. Consistent with the recommendations of FDA and its advisory committee, the Sponsor completed an additional pivotal study (Study 147) with the goal of demonstrating statistically significant improvements over placebo on two co-primary measures, SSEs and a validated and consistent instrument for measuring desire (FSFI-Desire), and on a key secondary measure of distress associated with low desire (FSDS-R13 (Distress)). Study 147 was successful on each of these required endpoints, as well as all other secondary measures of efficacy. Secondary endpoints for Studies 71 and 75 are also presented below, along with nominal p-values, to provide a sense of the consistency of the results across studies.

Across the pivotal program, flibanserin consistently demonstrated statistically robust improvements over placebo on changes in SSEs, desire and distress in three studies. The magnitude of those changes is remarkably reproducible (Table 13).

**Table 13 Mean Change from Baseline to Week 24 in Primary and Secondary Endpoints – Pivotal Phase 3 Studies in Premenopausal Women**

	Study Number								
	71			75			147		
	Placebo (N = 290)	Flibanserin 100 mg qhs (N = 280)	P-value	Placebo (N = 389)	Flibanserin 100 mg qhs (N = 380)	P-value	Placebo (N = 536)	Flibanserin 100 mg qhs (N = 532)	P-value
SSEs (SD)	0.8 (3.4)	1.6 (3.8)	0.0024 <sup>a</sup>	1.1 (3.4)	1.9 (5.3)	0.0081 <sup>a</sup>	1.5 (4.5)	2.5 (4.6)	<0.0001 <sup>a</sup>
FSFI-Desire (SE)	0.5 (0.1)	0.9 (0.1)	<0.0001	0.6 (0.1)	0.9 (0.1)	<0.0001	0.7 (0.1)	1.0 (0.1)	<0.0001 <sup>a</sup>
eDiary Desire (SE)	6.9 (0.9)	9.1 (1.0)	0.0660 <sup>a</sup>	6.8 (0.8)	8.5 (0.8)	0.1154 <sup>a</sup>	ND	ND	ND
FSDS-R13 (Distress) (SE)	-0.5 (0.1)	-0.8 (0.1)	0.0001	-0.5 (0.1)	-0.7 (0.1)	0.0006	-0.7 (0.1)	-1.0 (0.1)	0.0001

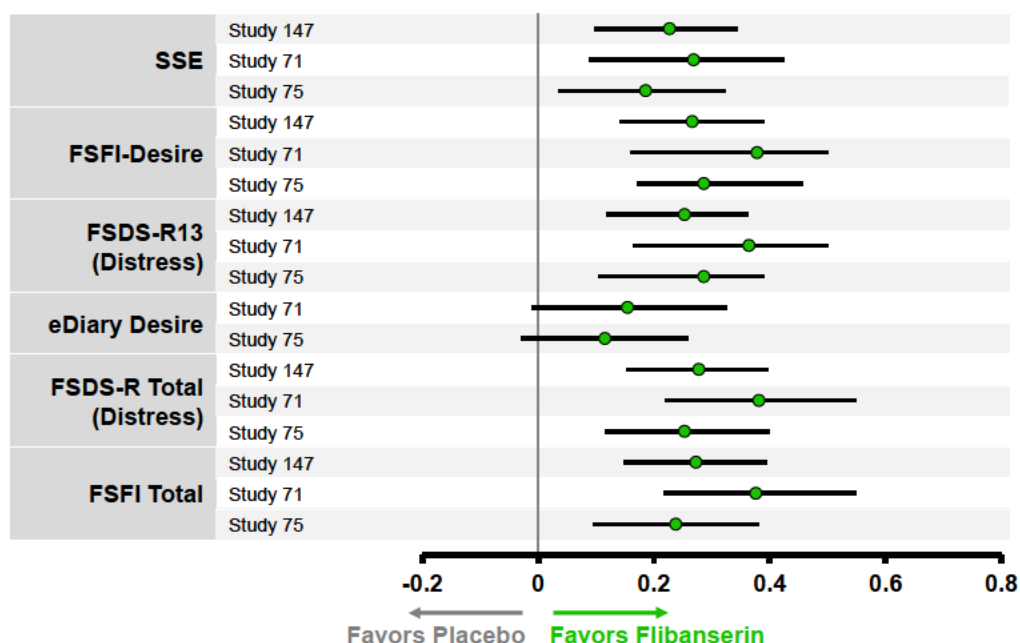
<sup>a</sup> Primary endpoint.

Notes: eDiary desire (range: 0-no upper limit); FSDS-R13 = Female sexual distress scale revised – Question 13 (range: 0-4); FSFI-Desire = Female sexual function index – sexual desire domain (range: 1-6); ND = Not done; SD = Standard deviation; SE = Standard error; SSE = Satisfying sexual events (range: 0-no upper limit).

Source: Module 2.7.3, Tables 5, 6, 7 (511.147); Tables 13, 14, 15, 17 (511.71); Tables 21, 22, 24, 25 (511.75).

Efficacy across these primary and secondary endpoints in the pivotal studies is shown in a Forest plot in Figure 16. Because each endpoint is measured on a different scale, mean differences from placebo and the upper and lower bounds of the 95% CI were transformed by dividing each variable by its standard deviation. The x-axis does not provide comparative treatment effect information across endpoints. What the diagram does illustrate are the consistent statistically significant improvements of flibanserin over placebo in all primary and secondary endpoints with the eDiary Desire measurement as the outlier.

**Figure 16 Differences from Placebo (95% CI) for Primary and Secondary Efficacy Endpoints (Standardized) – Pooled Pivotal Phase 3 Studies in Premenopausal Women (FAS, LOCF)**

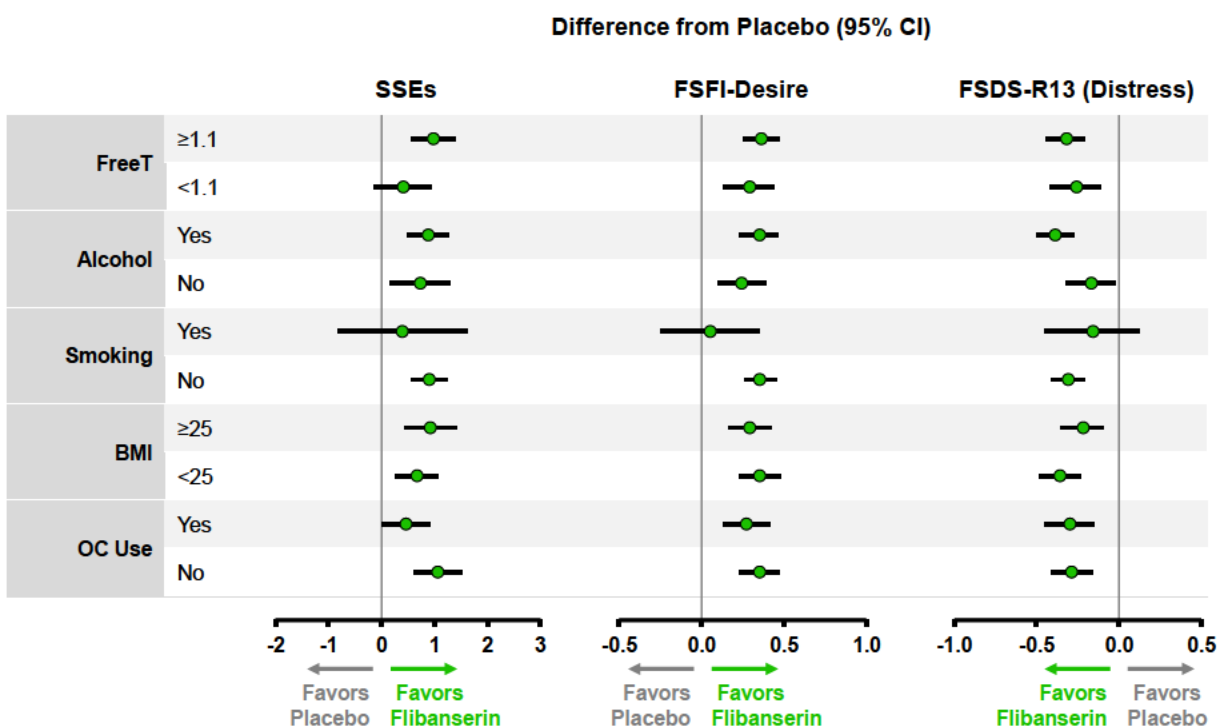


Notes: CI = Confidence interval; FAS = Full analysis set; FSDS-R (Distress) = Female sexual distress scale - revised; FSDS-R13 (Distress) = Female sexual distress scale - revised question 13; FSFI = Female sexual function index; FSFI-Desire = Female sexual function index – sexual desire domain; LOCF = Last observation carried forward; SSE = Satisfying sexual event.

Source: Summary of Clinical Efficacy Figure 30.

Efficacy was also assessed across subsets of patients by various baseline factors of interest: free testosterone levels, alcohol use, smoking status, body mass index (BMI), and oral contraceptive use. Only smoking status appeared to consistently affect efficacy across endpoints with current smokers showing a diminished effect of therapy (Figure 17).

**Figure 17 Forest Plot of Difference from Placebo in Mean Change (95% CI) from Baseline in SSEs, FSFI-Desire and FSDS-R13 (Distress) at Week 24 – Pooled Pivotal Phase 3 Studies in Premenopausal Women (FAS, LOCF)**



Notes: BMI=body mass index; CI=confidence interval; FreeT=free testosterone; FSDS-R13 (Distress)=Female Sexual Distress Scale – Revised Item 13; FSFI-Desire=Female Sexual Function Index – Sexual Desire Domain; OC=oral contraceptive; SSE=satisfying sexual event.

### 3.7 Clinically Meaningful Benefit in HSDD

#### 3.7.1 Benefit across Sexual Function Domains

The totality of the patient's perception of improvement in her condition is what ultimately determines treatment success. Because HSDD is a multifaceted disorder, predominantly, but not exclusively impacting sexual desire, various domains of sexual response such as arousal and orgasm, as well as desire, play a part in measuring overall satisfying and healthy sexuality. An assessment of the effect of flibanserin on instruments that take a broader view of sexual function permits a broader understanding of the overall benefit to the patients.

Across all pivotal studies, at Week 24, mean change from baseline for flibanserin 100 mg qhs was statistically superior to placebo for the FSFI Total Score, which includes domains assessing sexual desire, sexual arousal, lubrication, orgasm, sexual satisfaction and pain. In terms of absolute numbers, mean FSFI Total Scores in the flibanserin group increased to 24.3 in Study 147, 24.5 in Study 71, and 23.2 in Study 75 at the end of the 24-week study period approaching the clinical cut point of >26.5. With the exception of the pain domain which would

not be expected to correlate with HSDD, flibanserin demonstrated benefit over placebo in all individual domains including sexual satisfaction.

Across all pivotal trials, at Week 24, mean change from baseline for flibanserin 100 mg qhs was statistically superior to placebo for the FSDS-R (Distress) Total Score, which measures sexually-related personal distress including feelings of guilt, frustration, inferiority, inadequacy, embarrassment and dissatisfaction. In terms of absolute numbers, mean FSDS-R (Distress) Total Scores in the flibanserin group decreased to 23.4 in Study 147, 21.2 in Study 71, and 22.8 in Study 75 at the end of the 24-week study period coming closer to the clinical cut point of <15 on the 0 – 52 point scale of distress.

### **3.7.2 Pre-specified Responder Analysis**

Recognizing that even consistent, robust statistically significant efficacy measured via a numeric change on one or more PRO instruments may not adequately capture the potential treatment benefit to the patient, the clinical development program included a pre-specified analysis method (i.e., PGI-I-anchored responder analysis) for assessing the clinical meaningfulness of flibanserin's effects to patients suffering from HSDD. An anchored responder analysis provides objective evidence that the totality of the patient experience described above via secondary and exploratory analyses is meaningful and beneficial to the patient.

The pre-specified responder analysis was conducted in several steps. First, PGI-I results were collected from all subjects at all visits. The PGI-I provides ordinal responses from 1 (very much improved) to 7 (very much worse) to the question, "How is your condition – meaning decreased sexual desire and being bothered by it – today compared to when you started study medication?"

In the second step, each patient's PGI-I scores (regardless of time point or treatment group) was mapped to her corresponding score for each key endpoint (SSEs, FSFI-Desire, FSDS-R13 (Distress)). For each endpoint, the difference in mean improvement from baseline between the values that corresponds to a PGI-I of 3 (minimally improved) and the values that corresponds to a PGI-I of 4 (no change) across patients was used as the response threshold, or the point that begins to differentiate a responder from a non-responder.

This threshold served as the point cut-off between responders and non-responders. Taking distress based on the FSDS-R13 (Distress) in Study 147 as an example, a decrease of 0.5 (-0.5) on the 0 – 4 point scale defined a responder based on the difference in mean FSDS-R13 (Distress) scores that corresponded to a PGI-I of 3 versus 4. Thus, this method specifically anchored each key endpoint to patient self-identification of improvement.

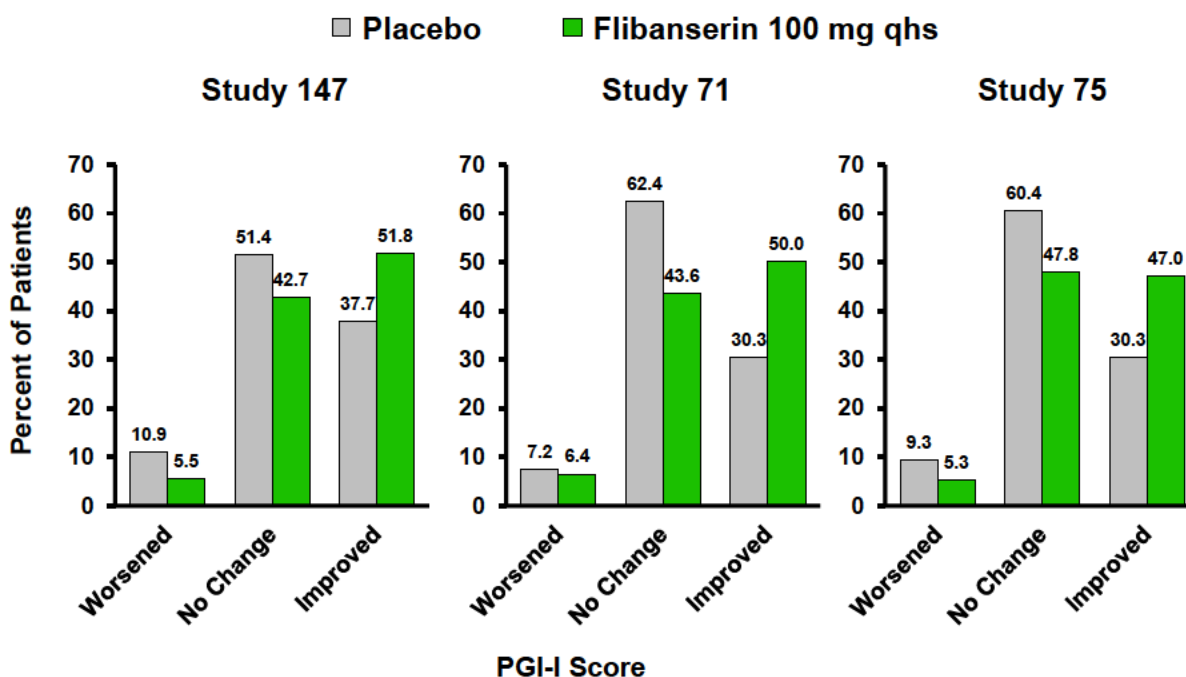
In the final step, for each endpoint, those response thresholds were applied across the entire study population to define a responder as a patient with a change from baseline at Week 24 equal to or greater than the response threshold for that endpoint: SSEs, FSFI-Desire, FSDS-R13 (Distress). Continuing with the example from the last paragraph, based on the responder



criterion of a 0.5 decrease in FSDS-R13 (Distress), 48.0% of placebo subjects and 59.7% of flibanserin subjects in Study 147 were classified as FSDS-R13 (Distress) responders and the difference between the two treatment groups was highly statistically significant ( $\Delta=11.8\%$ ;  $p=0.0001$ ).

Step one, PGI-I distribution, when applied across all studies and endpoints, consistently demonstrates that greater numbers of patients randomized to flibanserin report improvement and greater numbers of patients randomized to placebo reporting no change or worsening (Figure 18). This distribution is consistent with a treatment effect.

**Figure 18** Percent of Patients by Patient Global Impression of Improvement (PGI-I) Score at Week 24 – Pivotal Phase 3 Studies in Premenopausal Women (FAS, LOCF)



Notes: FAS = Full analysis set; Improved = Minimally improved, much improved and very much improved; LOCF = Last observation carried forward; PGI-I = Patient Global Impression of Improvement; qhs = Once every evening at bedtime; Worsened = Much worse and very much worse.

Results of step two – defining response thresholds based on the endpoint values that correspond to the difference between a PGI-I score of 3 versus a PGI-I score of 4 – are shown in Table 14.



**Table 14 Response Thresholds Established via PGI-I Anchoring – Pivotal Phase 3 Studies in Premenopausal Women**

	Study Number		
	147	71	75
SSE	$\geq 1.7$	$\geq 1.22$	$\geq 1.25$
FSFI-Desire	$\geq 0.9$	$\geq 0.83$	$\geq 0.74$
FSDS-R13 (Distress)	$\leq -0.5$	$\leq -0.44$	$\leq -0.41$

Notes: FSDS-R13 = Female sexual distress scale revised – Question 13; FSFI-Desire = Female sexual function index – sexual desire domain; PGI-I = Patient Global Impression of Improvement; SSE = Satisfying sexual events.

Results of the final step – application of these thresholds to the treatment groups to determine percent responders for each endpoint – shows that between 43% and 60% of flibanserin-treated patients were responders on one or more of the three important endpoints across all three pivotal studies with margins of responder superiority of 9.4% to 14.6% over placebo across endpoints (Table 15, Figure 19).

**Table 15 Number (%) of Responders (PGI-I Anchor Criteria) and Percent Differences across Efficacy Endpoints at Week 24 – Pivotal Phase 3 Studies in Premenopausal Women (FAS, LOCF)**

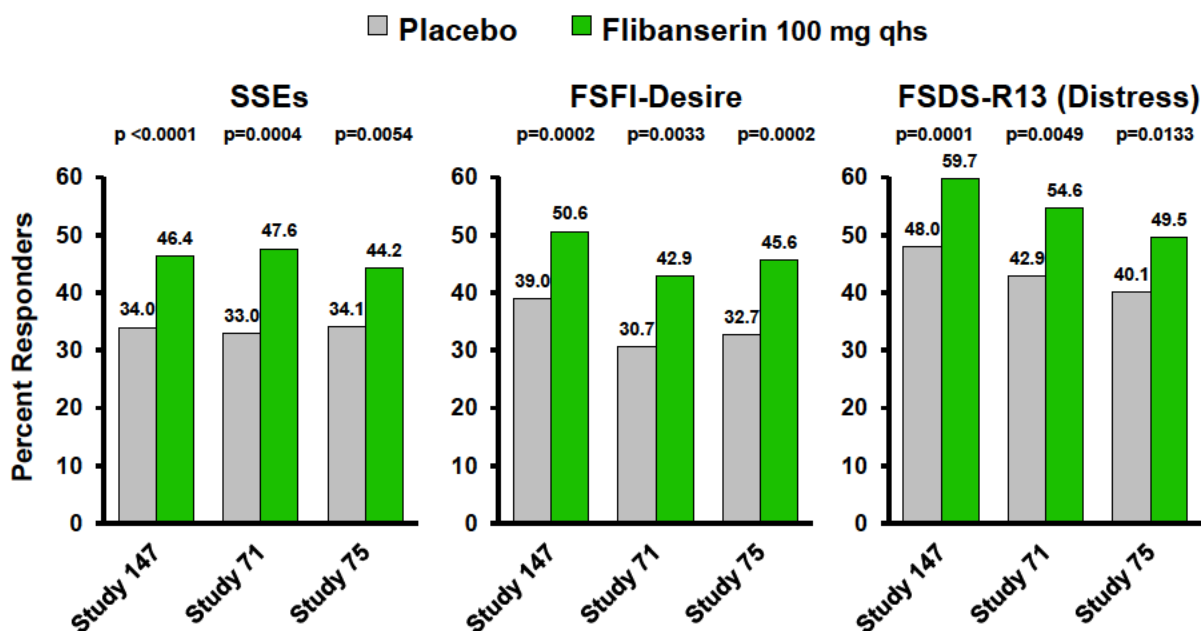
	Flibanserin 100 mg qhs		Placebo		Difference in Percent	P-value
	N	n (%)	N	n (%)		
147						
SSEs	500	232 (46.4)	521	177 (34.0)	12.4 <sup>a</sup>	<0.0001
FSFI-Desire	506	256 (50.6)	525	205 (39.0)	11.6 <sup>a</sup>	0.0002
FSDS-R13 (Distress)	506	302 (59.7)	525	252 (48.0)	11.7	0.0001
71						
SSEs	275	131 (47.6)	285	94 (33.0)	14.6 <sup>a</sup>	0.0004
FSFI-Desire	280	120 (42.9)	290	89 (30.7)	12.2	0.0033
FSDS-R13 (Distress)	280	153 (54.6)	289	124 (42.9)	11.7	0.0049
75						
SSEs	371	164 (44.2)	381	130 (34.1)	10.1 <sup>a</sup>	0.0054
FSFI-Desire	379	173 (45.6)	388	127 (32.7)	12.9	0.0002
FSDS-R13 (Distress)	380	188 (49.5)	389	156 (40.1)	9.4	0.0133

<sup>a</sup> Primary endpoint measure.

Notes: FAS = Full analysis set; FSDS-R13 = Female sexual distress scale revised – question 13; FSFI-Desire = Female sexual function index – sexual desire domain; LOCF = Last observation carried forward; N = Number of subjects; n = Number of subjects responding; qhs = Once every evening at bedtime; SSE = Satisfying sexual events (range: 0-no upper limit).

Source: Module 2.7.3 Table 57.

**Figure 19 Number (%) of Responders (PGI-I Anchor Criteria) across Efficacy Endpoints – Pivotal Phase 3 Studies in Premenopausal Women**

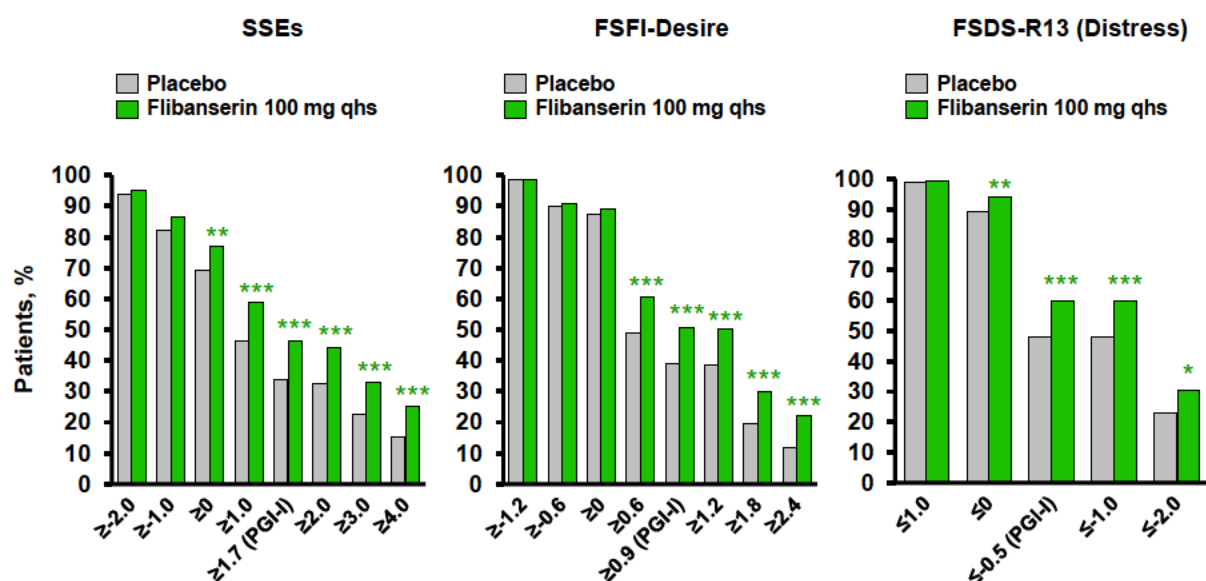


Endpoint		SSE			FSFI-Desire			FSDS-R13 (Distress)		
Study		147	71	75	147	71	75	147	71	75
Placebo	FAS (N)	521	285	381	525	290	388	525	289	389
	Completers (N)	361	219	278	380	236	290	426	235	290
	Responders (n)	177	94	134	205	89	127	252	124	156
Flibanserin	FAS (N)	500	275	371	506	280	379	506	280	380
	Completers (N)	329	196	245	343	208	261	391	208	261
	Responders (n)	232	131	165	256	120	173	302	153	188

Notes: FAS = Full analysis set; FSDS-R13 (Distress) = Female Sexual Distress Scale – Revised Question 13; FSFI-Desire = Female Sexual Function Index – Sexual Desire Domain; SSE = Satisfying sexual event.

The PGI-I effect is not an artifact of the PGI-anchored responder definition. For example, a responder based on PGI-I anchored distress in Study 147 was any patient with a decrease of 0.5 (-0.5), or a change equivalent to 10% of the overall 0-4 point scale of FSDS-R13 (Distress). Employing more stringent criteria such as a decrease of 1.0 or 2.0 (-1.0 or -2.0) on FSDS-R13 (Distress) (i.e., a change of 20% or 40% on the overall 0-4 scale) or looking at responders for SSEs or FSFI-D also resulted in significant differences between placebo and flibanserin 100 mg in all studies. Results from Study 147 are shown in Figure 20.

**Figure 20 Number (%) of Responders Using Various PGI-I Anchor Criteria across Efficacy Endpoints – Study 147**



Notes: \* $p \leq 0.05$ ; \*\* $p \leq 0.001$ ; \*\*\* $p \leq 0.0001$ .  
FSDS-R13=Female Sexual Distress Scale-Revised Item 13; FSFI-Desire=Female Sexual Function Index-Sexual Desire Domain; PGI-I=Patient Global Impression of Improvement; qhs=once every evening at bedtime; SSE=satisfying sexual event.

The large placebo response in the flibanserin studies is typical of symptom-improvement studies of CNS-active drugs in which study participation, behavioral modification, intensive contact with study staff and clinicians, and diary keeping play a role in perception of benefit. For conditions like HSDD in which a large placebo response is characteristic, drug development faces the risk that a clinical study that was considered to be adequately powered may nonetheless fail to show statistically significant results. In the case of flibanserin, however, response to flibanserin exceeded the response to placebo in all three pivotal studies and was consistent even when multiple alternative endpoints and time points were assessed in sensitivity analyses, indicating a statistically robust and generalizable effect. The consistency and magnitude of the placebo-corrected flibanserin effect is especially compelling in light of the strong placebo response.

The pre-specified PGI-I responder analysis allows patients with HSDD to personally determine the individual benefit of flibanserin's treatment effect. As shown in Table 15 above, 43 to 60% of flibanserin patients in the pivotal program exceeded the patient-anchored criteria for improvement for each measured endpoint. The 43% - 60% of patients who were flibanserin responders reported mean changes in key symptoms that often more than doubled the effect in the overall flibanserin population (Table 16) with an approximately two point increase on the 4.8-point desire scale and an approximately 1.8 point improvement on the 5-point distress scale and an increase of more than 5 SSEs per month over baseline.

**Table 16 Mean Change from Baseline at Week 24 on Primary and Secondary Endpoints – Flibanserin Group Pivotal Phase 3 Studies in Premenopausal Women (FAS and Responder Populations)**

	Study Number					
	147		71		75	
	FAS	Responder	FAS	Responder	FAS	Responder
SSEs	2.5 (n = 500)	5.7 (n=239)	1.6 (n = 275)	4.3 (n = 131)	1.9 (n = 371)	5.2 (n=164)
FSFI-Desire	1.0 (n = 506)	2.0 (n=256)	0.9 (n = 280)	2.0 (n = 120)	0.9 (n = 379)	1.9 (n=173)
FSDS-R13 (Distress)	-1.0 (n = 506)	-1.8 (n=302)	-0.8 (n = 280)	-1.8 (n = 153)	-0.7 (n = 380)	-1.7 (n=188)

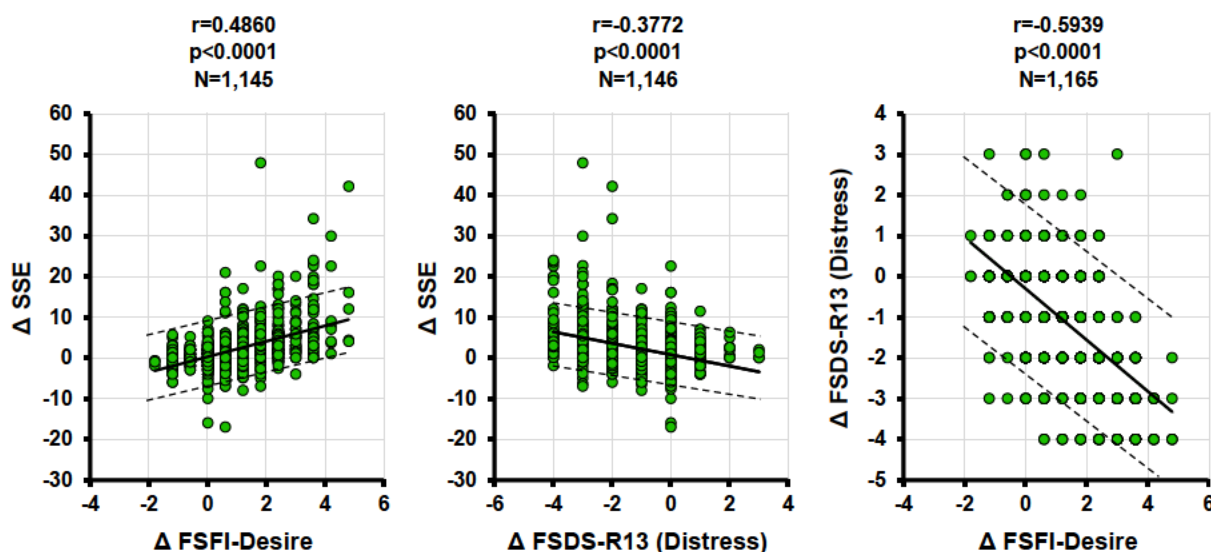
Notes: FAS = Full analysis set; FSDS-R13 = Female sexual distress scale revised – Question 13 (range: 0 - 4); FSFI-Desire = Female sexual function index – sexual desire domain (range: 1.2 - 6); SSE = Satisfying sexual events (range: 0-no upper limit).

Source: Ad hoc analysis.

### 3.7.3 Consistent Effect Across Symptoms

Exploratory correlation analyses of responders across the efficacy endpoints of SSE, FSFI-Desire and FSDS-R13 (Distress) as shown in Figure 21.

**Figure 21 Correlation between Key Efficacy Endpoints – Pooled Pivotal Phase 3 Studies in Premenopausal Women (FAS, LOCF)**



Notes: FSFI-Desire=Female Sexual Function Index – Desire Domain; FSDS-R13 (Distress)=Female Sexual Distress Scale – Revised Item 13;  $r$ =Pearson correlation coefficient; SSE=satisfying sexual event. Regression lines (solid) with the 95% prediction bands (dashed) are shown superimposed on the scatterplot.

Responders for each pair of these three endpoints were significantly correlated ( $p<0.0001$ ) with one another. In general, decreasing distress and increasing desire were both predictably

correlated with increasing SSEs. The strongest correlation was between the endpoints measuring desire (FSFI-Desire) and distress associated with low desire (FSDS-R13 (Distress)), which are the primary diagnostic characteristics for HSDD. As SSEs are a downstream manifestation of desire, correlations between SSE and the other two endpoints were less dramatic, as indicated by the lower Pearson correlation coefficients (see [Figure 21](#)). A alignment of response across the three symptoms suggests that flibanserin addresses the overall experience of the condition in a robust and meaningful way.

### **3.7.4 Other Indicators of Meaningfulness**

In 2004 FDA sought the advice of its advisory committee on the topic of clinically meaningful changes in SSEs [Intrinsic Reproductive Health Drugs Advisory Committee (RHDAC) Meeting, 2 December 2004, Transcript]. When asked to vote on the clinical meaningfulness of one additional SSE per month in postmenopausal women suffering from HSDD, 14 out of 17 RHDAC members noted that a single additional SSE per month was meaningful to patients, recognizing that large increases in frequency of events are not necessary for achievement of benefit. This view is supported in the published literature as well [Kingsberg, 2014; Symonds, 2007] with a survey of 450 women (306 premenopausal) with low sexual desire and associated distress in which 95% responded that a change of 1 - 2 SSEs per month was meaningful.

As was evident at FDA's 27 October 2014 PFDD Meeting, women suffering from HSDD seek sufficient improvement in their sexual desire to have it no longer be distressing. Flibanserin restores desire and reduces distress, thereby improving the two hallmark symptoms of HSDD. Women in the flibanserin pivotal program had suffered from HSDD symptoms for a mean of over 4 years at baseline – nearly half the mean length of their relationships. Across measures of sexual activity, desire and distress, 43-60% of the patients in the flibanserin pivotal trials saw improvement in their condition. The gains achieved with flibanserin in just 6 months are very clinically meaningful to these long-suffering women with HSDD who seek movement toward more satisfying sexual health that is more in line with their previous personal experience of unimpaired sexual function.

The feedback from HSDD patients and experts at the 27 - 28 October 2014 PFDD Meeting, the unmet need for non-hormonal, safe, effective and approved therapies for HSDD, the near-normalization of sexual desire and distress in the flibanserin pivotal program and the PGI-I analysis from the flibanserin pivotal studies, each provide evidence that the magnitude of effect demonstrated by flibanserin is clinically meaningful and an important improvement for HSDD.

## 4 SAFETY

### 4.1 Datasets

The extensive nature of the flibanserin development program has led to a large safety database with significant exposure experience at various doses, dosing regimens, and patient populations.

Overall, 17,940 subjects/patients have participated in the flibanserin development programs, including studies of healthy normal volunteers (1,427), patients with major depressive disorder (2,439) and patients with HSDD (14,074) patients. In these studies, 10,713 individuals have been exposed to flibanserin (1,122 healthy volunteers, 1,366 patients with major depressive disorder and 8,225 patients with HSDD). Of these 10,713 individuals exposed to flibanserin, 7,922 patients took 100 mg qd with 5,636 patients taking the recommended dosing regimen of 100 mg qhs. The size of this database is considerably in excess of the 1,500 subject minimum threshold required by FDA and other regulatory agencies for premarket assessment of novel drug therapies intended for chronic administration, and establishes a well-characterized safety profile for flibanserin [FDA, 2005; ICH, 1994].

Experience with longer-term flibanserin exposure is also fairly extensive. In long-term, open-label studies in pre and postmenopausal women, 2,521 patients have been exposed to flibanserin for at least six months (1,819 at flibanserin 100 mg qhs) and 1,096 patients have been exposed to flibanserin for at least one year (852 at flibanserin 100 mg qhs). Exposures limited to the premenopausal population are also extensive as shown in Table 17. These exposure levels, also significantly in excess of the established FDA minimum threshold for new chronic use drugs (i.e., 300 - 600 subjects exposed for 6 months and 100 subjects exposed for a year) serve to provide further information regarding long term effects [FDA, 2005; ICH, 1994].

**Table 17 Overall Exposure to Flibanserin – Phase 3 Studies in Premenopausal Women (Target Population Set) and Open Label Safety Studies**

Duration of Exposure	Flibanserin 100 mg qhs	Flibanserin Any Dose	Minimum FDA Threshold <sup>a</sup>
Overall Exposure	2997	5014	1500
≥6 months	1672	2257	300-600
≥12 months	850	1065	100
≥18 months	88	113	Not applicable

<sup>a</sup> FDA Guidance for Industry. Premarketing Risk Assessment. March 2005.

Notes: FDA = Food and Drug Administration; qhs = Once every evening at bedtime.

Source: ISS Ad Hoc Table 1.5.9.

The overall safety review in this briefing document is focused on data across all doses and dosing regimens from the 5 double-blind, randomized, placebo-controlled studies in the intended population: premenopausal women with HSDD (the Target Population Set). These five studies are comprised of the three pivotal studies discussed in the efficacy section (Studies 71, 75 and



147), as well as the Alternate Dose Study and the EU Study and include over 1500 patient years of flibanserin exposure. The 48-Week Withdrawal Study conducted in premenopausal patients is not included because its unique design has the potential to inflate placebo-associated AE rates while diminishing flibanserin-reported AE rates. The 12-Week SSRI/SNRI Study conducted in depressed patients is also not included because of population difference but is included in the overall summary of safety data across Phase 3 studies in the combined pre- and postmenopausal population (the Treated Set). Summary safety data for the Treated Set, comprising over 1800 patient years of exposure is provided in [Appendix F](#).

When discussing rare events, this safety review includes all available data from all Phase 3 studies including uncontrolled open label extension studies in an effort to increase signal detection power by looking across a larger data set.

Finally, this safety review summarizes safety data from Phase 1 studies in special populations or circumstances (e.g., drug-drug interaction studies) when appropriate to address specific safety questions. Included among these studies is the recently completed Next-Day Driving and Cognition Study requested by the FDA.

## 4.2 Overall Exposure

Across the five double-blind, randomized, placebo-controlled studies in the premenopausal HSDD population, a total of 3,973 women received flibanserin, 1,543 of these at the 100 mg qhs dose ([Table 18](#)).

**Table 18 Exposure by Non-overlapping Intervals - Phase 3 Studies in Premenopausal Women (Target Population Set) and Open Label Safety Studies**

Non-overlapping Interval, Days <sup>a</sup>	Placebo N = 1905	Flibanserin				Total N = 3973
		25 mg bid N = 733	50 mg qhs N = 969	50 mg bid N = 728	100 mg qhs N = 1543	
Exposure, Days, n (%)						
1-28	87 (4.6)	40 (5.5)	53 (5.5)	80 (11.0)	102 (6.6)	275 (6.9)
29-60	137 (7.2)	85 (11.6)	82 (8.5)	93 (12.8)	160 (10.4)	420 (10.6)
61-90	90 (4.7)	28 (3.8)	56 (5.8)	44 (6.0)	78 (5.1)	206 (5.2)
91-135	108 (5.7)	47 (6.4)	59 (6.1)	52 (7.1)	92 (6.0)	250 (6.3)
136-180	1299 (68.2)	465 (63.4)	605 (62.4)	411 (56.5)	1004 (65.1)	2485 (62.5)
≥181	184 (9.7)	68 (9.3)	114 (11.8)	48 (6.6)	106 (6.9)	336 (8.5)
Mean	147.4	141.4	144.0	127.6	139.0	138.6
SD	49.56	54.83	53.02	61.96	55.23	56.19
Exposure, Patient Years	768.5	283.8	382.1	254.3	586.7	1506.9

<sup>a</sup> Subjects may be included in multiple dose groups.

Notes: bid = Twice daily; qhs = Once every evening at bedtime; SD = Standard deviation.

Includes Studies 511.70, 511.71, 511.75, 511.77, 511.84, 511.118, 511.133, and 511.147.

Source: ISS Table 1.5.1, Module 5.3.5.3.

Exposures beyond 6 months were obtained via open-label, follow-on extension studies in which all Phase 3 subjects were eligible to roll over to flibanserin (flexible dose) regardless of their randomized treatment group in the randomized, double-blind study. The duration of flibanserin exposure in the open label extension studies is provided in [Table 19](#).

**Table 19 Overall Exposure to Flibanserin – Phase 3 Studies in Premenopausal Women (Target Population Set) and Open Label Safety Studies**

Duration of Exposure	Flibanserin Exposure Population (n)			
	All Doses Groups		100 mg qhs	
	Pre and Post-menopausal	Premenopausal	Pre and Post-menopausal	Premenopausal
>6 months	2394	2257	1809	1672
>12 months	1066	1065	851	850
>18 months	114	113	89	88

Notes: qhs = Once every evening at bedtime.

Includes Studies 511.70, 511.71, 511.75, 511.77, 511.84, 511.114, 511.118, 511.130, 511.133, 511.147 and 511.156.

Source: ISS Table 1.5.9.

Rollover study data were consistent with the flibanserin safety profile seen in the Phase 3 studies with no new safety signals detected.

### 4.3 Demographics

Integrated demographic and baseline characteristic data from 5 Phase 3 24-week double-blind, placebo-controlled studies in premenopausal patients are presented in [Table 20](#).

**Table 20 Demographic and Other Baseline Characteristics by Treatment - Phase 3 Studies in Premenopausal Women (Target Population Set)**

Characteristic	Placebo N = 1905	Flibanserin			
		25 mg bid N = 733	50 mg qhs N = 969	50 mg bid N = 728	100 mg qhs N = 1543
Age Group, n (%)					
18-34 years	811 (42.6)	341 (46.5)	441 (45.5)	310 (42.6)	662 (42.9)
35-44 years	867 (45.5)	322 (43.9)	415 (42.8)	344 (47.3)	675 (43.7)
≥45 years	227 (11.9)	70 (9.5)	113 (11.7)	74 (10.2)	206 (13.4)
Age, Years					
Mean	35.7	34.9	35.5	35.4	35.9
SD	7.24	7.06	7.16	6.97	7.40
Min, Max	18, 54	18, 52	18, 54	19, 51	19, 56
Race, n (%)					
White	1676 (88.0)	643 (87.7)	875 (90.3)	661 (90.8)	1364 (88.4)
Black or African American	171 (9.0)	79 (10.8)	63 (6.5)	56 (7.7)	134 (8.7)

Notes: bid = Twice daily; Max = Maximum; Min = Minimum; n = Total population size; N = Number of subjects; qhs = Once every evening at bedtime; SD = Standard deviation.



**Table 20 Demographic and Other Baseline Characteristics by Treatment - Phase 3 Studies in Premenopausal Women (Target Population Set) (Cont'd)**

Characteristic	Placebo N = 1905	Flibanserin			
		25 mg bid N = 733	50 mg qhs N = 969	50 mg bid N = 728	100 mg qhs N = 1543
Race, n (%) (Cont'd)					
Asian	24 (1.3)	11 (1.5)	9 (0.9)	11 (1.5)	21 (1.4)
American Indian or Alaskan native	7 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.1)
Native Hawaiian or other Pacific islander	2 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Missing	25 (1.3)	0 (0.0)	22 (2.3)	0 (0.0)	21 (1.4)
Ethnicity, n (%)					
Hispanic	135 (7.1)	39 (5.3)	53 (5.5)	40 (5.5)	126 (8.2)
Not Hispanic	1744 (91.5)	694 (94.7)	890 (91.8)	687 (94.4)	1394 (90.3)
Missing	26 (1.4)	0 (0.0)	26 (2.7)	1 (0.1)	23 (1.5)
Body Mass Index, kg/m <sup>2</sup> , n (%)					
Underweight (<18.5)	37 (1.9)	8 (1.1)	18 (1.9)	11 (1.5)	29 (1.9)
Normal (18.5 - <25)	936 (49.1)	330 (45.0)	510 (52.6)	346 (47.5)	753 (48.8)
Overweight/obese (≥25)	924 (48.5)	391 (53.3)	438 (45.2)	364 (50.0)	757 (49.0)
Missing	8 (0.4)	4 (0.5)	3 (0.3)	7 (1.0)	4 (0.3)
Weight, kg					
Mean	72.1	73.4	71.0	71.8	72.4
SD	17.19	17.61	17.01	16.01	17.23
Min, Max	43, 163	46, 166	40, 152	41, 140	36, 158
Height, cm					
Mean	165.0	165.1	164.8	164.5	165.1
SD	7.01	7.07	7.01	6.80	6.78
Min, Max <sup>a</sup>	132, 188	140, 183	132, 185	142, 185	137, 196
Alcohol Status, n (%)					
No use at baseline	693 (36.4)	200 (27.3)	269 (27.8)	176 (24.2)	645 (41.8)
Some use at baseline	1212 (63.6)	533 (72.7)	700 (72.2)	552 (75.8)	898 (58.2)
Smoking History, n (%)					
Never smoked	1260 (66.1)	493 (67.3)	633 (65.3)	471 (64.7)	1032 (66.9)
Ex-smoker	367 (19.3)	162 (22.1)	177 (18.3)	159 (21.8)	285 (18.5)
Current smoker	278 (14.6)	78 (10.6)	159 (16.4)	98 (13.5)	226 (14.6)

Notes: bid = Twice daily; Max = Maximum; Min = Minimum; n = Total population size; N = Number of subjects;

qhs = Once every evening at bedtime; SD = Standard deviation.

Includes Studies 511.70, 511.71, 511.75, 511.77 and 511.147.

Source: ISS Post Hoc Table 1.3.1b.

These demographic data are representative of the anticipated flibanserin patient population [Shifren et al., 2008; Rosen et al., 2012; Connor et al., 2011]. In these 5 studies, 1,905 subjects

received placebo and 3,973 received flibanserin (any dose). The mean age for subjects receiving placebo was 35.7 years (range 18 to 54 years) and for subjects receiving flibanserin (any dose) was 35.4 years (range 18 to 56 years).

In all treatment groups, from 87.7% to 90.8% of subjects were white. The next largest racial group was Black or African American ranging from 6.5% to 10.8%.

The distribution of BMI was similar across treatment groups. About half of subjects (range 45.0% to 52.6% across groups) were of normal BMI, about a quarter were overweight (range 25.0% to 28.8%), and about a fifth were obese (range 20.2% to 25.5%).

Reported alcohol use at baseline was also similar for placebo and across the flibanserin treatment groups with more than half of subjects in each treatment group reporting some alcohol use. Extent of alcohol use was self-reported and recorded as either estimated number of drinks per day (Study 147) or likely or unlikely to interfere with study participation in the investigator's opinion (all other studies).

For smoking history, the distribution was similar among subjects receiving placebo compared to those receiving flibanserin. Around two-thirds of subjects had never smoked.

#### **4.4 Concomitant Baseline Diagnoses**

In the Phase 3, double-blind, placebo-controlled studies in premenopausal women, a cumulative total of 78% of women in all treatment groups reported concomitant baseline diagnoses ([Table 21](#)). System organ classes for diagnosed baseline conditions occurring in at least 5% of study subjects are shown.

**Table 21 Number (%) of Subjects with Concomitant Baseline Diagnoses/Diseases (≥5% of Subjects) - Phase 3 Studies in Premenopausal Women (Target Population Set)**

<b>System Organ Class Preferred Term</b>	<b>Placebo N = 1905</b>	<b>Flibanserin 100 mg qhs N = 1543</b>	<b>Flibanserin Any Dose N = 3973</b>
Total number of subjects with concomitant diagnoses/diseases	1500 (78.7)	1183 (76.7)	3083 (77.6)
Endocrine Disorders	130 (6.8)	75 (4.9)	240 (6.0)
Hypothyroidism	103 (5.4)	57 (3.7)	190 (4.8)
Eye Disorders	192 (10.1)	150 (9.7)	377 (9.5)
Myopia	118 (6.2)	80 (5.2)	231 (5.8)
Gastrointestinal Disorders	324 (17.0)	232 (15.0)	628 (15.8)
Immune system Disorders	620 (32.5)	523 (33.9)	1327 (33.4)
Drug hypersensitivity	246 (12.9)	219 (14.2)	536 (13.5)
Seasonal allergy	341 (17.9)	281 (18.2)	709 (17.8)
Infections and Infestations	315 (16.5)	236 (15.3)	614 (15.5)
Investigations	93 (4.9)	4 (0.0)	211 (5.3)
Metabolism and Nutrition Disorders	135 (7.1)	111 (7.2)	277 (7.0)
Musculoskeletal and Connective Tissue Disorders	332 (17.4)	303 (19.6)	721 (18.1)
Back pain	106 (5.6)	103 (6.7)	227 (5.7)
Nervous System Disorders	584 (30.7)	486 (31.5)	1213 (30.5)
Headache	322 (16.9)	273 (17.7)	673 (16.9)
Migraine	192 (10.1)	150 (9.7)	366 (9.2)
Psychiatric Disorders	214 (11.2)	153 (9.9)	352 (8.9)
Reproductive System and Breast Disorders	143 (7.5)	128 (8.3)	320 (8.1)
Respiratory, Thoracic and Mediastinal Disorders	216 (11.3)	182 (11.8)	473 (11.9)
Asthma	108 (5.7)	95 (6.2)	259 (6.5)
Skin and Subcutaneous Tissue Disorders	223 (11.7)	172 (11.1)	465 (11.7)
Surgical and Medical Procedures	234 (12.3)	195 (12.6)	494 (12.4)
Vascular Disorders	106 (5.6)	104 (6.7)	225 (5.7)

Notes: N = Total population size; qhs = Once every evening at bedtime.

Includes Studies 511.70, 511.71, 511.75, 511.77, and 511.147.

MedDRA version used for reporting: 11.1.

Source: ISS Table 1.4.1.

As expected in this relatively young and otherwise generally healthy population, the majority of diagnoses and diseases were minor conditions, and the frequency and System Organ Classes (SOCs) involved for concomitant baseline diagnoses and diseases were comparable between placebo and flibanserin treatment groups.

In response to recommendations from FDA and its advisory committee, various cardiovascular agents, anticoagulants, triptans, respiratory agents, muscle relaxants, and additional CYP3A4

inhibitors were permitted in Study 147. In Studies 71 and 75, between 86% and 87% of women reported concomitant medication use, compared to over 94% in Study 147.

The rate of use for medications typically used in an otherwise healthy premenopausal female population (i.e., hormonal contraceptives, aspirin and non-steroidal anti-inflammatory drugs, and antihistamines) was comparable across the treatment groups (Table 22).

**Table 22 Number (%) of Subjects using Expected Concomitant Medications - Phase 3 Studies in Premenopausal Women (Target Population Set)**

Subjects with Use, n (%)	Placebo N = 1905	Flibanserin 100 mg qhs N = 1543	Flibanserin Any Dose N = 3973
Hormonal Contraceptive	807 (42.4)	659 (42.7)	1699 (42.8)
Aspirin, NSAID	589 (30.9)	507 (32.9)	1300 (32.7)
Antihistamine	329 (17.3)	279 (18.1)	723 (18.2)
SSRI/SNRI	32 (1.7)	38 (2.5)	80 (2.0)
Triptans	61 (3.2)	55 (3.6)	129 (3.2)

Notes: NSAID = Non-steroidal anti-inflammatory drugs; qhs = Once every evening at bedtime; SNRI = Serotonin/norepinephrine reuptake inhibitor; SSRI = Selective serotonin reuptake inhibitor.

Includes Studies 511.70, 511.71, 511.75, 511.77, and 511.147.

Source: ISS Tables 1.4.4, 5.2.1, 5.3.1, 5.4.1, 5.5.1, and 5.6.1, Module 5.3.5.3.

In addition, the Sponsor conducted a dedicated Phase 3 safety study of concomitant use of flibanserin with SSRIs and SNRIs in 111 premenopausal women with HSDD and mild or remitted depression. Results of this study are presented separately in Appendix E.

## 4.5 Safety in Premenopausal Women with HSDD

### 4.5.1 Overall AEs

For the Phase 3 double-blind, placebo-controlled studies in premenopausal women, 55.7% of placebo subjects had at least 1 AE compared with 66.9% of subjects who received flibanserin 100 mg qhs and 65.6% of subjects who received any dose of flibanserin (Table 23).

**Table 23 Overall Summary of Adverse Events – Phase 3 Studies in Premenopausal Women (Target Population Set)**

Subjects by Category n (%)	Placebo N = 1905	Flibanserin			
		25 mg bid N = 733	50 mg qhs N = 969	50 mg bid N = 728	100 mg qhs N = 1543
Any Adverse Event	1062 (55.7)	430 (58.7)	628 (64.8)	517 (71.0)	1033 (66.9)
Severe Adverse Events	90 (4.7)	32 (4.4)	69 (7.1)	44 (6.0)	106 (6.9)
Adverse Events leading to discontinuation	112 (5.9)	50 (6.8)	99 (10.2)	148 (20.3)	198 (12.8)
Serious Adverse Events	10 (0.5)	4 (0.5)	10 (1.0)	5 (0.7)	14 (0.9)

Notes: bid = Twice daily; N = Number of subjects; n = Total population size; qhs = Once every evening at bedtime.

Includes Studies 511.70, 511.71, 511.75, 511.77, and 511.147.

Source: ISS Table 2.1.2.

For subjects who received placebo, 24.7% of subjects had mild AEs, 26.3% had moderate AEs, and 4.7% had severe AEs with severity assessed by the investigator in all cases. For subjects who received any dose of flibanserin, 26.6% of subjects had mild AEs, 32.7% had moderate AEs, and 6.3% had severe AEs. For subjects receiving flibanserin 100 mg qhs, 26.8% of subjects had mild AEs, 33.2% had moderate AEs, and 6.9% had severe AEs.

#### 4.5.2 Common AEs

The most common AE occurring in Phase 3 double-blind studies in premenopausal women for the placebo group and the flibanserin 100 mg qhs treatment group was dizziness. The number of premenopausal subjects with AEs that occurred in  $\geq 2\%$  of subjects and at a frequency twice that in subjects receiving placebo are listed in descending order of frequency for Phase 3 double-blind, placebo-controlled studies in premenopausal women in [Table 24](#). Overall, 22.0% of subjects who received placebo were considered to have a drug-related AE compared with 37.4% of subjects who received any dose of flibanserin. Dose dependence and the negative impact of morning dosing are apparent across several AEs (e.g., dizziness, somnolence, nausea, fatigue). Adverse events occurring in greater than 1% of the population are presented in [Appendix M](#).

**Table 24**      **Number (%) of Subjects with Adverse Events Occurring at  $\geq 2.0\%$  and Twice that of Placebo by Treatment - Phase 3 Studies in Premenopausal Women (Target Population Set)**

Preferred Term	Placebo, n (%) N = 1905	Flibanserin, n (%)			
		25 mg bid N = 733	50 mg qhs N = 969	50 mg bid N = 728	100 mg qhs N = 1543
Dizziness	41 (2.2)	31 (4.2)	61 (6.3)	111 (15.2)	176 (11.4)
Somnolence	59 (3.1)	51 (7.0)	55 (5.7)	122 (16.8)	173 (11.2)
Nausea	71 (3.7)	41 (5.6)	68 (7.0)	90 (12.4)	161 (10.4)
Fatigue	95 (5.0)	35 (4.8)	59 (6.1)	101 (13.9)	142 (9.2)
Insomnia	46 (2.4)	14 (1.9)	19 (2.0)	20 (2.7)	75 (4.9)
Dry mouth	17 (0.9)	6 (0.8)	12 (1.2)	10 (1.4)	37 (2.4)
Anxiety	17 (0.9)	5 (0.7)	19 (2.0)	10 (1.4)	28 (1.8)
Metrorrhagia	24 (1.3)	10 (1.4)	25 (2.6)	13 (1.8)	22 (1.4)

Notes: bid = Twice daily; n = Total population size; N = Number of subjects; qhs = Once every evening at bedtime.

MedDRA version used for reporting: 11.1.

Includes Studies 511.70, 511.71, 511.75, 511.77 and 511.147.

Source: ISS Table 2.3.10.

Increasing overall AE rates occurring at higher doses of flibanserin provide evidence of a dose response relationship, particularly for AEs associated with the CNS (dizziness, somnolence and fatigue). Also evident in the comparison of the 50 mg bid and 100 mg qhs dose groups is the occurrence of higher rates of these sedation-related AEs with daytime versus nighttime dosing.

Adverse events were largely mild to moderate with severe AEs reported in 90 (4.7%) placebo subjects and 106 (6.9%) flibanserin 100 mg qhs subjects. Severe AEs reported at an incidence of  $\geq 0.5\%$  in either group were headache (0.6% v 0.6%), dizziness (0.2% v 0.6%), fatigue (0.1% v 0.6%), somnolence (0.2% v 0.5%), and nausea (0% v 0.7%) in the placebo and flibanserin 100 mg qhs groups, respectively.

For patients who received placebo, 5.9% had an AE that led to discontinuation. For patients who received any dose of flibanserin, 12.5% had an AE that led to discontinuation. For patients receiving flibanserin 100 mg qhs, 12.8% had an AE that led to discontinuation. Adverse events that led to discontinuation in  $\geq 1.0\%$  of patients in any treatment group are listed in [Table 25](#).

**Table 25 Number (%) of Subjects with Adverse Events Leading to Discontinuation in  $\geq 1.0\%$  of Subjects by Treatment - Phase 3 Studies in Premenopausal Women (Target Population Set)**

Preferred Term	Placebo, n (%) N = 1905	Flibanserin, n (%)				
		25 mg bid N = 733	50 mg qhs N = 969	50 mg bid N = 728	100 mg qhs N = 1543	Any Dose N = 3973
Patients with Adverse Events leading to discontinuation	112 (5.9)	50 (6.8)	99 (10.2)	148 (20.3)	198 (12.8)	495 (12.5)
Dizziness	3 (0.2)	2 (0.3)	9 (0.9)	29 (4.0)	26 (1.7)	66 (1.7)
Fatigue	7 (0.4)	7 (1.0)	7 (0.7)	37 (5.1)	14 (0.9)	65 (1.6)
Somnolence	9 (0.5)	3 (0.4)	4 (0.4)	29 (4.0)	17 (1.1)	53 (1.3)
Nausea	4 (0.2)	2 (0.3)	5 (0.5)	18 (2.5)	19 (1.2)	44 (1.1)
Headache	10 (0.5)	6 (0.8)	11 (1.1)	13 (1.8)	10 (0.6)	40 (1.0)
Anxiety	7 (0.4)	3 (0.4)	10 (1.0)	4 (0.5)	16 (1.0)	33 (0.8)
Insomnia	3 (0.2)	1 (0.1)	3 (0.3)	6 (0.8)	17 (1.1)	27 (0.7)

Notes: bid = Twice daily; n = Total population size; N = Number of subjects; qhs = Once every evening at bedtime.

MedDRA version used for reporting: 11.1.

Includes Trials 511.70, 511.71, 511.75, 511.77 and 511.147.

Source: ISS Table 2.3.7.

No observations raised concerns regarding cardiac, hepatic, renal or hematopoietic effects, ophthalmologic safety, hypersexuality, hormonal changes, suicide, depression, abuse potential or withdrawal effects.

#### 4.5.2.1 Sedation-related AEs

CNS depression, often presenting as sedation-related AEs, is the hallmark adverse effect of flibanserin and has been uniformly reported across the flibanserin clinical development program. This AE profile is consistent with flibanserin's mechanism of action as both a 5-HT<sub>1A</sub> agonist and a 5-HT<sub>2A</sub> antagonist. 5-HT<sub>1A</sub> agonists tend to promote wakefulness, while 5-HT<sub>2A</sub> antagonists tend to cause sedation [Monti, 2011].

The apparent dose-response relationship between flibanserin and frequency of sedation-related AE rates is consistent with the 5-HT<sub>2A</sub> antagonism. Bedtime dosing appeared to markedly decrease the incidence of these events as demonstrated by a comparison of AEs in the 50 mg bid versus 100 mg qhs flibanserin groups (Table 26).

**Table 26 Number (%) of Subjects with Sedation-Related Adverse Events – Phase 3 Studies in Premenopausal Women (Target Population Set)**

Preferred Term, n (%)	Placebo (N=1905)	Flibanserin 25 mg bid (N=733)	Flibanserin 50 mg qhs (N=969)	Flibanserin 50 mg bid (N=728)	Flibanserin 100 mg qhs (N=1543)
Any Sedation-Related Adverse Event	179 (9.4)	107 (14.6)	164 (16.9)	285 (39.1)	441 (28.6)
Dizziness	41 (2.2)	31 (4.2)	61 (6.3)	111 (15.2)	176 (11.4)
Somnolence	59 (3.1)	51 (7.0)	55 (5.7)	122 (16.8)	173 (11.2)
Fatigue	95 (5.0)	35 (4.8)	59 (6.1)	101 (13.9)	142 (9.2)
Sedation	3 (0.2)	1 (0.1)	6 (0.6)	10 (1.4)	20 (1.3)

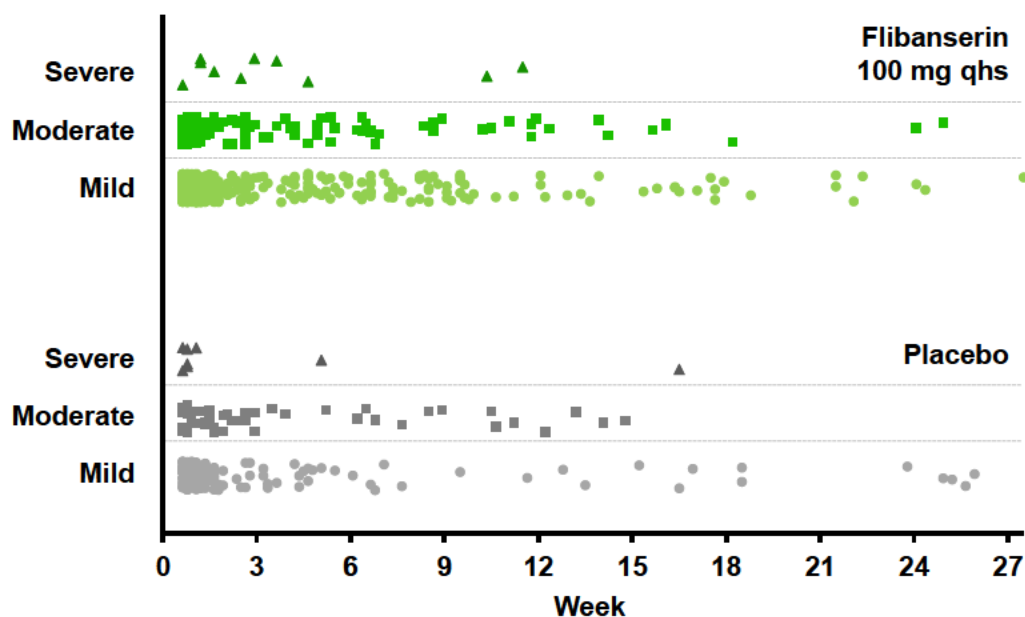
Notes: bid = Twice daily; n = Total number of subjects; N = Total population size; qhs = Once very evening at bedtime.

Includes Studies 511.70, 511.71, 511.75, 511.77 and 511.147.

Source: ISS Update Table 2.1.6, Module 5.3.5.3.

Onset for sedation-related AEs occurred most often during the first week of treatment with the incidence of new events decreasing over time. Median time to first onset was 5.5 days for dizziness, 2 days for somnolence, and 4 days for fatigue. An analysis of time of onset and severity of sedation-related AEs suggests an early-onset, and largely mild to moderate effect (Figure 22).

**Figure 22 Time to Onset of First Event of Sedation-related AEs with Severity – Phase 3 Studies in Premenopausal Women (Target Population Set)**



Notes: AE = Adverse event; qhs = Once every evening at bedtime.  
Sedation related AEs = Dizziness, somnolence, fatigue and sedation.

Median duration of dizziness of any intensity was 10 days for placebo and 11 days for flibanserin 100 mg qhs. Median duration of somnolence of any intensity was 35 days for placebo and



37 days for flibanserin 100 mg qhs. Median duration of fatigue of any intensity was 26 days for placebo and 29 days for flibanserin 100 mg qhs. Median duration of sedation of any intensity was 3 days for placebo and 26 days for flibanserin 100 mg qhs. Sedation-related AEs resolved within 9 days of discontinuing placebo and within 5 days of discontinuing flibanserin.

No sedation-related serious adverse events (SAEs) were reported during the Phase 3 double-blind studies in premenopausal women. Reported AEs were largely mild to moderate. Severe sedation-related AEs occurred in 0.1% to 0.6% of subjects taking placebo or flibanserin 100 mg qhs, respectively, with a tendency for greater frequency of severe events at higher dose or with morning dosing (Table 27).

**Table 27 Number (%) of Subjects with Severe Sedation-Related Adverse Events – Phase 3 Studies in Premenopausal Women (Target Population Set)**

Preferred Term, n (%)	Placebo (N=1905)	Flibanserin 25 mg bid (N=733)	Flibanserin 50 mg qhs (N=969)	Flibanserin 50 mg bid (N=728)	Flibanserin 100 mg qhs (N=1543)
Dizziness	3 (0.2)	1 (0.1)	6 (0.6)	3 (0.4)	9 (0.6)
Somnolence	3 (0.2)	0 (0.0)	2 (0.2)	8 (1.1)	8 (0.5)
Fatigue	2 (0.1)	0 (0.0)	3 (0.3)	7 (1.0)	9 (0.6)
Sedation	0	0	0	0	0

Notes: bid = Twice daily; n = Total number of subjects; N = Total population size; qhs = Once every evening at bedtime.

Source: ISS Update Table 2.2.18, Module 5.3.5.3.

Less than 2% of subjects randomized to flibanserin 100 mg qhs discontinued from the Phase 3 double-blind studies due to any individual sedation-related AE (Table 28). The apparent benefit of bedtime dosing is again notable in the difference in discontinuation rates between the 50 mg bid and 100 mg qhs flibanserin groups.

**Table 28 Number (%) of Subjects Who Discontinued Due to Sedation-related Adverse Events of Interest – Phase 3 Studies in Premenopausal Women (Target Population Set)**

Preferred Term n (%)	Placebo (N=1905)	Flibanserin 25 mg bid (N=733)	Flibanserin 50 mg qhs (N=969)	Flibanserin 50 mg bid (N=728)	Flibanserin 100 mg qhs (N=1543)
Dizziness	3 (0.2)	2 (0.3)	9 (0.9)	29 (4.0)	26 (1.7)
Somnolence	9 (0.5)	3 (0.4)	4 (0.4)	29 (4.0)	17 (1.1)
Fatigue	7 (0.4)	7 (1.0)	7 (0.7)	37 (5.1)	14 (0.9)
Sedation	0	0	0	1 (0.1)	3 (0.2)

Notes: bid = Twice daily; n = Total number of subjects; N = Total population size; qhs = Once every evening at bedtime.

Source: ISS Update Table 2.2.22, Module 5.3.5.3.

#### **4.5.2.1.1 Potential for Accidental Injury and Road Traffic Accidents**

The frequency and severity of flibanserin's sedation-related AEs are readily managed, as are similar sedative effects from over-the-counter antihistamines and other commonly used drug products with sedative properties. The Sponsor nonetheless investigated whether flibanserin's sedative effect could lead to additional AEs of greater concern such as accidental injuries, including from automobile collisions.

Together with FDA, the Sponsor considered road traffic accidents in the Phase 3 studies as well as AEs categorized under the Medical Dictionary for Regulatory Activities (MedDRA) Standard Medical Query (SMQ) for Accidents and Injuries. Consistent with examples provided by FDA during its review, these analyses were conducted in the flibanserin premenopausal database. The Sponsor then conducted a definitive simulated driving and cognition study designed with substantial input from FDA. Results of these analyses and study are presented here.

Road Traffic Accidents. In the Phase 3 studies in premenopausal women, a total of 12 subjects reported road traffic accidents. Two (<0.1%) were subjects receiving placebo, 3 (0.4%) were subjects receiving 25 mg flibanserin bid, 3 (0.3%) were subjects receiving flibanserin 50 mg qhs, 1 (0.1%) was a subject who received flibanserin 50 mg bid and 5 (0.2%) were subjects who received flibanserin 100 mg qhs. While there is no evidence that road accidents are significantly more common with subjects taking flibanserin than placebo, the rare incidence of such events prevents reaching any definitive conclusions from these studies.

Accidental Injury. Based on the MedDRA SMQ for Accidents and Injuries, 42 (2.7%) subjects reported accidental injuries with flibanserin 100 mg qhs versus 46 (2.4%) subjects with placebo during the Phase 3 studies in premenopausal women. There is a reassuring lack of clinically important imbalance in these numbers.

In assessing the extent to which these events may be associated with sedation, a further search was conducted for AE preferred terms that relate to sedation: dizziness, somnolence, fatigue, or sedation. Two additional preferred terms not indicative of sedation (i.e., hypotension and circulatory collapse) were also included per FDA's guidance. Where there was overlap between the date of accidental injury and the start and end dates of these sedation- or circulatory-related AEs, a possible association was deemed to exist. Using this analysis, 10 (0.65%) subjects in the flibanserin group and 4 (0.21%) in the placebo group (i.e., 14 of nearly 3500 total subjects) were deemed to have had accidental injuries possibly associated with this expansive definition of sedation.

The accidental injury AEs experienced by the 10 flibanserin subjects ranged from joint sprain (1), back injury (1), contusion and excoriation associated with falls (1), contusion associated with a road traffic accident (1) or contusion alone (1), concussion associated with circulatory collapse (1), to sunburn (2), muscle strain (1) and ear drum perforation in a subject with an ear infection

(1). Of these events, road traffic accident, excoriation and fall were also experienced in the 4 placebo subjects, along with ligament rupture/bursa injury and muscle spasms.

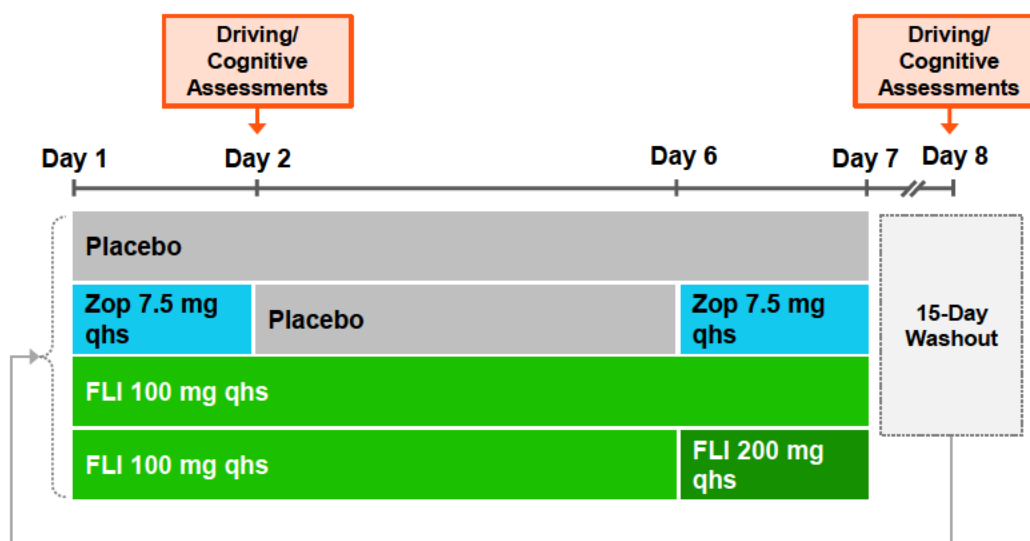
In half of these cases (5 flibanserin and 2 placebo), the sedation-related AE was mild in severity.

While this analysis shows a fairly even distribution of accidents experienced by subjects also experiencing sedation AEs (2.4% flibanserin 100 mg qhs versus 2.3% placebo), there is a potential imbalance when choosing the denominator of all accidents rather than all sedation (23.8% flibanserin versus 8.7% placebo). The small number of events prevents any conclusion that flibanserin-induced sedation meaningfully increases the risk of accidental injury. For instance, conducting the same analysis in the larger population of pre- and postmenopausal subjects results in 13 versus 6 (rather than 10 versus 4) events with flibanserin and placebo groups, respectively. The resulting percentage of all accidents that were temporally related to sedation decreases to 15.7% for flibanserin versus to 7.1% for placebo.

Although a contribution of flibanserin-related sedation to accidental injuries cannot be excluded, the small number of events also fails to establish a causal association. Results from a dedicated next-day driving assessment study (discussed below) provide additional assurance that accidents caused by next-day impairment are not a concern with flibanserin.

Dedicated Next-Day Driving and Cognition Study. The Sponsor designed a simulated driving impairment and cognition study, with substantial input from FDA, to evaluate next-day residual effects after acute (single bedtime dose) and steady state (7 nightly doses) exposure to flibanserin at the recommended 100 mg dose and acute exposure to a supratherapeutic dose (single bedtime dose at 200 mg after 6 nightly doses at 100 mg). The Driving and Cognition Study was a randomized, double-blind, placebo- and active hypnotic (zopiclone 7.5 mg)-controlled study with 4-way, 4-period cross-over Latin-square design assessing potential next-day residual effects of flibanserin on simulated driving performance in 83 healthy premenopausal female volunteers (Figure 23).

**Figure 23 Driving and Cognition Study Design**



Notes: FLI = Flibanserin; qhs = Once every evening at bedtime; Zop = Zopiclone.  
 Source: SPR 14-01 CTR.

Flibanserin was dosed 30 minutes before bedtime and all assessments were performed within 90 minutes of awakening after a 7-hour sleep period. Testing was performed on the morning of Day 2 and Day 8 for each treatment period. Subjects participated in all dosing groups with a minimum 7-day washout period between treatment arms.

The primary endpoint assessment was standard deviation of lateral position (SDLP) on the CRC-MiniSim driving simulator analyzed using a mixed model with fixed effects for sequence, period, and treatment, and a random effect for subject within sequence. The SDLP measures lane position control, that is the change in position within a driving lane relative to no movement (zero), which has been shown to be highly predictive of driving safety and impairment. A higher score on SDLP compared to placebo indicates poorer driving performance.

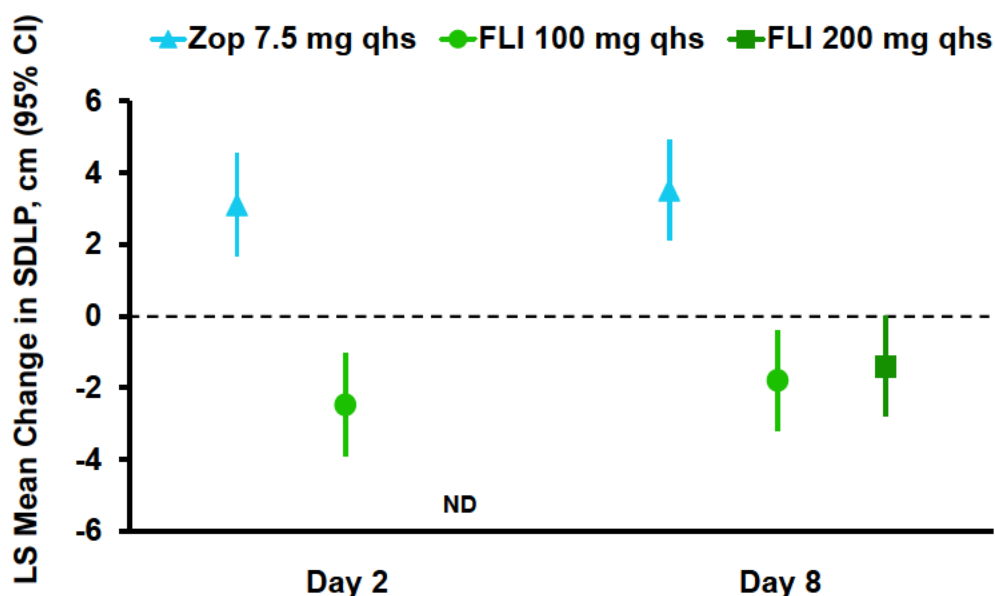
SDLP was significantly larger (+3.1 to +3.5 cm;  $p < 0.0001$ ) after zopiclone dosing than placebo, establishing the expected sensitivity of the simulated driving assessment. The effect of zopiclone on SDLP approached the increase in SDLP observed with a blood alcohol content (BAC) of 0.05% using the same driving simulator and driving scenario (+4.4 cm; Cognitive Research Corporation data on file). When subjects were dosed with flibanserin 100 mg qhs, SDLP values were significantly lower at both acute (-2.5 cm;  $p = 0.0009$ ) and steady state (-1.8 cm;  $p = 0.0126$ ) dosing when compared to placebo. Further, there was no significant difference between acute dosing at bedtime of 100 and 200 mg flibanserin (Table 29, Figure 24).

**Table 29 Mean and LS Mean Change (SD) in Standard Deviation of Lateral Position Difference from Placebo (ITT Population) – Driving and Cognition Study**

Assessment Day		Placebo N = 75	Flibanserin 100 mg N = 77	p-value (FLI 100 mg v PBO)	Flibanserin 200 mg N = 78	ZOP 7.5 mg N = 78
Day 2	Mean (SD)	31.2 (6.3)	28.9 (5.6)	0.0009	–	34.4 (8.9)
	LS Mean	31.4	29.0		–	34.6
Day 8	Mean (SD)	30.9 (8.1)	29.2 (5.8)	0.0126	29.5 (6.1)	34.5 (8.6)
	LS Mean	31.1	29.3		29.7	34.6

Notes: FLI = Flibanserin; LS = Least squares; N = Number of subjects; PBO = Placebo; SD = Standard deviation; ZOP = Zopiclone.  
Source: SPR-14-01 CTR, Table 14.2.2.1, Module 5.3.4.1.

**Figure 24 Mean Change (95% CI) in Standard Deviation of Lateral Position Difference from Placebo – Driving and Cognition Study**

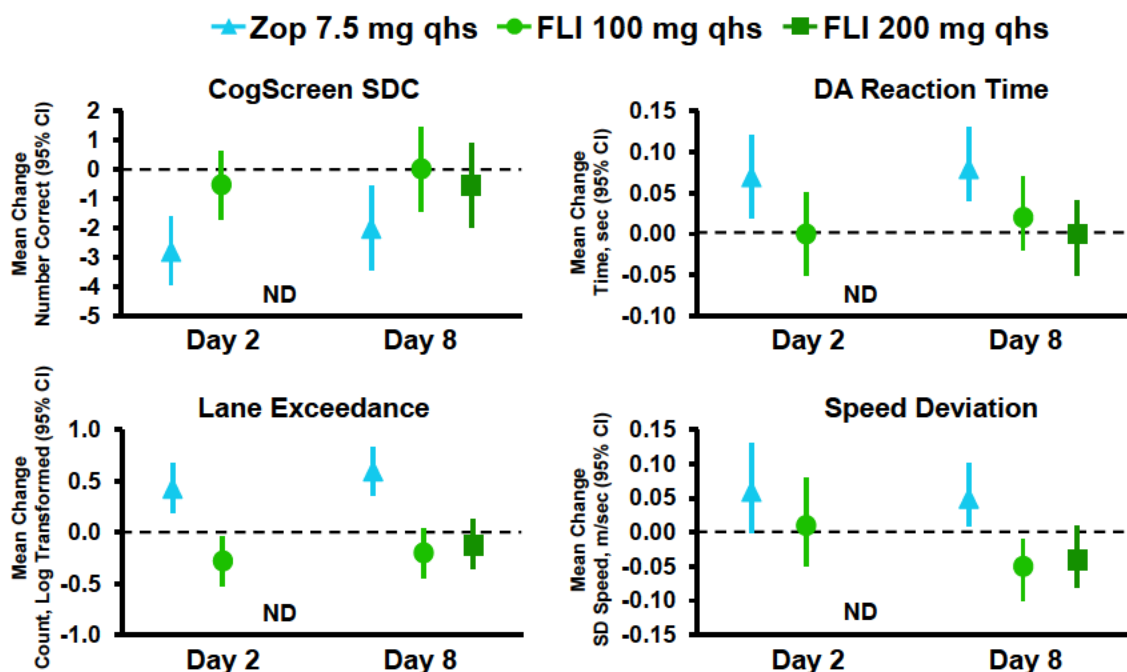


Notes: CI = Confidence interval; FLI = Flibanserin; LS = Least squares; ND = Not done; qhs = Once every evening at bedtime;  
SDLP = Standard deviation of lateral position; Zop = Zopiclone.  
Source: SPR 14-01 CTR Table 12.

Secondary sedation-sensitive driving endpoints included lane exceedance (the number of times a driver crosses over the boundary lines to her left or right) and speed deviation (intra-individual variability in speed). Secondary non-driving assessments of cognition included the CogScreen® Symbol Digit Coding test (a non-driving measure of cognitive function), and various Divided Attention assessments including reaction time. Acute (100 mg and 200 mg) and steady state (100 mg) flibanserin did not cause a significant increase in secondary driving events compared to placebo. Consistent with results on S DLP, the positive control showed deterioration in performance on each of these endpoints while all flibanserin arms performed similar to or better than placebo arms. Flibanserin also resulted in no significant impairment of next-day cognition

8.5 hours following dosing. In contrast, performance on various measures was significantly impaired by zopiclone (Figure 25). Other typical driving study secondary endpoints that are not informative for sedation (e.g., cornering speed) were also included in the study.

**Figure 25 Mean (95% CI) Difference from Placebo on Selected Secondary Driving Endpoints – Driving and Cognition Study**



Notes: CI=confidence interval; DA=divided attention; FLI=flibanserin; ND=not done; qhs=once every evening at bedtime; SD=speed deviation; SDC=symbol digit coding; Zop=zopiclone.

Additional endpoints included several self-report visual analog scale (VAS) measures of alertness and driving ability. On a measure of self-reported sleepiness, the Karolinska Sleepiness Scale, more subjects in the zopiclone (43.2%) and flibanserin 100 mg (38.3%) arms than in the placebo (26.0%) arm were dichotomized into “not alert” than “alert” prior to simulated driving on Day 2. There were no differences after the drive on Day 2 and no significant differences on Day 8. This subjective measure of sleepiness on Day 2 was the only endpoint in which subjects taking flibanserin reported less alertness than placebo although driving performance and other cognitive tests failed to show any impact.

The positive nature of the Driving and Cognition Study results is consistent with results of early cognition studies (described, along with other CNS properties of flibanserin, in Appendix M) and provides assurance that flibanserin use, even at elevated acute exposure levels up to twice the recommended dose, has effects no worse than placebo on next-day driving performance and cognitive assessments after 7 hours of sleep.

#### **4.5.2.1.2 Circumstances of Increased Risk for Sedation-Related AEs**

The safety profile from the Phase 3 experience demonstrates that flibanserin, when taken as directed in the proposed prescribing information, has a self-limiting and manageable risk of CNS depression. The impact of flibanserin's sedative effect was explored in the Driving and Cognition Study in which flibanserin demonstrated no tendency to impair next-day driving ability or cognition.

The potential for these otherwise readily managed risks to be exacerbated by uninformed and inappropriate use of flibanserin (i.e., concomitant use with certain medications or daytime dosing) has also been explored. CNS depression was more pronounced in several Phase 1 studies in which flibanserin was dosed in the morning and co-administered with certain concomitant medications that inhibit flibanserin metabolism or was co-administered with high concentrations of alcohol. In each of these studies flibanserin was administered during the daytime rather than at bedtime as recommended in the proposed labeling – a potentially significant departure from dosing in the Phase 3 studies that may result in a  $C_{max}$ -associated sedative effect during waking hours. The sedation-related AE experience from these studies is summarized below.

##### **4.5.2.1.2.1 High Exposure**

CYP3A4-mediated biotransformation is responsible for most of flibanserin elimination, with negligible or minimal (<10%) contributions from CYP2C9, CYP2C19 and/or CYP2D6. Phase 1 studies were conducted to assess the effects of hepatic impairment and CYP3A4 inhibitor co-administration on flibanserin pharmacokinetics and tolerability.

Flibanserin exposure (area under the plasma concentration time curve (AUC)) was increased 1.8- to 7.0-fold in studies of hepatically impaired subjects or that involved co-administration of a moderate to strong CYP3A4 inhibitor. In most but not all cases, flibanserin combined with a CYP3A4 inhibitor resulted in a greater frequency of some sedation-related AEs than flibanserin alone. [Table 30](#) presents the exposure increases and sedation-related AE information for each study. The individual studies are discussed in the subsequent bullets.



**Table 30 Summary of Sedation-Related AE Impact with Concomitant CYP3A4 Inhibitor Exposure or Hepatic Impairment**

Study	N	Fold Increase in AUC <sub>0-∞</sub>	Fold Increase in C <sub>max</sub>	Increase in Sedation-Related AEs?				Severe Sedation-Related AEs	SAEs
				Dizziness	Somnolence	Fatigue	Sedation		
Hepatic impairment	28	4.5	0.9	No	No	No	No	No	No
Itraconazole	12	2.6	1.7	Yes	No	Yes	No	No	No
Ketoconazole	24	4.5	1.8	Yes	No	No	No	No	No
Fluconazole	26	7.0	2.2	Yes	No	Yes	No	No	No
Grapefruit juice	26	1.4	1.1	No	No	Yes	No	No	No

Notes: AEs = Adverse events; SAE's = Serious adverse events.  
Includes Studies 511.111, 511.37, 511.67, SPR-12-01.

- Flibanserin exposure (AUC) increased 4.5-fold in subjects with mild to moderate liver impairment (Child-Pugh score of 6-8 points) in a dedicated morning-dosing study in 10 subjects. No increases in sedation-related AEs were noted in the hepatically impaired subjects. No SAEs or severe sedation-related AEs were reported in this study.
- Flibanserin exposure (AUC) increased 2.6-fold in the presence of itraconazole - a strong CYP3A4 inhibitor - in a dedicated morning-dosing study in 12 healthy volunteers. Concomitant administration of itraconazole and flibanserin increased the number of subjects reporting fatigue (50.0% versus 16.7% with flibanserin alone) or dizziness (25.0% versus 0% for flibanserin alone) but not somnolence (0% for both groups) or sedation (0% for both groups). No SAEs or severe sedation-related AEs were reported during this study.
- Flibanserin exposure (AUC) increased 4.5-fold in the presence of ketoconazole - another strong CYP3A4 inhibitor - in a dedicated morning-dosing study in 24 healthy female subjects. Concomitant administration of ketoconazole and flibanserin increased the number of subjects reporting dizziness (62.5% versus 23.8% with flibanserin alone) but not fatigue (45.8% versus 57.1% with flibanserin alone), somnolence (29.2% versus 28.6% with flibanserin alone) or sedation (4.2% versus 4.8% for flibanserin alone). No SAEs or severe sedation-related AEs were reported during this study.
- Flibanserin exposure (AUC) increased 7.0-fold in the presence of fluconazole - a moderate CYP3A4 inhibitor - in a morning-dosing study in 30 healthy female subjects. Concomitant administration of a high dose of fluconazole with flibanserin increased the number of subjects reporting fatigue (93.3% versus 69.2% with flibanserin alone) but not dizziness (20.0% versus 34.6% with flibanserin alone), somnolence (0% both groups) or sedation (0% both groups). No SAEs were reported during this study and no severe



sedation-related AEs were reported. One subject experienced severe hypotension and is discussed below in the context of hypotension and syncope-related events.

- Flibanserin exposure (AUC) was not affected by co-administration with grapefruit juice - a strong or moderate CYP3A4 inhibitor - in a morning-dosing study in 30 healthy female subjects. Concomitant administration of grapefruit juice and flibanserin increased the number of subjects reporting fatigue (84.6% versus 69.2% with flibanserin alone) but not dizziness (26.9% versus 34.6% with flibanserin alone), somnolence (0% for both groups) or sedation (0% for both groups). No SAEs were reported during this study and no severe sedation-related AEs were reported. One subject experienced a severe AE of abnormal dreams.
- Flibanserin exposure (AUC) increased by 44% in a pooled analysis of 2,506 premenopausal women concomitantly using flibanserin (morning dosing) and hormonal contraceptives which are weak CYP3A4 inhibitors. Oral contraceptive users taking flibanserin reported a higher frequency of dizziness (13.4% versus 9.9% with flibanserin alone), somnolence (12.3% versus 10.6% with flibanserin alone) and fatigue (11.4% versus 7.5% with flibanserin alone) but not sedation (1.4% versus 1.3% with flibanserin alone). In a sub-analysis of oral contraceptive users in the Driving and Cognition Study (42.3% of study subjects), which was conducted using bedtime dosing, no differences in trends were seen from those seen in the overall population. Compared to placebo, zopiclone 7.5 mg increased (worsened) SDLP (+2.9 to +3.2 cm;  $p < 0.05$ ), while flibanserin 100 mg decreased (improved) SDLP at both acute (-4.0 cm;  $p = 0.005$ ) and steady state (-2.6 cm;  $p = 0.038$ ) dosing. In oral contraceptive users, flibanserin 200 mg also decreased SDLP relative to placebo and was not significantly different from the 100 mg dose ( $p = 0.47$ ).

These studies, in which exposure to flibanserin was somewhat to substantially increased and  $C_{max}$  was experienced during waking hours, provide evidence for potential increases in rates of certain sedation-related AEs with high flibanserin exposure in the morning. Across all these studies, however, no SAEs or sedation-related severe AEs were reported despite high flibanserin exposure.

#### **4.5.2.1.2.2 Administration with Alcohol**

Co-administration of flibanserin (morning dosing) with significant quantities of alcohol may increase the risk of CNS depression and associated AEs. Analyses of the Phase 3 premenopausal database were conducted to gain insights into any effects in a real world setting. In addition, a dedicated Phase 1 alcohol interaction safety study was performed to gain an understanding of any negative effects under maximal stress conditions.

In the Phase 3 studies, extent of alcohol use was captured at baseline but not monitored during the 24-week studies. A total of 1527 (54.7%) subjects randomized to placebo and 898 (49.9%)

subjects randomized to flibanserin 100 mg qhs reported some alcohol use at baseline. All remaining subjects reported no alcohol use. The lack of real-time information regarding concomitant use of flibanserin and alcohol in the Phase 3 program, including any temporal relationship of such use to sedation-related AEs, limits the ability to draw meaningful conclusions from these data.

Higher overall AE rates were reported by flibanserin subjects who were alcohol users at baseline. AE rate differences between subjects reporting alcohol use versus those reporting no alcohol use at baseline were higher for fatigue and slightly higher for dizziness and sedation in the flibanserin group (Table 31). Because alcohol use was not actively monitored during the Phase 3 studies and no data are available regarding any temporal relationship of AEs with alcohol consumption, Phase 3 results are imperfect for definitive assessment of this risk.

**Table 31 Number (%) of Subjects with Adverse Events and Sedation-Related Adverse Events by Alcohol Use and Treatment – Phase 3 Studies in Premenopausal Women (Target Population Set)**

Preferred Term, n (%)	Baseline Alcohol Use			
	Placebo		Flibanserin 100 mg qhs	
	No N = 693	Yes N = 1212	No N = 645	Yes N = 898
Total with AE	367 (53.0)	695 (57.3)	396 (61.4)	637 (70.9)
Dizziness	15 (2.2)	26 (2.1)	61 (9.5)	115 (12.8)
Somnolence	26 (3.8)	33 (2.7)	75 (11.6)	98 (10.9)
Fatigue	26 (3.8)	69 (5.7)	45 (7.0)	97 (10.8)
Sedation	2 (0.3)	1 (<0.1)	5 (0.8)	15 (1.7)

Notes: AE = Adverse event; n = Total number of subjects; N = Total population size.

Source: ISS Table 5.8.1

More direct data on the safety and tolerability of 100 mg flibanserin (morning dosing) when administered concomitantly with significant concentrations of alcohol were sought via conduct of a dedicated Phase 1 randomized, double-blind, single-dose, five-way crossover alcohol interaction study in 25 healthy volunteers. The study was designed as an extreme challenge and included conditions unlikely to reflect actual alcohol use in flibanserin subjects in clinical practice. After an overnight fast (10 hours) and light breakfast, each subject consumed, within 10 minutes, either flibanserin 100 mg alone, or 0.4 g/kg or 0.8 g/kg of 95% ethanol diluted to 240 mL total volume with orange juice with 1 flibanserin 100 mg tablet or placebo. Mean baseline weight in the study was 79.8 kg. This required alcohol consumption equivalent to nearly a half (0.4 g/kg alcohol group) or full bottle (0.8 g/kg alcohol group) of 12% alcohol content wine in 10 minutes on a close-to-empty stomach. Potential study subjects who self-reported as light alcohol drinkers (<5 units of alcohol/week) were excluded from the study due to the high potential for emesis, in light of the quantity of alcohol to be consumed in a short time period.

The average peak plasma flibanserin concentration was attained at approximately 3 hours after dosing for flibanserin alone and flibanserin dosed with ethanol (0.4 or 0.8 g/kg). Administration of flibanserin with ethanol 0.4 g/kg and 0.8 g/kg had no effect on flibanserin partial AUC (AUC<sub>0-4</sub>).

Sedation was assessed both by self-report with a visual analog scale (VAS) for four hours post-dosing and by standard AE reporting. Regarding the VAS, an increase in self-reported sedation occurred in the first 1.5 to 2 hours in all five treatment groups. Concomitant administration of flibanserin with 0.4 g/kg ethanol or 0.8 g/kg ethanol caused a progressive increase in self-reported sedation throughout the four assessment hours of the study. At 4 hours, self-reported mean change from baseline on VAS sedation was highest after flibanserin + 0.8 g/kg ethanol (27.1 mm), followed by flibanserin + 0.4 g/kg ethanol (20.4 mm), flibanserin alone (14.6 mm), 0.8 g/kg ethanol alone (3.9 mm) and 0.4 g/kg ethanol alone (-2.9 mm).

Regarding sedation-related AEs, concomitant morning administration of flibanserin with significant concentrations of alcohol increased the number of subjects reporting dizziness and somnolence (Table 32). Fatigue was not consistently increased. Sedation was not reported as an AE in this study although reporting may have been affected by the separate capturing of VAS information on sedation.

**Table 32 Number (%) of Subjects with Sedation-Related Adverse Events – Alcohol Study**

Preferred Term, n (%)	Placebo + 0.4 g/kg Ethanol (N=24)	Placebo + 0.8 g/kg Ethanol (N=25)	Flibanserin 100 mg (N=24)	Flibanserin 100 mg + 0.4 g/kg Ethanol (N=23)	Flibanserin 100 mg + 0.8 g/kg Ethanol (N=24)
Dizziness	3 (12.5)	3 (12.0)	4 (16.7)	5 (21.7)	5 (20.8)
Somnolence	9 (37.5)	15 (60.0)	16 (66.7)	17 (73.9)	22 (91.7)
Fatigue	2 (8.3)	1 (4.0)	2 (8.3)	3 (13.0)	1 (4.2)
Sedation	0	0	0	0	0

Notes: n = Total number of subjects; N = Total population size.

Source: SPR-12-03 CTR Table 13, Module 5.3.4.1.

While there were no SAEs in the study, fifteen severe AEs, including some sedation-related AEs were reported by 6 subjects. The sedation-related severe AEs were as follows:

- Following dosing of 24 subjects with 0.4 g/kg ethanol + placebo, one subject experienced severe somnolence
- Following dosing of 24 subjects with flibanserin 100 mg, two subjects experienced severe somnolence

- Following dosing of 23 subjects with 0.4 g/kg ethanol + flibanserin 100 mg, one subject experienced severe somnolence and one subject experienced severe dizziness
- Following dosing of 24 subjects with 0.8 g/kg ethanol + flibanserin 100 mg, two subjects experienced severe somnolence and one subject experienced severe dizziness and asthenia

Additional severe AEs of nausea and headache were reported in 0.4 g/kg ethanol + placebo group, and severe AEs of orthostatic hypotension and syncope were reported in the 0.4 g/kg ethanol + flibanserin 100 mg group. These flibanserin events are discussed below in the context of hypotension and syncope-related events.

Combined daytime administration of high doses of ethanol and flibanserin 100 mg in subjects not accustomed to flibanserin therapy constitutes an extreme challenge. This dosing regimen resulted in additive effects on sedation-related AEs and hypotension-related AEs (discussed below), as well as self-assessed sedation. Because the pharmacokinetic profile of flibanserin is unaffected by ethanol it appears that ethanol independently exerts its inhibitory effects on the CNS to increase frequency of related AEs when taking flibanserin. The degree of additive CNS inhibition would likely be proportional to the amount of ethanol ingested, its rate of ingestion and any delay between alcohol and flibanserin ingestion.

Premenopausal women with HSDD who enrolled in the flibanserin Phase 3 program were motivated to improve their sexual health and engage in sexual activity with their partners. Despite concerns that such motivation might be associated with excessive consumption of alcohol, these subjects, who on average were in committed relationships for over four years, reported mostly light drinking habits. In the Target Population, 66.3% of subjects reported some alcohol use at baseline. In Study 147, the only study in which subjects were asked to quantify their drinking habits at baseline, no subjects reported consuming more than 1 - 3 drinks per day. There is no evidence to suggest that premenopausal women seeing treatment for their HSDD would exhibit the excessive alcohol consumption patterns tested in the Alcohol Study.

Moreover, flibanserin is to be taken at bedtime, not earlier in the evening when alcohol consumption is more likely to occur. Similar to other drugs with CNS depressant activity, flibanserin when used as directed in the proposed labeling and as it was in Phase 3 studies (subjects were instructed to take flibanserin at bedtime and were not prohibited from consuming alcohol per their usual habits), presented a manageable risk of sedation-related AEs.

In light of the results of the Alcohol Study, the proposed package insert warns that alcohol may increase the risk of CNS depression with flibanserin and that patients should avoid alcohol until they know how flibanserin affects them.

#### **4.5.2.1.3 Assessment of Overall Risk of Sedation-Related AEs**

Flibanserin has an acute sedative effect that is maximally evident 1.5 to 2.5 hours after dosing along with a pharmacodynamic CNS depressant effect. AEs of dizziness, somnolence, fatigue and sedation were common in the Phase 3 (bedtime dosing) studies, and more pronounced in certain Phase 1 (morning dosing and concomitant drug or alcohol use) studies. The frequency and severity of sedation-related AEs were largely dose dependent and transient. The flibanserin Phase 3 data suggest that increased exposure to flibanserin via moderate to strong CYP3A4 inhibition may also increase rates of fatigue and dizziness but does not appear to increase rates of somnolence and sedation. Results of the Driving and Cognition Study have confirmed an absence of next-day impairment on driving ability or cognition with bedtime dosing of flibanserin at acute, steady state or supratherapeutic (double) exposures.

Consistent with this profile, the Sponsor has developed flibanserin for bedtime dosing in an effort to minimize the clinical impact of these effects. In Phase 3 studies, with subjects taking flibanserin as directed in the proposed package insert, the risk of adverse effects related to CNS depression (e.g., dizziness, somnolence, fatigue and sedation) is consistent with or less than that of many over-the-counter medications.

More frequent and significant sedation-related AEs were seen in the Alcohol Study. Concomitant daytime administration of flibanserin with large quantities of alcohol in subjects not accustomed to flibanserin caused a progressive increase in self-reported sedation and an increase in the number of subjects reporting dizziness and somnolence. Severity of dizziness and somnolence also appeared to increase when flibanserin was co-administered with alcohol. However, both the rate of somnolence AEs (66.7%), and the rate of severe somnolence (2 of 24 subjects; 8.3%) in the flibanserin 100 mg (no alcohol) group in that study were markedly higher than the corresponding rates of somnolence (11.2%) and severe somnolence (8 of 1,543 subjects; 0.5%) in the subjects taking the same dose of flibanserin at bedtime in Phase 3 studies. This suggests that some portion of the sedation effects seen in the Alcohol Study may be attributable to the daytime dosing or other study design elements.

While the risk of sedation-related AEs with flibanserin may increase with daytime dosing, in the presence of strong or moderate concomitant CYP3A4 inhibitor use or use with alcohol, the risk is still readily manageable. Sedation-related risks will be minimized in clinical practice through patient and prescriber understanding of the flibanserin safety profile and the importance of bedtime dosing, skipping any missed dose, avoidance of concomitant strong or moderate CYP3A4 inhibitors and a warning that the patient should avoid alcohol consumption until she knows how flibanserin affects her.

The observed frequency of CNS adverse effects reported with flibanserin is routinely reflected in product labeling to alert prescribers and patients to avoid certain situations and to monitor for and take appropriate action if such events occur in an individual patient. The package insert is a

standard and effective tool for such communication and will be supplemented in the case of flibanserin with a Medication Guide and Communication Plan distributed in accordance with a Risk Evaluation and Mitigation Strategy (REMS) as discussed in Section 4.6.

### **4.5.3 Hypotension and Syncope (AEs of Special Interest)**

While no signal for syncope or hypotension was noted during conduct of the Phase 3 studies in premenopausal women, clinically significant AEs of hypotension and syncope were observed in three Phase 1 studies of flibanserin that involved daytime dosing and either high exposure or concomitant and significant alcohol use. No hypotension or syncope AEs were noted in other studies that involved high flibanserin exposure (e.g., supratherapeutic dose study, QT study, driving impairment study, hepatic impairment study).

This section considers all hypotension and syncope AEs (whether or not considered clinically significant) in Phase 1 (morning dose) studies which involved concomitant CYP3A4 inhibitor or alcohol administration, presents the results of a dedicated study conducted to assess the true rates of syncope with high flibanserin exposure, and reviews the Phase 3 (bedtime dosing) database for signals of hypotension and syncope in the target population taking flibanserin.

#### **4.5.3.1 CYP3A4 Inhibition**

Flibanserin combined with fluconazole resulted in large flibanserin exposure increases (AUC 7-fold;  $C_{max}$  2.24-fold). The Fluconazole Study was discontinued due to hypotension-related AEs seen in three subjects following dosing with flibanserin 100 mg and fluconazole 200 mg. One of these events was clinically significant with the subject becoming unresponsive with a blood pressure of 64/41 mm Hg. Each of these events occurred approximately 1 hour after dosing when serum levels of flibanserin were near their maximum. Pharmacokinetic data collected near the time of these events indicates that these three subjects had the three highest  $C_{max}$  values of subjects dosed with flibanserin while at steady-state on fluconazole. These values were 3 to 4 times in excess of the mean for subjects taking flibanserin alone in the study (e.g., 1,290 - 1,530 ng/mL versus 405 ng/mL mean for flibanserin alone). AUC values were 6 to 9 times in excess of the mean for subjects taking flibanserin alone in the study (e.g., 11,611 - 16,547 h\*ng/mL versus 1869 h\*ng/mL mean for flibanserin alone). This would support the conclusion that hypotension is more likely with excessive levels of flibanserin than with therapeutic levels. No subjects in the other treatment groups had hypotensive events.

Flibanserin combined with itraconazole resulted in no syncope or hypotension AEs despite mean exposure increases (AUC 2.57-fold;  $C_{max}$  1.69-fold) over flibanserin alone. Flibanserin combined with ketoconazole resulted in higher mean flibanserin exposure increases (AUC 4.50-fold;  $C_{max}$  1.84-fold) compared with flibanserin alone. Orthostatic hypotension (2 episodes) and syncope (2 episodes) were reported in a single subject receiving flibanserin plus ketoconazole. The second episode occurred 17 days after dosing. The events resolved without treatment but led to her discontinuation from the study. An additional report of moderate

syncope, and moderate circulatory collapse, both of which resolved without treatment occurred in a subject dosed with flibanserin alone. Because both subjects who experienced these episodes in the ketoconazole study vomited after flibanserin administration,  $C_{max}$  and AUC values recorded for these subjects are minimally informative.

Results across these studies are summarized in [Table 33](#).

**Table 33 Summary of Hypotension and Syncope AEs with Concomitant CYP3A4 Inhibitor Exposure or Hepatic Impairment**

Study	N	Fold Increase in $AUC_{0-\infty}$	Fold Increase in $C_{max}$	Subjects with Hypotension AEs	Subjects with Syncope AEs	SAEs
Hepatic impairment	28	4.5	0.9	0	0	0
Itraconazole	12	2.6	1.7	0	0	0
Ketoconazole	24	4.5	1.8	2	2	0
Fluconazole	15	7.0	2.2	3	0	0
Grapefruit juice	26	1.4	1.1	0	0	0

Notes: AEs = Adverse events; SAEs = Serious adverse events.  
Includes Studies 511.111, 511.37, 511.67, SPR-12-01.

#### 4.5.3.2 Dedicated High Dose Study

The High Dose Study was specifically conducted to understand the risk of syncope in the setting of supratherapeutic flibanserin exposure in the morning hours. This was a single center, 2-stage, double-blind, placebo-controlled, single-dose trial. Stage 1 included 3 cohorts of 4 subjects each. This stage followed a sequential, ascending-dose, crossover design, in which subjects received a single dose of placebo and single doses of 2 of 3 flibanserin dose levels (100, 150, or 200 mg). For each cohort, 1 dose was administered each morning on 3 successive days in the sequences shown below. Orthostatic changes and pharmacokinetic parameters were assessed for 48 hours after morning dosing.

##### Stage 1 (Three Cohorts)

Cohort	Number of Subjects	Period 1	Period 2	Period 3
1	4	Flibanserin 100 mg	Placebo	Flibanserin 200 mg
2	4	Placebo	Flibanserin 150 mg	Flibanserin 200 mg
3	4	Flibanserin 100 mg	Flibanserin 150 mg	Placebo

##### Stage 2 (Two Cohorts)

Cohort	Treatment Arm
4	Placebo (n=2) Flibanserin 250 mg (n=6)
5	Placebo (n=2) Flibanserin 300 mg (n=6)

No trends were noted in the mean changes from sitting to standing blood pressure during the study across the flibanserin and placebo treatment groups. During the first four hours of the treatment phase, clinically significant decreases in blood pressure ( $\geq 20$  mm Hg) occurred in three of the eight subjects after dosing with flibanserin 100 mg and one of the eight subjects after dosing with flibanserin 200 mg. In each of the flibanserin 100 mg and flibanserin 250 mg (N = 6) groups, one additional clinically significant decrease in Systolic Blood Pressure (SBP) was noted in the post-treatment period (48 h after dosing). Higher doses showed no tendency for greater effects.

A total of 41 clinically significant changes in sitting to standing pulse rate ( $\geq 20$  bpm) were observed during periods when subjects received flibanserin, compared to 8 clinically significant changes in sitting to standing pulse rate during periods when subjects received placebo. During the first four hours after dosing, the greatest number of events (16) occurred at the flibanserin 100 mg dose, with fewer events at 150 mg (11), 200 mg (12), 250 mg (10) doses and with placebo (5). One additional clinically significant increase in pulse rate was reported for each of the flibanserin 100 mg, 150 mg and 250 mg groups in the post-treatment period while 4 such events were reported for placebo. While flibanserin appears to have some effect on pulse rate, higher doses show no tendency for greater effects.

The most commonly reported AE during the study was dizziness, the frequency of which generally increased with higher doses. Dizziness was reported in 12.5% (1/8) of subjects when receiving 100 mg of flibanserin, 37.5% (3/8) of subjects receiving 150 mg of flibanserin, 85.7% (6/7) of subjects receiving 200 mg of flibanserin, 83.3% (5/6) of subjects in the 250 mg flibanserin group, and 7.1% (1/14) of subjects receiving placebo.

Dose escalation was stopped after the 250 mg cohort because a review of the blinded safety results showed that the protocol-specified stopping criteria had been met (i.e., if 3 of 8 subjects experienced moderate or severe AEs that were considered possibly or probably related to study medication, then escalation to the next higher dose group was not undertaken). All six subjects in the flibanserin group experienced an event which met these criteria. These events were dizziness, somnolence, nausea, fatigue, disorientation, muscular weakness and back pain.

A single additional mild syncope event lasting one minute was reported in a subject dosed with flibanserin 200 mg in a Phase 1, morning dosing study of flibanserin's potential for drug liking. The event occurred 56 minutes after dosing.

#### **4.5.3.3 Concomitant Use with Alcohol**

The primary objective of the Alcohol Study was to evaluate the effect of combined administration of flibanserin 100 mg and high doses of ethanol on seated blood pressure, orthostatic vital signs, and oxygen saturation. A five-way cross-over design compared morning dosing of flibanserin 100 mg alone to ethanol at two different concentrations (0.4 g/kg and 0.8 g/kg) with and without flibanserin 100 mg.



Signals of an effect on orthostatic hypotension were detected during the study:

- Seated vital signs were largely stable throughout the study. Flibanserin with 0.8 mg/kg ethanol produced a decrease in mean SBP (-10.8 to -12.0 mm Hg) at 6 and 8 hours. No other mean changes in systolic blood pressure, diastolic blood pressure or heart rate were seen in any other group.
- No mean changes in blood pressure met criteria for orthostatic hypotension (decrease of 20 mm Hg for systolic blood pressure or 15 mm Hg diastolic blood pressure upon standing up) with any treatment. On an individual basis, more subjects met criteria for orthostatic change in systolic and diastolic blood pressure when dosed with flibanserin 100 mg plus ethanol than when dosed with either flibanserin or alcohol alone.
- For pulse rate, treatment with ethanol (either concentration) and flibanserin led to mean increases that met the criterion for increased heart rate (increase of >20 bpm) at 3 of 4 time points (over 1.5 to 4 hours following dosing). The orthostatic hypotension criterion was met at one time point (3 hours) after 0.8 g/kg ethanol + placebo and at no time points following treatment with 0.4 g/kg ethanol + placebo or flibanserin 100 mg alone.
- The percentage of subjects with pulse rate increases  $\geq 20$  bpm upon moving from a sitting to standing position was generally higher after single dose of flibanserin 100 mg + ethanol 0.8 g/kg compared to other treatments, particularly during the 0.5 to 6 hour interval after dosing. A greater percentage of subjects (29.2% - 70.8%) met the criterion for clinically meaningful pulse rate increase at every time point through 6 hours after dosing during the periods when they received flibanserin 100 mg + ethanol 0.8 g/kg compared to flibanserin alone (8.3% - 50.0%).

In addition, rates of hypotension, syncope and dizziness reported as AEs in the study are shown below in [Table 34](#) with an effect on dizziness apparent upon concomitant daytime administration of flibanserin with these quantities of alcohol. AEs of severe syncope, dizziness and/or hypotension requiring medical intervention were reported in three subjects receiving 0.4 g/kg ethanol plus flibanserin and one event of severe dizziness was reported in a subject receiving 0.8 g/kg ethanol plus flibanserin.

**Table 34 Number (%) of Subjects with Adverse Events of Interest by Treatment Group and Preferred Term – Alcohol Study**

<b>Preferred Term, n (%)</b>	<b>Placebo + 0.4 g/kg Ethanol (N=24)</b>	<b>Placebo + 0.8 g/kg Ethanol (N=25)</b>	<b>Flibanserin 100 mg (N=24)</b>	<b>Flibanserin 100 mg + 0.4 g/kg Ethanol (N=23)</b>	<b>Flibanserin 100 mg + 0.8 g/kg Ethanol (N=24)</b>
Hypotension	0	0	0	1 (4.3)	0
Orthostatic hypotension	0	0	0	1 (4.3)	0
Syncope	0	0	0	1 (4.3)	0
Dizziness	3 (12.5)	3 (12.0)	4 (16.7)	5 (21.7)	5 (20.8)

Notes: n = Total number of subjects; N = Total population size.

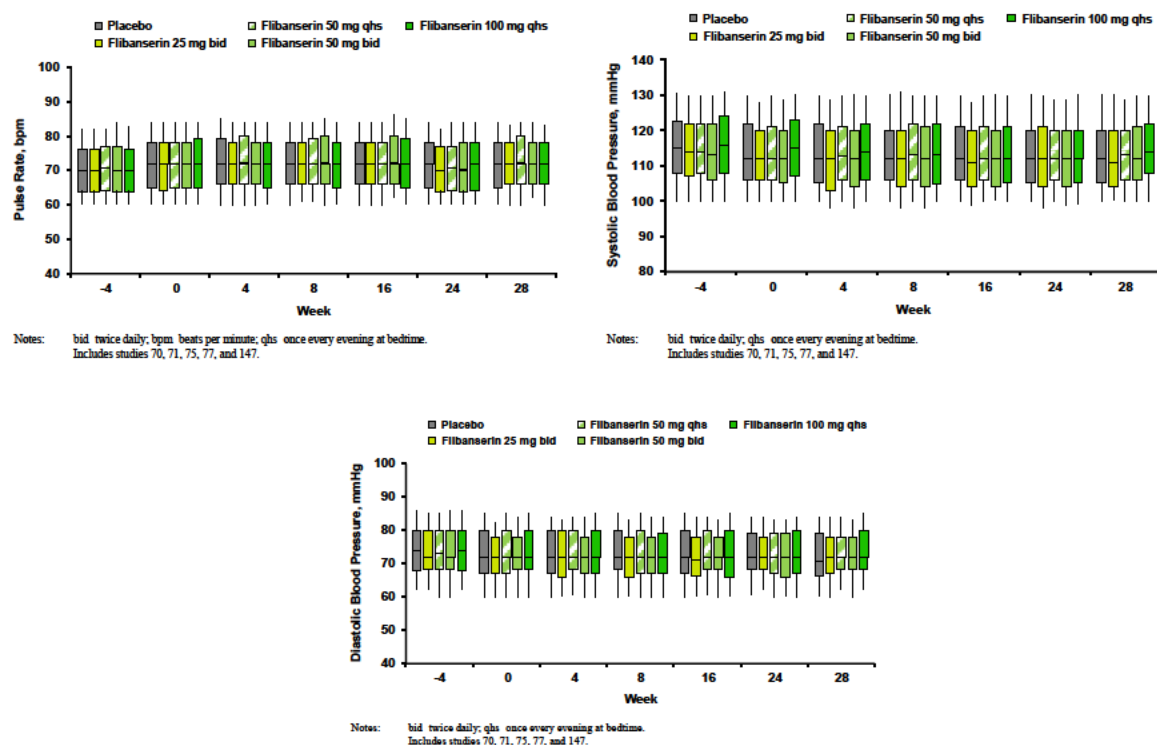
Source: SPR-12-03 CTR Table 14.3.1.2, Module 5.3.4.1

Rapid daytime consumption of high doses of ethanol and flibanserin 100 mg in subjects not accustomed to flibanserin therapy constitutes an extreme challenge. The Phase 3 study data were explored to compare rates of AEs in premenopausal subjects taking flibanserin 100 mg qhs in non-users of alcohol to rates in those who reported alcohol use at baseline. Hypotension- and syncope-related events (syncope, vasovagal syncope, postural dizziness, loss of consciousness, decreased blood pressure, hypotension, circulatory collapse) were reported in 6 (0.7%) of flibanserin 100 mg subjects reporting alcohol use at baseline, and 2 (0.3%) subjects reporting no alcohol use at baseline. The hypotension and syncope rates in placebo subjects were 3 (0.2%) and 2 (0.3%) for non-users versus users of alcohol, respectively.

#### **4.5.3.4 Phase 3 Studies in Premenopausal Women**

In the Phase 3, double-blind studies in premenopausal women, blood pressure and pulse rate were measured at each clinical study visit. The data reveal no trends toward mean changes in blood pressure or pulse rate across flibanserin dose groups over time ([Figure 26](#)). Similarly, no trends were seen in frequency of subjects with clinically relevant changes in those vital signs or frequency of syncope AEs.

**Figure 26 Mean Pulse Rate, Diastolic and Systolic Blood Pressure by Study Visit - Phase 3 Studies in Premenopausal Women (Target Population Set)**



Among premenopausal women enrolled in the double-blind Phase 3 clinical studies, a total of eight subjects out of 3,973 who received flibanserin at any dose (0.2%) reported eight episodes of syncope or vasovagal syncope (4 mild episodes, 3 moderate episodes and 1 severe episode). Four of 1,905 subjects (0.1%) who received placebo also reported experiencing four syncopal episodes (1 mild episode and 3 moderate episodes). There were two cases of circulatory collapse reported in the premenopausal Phase 3 studies: one each in the flibanserin 100 mg qhs (severe) and placebo (mild) groups. These few events do not suggest an association of flibanserin taken at bedtime and syncope.

The Sponsor also searched the Phase 3 premenopausal double-blind studies for any potential imbalance in number of other events potentially related to hypotension. A total of 9 subjects out of 3,973 who received flibanserin at any dose (0.2%) reported 10 other events potentially related to hypotension with AE terms of postural dizziness, loss of consciousness, decreased blood pressure and hypotension (4 mild episodes, 5 moderate episodes and 1 severe episode). One of 1,905 subjects who received placebo (<0.1%) also reported experiencing a single similar episode (mild).

Nineteen flibanserin subjects who reported events potentially signaling syncope or hypotension are listed in [Table 35](#).

**Table 35 Individual Hypotension, Syncope or Possible Hypotension-related Adverse Events - Phase 3 Studies in Premenopausal Women (Target Population Set)**

Event	Dose	Severity	Time from Dosing Start (Days)
Syncope	100 mg qhs	Severe	14-15
	50 mg bid	Moderate	5-5
	100 mg qhs	Mild	34-34
	100 mg qhs	Moderate	93-93
	50 mg bid	Mild	34-34
	50 mg qhs	Moderate	24-24
	100 mg qhs	Mild	23-23
Syncope, vasovagal	50 mg bid	Mild	150-200
Circulatory Collapse	100 mg qhs	Severe	11-12
Hypotension	50 mg bid	Moderate	3-9
	100 mg qhs	Mild	45
	100 mg qhs	Mild	86-125
	100 mg qhs	Mild	59-63
	100 mg qhs	Moderate	109
Blood Pressure Decreased	50 mg qhs	Mild	25
Postural Dizziness	50 mg qhs	Moderate	11-29
	50 mg qhs	Moderate	41-146
Loss of Consciousness	50 mg bid	Severe	79
	100 mg qhs	Moderate	34-48

Notes: bid = Twice daily; qhs = Once every evening at bedtime.

Source: ISS Table 2.1.10.

#### 4.5.3.5 Assessment of Overall Risk of Hypotension and Syncope

In general, flibanserin does not appear to have a significant pharmacological effect on blood pressure when used as directed. Isolated instances of both hypotension and syncope have been reported in the Phase 3 program and were largely characterized as mild or moderate in severity. While patients may experience hypotension and/or syncope with therapeutic doses of flibanserin, the risk is low.

The most prominent effects of flibanserin treatment on blood pressure were seen in the Phase 1 program. Individual subjects exposed to high doses of flibanserin, flibanserin and fluconazole, or flibanserin with very high concentrations of ethanol, all dosed in the morning, had episodes of clinically significant hypotension or syncope.

The proposed flibanserin package insert warns that taking flibanserin in the morning, taking doses higher than recommended, or taking flibanserin with moderate to strong CYP3A4 inhibitors or with CNS depressants such as ethanol can result in potentially dangerous incidents

of hypotension or syncope. Moderate to strong CYP3A4 use is contraindicated. Alcohol use is to be avoided until the patient knows how flibanserin affects her. Numerous statements reinforce the need to take flibanserin only at bedtime and to skip any missed bedtime dose. These messages are repeatedly reinforced through a Medication Guide and a REMS (discussed below) that serves to buttress physician, provider and patient understandings of flibanserin safe use.

#### 4.5.4 SAEs

Across all the Phase 3 double-blind studies in the flibanserin development program (over 8,000 women with HSDD), 2 subjects died: one subject randomized to placebo died as a passenger in an airplane crash on Day 19 of the double-blind period and one 54 year-old postmenopausal subject with HSDD and concomitant hypertension, asthma, high cholesterol and atherosclerotic cardiovascular disease died due to severe alcohol poisoning after 13 days on flibanserin 100 mg qhs. Neither death was considered treatment-related by investigators or the Sponsor.

Rates of SAEs were low in the Phase 3 premenopausal studies. For premenopausal subjects who received placebo, 10 women (0.5%) had an SAE compared with 33 women (0.8%) who received any dose of flibanserin and 14 women (0.9%) who received flibanserin 100 mg qhs ([Table 36](#)).

**Table 36 Overall Summary of Adverse Events - Phase 3 Studies in Premenopausal Women (Target Population Set)**

Subjects by Category n (%)	Placebo N = 1905	Flibanserin			
		25 mg bid N = 733	50 mg qhs N = 969	50 mg bid N = 728	100 mg qhs N = 1543
Any Adverse Events	1062 (55.7)	430 (58.7)	628 (64.8)	517 (71.0)	1033 (66.9)
Severe Adverse Events	90 (4.7)	32 (4.4)	69 (7.1)	44 (6.0)	106 (6.9)
Adverse Events leading to discontinuation	112 (5.9)	50 (6.8)	99 (10.2)	148 (20.3)	198 (12.8)
Serious Adverse Events	10 (0.5)	4 (0.5)	10 (1.0)	5 (0.7)	14 (0.9)

Notes: bid = Twice daily; N = Number of subjects; n = Total population size; qhs = Once every evening at bedtime.

Includes Studies 511.70, 511.71, 511.75, 511.77, and 511.147.

Source: ISS Table 2.1.2.

Treatment emergent SAEs are shown by system organ class in [Table 37](#).

**Table 37 Number (%) of Subjects with Treatment-Emergent Serious Adverse Events - Phase 3 Studies in Premenopausal Women (Target Population Set)**

System Organ Class	Placebo, n (%) N = 1905	Flibanserin, n (%)			
		25 mg bid N = 733	50 mg qhs N = 969	50 mg bid N = 728	100 mg qhs N = 1543
Any Serious Adverse Event	10 (0.5)	4 (0.5)	10 (1.0)	5 (0.7)	14 (0.9)
Gastrointestinal disorders	1 (<0.1)	0	1 (0.1)	0	3 (0.2)
Hepatobiliary disorders	2 (0.1)	0	1 (0.1)	1 (0.1)	2 (0.1)
Infections and Infestations	1 (<0.1)	1 (0.1)	3 (0.3)	3 (0.4)	1 (<0.1)
Injury, poisoning and procedural complications	0	1 (0.1)	1 (0.1)	0	4 (0.3)
Investigations	0	0	0	0	0
Metabolism and nutrition disorders	0	0	0	0	0
Musculoskeletal and connective tissue disorders	0	1 (0.1)	1 (0.1)	0	3 (0.2)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1 (<0.1)	0	1 (0.1)	1 (0.1)	1 (<0.1)
Nervous system disorders	0	0	1 (0.1)	0	1 (<0.1)
Psychiatric disorders	1 (<0.1)	0	0	0	1 (<0.1)
Renal and urinary disorders	1 (<0.1)	0	0	0	0
Reproductive system and breast disorders	2 (<0.1)	1 (0.1)	1 (0.1)	0	0
Respiratory, thoracic and mediastinal disorders	0	0	0	0	1 (<0.1)
Surgical and medical procedures	0	0	0	0	1 (<0.1)
Vascular disorders	1 (<0.1)	0	0	0	1 (<0.1)

Notes: bid = Twice daily; n = Total population size; N = Number of subjects; qhs = Once every evening at bedtime.

Includes Studies 511.70, 511.71, 511.75, 511.77, 511.147.

Source: ISS Table 2.2.34.

Six subjects experienced SAEs in the SOC of “Injury, poisoning and complications.” One each occurred in the flibanserin 25 mg bid and 50 mg qhs flibanserin groups and 4 in the flibanserin 100 mg qhs group. Because of the small number of total events in this SOC, the Sponsor expanded this inquiry to the Treated Set of studies in pre and postmenopausal women with HSDD. In that larger population, thirteen subjects experienced SAEs in the SOC of “Injury, poisoning and complications.” Four of these occurred in the placebo group, 1 each occurred in the 25 mg bid and 50 mg qhs flibanserin groups and 7 in the flibanserin 100 mg qhs group. In the flibanserin group there were 2 subjects who experienced SAEs of road traffic accidents (1 in flibanserin 100 mg qhs, 1 in flibanserin 25 mg bid). No SAEs of road traffic accident were reported in the placebo group. A dedicated study to assess next-day simulated driving performance (the Driving and Cognition Study) was conducted and demonstrated no next-day impairment with flibanserin 100 mg qhs at acute and chronic (steady state) dosing or at an acute dose of 200 mg qhs.

The only SAE reported in Phase 1 studies occurred during a 4-week pharmacokinetic study. A 47 year-old female experienced a severe depressive episode that required hospitalization while in the flibanserin 25 mg bid treatment arm. The SAE began on study Day 4 and resolved on study Day 8. While hospitalized, the subject experienced insomnia that also resolved by Day 8. The subject discontinued from the study after receiving 5 doses of flibanserin 25 mg. The subject had no previous history of depression, but indicated that the depressive episode was secondary to a difficult personal situation.

No SAEs were reported in Phase 2 studies.

## 4.5.5 Other AEs of Special Interest

### 4.5.5.1 Suicidal Ideation

Because flibanserin is a centrally-acting drug with serotonergic and dopaminergic activity, the Sponsor has given special consideration to AEs related to depression and suicide/self-injury.

In the Phase 3 trials in pre and postmenopausal subjects, the suicide/self-injury SMQ was reported by <1% of subjects in any treatment group. Suicide/self-injury was reported in 3 (0.12%) subjects in the flibanserin 100 mg qhs dose group (2 suicide ideations and 1 suicide attempt) compared with 4 (0.14%) subjects receiving placebo (4 suicide ideations) (Table 38). One of the two suicide ideations in the flibanserin 100 mg group was an SAE and one of the four suicide ideations in the placebo group was an SAE. Based on the data in completed studies, there was no increase of suicidal ideation in HSDD subjects treated with any dose of flibanserin compared to placebo.

**Table 38 Number (%) of Subjects with Adverse Events of Suicide/Self-Injury by Treatment and Preferred Term - Phase 3 Studies in Premenopausal Women (Treated Set)**

Subjects by Category n (%)	Placebo N = 2792	Flibanserin			
		25 mg bid N = 733	50 mg qhs N = 969	50 mg bid N = 728	100 mg qhs N = 2459
Suicide/Self-injury SMQ					
Suicidal ideation	4 (0.14)	0	2 (0.21)	0	2 (0.08)
Suicide attempt	0	0	0	0	1 (0.04)

Notes: bid = Twice daily; N = Number of subjects; n = Total population size; qhs = Once every evening at bedtime.

Includes Studies 511.70, 511.71, 511.75, 511.77, 511.114, 511.130, 511.147 and 511.156.

Source: ISS Table 2.10.3.

The Beck Scale for Suicide Ideation (BSS) was administered in 4 of the 5 Phase 3 studies of flibanserin in premenopausal women at screening, baseline, Week 24 (on treatment) and Week 28 (post-treatment) visits. The BSS is a validated 21-item instrument (self-reported or administered by a paraprofessional) for detection and assessment of severity of suicidal ideation

in adults. Based on the evaluation using the BSS no signal was detected that flibanserin at any dose could lead to increase of suicidal ideation in premenopausal women.

#### 4.5.5.2 Neoplasms

FDA expressed special interest in breast neoplasms based on the results of one of two rodent carcinogenicity studies showing no significantly increased incidence of the individual mammary gland tumor types in female mice, but a statistically significant increase in combined mammary tumors in female mice treated with the 2 highest doses of flibanserin (200 and 1200 mg/kg/day). No tumors were observed in the mammary glands of male mice.

In all Phase 3 double-blind, placebo-controlled studies, there were 4 cases of breast cancer or breast cancer in situ all of which were SAEs. An additional case of breast cancer in situ was reported on Day 18 of an open-label extension study. Two of the reports of breast cancer in situ were further specified as ductal carcinoma in situ. No additional breast cancer AEs were reported in any of the Phase 2, Phase 3 double-blind pre- or postmenopausal, Phase 3 premenopausal randomized withdrawal or the open-label extension studies (Table 39).

**Table 39 Individual Subjects with Breast Cancer Adverse Events – Flibanserin HSDD Development Program**

System Organ Class Preferred Term	Study No.	Subject	Age (Years)	Days on Therapy at Onset	Actions/Outcome
<b>Placebo</b>					
Breast Cancer	75	31652	42	91	D/Not Yet Recovered
<b>Flibanserin 50 mg bid</b>					
Breast Cancer in situ	70	17636	43	81	D/Not Yet Recovered
<b>Flibanserin 100 mg qhs</b>					
Breast Cancer	77	37755 <sup>a</sup>	27	3	Unknown
Breast Cancer in situ	156	20326	52	105	D/Not Yet Recovered
Breast Cancer in situ	118	36459 <sup>b</sup>	45	18	D/Recovered

<sup>a</sup> Breast cancer was diagnosed 3 months after subject discontinued from the study due to an adverse event of vertigo on treatment Day 3. This breast cancer event is not included in the ISS Summary Tables.

<sup>b</sup> Subject rolled over from Study 511.77 in which she was randomized to placebo. An AE of microcalcification in the same breast was reported in that trial while the subject was on placebo.

Notes: bid = Twice per day; D = Discontinued study; HSDD = Hypoactive sexual desire disorder; qhs = Once every evening at bedtime. Includes Studies 511.68, 511.69, 511.70, 511.71, 511.74, 511.75, 511.77, 511.84, 511.114, 511.118, 511.130, 511.133, 511.147 and 511.156.

Source: ISS Table 2.5.7; ISS Table 2.5.8; ISS Table 2.1.13.

No cases were reported later than 6 months after initiation of therapy. Events were too infrequent to establish any pattern in time of onset. Onset of each event prior to 120 days after start of therapy makes an association with flibanserin unlikely.



The Sponsor has submitted a protocol synopsis for a post-approval, observational, pharmacoepidemiologic safety study using administrative healthcare claims data to monitor for and evaluate any potential signal of breast cancer.

#### **4.5.5.3 Appendicitis**

A total of eight subjects reported appendicitis across the flibanserin HSDD development program. The incidence of appendicitis reported in the Phase 3 double-blind, placebo-controlled studies in premenopausal and postmenopausal women was 1 case (0.1%) for flibanserin 25 mg bid, 2 cases (0.2%) for flibanserin 50 mg qhs, and 3 cases (0.4%) for flibanserin 50 mg bid, while there were no cases reported for women treated with placebo or flibanserin 100 mg qhs. In open-label studies, in which all subjects took flibanserin 100 mg qhs, there were two reported cases of appendicitis. All episodes resulted in surgery (appendectomy) and there was no apparent pattern of first onset of appendicitis.

The estimated annual incidence of appendicitis among women aged 20 - 44 years ranges from 152 per 100,000 (ages 20 - 24) to 74 per 100,000 (ages 40 - 44), for an annual risk of 0.074% - 0.15%. A total of 0.13% of flibanserin-treated subjects in the premenopausal Phase 3 studies experienced appendicitis over a potential six-month exposure period. This incidence is slightly greater than would be expected based on background risk. The reason for the apparent excess prevalence of appendicitis among flibanserin-treated subjects is not clear. While the published literature on this point are not informative, FDA has advised that it may represent a class effect of drugs with 5-HT<sub>2A</sub> antagonism. The Sponsor has submitted a protocol synopsis for a post-approval, observational, pharmacoepidemiologic safety study using administrative healthcare claims data to continue to monitor any risk of appendicitis.

### **4.6 Risk Management**

The Sponsor has developed a comprehensive risk management program to ensure safe use of flibanserin. The safety of flibanserin is optimized when it is taken at bedtime by patients who understand that flibanserin can cause dizziness, syncope or hypotension in addition to sedation. Appropriate patients are those who are premenopausal, have been diagnosed with HSDD, are not taking moderate or strong CYP3A4 inhibitors, and have been cautioned about the risks of concomitant alcohol use. These considerations form the basis of the flibanserin package insert, REMS, and voluntary risk mitigation activities.

In addition, the Sponsor intends to conduct post-approval, observational, pharmacoepidemiologic safety studies using administrative healthcare claims data to continue to monitor for any risk for appendicitis or neoplasms in women taking flibanserin.

#### **4.6.1 Safety Messages**

Various risk management tools (discussed below) have been developed to effectively reinforce and strengthen key flibanserin safety messages. Those messages are delineated here.

#### **4.6.1.1 Risks of Flibanserin**

The risk management program emphasizes flibanserin's CNS depressant effects. Based on sedation-related AEs seen in the clinical development program, it cautions patients, prescribers and dispensers that flibanserin may impair cognition or motor skills. It specifically notes that patients should not operate heavy machinery, including automobiles, until they know how flibanserin affects them.

The risk management program also makes clear that flibanserin can cause dizziness, hypotension and/or syncope.

#### **4.6.1.2 Importance of Bedtime Dosing**

The risk management tools emphasize the importance of bedtime dosing with flibanserin and stress that a missed dose should be skipped rather than taken the next day. Physician-based tools provide information regarding the increased risk of severe AEs if flibanserin is taken during waking hours or when the approved dose is exceeded, and patients are cautioned to avoid driving until the next morning.

#### **4.6.1.3 Avoidance of Moderate to Strong CYP3A4 inhibitors**

The Sponsor has proposed a contraindication for flibanserin with moderate to strong CYP3A4 inhibitors. Both physician and pharmacist communication tools reinforce this contraindication. In addition, patient-facing information has been carefully drafted to ensure patients are aware of the need to stop their flibanserin use during any course of oral antifungal therapy for yeast infections as these are the most likely CYP3A4 inhibitors to be prescribed in the premenopausal HSDD population. Patients are also encouraged to tell their physician if they are taking other nonprescription medicines, vitamins and herbal supplements because of the risk for interactions and serious side effects.

#### **4.6.1.4 Caution When Used with Alcohol**

Flibanserin risk management tools make clear that there is a risk of intensified severe AEs with concomitant use of flibanserin and alcohol or another CNS depressant. Those tools caution against drinking alcoholic beverages or taking other medications that may cause sleepiness until the patient knows how flibanserin affects her.

#### **4.6.1.5 Appropriate Patient Selection**

Flibanserin use should be limited to premenopausal women suffering from HSDD. Multiple risk management tools are designed to discourage use in other populations and explicitly state that flibanserin has not been demonstrated to be safe or effective for the treatment of other forms of FSD.

Several specific tools, discussed below, are designed to assist physicians in quickly and effectively diagnosing HSDD and identifying patients who should not be treated with flibanserin.

Flibanserin will not be effective for all premenopausal patients suffering from HSDD. Its use should also be reserved for only those patients who derive benefit from the therapy. As such, physicians and patients are explicitly advised to discontinue flibanserin in patients who experience inadequate clinical response (increase in sexual desire and/or decrease in distress due to low sexual desire) by 12 weeks of treatment. This message is designed to encourage physicians to make informed decisions about treatment continuation.

#### **4.6.2 Tools**

Each of the messages discussed above is reinforced through multiple risk management tools, some of which form a REMS program.

##### **4.6.2.1 Package Insert**

The proposed flibanserin package insert is intended to prominently put forth responsible messaging and includes, among other things:

- A limitation on use in the Indications & Usage section
- Instructions to stop treatment if adequate clinical response is not achieved by 12 weeks in the Dosage and Administration Section
- Explicit instruction to avoid daytime dosing or double dosing in the Dosing and Administration section
- A Contraindication for use with moderate to strong CYP3A4 inhibitors
- Clear language about the potential risks of sedation, dizziness, hypotension and syncope

A copy of the proposed package insert is provided in [Appendix O](#).

##### **4.6.2.2 Medication Guide**

A Medication Guide, intended to be distributed with each package insert, presents the key risks, necessary precautions and mitigation activities in non-professional language designed for patient comprehension. Clear, patient-friendly language is included regarding bedtime dosing, avoidance of driving until the next morning, discontinuation of therapy if an adequate response is not achieved, avoidance of alcohol until flibanserin's effects are understood and the importance of disclosing other medication use. A copy of the Medication Guide is appended to the proposed package insert in [Appendix O](#).

#### **4.6.2.3 Communication Plan REMS**

The Sponsor recognizes that REMS can be burdensome to the healthcare system and, in part for that reason, numerous approved drugs with somnolence effects sufficient to impair driving ability (e.g., Belsomra (suvorexant), Ambien (zolpidem), Rozerem (ramelteon)) are available without a REMS. The same is true for other CNS active drugs (e.g., Pristiq (desvenlafaxine), Silenor (doxepin)).

A Communication Plan REMS has nonetheless been included as part of flibanserin's risk management program in an effort to assure enhanced awareness of safe use and appropriate prescribing by prescribers, pharmacists and patients. The Sponsor believes this REMS improves patient safety while largely avoiding the potential unintended consequences of Elements to Assure Safe Use (ETASU) - reduction in drug access that may cause HSDD patients to experience an ongoing unmet medical need. Communication Plan REMS, without ETASU, are in place for numerous products with risks of anaphylaxis, fatal neurological toxicity, and severe ischemic events.

##### **4.6.2.3.1 Communication Plan Letters**

The REMS Communication Plan includes annual letters to healthcare providers, pharmacists and professional organizations (prescriber and pharmacist) which are intended to be accompanied by the full package insert and Medication Guide. The healthcare provider letter will also be accompanied by tools for correctly diagnosing HSDD and identifying appropriate versus inappropriate patients for flibanserin. These communications are intended to disseminate the key messages discussed above broadly to family physicians, general practitioners, internists, physician assistants, nurse practitioners, gynecologists, psychiatrists, sexual health practitioners, and pharmacists via both direct outreach and outreach to professional organizations for these practitioners.

##### **4.6.2.3.2 Decreased Sexual Desire Screener (DSDS)**

The Decreased Sexual Desire Screener (DSDS), a copy of which is provided in [Appendix P](#), is a validated aid for identifying women suffering from HSDD. Together with the Appropriate Use Checklist, the DSDS is designed to limit flibanserin use to appropriate patients.

The DSDS was developed consistent with FDA's recommendation to allow easy and accurate identification of patients who would, and those who would not, be appropriate candidates for flibanserin treatment. HSDD is a persistent or recurrent deficiency in or absence of sexual fantasies and desire for sexual activity, which causes marked distress or interpersonal difficulty, and which is not better accounted for by a medical, substance-related, psychiatric, or other sexual condition. Not all women who present with low sexual desire have HSDD. The DSDS is a brief tool designed to facilitate efficient clinical diagnosis of HSDD by obtaining relevant patient history and identifying causative or confounding conditions and important psychosocial information.

The DSDS has been included as part of the REMS to provide expert and non-expert clinicians in the field of sexual medicine with a validated, brief, and reliable, standardized diagnostic tool for HSDD. While not necessary for diagnosis, the DSDS is intended to facilitate and confirm HSDD diagnosis. The Sponsor intends to utilize the DSDS in educational campaigns directed toward healthcare providers likely to prescribe flibanserin in an effort to limit prescribing to premenopausal women with HSDD who are appropriate candidates for flibanserin.

#### **4.6.2.3.3 Appropriate Use Checklist**

The flibanserin Appropriate Use Checklist, a copy of which is provided in [Appendix Q](#), is designed as an aid to HCPs assessing patient appropriateness for treatment with flibanserin and to guide patient counseling regarding the serious risks and safe use of flibanserin. The first page serves as a reminder to physicians to ensure that the patient:

1. Has HSDD
2. Is a premenopausal adult woman
3. Is not pregnant or breastfeeding
4. Does not have impaired hepatic function
5. Is not currently taking a moderate-to-strong CYP3A4 inhibitor

The second page provides a brief and easy-to-follow guideline for counseling patients on the safe use of flibanserin. The Appropriate Use Checklist is included as part of the REMS.

#### **4.6.2.3.4 REMS Website**

The Sponsor intends to establish a flibanserin REMS program website which will make available all key REMS materials: full Prescribing Information, Medication Guide, Dear HCP Letter, DSDS, Flibanserin Appropriate Use Checklist, Dear Pharmacist Letter and Dear Professional Organization Letters (Prescriber and Pharmacist).

#### **4.6.2.4 Non-REMS tools**

##### **4.6.2.4.1 Metered Launch**

Recognizing that specific patient requests for a new drug may put pressure on prescribers, upon approval of flibanserin the Sponsor plans a focused product launch, without use of direct to consumer television and radio advertising of flibanserin for at least 18 months, with a concerted educational effort for prescribers in order to ensure a clear understanding of the appropriate population for flibanserin treatment. The package insert and REMS program, including the Medication Guide and Limitation on Use language are designed to further aid educational efforts.

Based on historical use of some male sexual dysfunction drugs, there may be concern about recreational use of flibanserin by women or couples who suffer no impaired sexual desire but wish to experiment with enhancement of normal desire. In stark contrast to approved phosphodiesterase-5 (PDE-5) inhibitors that act almost immediately after single dose administration and are perceived to enhance sexual performance in men not suffering from erectile dysfunction, flibanserin does not produce on-demand changes in sexual desire, behavior or performance. Flibanserin's effect, which only occurs after chronic dosing, and which is not physically evident, makes the drug an unlikely candidate for experimentation in the non-HSDD population.

Thus, the Sponsor believes that a metered launch coupled with the proposed labeling and risk mitigation activities will enhance appropriate prescribing of flibanserin limited to on-label use, and that flibanserin's mode of action will make it unattractive for recreational use.

#### **4.6.2.4.2 Physician Training**

The Sponsor is preparing a physician training slide deck to again reinforce key messages regarding safe use of flibanserin. HCP training will focus on flibanserin's safety profile and appropriate patient selection. Training will be distributed by the Sponsor's field personnel and Medical Information Department, and will be available on the flibanserin brand website. By presenting appropriate use and safety messages through a different vehicle, physician training provides an additional avenue for reinforcement of those messages.

#### **4.6.2.5 Phase 4 Studies**

The Sponsor intends to conduct post-approval, observational, pharmacoepidemiologic safety studies using administrative healthcare claims data to continue to monitor for any risk of appendectomy or invasive breast cancer in women taking flibanserin.

A case crossover design study will be conducted to determine if there is a positive association between flibanserin and appendectomy (surgery for acute appendicitis). The background incidence of acute appendicitis ranges from 6.3 to 15.2 cases per 10,000 person-years, necessitating the use of a large healthcare claims database and at least 3 years of observation. Cases will be defined as any woman who has received one or more prescriptions for flibanserin during the study period and has an appendectomy (open or laparoscopic) during the follow-up period. Exposure to flibanserin will be determined for a hazard period, defined as the 30 days immediately prior to the date of appendectomy surgery, and for a randomly selected 30-day control period that is a minimum of least 120 days (4 months) prior to surgery. Conditional logistic regression will be used to compare the odds of exposure to flibanserin in the hazard and control periods. If flibanserin causes an increase in the short-term risk of appendectomy, exposures should be more prevalent immediately prior to the surgery and the odds ratio would be >1.0. Because cases serve as their own controls, they are matched on factors that are static during the observation period.

The proposed plan for assessing any increase risk of invasive breast cancer includes a surveillance program to determine if a clinical signal exists, as well as a comparison to a frequency-matched cohort of unexposed women to quantify any risk and explore the role of the treatment on that risk. Because there is limited relevant clinical data at this time, ongoing (annual) surveillance will be initiated immediately upon product distribution to monitor women with flibanserin exposure for subsequent breast cancer diagnoses and rapidly identify any departure in invasive breast cancer incidence from a contemporaneous population-based comparator group. Because any correlation between breast cancer and HSDD itself is unknown, an HSDD cohort (independent of flibanserin exposure) will be assessed for comparison. If determined feasible, a nested case control study will also be conducted to assess any association between flibanserin exposure and breast cancer among women diagnosed with HSDD.

#### **4.6.2.6 Enhanced Pharmacovigilance**

The Sponsor is developing an Enhanced Pharmacovigilance Plan for the collection, reporting and analysis of identified AEs of special interest (AESI) including hypotension, syncope, dizziness, and accidental injuries. Reports may originate from spontaneous sources including HCPs and patients, post-marketing surveillance, Individual Case Safety Reports (ICSRs) from literature sources and ICSRs from websites for which the Sponsor has responsibility (e.g., corporate website, product website). The Sponsor's pharmacovigilance staff will collect as much information as possible about these events in a standardized fashion, including by active follow-up queries when necessary. Further, focused questionnaires will be used to determine if other factors, such as alcohol use, concomitant use of OTC or prescription CNS depressant, concomitant use of a moderate or strong CYP3A4 inhibitor and/or timing of dosing may have contributed to the spontaneous event reported. The Sponsor's pharmacovigilance staff will specifically look for trends linking AEs to alcohol intake, concomitant use of CNS depressants, concomitant use of a moderate or strong CYP3A4 inhibitors and/or the timing of dosing on a quarterly basis. Additionally, routine safety signal activity detection will be conducted at the time of the periodic safety reporting.

The enhanced pharmacovigilance program will be implemented through standard operating procedures (SOPs) to ensure a robust, systematic process for capturing, evaluating, investigating, responding to and reporting AEs. A diverse event reports will be individually reviewed and collectively evaluated to determine if changes to the REMS messages could help to further mitigate the risks.

#### **4.6.3 Assessments**

The effect of the REMS and other risk management tools, on HCP and patient understanding of the serious risks of flibanserin and the importance of the risk mitigation strategies will be regularly assessed through multiple measurement tools. Self-administered internet-based survey tools will assess HCP awareness, understanding and use of the DSDS, flibanserin safe use conditions including bedtime dosing, and the need to counsel patients regarding flibanserin AEs.

The medical specialties surveyed will be representative of those prescribing flibanserin for the 3 month period immediately prior to conducting the survey. Flibanserin use patterns will also be evaluated using prescribing information from IMS Health or Symphony Health Solutions to assess age distribution of patients receiving a flibanserin prescription (as a rough indicator of menopausal status), percent of prescriptions written with bedtime or other dosing instructions, and percent of prescriptions written for patients using other prescription drugs.

Patient focused assessment tools will be designed to obtain demographic information for patients who receive a flibanserin prescription and also to assess patient awareness and understanding of common flibanserin AEs and safe use conditions. Semi-annual, self-administered in-depth telephone- and web-based surveys will also assess whether patients received physician counseling specific to safe use conditions, including alcohol use, and adverse events.

Results of these assessment tools will provide critical information regarding the impact of the flibanserin risk management program and any need to change or refine messages or delivery tools.

## **5 BENEFIT RISK PROFILE**

### **5.1 Benefits**

Flibanserin has shown the ability to restore desire, reduce distress and increase SSEs in premenopausal women with HSDD. These benefits have been reproduced across multiple studies, endpoints and time points. They have been shown to be robustly meaningful to women with HSDD – a condition which significantly impacts many aspects of patient well-being and for which no other therapies are approved. These benefits come at the cost of modest and transient common side effects when flibanserin is used as directed. Those same side effects can be exacerbated with inappropriate dosing or concomitant medication use, but, even then, can be readily managed. The Sponsor has taken care to draft clear labeling and has proposed a risk mitigation plan designed specifically to minimize these risks. Flibanserin's efficacy far outweighs its AE profile, especially when viewed in light of the risk mitigation activities. Flibanserin should be made available for the benefit of premenopausal women with HSDD.

Premenopausal women with acquired HSDD have lost their previously satisfactory level of sexual desire for a significant period of time and experience significant distress and frustration with their inability to feel sexual desire. HSDD is a serious disorder with impacts far beyond the bedroom affecting relationships, self-confidence and self-image. Women suffering from HSDD are eight to ten times more likely than women with normal desire/distress to report often, very often or always feeling unhappy, disappointed, upset, frustrated, sad, ashamed and bitter, as well as feeling low self-esteem [Leiblum et al., 2006].

Their suffering is exacerbated by the lack of pharmacologic therapies approved for the treatment of HSDD in the U.S. Testosterone is commonly prescribed off-label despite the contrary



recommendations of the American Endocrine Society and FDA. The common use of pharmacy compounded low dose testosterone, much of it dispensed by “anti-aging” clinics, makes a realistic estimate of female testosterone use in HSDD difficult. Bupropion, approved by FDA for the treatment of major depressive disorder and as an aid to smoking cessation has also been used off-label for the treatment of HSDD despite a lack of evidence of efficacy. These unproven treatments expose patients to numerous side effects, arguably of greater concern than CNS depression. HSDD patients are often victims of unscrupulous internet advertisements for products such as “Mami's Estro - Female Sexual Enhancer,” whose name suggests a hormonal ingredient and whose advertisements boast “active ingredients” but whose ingredient list contains neither.

The impact and seriousness of HSDD, the lack of approved therapies and the common use of untested and misleading products for its treatment combine to create a tremendous need for a proven, properly labeled medication that provides quantifiable benefit that patients deem meaningful.

Flibanserin therapy resulted in meaningful improvements over placebo on SSEs, and, more importantly, on desire and distress in three pivotal studies. Flibanserin therapy also demonstrated significant improvements over placebo in all other secondary endpoints no later than Week 16 and continuing through Week 24 with daily eDiary desire as the only outlier in any of these studies (and only when not pooled in these studies).

Substantial weight should be given to the pre-specified PGI-I results as the mechanism for assessing clinical meaningfulness. This method allows patients with HSDD to evaluate the personal impact of flibanserin's treatment effect. Forty-three to 60% of flibanserin subjects in the pivotal program exceeded the patient-anchored criteria for improvement for each measured endpoint, and those patients reported mean changes in defining symptoms that often more than doubled the flibanserin effect in the overall population. This change is noteworthy in the study population who had suffered symptoms of HSDD for a mean of over 4 years and had been in their current relationship for over 10 years.

A substantial portion of the premenopausal HSDD patient population in the pivotal studies consistently found the effects of flibanserin to be clinically meaningful and important to their condition. This view is consistent with the statements of numerous patients at the 27 October 2014 PFDD meeting.

The benefits of flibanserin are meaningful and significant and would provide a welcome treatment option for many premenopausal women suffering from HSDD.

## **5.2 Risks**

Flibanserin safety has been extensively studied across a large Phase 2 and 3 program as well as in dedicated Phase 1 studies. The drug has been tested in a simulated driving and cognition

study, and both the on- and off-label potential for flibanserin to interact with various other drugs and substances has been extensively characterized through Phase 1 studies.

Among the most frequent flibanserin AEs are those consistent with the drug's CNS activity:

Dizziness, somnolence and fatigue with median duration of 11, 37 and 26 days respectively for flibanserin 100 mg qhs, all of which were similar to placebo. There were no SAEs associated with these events in the Phase 3 program. Events were considered "severe" in only 0.5 to 0.7% of the population taking flibanserin 100 mg qhs. Onset of these events was most often during the first week of treatment. In a dedicated study, flibanserin did not impair next-day driving ability.

Flibanserin's safety profile, when the drug is taken as indicated, is no worse than that of many over-the-counter medications such as antihistamines, antidiarrheals and antiemetics, the safety of which is managed by advising the general public to read and carefully follow the drugs' labeling. The adverse events that occur with flibanserin in patients taking 100 mg at bedtime are largely mild sedative effects that would not require significant risk mitigation and, if deemed unacceptable to a given patient, would lead to appropriate discontinuation of therapy. Resolution of these effects occurs within 3 days of drug discontinuation.

These same events can be more pronounced, and rare events of hypotension and syncope can occur, in the off-label setting of daytime dosing, concomitant use of certain drugs and use in combination with significant alcohol consumption – situations that are well-described in the proposed package insert and that are mitigated against by the REMS and other risk management activities being adopted by the Sponsor. Risks are also mitigated by the target population itself which is generally healthy and thus unlikely to use many other drugs.

### **5.3 Risk Benefit Considerations**

The safety profile of flibanserin is consistent with that of other drugs approved on the basis of benefits some may deem modest in indications that, like HSDD, do not result in significant morbidity. One of several examples in the area of bone, reproductive and urologic products is Rapaflo (silodosin) - a new molecular entity approved in 2008 for the chronic treatment of benign prostatic hyperplasia (BPH), a non-life-threatening, male-specific disorder that, while inconvenient and potentially embarrassing, leads to no significant morbidity. Approval was granted on the basis of what FDA referred to as "modest" PRO-based efficacy data: mean changes of 2.9 points over 12 weeks on a 35-point symptom PRO in 2 pivotal trials. Maximum urine flow rate, a key secondary endpoint, also showed modest median improvements of 1 mL/sec over baseline flow rates of 8.4 - 9 mL/sec.

The silodosin labeling contains a warning regarding postural hypotension and the potential for syncope. That warning notes that "[P]atients should be cautioned about driving, operating machinery, or performing hazardous tasks when initiating therapy." Another warning reports the results of a DDI study that showed a 3.8-fold increase in  $C_{max}$  and a 3.2-fold increase in AUC

upon co-administration with ketoconazole. The drug is contraindicated for concomitant administration with strong CYP3A4 inhibitors. No DDI studies were submitted to inform prescribing with moderate CYP3A4 inhibitors.

#### **5.4 Balance of Flibanserin Benefit and Risk for Premenopausal Women with HSDD**

The most significant regulatory differences between silodosin and flibanserin appear to be the prior approval of other therapies for BPH and the relatively small BPH patient population. The resulting larger unmet need in HSDD is compelling in the flibanserin benefit risk determination.

FDA has recognized HSDD as a significant condition for which therapies are needed. FDA has also recognized that flibanserin has demonstrated consistent and meaningful efficacy in the treatment of HSDD. That efficacy is evident across all measured symptoms, on validated instruments across multiple time points, and in a pre-specified responder analysis. The treatment effect has been deemed meaningful by patients. In the arena of female sexual disorders, FDA has repeatedly called for development of the lowest effective dose – that is, drugs that provide a meaningful benefit but that are administered at a dose that may sacrifice additional benefit in favor of maintaining a more favorable side effect profile. Flibanserin was the subject of numerous studies examining different doses and dosing regimens which resulted in the selection of the 100 mg qhs dose as optimal because it has an effect that is clinically significant and it demonstrated a favorable AE profile when compared with higher doses and different dosing regimens.

At 100 m g qhs, 43%-60% of flibanserin patients in the pivotal program exceeded the patient-anchored criteria for improvement for each measured endpoint, and those patients reported mean changes in important symptoms that often more than doubled the effect in the overall population. The proposed package insert language instructing that patients should discontinue therapy if improvement is not seen within 12 weeks is designed to increase the likelihood that women who take flibanserin chronically will experience this magnitude of effect.

The large flibanserin Phase 1, Phase 2 and Phase 3 programs have allowed for extensive characterization of drug-related adverse effects, including effects in specific unintended situations. Serious risks are, for the most part, theoretical and can be managed through labeling and other risk management tools as they are for other drugs. The concern for side effects is somewhat ameliorated in the setting of a symptomatic disease like HSDD in which patients will stop taking medication if not receiving benefit or if they experience unacceptable side effects.

The Sponsor has sought to develop draft labeling and risk management measures that adequately instruct physicians and patients on the appropriate use of flibanserin and looks forward to working with FDA to refine these tools. Patients at the 27 October 2014 patient-focused drug development meeting reported a willingness to risk serious (and often unknown) adverse effects

and even to undergo periodic minor surgery with its related risk of serious infection in order to obtain relief from HSDD symptoms.

In summary, flibanserin has shown statistically significant, rapid, consistent, sustained, clinically meaningful improvements in HSDD symptoms in premenopausal women. Its known common safety risks are recognizable and manageable. Less common events which are potentially clinically relevant and drug-drug interactions are well-characterized and are readily avoided through appropriate prescribing information and a REMS. The benefit-risk profile of flibanserin for the treatment of premenopausal women with HSDD is highly positive and warrants approval.

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## **APPENDICES**

## **APPENDIX A FDA MINUTES OF FLIBANSERIN 2010 ADVISORY COMMITTEE**



U.S. Food and Drug Administration

## **Notice: Archived Document**

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**Summary Minutes of the  
Advisory Committee for Reproductive Health Drugs  
June 18, 2010**

**Location: Hilton Washington DC North/Gaithersburg, 620 Perry Parkway,  
Gaithersburg, Maryland**

**All external requests for the meeting transcripts should be submitted to the CDER,  
Freedom of Information office.**

**These summary minutes for the June 18, 2010 Meeting of the Advisory Committee  
for Reproductive Health Drugs of the Food and Drug Administration were  
approved on August 24, 2010.**

**I certify that I attended the June 18, 2010, Meeting of the Advisory Committee for  
Reproductive Health Drugs of the Food and Drug Administration and that these  
minutes accurately reflect what transpired.**

\_\_\_\_\_/s/\_\_\_\_\_  
Kalyani Bhatt  
Designated Federal Official, ACHRD

\_\_\_\_\_/s/\_\_\_\_\_  
Julia V. Johnson, M.D.  
Committee Chair

The Advisory Committee for Reproductive Health Drugs of the Center for Drug Evaluation and Research met on June 18, 2010 at the Hilton Washington DC North/Gaithersburg, The Ballrooms, 620 Perry Parkway, Gaithersburg, Maryland. Prior to the meeting, members and invited consultants were provided background material from the FDA and Sponsor. The meeting was called to order by Julia V. Johnson, M.D., Acting Chair; the conflict of interest statement was read into the record by Kalyani Bhatt (Designated Federal Official). There were approximately two hundred (200) persons in attendance. There were twelve (12) speakers for the Open Public Hearing Session.

**Issue:** New drug application (NDA) 22-526, (flibanserin) tablets, 100 milligrams (mg), Boehringer Ingelheim Pharmaceuticals, Inc., for the proposed indication of the treatment of hypoactive sexual desire disorder (HSDD) in premenopausal women.

**Attendance:**

**Advisory Committee for Reproductive Health Drugs Members (Voting):**

Julia V. Johnson, M.D. (Acting Chair), Kathleen Hoeger, M.D., M.P.H., John Kittelson, Ph.D., Valerie Montgomery Rice, M.D.

**Industry Representative Member (Non-Voting):** Industry Representative was not present at the meeting.

**Patient Representative:** Patient Representative was not present at the meeting.

**Special Government Employee Consultants (Temporary Voting Members):**

Diane Aronson (Acting Consumer Representative); Marianne Brandon, Ph.D., Scott Emerson, M.D., Ph.D., Julia R. Heiman, Ph.D., Paula Hillard, M.D., Bryce B. Reeve, Ph.D., Matthew V. Rudorfer, M.D.

**FDA Participants (Non-Voting):** Julie Beitz, M.D., Scott Monroe, M.D., Lisa Soule, M.D., Dan Davis, M.D., Olivia Easley, M.D., LaiMing Lee, Ph.D., Lisa Kammerman, Ph.D.

**Advisory Committee for Reproductive Health Drugs Members Not Present:** Sandra Carson, M.D., Paul Blumenthal, M.D., M.P.H., Richard Bockman, M.D., Maria Bustillo, M.D., Bart Clarke, M.D., Daniel L. Gillen, Ph.D., Melissa Gilliam, M.D., Robert Gut, M.D., Ph.D., James H. Liu, M.D.

**Designated Federal Official:** Kalyani Bhatt, B.S., M.S.

**Open Public Hearing Speakers:**

1. Sue Goldstein
2. Irwin Goldstein, MD, Director, Sexual Medicine, Alvarado Hospital, San Diego, CA  
Clinical Professor of Surgery, University of California at San Diego  
Editor-in-Chief, The Journal of Sexual Medicine
3. Leonore Tiefer, PhD, Clinical Assoc. Professor  
Department of Psychiatry  
NYU School of Medicine
4. Dr. Thea Cacchioni, Lecturer, Sociology  
Irving K. Barber School of Arts & Sciences  
University of British Columbia Okanagan
5. Michelle King Robson, Founder/CEO EmpowHER
6. Karen M. Hicks, Ph.D.
7. Susan Wysocki, The National Association of Nurse Practitioners in Women's Health (NPWH)
8. Adriane Fugh-Berman, MD, Associate Professor, Georgetown University Medical Center and Director of PharmedOut  
Elena Yanchar and Antonie Meixel
9. Liz Canner, Director  
Astrea Media, Inc.
10. Wayne C. Shields  
President and CEO, Association of Reproductive Health Professionals
11. Amy Allina, Program Director  
National Women's Health Network
12. Kim Whittemore

## AGENDA

Call to Order and Introductions	Julia Johnson, M.D., Acting Chair Advisory Committee for
Reproductive	Health Drugs (ACRHD)
Conflict of Interest Statement	Kalyani Bhatt, B.S., M.S. Designated Federal Official,
ACRHD	
Welcome and Comments	Scott Monroe, M.D. Director, Division of Reproductive and Urologic Products (DRUP)
Sponsor Presentation	Boehringer Ingelheim Pharma., Inc. Sabine Luik, M.D. Corporate Senior Vice President Quality, Regulatory, Pharmacovigilance and Epidemiology Boehringer Ingelheim GmbH
	Anita Clayton, M.D David C. Wilson Professor of Psychiatry & Neurobehavioral Professor of Clinical Obstetrics & Gynecology University of Virginia
	Michael Sand, Ph.D., M.P.H. Global Strategic Leader, flibanserin Director, General Medicine Boehringer Ingelheim
Pharmaceuticals	
	Lutz Hilbrich, M.D. Executive Director, General Boehringer Ingelheim
Medicine Pharmaceuticals	
	Anita Clayton, M.D
FDA Presentation	

Daniel Davis, M.D.  
Medical Officer  
DRUP

Safety

Olivia Easley, M.D.  
Medical Officer  
DRUP

Clinical Pharmacology

LaiMing Lee, Ph.D.  
Clinical Pharmacologist  
Office of Clinical Pharmacology  
(OCP)

Questions from the Committee to  
Sponsor and FDA

Open Public Hearing

Committee Discussion and Voting  
Adjournment



## Questions to the Committee

- 
1. Considering that the two primary US efficacy studies did not demonstrate efficacy for the prespecified co-primary endpoint of sexual desire as measured by the daily eDiary:
- a. Do you agree with the Applicant that the impact of flibanserin on sexual desire is better evaluated with the desire domain of the FSFI using 28-day recall?

**(Vote)**

Yes- 2      No - 9      Abstain- 0

*Overall, those that voted yes noted that the FSFI (Female Sexual Function Index) is a standardized tool and although imperfect, it is a standardized tool for looking at sexual desire. The daily diary is not a verified tool, while the FSFI is a well-known and published tool where as the daily diary is a non-standardized tool.*

*Overall, those that voted no recognized that the Sponsor and FDA had agreed a priori on the use of the eDiary. The group as a whole felt that some form of daily measurement is of greater value than the 28-day recall used by the FSFI. It was also mentioned that for future consideration utilizing the daily diary and putting it into a monthly format may offer some valuable information.*

*Please see the transcript for detailed discussion.*

- b. Is it appropriate to alter the prespecified method of assessing sexual desire?

**(Vote)**

Yes- 2      No - 9      Abstain- 0

*Overall, those that voted yes stated that it was appropriate to alter the pre-specified method of assessing sexual desire from the eDiary (electronic diary) to the FSFI (Female Sexual Function Index) as they reasoned that the FSFI is a standardized and tested tool.*

*Overall, those that voted no felt that altering the pre-specified method of assessing sexual desire during the clinical trial did not maintain the integrity of the trial. Those that voted no also felt that changing the method should have been addressed earlier than the Phase 3 trial.*

*Please see the transcript for detailed discussion.*

2. Has the Applicant provided sufficient evidence of overall efficacy for flibanserin for the treatment of hypoactive sexual desire disorder (HSDD) compared to placebo?

**(Vote)**

Yes- 1      No - 10      Abstain- 0

*The committee's consensus was that the applicant did not provide sufficient evidence of the overall efficacy for flibanserin for the treatment of hypoactive sexual desire disorder (HSDD) as concerns were raised that improvement was not shown in sexual desire through the eDiary between flibanserin and placebo. It was recognized that there was a significant improvement in SSE between flibanserin and placebo, and patient satisfaction with the treatment was noted*

*The committee raised concerns regarding the number of individuals who dropped out due to adverse events. Due to the high drop out rate and the design of the study for those who dropped out to consider themselves as being closed out of the study, the Committee did not feel that they had the necessary information to evaluate this medication effectively. During discussion, it was identified that HSDD is a real condition; however, the diagnosis is still challenging. The committee acknowledged that indeed there is a significant need for women to have a treatment for HSDD and that efforts need to be put forth to continue to find ways to treat this disorder.*

*Please see the transcript for detailed discussion.*

3. Considering the available data on efficacy and safety, has the Applicant demonstrated that the overall risk/benefit profile of flibanserin for the treatment of HSDD in premenopausal women is acceptable?

**(Vote)**

Yes-0      No -11      Abstain-0

*The Committee felt that that the efficacy of flibanserin was not sufficiently robust to justify the risks. Overall, the Committee was concerned over the safety signals seen. Concerns were also raised regarding potential drug interactions with flibanserin. The Committee felt that data needed to be provided on the long term use of flibanserin. Further documentation of improved sexual desire is critical for reconsideration of this medication for treatment of HSDD.*

*Please see the transcript for detailed discussion.*

*The meeting adjourned at approximately 3:30 PM.*

## **APPENDIX B FLIBANSERIN REGULATORY HISTORY**

## FLIBANSERIN REGULATORY HISTORY

Key Communications	Date
IND submitted	15 October 1996
IND transferred to current review division	7 May 2002
Type C Meeting	28 April 2004
End-of-Phase-2 meeting	21 April 2005
Type C Meeting	28 June 2005
Responses to Type C Meeting Questions	9 October 2007
Pre-NDA Meeting	10 October 2007
Type C Meeting	8 January 2009
NDA Submission	27 October 2009
Advisory Committee Meeting	18 June 2010
Type A Meeting	22 July 2010
Complete Response Letter:	27 August 2010
<ul style="list-style-type: none"> <li>Conduct one additional Phase 3 efficacy study on SSEs, desire and distress</li> <li>A validated endpoint of desire could be used to replace eDiary Desire</li> <li>Use less restrictive entry criteria in new Phase 3 study</li> <li>Complete safety study on co-use with SSRI/SNRI to look for exacerbation of depression</li> <li>Conduct co-use study with alcohol</li> <li>Conduct supratherapeutic dose study to assess potential for syncope at high doses</li> <li>Conduct drug-drug interaction study with moderate CYP3A4 inhibitor</li> <li>Conduct a drug-drug interaction study with moderate CYP3A4 inducer</li> <li>Conduct metanalysis of Phase 1 PK and safety data in oral contraceptive users</li> <li>Assess risk of accidental injury in ongoing and future studies</li> </ul>	
Transfer of Ownership Acknowledgement	17 February 2012
Pre-NDA meeting	26 April 2012
NDA Resubmission	28 March 2013
<ul style="list-style-type: none"> <li>Included Study 147, SSRI/SNRI Study, Alcohol Study, Supratherapeutic Dose Study, Fluconazole Study, Etravirine Study, metanalysis in oral contraceptive users, assessment of accidental injury risk</li> </ul>	
Complete Response Letter	27 September 2013
<ul style="list-style-type: none"> <li>Concern regarding magnitude of treatment effect</li> <li>Explore ways to improve measure of desire</li> <li>Propose method for easy diagnosis of HSDD</li> <li>Clarify how risks of CNS depression, syncope, hypotension and accidental injury will be minimized in clinical practice</li> <li>Propose strategies for avoidance of important drug-drug interactions</li> <li>Conduct a driving impairment study</li> <li>Conduct study to assess effects of CYP2C19 and CYP2C9 enzymes on metabolism</li> </ul>	
Appeal Request	3 December 2013
Appeal Meeting	10 January 2014
Denial of Appeal	7 February 2014
<ul style="list-style-type: none"> <li>Conduct a driving impairment study</li> <li>Conduct study to assess effects of CYP2C19 and CYP2C9 enzymes on metabolism</li> </ul>	
Type A Meeting	12 March 2014
Pre-NDA Meeting	15 January 2015
NDA Resubmission	18 February 2015
<ul style="list-style-type: none"> <li>Included Driving and Cognition Study, CYP2C9/CYP2C19 Study, Updated package insert and REMS regarding adverse event risks and drug-drug interactions, information regarding DSDDS, FSFI-Desire and magnitude of effect</li> </ul>	

## **APPENDIX C SUMMARY OF 27 OCTOBER 2014 PATIENT FOCUSED DRUG DEVELOPMENT MEETING**

**RADM SANDRA KWEDER, M.D.**  
**DEPUTY DIRECTOR OFFICE OF NEW DRUGS**  
**SUMMARY OF 27 OCTOBER 2014 PATIENT FOCUSED DRUG**  
**DEVELOPMENT MEETING**

Well, good afternoon, everyone. And I recognize that we are ten minutes before your opportunity to stand up and stretch. So I'm going to try and summarize what we heard today. And I hope you can bear with me because I am looking at my little laptop screen. But I did try to divide my comments into a couple of areas. One of which is separated first by the two panels and also acknowledging some of the general comments that were made. First I want to thank you for all my colleagues here for being here and spending the day in a room that is sometimes a little dark and seats that are often a little uncomfortable. And in particular for expressing yourselves and a willingness to listen if you didn't express yourself to a discussion about a topic that is sometimes a little uncomfortable. And if you have any doubt about that I ask you to think back to the first panel that got up when Sara got up and tried to generate some discussion. I could see people shifting in their seats. There was a little silence and people are thinking oh my gosh how are we going to fill this afternoon. But quickly you arose to the occasion and I am really glad that you did. I found it very informative and I think I speak for my colleagues in that manner as well. We are not here to solve all the world's problems. That is way beyond any of our pay grades. But we are here to listen and try and respond professionally and thoughtfully to concerns raised by patients who have conditions or concerns that you think that we need to hear about. And you certainly outdid yourselves today in expressing that.

I do want to acknowledge and we heard this throughout the comments peppered during the day and at the end in the open public hearing that -- I want to acknowledge that there is a breadth of perspective on the issues that we discussed today. I would be gravely disappointed if there were not a breadth of perspective. And any time we at the agency tackle something that is difficult there is a wide breadth of perspective and people feel very passionately along that full spectrum. That is just fine. So I will acknowledge that there remains some who are concerned that we need more attention to the etiologies and I use plural and physiology of female sexual disorder conditions that have been the focus of today's discussion particularly they expressed concern about the need to consider the natural variation in sexual desire from one person to the next or over the course of any individual's lifetime and life experiences. A nother concern that was expressed was that we always take care not to allow undue influence from the pharmaceutical industry in any discussions of any particular medical condition. And other speakers expressed concern that not enough attention has been paid to addressing treatments for women who experiencing this condition that we discussed today and there is actually probably a spectrum of conditions based on the kinds of things people raised their hands about in describing their own circumstances. But acknowledging all that I'd like to try and summarize what we heard from Panel 1 that was so eloquently expressed by the panel members.

What was most striking to me was how similar the experiences described by the four panelists seemed to be to those who subsequently expressed themselves in the discussion portion following that panel. I would just recount that 75 percent of you who voted cited no or reduced excitement or pleasure during sexual activity. 75 percent expressed no or reduced non genital sensation during sexual activity. And a large number of you as well particularly made a point to express that your major issue of concern is a lack of any desire to even contemplate sexual activity in the first place. And I would say that was one of the important messages for us today was that this complete lack of interest in sexual activity seems to be a really predominant feature that many of you shared often to the point of working hard in your life to avoid any experience in life or circumstance in your day-to-day existence that might result in pressure to engage in sexual activity. There was an expression by many of having great difficulty in becoming sexually aroused at all with some noting that they can't reach orgasm; although most expressed the difficulty in becoming aroused at all as more important than any orgasmia. Many of you expressed a point in time in your life when you recognized that suddenly something changed. For some people it was the birth of a child, for some people it was surgical intervention. There were a variety of things expressed. But you referred to what was -- had always been for most of your life normal very suddenly became different. Although others of expressed that the onset of this was different. And some who spoke expressed the importance of factoring in age, the variation in that according to a particular age or period of physiologic differences in a woman's life.

One of the things that I heard was that interest is different from arousal. Interest is different from the physiologic process of arousal itself. And arousal may often be generated by interest or physical stimulation but many women experience difficulty in both of those spheres. There is like a Venn diagram where they overlap but they are different. With regard to signs and symptoms it was interesting when Sara brought up the issue with regard to signs and symptoms this discussion of what constitutes a satisfying sexual experience. And some of you expressed that a satisfying sexual experience is not something that is easy to measure. It means different things to different people. But you all raised your hands to indicate that having satisfying sex is different but it is highly different depending on the individual. Overall I think there seemed to be a convergence on satisfaction being related to some sense of emotional positivity and sense of self worth. To me this is an important component. I think we are going to hear more about that tomorrow when we talk about the aspect of being able to measure sexual satisfaction in clinical studies of new drugs. It is something that is often prominent in the scoring system used. So understanding what is behind those is really, really important.

In terms of the effect of the disorder or variations in the disorder on people's lives and functionings all who spoke and this was quite striking indicated what a profound affect this has had on your lives beginning with stressing the effect on your sense of self-worth but in particular your relationships. Not and most prominently your relationship with your spouse or significant other or sexual partner but also how that affect impacted you beyond just that one-on-one

relationship. It affected oftentimes your family lives, your relationships with your family, how you felt about yourself in your ability to do other things in your life. Some described a cycle of anxiety and disappointment associated with coping with the condition. And it was noted and duly noted on our part that having some input as we think about measures to assess this condition getting input from partners of women with this disorder may be important in our understanding its impact on people's lives.

So to move on to Panel 2 and trying to grasp current approaches to treatment, current treatments and how well they worked I did note among the four panelists there was one panelist who focused most particularly on the facilitated work on relationships and developing a sense of really understanding intimacy itself as part of addressing this disorder. And interestingly it was about one in four and also about 25 percent of the people in the room who had done some sort of work like that in seeking to address this disorder. So it seems like the panel was quite representative of the people in the room. The types of things that were mentioned included estrogen treatments, various forms of testosterone, a lot of emphasis and discussion on testosterone. And you really reflected a gamut of experience from topical, injected or pellets. And what was also striking was there was a great variation in people's experiences and success in treatment with testosterone which does suggest that there may be different underlying etiologies of this condition that may respond differently to different hormonal interventions. Estrogens I think we can say that the responses were similarly varied. Several of you mentioned systemic use, noticing improvement in symptoms including more widespread affects that go beyond just sexual function but to other aspects of functioning in day-to-day life particularly those women who had experienced surgical menopause or menopause again going back to the spectrum affects, impacts that different stages in life can have on sexual functioning. Interesting that PDE5 inhibitors, the Viagras, the sildenafil, Cialis and the other things, some have tried them. Those who mentioned them seemed to be not particularly enamored with their effectiveness. And several of you mentioned trying a variety of over-the-counter products to try and address your concerns. Several in the room have participated in clinical trials for flibanserin and those who did mentioned that they had participated indicated that they had had positive effects from that drug on sexual desire.

The side effects that were mentioned were not surprising, in particular I would say the most prominent one was undesired hair growth with testosterone was the one that was mentioned most often and a variety of other things but didn't seem to have any patterns. As far as an ideal treatment I thought that discussion was interesting. Overall a subjective -- what most people seemed to desire most was something that would bring them back to what they saw as having a healthy sexual life and desire to engage in sexual activity. It seems to be the most elusive aspect of successful treatment from what I heard today and probably one that needs the most focus in developing therapies. Favor was expressed by some for treatments that can be managed on an as needed basis. But it was also important to some of you that this isn't something that comes and goes, this sense of self-worth that one has from being able to have a sense of being a sexual



being isn't something that comes and goes, it is kind of a continuum or a continuous desire to feel what one perceives as normal. So I'm not sure there is one ideal. I don't think I came away with a sense that there is one ideal but that there is probably breadth in perspective on this issue. And I think as we proceed and encourage companies to proceed considering therapies in this area and using measure and considering clinical trials for any products that are developed in this field; those are factors that we all collectively in here at FDA and academia where people, and in clinical medicine and in the pharmaceutical industry are going to have to probe these issue a little bit further.

So I couldn't capture absolutely everything that you expressed. I would have been up here all afternoon because that is how long it took to express these things. But I do hope that I've touched on some of the major themes. I think -- I hope that most of you are planning on being here tomorrow because the discussion will be expanded from this to taking what was said today to thinking about how to measure these things; how to take them into consideration in clinical studies; how to develop a study end point and measures of this of these factors that are so important to you as patients so that in any clinical trial we can do you justice and really assess therapies and whether they really do achieve the things that you find most important in meeting your needs. So again thank you for your attention. Thank you for your serious consideration of the plethora of issues that we have before us. And I hope many of you will be joining us tomorrow. Thanks very much.

## **APPENDIX D - SUMMARY EFFICACY DATA FROM NON-PIVOTAL PHASE 3 STUDIES IN PREMENOPAUSAL WOMEN WITH HSDD**

## TABLE OF CONTENTS

	Page
<b>TABLE OF CONTENTS .....</b>	<b>2</b>
<b>LIST OF TABLES .....</b>	<b>3</b>
<b>LIST OF ABBREVIATIONS .....</b>	<b>4</b>
<b>1 SUMMARY EFFICACY DATA FROM NON-PIVOTAL PHASE 3 STUDIES IN PREMENOPAUSAL WOMEN WITH HSDD .....</b>	<b>5</b>
1.1 The Alternate Dosing Study.....	5
1.2 The EU Study.....	7
1.3 Withdrawal Study .....	9

## LIST OF TABLES

	Page
Table 1 SSEs (Standardized) Change from Baseline at Week 24 – Alternate Dosing Study (FAS, LOCF) .....	6
Table 2 eDiary Desire Total Monthly Score Change from Baseline at Week 24 – Alternate Dosing Study (FAS, LOCF).....	6
Table 3 FSFI-Desire Change from Baseline at Week 24 – Alternate Dosing Study (FAS, LOCF) .....	6
Table 4 FSDS-R13 (Distress) Change from Baseline at Week 24 – Alternate Dosing Study (FAS, LOCF) .....	7
Table 5 SSEs (Standardized) Change from Baseline at Week 24 – EU Study (FAS, LOCF) .....	8
Table 6 FSFI-Desire Change from Baseline at Week 24 – EU Study (FAS, LOCF) .....	8
Table 7 eDiary Desire Total Monthly Score Change from Baseline at Week 24 – EU Study (FAS, LOCF) .....	8
Table 8 FSDS-R13 (Distress) Change from Baseline at Week 24 – EU Study (FAS, LOCF) .....	9
Table 9 SSEs (Standardized) Change from Week 24 Baseline at Week 48 – Withdrawal Study (FAS2, LOCF) .....	10
Table 10 eDiary Desire Total Monthly Score Change from Week 24 Baseline at Week 48 – Withdrawal Study (FAS2, LOCF) .....	11
Table 11 FSFI-Desire Change from Week 24 Baseline at Week 48 – Withdrawal Study (FAS2, LOCF) .....	11
Table 12 FSDS-R13 (Distress) Change from Week 24 Baseline at Week 48 – Withdrawal Study (FAS2, LOCF) .....	11

## **LIST OF ABBREVIATIONS**

ANCOVA	Analysis of Covariance
bid	Twice Daily
eDiary Desire	Daily Electronic Desire Measure
EoT	End of Trial
EU	European Union
FAS	Full Analysis Set
FAS2	Full Analysis (population) set during the Second Period
FSDR-R13 (Distress)	Female Sexual Distress Scale – Revised Question 13
FSFI-Desire	Female Sexual Function Index – Sexual Desire Domain
HSDD	Hypoactive Sexual Desire Disorder
LOCF	Last Observation Carried Forward
N	Number of Subjects
Q1	First Quartile
Q3	Third Quartile
qhs	Once Daily at Bedtime
SD	Standard Deviation
SE	Standard Error
SSE	Satisfying Sexual Event
US	United States of America

## **1 SUMMARY EFFICACY DATA FROM NON-PIVOTAL PHASE 3 STUDIES IN PREMENOPAUSAL WOMEN WITH HSDD**

The three non-pivotal Phase 3 studies provided additional clinical and statistical support for the findings arising from the pivotal Phase 3 studies despite differences in dosing levels/regimens, patient populations and/or study design.

### **1.1 The Alternate Dosing Study**

The Alternate Dosing Study was a 24-week, randomized, double-blind, placebo-controlled study in premenopausal women with HSDD designed to evaluate safety and efficacy of flibanserin 25 mg bid, flibanserin 50 mg qhs, and flibanserin 50 mg bid. Co-primary endpoints were mean change from baseline to Week 24 in the frequency of SSEs and mean change from baseline to Week 24 in daily eDiary Desire. Mean change from baseline to Week 24 in FSFI-Desire and FSDS-R13 (Distress) were among the secondary endpoints.

The treated group included 1385 patients, 337 randomized to flibanserin 25 mg bid, 363 randomized to flibanserin 50 mg qhs, 336 randomized to flibanserin 50 mg bid, and 349 randomized to placebo. The efficacy FAS population, with at least 1 dose of trial medication and at least 1 post-dose on-treatment efficacy assessment, included 1316 patients, 324 randomized to flibanserin 25 mg bid, 342 randomized to flibanserin 50 mg qhs, 315 randomized to flibanserin 50 mg bid, and 335 randomized to placebo. Demographic data for the flibanserin and placebo groups were similar for all variables. Baseline scores for efficacy endpoints were comparable in the flibanserin and placebo groups.

In this study, no flibanserin dose was shown to be better than placebo based on either of the co-primary endpoints or on the FSDS-R13 (Distress). For the FSFI-Desire at Week 24, flibanserin 25 mg bid and 50 mg bid treatment groups experienced statistically superior improvements compared to placebo. The lack of a 100 mg qhs flibanserin dose group likely limited the ability of this study to demonstrate efficacy consistent with other studies.

For SSEs (standardized) at Week 24, no flibanserin treatment groups had increases compared with the placebo group ([Table 1](#)).

**Table 1 SSEs (Standardized) Change from Baseline at Week 24 – Alternate Dosing Study (FAS, LOCF)**

Endpoint	Treatment	N	Change from Baseline		
			Mean (SD)	Median (Q1, Q3)	P-value <sup>a</sup>
SSEs (Standardized)	Placebo	325	1.6 (4.3)	0.8 (-0.8, 2.5)	
	Flibanserin 25 mg bid	320	1.5 (3.4)	1.0 (-0.2, 3.0)	0.6085
	Flibanserin 50 mg qhs	334	1.6 (4.2)	1.0 (-0.1, 2.8)	0.6981
	Flibanserin 50 mg bid	291	1.6 (3.5)	1.0 (0.0, 3.0)	0.2517

<sup>a</sup> P-value based on Wilcoxon rank sum test.

Notes: bid = Twice daily; FAS = Full analysis set; LOCF = Last observation carried forward; Q1 = First quartile; Q3 = Third quartile;

N = Number of subjects; qhs = Once every evening; SD = Standard deviation; SSE = Satisfying sexual event.

Source: 511.70 CTR Table 15.2.1: 2, Module 5.3.5.1.

Change in sexual desire per eDiary scores was not statistically improved at Week 24 for any flibanserin treatment group as compared to placebo (Table 2).

**Table 2 eDiary Desire Total Monthly Score Change from Baseline at Week 24 – Alternate Dosing Study (FAS, LOCF)**

Endpoint	Treatment	N	Change from Baseline		
			LS Mean (SE)	LS Diff (SE)	P-value <sup>a</sup>
eDiary Desire	Placebo	325	7.5 (0.9)		
	Flibanserin 25 mg bid	320	8.8 (0.9)	1.3 (1.2)	0.2627
	Flibanserin 50 mg qhs	334	7.0 (0.9)	-0.5 (1.2)	0.6838
	Flibanserin 50 mg bid	291	7.7 (0.9)	0.2 (1.2)	0.8609

<sup>a</sup> P-value based on ANCOVA model with main effect terms treatment and pooled center and using baseline as a covariate.

Notes: bid = Twice daily; FAS = Full analysis set; LS = Least squares; LOCF = Last observation carried forward;

N = Number of subjects; qhs = Once every evening; SE = Standard error.

Source: 511.70 CTR Table 15.2.1: 5, Module 5.3.5.1.

Two flibanserin treatment groups (25 mg bid and 50 mg bid) demonstrated statistically significantly greater increases in the FSFI-Desire at Week 24, as compared to placebo (Table 3).

**Table 3 FSFI-Desire Change from Baseline at Week 24 – Alternate Dosing Study (FAS, LOCF)**

Endpoint	Treatment	N	Change from Baseline		
			LS Mean (SE)	LS Diff (SE)	P-value <sup>a</sup>
FSFI-Desire	Placebo	335	0.6 (0.1)		
	Flibanserin 25 mg bid	324	0.8 (0.1)	0.2 (0.1)	0.0087
	Flibanserin 50 mg qhs	342	0.6 (0.1)	-0.0 (0.1)	0.9998
	Flibanserin 50 mg bid	315	0.8 (0.1)	0.2 (0.1)	0.0365

<sup>a</sup> P-value based on ANCOVA model with main effect terms treatment and pooled center and using baseline as a covariate.

Notes: bid = Twice daily; FAS = Full analysis set; FSFI-Desire = Female sexual function index – desire domain;

LOCF = Last observation carried forward; LS = Least square; N = Number of subjects; qhs = Once every evening;

SE = Standard error.

Source: 511.70 CTR Table 15.2.1: 11, Module 5.3.5.1.

No flibanserin treatment group demonstrated statistically significant greater decreases in FSDS-R13 (Distress) at Week 24 than the placebo group (Table 4) at Week 24.

**Table 4 FSDS-R13 (Distress) Change from Baseline at Week 24 – Alternate Dosing Study (FAS, LOCF)**

Endpoint	Treatment	N	Change from Baseline		
			LS Mean (SE)	LS Diff (SE)	P-value <sup>a</sup>
FSDS-R13 (Distress)	Placebo	335	-0.6 (0.1)		
	Flibanserin 25 mg bid	324	-0.7 (0.1)	-0.1 (0.1)	0.1845
	Flibanserin 50 mg qhs	342	-0.5 (0.1)	0.1 (0.1)	0.5259
	Flibanserin 50 mg bid	315	-0.7 (0.1)	-0.2 (0.1)	0.0644

<sup>a</sup> P-value based on ANCOVA model with main effect terms treatment and pooled center and using baseline as a covariate.

Notes: bid = Twice daily; FAS = Full analysis set; FSDS-R13 (Distress) = Female sexual distress scale-revised Item 13;  
LOCF = Last observation carried forward; LS = Least square; N = Number of subjects; qhs = Once every evening;  
SE = Standard error.

Source: 511.70 CTR Table 15.2.2.2: 4, Module 5.3.5.1.

## 1.2 The EU Study

The EU Study was a 24-week, randomized, double-blind, placebo-controlled study in premenopausal women with HSDD designed to evaluate safety and efficacy of 50 mg qhs or 100 mg qhs regimens of flibanserin over 24 weeks of treatment in premenopausal women from 13 European countries. The primary endpoint was mean change from baseline to Week 24 in the number of SSEs. Secondary endpoints included mean change from baseline to Week 24 in the FSFI-Desire, FSDS-R13 (Distress) and eDiary Desire.

The treatment group for EU Study included 945 patients, 311 randomized to flibanserin 50 qhs, 316 randomized to flibanserin 100 mg qhs, and 318 randomized to placebo. The efficacy FAS population with at least one dose of trial medication and at least one post-dose on-treatment efficacy assessment included 926 patients, 305 randomized to flibanserin 50 qhs, 308 randomized to flibanserin 100 mg qhs, and 313 randomized to placebo. Baseline scores for efficacy endpoints were comparable in the flibanserin and placebo groups

In this study flibanserin 50 mg qhs and 100 mg qhs demonstrated efficacy on the FSDS-R13 (Distress) and the eDiary Desire score but not on SSEs and FSFI-Desire. Cultural differences in European versus North American approaches to sexuality render this study difficult to generalize to the intended US population.



For SSE (standardized) at Week 24, neither flibanserin treatment group demonstrated a statistically significant improvement over placebo (Table 5).

**Table 5 SSEs (Standardized) Change from Baseline at Week 24 – EU Study (FAS, LOCF)**

Endpoint	Treatment	N	Change from Baseline		
			Mean (SD)	Median (Q1, Q3)	P-value <sup>a</sup>
SSE (Standardized)	Placebo	307	0.9 (3.2)	0.0 (-1.0, 2.0)	
	Flibanserin 50 mg qhs	297	1.2 (3.7)	0.1 (0.0, 2.0)	0.5413
	Flibanserin 100 mg qhs	299	1.5 (4.0)	1.0 (-0.5, 3.0)	0.1403

<sup>a</sup> P-value based on Wilcoxon rank sum test.

Notes: FAS = Full analysis set; LOCF = Last observation carried forward; Q1 = First quartile; Q3 = Third quartile;  
N = Number of subjects; qhs = Once every evening; SD = Standard deviation; SSE = Satisfying sexual event.

Source: 511.77 CTR Table 15.2.1: 2, Module 5.3.5.1.

Changes in FSFI-Desire similarly did not achieve statistical significance at Week 24 for either flibanserin treatment group compared with placebo (Table 6).

**Table 6 FSFI-Desire Change from Baseline at Week 24 – EU Study (FAS, LOCF)**

Endpoint	Treatment	N	Change from Baseline		
			LS Mean (SE)	LS Diff (SE)	P-value <sup>a</sup>
FSFI-Desire	Placebo	313	0.5 (0.1)		
	Flibanserin 50 mg qhs	305	0.5 (0.1)	-0.0 (0.1)	0.9409
	Flibanserin 100 mg qhs	308	0.7 (0.1)	0.1 (0.1)	0.0816

<sup>a</sup> P-value based on ANCOVA model with main effect terms treatment and pooled center and using baseline as a covariate.

Notes: FAS = Full Analysis Set; FSFI-Desire = Female sexual function index – desire domain; LOCF = Last observation carried forward;  
LS = Least square; N = Number of subjects; qhs = Once every evening; SE = Standard error.

Source: 511.77 CTR Table 15.2.1: 9, Module 5.3.5.1.

The 100 mg flibanserin qhs treatment resulted in statistically significant increases in eDiary Desire scores at Week 24 compared to placebo (Table 7).

**Table 7 eDiary Desire Total Monthly Score Change from Baseline at Week 24 – EU Study (FAS, LOCF)**

Endpoint	Treatment	N	Change from Baseline		
			LS Mean (SE)	LS Diff (SE)	P-value <sup>a</sup>
eDiary Desire	Placebo	307	5.4 (0.8)		
	Flibanserin 50 mg qhs	297	5.6 (0.8)	0.2 (1.0)	0.8642
	Flibanserin 100 mg qhs	299	7.7 (0.8)	2.3 (1.0)	0.0240

<sup>a</sup> P-value based on ANCOVA model with main effect terms treatment and pooled center and using baseline as a covariate.

Notes: EoT = End of trial; FAS = Full analysis set; LOCF = Last observation carried forward; LS = Least square;  
N = Number of subjects; qhs = Once every evening; SE = Standard error.

Source: 511.77 CTR Table 15.2.1: 4, Module 5.3.5.1.

At Week 24, the flibanserin 100 mg qhs-treated group experienced a statistically greater decrease FSDS-R13 (Distress) as compared to the placebo treated group (Table 8).

**Table 8 FSDS-R13 (Distress) Change from Baseline at Week 24 – EU Study (FAS, LOCF)**

Endpoint	Treatment	N	Change from Baseline		
			LS Mean (SE)	LS Diff (SE)	P-value <sup>a</sup>
FSDS-R13 (Distress)	Placebo	313	-0.4 (0.1)		
	Flibanserin 50 mg qhs	304	-0.5 (0.1)	-0.1 (0.1)	0.1583
	Flibanserin 100 mg qhs	308	-0.6 (0.1)	-0.2 (0.1)	0.0163

<sup>a</sup> P-value based on ANCOVA model with main effect terms treatment and pooled center and using baseline as a covariate.

Notes: FAS = Full analysis set; FSDS-R13 (Distress) = Female sexual distress scale-revised Item 13;

LOCF = Last observation carried forward; LS = Least square; qhs = Once every evening; SE = Standard error.

Source: 511.77 CTR Table 15.2.2.2: 4, Module 5.3.5.1.

### 1.3 Withdrawal Study

The Withdrawal Study was conducted in premenopausal women with HSDD and consisted of an open-label, flexible dose period for 24 weeks, followed by a placebo-controlled, double-blind, randomized withdrawal period for an additional 24 weeks. The study was designed to observe the persistence of flibanserin efficacy.

During the first 4 weeks of the open-label period, all patients received flibanserin 50 mg qhs. At Week 4, a flexible dosing period commenced, during which patients could remain at the 50 mg qhs dosage regimen, or titrate to flibanserin 100 mg qhs or 50 mg bid. From Week 16 through Week 24, patients were required to remain on one of the 3 dosage regimens that had been reached at the end of the flexible dosing period.

After completing the open-label period, patients who met pre-specified enrichment criteria (i.e., increase from baseline of at least 2 SSEs per month or at least 4 desire days per month) were randomized to the controlled part of the trial. More than two-thirds of patients met the enrichment criteria. At the time of randomization 73 patients (21.9%) were on 50 mg qhs; 231 patients (69.4%) on 100 mg qhs; and 29 patients (8.7%) on 50 mg bid. Of these, 170 patients (51.1%) were randomized to placebo and 163 patients (48.9%) to their Week 24 flibanserin dosing regimen. The FAS2 consisted of patients who were randomized to a treatment group and received at least one dose of placebo or flibanserin during the double-blind portion of the study.

Co-primary endpoints for the double-blind period were change from Week 24 (randomization/baseline) to Week 48 in the number of SSEs and eDiary Desire. Secondary endpoints included change from Week 24 to Week 48 in FSDS-R13 (Distress).

Demographic data for the flibanserin and placebo groups were similar for all variables. Baseline scores for all efficacy endpoints were comparable between the flibanserin and placebo groups.

‘Baseline’ scores for the randomized portion of the trial are based on patients’ taking their optimized dose from three possible flibanserin regimens during the 24-week open-label portion of the study. Consistent with a randomized withdrawal study design, because an elevated ‘baseline’ is used for the Week 48 outcomes data, further increases from baseline are not expected. Instead, maintaining baseline scores would amount to a positive treatment effect.

Flibanserin benefited premenopausal women with HSDD based on 24-week open-label responses and on comparisons of effects in patients continued on drug to those switched to placebo for a second 24 weeks (maintenance of effect). Women who were randomized to remain on flibanserin therapy during the second portion of the study maintained significant improvement over placebo for sexual desire as assessed by both the eDiary Desire and FSFI-Desire, and distress assessed by FSDS-R13 (Distress) and SSEs.

Decline in SSEs from Week 24 to Week 48 was significantly greater for placebo patients than with flibanserin treatment indicating better persistence of effect with flibanserin compared to placebo (Table 9).

**Table 9**      **SSEs (Standardized) Change from Week 24 Baseline at Week 48 – Withdrawal Study (FAS2, LOCF)**

Endpoint	Treatment	N	Change from Baseline		
			LS Mean (SE)	LS Diff	P-value <sup>a</sup>
SSEs (Standardized)	Placebo	170	-2.3 (0.3)		
	Flibanserin	163	-1.4 (0.3)	-1.0	0.0141

<sup>a</sup> P-value based on ANCOVA model with main effect terms treatment and using baseline as a covariate.

Notes: FAS2 = Full analysis (population) set during the second period (double-blind placebo-controlled period) of 511.74;

LOCF = Last observation carried forward; LS = Least squares; N = number of subjects; SE = Standard error;

SSE = Satisfying sexual event.

Source: 511.74 CTR Table 15.2.1.1: 4, Module 5.3.5.1.

At Week 48, the eDiary daily desire score also significantly favored flibanserin over placebo (Table 10).

**Table 10 eDiary Desire Total Monthly Score Change from Week 24 Baseline at Week 48 – Withdrawal Study (FAS2, LOCF)**

Endpoint	Treatment	N	Change from Baseline		
			LS Mean (SE)	LS Diff	P-value <sup>a</sup>
eDiary Desire	Placebo	137	25.4 (1.2)		
	Flibanserin	115	29.2 (1.2)	-3.8	0.0283

<sup>a</sup> P-value based on mixed model with baseline as a covariate.

Notes: FAS2 = Full analysis (population) set during the second period (double-blind placebo-controlled period) of 511.74;

LOCF = Last observation carried forward; LS = Least squares; N = number of subjects; SE = Standard error;

SSE = Satisfying sexual event.

Source: 511.74 CTR Table 11.4.1.1:5, Module 5.3.5.1.

The adjusted mean LOCF decline in FSFI-Desire score from Week 24 to Week 48 was significantly greater for placebo than for flibanserin patients (Table 11).

**Table 11 FSFI-Desire Change from Week 24 Baseline at Week 48 – Withdrawal Study (FAS2, LOCF)**

Endpoint	Treatment	N	Change from Baseline		
			LS Mean (SE)	LS Diff	P-value <sup>a</sup>
FSFI-Desire	Placebo	170	-0.8 (0.1)		
	Flibanserin	163	-0.5 (0.1)	-0.3	0.0074

<sup>a</sup> P-value based on ANCOVA model with main effect terms treatment and using baseline as a covariate.

Notes: FAS2 = Full analysis (population) set during the second period (double-blind placebo-controlled period) of 511.74;

FSFI-Desire = Female sexual function index – desire domain; LOCF = Last observation carried forward;

LS = Least square; N = Number of subjects; qhs = Once every evening; SE = Standard error.

Source: 511.74 CTR Table 15.2.2.4: 4, Module 5.3.5.1.

At Week 48, the increase in FSDS-R13 (Distress) for flibanserin patients was significantly less than that for observed on average in placebo patients (Table 12).

**Table 12 FSDS-R13 (Distress) Change from Week 24 Baseline at Week 48 – Withdrawal Study (FAS2, LOCF)**

Endpoint	Treatment	N	Change from Baseline		
			LS Mean (SE)	LS Diff (SE)	P-value <sup>a</sup>
FSDS-R13 (Distress)	Placebo	170	0.5 (0.1)		
	Flibanserin	163	0.2 (0.1)	0.3	0.0143

<sup>a</sup> P-value based on ANCOVA model with main effect terms treatment and using baseline as a covariate.

Notes: FAS2 = Full analysis (population) set during the second period (double-blind placebo-controlled period) of 511.74;

FSDS-R13 (Distress) = Female sexual distress scale-revised Item 13; LOCF = Last observation carried forward; LS = Least square;

N = Number of subjects; qhs = Once every evening; SE = Standard error.

Source: 511.74 CTR Table 15.2.2.3: 4, Module 5.3.5.1.

## **APPENDIX E SUMMARY OF PHASE 3 SAFETY STUDY OF CONCOMITANT SSRI/SNRI USE**

## **SUMMARY OF PHASE 3 SAFETY STUDY OF CONCOMITANT SSRI/SNRI USE**

### **Study 114: A 12-week, Randomized, Double-blind, Placebo-controlled, Phase 3 Safety Study of Flibanserin Tablets (100 mg daily) in Women Taking a Selective Serotonin or Serotonin-Norepinephrine Reuptake Inhibitor with Decreased Sexual Desire and Distress**

Study 114 was a 12-week, randomized, double-blind, placebo-controlled, Phase 3 safety trial of flibanserin tablets (100 mg daily) in women taking a selective serotonin or serotonin-norepinephrine reuptake inhibitor (SSRI/SNRI) with decreased sexual desire and distress. The study was designed to assess the safety of flibanserin treatment compared to double-blind placebo over 12 weeks in subjects taking an SSRI/SNRI who had symptoms of mild or remitted depressive disorder (and may also have had concurrent mild anxiety) and had symptoms of decreased sexual desire and related distress. Safety assessment included assessment of withdrawal from flibanserin treatment.

Following screening, subjects were randomized to flibanserin (either 50 mg qhs for two weeks with up-titration to 100 mg qhs or 100 mg qhs) or placebo qhs orally for twelve weeks of treatment. A total of 45 subjects were randomized to 50 mg flibanserin up-titrated to 100 mg, 28 subjects were randomized to 100 mg flibanserin qhs fixed dose and 38 subjects were randomized to placebo.

There were no primary or secondary efficacy endpoints in this study. Measures of sexual function were however collected by various instruments (FSFI, FSFI Desire, FSDS-R (Distress), FSDS-R13 (Distress), Changes in Sexual Functioning-Female Questionnaire (CSFQ-F) total score, CSFQ-F desire domain, CSFQ-F desire frequency, CSFQ-F desire interest, PGI-I and clinician global impression of improvement (CGI-I)) none of which resulted in statistical separation of flibanserin 100 mg qhs from placebo.

Safety was assessed via the following measures: adverse events, concomitant therapies, 16-Item Quick Inventory of Depressive Symptomatology (QIDS-SR16), Beck Anxiety Inventory, Columbia-Suicide Severity Rating Scale (C-SSRS), routine laboratory tests, 12-lead electrocardiograms, blood pressure and pulse rate, weight and medication compliance.

No deaths or serious adverse events were reported in this trial. Slightly more subjects in the placebo group (71.1%) experienced adverse events (vs. 65.8% in the flibanserin total group). Overall, very few subjects reported expected adverse events (fewer than 18% in the placebo group and 5.5% or less in the flibanserin total group). In the placebo group 2 subjects (5.3%) discontinued due to an adverse event compared to 2 subjects (2.7%) in the flibanserin total group. Few subjects in each treatment group experienced severe adverse events (2.6% in the placebo group vs 2.7% in the flibanserin total group). Subjects considered to have had an adverse event related to study medication were comparable between treatment groups, 36.8% in the placebo group vs 39.7% in the flibanserin total group.

During the double-blind treatment and post-treatment periods, no subjects indicated a positive response on the C-SSRS for suicide behavior or suicidal ideation. At Week 12 (end of treatment), almost 15% fewer subjects worsened in the flibanserin 100 mg qhs group when compared to the placebo group as assessed by the severity of depression using the QIDS-SR16. At Week 12, only 1 subject each in the flibanserin 100 mg qhs group (1.4%) and in the placebo group (2.7%) worsened in the severity of anxiety as assessed by using the Beck Anxiety Inventory.

Study 114 identified no risk for depression, anxiety or suicidality with the addition of flibanserin 100 mg qhs to either an SSRI or SNRI in a population of mild or remitted depressed pre-menopausal women. This trial showed no evidence of withdrawal adverse events after abrupt discontinuation of flibanserin 100 mg per day after 12 weeks of use in combination with an SSRI or an SNRI. Other safety measures (routine laboratory tests, hormonal laboratory tests, ECG, blood pressure, pulse, weight and pregnancy) did not demonstrate any clinically important differences between flibanserin and placebo.

In summary, the dose regimens of 50 mg flibanserin qhs up-titrated to 100 mg flibanserin qhs and 100 mg flibanserin qhs were very well tolerated and did not increase risk as an addition to an SSRI or SNRI in this population of premenopausal women with mild or remitted depression.

## **APPENDIX F SUMMARY SAFETY DATA FROM PHASE 3 STUDIES IN PREMENOPAUSAL AND POSTMENOPAUSAL WOMEN WITH HSDD**



## TABLE OF CONTENTS

	Page
<b>TABLE OF CONTENTS .....</b>	<b>2</b>
<b>LIST OF TABLES .....</b>	<b>3</b>
<b>LIST OF ABBREVIATIONS .....</b>	<b>4</b>
<b>1 SUMMARY SAFETY DATA FROM PHASE 3 STUDIES IN PREMENOPAUSAL AND POSTMENOPAUSAL WOMEN WITH HSDD.....</b>	<b>5</b>
1.1 Overall Extent of Exposure for All Phase 3 Studies.....	5
1.2 Subject Disposition for All Phase 3 Double-blind Studies.....	5
1.3 Subject Exposure for All Phase 3 Double-blind Studies in Women with HSDD .....	6
1.4 Demographic and Other Baseline Characteristic Data for All Phase 3 Double-blind Studies in Women with HSDD .....	7
1.5 Concomitant Baseline Diagnoses/Diseases ( $\geq 5\%$ of subjects) for All Phase 3 Double-blind Studies in Women with HSDD.....	8
1.6 Adverse Events .....	10
1.7 Common Adverse Events .....	10
1.8 Adverse Events by Severity .....	13
1.9 Adverse Events Leading to Discontinuation.....	13

## LIST OF TABLES

	Page
Table 1 Subject Disposition - All Phase 3 Double-blind Studies .....	5
Table 2 Exposure by Non-overlapping Intervals - All Phase 3 Double-blind Studies (Treated Set).....	6
Table 3 Demographic and Other Baseline Characteristics by Treatment - All Phase 3 Double-blind Studies (Treated Set) .....	7
Table 4 Number (%) of Subjects with Concomitant Baseline Diagnoses/Diseases ( $\geq 5\%$ of Subjects) - All Phase 3 Double-blind Studies (Treated Set) .....	9
Table 5 Overall Summary of Adverse Events - All Phase 3 Double-blind Studies (Treated Set).....	10
Table 6 Number (%) of Adverse Events $\geq 2.0\%$ and Twice that of Placebo by Treatment - All Phase 3 Double-blind Studies (Treated Set).....	11
Table 7 Number (%) of Subjects with Adverse Events Occurring in $\geq 1.0\%$ and Twice the Rate of Placebo by Treatment - All Phase 3 Double-blind Studies (Treated Set).....	12
Table 8 Adverse Events Leading to Discontinuation in $\geq 1.0\%$ of Subjects in Any Treatment Group - All Phase 3 Double-blind Studies (Treated Set).....	13

## **LIST OF ABBREVIATIONS**

AE	Adverse event
bid	Twice daily
HSDD	Hypoactive sexual desire disorder
ISS	Integrated Summary of Safety
Max	Maximum
MedDRA	Medical Dictionary for Regulatory Activities
Min	Minimum
qhs	Once every evening at bedtime
SAE	Serious Adverse Event
SD	Standard Deviation
SNRI	Serotonin Norepinephrine Reuptake Inhibitor
SSRI	Selective Serotonin Reuptake Inhibitor

# 1 SUMMARY SAFETY DATA FROM PHASE 3 STUDIES IN PREMENOPAUSAL AND POSTMENOPAUSAL WOMEN WITH HSDD

## 1.1 Overall Extent of Exposure for All Phase 3 Studies

Safety data from two Phase 3, double-blind, placebo-controlled studies in postmenopausal women with HSDD and a Phase 3 double-blind, placebo-controlled safety study of concomitant SSRI/SNRI use in premenopausal women with HSDD were integrated with safety data from the five double-blind, placebo-controlled Phase 3 studies in premenopausal women presented in the main body of this briefing document. The combined safety database from these eight studies is referred to herein as “All Phase 3 Double-blind Studies.”

## 1.2 Subject Disposition for All Phase 3 Double-blind Studies

Subject disposition for all Phase 3 double-blind studies in women with HSDD is summarized in Table 1. Most randomized subjects entered the treatment phase of the studies. The discontinuation rates of 28.7% for placebo and 35.1% for flibanserin 100 mg qhs reflect the Sponsor’s early termination of one of the postmenopausal studies prior to its completion. The study was terminated for commercial reasons and not due to any safety concerns. Discontinuation rates due to AEs for all Phase 3 double-blind studies in women with HSDD were 5.8% for the placebo group and 11.3% for the flibanserin 100 mg qhs group.

**Table 1 Subject Disposition - All Phase 3 Double-blind Studies**

Characteristic	Placebo, N (%)	Flibanserin, N (%)			
		25 mg bid	50 mg qhs	50 mg bid	100 mg qhs <sup>a</sup>
Enrolled	2800	736	974	730	2463
Treated	2792 (100.0)	733 (100.0)	969 (100.0)	728 (100.0)	2459 (100.0)
Discontinued	800 (28.7)	224 (30.6)	280 (28.9)	289 (39.7)	864 (35.1)
Adverse event	163 (5.8)	51 (7.0)	100 (10.3)	150 (20.6)	279 (11.3)
AE study disease worse	2 (<0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
AE other disease worse	10 (0.4)	5 (0.7)	10 (1.0)	5 (0.7)	16 (0.7)
AE other	151 (5.4)	46 (6.3)	90 (9.3)	145 (19.9)	263 (10.7)
Lack of efficacy	64 (2.3)	13 (1.8)	31 (3.2)	20 (2.7)	52 (2.1)
Noncompliance	75 (2.7)	22 (3.0)	35 (3.6)	20 (2.7)	77 (3.1)
Lost to follow up	99 (3.5)	37 (5.0)	39 (4.0)	35 (4.8)	89 (3.6)
Consent withdrawn	132 (4.7)	81 (11.1)	55 (5.7)	51 (7.0)	81 (3.3)
Study terminated by Sponsor <sup>b</sup>	181 (6.5)	0 (0.0)	0 (0.0)	0 (0.0)	193 (7.8)
Other <sup>c</sup>	87 (3.1)	20 (2.7)	20 (2.1)	13 (1.8)	92 (3.7)
Completed	1992 (71.3)	509 (69.4)	689 (71.1)	439 (60.3)	1595 (64.9)

<sup>a</sup> Includes both fixed and up-titrated 100 mg qhs doses.

<sup>b</sup> Study 511.156 was terminated early by the sponsor due to commercial reasons.

<sup>c</sup> Other includes pregnancy, personal reasons, moving away, etc.

Notes: AE = Adverse event; bid = Twice daily; HSDD = Hypoactive sexual desire disorder; N = Total population size; qhs = Once every evening at bedtime; y = Year.

Includes Studies 511.70, 511.71, 511.75, 511.77, 511.114, 511.130, 511.147 and 511.156.

Source: ISS Table 1.1.3.

### 1.3 Subject Exposure for All Phase 3 Double-blind Studies in Women with HSDD

Subject exposure to flibanserin in all Phase 3 randomized, double-blind, placebo-controlled efficacy studies in women with HSDD by cumulative exposure intervals is presented in [Table 2](#). Overall, a total of 2982 women with HSDD have received flibanserin from 136 up to 180 days (6 months) in all Phase 3 double-blind studies, 1501 of these at the 100 mg qhs dose.

The mean duration of exposure during double-blind treatment for women for all Phase 3 placebo-controlled studies was 143.1 days (approximately 20 weeks) in the placebo group and 136.2 days (approximately 19.5 weeks) in the flibanserin group (any dose). Exposure to flibanserin (any dose) was 1823.1 patient-years. Cumulatively, the length of exposure to flibanserin (any dose) for approximately 85% of subjects was between 56 and 83 days and for approximately 78% of subjects was between 85 and 181 days.

**Table 2 Exposure by Non-overlapping Intervals - All Phase 3 Double-blind Studies (Treated Set)**

Non-overlapping Interval <sup>a</sup>	Placebo N = 2792	Flibanserin				Total N = 4889
		25 mg bid N = 733	50 mg qhs N = 969	50 mg bid N = 728	100 mg qhs N = 2459	
Exposure, Days, n (%)						
1-28	144 (5.2)	40 (5.5)	53 (5.5)	80 (11.0)	182 (7.4)	355 (7.3)
29-60	215 (7.7)	85 (11.6)	82 (8.5)	93 (12.8)	260 (10.6)	520 (10.6)
61-90	154 (5.5)	28 (3.8)	56 (5.8)	44 (6.0)	167 (6.8)	295 (6.0)
91-135	228 (8.2)	47 (6.4)	59 (6.1)	52 (7.1)	216 (8.8)	374 (7.6)
136-180	1844 (66.0)	465 (63.4)	605 (62.4)	411 (56.5)	1501 (61.0)	2982 (61.0)
≥181	207 (7.4)	68 (9.3)	114 (11.8)	48 (6.6)	132 (5.4)	362 (7.4)
Mean, Days	143.1	141.4	144.0	127.6	134.2	136.2
SD	50.62	54.83	53.02	61.96	55.84	56.35
Minimum	1	2	2	2	1	1
Median	168	169	169	168	168	168
Maximum	251	235	241	208	226	241
Exposure, patient years	1094.0	283.8	382.1	254.3	902.9	1823.1

<sup>a</sup> Subjects may be included in multiple dose groups.

Notes: bid = Twice daily; HSDD = Hypoactive sexual desire disorder; n = Total population size; N = Number of subjects;  
qhs = Once every evening at bedtime; SD = Standard deviation.

Includes Studies 511.70, 511.71, 511.75, 511.77, 511.114, 511.130, 511.147, and 511.156.

Source: ISS Table 1.5.3.

## 1.4 Demographic and Other Baseline Characteristic Data for All Phase 3 Double-blind Studies in Women with HSDD

Integrated demographic and baseline characteristic data for all Phase 3 24-week double-blind, placebo-controlled studies of flibanserin in women with HSDD are presented in [Table 3](#). Summary data for the overall population of women with HSDD was consistent with that reported above for the premenopausal and postmenopausal populations.

**Table 3 Demographic and Other Baseline Characteristics by Treatment - All Phase 3 Double-blind Studies (Treated Set)**

Characteristic	Placebo N = 2792	Flibanserin			
		25 mg bid N = 733	50 mg qhs N = 969	50 mg bid N = 728	100 mg qhs <sup>a</sup> N = 2459
Age group, n (%)					
18-34 years	824 (29.5)	341 (46.5)	441 (45.5)	310 (42.6)	688 (28.0)
35-44 years	896 (32.1)	322 (43.9)	415 (42.8)	344 (47.3)	718 (29.2)
≥45 years	1072 (38.4)	70 (9.5)	113 (11.7)	74 (10.2)	1053 (42.8)
Age, years					
Mean	41.9	34.9	35.5	35.4	42.7
SD	11.46	7.06	7.16	6.97	11.49
Min, Max	18, 79	18, 52	18, 54	19, 51	19, 80
Race, n (%)					
White	2489 (89.1)	643 (87.7)	875 (90.3)	661 (90.8)	2196 (89.3)
Black or African American	228 (8.2)	79 (10.8)	63 (6.5)	56 (7.7)	200 (8.1)
Asian	32 (1.1)	11 (1.5)	9 (0.9)	11 (1.5)	35 (1.4)
American Indian or Alaskan native	13 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)	6 (0.2)
Native Hawaiian or other Pacific islander	5 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.0)
Missing	25 (0.9)	0 (0.0)	22 (2.3)	0 (0.0)	21 (0.9)
Ethnicity, n (%)					
Hispanic	190 (6.8)	39 (5.3)	53 (5.5)	40 (5.5)	181 (7.4)
Not Hispanic	2575 (92.2)	694 (94.7)	890 (91.8)	687 (94.4)	2255 (91.7)
Missing	27 (1.0)	0 (0.0)	26 (2.7)	1 (0.1)	23 (0.9)
Body mass index, kg/m <sup>2</sup> , n (%)					
Underweight (<18.5)	55 (2.0)	8 (1.1)	18 (1.9)	11 (1.5)	42 (1.7)
Normal (18.5-<25)	1267 (45.4)	330 (45.0)	510 (52.6)	346 (47.5)	1090 (44.3)
Overweight (25-<30)	806 (28.9)	204 (27.8)	242 (25.0)	210 (28.8)	727 (29.6)
Obese (≥30)	656 (23.5)	187 (25.5)	196 (20.2)	154 (21.2)	596 (24.2)
Missing	8 (0.3)	4 (0.5)	3 (0.3)	7 (1.0)	4 (0.2)

<sup>a</sup> Includes both fixed and up-titrated 100 mg qhs doses.

**Table 3 Demographic and Other Baseline Characteristics by Treatment - All Phase 3 Double-blind Studies (Treated Set) (Cont'd)**

Characteristic	Placebo N = 2792	Flibanserin			
		25 mg bid N = 733	50 mg qhs N = 969	50 mg bid N = 728	100 mg qhs <sup>a</sup> N = 2459
Weight, kg					
Mean	72.3	73.4	71.0	71.8	72.7
SD	16.67	17.61	17.01	16.01	16.64
Min, Max	38, 163	46, 166	40, 152	41, 140	36, 158
Height, cm <sup>b</sup>					
Mean	164.4	165.1	164.8	164.5	164.4
SD	7.07	7.07	7.01	6.80	7.38
Min, Max	132, 193	140, 183	132, 185	142, 185	65, 196
Alcohol status, n (%)					
Non-drinker	1265 (45.3)	200 (27.3)	269 (27.8)	176 (24.2)	1232 (50.1)
Drinker – no interference <sup>c</sup>	1521 (54.5)	533 (72.7)	699 (72.1)	548 (75.3)	1222 (49.7)
Drinker – interference <sup>c</sup>	6 (0.2)	0	1 (0.1)	4 (0.5)	5 (0.2)
Smoking history, n (%)					
Never smoked	1814 (65.0)	493 (67.3)	633 (65.3)	471 (64.7)	1589 (64.6)
Ex-smoker	605 (21.7)	162 (22.1)	177 (18.3)	159 (21.8)	534 (21.7)
Current smoker	373 (13.4)	78 (10.6)	159 (16.4)	98 (13.5)	336 (13.7)

<sup>a</sup> Includes both fixed and up-titrated 100 mg qhs doses.

<sup>b</sup> Data entry error in CTR source documentation [Errata Reviewer's Guide].

<sup>c</sup> Based on investigator's judgment of whether drinking would interfere with study participation.

Notes: bid = Twice daily; HSDD = Hypoactive sexual desire disorder; Max = maximum; Min = Minimum; n = Total population size; N = number of subjects; qhs = Once every evening at bedtime; SD = Standard deviation.

Includes Studies 511.70, 511.71, 511.75, 511.77, 511.114, 511.130, 511.147, and 511.156.

Source: ISS Post Hoc Table 1.3.3.

## 1.5 Concomitant Baseline Diagnoses/Diseases (≥5% of subjects) for All Phase 3 Double-blind Studies in Women with HSDD

Concomitant baseline diagnoses and diseases reported in ≥5% of subject in all Phase 3 double-blind, placebo-controlled studies in women with HSDD were consistent with those described above for the premenopausal and postmenopausal populations (Table 4).

**Table 4 Number (%) of Subjects with Concomitant Baseline Diagnoses/Diseases (≥5% of Subjects) - All Phase 3 Double-blind Studies (Treated Set)**

<b>System Organ Class, Preferred Term</b>	<b>Placebo N = 2792 n (%)</b>	<b>Flibanserin N = 4889 n (%)</b>	<b>Total N = 7681 n (%)</b>
Total number of subjects with concomitant diagnoses/diseases	2324 (83.2)	3947 (80.7)	6271 (81.6)
Endocrine disorders	250 (9.0)	391 (8.0)	641 (8.3)
Hypothyroidism	210 (7.5)	321 (6.6)	531 (6.9)
Eye disorders	358 (12.8)	547 (11.2)	905 (11.8)
Myopia	177 (6.3)	299 (6.1)	476 (6.2)
Gastrointestinal disorders	592 (21.2)	913 (18.7)	1505 (19.6)
Gastroesophageal reflux disease	219 (7.8)	318 (6.5)	537 (7.0)
Immune system disorders	930 (33.3)	1681 (34.4)	2611 (34.0)
Drug hypersensitivity	412 (14.8)	707 (14.5)	1119 (14.6)
Seasonal allergy	492 (17.6)	898 (18.4)	1390 (18.1)
Infections and infestations	474 (17.0)	785 (16.1)	1259 (16.4)
Injury, poisoning and procedural complications	146 (5.2)	244 (5.0)	390 (5.1)
Investigations	189 (6.8)	320 (6.5)	509 (6.6)
Metabolism and nutrition disorders	341 (12.2)	493 (10.1)	834 (10.9)
Musculoskeletal and connective tissue disorders	756 (27.1)	1088 (22.3)	1844 (24.0)
Back pain	173 (6.2)	281 (5.7)	454 (5.9)
Nervous system disorders	854 (30.6)	1473 (30.1)	2327 (30.3)
Headache	421 (15.1)	772 (15.8)	1193 (15.5)
Migraine	274 (9.8)	441 (9.0)	715 (9.3)
Psychiatric disorders	426 (15.3)	603 (12.3)	1029 (13.4)
Depression	139 (5.0)	222 (4.5)	361 (4.7)
Insomnia	183 (6.6)	225 (4.6)	408 (5.3)
Renal and urinary disorders	180 (6.4)	278 (5.7)	458 (6.0)
Reproductive system and breast disorders	238 (8.5)	405 (8.3)	643 (8.4)
Respiratory, thoracic and mediastinal disorders	359 (12.9)	617 (12.6)	976 (12.7)
Asthma	152 (5.4)	314 (6.4)	466 (6.1)
Skin and subcutaneous tissue disorders	322 (11.5)	584 (11.9)	906 (11.8)
Surgical and medical procedures	393 (14.1)	669 (13.7)	1062 (13.8)
Vascular disorders	333 (11.9)	482 (9.9)	815 (10.6)
Hypertension	248 (8.9)	361 (7.4)	609 (7.9)

Notes: MedDRA version used for reporting: 11.1.

Includes Studies 511.70, 511.71, 511.75, 511.77, 511.114, 511.130, 511.147, and 511.156.

Source: ISS Table 1.4.3.



## 1.6 Adverse Events

An overall summary of adverse events for all Phase 3 double-blind studies in women with HSDD is presented in [Table 5](#).

**Table 5 Overall Summary of Adverse Events - All Phase 3 Double-blind Studies (Treated Set)**

Subjects by Category, n (%)	Placebo N = 2792	Flibanserin				Flibanserin Total N = 4889
		25 mg bid N = 733	50 mg qhs N = 969	50 mg bid N = 728	100 mg qhs N = 2459	
Any AE	1519 (54.4)	430 (58.7)	628 (64.8)	517 (71.0)	1588 (64.6)	3163 (64.7)
Severe AEs	124 (4.4)	32 (4.4)	69 (7.1)	44 (6.0)	162 (6.6)	307 (6.3)
Investigator-defined drug-related AEs	566 (20.3)	197 (26.9)	288 (29.7)	356 (48.9)	912 (37.1)	1753 (35.9)
AEs leading to discontinuation	158 (5.7)	50 (6.8)	99 (10.2)	148 (20.3)	277 (11.3)	574 (11.7)
SAEs	17 (0.6)	4 (0.5)	10 (1.0)	5 (0.7)	26 (1.1)	45 (0.9)

Notes: AE = Adverse event; bid = Twice daily; HSDD = Hypoactive sexual desire disorder; n = Total population size; N = Number of subjects; qhs = Once every evening at bedtime; SAE = Serious adverse event.

Includes Studies 511.70, 511.71, 511.75, 511.77, 511.114, 511.130, 511.147, and 511.156.

Source: ISS Table 2.1.4.

## 1.7 Common Adverse Events

Across all Phase 3 double-blind studies in women with HSDD, AEs that occurred for  $\geq 2.0\%$  and twice that of placebo in all women with HSDD were dizziness, somnolence, nausea, fatigue, insomnia, dry mouth, anxiety, metrorrhagia, and dysmenorrhea ([Table 6](#)).

**Table 6      Number (%) of Adverse Events  $\geq 2.0\%$  and Twice that of Placebo by Treatment - All Phase 3 Double-blind Studies (Treated Set)**

Preferred Term, n (%)	Placebo N = 2792	Flibanserin			
		25 mg bid N = 733	50 mg qhs N = 969	50 mg bid N = 728	100 mg qhs N = 2459
Dizziness	69 (2.5)	31 (4.2)	61 (6.3)	111 (15.2)	249 (10.1)
Somnolence	77 (2.8)	51 (7.0)	55 (5.7)	122 (16.8)	241 (9.8)
Nausea	105 (3.8)	41 (5.6)	68 (7.0)	90 (12.4)	216 (8.8)
Fatigue	128 (4.6)	35 (4.8)	59 (6.1)	101 (13.9)	171 (7.0)
Insomnia	75 (2.7)	14 (1.9)	19 (2.0)	20 (2.7)	132 (5.4)
Dry mouth	31 (1.1)	6 (0.8)	12 (1.2)	10 (1.4)	61 (2.5)
Metrorrhagia	24 (0.9)	10 (1.4)	25 (2.6)	13 (1.8)	23 (0.9)
Dysmenorrhea <sup>a</sup>	29 (1.0)	9 (1.2)	14 (1.4)	15 (2.1)	20 (0.8)

<sup>a</sup> Met drug-related AE criteria only in all Phase 3 double-blind data set for flibanserin 50 mg bid; onset not analyzed.

Notes: bid = Twice daily; HSDD = Hypoactive sexual desire disorder; n = Total population size; N = Number of subjects;

qhs = Once every evening at bedtime.

MedDRA version used for reporting: 11.1.

Includes Studies 511.70, 511.71, 511.75, 511.77, 511.114, 511.130, 511.147, and 511.156.

Source: ISS Table 2.3.12.

Across all Phase 3 double-blind studies in women with HSDD, AEs that occurred in  $\geq 1\%$  of subjects and at a frequency twice that in subjects receiving placebo are listed in descending order of frequency in [Table 7](#). The most common AEs for both the placebo group and the flibanserin-treated groups were dizziness, somnolence, nausea, fatigue, and insomnia.

**Table 7      Number (%) of Subjects with Adverse Events Occurring in  $\geq 1.0\%$  and Twice the Rate of Placebo by Treatment - All Phase 3 Double-blind Studies (Treated Set)**

Preferred Term, n (%)	Placebo N = 2792	Flibanserin			
		25 mg bid N = 733	50 mg qhs N = 969	50 mg bid N = 728	100 mg qhs N = 2459
Dizziness	69 (2.5)	31 (4.2)	61 (6.3)	111 (15.2)	249 (10.1)
Somnolence	77 (2.8)	51 (7.0)	55 (5.7)	122 (16.8)	241 (9.8)
Nausea	105 (3.8)	41 (5.6)	68 (7.0)	90 (12.4)	216 (8.8)
Fatigue	128 (4.6)	35 (4.8)	59 (6.1)	101 (13.9)	171 (7.0)
Insomnia	75 (2.7)	14 (1.9)	19 (2.0)	20 (2.7)	132 (5.4)
Dry mouth	31 (1.1)	6 (0.8)	12 (1.2)	10 (1.4)	61 (2.5)
Constipation	25 (0.9)	4 (0.5)	4 (0.4)	9 (1.2)	47 (1.9)
Abdominal pain	20 (0.7)	5 (0.7)	17 (1.8)	8 (1.1)	30 (1.2)
Rash	20 (0.7)	13 (1.8)	14 (1.4)	9 (1.2)	29 (1.2)
Vertigo	11 (0.4)	1 (0.1)	3 (0.3)	5 (0.7)	29 (1.2)
Sleep disorder	8 (0.3)	1 (0.1)	3 (0.3)	3 (0.4)	28 (1.1)
Oedema peripheral	11 (0.4)	0 (0.0)	2 (0.2)	0 (0.0)	24 (1.0)
Sedation	5 (0.2)	1 (0.1)	6 (0.6)	10 (1.4)	24 (1.0)
Metrorrhagia	24 (0.9)	10 (1.4)	25 (2.6)	13 (1.8)	23 (0.9)
Migraine	26 (0.9)	13 (1.8)	12 (1.2)	7 (1.0)	21 (0.9)
Dysmenorrhoea	29 (1.0)	9 (1.2)	14 (1.4)	15 (2.1)	20 (0.8)
Pain in extremity	14 (0.5)	8 (1.1)	5 (0.5)	4 (0.5)	20 (0.8)
Acne	18 (0.6)	9 (1.2)	15 (1.5)	6 (0.8)	18 (0.7)
Polymenorrhoea	9 (0.3)	9 (1.2)	9 (0.9)	6 (0.8)	12 (0.5)
Vulvovaginal mycotic infection	17 (0.6)	3 (0.4)	16 (1.7)	7 (1.0)	12 (0.5)
Breast tenderness	18 (0.6)	11 (1.5)	8 (0.8)	5 (0.7)	11 (0.4)
Dyspepsia	17 (0.6)	7 (1.0)	7 (0.7)	9 (1.2)	11 (0.4)
Genital haemorrhage	12 (0.4)	7 (1.0)	3 (0.3)	0 (0.0)	11 (0.4)
Vaginitis bacterial	10 (0.4)	7 (1.0)	2 (0.2)	5 (0.7)	7 (0.3)
Hypomenorrhoea	8 (0.3)	4 (0.5)	2 (0.2)	7 (1.0)	4 (0.2)
Pharyngitis streptococcal	10 (0.4)	7 (1.0)	5 (0.5)	7 (1.0)	5 (0.2)

Notes: bid = Twice daily; HSDD = Hypoactive sexual desire disorder; n = total population size; N = Number of subjects;  
qhs = Once every evening at bedtime.

MedDRA version used for reporting: 11.1.

Includes Studies 511.70, 511.71, 511.75, 511.77, 511.114, 511.130, 511.147, and 511.156.

Source: ISS Table 2.2.3.

## 1.8 Adverse Events by Severity

In the Phase 3 double-blind, placebo-controlled studies in all women with HSDD, among subjects who received placebo, 25.0% of subjects had mild AEs, 25.0% had moderate AEs, and 4.4% had severe AEs. For subjects who received any dose of flibanserin, using the highest level of severity, 26.9% of subjects had mild AEs, 31.5% had moderate AEs, and 6.3% had severe AEs. For subjects receiving flibanserin 100 mg qhs, using the highest level of severity, 27.4% of subjects had mild AEs, 30.6% had moderate AEs, and 6.6% had severe AEs.

## 1.9 Adverse Events Leading to Discontinuation

In the Phase 3 double-blind, placebo-controlled studies in all women with HSDD, among subjects who received placebo, 5.7% had an AE that led to discontinuation. For subjects who received any dose of flibanserin, 11.7% had an AE that led to discontinuation. Adverse events that led to discontinuation in  $\geq 1.0\%$  of subjects in any treatment group are listed in [Table 8](#).

**Table 8 Adverse Events Leading to Discontinuation in  $\geq 1.0\%$  of Subjects in Any Treatment Group - All Phase 3 Double-blind Studies (Treated Set)**

Preferred Term	Placebo N = 2792	Flibanserin				Total N = 4889
		25 mg bid N = 733	50 mg qhs N = 969	50 mg bid N = 728	100 mg qhs N = 2459	
Subjects with AEs leading to discontinuation, n (%)	158 (5.7)	50 (6.8)	99 (10.2)	148 (20.3)	277 (11.3)	574 (11.7)
Dizziness	6 (0.2)	2 (0.3)	9 (0.9)	29 (4.0)	33 (1.3)	73 (1.5)
Fatigue	12 (0.4)	7 (1.0)	7 (0.7)	37 (5.1)	20 (0.8)	71 (1.5)
Somnolence	10 (0.4)	3 (0.4)	4 (0.4)	29 (4.0)	22 (0.9)	58 (1.2)
Nausea	7 (0.3)	2 (0.3)	5 (0.5)	18 (2.5)	23 (0.9)	48 (1.0)
Anxiety	12 (0.4)	3 (0.4)	10 (1.0)	4 (0.5)	26 (1.1)	43 (0.9)
Headache	12 (0.4)	6 (0.8)	11 (1.1)	13 (1.8)	16 (0.7)	46 (0.9)
Insomnia	7 (0.3)	1 (0.1)	3 (0.3)	6 (0.8)	30 (1.2)	40 (0.8)

Notes: AE = Adverse event; bid = Twice daily; n = Total population size; N = Number of subjects; qhs = Once every evening at bedtime.

MedDRA version used for reporting: 11.1.

Includes Studies 511.70, 511.71, 511.75, 511.77, 511.114, 511.130, 511.147, and 511.156.

Source: ISS Table 2.3.9.

## **APPENDIX G QUICK REFERENCE GUIDE FOR EFFICACY INSTRUMENTS**

## QUICK REFERENCE GUIDE FOR EFFICACY INSTRUMENTS

Please see [Table 1](#) below.

**Table 1 Summary of Patient Reported Outcome Instruments**

Efficacy Endpoint	No. of Items	Response Range	Clinical Cut Point	Recall Period (Days)	Volunteers without FSD
SSEs (Standardized)	2	0 – NUL	-	3	13.9 ±8.8
FSFI Total Score	19	2 – 36	>26.6	28	33.0 ±4.2
FSFI-Desire	2	1.2 – 6 <sup>a</sup>	>3.0	28	4.6 ±1.1
FSDS-R (Distress) Total Score	13	0-52	<15	7	2.2 ±4.1
FSDS-R13 (Distress)	1	0 - 4	-	7	0.3 ±0.6
PGI-I	1	1 – 7	-	-	-
eDiary Desire (Total Monthly Score)	1	0 - 84	-	1	48.7 ±18.3

<sup>a</sup> Standardized domain score derived from total raw score of two items (score range of each item is 1 to 5) and then multiplied by 0.6.  
Notes: FSDS-R = Female sexual distress scale-revised; FSDS-R13 = Female sexual distress scale-revised Question 13; FSFI = Female sexual function index; FSFI-Desire = Female sexual function index – desire domain; NUL = No upper limit; PGI-I = Patient Global Impression of Improvement; SSE = Satisfying sexual event.

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## **APPENDIX H FEMALE SEXUAL FUNCTION INDEX (FSFI) VALIDATION STUDIES**

## TABLE OF CONTENTS

	Page
<b>TABLE OF CONTENTS .....</b>	<b>2</b>
<b>LIST OF TABLES .....</b>	<b>2</b>
<b>LIST OF ABBREVIATIONS .....</b>	<b>3</b>
<b>1 FEMALE SEXUAL DYSFUNCTION INDEX (FSFI) VALIDATION STUDIES.....</b>	<b>4</b>
1.1 FSFI-Desire – Background .....	4
1.2 Development and Validation Results.....	5
1.3 Publications: Original Development and Validation in HSDD .....	5
1.4 Studies Conducted for NDA Submission .....	7
1.4.1 Study 144 .....	8
1.4.2 Study 151 .....	10
1.4.3 Study 147 .....	11
1.5 Literature Review.....	13
1.6 28-Day Recall Period.....	13

## LIST OF TABLES

	Page
Table 1 Standardized Cronbach Coefficient Alpha at Baseline and End of Treatment – Pivotal Phase 3 Studies in Premenopausal Women.....	7
Table 2 Reliability Characteristics of FSFI-Desire 7-day versus 28-day Recall Comparison – Study 147.....	12



## **LIST OF ABBREVIATIONS**

ANOVA	Analysis of Variance
Cohen's D	Standardised Difference between 2 Means
eDiary Desire	Daily Electronic Desire Measure
FDA	U.S. Food & Drug Administration
FSAD	Female Sexual Arousal Disorder
FSDS-R	Female Sexual Distress Scale – Revised
FSFI	Female Sexual Function Index
FSFI-Desire	Female Sexual Function Index – Sexual Desire Domain
HSDD	Hypoactive Sexual Desire Disorder
ICC	Intra-Class Correlation Coefficient
LS	Least Square
NDA	New Drug Application
PRO	Patient Reported Outcome

# 1 FEMALE SEXUAL DYSFUNCTION INDEX (FSFI) VALIDATION STUDIES

This Appendix discusses the validity of FSFI-Desire and its superiority to eDiary Desire as a tool for measuring sexual desire.

## 1.1 FSFI-Desire – Background

The Female Sexual Function Index (FSFI) is a patient reported outcome (PRO) instrument developed by a multi-disciplinary investigator group in response to the need for a valid and reliable tool for use in clinical research and practice for the assessment of female sexual dysfunction. The FSFI was developed in 1999-2000 prior to issuance of the FDA draft or final guidance's for industry regarding PRO development, but followed the well-known principles of:

1. Initial conceptual framework development
2. Open-ended qualitative interviews for generation of item content, content finalization, and documentation of content validity, and
3. Rigorous psychometric evaluation of reliability (test-retest, internal consistency), construct validity and ability to detect changes

FSFI has since become the established standard instrument for the assessment of female sexual dysfunction, has been shown to be valid in multiple cultures and languages, and has been adopted for use by well-established and leading sexual medicine societies [Lue et al., 2004].

The final version of the FSFI consists of 19 questions applicable to the domains of desire, arousal, lubrication, orgasm, satisfaction, and pain based on a 28-day recall period. FSFI-Desire consists of 2 questions with associated response options:

“Q1: Over the past 4 weeks, how **often** did you feel sexual desire or interest?

Response options:

- 5 = Almost always or always
- 4 = Most times (more than half the time)
- 3 = Sometimes (about half the time)
- 2 = A few times (less than half the time)
- 1 = Almost never or never

and

“Q2. Over the past 4 weeks, how would you rate your **level** (degree) of sexual desire or interest?”

Response options:

5 = Very high

4 = High

3 = Moderate

2 = Low

1 = Very low or none at all

FSFI-Desire was developed prior to initiation of the flibanserin pivotal program and was an endpoint in pivotal Studies 71 and 75. The protocols, however, utilized eDiary Desire as the measure for primary assessment of sexual desire in response to FDA’s stated concern that only daily assessment of desire would be acceptable. FSFI-Desire was utilized as a co-primary endpoint in pivotal Study 147.

## **1.2 Development and Validation Results**

FSFI was developed, and first published based on a psychometric evaluation study in women with female sexual arousal disorder (FSAD) performed in 1999-2000 [Rosen et al., 2000]. A subsequent study demonstrated the reliability and validity of FSFI domains and total scores in HSDD [Meston, 2003]. Additional HSDD studies were performed in connection with flibanserin development specifically to address FDA recommendations for validation of preexisting instruments once the Agency’s draft Guidance for Industry: Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims (the PRO Guidance) [FDA, 2006] was published in 2006. Across these studies the FSFI has consistently demonstrated strong reliability (test-retest and internal consistency), and robust discriminant and convergent validity (i.e., construct validity), in addition to the ability to detect clinically relevant changes during treatment. The key validation studies submitted to the NDA are summarized below.

## **1.3 Publications: Original Development and Validation in HSDD**

The NDA contained the original publication that detailed the development and validation of FSFI. A panel of international experts and clinicians reviewed available literature on female sexual dysfunction in order to develop a suitable conceptual framework for a PRO instrument [Rosen et al., 2000]. The resulting draft instrument and discussion guide was intended to sample each of 5 domains (arousal, desire, pain, orgasm and satisfaction) and to meet basic psychometric criteria. The concept model was supported by both factor analyses of initial draft items and open-ended concept elicitation interviews with a focus group sample of 30 female volunteers at 3 investigational sites.

The factor loadings of the individual items fit the expected pattern, supporting the content validity of the instrument. Based on the initial results of this testing, the authors further refined the FSFI through item reduction with the goal of minimizing redundancy and creating a shorter 19-item instrument. Based on the qualitative and quantitative data, the initial conceptual framework of the instrument was modified and items were assigned to six domains: desire, arousal, lubrication, orgasm, global satisfaction and pain. A scoring system was implemented for determining domain scores and a composite full-scale score.

The 19-item questionnaire was then formally evaluated in a large psychometric evaluation study of 259 women (128 age-matched patients with a primary diagnosis of FSAD and 131 sexually active normal controls in stable heterosexual relationships) at 5 clinical sites. While HSDD patients were not specifically enrolled, many of the participants had concomitant lack of desire and distress. The objective of the first validation study was to assess the psychometric characteristics of the FSFI, including reliability (internal consistency and test-retest reliability) and construct validity (discriminant validity, convergent validity) and to confirm the factor structure of the instrument. The FSFI, as well as a validated measure of marital and relationship satisfaction, was administered twice (2 to 4 weeks apart).

Reliability. Regarding internal consistency, high inter-item correlations were observed for all six domains (Cronbach's alpha,  $\alpha \geq 0.82$ ; for the desire domain  $\alpha = 0.83$ ). Regarding test-retest reliability, Pearson product-moment correlation coefficients of each item from Visit 1 to Visit 2 were relatively high for each domain ( $r = 0.79 - 0.86$ ; for the desire domain  $r = 0.83$ ) and for the total score ( $r = 0.88$ ) and were statistically significant across all domains and groups.

Construct validity. Regarding discriminant validity, highly significant mean difference scores between the FSAD and control groups were seen for each domain ( $p \leq 0.001$ ) and for the full scale score ( $p \leq 0.001$ ), demonstrating the ability of each domain to differentiate between controls and FSAD patients. As expected, convergent validity testing demonstrated only modest correlations between the FSFI and a marital satisfaction instrument that measures a different but related construct.

These results established the validity and psychometric properties of the FSFI, and demonstrated content validity and acceptability by study participants. As noted by the authors, the instrument marked a significant advance over previous measures and the study confirmed the final conceptual framework of the instrument.

An additional published study extended the FSFI validation to include patients with a primary clinical diagnosis of HSDD ( $n = 88$ ) [Meston, 2003]. Participants, including 44 normal controls completed a demographics questionnaire and a number of sexuality questionnaires including the FSFI.

**Reliability.** Regarding internal consistency, high inter-item correlations were noted for the FSFI total score ( $\alpha = 0.92$ ) and for all domain scores ( $\alpha \geq 0.74$ ) with the exception of the desire component which had a moderate correlation ( $\alpha = 0.58$ ).

**Construct validity.** Regarding discriminant validity, FSFI differentiated between clinical and nonclinical samples showing significant differences in mean responses on total score and each of the six domains between participants with HSDD and controls. Finally, no significant correlations were found between the FSFI (total score or any individual domain with the exception of satisfaction) and a related construct (marital satisfaction) instrument that measures a different but related construct.

The authors concluded that “FSFI is a reliable and valid measure of sexual functioning in women with [female orgasmic disorder] and HSDD.”

Finally, to ensure that the FSFI-Desire had adequate internal consistency, the Sponsor calculated Cronbach alpha scores at baseline and end of treatment for patients across the 3 pivotal HSDD Phase 3 studies in premenopausal women.

**Table 1 Standardized Cronbach Coefficient Alpha at Baseline and End of Treatment – Pivotal Phase 3 Studies in Premenopausal Women**

Study Number	Time Point	N	Alpha
71	Baseline	863	0.7917
	End of treatment	678	0.9160
75	Baseline	1531	0.7740
	End of treatment	1109	0.9087
147	Baseline	1068	0.8020
	End of treatment	723	0.9334

These data establish that FSFI-Desire has sufficient reliability in HSDD.

## 1.4 Studies Conducted for NDA Submission

In support of the original NDA, the Sponsor conducted two content validity studies of the FSFI instrument in HSDD patients to comply with the PRO Guidance recommendation that additional content validity studies may be needed when a PRO instrument is applied to a new patient population not specifically enrolled in initial validation studies. Open-ended concept elicitation questions were utilized at the outset of these two studies to confirm content validity. These two content validity studies were reported separately in final study reports in the NDA and published together in a single paper after the 2010 advisory committee meeting [Revicki et al., 2011]. Concept saturation was achieved with 15 subjects in the first study and the qualitative data confirmed the conceptual framework of the FSFI. A second study enrolled 30 premenopausal and 30 postmenopausal subjects with HSDD to address FDA’s request for replication in a greater

number of subjects. While these studies enrolled a relatively small number of subjects compared to the 259 participant initial validation study, they were sufficiently sized to evaluate the content validity of an existing instrument which had extensive prior evidence supporting reliability and validity in HSDD and related populations. These two studies are summarized below.

#### **1.4.1 Study 144**

Study 144 was conducted to evaluate the content validity of FSFI in premenopausal women with HSDD with particular focus on the content validity of FSFI-Desire. The 15 participants were premenopausal female patients, aged 22 to 46, diagnosed with HSDD and a FSDS-R score  $\geq 15$  (indicating distress regarding sexual function) in stable, monogamous heterosexual relationships. As noted above, one-on-one interviews with 15 participants resulted in saturation – the point at which no substantially new themes, descriptions or terms are introduced as new interviews are conducted. Specifically, the content validity interviews confirmed the suitability and comprehensiveness of the existing item content of the FSFI.

During the single study visit, each enrolled subject participated in an initial cognitive interview, completed the FSFI, participated in a second cognitive interview and completed a socio-demographic form. The initial cognitive interview involved general questions about HSDD:

- What led you to talk to us about your decreased sexual desire?
- What are some of your complaints about decreased sexual desire?
- When did you first notice that you may have some sort of problem?
- What bothers you the most about your feelings of decreased desire?
- Have you discussed these concerns with a doctor?
- Are you currently receiving any treatment for your decreased sexual desire (e.g., counseling, psychotherapy and medication)?
- How would you describe the severity of your decreased desire?
- How has your condition affected you in your personal life?
- Relationships?
- Emotional well-being? (Probe for specific emotional feelings e.g., frustration, guilt, etc.).
- Is there anything else about your decreased sexual desire that you feel is important for us to know?

The second cognitive interview, which occurred after the subject completed the FSFI, involved questions about the participants' perception and interpretation of each FSFI item. During the second cognitive interview, the participants were asked about their feelings and perceptions of the desire items in particular, and whether the FSFI-Desire was able to adequately capture their experience of decreased sexual desire. Content analysis and descriptive statistics were used to analyze responses collected during cognitive debriefing interviews. The findings for FSFI-Desire domain only are summarized here.

The two questions were clear and easy to understand to almost all participants (n = 14; 93%). Ninety percent of participants rated item 1 and 100% rated item 2 as relevant to their sexual desire. In addition, 10 participants (67%) agreed that the two questions together reflected all of their concerns related to decreased sexual desire. Responses from the subjects who did not believe that these questions reflected all of their desire problems indicated that the participants were in fact seeking additional questions regarding physical and emotional issues, not desire. Specifically, subjects who responded "no" to the question, "Do questions 1 and 2 together reflect all of your problems with decreased sexual desire or interest?" were asked "Why not?" They responded:

- "Because there's more to it than that. [laughter]" *Can you give me an example?* "Yeah. The arousal level that went—there was that one question—the emotional closeness, 14. That's part of the more to it than—"Okay—"just the physical". *But arousal level as well?* "Yes".
- "Because the emotional part is missing. The physical part is missing. Those two pieces also need to be included".
- "I think you've already sort of talked about that" (earlier in transcript): "I think it's very, very similar to—1 and 2 are extremely similar and I don't think that I would ever differentiate between feeling sexual desire and rating my level of sexual desire. They may have made them differently in the hopes that they would tweak something different out of it. I'm sure they did because I'm sure they pay an awful lot of people a lot of money but for me they're the same".
- "It's too general".

Regarding the adequacy of the recall period for the FSFI-D questions, nearly all participants (n=14; 93%) indicated that they were able to think about their experience and report accurately over the past 4 weeks with only one subject indicating that she could only reflect upon the current day and had difficulty recalling longer time periods. Ninety-three percent thought that a 24-hour recall period was not suitable or relevant for capturing their sexual desire experience in item 1. When asked about the preferred recall period for assessing sexual desire, most participants endorsed a 1-2 week (Q1. n=5; Q2. n=6) or 4 week (Q1. n=4; Q2. n=2) recall period;

one participant each preferred a recall period longer than 4 weeks and 24 hours for item 1, and two participants preferred daily recall for item 2. Even though the majority of participants reported that a longer recall period (1 to 4 weeks) was relevant for reporting their state of sexual desire, there was no clear preference for a 1-, 2-, or 4-week recall period.

Study 144 concluded that the FSFI-Desire had good content validity, was clearly worded, easy to understand and relevant for 93% of the premenopausal HSDD participants.

### 1.4.2 Study 151

Study 151 was conducted to evaluate and confirm the content validity of FSFI in a larger sample of premenopausal women and in postmenopausal women with HSDD. As with the earlier study, particular focus was placed on the content validity of FSFI-Desire. The discussion below involves the separately analyzed cohort of premenopausal women only.

The 30 premenopausal participants were aged 22 to 50, diagnosed with HSDD and an FSDS-R score  $\geq 15$  and were in stable, monogamous heterosexual relationships. The study visit procedures were identical to those described above for Study 144.

The two FSFI-Desire questions were clear and easy to understand to almost all participants (Q1. n = 30, 100%; Q2. n = 29, 97%). Ninety to 100% of participants thought that the two sexual desire questions were relevant to their experience. In addition 16 participants (53%) agreed that the two questions together reflect all of their problems with decreased sexual desire. The subjects who did not believe that these questions reflected all of their desire problems indicated that additional questions on emotional distress and functioning and physical problems were needed. Specifically, subjects who responded “no” to the question, “Do questions 1 and 2 together reflect all of your problems with decreased sexual desire or interest?” were asked “Why not?” They responded:

- “No. It says if you have the desire, that doesn’t mean that you’re aroused or lubricated. One, I think, is dealing with the mind and the other is dealing with the physical aspect of it”.
- “I just – I don't know why I have the decrease. I don't know, again, if it’s hormonal or if it’s things that’s just going on in my life, day to day life”.
- I would think that um, you know, orgasm and erot – and – and wetness is a concern too. But like I said, if the sexual desire was there, I think that the wetness and orgasm would be just fine, if I was in the mood. [laughter]”
- “Because for me, it’s not just physical, it’s mental”.
- “Because I don't think it gets to feelings about why you have no desire”.



- “Because it’s not the only problem is – is interest or the desire”.
- “They don’t touch on – really, I don’t think they touch on any problem. They’re just asking – they’re just getting a feel for level of desire”.
- “Um, I think it’s a good place to start, but it doesn’t, it’s not comprehensive”.
- “I do not think they do because it – it’s only a – they’re not as, um, specific about reasons”.
- “But a majority. I think they don’t because I think they, you know, the questions about, I think you need to know if something satisfies or how confident or how often and how difficult are relevant”.
- “Because you still haven’t gotten to why –” *Okay.* “– the cause”.

Regarding the adequacy of the recall period for the FSFI-Desire questions, nearly all participants (n=29; 97%) indicated that they were able to think about their experience and feelings, or state of desire, over the past 4 weeks with only one subject reporting that she could only reflect upon the past 2 weeks and had difficulty recalling longer time periods. When asked about their preferred recall period for assessing sexual desire, most participants endorsed longer recall periods with only 3 participants (10%) showing a preference for a shorter (i.e., 24-hour) recall period. Even though the majority of participants thought a longer recall period was most relevant for reporting their state of sexual desire, there was no clear preference for a 1-, 2-, or 4-week recall period.

Study 151 concluded that the FSFI-Desire had good content validity and was clear, easy to understand and relevant for 95% of the premenopausal HSDD participants. The findings served to confirm the content validity of FSFI-Desire from Study 144.

These two studies, taken together demonstrate that FSFI-Desire meets the criteria for clarity, relevance and completeness in premenopausal women with HSDD, supporting the content validity of the FSFI-Desire.

### **1.4.3 Study 147**

Study 147, a large pivotal Phase 3 trial of premenopausal HSDD subjects, included a nested controlled, within-patient, crossover sub-study comparing 7-day with 28-day recall on FSFI-Desire means, variances and intra-class correlations. The specific question to be addressed was whether a shorter (1-week) recall period would provide better or more reliable data than a 4-week recall period. One hundred seventy five enrolled patients who had not yet completed Visit 8 (Week 20) were centrally assigned to 2 groups in a 1:1 ratio. One group completed the Visit 8 FSFI-Desire with a 28-day recall period and the other completed a modified version of the FSFI-Desire with a 7-day recall period. At Visit 9 (Week 24), patients within the sub-study

who had completed the FSFI-Desire with 28-day recall were crossed over to complete the FSFI-Desire with the 7-day recall period while all other patients completed the FSFI-Desire with the 28-day recall.

Comparisons between 7-day and 28-day recall for FSFI- Desire were to be assessed using the following analyses:

- An equivalence test approach via ANOVA to examine mean differences between the two recall periods, taking treatment, sequence and period effect into account in the model. The mean difference was to be assessed using a value of 0.6 which is the smallest increment on FSFI- Desire.
- Cohen's D was to be calculated to compare the 28-day to 7-day recall assessment relative to the standard deviation.
- The ratio of the within-patient assessment of the two different recall periods was to be examined. This approach was to determine whether the 95% confidence interval of the ratio was within 80% - 125%.
- Correlation between 28-day and 7-day recall periods and the intra-class correlation coefficient (ICC) were to be examined.

The LS mean difference (-0.11) was not significant for 7- versus 28-day recall (Cohen's D [ $\pm 0.6$  equivalence test threshold] = 0.20) [Cortina et al., 1999]. The within-patient ratio estimate (0.95) was well within the pre-specified boundaries (80% - 125%). The ICC assessment of rater reliability was high (0.78).

**Table 2 Reliability Characteristics of FSFI-Desire 7-day versus 28-day Recall Comparison – Study 147**

	FSFI-Desire 7-day versus 28-day Recall
Number of patients	175
Mean difference (95% CI)	-0.11 (-0.23, 0.01) <sup>a</sup>
Cohen's D	0.20
Ratio (95% CI)	0.95 (0.90, 0.99) <sup>b</sup>
ICC (95% CI)	0.78 (0.72, 0.83)

<sup>a</sup> ANOVA adjusting for period, sequence, and treatment.

<sup>b</sup> Log transformed ANOVA for period, sequence, and treatment.

Notes: CI = Confidence interval, FSFI-D = Female Sexual Function Index – Desire Domain; ICC = Intra-class correlation coefficient.

Source: 511.147 CTR Table 15.2.4: 3; Table 15.2.4: 4; Table 15.2.4: 5.

In summary, no significant differences or meaningful trends were observed between the two recall periods. The FSFI-Desire scores for the 28-day recall period demonstrated equivalent means and distribution of responses when compared to the FSFI-Desire scores for the 7-day

recall period. The strong correlation between FSFI-Desire scores across recall periods and the small and non-significant mean differences suggest that similar results would be obtained with either 7-day or 28-day recall of the FSFI-Desire.

## **1.5 Literature Review**

In addition to the studies summarized above, the literature review provides an overview of additional FSFI validation in connection with a large HSDD registry [Connor et al., 2011], across diverse clinical and cultural settings and geographic locations [Takahashi et al., 2011; Sun et al., 2011; Boehmer et al., 2011; Nappi et al., 2012; Fakhri et al., 2012], and in women with serious medical comorbidities or with other sexual dysfunctions [Baser et al., 2012; Rodriquez et al., 2012; Nappi et al., 2012; Bond et al., 2009]. The authors note the “burgeoning accumulation of evidence in support of the factor structure, item reliability and discriminant validity of the FSFI across multiple study populations and clinical settings”.

## **1.6 28-Day Recall Period**

FDA has expressed concern with FSFI-Desire’s 28-day recall window and the potential that such a window could result in systematically inaccurate data due to inaccurate or incomplete recollections of study participants regarding experiences from the past 4 weeks – otherwise known as “recall bias.” For instance, at the 2010 Flibanserin Advisory Committee meeting, FDA stated that an accurate recall of the “emotional state” of desire required a short time period. No evidence to support this hypothesis was presented in the Draft FSD Guidance, FDA’s briefing book to the advisory committee or in meetings or correspondence with the Sponsor.

Sexual desire is a cognitive/emotional state - a sense of longing - that derives from a fundamental appetitive drive in humans – the sex drive [DeLaMater and Sill, 2005]. It is an aspect of one’s consciousness, not a discrete episodic cognitive event that lends itself to daily counting. Like appetitive drives in general (hunger, thirst, etc), sexual desire waxes and wanes through time and is represented experientially as a cumulative gestalt phenomenon. Consistent with this understanding, the results of Studies 144 and 151, both of which had been submitted to the NDA respectively showed that:

- 93% and 97% of participants were able to think about their experiences associated with sexual desire over the past 4 weeks
- 93% and 90% of participants thought that a 24-hour recall period was not relevant for capturing their sexual desire experience in FSFI-D item 1, and
- 87% and 90% of participants thought a longer recall period (1 to 4 weeks) was best for assessing sexual desire

The Study 147 crossover sub-study further demonstrated the lack of any significant difference or meaningful trend between 7-day and 28-day recall periods.

FDA has also questioned the existence of the FSFI-D's first question "Over the past 4 weeks, how **often** did you feel sexual desire or interest?" as suggesting that desire exists as a discrete, countable set of events that must be recorded with great frequency so as not to be affected by recall bias. Instead, the question appropriately measures the frequency with which the respondent has sensed desire over the past 4 weeks. The responses are qualified in terms of more or less than half the time. The frequency question is not intended to elicit integer values (e.g., "4", "6", or "7") but rather gestalt gradations ranging from "not at all" to "very often", which are then assigned ordinal number values to facilitate quantitative analyses.

FDA asked an important, if rhetorical, question at the 28 October 2014 scientific workshop: If a woman's state of desire is changing in response to drug treatment, would a 28-day instrument detect that change? The FSFI validation inherently demonstrates the ability of a 28-day instrument to detect a change. The flibanserin Phase 3 studies themselves also answer this question. The FSFI-Desire has, in fact, detected the flibanserin effect on desire with remarkable consistency across three pivotal trials – a result that would be a statistical near impossibility if either 28-day recall were inaccurate or if flibanserin were not effective.

## **APPENDIX I   EDIARY DESIRE VALIDATION AND IMPLEMENTATION LIMITATIONS**

# 1 EDIARY DESIRE VALIDATION AND IMPLEMENTATION LIMITATIONS

eDiary Desire has not been validated for use in 24-week studies but was used during the pivotal program in an effort to address FDA's suggestion that daily recall would serve to improve measurement of desire. No published data establish or even suggest that a shorter recall period would improve measurement of the concept of desire. Consistent with this, no PRO instrument for sexual desire has been validated with the suggested short recall period. Because women conceptualize desire as a consistent state with little to no change over a period of weeks to months, longer recall is more appropriate and necessary to the collection of accurate data. This is borne out by the demonstrated variability seen in daily eDiary Desire recording where the excessive frequency of the question being asked may either negatively affect the woman's state of desire or cause her to inappropriately associate her response with her daily recording of SSEs. Not surprisingly, the experts at FDA's 28 October 2014 scientific workshop supported a 28-day recall period based on their view of desire as a state.

Similarly, HSDD patients at the 27 October 2014 patient-focused drug development meeting were not receptive to repeated questions from FDA about whether they think about their desire daily. Participants noted that they want to feel desire "all the time" as opposed to "every day".<sup>1</sup> Two participants who were treated with depot testosterone formulations noted their awareness of an increase or decrease in desire near the beginning or end of a treatment cycle. Even that awareness was not described as day-to-day but a sense over time that desire has increased or diminished. A patient's ability to sense her state of desire increasing or waning in response to hormonal therapy does not establish desire as a set of discrete events for which daily recall is needed.

## 1.1 Collection of Subjective Data Regarding an Emotional State

Desire is most accurately experienced and described as a cognitive/emotional/physiologic state and HSDD patients report that daily measures are not appropriate for capturing this state. The state of sexual desire in women with HSDD is perceived as an overall gestalt that is not subject to fluctuation over a matter of days. As a result, too short or discrete a measurement interval could be easily confounded by multiple unrelated situational factors occurring within the limited timeframe within which the HSDD patient is compelled to consider her current level of desire (i.e., 24-72 hours). Event logs or diary measures are most useful for enumerating discrete and readily observable events and/or counting frequencies of activity, for example in measuring

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<sup>1</sup> The following statement was in response to FDA questions regarding participants' interest in a PRN therapy or "taking something when you want to feel more desire as opposed to something you take everyday" (Transcript p. 179, lines 3-5): "But I don't even think about sex. So for me it's not like I'd want to just take a pill right before having sex with my husband. I want to feel it all the time ... I want that part of my life back because just thinking about sex, not having it but even just thinking about it impacts the rest of me too. It makes me feel like a more sexual person. It makes me feel like a woman". Katherine, Transcript p. 181, line 22, p. 182, lines 1-13.

incontinence, falls or sexual performance (as distinct from desire). Sexual events are more readily quantified than the state of sexual desire. In fact, reflecting daily on a state such as desire can cause too close a focus and result in a skewed view – similar to observing a large object under a microscope. The effects of travel circumstance, partner availability and relationship factors as well as menstrual cycles may further distort daily assessments of desire. A 4-week self-evaluation period provides a useful window for the patient to notice gradual sustained clinically relevant changes which would be difficult to discern in the context of day-to-day thinking. In clinical practice, healthcare providers do not typically query patients about their level or intensity of desire at the moment or time of the exam or even during the 24 hours prior. It is, however, common practice to query patients about sexual desire changes in the previous month or since the last clinic visit.

This view is also consistent with the regulatory approach to emotional states related to male sexuality. The International Index of Erectile Function (IIEF) erectile function domain, an instrument utilized as the efficacy measure for approval and/or labeling in the review of several drugs for erectile dysfunction includes the question, “Over the past 4 weeks, how do you rate your **confidence** that you can get and keep an erection?” Confidence, like desire, is an emotional state that is appropriately assessed over 4 weeks.

## **1.2 Patient Burden and Lack of Compliance**

Patient burden and lack of compliance are significant issues with daily diaries and lead to a high degree of missing data with daily assessments. These burdens may be exacerbated when collecting data regarding a highly sensitive aspect of the participant’s life such as sexual function. A study of testosterone replacement therapy in oophorectomized women showed marked discrepancies between a telephone-based daily diary measure of sexual desire and the results obtained from the monthly Brief Index of Sexual Functioning. The diary method was found to be more intrusive, bothersome and less sensitive to treatment effects, and suffered from serious compliance difficulties throughout the study [Shifren et al., 2000].

Similarly, in practice, eDiary Desire resulted in high non-completion rates and very high placebo response rates (59-67%) across the flibanserin clinical program. Of the patients who were active at the end of pivotal Studies 71 and 75, only 44.4% of placebo subjects and 43.6% of flibanserin subjects had eDiary Desire entries on 26 or more days of the six month study period. Nearly 10% of subjects failed to achieve 50% compliance with eDiary Desire over the entire trial and were thereby ineligible for the prespecified primary analysis.

There are no publicly available data to support FDA’s repeated assertion, since 2000, that daily desire recording is a better tool for assessing sexual desire in women with HSDD because of presumed recall bias or, for that matter, that recall bias is the most pressing issue to be considered in evaluating various measures of desire. Not only is daily testing not essential, a growing body of evidence suggests that it is detrimental to accurate data collection for this indication.

## **APPENDIX J FEMALE SEXUAL DISTRESS SCALE – REVISED (FSDS-R (DISTRESS)) VALIDATION STUDIES**



## TABLE OF CONTENTS

Page

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## **LIST OF TABLES**

Page

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## LIST OF FIGURES

Page

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Pages 175-188 redacted. Derogatis LR, Rosen R, Leiblum S, et al. The Female Sexual Distress Scale (FSDS): Initial validation of a standardized scale for assessment of sexually related personal distress in women. J Sex Marital Therapy; 2002; 28: 317-330. A copy of this reference is not included in the Briefing Book for copyright reasons, but has been provided to Panel Members.

## **APPENDIX K OVERVIEW OF PHASE 3 STUDY STATISTICAL PRINCIPLES AND ANALYSES**

## TABLE OF CONTENTS

	Page
<b>TABLE OF CONTENTS .....</b>	<b>2</b>
<b>LIST OF TABLES .....</b>	<b>3</b>
<b>LIST OF FIGURES .....</b>	<b>5</b>
<b>LIST OF ABBREVIATIONS .....</b>	<b>6</b>
<b>STATISTICAL METHODOLOGY.....</b>	<b>7</b>
<b>1 ANALYSIS SETS.....</b>	<b>7</b>
<b>2 DETERMINATION OF SAMPLE SIZE .....</b>	<b>7</b>
2.1 Study 147 .....	7
2.2 Studies 71 and 75 .....	8
<b>3 ANALYSIS OF EFFICACY ENDPOINTS.....</b>	<b>9</b>
3.1 SSE.....	9
3.2 FSFI-Desire.....	9
3.3 eDiary Desire .....	9
3.4 FSDS-R13 (Distress) .....	10
3.5 FSDS-R Total Score (Distress).....	10
3.6 FSFI Total Score.....	10
3.7 Responder Analysis .....	10
<b>4 ADJUSTMENT FOR MULTIPLE COMPARISONS .....</b>	<b>10</b>
4.1 Study 71 .....	10
4.2 Study 75 .....	11
<b>5 NULL AND ALTERNATIVE HYPOTHESES .....</b>	<b>12</b>
<b>6 ANALYSIS OF SAFETY DATA.....</b>	<b>12</b>
<b>7 INTERIM ANALYSES .....</b>	<b>12</b>
<b>8 MISSING DATA.....</b>	<b>12</b>
8.1 Preplanned Sensitivity Analyses.....	12
8.2 Additional Sensitivity Analyses and General Assumptions .....	13
8.3 Sensitivity Analyses for SSEs.....	14
8.4 Sensitivity Analyses for FSFI-Desire .....	18
8.5 Sensitivity Analyses for FSDS-R13.....	23
<b>9 ANALYSIS OF COMPLETERS DATA.....</b>	<b>27</b>
9.1 Satisfying Sexual Events.....	27
9.2 FSFI-Desire.....	28
9.3 FSDS-R13 (Distress) .....	29

## LIST OF TABLES

	Page
Table 1 Mean Change from Baseline to Week 24 in SSE – Pivotal Phase 3 Studies in Premenopausal Women (FAS, LOCF) .....	15
Table 2 Mean Change from Baseline to Week 24 in SSE – Pivotal Phase 3 Studies in Premenopausal Women (FAS, BOCF) .....	15
Table 3 Mean Change from Baseline to Week 24 in SSE – Pivotal Phase 3 Studies in Premenopausal Women (Treated Set, BOCF) .....	15
Table 4 Mean Change from Baseline to Week 24 in SSE – Pivotal Phase 3 Studies in Premenopausal Women (FAS, MMRM) .....	16
Table 5 Mean Change from Baseline to Week 24 in SSE – Pivotal Phase 3 Studies in Premenopausal Women (FAS, MAR) .....	16
Table 6 Mean Change from Baseline to Week 24 in SSE – Pivotal Phase 3 Studies in Premenopausal Women (FAS, CBI) .....	16
Table 7 Mean Change from Baseline to Week 24 in SSE – Pivotal Phase 3 Studies in Premenopausal Women (FAS, J2R) .....	17
Table 8 Tipping Point Analysis for SSE – Study 71 .....	17
Table 9 Tipping Point Analysis for SSE – Study 75 .....	18
Table 10 Tipping Point Analysis for SSE – Study 147 .....	18
Table 11 Mean Change from Baseline to Week 24 in FSFI-Desire – Pivotal Phase 3 Studies in Premenopausal Women (FAS, LOCF) .....	19
Table 12 Mean Change from Baseline to Week 24 in FSFI-Desire – Pivotal Phase 3 Studies in Premenopausal Women (FAS, BOCF) .....	19
Table 13 Mean Change from Baseline to Week 24 in FSFI-Desire – Pivotal Phase 3 Studies in Premenopausal Women (Treated Set, BOCF) .....	20
Table 14 Mean Change from Baseline to Week 24 in FSFI-Desire – Pivotal Phase 3 Studies in Premenopausal Women (FAS, MMRM) .....	20
Table 15 Mean Change from Baseline to Week 24 in FSFI-Desire – Pivotal Phase 3 Studies in Premenopausal Women (FAS, MAR) .....	20
Table 16 Mean Change from Baseline to Week 24 in FSFI-Desire – Pivotal Phase 3 Studies in Premenopausal Women (FAS, CBI) .....	21
Table 17 Mean Change from Baseline to Week 24 in FSFI-Desire – Pivotal Phase 3 Studies in Premenopausal Women (FAS, J2R) .....	21
Table 18 Tipping Point Analysis for FSFI-Desire – Study 71 .....	22
Table 19 Tipping Point Analysis for FSFI-Desire – Study 75 .....	22
Table 20 Tipping Point Analysis for FSFI-Desire – Study 147 .....	22
Table 21 Mean Change from Baseline to Week 24 in FSDS-R13 (Distress) – Pivotal Phase 3 Studies in Premenopausal Women (FAS, LOCF) .....	23
Table 22 Mean Change from Baseline to Week 24 in FSDS-R13 (Distress) – Pivotal Phase 3 Studies in Premenopausal Women (FAS, BOCF) .....	24

Table 23	Mean Change from Baseline to Week 24 in FSDS-R13 (Distress) – Pivotal Phase 3 Studies in Premenopausal Women (Treated Set, BOCF).....	24
Table 24	Mean Change from Baseline to Week 24 in FSDS-R13 (Distress) – Pivotal Phase 3 Studies in Premenopausal Women (FAS, MMRM).....	24
Table 25	Mean Change from Baseline to Week 24 in FSDS-R13 (Distress) – Pivotal Phase 3 Studies in Premenopausal Women (FAS, MAR).....	25
Table 26	Mean Change from Baseline to Week 24 in FSDS-R13 (Distress) – Pivotal Phase 3 Studies in Premenopausal Women (FAS, CBI).....	25
Table 27	Mean Change from Baseline to Week 24 in FSDS-R13 (Distress) – Pivotal Phase 3 Studies in Premenopausal Women (FAS, J2R).....	25
Table 28	Tipping Point Analysis for FSDS-R13 (Distress) – Study 71 .....	26
Table 29	Tipping Point Analysis for FSDS-R13 (Distress) – Study 75 .....	26
Table 30	Tipping Point Analysis for FSDS-R13 (Distress) – Study 147 .....	27
Table 31	SSEs (Standardized) Change from Baseline at Week 24 – Pivotal Phase 3 Studies in Premenopausal Women (Completers) .....	27
Table 32	FSFI-Desire Change from Baseline at Week 24 – Pivotal Phase 3 Studies in Premenopausal Women (Completers) .....	28
Table 33	FSDS-R13 (Distress) Change from Baseline at Week 24 – Pivotal Phase 3 Studies in Premenopausal Women (Completers) .....	29

## LIST OF FIGURES

	Page
Figure 1 SSE Data Comparison Using Various Methods for Handling Missing Data – Pivotal Phase 3 Studies in Premenopausal Women.....	14
Figure 2 Summary of Tipping Point Analysis for SSE - Pivotal Phase 3 Studies in Premenopausal Women .....	17
Figure 3 FSFI-Desire Data Comparison Using Various Methods for Handling Missing Data – Pivotal Phase 3 Studies in Premenopausal Women .....	19
Figure 4 Summary of Tipping Point Analysis for FSFI-Desire - Pivotal Phase 3 Studies in Premenopausal Women .....	21
Figure 5 FSDS-R13 (Distress) Data Comparison Using Various Methods for Handling Missing Data – Pivotal Phase 3 Studies in Premenopausal Women .....	23
Figure 6 Summary of Tipping Point Analysis for FSDS-R13 (Distress) - Pivotal Phase 3 Studies in Premenopausal Women.....	26
Figure 7 SSEs (Standardized) Change from Baseline at Week 24 – Pivotal Phase 3 Studies in Premenopausal Women (Completers) .....	28
Figure 8 FSFI-Desire Change from Baseline at Week 24 – Pivotal Phase 3 Studies in Premenopausal Women (Completers) .....	29
Figure 9 FSDS-R13 (Distress) Change from Baseline at Week 24 – Pivotal Phase 3 Studies in Premenopausal Women (Completers) .....	30

## LIST OF ABBREVIATIONS

AE	Adverse Event
ANCOVA	Analysis of Covariance
AR(1)	First Order Autoregressive Covariance Structure
bid	Twice Daily
BOCF	Baseline Observation Carried Forward
CBI	Control Based Imputation
CID	Clinically Important Difference
CMH	Cochran-Mantel-Haenszel
CS	Compound Symmetry Covariance Structure
eDiary	Daily Electronic Desire Measure
FAS	Full Analysis Set
FLI	Flibanserin
FSDS-R (Distress)	Female Sexual Distress Scale - Revised
FSDS-R13 (Distress)	Female Sexual Distress Scale – Revised Question 13
FSFI-Desire	Female Sexual Function Index – Sexual Desire Domain
HSDD	Hypoactive Sexual Desire Disorder
J2R	Jump to Reference
LOCF	Last Observation Carried Forward
LS	Least Square
MAR	Missing at Random
MCMC	Markov Chain Monte Carlo
MMRM	Mixed Model Repeated Measures
PGI-I	Patient Global Impression of Improvement
qhs	Once Daily at Bedtime
SD	Standard Deviation
SE	Standard Error
SSE	Satisfying Sexual Event
TS	Efficacy Treated Set
UN	Unstructured Covariance Structure

## STATISTICAL METHODOLOGY

This appendix describes key statistical design elements of the pivotal Phase 3 studies of flibanserin in premenopausal women with HSDD (Studies 147, 71, and 75). The statistical design and analyses were similar for the three pivotal efficacy studies.

### 1 ANALYSIS SETS

Two analysis population sets were analyzed in each of the studies:

1. The Treated Set, and
2. The Full Analysis Set (FAS)

The Treated Set consisted of those patients who were randomized to a treatment group and received at least one dose of study medication. The FAS consisted of those patients who were randomized to a treatment group, received at least one dose of study medication, and had at least one on-treatment efficacy assessment.

The Treated Set was primarily analyzed for safety, but is also used to analyze demographic data or baseline characteristics. The FAS was analyzed for efficacy using the last observation carried forward (LOCF) method of handling missing data. Additional sensitivity analyses were also utilized as discussed below.

### 2 DETERMINATION OF SAMPLE SIZE

#### 2.1 Study 147

Study 147 was a 24-week, randomized, double-blind, parallel group study comparing the efficacy of flibanserin 100 mg qhs to placebo in premenopausal women with HSDD.

The upper bound of the 90% confidence interval of the standard deviation of the change from baseline in FSFI-Desire score in the previous North American studies that included flibanserin 100 mg qhs (Studies 71 and 75) was 1.15. Assuming a similar standard deviation, it was determined that 450 subjects per treatment arm would detect a treatment difference in FSFI-Desire score of 0.25 with 90% power using a 2-sided 5% level of significance.

Similarly, the upper bound of the 90% confidence interval of the standard deviation of the change from baseline in monthly SSE from previous North American studies was 4.2. Assuming SSE is a continuous variable, a difference of 1 SSE per month between flibanserin and placebo and a common standard deviation of 4.2 across treatment groups corresponds to a probability of 0.567 that an observation in placebo is less than an observation from flibanserin when the alternative hypothesis (probability not equal to 0.5) is true. These assumptions indicate that a sample size of 420 subjects per treatment arm would be needed to have at least 90% power at the



5% level of significance to detect the difference of 1 SSE between treatments using a Wilcoxon rank sum test.

A sample size of 450 per group was estimated to accommodate a dropout rate during the first month as high as 7% (a rate of 5% was observed in each previous North American study). Thus, for Study 147, approximately 900 patients were pre-specified to be centrally randomized to two treatment groups in a 1:1 allocation ratio, stratified by center.

## 2.2 Studies 71 and 75

Studies 71 and 75 were 24-week, randomized, double-blind, parallel group studies that compared the efficacy of flibanserin to placebo in premenopausal women with HSDD. Study 71 included flibanserin treatment arms with dosing at 50 mg qhs and 100 mg qhs, while Study 75 included flibanserin dosing at 25 mg bid, 50 mg bid and 100 mg qhs.

Sample size estimates were based on the co-primary endpoint of monthly total of SSEs at 24 weeks. Of the two co-primary endpoints, this endpoint required a larger sample size. Assuming normality, a difference of 1 SSE per month between flibanserin and placebo and a common standard deviation of 3.25 across treatment groups corresponded to a probability of 0.586 that an observation in placebo was less than an observation from flibanserin when the alternative hypothesis (probability not equal to 0.5) was true. The standard deviation was estimated using the root mean squared errors from ANCOVA models in previous 12-week HSDD proof-of-concept studies for flibanserin (Studies 68 and 69).

In order to detect a difference under the above assumptions using a Wilcoxon rank sum test, a sample size of 279 patients per treatment group was determined to have 90% power at the two-sided  $\alpha = 0.025$  level of significance for Study 71. Similarly, a sample size of 304 patients per treatment group was determined to have 90% power at the two-sided  $\alpha = 0.0167$  level of significance for Study 75. The sample size calculations were performed using nQuery Advisor 4.0, allowing for a dropout rate of approximately 10% before the first complete month of eDiary data collection.

Sample size considerations could not be adequately determined for the co-primary endpoint of desire at the time of protocol writing for Studies 71 and 75. Only distribution-based data were available. In the absence of anchor-based data, a difference between flibanserin and placebo of 5.4 was calculated to be detectable with 90% power given a sample size of 279, assuming a standard deviation of 18 for Study 71. Similarly, a difference between flibanserin and placebo of 5.4 was calculated to be detectable with 90% power given a sample size of 304, assuming a standard deviation of 18 for Study 75. For both studies, the standard deviation was estimated by taking 150% of the standard deviation of 12 that was observed in HSDD patients in a pilot study (unpublished data from validation study).

### **3 ANALYSIS OF EFFICACY ENDPOINTS**

Each of the three pivotal Phase 3 studies in premenopausal women with HSDD included a 24-week, placebo-controlled, double-blind, parallel-group study. Different flibanserin doses and regimens were investigated in several studies. Efficacy comparisons were made between the 4-week screening period and Week 21 to 24 of the treatment period. Management of missing data is described specifically for eDiary data (SSEs and sexual desire) in this section, but is more generally discussed for primary and secondary endpoints below. For studies with co-primary endpoints, both had to be statistically significant at a level of  $\alpha = 0.05$  in order for the study to be deemed positive.

#### **3.1 SSE**

SSEs were measured by daily eDiary entries, data were standardized by normalizing the total number of SSEs between monthly clinic visits to 28 day periods. The total number of SSEs was divided by the total number of available days between clinic visits and then multiplied by 28. Patients were required to record SSE data within three consecutive days. The eDiary SSE data were analyzed only if at least 14 days of diary data were available. If less than 14 days of diary data were available for a given month, the most recent 28-day period with at least 14 days of available diary data was used for imputation for that month. The change from baseline was compared using a stratified Wilcoxon rank sum test where strata were the pooled centers. The adjustment for baseline SSEs was taken into account by using mean change from baseline in the number of SSEs.

#### **3.2 FSFI-Desire**

For sexual desire assessed by the FSFI-Desire, mean change from baseline in the score was compared using ANCOVA with treatment and pooled center as fixed effects and baseline score as a covariate.

#### **3.3 eDiary Desire**

For sexual desire assessed daily eDiary Desire, responses rating intensity of desire were recorded. The eDiary Desire asks a patient to “Indicate your most intense level of sexual desire in the last 24 hours [or] since your last visit”. Possible responses were “strong”, “moderate” or “low” or “none.” A measure of sexual desire was recorded by eDiary on a daily basis. Reporting of sexual desire information was limited to a 24-hour retrospective period. The eDiary Desire data were analyzed only if at least 14 days of diary data were available. If less than 14 days of diary data were available for a given month, the most recent 28-day period with at least 14 days of available diary data was used for imputation for that month. The change from baseline in the monthly sum of responses was compared using analysis of covariance (ANCOVA) with treatment and center as fixed effects and baseline score as covariates.

### **3.4 FSDDS-R13 (Distress)**

For FSDDS-R13 (Distress), mean change from baseline to Week 24 for flibanserin and placebo was compared using the ANCOVA with treatment and center as fixed effects and baseline score as a covariate.

### **3.5 FSDDS-R Total Score (Distress)**

For the FSDDS-R Total Score (Distress), mean change from baseline to Week 24 for flibanserin and placebo was compared using ANCOVA with treatment and pooled center as fixed effects and baseline score as a covariate.

### **3.6 FSFI Total Score**

For the FSFI Total Score, mean change from baseline to Week 24 for flibanserin and placebo was compared using ANCOVA with treatment and pooled center as fixed effects and baseline score as a covariate.

### **3.7 Responder Analysis**

For the responder analyses, the difference between the percentages of responders in the placebo and flibanserin treatment groups was compared using the Chi-square test for the SSE endpoint (no adjustment for center) and the Cochran-Mantel-Haenszel (CMH) test adjusting for center for all other endpoints. For each pivotal study, this analysis was based on defining a responder as a patient with a change from baseline in an endpoint value greater than the minimal response threshold observed in the PGI-I assessment i.e., between “minimally improved” (score of 3) and “no change” (score of 4) on the PGI-I. Thus, changes in the endpoints were linked to the responses of the patients on the PGI-I instrument.

## **4 ADJUSTMENT FOR MULTIPLE COMPARISONS**

In Studies 71 and 75 that assessed multiple doses of flibanserin, adjustments for multiple comparisons for each flibanserin treatment regimen to placebo were made using the Hochberg multiplicity adjustment.

### **4.1 Study 71**

For Study 71 which included two different dosing regimens of flibanserin, pairwise comparisons of the Wilcoxon rank sum test for SSEs (first co-primary endpoint) were performed for each dose of flibanserin vs. placebo. The p-values for each dose of flibanserin compared to placebo were ordered [ $p_{(1)} \leq p_{(2)}$ ].

1. If  $p_{(2)} \leq 0.05$ , then reject all null hypotheses and conclude all treatment comparisons are statistically significant, else if  $p_{(2)} > 0.05$ , proceed to Step 2.

2. If  $p_{(1)} \leq 0.025$ , then reject the null hypotheses corresponding to p-value  $p_{(1)}$ , and conclude that the corresponding treatment comparisons are statistically significant.

For monthly sum of responses to the eDiary daily desire question (second co-primary endpoint), pairwise comparisons were performed for each dose of flibanserin vs. placebo in the ANCOVA model for the desire monthly score. For the doses that were statistically significant with the first co-primary endpoint, p-values for each dose compared to placebo for the desire endpoint were ordered and the same procedure as described above (for the satisfying sexual event endpoint) were used to evaluate statistical significance, if both doses were significant for the first co-primary endpoint. If only one dose was significant on the first co-primary, the Hochberg procedure started at Step 2. The p-value  $p_{(1)}$  at Step 2 refers to the comparison of only the flibanserin dose that was significant on the first co-primary endpoint vs. placebo.

## 4.2 Study 75

For Study 75 that included three different dosing regimens of flibanserin, pairwise comparisons of the Wilcoxon rank sum test for SSEs (first co-primary endpoint) were performed for each dose of flibanserin vs. placebo. The p-values for each dose of flibanserin compared to placebo were ordered [ $p_{(1)} \leq p_{(2)} \leq p_{(3)}$ ].

1. If  $p_{(3)} \leq 0.05$ , then reject all null hypotheses and conclude all treatment comparisons are statistically significant, else if  $p_{(3)} > 0.05$ , proceed to Step 2.
2. If  $p_{(2)} \leq 0.025$ , then reject the null hypotheses corresponding to p-values  $p_{(1)}$  and  $p_{(2)}$ , and conclude that the corresponding treatment comparisons are statistically significant, else if  $p_{(2)} > 0.025$ , proceed to Step 3.
3. If  $p_{(1)} \leq 0.0167$ , then reject the null hypotheses corresponding to p-value  $p_{(1)}$ , and conclude that the corresponding treatment comparison is statistically significant, else if  $p_{(1)} > 0.0167$ , then conclude that no dose comparisons to placebo are statistically significant.

For monthly sum of responses to the eDiary daily desire question (second co-primary endpoint), pairwise comparisons were performed for each dose of flibanserin vs. placebo in the ANCOVA model for the desire monthly score. For the doses that were statistically significant with the first co-primary endpoint, p-values for each dose compared to placebo for the desire endpoint were ordered and the same procedure as described above (for the satisfying sexual event endpoint) were used to evaluate statistical significance, if all three doses were significant for the first co-primary endpoint. If only two doses were significant on the first co-primary, the Hochberg procedure started at Step 2. If only one dose was significant on the first co-primary, the Hochberg procedure started at Step 3.

## 5 NULL AND ALTERNATIVE HYPOTHESES

The null hypothesis was that the mean change from baseline was equal for patients treated with flibanserin and placebo. The alternative hypothesis was that the mean change from baseline was not equal for patients treated with flibanserin and placebo. All hypothesis tests were 2-sided with an overall study Type I error of 0.05.

## 6 ANALYSIS OF SAFETY DATA

Safety data were assessed through AEs, laboratory tests, and vital signs are recorded in clinical site reports. AEs occurring on the day of randomization and within one day after the final dose of study medication were considered to be on-treatment. AEs occurring 2 to 7 days after the final dose of study medication (until the 1-week post-treatment visit) were defined as post-treatment events. Other AEs were assigned to the Screen or post-study period. Laboratory values, blood pressure, pulse, and weight were analyzed in terms of means and mean changes from baseline. Clinically significant laboratory abnormalities and transitions relative to the reference range were listed separately.

## 7 INTERIM ANALYSES

No interim analyses were planned and none were performed.

## 8 MISSING DATA

The primary method for handling missing data in the FAS was the LOCF method. This analysis imputes missing data by using a patient's data from their most recent previous visit. The underlying assumption of this approach is that the best estimate of the patient's response to an item on a visit is that patient's most recent previous response to that item. For the LOCF analysis, no data were carried forward from a baseline or pre-drug state to a post-drug state. In the case of a missing item of a multi-item scale, only the individual component is carried forward, not the overall total.

### 8.1 Preplanned Sensitivity Analyses

The following sensitivity analyses were conducted to assess the impact of alternative missing data imputation methods: 1) baseline observation carried forward (BOCF), alternatively called the LOCF-zero method, and 2) mixed model repeated measures (MMRM).

*BOCF:* In the first sensitivity analysis, BOCF was applied to the change from baseline endpoints. These analyses imputed a value of zero representing no change from baseline for the missing visits. BOCF is a conservative method for missing data, particularly if the flibanserin treatment group had more dropouts compared to placebo. The same statistical methods used for the primary, key secondary, and other secondary endpoints were used with this imputation method.

*MMRM*: In the second sensitivity analysis, MMRM analyses were performed without any data imputation and used only the observed cases. The MMRM analyses were performed to mirror the ANCOVA analysis (except for the repeated measures aspect); therefore, these analyses used baseline as a covariate and pooled center. The model included the treatment-by-visit interaction term from which the treatment versus placebo contrast at a given visit was reported. The first order autoregressive [AR(1)] covariance structure was used. If AR(1) did not converge, the unstructured (UN) and compound symmetry (CS) covariance structures were examined.

## 8.2 Additional Sensitivity Analyses and General Assumptions

Additional sensitivity analyses were conducted for SSEs, FSFI-Desire and FSDS-R13 (Distress) for the three pivotal phase 3 studies, as discussed below.

In general, non-monotone missing data were first imputed to be monotone missing. The non-monotone missing data were assumed to be missing at random (MAR) and were imputed using the Markov chain Monte Carlo (MCMC) method in the SAS MI procedure (SAS Version 9.4, SAS Institute) method using a multivariate normal distribution model over all variables including treatment arm.

Following the MCMC imputation, the monotone missing data was imputed with the assumptions below respectively by SAS MI procedure with sequential regression method by visit.

1. *Missing at Random (MAR)*: This approach assumes unobserved data are predictable by observed data.
2. *Control Based Imputation (CBI)*: This approach assumes that a subject who had been benefitting from the test treatment maintains its benefit for outcome at drop-out and from then on performs like a subject in the placebo arm because of discontinuing medication. The efficacy trajectory after drop-out was assumed to be similar to a subject in the placebo treatment. The missing values were modeled as a function of age, pooled center, baseline and previous observed visits.
3. *Jump to Reference (J2R)*: This approach assumes that the withdrawals from the test treatment have the same distribution as the placebo arm. An additional level of stringency specifies that subjects who withdrew from the test treatment lost the benefit they obtained from previous visits immediately. Missing values were modeled as a function of age, pooled center, and baseline.
4. *Tipping Point Analysis* using delta adjustment for selected reasons: This approach assumes that withdrawal from the test treatment due to AE or due to lack of efficacy would be immediately worse than the MAR imputed values by some value in the first withdrawal visit. Other reasons for withdrawal had similar proportions in the test

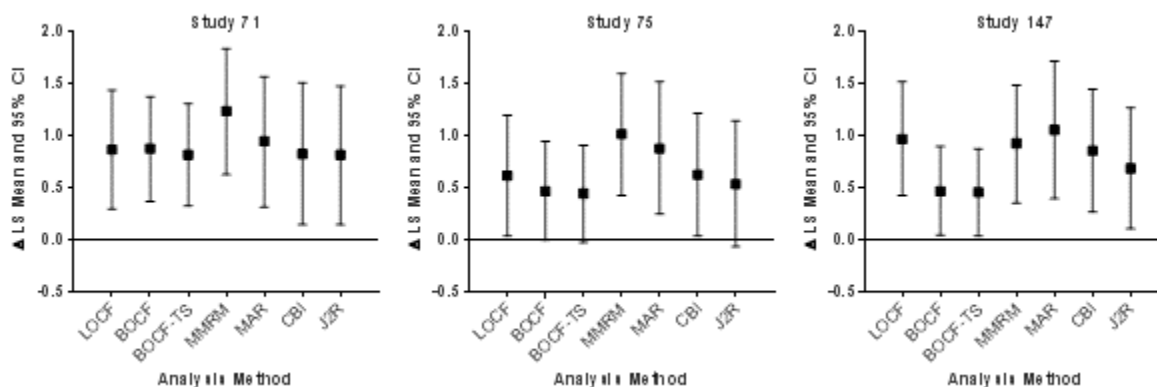
treatment group and in the placebo group, so those reasons are assumed to be unrelated to the efficacy of the treatment, and are considered sufficiently modeled by the MAR imputation. The difference between ‘minimally improved’ and ‘no change’ on PGI-I anchoring of the FSFI desire domain is identified as the clinically important difference (CID). In the tipping point analysis, a sequence of delta values, from 0.5 CID to 2 CID in increments of 0.5 CID (or until the primary statistical test has  $p > 0.05$ ) are imposed as the worsening values are invoked for the test treatment group.

### 8.3 Sensitivity Analyses for SSEs

For each pivotal study, the statistical analysis plans for analyzing SSEs pre-specified the stratified Wilcoxon rank sum test where strata were the pooled centers. However, the pre-specified MMRM and the post-hoc sensitivity analyses shown in this Appendix used the ANCOVA model. For LOCF and BOCF, the Wilcoxon test and ANCOVA analyses produced similar conclusions.

Summary graphs for the various sensitivity analyses are shown for each study. All values in the tables are from the last visit at the end of the treatment period for placebo and flibanserin 100 mg qhs. All analyses were applied to the FAS and BOCF was also applied to the Efficacy Treated Set (TS).

**Figure 1 SSE Data Comparison Using Various Methods for Handling Missing Data – Pivotal Phase 3 Studies in Premenopausal Women**



Notes: BOCF = Baseline observation carried forward; CBI = control based imputation; J2R = Jump to reference; LOCF = Last observation carried forward; MAR = Missing at random; MMRM = Mixed models repeated measures. All analyses were performed on the Full Analysis Set. BOCF was also performed on the Treated Set (BOCF-TS).

**Table 1 Mean Change from Baseline to Week 24 in SSE – Pivotal Phase 3 Studies in Premenopausal Women (FAS, LOCF)**

Study	Treatment	Change from Baseline		Difference from Placebo				
		LS Mean	SE	LS Mean	SE	Lower CL	Upper CL	P-value
71	Placebo	1.10	0.23	.	.	.	.	.
	Flibanserin	1.97	0.24	0.87	0.29	0.30	1.44	0.0030
75	Placebo	1.31	0.24	.	.	.	.	.
	Flibanserin	1.93	0.24	0.62	0.30	0.04	1.20	0.0374
147	Placebo	1.46	0.22	.	.	.	.	.
	Flibanserin	2.43	0.22	0.97	0.28	0.43	1.52	0.0005

**Table 2 Mean Change from Baseline to Week 24 in SSE – Pivotal Phase 3 Studies in Premenopausal Women (FAS, BOCF)**

Study	Treatment	Change from Baseline		Difference from Placebo				
		LS Mean	SE	LS Mean	SE	Lower CL	Upper CL	P-value
71	Placebo	0.58	0.21	.	.	.	.	.
	Flibanserin	1.45	0.21	0.88	0.26	0.37	1.38	0.0007
75	Placebo	0.87	0.19	.	.	.	.	.
	Flibanserin	1.34	0.19	0.47	0.24	-0.00	0.95	0.0518
147	Placebo	0.98	0.17	.	.	.	.	.
	Flibanserin	1.46	0.17	0.47	0.22	0.05	0.90	0.0296

**Table 3 Mean Change from Baseline to Week 24 in SSE – Pivotal Phase 3 Studies in Premenopausal Women (Treated Set, BOCF)**

Study	Treatment	Change from Baseline		Difference from Placebo				
		LS Mean	SE	LS Mean	SE	Lower CL	Upper CL	P-value
71	Placebo	0.58	0.20	.	.	.	.	.
	Flibanserin	1.40	0.21	0.82	0.25	0.33	1.31	0.0012
75	Placebo	0.84	0.19	.	.	.	.	.
	Flibanserin	1.29	0.19	0.45	0.24	-0.02	0.91	0.0586
147	Placebo	0.97	0.17	.	.	.	.	.
	Flibanserin	1.43	0.17	0.46	0.21	0.04	0.88	0.0321



**Table 4 Mean Change from Baseline to Week 24 in SSE – Pivotal Phase 3 Studies in Premenopausal Women (FAS, MMRM)**

Study	Treatment	Change from Baseline		Difference from Placebo				
		LS Mean	SE	LS Mean	SE	Lower CL	Upper CL	P-value
71	Placebo	0.71	0.23					
	Flibanserin	1.95	0.24	1.24	0.31	0.63	1.84	0.0001
75	Placebo	1.16	0.22					
	Flibanserin	2.17	0.23	1.02	0.30	0.43	1.60	0.0007
147	Placebo	1.42	0.21					
	Flibanserin	2.35	0.22	0.93	0.29	0.36	1.49	0.0013

**Table 5 Mean Change from Baseline to Week 24 in SSE – Pivotal Phase 3 Studies in Premenopausal Women (FAS, MAR)**

Study	Treatment	Change from Baseline		Difference from Placebo				
		LS Mean	SE	LS Mean	SE	Lower CL	Upper CL	P-value
71	Placebo	0.77	0.24					
	Flibanserin	1.71	0.27	0.95	0.32	0.32	1.57	0.0031
75	Placebo	1.35	0.23					
	Flibanserin	2.23	0.28	0.88	0.32	0.25	1.52	0.0069
147	Placebo	1.36	0.25					
	Flibanserin	2.42	0.24	1.06	0.33	0.40	1.72	0.0021

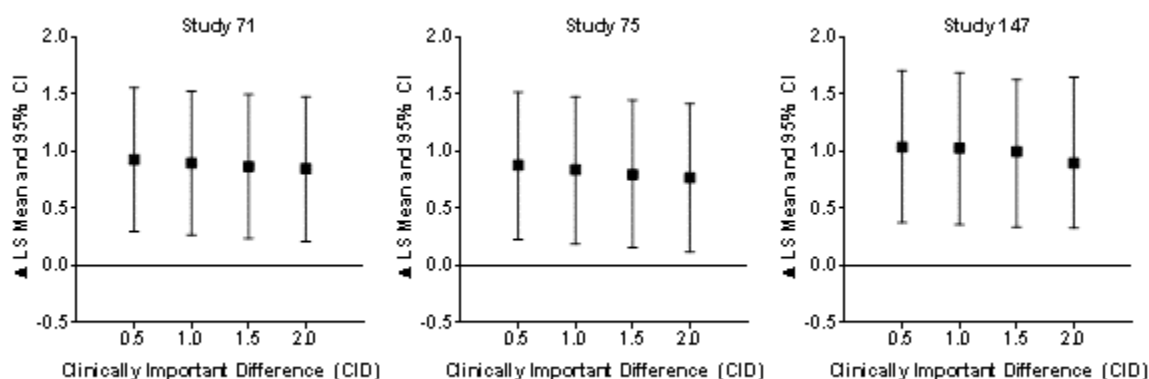
**Table 6 Mean Change from Baseline to Week 24 in SSE – Pivotal Phase 3 Studies in Premenopausal Women (FAS, CBI)**

Study	Treatment	Change from Baseline		Difference from Placebo				
		LS Mean	SE	LS Mean	SE	Lower CL	Upper CL	P-value
71	Placebo	0.73	0.25					
	Flibanserin	1.56	0.27	0.83	0.34	0.15	1.51	0.0164
75	Placebo	1.35	0.25					
	Flibanserin	1.98	0.25	0.63	0.30	0.04	1.22	0.0374
147	Placebo	1.40	0.23					
	Flibanserin	2.26	0.24	0.86	0.30	0.27	1.45	0.0043

**Table 7 Mean Change from Baseline to Week 24 in SSE – Pivotal Phase 3 Studies in Premenopausal Women (FAS, J2R)**

Study	Treatment	Change from Baseline		Difference from Placebo				
		LS Mean	SE	LS Mean	SE	Lower CL	Upper CL	P-value
71	Placebo	0.76	0.25					
	Flibanserin	1.58	0.29	0.82	0.34	0.15	1.48	0.0161
75	Placebo	1.26	0.22					
	Flibanserin	1.80	0.25	0.54	0.31	-0.06	1.15	0.0779
147	Placebo	1.35	0.26					
	Flibanserin	2.04	0.25	0.69	0.30	0.11	1.27	0.0195

**Figure 2 Summary of Tipping Point Analysis for SSE - Pivotal Phase 3 Studies in Premenopausal Women**



Notes: Clinically important difference (CID) was defined as the mean endpoint value for patients recording a “minimally improved” response on the PGI-I scale. The x-axis shows various multiples of the CID from 0.5 x CID to 2 x CID.

**Table 8 Tipping Point Analysis for SSE – Study 71**

CID	Treatment	Change from Baseline		Difference from Placebo				
		LS Mean	SE	LS Mean	SE	Lower CL	Upper CL	P-value
0.5	Placebo	0.76	0.24					
	Flibanserin	1.69	0.27	0.93	0.32	0.30	1.56	0.0038
1.0	Placebo	0.76	0.24					
	Flibanserin	1.66	0.27	0.90	0.32	0.27	1.53	0.0051
1.5	Placebo	0.76	0.25					
	Flibanserin	1.63	0.27	0.87	0.32	0.24	1.50	0.0067
2.0	Placebo	0.76	0.25					
	Flibanserin	1.60	0.27	0.85	0.32	0.22	1.48	0.0086

**Table 9 Tipping Point Analysis for SSE – Study 75**

CID	Treatment	Change from Baseline		Difference from Placebo				
		LS Mean	SE	LS Mean	SE	Lower CL	Upper CL	P-value
0.5	Placebo	1.35	0.23					
	Flibanserin	2.22	0.28	0.88	0.33	0.23	1.52	0.0080
1.0	Placebo	1.35	0.23					
	Flibanserin	2.19	0.28	0.84	0.33	0.19	1.48	0.0112
1.5	Placebo	1.35	0.23					
	Flibanserin	2.15	0.28	0.80	0.33	0.16	1.45	0.0152
2.0	Placebo	1.35	0.23					
	Flibanserin	2.12	0.28	0.77	0.33	0.12	1.42	0.0198

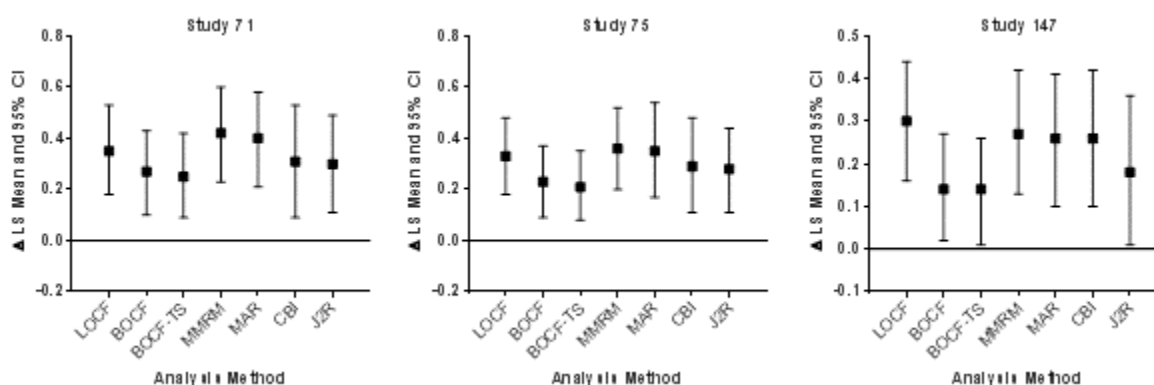
**Table 10 Tipping Point Analysis for SSE – Study 147**

CID	Treatment	Change from Baseline		Difference from Placebo				
		LS Mean	SE	LS Mean	SE	Lower CL	Upper CL	P-value
0.5	Placebo	1.36	0.25					
	Flibanserin	2.40	0.24	1.04	0.33	0.38	1.71	0.0024
1.0	Placebo	1.36	0.25					
	Flibanserin	2.38	0.24	1.02	0.33	0.36	1.69	0.0029
1.5	Placebo	1.36	0.25					
	Flibanserin	2.36	0.24	1.00	0.33	0.34	1.67	0.0035
2.0	Placebo	1.36	0.25					
	Flibanserin	2.35	0.24	0.99	0.33	0.32	1.65	0.0040

## 8.4 Sensitivity Analyses for FSFI-Desire

Summary graphs for the various sensitivity analyses are shown for each study. All values in the tables are from the last visit at the end of the treatment period for placebo and flibanserin 100 mg qhs.

**Figure 3 FSFI-Desire Data Comparison Using Various Methods for Handling Missing Data – Pivotal Phase 3 Studies in Premenopausal Women**



Notes: BOCF = Baseline observation carried forward; CBI = Control based imputation; J2R = Jump to reference; LOCF = Last observation carried forward; MAR = Missing at random; MMRM = Mixed models repeated measures.  
All analyses were performed on the Full Analysis Set. BOCF was also performed on the Treated Set (BOCF-TS).

**Table 11 Mean Change from Baseline to Week 24 in FSFI-Desire – Pivotal Phase 3 Studies in Premenopausal Women (FAS, LOCF)**

Study	Treatment	Change from Baseline		Difference from Placebo				
		LS Mean	SE	LS Mean	SE	Lower CL	Upper CL	P-value
71	Placebo	0.52	0.07	.	.	.	.	.
	Flibanserin	0.87	0.07	0.35	0.09	0.18	0.53	0.0001
75	Placebo	0.55	0.06	.	.	.	.	.
	Flibanserin	0.88	0.06	0.33	0.08	0.18	0.48	<0.0001
147	Placebo	0.68	0.06	.	.	.	.	.
	Flibanserin	0.98	0.06	0.30	0.07	0.16	0.44	<0.0001

**Table 12 Mean Change from Baseline to Week 24 in FSFI-Desire – Pivotal Phase 3 Studies in Premenopausal Women (FAS, BOCF)**

Study	Treatment	Change from Baseline		Difference from Placebo				
		LS Mean	SE	LS Mean	SE	Lower CL	Upper CL	P-value
71	Placebo	0.37	0.07	.	.	.	.	.
	Flibanserin	0.64	0.07	0.27	0.09	0.10	0.43	0.0019
75	Placebo	0.42	0.06	.	.	.	.	.
	Flibanserin	0.65	0.06	0.23	0.07	0.09	0.37	0.0012
147	Placebo	0.50	0.05	.	.	.	.	.
	Flibanserin	0.64	0.05	0.14	0.06	0.02	0.27	0.0280

**Table 13 Mean Change from Baseline to Week 24 in FSFI-Desire – Pivotal Phase 3 Studies in Premenopausal Women (Treated Set, BOCF)**

Study	Treatment	Change from Baseline		Difference from Placebo				
		LS Mean	SE	LS Mean	SE	Lower CL	Upper CL	P-value
71	Placebo	0.37	0.07	.	.	.	.	.
	Flibanserin	0.62	0.07	0.25	0.08	0.09	0.42	0.0026
75	Placebo	0.41	0.05	.	.	.	.	.
	Flibanserin	0.62	0.06	0.21	0.07	0.08	0.35	0.0020
147	Placebo	0.49	0.05	.	.	.	.	.
	Flibanserin	0.63	0.05	0.14	0.06	0.01	0.26	0.0300

**Table 14 Mean Change from Baseline to Week 24 in FSFI-Desire – Pivotal Phase 3 Studies in Premenopausal Women (FAS, MMRM)**

Study	Treatment	Change from Baseline		Difference from Placebo				
		LS Mean	SE	LS Mean	SE	Lower CL	Upper CL	P-value
71	Placebo	0.51	0.07					
	Flibanserin	0.92	0.07	0.42	0.10	0.23	0.60	<0.0001
75	Placebo	0.57	0.06					
	Flibanserin	0.93	0.06	0.36	0.08	0.20	0.52	<0.0001
147	Placebo	0.72	0.06					
	Flibanserin	0.99	0.06	0.27	0.08	0.13	0.42	0.0003

**Table 15 Mean Change from Baseline to Week 24 in FSFI-Desire – Pivotal Phase 3 Studies in Premenopausal Women (FAS, MAR)**

Study	Treatment	Change from Baseline		Difference from Placebo				
		LS Mean	SE	LS Mean	SE	Lower CL	Upper CL	P-value
71	Placebo	0.49	0.07					
	Flibanserin	0.89	0.08	0.40	0.10	0.21	0.58	<0.0001
75	Placebo	0.58	0.06					
	Flibanserin	0.93	0.08	0.35	0.09	0.17	0.54	0.0002
147	Placebo	0.71	0.06					
	Flibanserin	0.97	0.06	0.26	0.08	0.10	0.41	0.0010

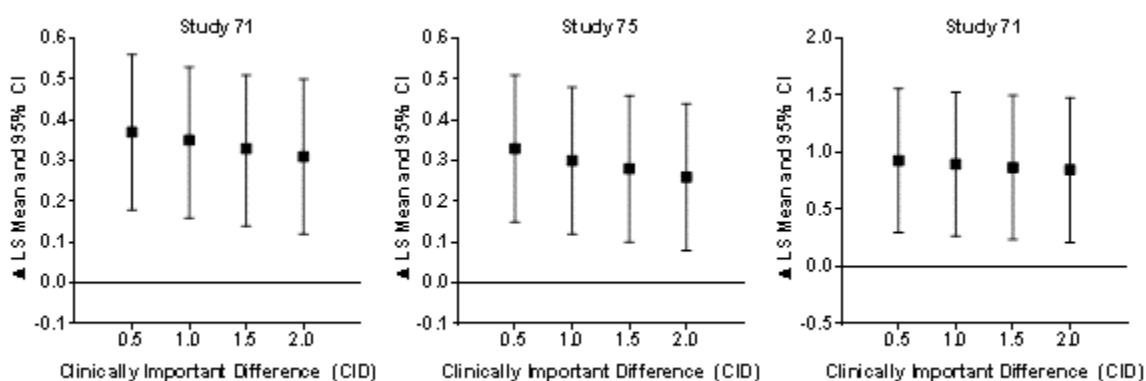
**Table 16 Mean Change from Baseline to Week 24 in FSFI-Desire – Pivotal Phase 3 Studies in Premenopausal Women (FAS, CBI)**

Study	Treatment	Change from Baseline		Difference from Placebo				
		LS Mean	SE	LS Mean	SE	Lower CL	Upper CL	P-value
71	Placebo	0.52	0.08					
	Flibanserin	0.83	0.08	0.31	0.11	0.09	0.53	0.0072
75	Placebo	0.58	0.09					
	Flibanserin	0.87	0.07	0.30	0.09	0.11	0.48	0.0019
147	Placebo	0.71	0.06					
	Flibanserin	0.97	0.06	0.26	0.08	0.10	0.42	0.0013

**Table 17 Mean Change from Baseline to Week 24 in FSFI-Desire – Pivotal Phase 3 Studies in Premenopausal Women (FAS, J2R)**

Study	Treatment	Change from Baseline		Difference from Placebo				
		LS Mean	SE	LS Mean	SE	Lower CL	Upper CL	P-value
71	Placebo	0.50	0.07					
	Flibanserin	0.81	0.08	0.30	0.10	0.11	0.49	0.0019
75	Placebo	0.58	0.06					
	Flibanserin	0.85	0.07	0.28	0.08	0.11	0.44	0.0008
147	Placebo	0.71	0.06					
	Flibanserin	0.89	0.07	0.18	0.08	0.01	0.36	0.0426

**Figure 4 Summary of Tipping Point Analysis for FSFI-Desire - Pivotal Phase 3 Studies in Premenopausal Women**



Notes: Clinically important difference (CID) was defined as the mean endpoint value for patients recording a “minimally improved” response on the PGI-I scale. The x-axis shows various multiples of the CID from 0.5 x CID to 2 x CID.

**Table 18 Tipping Point Analysis for FSFI-Desire – Study 71**

CID	Treatment	Change from Baseline		Difference from Placebo				
		LS Mean	SE	LS Mean	SE	Lower CL	Upper CL	P-value
0.5	Placebo	0.49	0.07					
	Flibanserin	0.86	0.08	0.37	0.10	0.18	0.56	0.0001
1.0	Placebo	0.49	0.07					
	Flibanserin	0.84	0.08	0.35	0.10	0.16	0.53	0.0003
1.5	Placebo	0.49	0.07					
	Flibanserin	0.82	0.08	0.33	0.10	0.14	0.51	0.0007
2.0	Placebo	0.49	0.07					
	Flibanserin	0.80	0.08	0.31	0.10	0.12	0.50	0.0012

**Table 19 Tipping Point Analysis for FSFI-Desire – Study 75**

CID	Treatment	Change from Baseline		Difference from Placebo				
		LS Mean	SE	LS Mean	SE	Lower CL	Upper CL	P-value
0.5	Placebo	0.58	0.06					
	Flibanserin	0.91	0.08	0.33	0.09	0.15	0.51	0.0005
1.0	Placebo	0.58	0.06					
	Flibanserin	0.88	0.08	0.30	0.09	0.12	0.48	0.0014
1.5	Placebo	0.57	0.06					
	Flibanserin	0.85	0.08	0.28	0.09	0.10	0.46	0.0030
2.0	Placebo	0.57	0.06					
	Flibanserin	0.83	0.08	0.26	0.09	0.08	0.44	0.0054

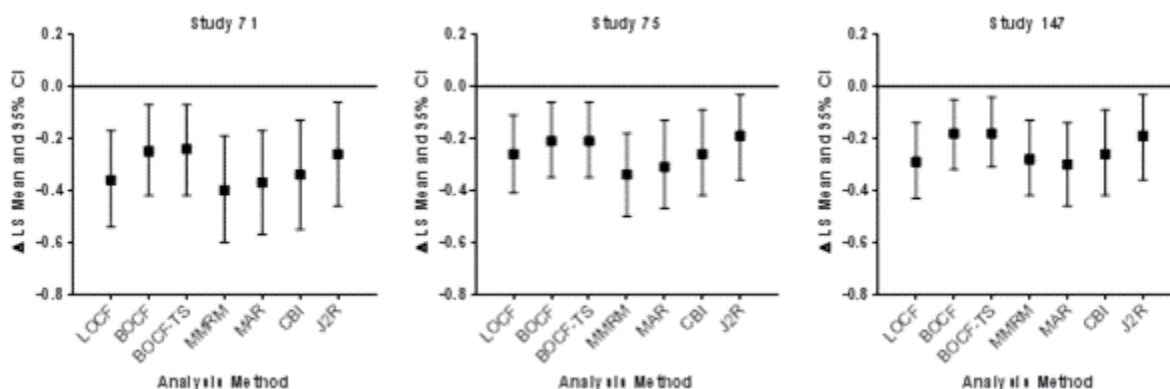
**Table 20 Tipping Point Analysis for FSFI-Desire – Study 147**

CID	Treatment	Change from Baseline		Difference from Placebo				
		LS Mean	SE	LS Mean	SE	Lower CL	Upper CL	P-value
0.5	Placebo	0.72	0.06					
	Flibanserin	0.96	0.06	0.24	0.08	0.09	0.39	0.0020
1.0	Placebo	0.72	0.06					
	Flibanserin	0.95	0.06	0.23	0.08	0.08	0.38	0.0034
1.5	Placebo	0.72	0.06					
	Flibanserin	0.94	0.06	0.22	0.08	0.07	0.37	0.0052
2.0	Placebo	0.72	0.06					
	Flibanserin	0.93	0.06	0.21	0.08	0.06	0.36	0.0070

## 8.5 Sensitivity Analyses for FSDS-R13

Summary graphs for the various sensitivity analyses are shown for each study. All values in the tables are from the last visit at the end of the treatment period for placebo and flibanserin 100 mg qhs.

**Figure 5 FSDS-R13 (Distress) Data Comparison Using Various Methods for Handling Missing Data – Pivotal Phase 3 Studies in Premenopausal Women**



Notes: BOCF = Baseline observation carried forward; CBI = Control based imputation; J2R = jump to reference; LOCF = Last observation carried forward; MAR = Missing at random; MMRM = Mixed models repeated measures. All analyses were performed on the Full Analysis Set. BOCF was also performed on the Treated Set (BOCF-TS).

**Table 21 Mean Change from Baseline to Week 24 in FSDS-R13 (Distress) – Pivotal Phase 3 Studies in Premenopausal Women (FAS, LOCF)**

Study	Treatment	Change from Baseline		Difference from Placebo				
		LS Mean	SE	LS Mean	SE	Lower CL	Upper CL	P-value
71	Placebo	-0.45	0.08	.	.	.	.	.
	Flibanserin	-0.81	0.08	-0.36	0.09	-0.54	-0.17	0.0002
75	Placebo	-0.45	0.06	.	.	.	.	.
	Flibanserin	-0.72	0.06	-0.26	0.08	-0.41	-0.11	0.0007
147	Placebo	-0.72	0.06	.	.	.	.	.
	Flibanserin	-1.01	0.06	-0.29	0.07	-0.43	-0.14	0.0001



**Table 22 Mean Change from Baseline to Week 24 in FSDS-R13 (Distress) – Pivotal Phase 3 Studies in Premenopausal Women (FAS, BOCF)**

Study	Treatment	Change from Baseline		Difference from Placebo				
		LS Mean	SE	LS Mean	SE	Lower CL	Upper CL	P-value
71	Placebo	-0.36	0.07	.	.	.	.	.
	Flibanserin	-0.61	0.07	-0.25	0.09	-0.42	-0.07	0.0056
75	Placebo	-0.35	0.06	.	.	.	.	.
	Flibanserin	-0.56	0.06	-0.21	0.07	-0.35	-0.06	0.0048
147	Placebo	-0.57	0.05	.	.	.	.	.
	Flibanserin	-0.75	0.05	-0.18	0.07	-0.32	-0.05	0.0090

**Table 23 Mean Change from Baseline to Week 24 in FSDS-R13 (Distress) – Pivotal Phase 3 Studies in Premenopausal Women (Treated Set, BOCF)**

Study	Treatment	Change from Baseline		Difference from Placebo				
		LS Mean	SE	LS Mean	SE	Lower CL	Upper CL	P-value
71	Placebo	-0.35	0.07	.	.	.	.	.
	Flibanserin	-0.59	0.07	-0.24	0.09	-0.42	-0.07	0.0051
75	Placebo	-0.34	0.06	.	.	.	.	.
	Flibanserin	-0.54	0.06	-0.21	0.07	-0.35	-0.06	0.0044
147	Placebo	-0.56	0.05	.	.	.	.	.
	Flibanserin	-0.74	0.05	-0.18	0.07	-0.31	-0.04	0.0099

**Table 24 Mean Change from Baseline to Week 24 in FSDS-R13 (Distress) – Pivotal Phase 3 Studies in Premenopausal Women (FAS, MMRM)**

Study	Treatment	Change from Baseline		Difference from Placebo				
		LS Mean	SE	LS Mean	SE	Lower CL	Upper CL	P-value
71	Placebo	-0.46	0.08	.	.	.	.	.
	Flibanserin	-0.85	0.08	-0.40	0.10	-0.60	-0.19	0.0001
75	Placebo	-0.48	0.06	.	.	.	.	.
	Flibanserin	-0.82	0.06	-0.34	0.08	-0.50	-0.18	<0.0001
147	Placebo	-0.73	0.06	.	.	.	.	.
	Flibanserin	-1.0	0.06	-0.28	0.07	-0.42	-0.13	0.0002

**Table 25 Mean Change from Baseline to Week 24 in FSDS-R13 (Distress) – Pivotal Phase 3 Studies in Premenopausal Women (FAS, MAR)**

Study	Treatment	Change from Baseline		Difference from Placebo				
		LS Mean	SE	LS Mean	SE	Lower CL	Upper CL	P-value
71	Placebo	-0.50	0.07					
	Flibanserin	-0.87	0.09	-0.37	0.10	-0.57	-0.17	0.0003
75	Placebo	-0.52	0.07					
	Flibanserin	-0.83	0.08	-0.31	0.09	-0.47	-0.14	0.0005
147	Placebo	-0.76	0.06					
	Flibanserin	-1.06	0.06	-0.30	0.08	-0.46	-0.14	0.0002

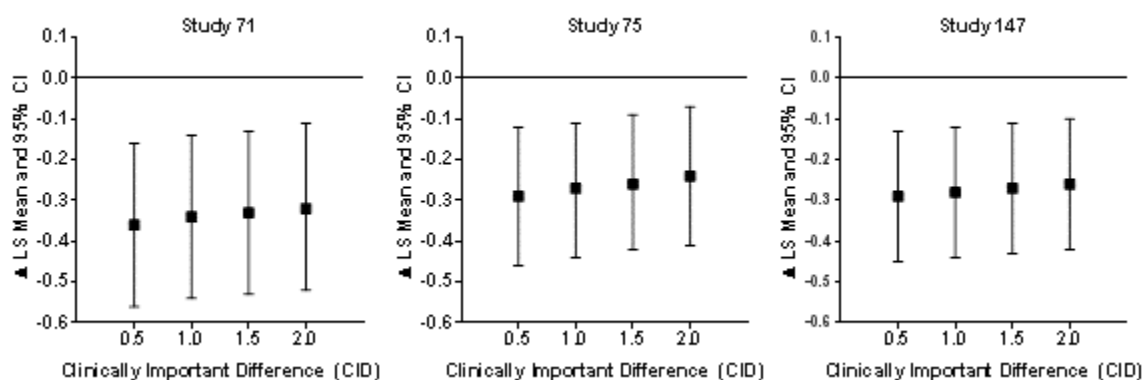
**Table 26 Mean Change from Baseline to Week 24 in FSDS-R13 (Distress) – Pivotal Phase 3 Studies in Premenopausal Women (FAS, CBI)**

Study	Treatment	Change from Baseline		Difference from Placebo				
		LS Mean	SE	LS Mean	SE	Lower CL	Upper CL	P-value
71	Placebo	-0.48	0.08					
	Flibanserin	-0.82	0.08	-0.34	0.11	-0.55	-0.13	0.0014
75	Placebo	-0.54	0.07					
	Flibanserin	-0.80	0.07	-0.26	0.09	-0.43	-0.09	0.0027
147	Placebo	-0.76	0.07					
	Flibanserin	-1.02	0.06	-0.26	0.08	-0.42	-0.09	0.0020

**Table 27 Mean Change from Baseline to Week 24 in FSDS-R13 (Distress) – Pivotal Phase 3 Studies in Premenopausal Women (FAS, J2R)**

Study	Treatment	Change from Baseline		Difference from Placebo				
		LS Mean	SE	LS Mean	SE	Lower CL	Upper CL	P-value
71	Placebo	-0.50	0.07					
	Flibanserin	-0.76	0.08	-0.26	0.10	-0.46	-0.06	0.0119
75	Placebo	-0.52	0.07					
	Flibanserin	-0.76	0.07	-0.24	0.08	-0.40	-0.08	0.0039
147	Placebo	-0.76	0.06					
	Flibanserin	-0.96	0.07	-0.19	0.08	-0.36	-0.03	0.0203

**Figure 6 Summary of Tipping Point Analysis for FSDS-R13 (Distress) - Pivotal Phase 3 Studies in Premenopausal Women**



Notes: Clinically important difference (CID) was defined as the mean endpoint value for patients recording a “minimally improved” response on the PGI-I scale. The x-axis shows various multiples of the CID from 0.5 x CID to 2 x CID.

**Table 28 Tipping Point Analysis for FSDS-R13 (Distress) – Study 71**

CID	Treatment	Change from Baseline		Difference from Placebo				
		LS Mean	SE	LS Mean	SE	Lower CL	Upper CL	P-value
0.5	Placebo	-0.50	0.07					
	Flibanserin	-0.86	0.09	-0.36	0.10	-0.56	-0.16	0.0006
1.0	Placebo	-0.50	0.07					
	Flibanserin	-0.84	0.09	-0.34	0.10	-0.54	-0.14	0.0009
1.5	Placebo	-0.50	0.07					
	Flibanserin	-0.83	0.09	-0.33	0.10	-0.53	-0.13	0.0015
2.0	Placebo	-0.50	0.07					
	Flibanserin	-0.81	0.09	-0.32	0.10	-0.52	-0.11	0.0023

**Table 29 Tipping Point Analysis for FSDS-R13 (Distress) – Study 75**

CID	Treatment	Change from Baseline		Difference from Placebo				
		LS Mean	SE	LS Mean	SE	Lower CL	Upper CL	P-value
0.5	Placebo	-0.52	0.07					
	Flibanserin	-0.82	0.07	-0.29	0.09	-0.46	-0.12	0.0007
1.0	Placebo	-0.52	0.07					
	Flibanserin	-0.80	0.07	-0.27	0.09	-0.44	-0.11	0.0015
1.5	Placebo	-0.52	0.07					
	Flibanserin	-0.78	0.07	-0.26	0.09	-0.42	-0.09	0.0030
2.0	Placebo	-0.52	0.07					
	Flibanserin	-0.76	0.07	-0.24	0.09	-0.41	-0.07	0.0057

**Table 30 Tipping Point Analysis for FSDS-R13 (Distress) – Study147**

CID	Treatment	Change from Baseline		Difference from Placebo				
		LS Mean	SE	LS Mean	SE	Lower CL	Upper CL	P-value
0.5	Placebo	-0.76	0.06					
	Flibanserin	-1.05	0.06	-0.29	0.08	-0.45	-0.13	0.0003
1.0	Placebo	-0.76	0.06					
	Flibanserin	-1.04	0.06	-0.28	0.08	-0.44	-0.12	0.0005
1.5	Placebo	-0.76	0.06					
	Flibanserin	-1.03	0.06	-0.27	0.08	-0.43	-0.11	0.0008
2.0	Placebo	-0.76	0.06					
	Flibanserin	-1.02	0.06	-0.26	0.08	-0.42	-0.10	0.0012

## 9 ANALYSIS OF COMPLETERS DATA

In addition to sensitivity analysis using various imputation methods for missing data, efficacy data were also analyzed for the subset of subjects who completed the study at Week 24 (Completers).

### 9.1 Satisfying Sexual Events

Mean Change from Baseline in SSEs at Week 24 was a co-primary endpoint in all three pivotal studies. The flibanserin 100 mg qhs treatment group in each study experienced a statistically significant increase in SSEs (standardized) compared with the placebo group at Week 24.

**Table 31 SSEs (Standardized) Change from Baseline at Week 24 – Pivotal Phase 3 Studies in Premenopausal Women (Completers)**

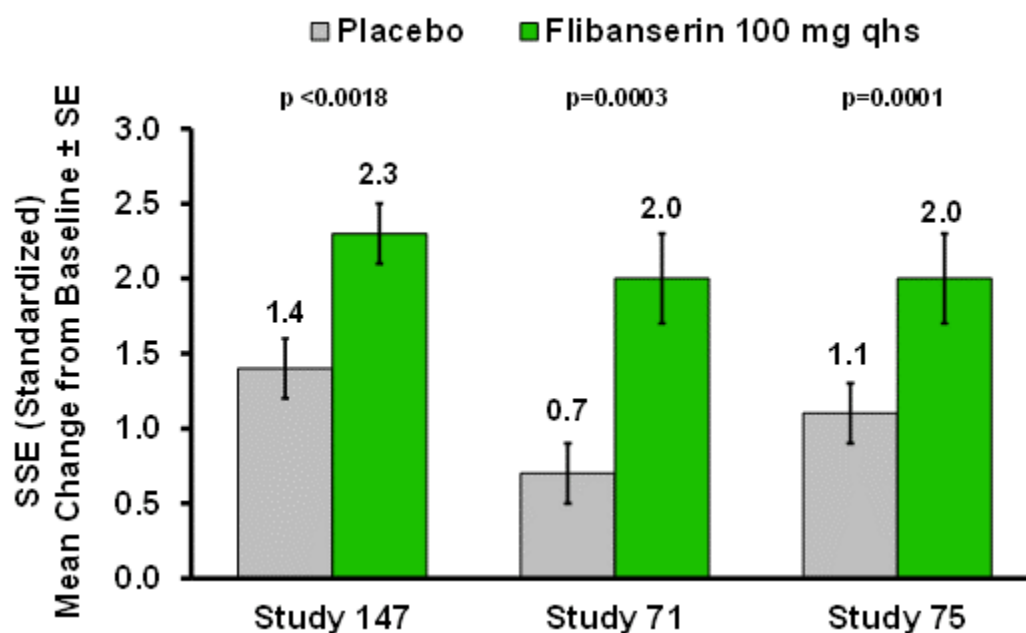
	Treatment	N	Change from Baseline	
			Mean (SD)	P-value <sup>a</sup>
Study 147	Placebo	361	1.4 (4.0)	
	FLI 100 mg qhs	329	2.3 (4.4)	0.0018
Study 71	Placebo	219	0.7 (3.0)	
	FLI 100 mg qhs	196	2.0 (4.0)	0.0003
Study 75	Placebo	278	1.1 (3.3)	
	FLI 100 mg qhs	245	2.0 (4.8)	0.0001

<sup>a</sup> P-value based on Wilcoxon rank sum test.

Notes: SD = Standard deviation; SSE = Satisfying sexual event.

Source: Post Hoc Analysis.

**Figure 7 SSEs (Standardized) Change from Baseline at Week 24 – Pivotal Phase 3 Studies in Premenopausal Women (Completers)**



Notes: qhs = Once every evening at bedtime; SE = Standard error; SSE = Satisfying sexual event.

## 9.2 FSFI-Desire

Low desire is one of the two hallmark features of HSDD and the 4.8-point FSFI-Desire domain which queries frequency and intensity of desire (scale range: 1.2 – 6.0) is the validated standard instrument for measuring female sexual desire. Mean Change from Baseline in FSFI-Desire at Week 24 was a co-primary endpoint in Study 147. It was also a secondary endpoint in Studies 71 and 75. The flibanserin 100 mg qhs treatment group in each study experienced a statistically significant mean increase in FSFI-Desire compared with the placebo group at Week 24.

**Table 32 FSFI-Desire Change from Baseline at Week 24 – Pivotal Phase 3 Studies in Premenopausal Women (Completers)**

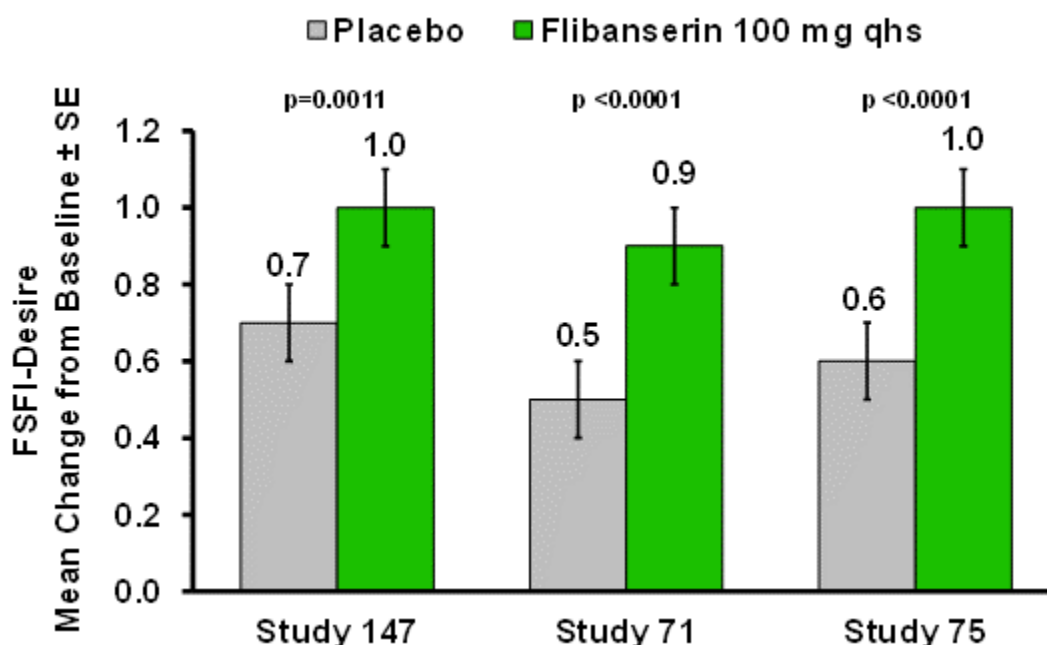
	Treatment	N	Change from Baseline		
			LS Mean (SE)	LS Diff (SE)	P-value <sup>a</sup>
Study 147	Placebo	380	0.7 (0.1)		
	FLI 100 mg qhs	343	1.0 (0.1)	0.3 (0.1)	0.0011
Study 71	Placebo	236	0.5 (0.1)		
	FLI 100 mg qhs	208	0.9 (0.1)	0.4 (0.1)	<0.0001
Study 75	Placebo	290	0.6 (0.1)		
	FLI 100 mg qhs	261	1.0 (0.1)	0.4 (0.1)	<0.0001

<sup>a</sup> P-value based on ANCOVA model with main effect terms treatment and pooled center and using baseline as a covariate.

Notes: FLI = Flibanserin; FSFI-Desire = Female sexual function index – desire domain (score range 1.2 – 6); LS = Least square; N = Number of subjects; qhs = Once every evening at bedtime; SE = Standard error.

Source: Post Hoc Analysis.

**Figure 8 FSFI-Desire Change from Baseline at Week 24 – Pivotal Phase 3 Studies in Premenopausal Women (Completers)**



Notes: FSFI-Desire = Female sexual function index – desire domain; qhs = Once every evening at bedtime; SE = Standard error.

### 9.3 FSIDS-R13 (Distress)

Mean Change from Baseline in FSIDS-R13 (Distress) at Week 24 was a secondary endpoint in all three pivotal studies. Distress associated with low desire is one of the two hallmark PRO question for measuring that distress. The flibanserin 100 mg qhs treatment group in each study experienced a statistically significant decrease in FSIDS-R13 (Distress) as compared with placebo.

**Table 33 FSIDS-R13 (Distress) Change from Baseline at Week 24 – Pivotal Phase 3 Studies in Premenopausal Women (Completers)**

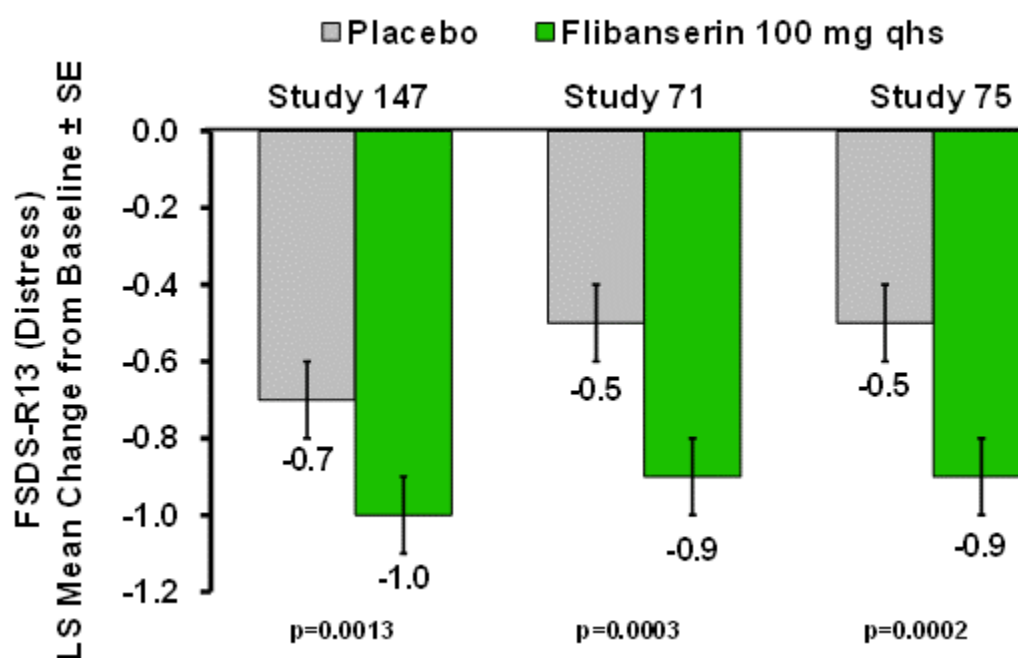
	Treatment	N	Change from Baseline		
			LS Mean (SE)	LS Diff (SE)	P-value <sup>a</sup>
Study 147	Placebo	426	-0.7 (0.1)		
	FLI 100 mg qhs	391	-1.0 (0.1)	-0.3 (0.1)	0.0013
Study 71	Placebo	235	-0.5 (0.1)		
	FLI 100 mg qhs	208	-0.9 (0.1)	-0.4 (0.1)	0.0003
Study 75	Placebo	290	-0.5 (0.1)		
	FLI 100 mg qhs	261	-0.9 (0.1)	-0.4 (0.1)	0.0002

<sup>a</sup> P-value based on ANCOVA model with main effect terms treatment and pooled center and using baseline as a covariate.

Notes: FLI = Flibanserin; FSIDS-R13 = Female sexual distress scale-revised Question 13 (range 0 – 4); LS = Least squares; n = Number of subjects; qhs = Once every evening at bedtime; SE = Standard error.

Source: Post Hoc Analysis.

**Figure 9 FSDS-R13 (Distress) Change from Baseline at Week 24 – Pivotal Phase 3 Studies in Premenopausal Women (Completers)**



Notes: FSDS-R13 = Female sexual distress scale - revised item 13; LS = Least squares; qhs = Once every evening at bedtime; SE = Standard error.

## **APPENDIX L STUDY 75 EFFICACY RESULTS EXCLUDING 2 STUDY SITES**



## TABLE OF CONTENTS

	Page
<b>TABLE OF CONTENTS .....</b>	<b>2</b>
<b>LIST OF TABLES .....</b>	<b>3</b>
<b>LIST OF FIGURES .....</b>	<b>4</b>
<b>LIST OF ABBREVIATIONS .....</b>	<b>5</b>
<b>EFFICACY DATA FROM STUDY 75 EXCLUDING PATIENTS FROM TWO STUDY SITES.....</b>	<b>6</b>
<b>1 DEMOGRAPHICS AND BASELINE CHARACTERISTICS - PIVOTAL STUDIES.....</b>	<b>6</b>
1.1 Demographics .....	6
1.2 Baseline Characteristics .....	7
<b>2 PRINCIPAL EFFICACY DATA – STUDY 75<sup>†</sup>.....</b>	<b>8</b>
2.1 Satisfying Sexual Events.....	8
2.2 Sexual Desire .....	10
2.2.1 FSFI-Desire .....	10
2.2.2 eDiary Desire .....	12
2.3 FSDS-R13 (Distress) .....	14
2.4 Results Across all Efficacy Measures .....	16
2.5 Pre-specified Responder Analysis .....	17
2.5.1 Consistent Effect Across Symptoms.....	19

## LIST OF TABLES

	Page
Table 1 Patient Disposition - Pivotal Phase 3 Studies in Premenopausal Women with Study 75† (Efficacy Treated Set).....	6
Table 2 Demographic Characteristics of Patients - Pivotal Phase 3 Studies in Premenopausal Women - Study 75† (Efficacy Treated Set) .....	7
Table 3 Baseline Characteristics for Efficacy Endpoints - Pivotal Phase 3 Studies in Premenopausal Women with Study 75† (FAS).....	8
Table 4 SSEs (Standardized) Change from Baseline at Week 24 – Pivotal Phase 3 Studies in Premenopausal Women - Study 75† (FAS, LOCF).....	9
Table 5 FSFI-Desire Change from Baseline at Week 24 – Pivotal Phase 3 Studies in Premenopausal Women - Study 75† (FAS, LOCF).....	11
Table 6 eDiary Desire (Total Monthly Score) Change from Baseline at Week 24 – Study 75† (FAS, LOCF).....	13
Table 7 FSDS-R13 (Distress) Change from Baseline at Week 24 - Study 75† (FAS, LOCF) .....	15
Table 8 Number (%) of Responders (PGI-I Anchor Criteria) and Percent Differences across Efficacy Endpoints at Week 24 – Study 75† (FAS, LOCF).....	17
Table 9 Mean Change from Baseline at Week 24 on Primary and Secondary Endpoints – Flibanserin Group – Study 75† (FAS, and Responder Populations) .....	19

## LIST OF FIGURES

	Page
Figure 1 SSEs (Standardized) Change from Baseline at Week 24 – Pivotal Phase 3 Studies in Premenopausal Women - Study 75† (FAS, LOCF).....	9
Figure 2 SSEs (Standardized) Change from Baseline by Visit – Pivotal Phase 3 Studies in Premenopausal Women - Study 75† (FAS, LOCF) .....	10
Figure 3 FSFI-Desire Change from Baseline at Week 24 – Pivotal Phase 3 Studies in Premenopausal Women - Study 75† (FAS, LOCF).....	11
Figure 4 FSFI-Desire Change from Baseline by Visit – Pivotal Phase 3 Studies in Premenopausal Women - Study 75† (FAS, LOCF).....	12
Figure 5 eDiary Desire (Standardized) Change from Baseline at Week 24 - Study 75† (FAS, LOCF) .....	13
Figure 6 eDiary Desire (Standardized) Change from Baseline by Visit - Study 75† (FAS, LOCF).....	14
Figure 7 FSDS-R13 (Distress) Change from Baseline at Week 24 – - Study 75† (FAS, LOCF) .....	15
Figure 8 FSDS-R13 (Distress) Change from Baseline by Visit - Study 75† (FAS, LOCF).....	16
Figure 9 Differences from Placebo (95% CI) for Primary and Secondary Efficacy Endpoints (Standardized) – Study 75† (FAS, LOCF) .....	17
Figure 10 Number (%) of Responders (PGI-I Anchor Criteria) across Efficacy Endpoints – Study 75† (FAS, LOCF) .....	18
Figure 11 Correlation between Key Efficacy Endpoints – Pooled Pivotal Phase 3 Studies in Premenopausal Women with Study 75† (FAS, LOCF).....	19

## LIST OF ABBREVIATIONS

ANCOVA	Analysis of Covariance
CI	Confidence Interval
eDiary Desire	Daily Electronic Desire Measure
FAS	Full Analysis Set
FLI	Flibanserin
FSDS-R (Distress)	Female Sexual Distress Scale-Revised
FSDS-R13 (Distress)	Female Sexual Distress Scale – Revised Question 13
FSFI	Female Sexual Function Index
FSFI-Desire	Female Sexual Function Index – Sexual Desire Domain
HSDD	Hypoactive Sexual Desire Disorder
LS	Least Squares
LOCF	Last Observation Carried Forward
N	Number of Subjects
NDA	New Drug Application
PRO	Patient Reported Outcome
Q1	1st Quartile
Q3	3rd Quartile
qhs	Once Daily at Bedtime
SD	Standard Deviation
SE	Standard Error
SSE	Satisfying Sexual Event
CI	Analysis of Covariance

## EFFICACY DATA FROM STUDY 75 EXCLUDING PATIENTS FROM TWO STUDY SITES

Data presentations in the main body of this begin document present data for the Full Analysis Set (FAS) population for the three pivotal studies. Due to data integrity issues detected and reported by the Sponsor at two sites in Study 75 (Sites 1013 and 1024), a sensitivity analysis of data from Study 75 excluding the 69 subjects enrolled at those two sites was included in the original 2009 NDA and is presented here. Study 75 with these two sites excluded is referred to herein as Study 75<sup>†</sup>. Information across studies is presented for demographic and baseline criteria to match the format in the main body of the briefing document. Efficacy data are presented for Study 75<sup>†</sup> alone (not pooled) again to match previously displayed graphs and tables.

### 1 DEMOGRAPHICS AND BASELINE CHARACTERISTICS - PIVOTAL STUDIES

#### 1.1 Demographics

A total of 1229 patients received flibanserin 100 mg qhs and 1241 received placebo in the pivotal Phase 3 studies using Study 75<sup>†</sup>. The overall completion rates for flibanserin 100 mg qhs and placebo treatment groups were 70.1% and 78.2%, respectively. Discontinuations were attributed primarily to adverse events with more discontinuations on drug than placebo ([Table 1](#)).

**Table 1 Patient Disposition - Pivotal Phase 3 Studies in Premenopausal Women with Study 75<sup>†</sup> (Efficacy Treated Set)**

	Placebo N (%)	Flibanserin 100 mg qhs N (%)
Randomized	1224	1212
Treated	1221 (100)	1210 (100)
Discontinued	266 (21.8)	362 (29.9)
Adverse Event	70 (5.7)	145 (12.0)
Lost to Follow-up	54 (4.4)	67 (5.5)
Consent Withdrawn	66 (5.4)	50 (4.1)
Noncompliance	22 (1.8)	33 (2.7)
Lack of Efficacy	22 (1.8)	20 (1.7)
Other <sup>a</sup>	32 (2.6)	46 (3.8)
Completed	955 (78.2)	848 (70.1)

<sup>a</sup> Other includes pregnancy, personal reasons, moving away, etc.

Notes: qhs = Once every evening at bedtime.

Study 75<sup>†</sup>excludes subjects enrolled at sites 1013 and 1024.

Includes Studies 511.71, 511.75<sup>†</sup> and 511.147.

Source: ISE Appendix 6 Table 3.1.1.5, 3.1.1.6; 511.147 CTR Table 15.1.1:1.

Demographic data for the flibanserin and placebo groups were similar for all variables ([Table 2](#)).

**Table 2      Demographic Characteristics of Patients - Pivotal Phase 3 Studies in Premenopausal Women - Study 75† (Efficacy Treated Set)**

	<b>Placebo N = 1221</b>	<b>Flibanserin 100 mg qhs N = 1210</b>
Age, Years		
Mean	36.2	35.9
Min, Max	19, 54	19, 55
Race, n (%)		
White	1072 (87.8)	1057 (87.4)
Black or African American	119 (9.7)	130 (10.7)
Asian	21 (1.7)	20 (1.7)
Other	9 (0.7)	3 (0.2)
Body Mass Index, kg/m <sup>2</sup> , n (%)		
Underweight (<18.5)	23 (1.9)	19 (1.6)
Normal (18.5 - <25)	558 (45.9)	551 (45.7)
Overweight/Obese (≥25)	636 (52.2)	636 (52.7)
Missing	4 (0.3)	4 (0.3)

Notes: SD = Standard deviation.  
Study 75†excludes subjects enrolled at sites 1013 and 1024.  
Includes Studies 511.71, 511.75† and 511.147.  
Source: ISS Post Hoc Table 1.3.1.

## 1.2 Baseline Characteristics

The population demonstrated clinically relevant symptoms of HSDD ([Table 3](#)).

**Table 3 Baseline Characteristics for Efficacy Endpoints - Pivotal Phase 3 Studies in Premenopausal Women with Study 75† (FAS)**

	147		71		75	
	FLI		FLI		FLI	
	Placebo	100 mg qhs	Placebo	100 mg qhs	Placebo	100 mg qhs
<b>Number of Patients</b>	<b>536</b>	<b>532</b>	<b>290</b>	<b>280</b>	<b>381</b>	<b>378</b>
<b>Baseline SSE (Standardized)</b>						
N	532	528	288	280	371	362
Mean (SD)	2.7 (2.9)	2.5 (2.5)	2.7 (2.8)	3.0 (2.8)	2.7 (2.8)	2.6 (2.9)
<b>Baseline FSFI-Desire</b>						
N	536	532	290	280	371	365
Mean (SE)	1.9 (0.7)	1.9 (0.7)	1.9 (0.7)	1.9 (0.7)	1.8 (0.7)	1.8 (0.7)
<b>Baseline FSDS-R13 (Distress)</b>						
N	536	532	290	280	372	365
Mean (SD)	3.4 (0.7)	3.4 (0.7)	3.2 (0.8)	3.2 (0.9)	3.2 (0.8)	3.2 (0.7)
<b>Baseline FSDS-R (Distress) Total Score</b>						
N	536	532	290	280	372	365
Mean (SD)	32.5 (8.7)	32.8 (9.0)	30.1 (9.9)	30.1 (10.0)	30.2 (9.8)	30.5 (9.3)
<b>Baseline FSFI Total Score</b>						
N	536	532	290	280	371	365
Mean (SE)	19.0 (6.1)	19.0 (6.0)	19.8 (7.0)	19.5 (6.6)	19.4 (6.3)	19.1 (6.0)

Notes: FAS = Full analysis set; FLI = Flibanserin; FSDS-R (Distress) = Female sexual distress scale-revised (score range 0 – 52; clinical cut point <15); FSDS-R13 = Female sexual distress scale-revised Question 13 (score range 0 – 4); FSFI = Female sexual function index (score range 2 – 36; clinical cut point >26.6); FSFI-Desire = Female sexual function index- desire domain (score range 1.2 – 6; clinical cut point >3); N = Number of subjects; SD = Standard deviation; SE = Standard error; SSE = Satisfying sexual event.  
Study 75†excludes subjects enrolled at sites 1013 and 1024.  
Source: 511.147, 511.71 and 511.75 CTRs, Tables 15.1.4: 4.

## 2 PRINCIPAL EFFICACY DATA – STUDY 75†

### 2.1 Satisfying Sexual Events

Mean Change from Baseline in SSEs at Week 24 was a co-primary endpoint in Study 75. The flibanserin 100 mg qhs treatment group experienced a statistically significant increase in SSEs (standardized) compared with the placebo group at Week 24 (Table 4; Figure 1).

**Table 4**      **SSEs (Standardized) Change from Baseline at Week 24 – Pivotal Phase 3 Studies in Premenopausal Women - Study 75† (FAS, LOCF)**

Endpoint SSEs (Standardized)	Treatment	N	Change from Baseline	
			Mean (SD)	P-value <sup>a</sup>
Study 75†	Placebo	365	1.1 (3.4)	0.0145
	FLI 100 mg qhs	358	1.8 (5.4)	

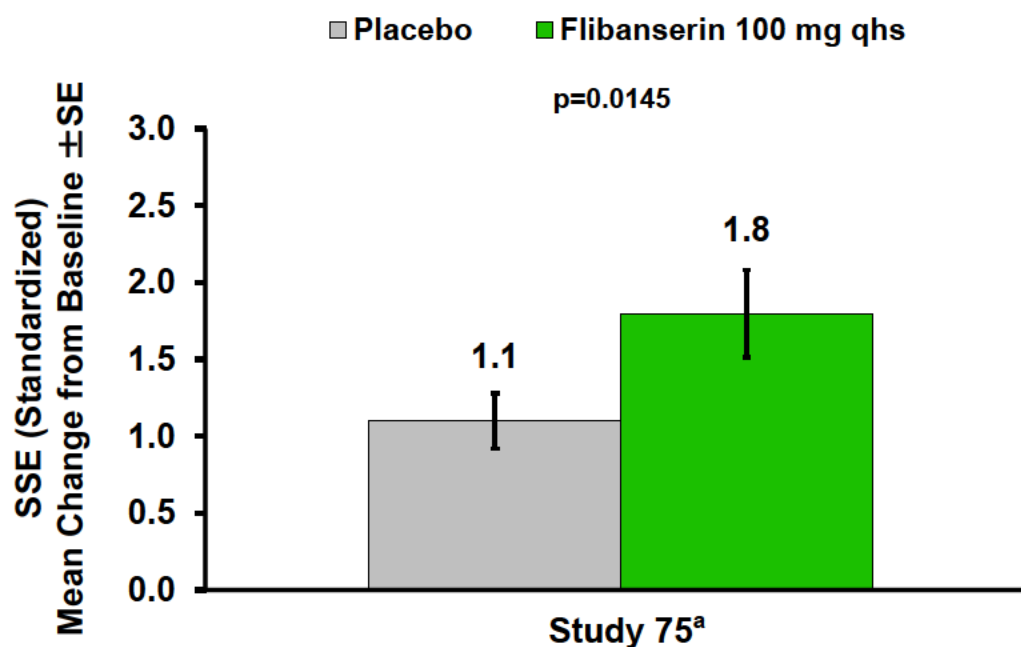
<sup>a</sup> P-value based on Wilcoxon rank sum test.

Notes: FAS = Full analysis set; LOCF = Last observation carried forward; Q1 = 1<sup>st</sup> quartile; Q3 = 3<sup>rd</sup> quartile; SD = Standard deviation; SSE = Satisfying sexual event.

Study 75† excludes subjects enrolled at sites 1013 and 1024.

Source: 511.71 CTR Table 15.2.1: 2, Module 5.3.5.1; 511.75 CTR Table 15.2.1: 2, Module 5.3.5.1; 511.147 CTR Table 15.2.1: 4, Module 5.3.5.1.

**Figure 1**      **SSEs (Standardized) Change from Baseline at Week 24 – Pivotal Phase 3 Studies in Premenopausal Women - Study 75† (FAS, LOCF)**



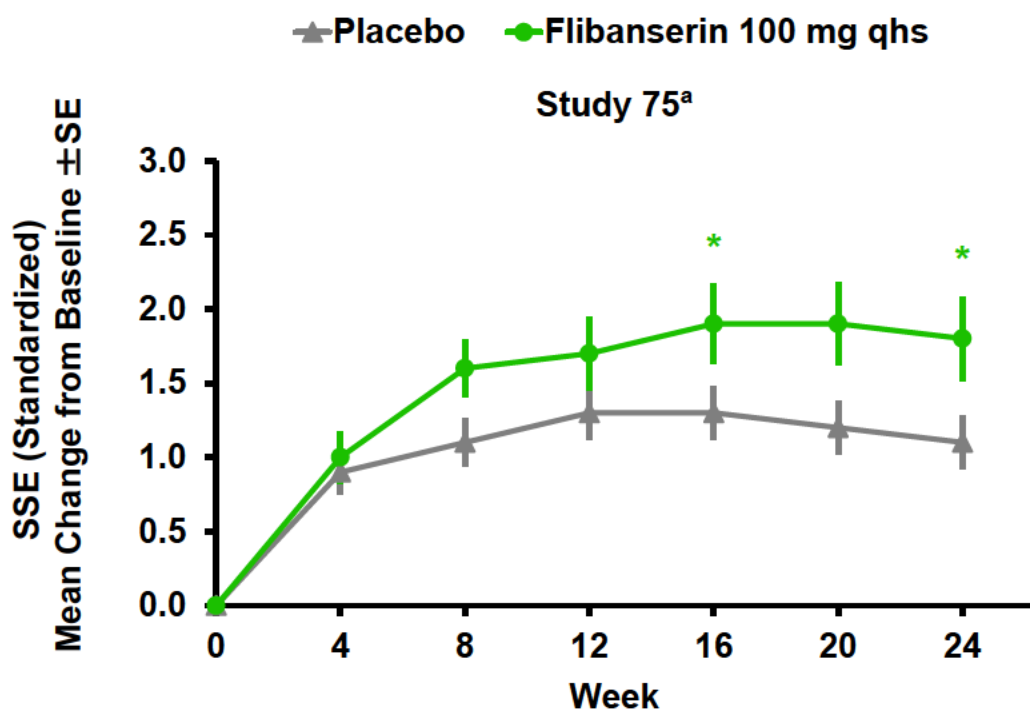
<sup>a</sup> Sites 01013 and 01024 excluded.

Notes: qhs = Once every evening at bedtime; SE = Standard error; SSE = Satisfying sexual event.

Early separation from placebo on mean change from baseline in SSEs was evident (Figure 2).



**Figure 2** SSEs (Standardized) Change from Baseline by Visit – Pivotal Phase 3 Studies in Premenopausal Women - Study 75<sup>†</sup> (FAS, LOCF)



<sup>a</sup> Sites 01013 and 01024 excluded.

Notes: \*p<0.05.

qhs = Once every evening at bedtime; SE = Standard error; SSE = Satisfying sexual event.

## 2.2 Sexual Desire

### 2.2.1 FSFI-Desire

Low desire is one of the two hallmark features of HSDD and the 4.8-point FSFI-Desire domain which queries frequency and intensity of desire (scale range: 1.2 – 6.0) is the validated standard instrument for measuring female sexual desire. Mean Change from Baseline in FSFI-Desire at Week 24 was a secondary endpoint in Study 75. The flibanserin 100 mg qhs treatment group experienced a statistically significant mean increase in FSFI-Desire compared with the placebo group at Week 24 (Table 5; Figure 3).

**Table 5 FSFI-Desire Change from Baseline at Week 24 – Pivotal Phase 3 Studies in Premenopausal Women - Study 75† (FAS, LOCF)**

Endpoint FSFI-Desire	Treatment	N	Change from Baseline		
			LS Mean (SE)	LS Diff (SE)	P-value <sup>a</sup>
Study 75†	Placebo	371	0.6 (0.1)		
	FLI 100 mg qhs	364	0.9 (0.1)	0.3 (0.1)	<0.0001

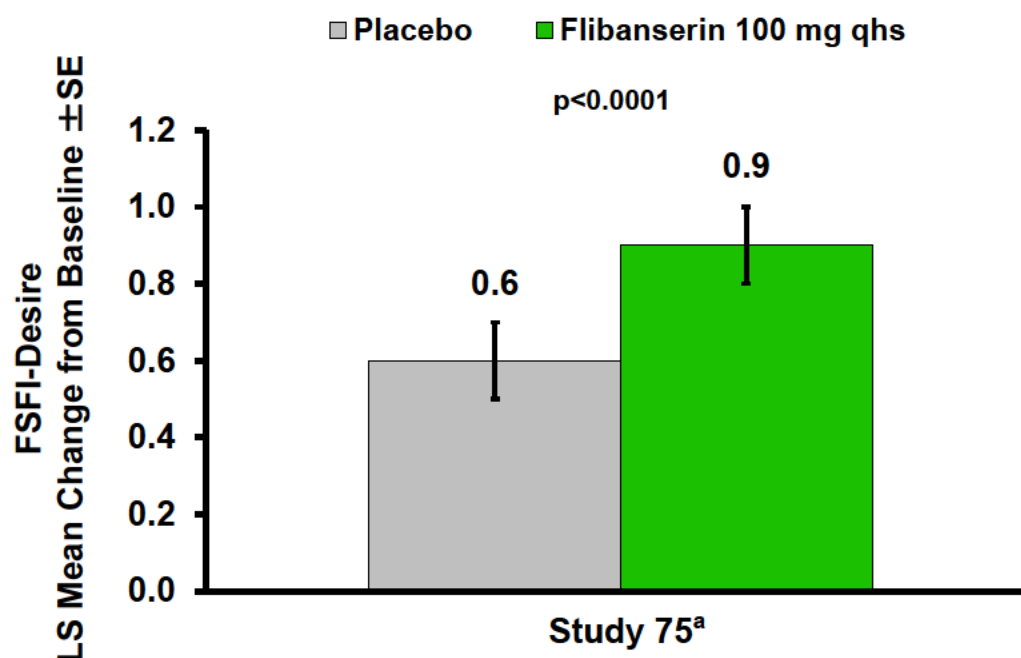
<sup>a</sup> P-value based on ANCOVA model with main effect terms treatment and pooled center and using baseline as a covariate.

Notes: FAS = Full analysis set; FLI = Flibanserin; FSFI-Desire = Female sexual function index – desire domain (score range 1.2 – 6); LOCF = Last observation carried forward; LS = Least square; N = Number of subjects; qhs = Once every evening at bedtime; SE = Standard error.

Study 75† excludes subjects enrolled at sites 1013 and 1024.

Source: 1.71 CTR Table 15.2.1: 11, Module 5.3.5.1; 511.75 CTR Table 15.2.2.3: 5, Module 5.3.5.1; 511.147 CTR Table 15.2.1: 2, Module 5.3.5.1.

**Figure 3 FSFI-Desire Change from Baseline at Week 24 – Pivotal Phase 3 Studies in Premenopausal Women - Study 75† (FAS, LOCF)**

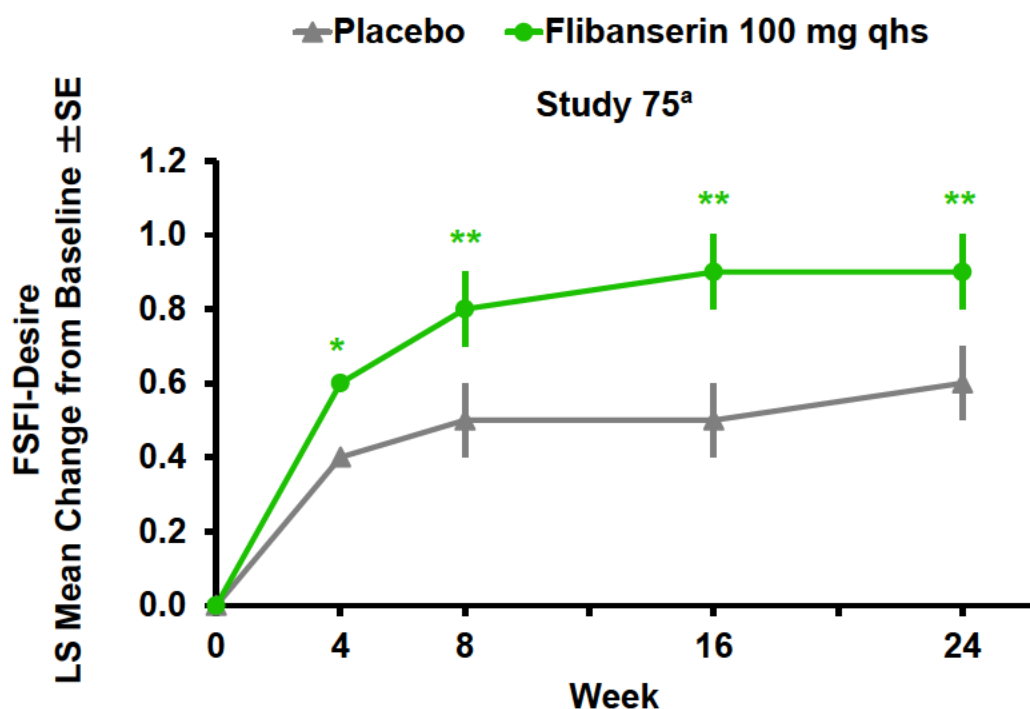


<sup>a</sup> Sites 01013 and 01024 excluded.

Notes: FSFI-Desire = Female sexual function index - desire domain; LS = Least squares; qhs = Once every evening at bedtime; SE = Standard error.

Early separation from placebo on mean change from baseline in FSFI-Desire was evident (Figure 4).

**Figure 4 FSFI-Desire Change from Baseline by Visit – Pivotal Phase 3 Studies in Premenopausal Women - Study 75† (FAS, LOCF)**



<sup>a</sup> Sites 01013 and 01024 excluded.

Notes: \*p<0.05; \*\*p<0.01.

FSFI-Desire = Female sexual function index - desire domain; LS = Least squares; qhs = Once every evening at bedtime;  
 SE = Standard error.

## 2.2.2 eDiary Desire

Mean Change from Baseline in eDiary Desire at Week 24 was a co-primary endpoint in Study 75. Poor compliance with this instrument was a consistent issue. Daily recording is inconsistent with the symptom of low desire in HSDD and has repeatedly failed to correlate with other validated instruments in flibanserin clinical studies when all other endpoints showed efficacy. The flibanserin 100 mg qhs treatment group in Study 75 experienced a numerically but not statistically significant mean increase in eDiary Desire compared with the placebo group at Week 24 (Table 6, Figure 5).

**Table 6 eDiary Desire (Total Monthly Score) Change from Baseline at Week 24 – Study 75† (FAS, LOCF)**

Endpoint eDiary Desire	Treatment	N	Change from Baseline		
			LS Mean (SE)	LS Diff (SE)	P-value <sup>a</sup>
Study 75†	Placebo	371	6.8 (0.8)		
	FLI 100 mg qhs	362	8.6 (0.8)	1.8 (1.1)	0.0996

<sup>a</sup> P-value based on ANCOVA model with main effect terms treatment and pooled center and using baseline as a covariate.

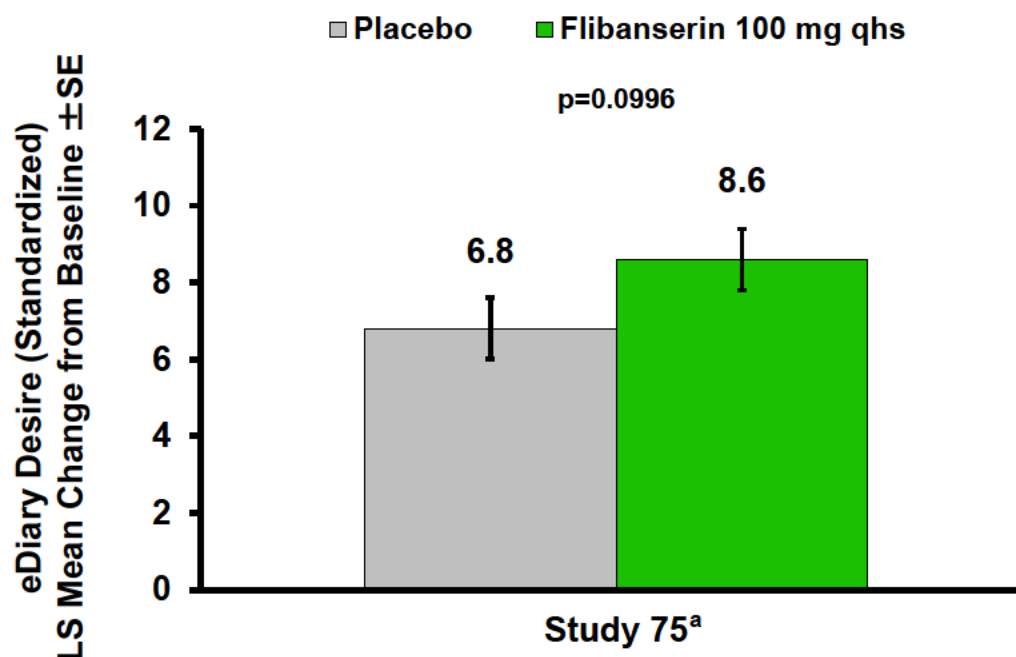
Notes: FAS = Full analysis set; FLI = Flibanserin; LS = Least squares; LOCF = Last observation carried forward; LS = Least squares;

N = Number of subjects; qhs = Once every evening at bedtime; SE = Standard error.

Study 75† excludes subjects enrolled at sites 1013 and 1024.

Source: 511.71 CTR, Table 15.2.1: 5, Module 5.3.5.1; 511.75 CTR Table 15.2.1: 5, Module 5.3.5.1.

**Figure 5 eDiary Desire (Standardized) Change from Baseline at Week 24 - Study 75† (FAS, LOCF)**

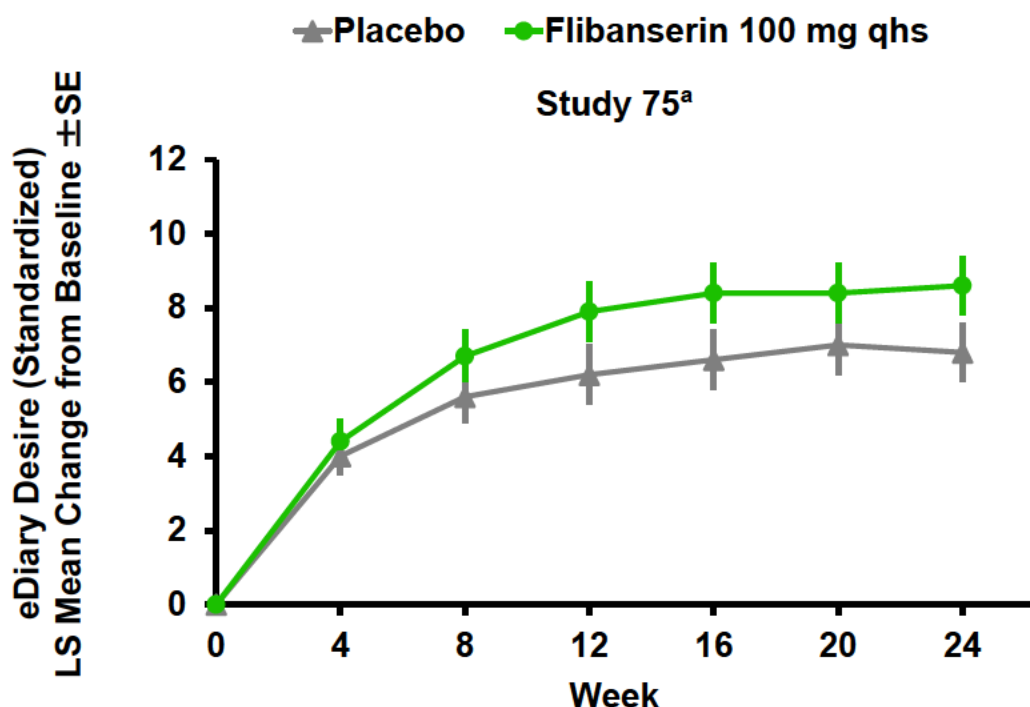


<sup>a</sup> Sites 01013 and 01024 excluded.

Notes: eDiary = Electronic diary; LS = Least squares; qhs = Once every evening at bedtime; SE = Standard error.

Early separation from placebo on mean change from baseline in eDiary Desire was evident but not significant (Figure 6).

**Figure 6 eDiary Desire (Standardized) Change from Baseline by Visit - Study 75†  
 (FAS, LOCF)**



<sup>a</sup> Sites 01013 and 01024 excluded.

Notes: eDiary = Electronic diary; LS = Least squares; qhs = Once every evening at bedtime; SE = Standard error.

## 2.3 FSDS-R13 (Distress)

Mean Change from Baseline in FSDS-R13 (Distress) at Week 24 was a secondary endpoint in Study 75. Distress associated with low desire is one of the two hallmark PRO question for measuring that distress. The flibanserin 100 mg qhs treatment group experienced a statistically significant decrease in FSDS-R13 (Distress) as compared with placebo (Table 7, Figure 7).

**Table 7 FSDS-R13 (Distress) Change from Baseline at Week 24 - Study 75†  
(FAS, LOCF)**

Endpoint FSDS-R13 (Distress)	Treatment	N	Change from Baseline		
			LS Mean (SE)	LS Diff (SE)	P-value <sup>a</sup>
Study 75†	Placebo	372	-0.5 (0.1)		
	FLI 100 mg qhs	365	-0.7 (0.1)	-0.3 (0.1)	0.0014

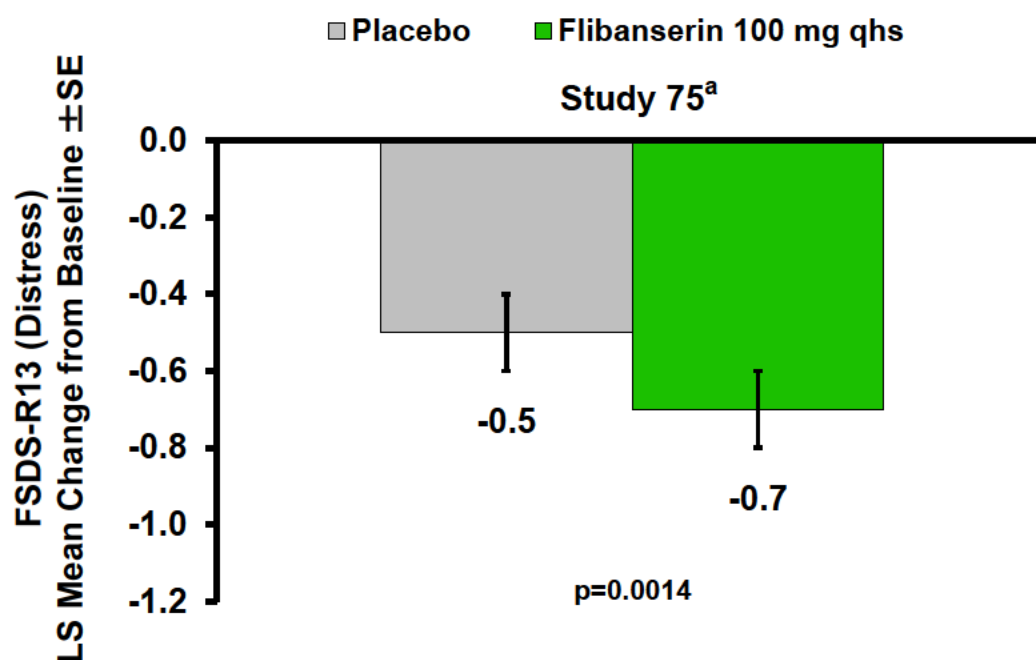
<sup>a</sup> P-value based on ANCOVA model with main effect terms treatment and pooled center and using baseline as a covariate.

Notes: FAS = Full analysis set; FLI = Flibanserin; FSDS-R13 = Female sexual distress scale-revised Question 13 (range 0 - 4);  
LOCF = Last observation carried forward; LS = Least squares; n = Number of subjects; qhs = Once every evening at bedtime;  
SE = Standard error.

Study 75†excludes subjects enrolled at sites 1013 and 1024.

Source: 511.71 CTR Table 15.2.2.2: 4, Module 5.3.5.1; 511.75 CTR Table 15.2.2.2: 4, Module 5.3.5.1.; 511.147 CTR Table 15.2.1: 6, Module 5.3.5.1.

**Figure 7 FSDS-R13 (Distress) Change from Baseline at Week 24 – - Study 75†  
(FAS, LOCF)**

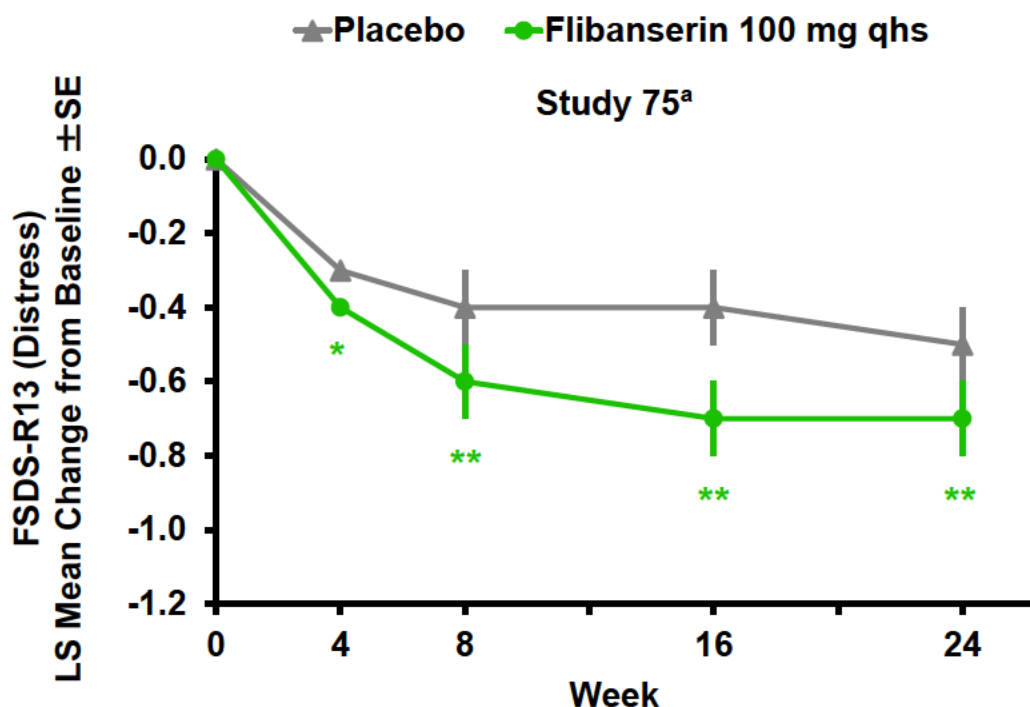


<sup>a</sup> Sites 01013 and 01024 excluded.

Notes: FSDS-R13 (Distress) = Female sexual distress scale - revised Item 13; LS = Least squares; qhs = Once every evening at bedtime;  
SE = Standard error.

Early separation from placebo on mean change from baseline in FSDS-R13 (Distress) was evident (Figure 8).

**Figure 8 FSDS-R13 (Distress) Change from Baseline by Visit - Study 75<sup>†</sup> (FAS, LOCF)**



<sup>a</sup> Sites 01013 and 01024 excluded.

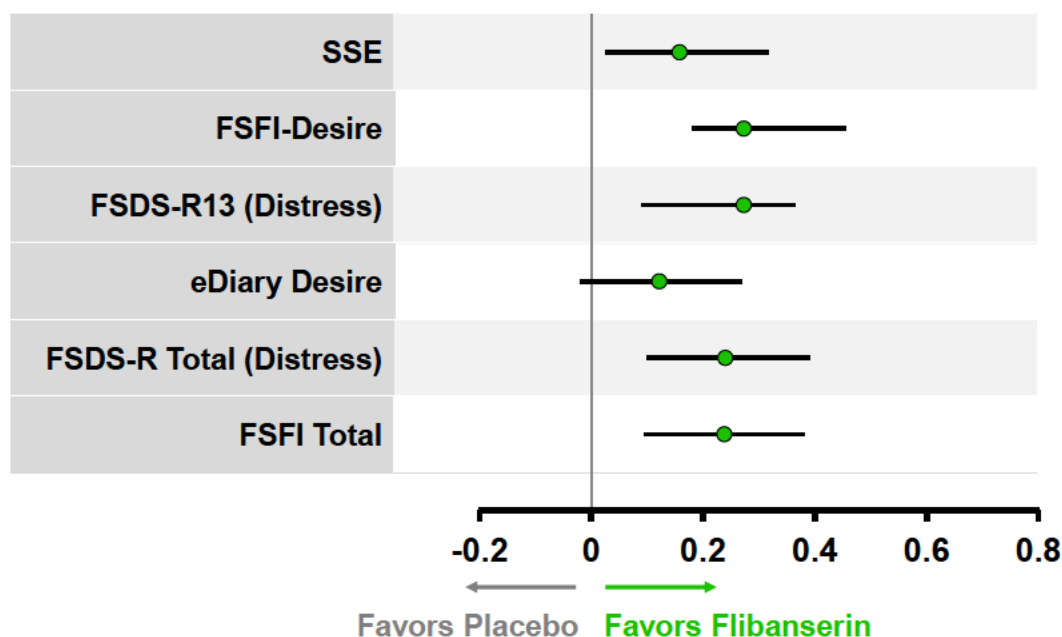
Notes: \*p<0.05; \*\*p<0.01.

FSDS-R13 (Distress) = Female sexual distress scale - revised Item 13; LS = Least squares; qhs = Once every evening at bedtime;  
 SE = Standard error.

## 2.4 Results Across all Efficacy Measures

Efficacy across these primary and secondary endpoints in Study 75<sup>†</sup> is shown in a Forest plot in [Figure 9](#). Because each endpoint is measured on a different scale, mean differences from placebo and the upper and lower bounds of the 95% CI were transformed by dividing each variable by its standard deviation. The x-axis does not provide comparative treatment effect information across endpoints.

**Figure 9 Differences from Placebo (95% CI) for Primary and Secondary Efficacy Endpoints (Standardized) – Study 75† (FAS, LOCF)**



Notes: FSDS-R (Distress) = Female sexual distress scale - revised; FSDS-R13 (Distress) = Female sexual distress scale - revised Item 13; FSFI = Female sexual function index; FSFI-Desire = Female sexual function index – desire domain; SSE = Satisfying sexual event.

## 2.5 Pre-specified Responder Analysis

Application of PGI-I anchored responder thresholds to the treatment groups to determine percent responders is shown in Table 8 and Figure 10.

**Table 8 Number (%) of Responders (PGI-I Anchor Criteria) and Percent Differences across Efficacy Endpoints at Week 24 – Study 75† (FAS, LOCF)**

	Flibanserin 100 mg qhs		Placebo		Difference in Percent	P-value
	N	n (%)	N	n (%)		
<b>75</b>						
SSEs	358	158 (44.1)	365	127 (34.8)	9.3	0.0114
FSFI-Desire	364	165 (45.3)	371	121 (32.6)	12.7	0.0003
FSDS-R13 (Distress)	365	181 (49.6)	372	152 (40.9)	8.7	0.0243

<sup>a</sup> Primary endpoint measure.

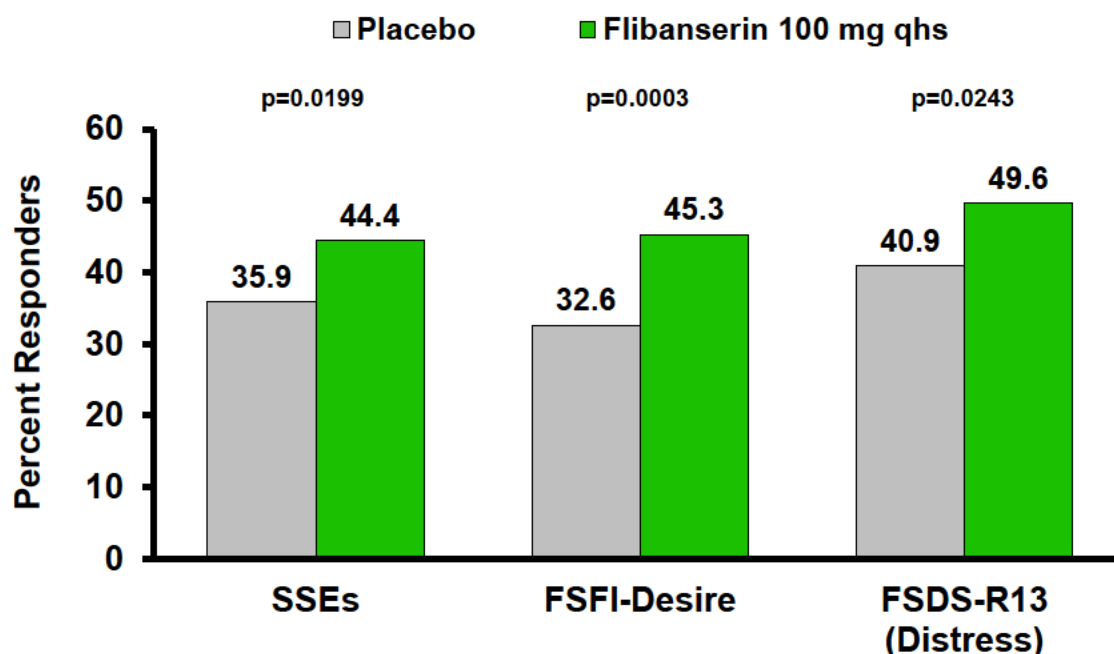
Notes: FSDS-R13 = Female sexual distress scale revised – Question 13; FSFI-Desire = Female sexual function index – sexual desire domain; qhs = Once every evening at bedtime; SSE = Satisfying sexual events (range: 0-no upper limit).

Study 75† excludes subjects enrolled at sites 1013 and 1024.

Source: Table 30 (511.75).



**Figure 10 Number (%) of Responders (PGI-I Anchor Criteria) across Efficacy Endpoints – Study 75† (FAS, LOCF)**



Notes: FSDS-R13 (Distress) = Female sexual distress scale - revised Item 13; FSFI-Desire = Female sexual function index – desire domain; qhs = Once every evening at bedtime; SSE = Satisfying sexual event.

The patients who were flibanserin responders in Study<sup>†</sup> 75 reported mean changes in key symptoms that often more than doubled the effect in the overall flibanserin population (Table 9) with an approximately two point increase on the 4.8-point desire scale and an approximately 1.7 point improvement on the 5-point distress scale and an increase of more than 5 SSEs per month over baseline. While not surprising, patients who self-report experiencing improvement have a much greater magnitude of response to treatment when compared to the overall population.

**Table 9 Mean Change from Baseline at Week 24 on Primary and Secondary Endpoints – Flibanserin Group – Study 75† (FAS, and Responder Populations)**

	Study Number	
	75	
	FAS	Responder
SSEs	1.8 (n = 358)	5.2 (n = 158)
FSFI-Desire	0.9 (n = 364)	1.9 (n = 165)
FSDS-R13 (Distress)	-0.8 (n = 365)	-1.7 (n = 181)

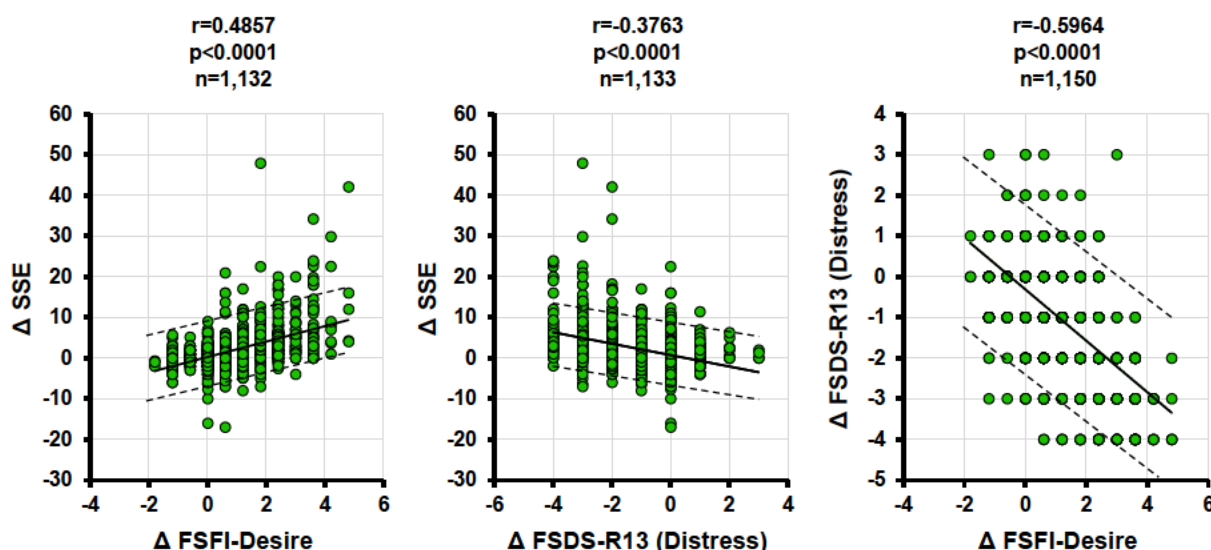
Notes: FSDS-R13 = Female sexual distress scale revised – Question 13 (range: 0 - 4); FSFI-Desire = Female sexual function index – sexual desire domain (range: 1.2 - 6); SSE = Satisfying sexual events (range: 0-no upper limit).  
 Study 75† excludes subjects enrolled at sites 1013 and 1024.

Source: Ad hoc analysis.

### 2.5.1 Consistent Effect Across Symptoms

Exploratory correlation analyses of responders across the efficacy endpoints of SSE, FSFI-Desire and FSDS-R13 (Distress) as shown in Figure 11.

**Figure 11 Correlation between Key Efficacy Endpoints – Pooled Pivotal Phase 3 Studies in Premenopausal Women with Study 75† (FAS, LOCF)**



Notes: FSDS-R13 (Distress) = Female sexual distress scale - revised Item 13; FSFI-Desire = Female sexual function index – desire domain;  $r$  = Pearson correlation coefficient; SSE = Satisfying sexual event.

Regression lines (solid) with the 95% prediction bands (dashed) are shown superimposed on the scatterplot.

All data (N = 3,368) are expressed as the change from baseline for each key endpoint and includes Studies 147 (pooled), 71 and 75.

**APPENDIX M NUMBER (%) OF SUBJECTS WITH ADVERSE  
EVENTS OCCURRING IN  $\geq 1.0\%$  IN PHASE 3  
DOUBLE-BLIND STUDIES IN  
PREMENOPAUSAL WOMEN**

**Table 1 Number (%) of Subjects with Adverse Events Occurring in  $\geq 1.0\%$  by Treatment, System Organ Class, and Preferred Term - Phase 3 Double-blind Studies in Premenopausal Women (Treated Set)**

System Organ Class Preferred Term	Placebo, n (%) N = 1905	Flibanserin, n (%)				Total N = 3973
		25 mg bid N = 733	50 mg qhs N = 969	50 mg bid N = 728	100 mg qhs N = 1543	
Subjects with any adverse event	1062 (55.7)	430 (58.7)	628 (64.8)	517 (71.0)	1033 (66.9)	2608 (65.6)
Ear and labyrinth disorders	10 (0.5)	8 (1.1)	9 (0.9)	8 (1.1)	27 (1.7)	52 (1.3)
Vertigo	6 (0.3)	1 (0.1)	3 (0.3)	5 (0.7)	16 (1.0)	25 (0.6)
Gastrointestinal disorders	218 (11.4)	92 (12.6)	150 (15.5)	148 (20.3)	315 (20.4)	705 (17.7)
Nausea	71 (3.7)	41 (5.6)	68 (7.0)	90 (12.4)	161 (10.4)	360 (9.1)
Diarrhoea	35 (1.8)	18 (2.5)	17 (1.8)	17 (2.3)	36 (2.3)	88 (2.2)
Vomiting	27 (1.4)	12 (1.6)	14 (1.4)	12 (1.6)	34 (2.2)	72 (1.8)
Dry mouth	17 (0.9)	6 (0.8)	12 (1.2)	10 (1.4)	37 (2.4)	65 (1.6)
Abdominal pain	15 (0.8)	5 (0.7)	17 (1.8)	8 (1.1)	23 (1.5)	53 (1.3)
Constipation	9 (0.5)	4 (0.5)	4 (0.4)	9 (1.2)	25 (1.6)	42 (1.1)
Dyspepsia	12 (0.6)	7 (1.0)	7 (0.7)	9 (1.2)	5 (0.3)	28 (0.7)
General disorders and administration site conditions	159 (8.3)	56 (7.6)	100 (10.3)	124 (17.0)	233 (15.1)	513 (12.9)
Fatigue	95 (5.0)	35 (4.8)	59 (6.1)	101 (13.9)	142 (9.2)	337 (8.5)
Irritability	22 (1.2)	7 (1.0)	16 (1.7)	8 (1.1)	35 (2.3)	66 (1.7)
Immune system disorders	19 (1.0)	10 (1.4)	10 (1.0)	7 (1.0)	14 (0.9)	41 (1.0)
Seasonal allergy	12 (0.6)	7 (1.0)	4 (0.4)	2 (0.3)	8 (0.5)	21 (0.5)
Infections and infestations	454 (23.8)	168 (22.9)	271 (28.0)	169 (23.2)	368 (23.8)	976 (24.6)
Nasopharyngitis	101 (5.3)	41 (5.6)	86 (8.9)	31 (4.3)	78 (5.1)	236 (5.9)
Upper respiratory tract infection	59 (3.1)	36 (4.9)	37 (3.8)	30 (4.1)	70 (4.5)	173 (4.4)
Sinusitis	64 (3.4)	23 (3.1)	35 (3.6)	29 (4.0)	45 (2.9)	132 (3.3)
Urinary tract infection	44 (2.3)	16 (2.2)	22 (2.3)	10 (1.4)	36 (2.3)	84 (2.1)
Bronchitis	23 (1.2)	10 (1.4)	16 (1.7)	14 (1.9)	25 (1.6)	65 (1.6)
Influenza	29 (1.5)	10 (1.4)	17 (1.8)	14 (1.9)	21 (1.4)	62 (1.6)
Gastroenteritis viral	32 (1.7)	11 (1.5)	9 (0.9)	6 (0.8)	20 (1.3)	46 (1.2)
Gastroenteritis	22 (1.2)	1 (0.1)	11 (1.1)	6 (0.8)	19 (1.2)	37 (0.9)
Vulvovaginal mycotic infection	15 (0.8)	3 (0.4)	16 (1.7)	7 (1.0)	10 (0.6)	36 (0.9)
Fungal infection	19 (1.0)	6 (0.8)	5 (0.5)	5 (0.7)	12 (0.8)	28 (0.7)
Pharyngitis streptococcal	10 (0.5)	7 (1.0)	5 (0.5)	7 (1.0)	5 (0.3)	24 (0.6)
Vaginitis bacterial	8 (0.4)	7 (1.0)	2 (0.2)	5 (0.7)	6 (0.4)	20 (0.5)
Investigations	41 (2.2)	23 (3.1)	23 (2.4)	21 (2.9)	38 (2.5)	105 (2.6)
Weight increased	15 (0.8)	9 (1.2)	7 (0.7)	3 (0.4)	5 (0.3)	24 (0.6)

System Organ Class Preferred Term	Placebo, n (%) N = 1905	Flibanserin, n (%)				Total N = 3973
		25 mg bid N = 733	50 mg qhs N = 969	50 mg bid N = 728	100 mg qhs N = 1543	
Musculoskeletal and connective tissue disorders	129 (6.8)	52 (7.1)	72 (7.4)	30 (4.1)	98 (6.4)	252 (6.3)
Back pain	41 (2.2)	12 (1.6)	21 (2.2)	6 (0.8)	30 (1.9)	69 (1.7)
Arthralgia	16 (0.8)	13 (1.8)	16 (1.7)	4 (0.5)	14 (0.9)	47 (1.2)
Pain in extremity	9 (0.5)	8 (1.1)	5 (0.5)	4 (0.5)	13 (0.8)	30 (0.8)
Muscle spasms	10 (0.5)	7 (1.0)	10 (1.0)	2 (0.3)	8 (0.5)	27 (0.7)
Nervous system disorders	278 (14.6)	142 (19.4)	211 (21.8)	273 (37.5)	479 (31.0)	1105 (27.8)
Somnolence	59 (3.1)	51 (7.0)	55 (5.7)	122 (16.8)	173 (11.2)	401 (10.1)
Dizziness	41 (2.2)	31 (4.2)	61 (6.3)	111 (15.2)	176 (11.4)	379 (9.5)
Headache	144 (7.6)	51 (7.0)	93 (9.6)	61 (8.4)	146 (9.5)	351 (8.8)
Migraine	19 (1.0)	13 (1.8)	12 (1.2)	7 (1.0)	17 (1.1)	49 (1.2)
Sedation	3 (0.2)	1 (0.1)	6 (0.6)	10 (1.4)	20 (1.3)	37 (0.9)
Psychiatric disorders	150 (7.9)	50 (6.8)	107 (11.0)	71 (9.8)	217 (14.1)	445 (11.2)
Insomnia	46 (2.4)	14 (1.9)	19 (2.0)	20 (2.7)	75 (4.9)	128 (3.2)
Anxiety	17 (0.9)	5 (0.7)	19 (2.0)	10 (1.4)	28 (1.8)	62 (1.6)
Abnormal dreams	18 (0.9)	7 (1.0)	8 (0.8)	6 (0.8)	21 (1.4)	42 (1.1)
Depression	16 (0.8)	6 (0.8)	10 (1.0)	7 (1.0)	16 (1.0)	39 (1.0)
Reproductive system and breast disorders	195 (10.2)	85 (11.6)	113 (11.7)	79 (10.9)	169 (11.0)	446 (11.2)
Menorrhagia	44 (2.3)	19 (2.6)	28 (2.9)	22 (3.0)	40 (2.6)	109 (2.7)
Metrorrhagia	24 (1.3)	10 (1.4)	25 (2.6)	13 (1.8)	22 (1.4)	70 (1.8)
Dysmenorrhoea	29 (1.5)	9 (1.2)	14 (1.4)	15 (2.1)	19 (1.2)	57 (1.4)
Polymenorrhoea	9 (0.5)	9 (1.2)	9 (0.9)	6 (0.8)	12 (0.8)	36 (0.9)
Breast tenderness	11 (0.6)	11 (1.5)	8 (0.8)	5 (0.7)	8 (0.5)	32 (0.8)
Genital haemorrhage	9 (0.5)	7 (1.0)	3 (0.3)	0	9 (0.6)	19 (0.5)
Hypomenorrhoea	8 (0.4)	4 (0.5)	2 (0.2)	7 (1.0)	4 (0.3)	17 (0.4)
Respiratory, thoracic and mediastinal disorders	90 (4.7)	34 (4.6)	44 (4.5)	36 (4.9)	86 (5.6)	200 (5.0)
Oropharyngeal pain	24 (1.3)	7 (1.0)	15 (1.5)	10 (1.4)	19 (1.2)	51 (1.3)
Cough	19 (1.0)	5 (0.7)	14 (1.4)	8 (1.1)	18 (1.2)	45 (1.1)
Skin and subcutaneous tissue disorders	82 (4.3)	33 (4.5)	60 (6.2)	32 (4.4)	87 (5.6)	212 (5.3)
Rash	13 (0.7)	13 (1.8)	14 (1.4)	9 (1.2)	20 (1.3)	56 (1.4)
Acne	18 (0.9)	9 (1.2)	15 (1.5)	6 (0.8)	17 (1.1)	47 (1.2)

Notes: bid = Twice daily; n = Total population size; N = Number of subjects; qhs = Once every evening at bedtime.

MedDRA version used for reporting: 11.1.

Includes Studies 511.70, 511.71, 511.75, 511.77 and 511.147.

Source: ISS Table 2.2.4.

## **APPENDIX N CENTRAL NERVOUS SYSTEM EFFECTS OF FLIBANSERIN**

## TABLE OF CONTENTS

	Page
<b>TABLE OF CONTENTS .....</b>	<b>2</b>
<b>LIST OF TABLES .....</b>	<b>3</b>
<b>LIST OF ABBREVIATIONS .....</b>	<b>4</b>
<b>1 FLIBANSERIN IS AN AGENT THAT IS ACTIVE IN THE CENTRAL NERVOUS SYSTEM (CNS) .....</b>	<b>6</b>
1.1 Pathogenesis of HSDD .....	6
1.1.1 Presumed Mechanism of Action of Flibanserin in the Treatment of HSDD .....	7
1.2 Other CNS considerations.....	7
1.2.1 Depression and Suicidality.....	8
1.2.1.1 Data from the Flibanserin Clinical Development Program Related to Depression and Suicide Risk .....	8
1.2.2 Effect of Flibanserin on Wakefulness .....	10
1.2.2.1 Phase 1 and Phase 2 Cognition Studies .....	11
1.2.2.2 Summary of Individual Cognitive Studies with a Listing of their Key Results .....	13
1.2.2.3 Summary of Results from Cognitive Studies.....	17
1.2.2.4 Dedicated Next Day Driving Study .....	18
1.2.3 Risk of Serotonin Syndrome .....	21
1.2.4 Serotonin and Hypotension .....	27
<b>REFERENCES.....</b>	<b>30</b>

## LIST OF TABLES

	Page
Table 1	Number (%) of Subjects with Depression-related AEs by Preferred Term - Phase 3 Studies in Pre- and Post-menopausal Women (Treated Set).....9
Table 2	Number (%) of Subjects with Suicide/Self-injury Related AEs - Phase 3 Studies in Pre- and Post-menopausal Women (Treated Set) .....10
Table 3	Number (%) of Subjects with Sedation-related AEs by Preferred Term – Phase 3 Double-blind Studies in Pre-menopausal Women (Targeted Population Set) .....11
Table 4	Mean and LS Mean Standard Deviation of Lateral Position - Study SPR-14-01 .....20
Table 5	Number (%) of Subjects with Selected Adverse Events - Phase 3 Studies in Pre- and Post-menopausal Women (Treated Set) .....23
Table 6	Number (%) of Subjects with Selected Adverse Events Seen More Frequently in Flibanserin Treated Patients, Analyzed based on SSRI/SNRI Use - Phase 3 Studies in Pre- and Post-menopausal Women (Treated Set) .....24
Table 7	Number (%) of Subjects with Selected Adverse Events Seen More Frequently in Flibanserin Treated Patients, Analyzed based on T riptan Use - Phase 3 Studies in Pre- and Post-menopausal Women (Treated Set) .....25
Table 8	Number (%) of Subjects with Adverse Events by Primary System Organ Class and Preferred Term – Study 114 .....26
Table 9	N (%) of subjects with Serotonin Specific Adverse Events – Study 114 .....27



## LIST OF ABBREVIATIONS

AE	Adverse Event
Ay	Excessive Speed in Corners
bid	Twice Daily
CFF	Critical Flicker Fusion
Cm	Centimeter
Cmax	Maximum Plasma Concentrations
CNS	Central Nervous System
CRCDS	Cognitive Research Corporation Driving Simulator
CRT	Choice Reaction Time
CVDA	Country Vigilance-Divided Attention
EEG	Electroencephalogram
FDA	US Food and Drug Administration
FLI	Flibanserin
GABA	Gamma AMINO Butyric Acid
HSDD	Hypoactive Sexual Desire Disorder
HT	Hydroxytryptamine
Kg	Kilogram
LS	Least Square
MDD	Major Depressive Disorder
Mg	Miligrams
Mm	Millimetre
MRI	Magnetic Resonance Imaging
PBO	placebo
PET	Positron Emission Tomography
QEEG	Quantitative Electroencephalography
qhs	Once daily at bedtime
REM	Rapid Eye Movement
SBP	Systolic Blood Pressure
SD	Standard Deviation
SDC	Symbol Digit Coding
SDLP	Standard deviation of lateral position
SNRI	Serotonin and Norepinephrine Reuptake Inhibitor
SAE	Serious Adverse Event

SSRI	Selective Serotonin Reuptake Inhibitor
TCA	Tricyclic Antidepressants
Tid	Three times a Day
TRT	Total Reaction Time
VAS	Visual Analog Scale
ZOP	Zopiclone

## 1 FLIBANSERIN IS AN AGENT THAT IS ACTIVE IN THE CENTRAL NERVOUS SYSTEM (CNS)

Fibanserin is a compound that is primarily active in the central nervous system where it selectively binds to 5-HT<sub>1A</sub> and 5-HT<sub>2A</sub> serotonin receptors. Serotonin (5-hydroxytryptamine or 5-HT) is a neurotransmitter that is implicated in a large variety of behavioral and emotional processes. The 5-HT receptors are classified into seven subfamilies, 5-HT<sub>1</sub> to 5-HT<sub>7</sub>, which are further divided into at least 14 receptor subtypes. 5-HT<sub>1A</sub> serotonin receptor subtypes are located postsynaptically in many different brain regions, where they tend to regulate the release of other neurotransmitters. In addition, 5-HT<sub>1A</sub> receptors also exist as presynaptic somatodendritic autoreceptors on serotonin neurons where they serve to regulate 5-HT neurotransmission. 5-HT<sub>1A</sub> receptors are widely expressed in the prefrontal cortex, hippocampus, septum and the raphe nucleus of the brain stem (which is the primary location of serotonergic neuron cell bodies in the CNS). 5-HT<sub>2A</sub> receptors are also found in multiple brain regions, but in particular in the prefrontal cortex, where they are located on postsynaptic neurons.

Flibanserin acts as an **agonist** that selectively binds to the postsynaptic 5-HT<sub>1A</sub> receptor, activating neurons that express that receptor, and stimulating the release of either excitatory (glutamate) or inhibitory (Gamma Amino Butyric Acid or GABA) neurotransmitters depending upon the function of the particular postsynaptic neuron. At the same time, flibanserin acts as an **antagonist** when binding to 5-HT<sub>2A</sub> receptors, and inhibits the activity of neurons that express the 5-HT<sub>2A</sub> receptor.

### 1.1 Pathogenesis of HSDD

Although the underlying pathophysiology of HSDD is not well defined, functional MRI studies and studies of gray matter volume comparing women with HSDD versus healthy controls, offer insight into some of the neurophysiological abnormalities that might be responsible [Arnow, 2009; Bianchi-Demicheli, 2011; Bloemers, 2013; Woodward, 2013]. These studies suggest that excessive neuronal activity in portions of the prefrontal cortex, an area of the brain that exercises executive inhibitory control over subcortical reward structures of the brain, may play an important role in the pathophysiology of HSDD.

Pyramidal neurons in the prefrontal cortex project to three nuclei in the brainstem: the dorsal raphe nucleus which expresses the neurotransmitter serotonin, and serves to inhibit brain activity in a variety of CNS areas; the ventral tegmental area which expresses the neurotransmitter dopamine and plays an important excitatory role in reward circuits in the brain; and the locus coeruleus, which expresses norepinephrine (noradrenergic neurons) and plays a central excitatory role in promoting conscious arousal. Under normal conditions, there is a healthy balance between the inhibitory activity of the serotonergic neurons and the excitatory activity of dopaminergic and noradrenergic neurons, that allows the generation of sexual desire through controlled stimulation of portions of the brain's limbic system (which manages emotion), such as

the amygdala, ventral tegmental area, medial preoptic area, and the nucleus accumbens. The prefrontal cortex regulates this balance through inhibition of the dopaminergic and noradrenergic neurons, and activation of the brainstem serotonergic neurons [Puig, 2011].

The pyramidal cells in the prefrontal cortex express 5-HT<sub>1A</sub> and 5-HT<sub>2A</sub> serotonin receptors which have opposing effects. Activation of the 5-HT<sub>1A</sub> receptors in the prefrontal cortex creates an inhibitory signal on the pyramidal neurons. Activation of the 5-HT<sub>2A</sub> receptor results in an excitatory signal. Through activation of these two receptors, the pyramidal neurons in the prefrontal cortex regulate the activity of the serotonergic, dopaminergic and noradrenergic neurons in the brain stem nuclei. Excitatory signals from 5-HT<sub>2A</sub> expressing neurons in the prefrontal cortex stimulate serotonin release (which is inhibitory in many brain regions), and through inhibitory interneurons inhibit the release of dopamine and norepinephrine (which would be excitatory in many brain regions). Inhibitory signals from the 5-HT<sub>1A</sub> expressing pyramidal neurons would do the opposite, and prevent release of the inhibitory neurotransmitter serotonin and allow for increases in the activity of the excitatory neurotransmitters dopamine and norepinephrine.

### **1.1.1 Presumed Mechanism of Action of Flibanserin in the Treatment of HSDD**

The precise mechanism of action by which flibanserin enhances sexual desire in patients with HSDD is not known. What is known is that flibanserin is a highly selective postsynaptic 5-HT<sub>1A</sub> agonist and 5-HT<sub>2A</sub> antagonist. Since these two serotonergic receptors have opposing actions (i.e., the 5-HT<sub>1A</sub> receptors are inhibitory and the 5-HT<sub>2A</sub> receptors excitatory) combining an agonist for one and an antagonist for the other results in synergistic inhibition in the prefrontal cortex. As a result, it is postulated that flibanserin serves to inhibit the stimulation of serotonergic activity in the dorsal raphe nucleus (effectively reducing its inhibitory effects on the limbic system) and enhances the excitatory activity of dopaminergic neurons in the ventral tegmental area and noradrenergic activity in the locus coeruleus which enhance reward circuits and general conscious arousal [Stahl, 2011; Stahl, 2015]. This restores an appropriate balance between inhibitory and excitatory neurotransmitters. The net result is a greater response to sexual cues and a heightened awareness of desire on the part of the patient with HSDD.

## **1.2 Other CNS considerations**

Given the widespread expression of 5-HT<sub>1A</sub> and 5-HT<sub>2A</sub> receptors in the brain, and the direct or indirect impact of the prefrontal serotonergic neurons expressing them on different neuronal populations, the question arises, as with many other CNS acting drugs, of other possible CNS effects associated with the use of flibanserin apart from enhancing normal sexual desire (e.g., on mood, cognition, sleep, etc.).

### **1.2.1 Depression and Suicidality**

Flibanserin was initially studied as a potential treatment for major depressive disorder (MDD). The monoamine hypothesis of depression, posits that depression results from a deficiency of serotonin, norepinephrine and dopamine activity in the brain [Morrissette, 2014; Cowen, 2013]. Since serotonergic neurons influence the activity of other neurotransmitter systems as described above, as well as engage in self-modulation of other serotonergic neuronal systems through 5-HT<sub>1A</sub> presynaptic autoreceptors, serotonergic neurons may play a primary role in regulating mood. Serotonin has been implicated in many psychiatric disorders, including MDD. Stimulation of postsynaptic 5-HT<sub>1A</sub> receptors in corticolimbic networks appears to mediate the antidepressant effects of many antidepressants in clinical use [Morrissette, 2014]. Stimulation of 5-HT<sub>2A</sub> receptors on the other hand appears to have a depression enhancing effect, but 5-HT<sub>2A</sub> antagonists have been used to effectively improve the efficacy of selective serotonin reuptake inhibitor (SSRI) antidepressants in drug-resistant patients [Artigas, 2013]. Since flibanserin has both 5-HT<sub>1A</sub> agonist and 5-HT<sub>2A</sub> antagonist activity, it was originally developed to treat symptoms of depression in patients with MDD. Signals of antidepressant activity were mixed in the early clinical development program for flibanserin, and reports of increased sexual desire in patients suggested that the drug might be even more effective as a treatment for HSDD.

Serotonergic antidepressants have paradoxically been associated with increasing the risk of suicidality in some individuals (suicidal thoughts, but not necessarily suicide attempts). A Food and Drug Administration meta-analysis of placebo-controlled antidepressant trials found that there was a significantly higher rate of suicidal behavior among children and adults aged 24 years and younger, who were randomized to receive antidepressant medication versus placebo [FDA, 2003; Miller, 2014]. Rates of suicidality were similar for subjects aged 25-64 years whether they received antidepressant or placebo, and subjects aged 65 years or older had reduced risk of suicidality with antidepressant use than with placebo. In one postmortem study, depressed suicide victims had reduced expression of 5-HT<sub>1A</sub> receptors and lower receptor affinity in the hippocampus and amygdala [Cheetham, 1990], suggesting that 5-HT<sub>1A</sub> activation might protect against suicidality. A number of studies have looked to see if there was a similar finding related to 5-HT<sub>2A</sub> receptors, but no consistent findings have been reported [Antypa, 2013]. The potential for flibanserin to exacerbate depression and suicidality was evaluated in depressed patients.

#### **1.2.1.1 Data from the Flibanserin Clinical Development Program Related to Depression and Suicide Risk**

The frequency of all possible depression related adverse events in the Treated Set (which includes pre- and postmenopausal women in Studies 70, 71, 77, 114, 130, 147 and 156) suggests no effect of flibanserin on depression related adverse events in patients receiving flibanserin (Table 1).

**Table 1**      **Number (%) of Subjects with Depression-related AEs by Preferred Term - Phase 3 Studies in Pre- and Post-menopausal Women (Treated Set)**

Preferred Term	Placebo (N=2792) n (%)	Fli 25mg bid (N=733) n (%)	Fli 50mg qhs (N=969) n (%)	Fli 50mg qhs (N=728) n (%)	Fli 100mg qhs (N=2459) n (%)
<b>Total</b>	76 (2.7)	20 (2.7)	41 (4.2)	30 (4.1)	98 (4.0)
Depression	24 (0.9)	6 (0.8)	10 (1.0)	7 (1.0)	20 (0.8)
Depressed mood	10 (0.4)	0	5 (0.5)	3 (0.4)	12 (0.5)
Disturbed Attention	8 (0.3)	2 (0.3)	3 (0.3)	6 (0.8)	10 (0.4)
Poor quality sleep	1 (<0.1)	0	0	1 (0.1)	10 (0.4)
Mood altered	11 (0.4)	3 (0.4)	3 (0.3)	4 (0.5)	9 (0.4)
Mood swings	5 (0.2)	3 (0.4)	8 (0.8)	0	7 (0.3)
Affect lability	3 (0.1)	2 (0.3)	1 (0.1)	0	6 (0.2)
Emotional disorder	3 (0.1)	0	3 (0.3)	2 (0.3)	6 (0.2)
Early morn awakening	0	0	2 (0.2)	1 (0.1)	5 (0.2)
Postmenopause bleed	1 (<0.1)	0	0	0	5 (0.2)
Crying	4 (0.1)	0	1 (0.1)	1 (0.1)	4 (0.2)
Memory impairment	3 (0.1)	0	1 (0.1)	2 (0.3)	4 (0.2)
Major depression	3 (0.1)	0	1 (0.1)	0	2 (<0.1)
Apathy	1 (<0.1)	0	0	2 (0.3)	1 (<0.1)
Depressive symptoms	0	1 (0.1)	0	0	1 (<0.1)
Dysphoria	0	2 (0.3)	0	1 (0.1)	1 (<0.1)
Emotional distress	0	0	1 (0.1)	0	1 (<0.1)
Tearfulness	2 (<0.1)	0	0	1 (0.1)	1 (<0.1)
Affective disorder	0	1 (0.1)	2 (0.2)	1 (0.1)	0
Blunted Affect	2 (<0.1)	0	0	0	0
Decreased interest	2 (<0.1)	0	1 (0.1)	0	0
Decreased consciousness	1 (<0.1)	0	1(0.1)	0	0
Listless	0	0	1 (0.1)	0	0
Psychomotor hyperactivity	1 (<0.1)	0	0	1 (0.1)	0

Notes: bid = Twice daily; Fli = Flibanserin; qhs = Once daily at bedtime.

The incidence of suicidal ideation was also examined in the Treated Set, and the results are summarized in [Table 2](#).

**Table 2 Number (%) of Subjects with Suicide/Self-injury Related AEs - Phase 3 Studies in Pre- and Post-menopausal Women (Treated Set)**

Preferred Term	Placebo (N=2792) n (%)	Fli 25mg bid (N=733) n (%)	Fli 50mg qhs (N=969) n (%)	Fli 50mg qhs (N=728) n (%)	Fli 100mg qhs (N=2459) n (%)
Total	4 (0.1)	0	2 (0.2)	0	3 (0.1)
Suicidal ideation	4 (0.1)	0	2 (0.2)	0	2 (<0.1)
Suicide attempt	0	0	0	0	1 (<0.1)

Notes: bid = Twice daily; Fli = Flibanserin; qhs = Once daily at bedtime.

Recognizing that these numbers are small, no increase in the risk of suicidal ideation is evident with flibanserin use.

The Columbia Suicide Severity Rating Scale was included in the new pivotal study in premenopausal women, the SSRI/SNRI co-use study and 2 studies in postmenopausal women with HSDD (Studies 114, 130 147, and 156). At Baseline there were 0 subjects who were detected as having suicidal ideation in both the placebo (N=1432) and flibanserin 100 mg (N=1458) groups. At the end of therapy (12 weeks for Study 114 and 28 weeks for all other studies), 4 placebo treated subjects (0.3%) and 2 flibanserin 100 mg treated subjects (0.1%) had suicidal ideation. These results support the general observation that flibanserin administration did not increase the risk for suicidal ideation.

### 1.2.2 Effect of Flibanserin on Wakefulness

Serotonin systems have been extensively studied in an attempt to define their complicated role in the sleep wake cycle. Earlier simplistic ideas regarding a straightforward role of serotonin in promoting either sleep or wakefulness, have been challenged by numerous studies which suggest that the role of serotonin is highly variable depending on the specific neuronal populations being activated and depending on what other non-serotonergic neuronal populations are involved [Monti, 2011; Monti, 2008]. Most researchers have concluded that serotonin functions predominantly to promote wakefulness and inhibit REM sleep, although there are specific circumstances when serotonin promotes sleep [Monti, 2011]. Activation of 5-HT<sub>1A</sub> receptors has been shown to generally promote wakefulness and inhibit sleep, although the precise mechanism by which it does so is poorly understood [Monti, 2011; Monti, 2008]. Activation of 5-HT<sub>1A</sub> receptors may result in the inhibition of relevant GABAergic neurons, and this inhibition of inhibitory neurons may result in activation of noradrenergic neurons in the arousal systems, resulting in increased wakefulness. Activation of the 5-HT<sub>2A</sub> receptor has similar effects in promoting wakefulness, and reducing slow wave sleep. Inhibition of 5-HT<sub>2A</sub> receptors through administration of 5-HT<sub>2A</sub> antagonists significantly increases slow wave sleep, and reduces both wakefulness and REM sleep.

From the outset of the flibanserin clinical development program, it has been clear that flibanserin induces sedation in a proportion of subjects. [Table 3](#) summarizes the frequency with which sedation or related adverse events were reported in the Targeted Population Set of premenopausal women who were enrolled in the phase 3 double-blind clinical trials.

**Table 3      Number (%) of Subjects with Sedation-related AEs by Preferred Term – Phase 3 Double-blind Studies in Pre-menopausal Women (Targeted Population Set)**

Preferred Term	Placebo Treated N=1905	Total Flibanserin N=3973
Sedation	3 (0.2%)	37 (0.9%)
Fatigue	95 (5.0%)	337 (8.5%)
Somnolence	59 (3.1%)	401 (10.1%)
Subjects with any of the 3 AEs	150 (7.9%)	741 (18.7%)

Note: Includes studies 511.70, 511.71, 511.75, 511.77, and 511.147.

Flibanserin-treated subjects reported a dose dependent increase in the incidence of sedation-related adverse events. The sedative effect was observed to be mostly mild or moderate in severity. Dosing flibanserin 100 mg qhs (at bedtime) resulted in fewer reports of sedation related adverse events than was reported by subjects dosed with 50 mg bid, which included day time dosing. Not surprisingly, night time dosing (100 mg flibanserin at bedtime) reduced the impact of sedation.

### 1.2.2.1 Phase 1 and Phase 2 Cognition Studies

The effects of flibanserin on sedation and cognitive function were evaluated in both healthy male and female subjects and in young and elderly depressed patients in the course of six phase 1 or phase 2 studies during the early phase of the clinical development program, when the target indication for flibanserin development was MDD. These studies are briefly summarized individually in [Section 1.2.2.2](#) below. A description of the cognitive assessments that were conducted in the course of these studies, along with a brief summary of their results is presented here:

**Quantitative Electroencephalography (QEEG):** QEEG records regional electrical activity over different cortical areas of the brain, and can be used to quantitatively measure the abundance of different electrical rhythms. For example, seeing an increase in slow wave patterns (lower frequency, higher wavelength and amplitude) following treatment than before treatment could be indicative of a sedative effect. QEEG was measured in the following studies: 511.2, 511.3 and 511.5. In these studies, dose dependent changes in the QEEG, suggestive of sedation were seen with doses as low as 2mg and 20 mg, but the changes were seen more consistently following doses of 50 and 100 mg. The changes which were consistent with a sedative effect (e.g., increased theta rhythm power and increased slow wave activity), were generally maximal



between 1.25 and 2.25 hours following dosing, a time period that coincided with  $C_{max}$  for flibanserin. The effect attenuated or disappeared by about 6 hours following dosing. In one study (511.3) a sleep EEG was also performed and demonstrated an increase in latency to the first Rapid Eye Movement (REM) period. The increase in slow wave activity and the prolongation of the latency to the first REM period during sleep are both consistent with the established effects of drugs that are 5-HT<sub>2A</sub> antagonists [Monti, 2011].

**Critical Flicker Fusion (CFF):** The CFF is a test that serves as a surrogate measure of alertness. Subjects are exposed to intermittent light flashes at different frequencies. The frequency at which the flickering light appears to fuse to a constant light is defined as the flicker fusion threshold. As a general rule, the more alert the subject is, the higher the frequency of flashes that will be necessary to cause the flickering light to fuse to a constant light (defining the flicker fusion threshold). If a subject is less alert, the flicker fusion threshold will be achieved with a lower frequency of flashes. CFF was measured in the following studies: 511.2, 511.3, 511.10, 511.28, and 511.110. In most of these studies a reduction in CFF threshold (less alert) was observed maximally about 1 – 2 hours following administration of flibanserin, compared with baseline values and the placebo control. The reduction in threshold usually recovered by 5 or 6 hours following dosing. In several of these studies, the CFF threshold significantly increased after 6 hours suggesting the possibility of heightened alertness compared with baseline and with subjects taking placebo.

**Choice Reaction Time (CRT):** The CRT is a widely used assessment tool in psychopharmacological studies to determine if a drug has an effect on alertness. Subjects are asked to react to fixed combinations of light-emitting diodes, illuminated at random, by touching the appropriate contingent response button. The time it takes them to respond is recorded as the total reaction time (TRT). A prolongation of reaction time could be interpreted as a surrogate for lack of alertness. CRT was measured in the following studies: 511.2, 511.3, 511.10, 511.28, and 511.110. Flibanserin administration at doses ranging from 2 mg to 100 mg slowed TRT maximally between 1 and 2.5 hours following dosing. The slowing of TRT was significant for subjects receiving 50 or 100 mg flibanserin compared with placebo. The slowing was markedly attenuated or absent by 6 hours following dosing, and in some studies reaction time appeared to improve after 6 hours compared with baseline measures and the performance of the placebo group.

**Visual Analog Scale (VAS) of Mood States:** Subjects in studies 511.10, 511.110, and 511.115 were asked to score the magnitude of various mood descriptors by drawing a perpendicular line that intersected a 10 cm line, which was anchored by “not at all” over the 0 cm to 2cm portion of the line and “extremely (most ever)” over the 8 cm to 10 cm portion of the line. The 100 mg dose of flibanserin resulted in a clear and consistent increase in VAS score for “drowsiness”, which was maximal from 15 minutes to 2 hours following drug administration compared with baseline scores obtained a day prior to drug administration. The scores then decreased until 4 -6 hours following dosing, by which time the increase had largely resolved.

**EWL 60-S Adjective Checklist:** The EWL 60-S Adjective checklist lists 60 adjectives, which subjects are asked to rate how well they describe their current state on a 4-point Likert Scale ranging from “not at all” to “strongly”. The EWL 60-S was used to measure mood in a single trial, 511.2. Among the 6 mood scales assessed by this scale (performance oriented activation, general disactivation, extra-/introversion, general well-being, irritability and depression/anxiety) only the general disactivation scale (which can indicate sedation) indicated a dose response effect, with reduced activation associated with  $C_{max}$  levels after a single dose and after 14 days of treatment. With flibanserin treatment the maximum reduction occurred around 1.5 hours after treatment and then returned to placebo levels at 6 – 8 hours following dosing.

**Ingelheim Symptoms Checklist 91 Items (SCL 91i):** The SCL 91i is a 91 item list of symptoms which subjects rate on a 4-point Likert Scale ranging from “not at all” to “strongly”. This too was used in a single study, 511.2. The acute placebo-corrected mean sum scores of the SCL 91i on Days 1 and 14 revealed a drug-related picture of the subject’s subjective state of sedation and fatigue. There was a clear dose-dependent increase of scores with acute treatment, which was less pronounced on Day 14 and declined to near placebo level on Day 18. At all flibanserin doses except the 50 mg bid dose, the maximum effects occurred 1.5 hours post dosing. After that the effect generally decreased to baseline levels by 8 hours post dosing.

**Actigraph Recording:** The actigraph is a device, worn on the non-dominant wrist like a watch that continuously measures movement. It can be used as a surrogate measure of sedation by recording daytime activity. The actigraph was used to record movement in trial 511.3. The recordings revealed no significant difference from placebo in mean activity duration for any dose of flibanserin.

### **1.2.2.2 Summary of Individual Cognitive Studies with a Listing of their Key Results**

Study 511.2: This was a double-blind, placebo-controlled, phase 1 study in which 81 healthy volunteers were randomized to one of five flibanserin dose regimens: 20 mg tid, 50 mg bid, 50 mg tid, 100 mg bid, and 100 mg tid. In each treatment group, six male and six female subjects received active treatment, and two subjects of each gender received placebo, over 14 days.

#### **Key Cognitive Results:**

- Dose dependent effects on the QEEG consistent with sedation were associated with  $C_{max}$ , following single and repeated dosing over 14 days. Maximum effects were observed 1.5 hours after dosing with flibanserin.
- The mean CFF threshold frequency decreased within the first 2 hours after treatment in both the flibanserin and placebo treated groups. In the 50 and 100 mg flibanserin treated groups, the CFF threshold increased above baseline values at 5.5 and 8 hours following dosing, suggesting the possibility of increased vigilance at later time points.

- The EWL 60-S general disactivation scale indicated a dose response effect, with reduced activation associated with flibanserin  $C_{max}$  levels after a single dose and after 14 days of treatment. With flibanserin treatment the maximum reduction occurred around 1.5 hours after treatment and then returned to placebo levels at 6 – 8 hours following dosing.
- The SCL 91i Symptom Scale demonstrated a clear dose-dependent increase of scores in symptoms related to sedation with acute treatment, which was less pronounced on Day 14 and declined to near placebo level on Day 18. At all flibanserin doses except the 50 mg bid dose, the maximum effects occurred 1.5 hours following each dose, after that the effect generally decreased to baseline levels by 8 hours post dosing.

**Study 511.3:** This was a double-blind, placebo-controlled, 5-way crossover study in which healthy male volunteers received single oral doses of 2, 20, 50 and 100 mg doses of flibanserin or placebo separated by washout periods of two to three weeks. **Key Cognitive Results:**

- Measurement of QEEG results revealed a significant increase in theta power across all leads with administration of the 50 and 100 mg doses of flibanserin, and small, non-statistically significant increases in delta power which were maximal about 1.5 hours after dosing. These effects are consistent with those seen with administration of imipramine like tricyclic antidepressants (TCA) as a class, and may indicate mild sedating effects. The QEEG findings differed however, from classical effects of TCA antidepressants in that there was no effect on absolute alpha power, a parameter that is increased with TCA administration.
- Sleep EEG revealed little effect of flibanserin on overall sleep architecture, with the exception of a prolonged latency to first REM period. This finding is consistent with 5-HT<sub>2A</sub> antagonism, and is typically seen with antidepressants that have neither sedating nor stimulant effects.
- CFF threshold was lowered during the first 2.5 hours following dosing with all doses, indicating likely sedation. The difference approached significance at one hour for the 50 and 100 mg doses of flibanserin compared with placebo. The lowered threshold began to recover after 2 hours, and by 5.5 hours the 50 mg flibanserin treated group showed increased thresholds compared with placebo that approached significance. At 11.5 hours, both the 50 mg and the 100 mg flibanserin groups had significantly higher thresholds than placebo suggesting the possibility of enhanced alertness. The elevated thresholds are consistent with the effects of SSRIs which have been reported to raise CFF threshold in both patients with MDD and healthy volunteers.
- Flibanserin was found to have a small negative effect on CRT that did not meet statistical significance. The effects were seen for all doses and were maximal at 2.5 to 3.5 hours, and were suggestive of a mild sedative effect.

**Study 511.5:** This was a parallel group, single-blind, single-dose, trial of the effect of flibanserin on regional brain metabolism (PET scan) and QEEG in 43 males with major depressive disorder. Patients underwent baseline assessments and then received a single dose of 2, 20 or 100 mg flibanserin followed by PET and QEEG assessments for two days. They were then treated with paroxetine for 40 days, and had a final assessment on Day 42 of the study.

**Key Cognitive Results:**

- PET scans following acute dosing with flibanserin showed a clear dose response with the three tested doses. The most significant effects were reduced glucose metabolism in the frontal regions, particularly the right medial frontal area and an increase in activity in the temporal regions. There were similar but less prominent changes associated with chronic paroxetine administration. These changes may reflect the predicted ability of flibanserin to inhibit neuronal activity in the prefrontal cortex, with resultant increased dopaminergic and noradrenergic activity in other cortical regions.
- QEEG changes were seen only with 50 and 100 mg dosing, and included a significant increase in theta power with both 50 and 100 mg dosing, which was maximal about 1.25 – 2.5 hours after dosing, and were significantly reduced by 6 hours following dosing. There was an increase in both absolute and relative alpha power with the 50 mg dose, but not the 100 mg dose, and these changes were also maximal around 1.25 hours and reduced by 6 hours. In addition, there was also an increase in slow wave activity consistent with a sedative effect that was maximal around  $C_{max}$  and attenuated around 6 hours.

**Study 511.10:** This was a double-blind, placebo-controlled, multiple dose study of 71 male and female patients with MDD who were randomized to receive placebo, 20, 50, or 100 mg flibanserin bid for 14 days. Cognitive assessments were done following the first dose, and again on Days 7 and 14. The primary cognitive outcome measure was CFF threshold; however, for this study CFF was measured through a 3 mm aperture as well as a 25 mm aperture. The more standard 25 mm aperture does not control for effects the drug might have on pupil size (serotonergic drugs can increase pupil size), so the assessment was conducted with a smaller 3 mm aperture as well, which was thought to control for any changes to pupil size. The 3 mm CFF was designated as the primary outcome measure for the study.

**Key Cognitive Results:**

- At 2 hours following the first dose, all flibanserin treatment groups showed mild reductions in 3 mm CFF threshold compared with baseline, but only the 100 mg group had a statistically significant decrease from baseline compared with placebo (consistent with reduced alertness). At 6 hours there were no longer any differences between any flibanserin group and placebo. On Days 7 and 14 there were no significant differences

between flibanserin at any dose and placebo, suggesting possible accommodation of the sedative effect at these time points than following the first dose.

- With the 25 mm CFF, each of the flibanserin treatment groups demonstrated significant decreases in CFF threshold from baseline at 2 hours, but these differences disappeared by 6 hours. On Day 7 and 14 there were significant differences at 2 hours between the 100 mg flibanserin group and placebo, but not with the lower doses.
- At 2 hours post-dose on Day 0, the 50 mg flibanserin treated group showed significant slowing in CRT, as well as reduced performance in a battery of other cognitive tests (Digit Vigilance Accuracy, Digit Vigilance Speed, Picture Recognition speed, and Picture Recognition Sensitivity). At 6 hours post-dose there were no significant reductions in any cognitive test, instead the 100 mg treated group increased speed significantly on the CRT and the Spatial Working Memory Speed at 6 hours. The only significant differences seen with any dose on Days 7 and 14 was a slowing of CRT by the 50 mg group on Day 7.

Study 511.28: This was a double-blind, placebo-controlled, study of 70 geriatric (65 years or older) patients with major depressive disorder who were randomized to receive either placebo, 20, 50 or 100 mg flibanserin bid for 14 days. Change in the 3 mm CFF threshold at 2 and 6 hours following the first dose was the primary endpoint.

#### **Key Cognitive Results:**

- There were no significant differences between any flibanserin groups and placebo for the primary endpoint (change in 3 mm CFF threshold).
- With the 25 mm CFF, both the 50 and 100 mg doses significantly lowered the CFF threshold at 2 hours post-dose on Day 0. Patients who received 100 mg flibanserin seemed to recover on Days 7 and 14, whereas the group receiving 50 mg continued to significantly lower the threshold at 2 hours on both those days.
- Pupil size was measured in this study and flibanserin had no effect on pupil size.
- 14 other cognitive tests were measured including CRT. The 100 mg dose was significantly different from placebo in 4 of the 14 of the cognitive tests at 2 hours following the first dose (Digit Vigilance speed, Simple Reaction Time, Numeric Working Memory Speed, and Picture Recognition Sensitivity Index), suggesting there was some mildly sedating effect. All of these changes reversed by 6 hours following dosing. CRT showed no effect.

- VAS of Mood States for “drowsy” demonstrated that patients receiving 100 mg flibanserin were significantly drowsier than placebo at 2 hours post-dose on Day 0. This was completely reversed by 6 hours post-dosing.

**Study 511.110:** This was a phase 1 study to compare the bioavailability and sedative effects of three 100 mg modified release formulations of flibanserin with the 100 mg immediate release formulation as single doses administered to healthy male and female volunteers, under fed and fasting conditions. The study was designed as a randomized, six-way crossover study involving 24 healthy male and female subjects with seven day washout periods. Subjects received one of the following treatment regimens: 100 mg flibanserin modified release matrix tablet in a fasted state; 100 mg flibanserin modified release pellet (C2 formulation) in fasted state; 100 mg flibanserin modified release pellet (B formulation), in the fasted state; 100 mg flibanserin matrix modified release formulation in fasted state; 100 mg flibanserin modified release pellet (C2 formulation) in fed state; and 100 mg flibanserin immediate release formulation in fasted state.

#### **Key Cognitive Results:**

- A significant increase in mean VAS Mood States for Drowsiness was seen for the immediate release tablet from 15 minutes to 2 hours post-dose, that decreased afterwards and reached baseline at 4 hours. No increase was seen for the modified release formulations.
- There did not appear to be any significant effect on C RT by any formulation of flibanserin and at any time point.
- There was no effect of any formulation on the CFF threshold at any time point in this study.

#### **1.2.2.3 Summary of Results from Cognitive Studies**

Flibanserin had been extensively studied to better understand the sedative and other cognitive effects of the drug early in the clinical development program. In 6 studies, using a wide variety of cognitive measures, several consistent observations emerge.

- Most studies show a fairly consistent mild to moderate sedative effect that is usually detectable shortly after dosing with flibanserin, and tends to peak in concert with the  $C_{max}$ , between 1 and 3 hours after dosing.
- Most studies and a variety of assessments demonstrate that the maximum period of sedation ends quickly, with the effect either completely gone or markedly attenuated by 5.5 - 6 hours following dosing.

- In several studies, surrogate measures of sedation such as the CFF threshold and the CRT, actually improve beyond baseline and placebo group values suggesting the possibility of an enhanced alertness state after the initial sedative effects of the drug wear off. These studies were not designed to determine if there is in fact a hypervigilant state, and there may be other explanations for these results. It is nonetheless interesting to note that 5-HT<sub>1A</sub> agonism results in the stimulation of wakefulness, and drugs such as SSRIs which stimulate 5-HT<sub>1A</sub> receptors, may be expected to yield similar enhanced wakefulness results on this type of cognitive testing. Sedation may be caused by 5-HT<sub>2A</sub> antagonism, and it is possible that after the 5-HT<sub>2A</sub> antagonism wears off, there is a longer lasting period of continued 5-HT<sub>1A</sub> agonism, resulting in an increased level of wakefulness and alertness.
- Several, but not all, of the studies yielded results suggesting that the magnitude of the sedative effect of flibanserin might be significantly diminished with continued dosing. While there is evidence that the sedative effects of flibanserin are still present on Days 7 and 14, the magnitude of those effects seem to have decreased, suggesting that the effect itself may be somewhat transient and will improve with continued dosing.

#### **1.2.2.4 Dedicated Next Day Driving Study**

The intent bedtime flibanserin dosing is to minimize this risk and to minimize the impact of sedation as a side effect in patients with HSDD. Based on the results of the cognition studies described above, any sedation related side effects would be expected to either be largely reduced or entirely gone by the next morning, when the patient is more likely to operate an automobile. Among patients enrolled in the phase 3 clinical trials there were 12 reports of automobile accidents. Two events occurred with patients receiving placebo (<0.1%), 3 among subjects receiving flibanserin 25 mg bid (0.4%), 3 among those receiving 50 mg qhs (0.1%), 1 individual who received 50 mg bid (0.1%) and 5 among those who received 100 mg qhs (0.2%). A dedicated driving study was conducted to ensure that residual sedation from bedtime dosing did not impair driving ability the following morning.

Study SPR-14-01, was a randomized, multiple-dose, double-blind, placebo-controlled, Latin-square design study with 4-way, 4-period crossover designed to determine the next-day residual effects of acute and steady-state bedtime doses of flibanserin 100 mg and the acute effect of a supratherapeutic dose of flibanserin (200 mg) compared to placebo and a positive hypnotic control (zopiclone 7.5 mg) on simulated driving performance in healthy premenopausal female subjects who were active drivers (>10,000 miles per year) for three years prior to study start. Two hundred fifty-seven subjects were screened to enroll and randomize 83 subjects. Seventy-two subjects completed the study.

The treatment groups were as follows:

- Treatment A: flibanserin 100 mg + zopiclone placebo, night 1; flibanserin only on nights 2 – 6; flibanserin 100 mg + flibanserin placebo + zopiclone placebo on night 7
- Treatment B: zopiclone 7.5 mg + flibanserin placebo, night 1; flibanserin placebo only on nights 2 – 6; flibanserin placebo + zopiclone 7.5 mg on night 7
- Treatment C: zopiclone placebo + flibanserin placebo, night 1; flibanserin placebo only on nights 2 – 6; flibanserin placebo + zopiclone placebo on night 7
- Treatment D: flibanserin 100 mg + zopiclone placebo, night 1; flibanserin only on nights 2 – 6; flibanserin 100 mg + zopiclone placebo on night 7

Each Treatment Period was 1 week in duration. The washout between Treatment Periods was 5-7 days.

Subjects were evaluated following a single dose and at steady-state (7 days) dosing. Testing was conducted in the morning (on Days 2 and 8) following bedtime doses administered by site staff on the evening of Days 1 and 7. Subjects went to bed 30 minutes after dosing (lights out) and were awakened (lights on) approximately 7.5 hours after dosing.

Within approximately 1 hour of waking, subjects performed the non-driving cognitive tests including the CogScreen Symbol Digit Coding (SDC) Test. Subjects then performed the Country Vigilance-Divided Attention (CVDA) driving scenario (requiring the driver to drive 100 km at 95 kph on a simulated 2-lane highway) on the Cognitive Research Corporation Driving Simulator (CRCDS)-MiniSim commencing 9 hours post-dosing.

Endpoints for the study included measures of driving performance, including measures likely to be affected by sedation, as well as cognitive endpoints as described below.

### **Primary Endpoint**

- Standard deviation of lateral position (SDLP) which is a measure of lane position control, and has been shown to be highly predictive of driving safety impairment

### **Secondary Endpoints**

- Driving Performance Endpoints
  - Lane exceedance; including number, maximum, duration, and area of exceedance
  - Ratio above speed limit, excessive speed count, excessive speed ratio
  - Average speed, speed deviation, speeding count, speeding ratio



- Excessive Ay (cornering speed threshold exceeded)
- Collision count, off-road crashes, total collisions
- CogScreen Symbol Digit Coding (SDC)

## Key Study Results

### Primary Outcome: Standard Deviation of Lateral Position (SDLP)

The results for SDLP, are summarized in [Table 4](#).

**Table 4 Mean and LS Mean Standard Deviation of Lateral Position - Study SPR-14-01**

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

Notes: FLI = Flibanserin; PBO = Placebo; SD = Standard deviation; ZOP = Zopiclone.

The LS mean for SDLP was significantly higher after zopiclone administration compared to placebo on Day 2 ( $p < 0.0001$ ) and on Day 8 ( $p < 0.0001$ ). These changes indicate worsening of driving performance with zopiclone and confirm the sensitivity of the test paradigm. Compared to placebo, the LS mean for SDLP was significantly lower after acute ( $p = 0.0009$ ) or steady-state dosing ( $p = 0.0126$ ) of flibanserin 100 mg. Compared to placebo, SDLP for the suprathreshold 200 mg dose of flibanserin was also lower with an LS mean difference approaching statistical significance ( $p = 0.0502$ ).

## Key Secondary Driving Performance Outcomes

### Lane Exceedances, Total Collisions and Excessive Cornering Speed

Zopiclone significantly impaired the frequency of Lane Exceedances compared with placebo on Day 2 ( $p = 0.0004$ ) and Day 8 ( $p < 0.0001$ ). In contrast, flibanserin 100 mg reduced the frequency of Lane Exceedance compared to placebo on both Day 2 ( $p = 0.0213$ ) and Day 8 ( $p = 0.0963$ ). There was no significant difference between placebo and flibanserin 200 mg or between flibanserin 100 mg and flibanserin 200 mg.

There were no significant differences in the number of collisions among the 4 treatment groups, although there were numerically slightly more collisions with zopiclone than with placebo, and slightly fewer with flibanserin 100 mg.

Excessive speed in corners (Excessive Ay), as measured by lateral g force is considered a measure of driving safety. Compared to placebo, there was significantly less excessive cornering force following both acute ( $p=0.031$ ) and steady-state treatment ( $p=0.0076$ ) with flibanserin 100 mg, and with flibanserin 200 mg ( $p=0.0052$ ). Following zopiclone dosing, there was numerically poorer performance on Day 2 and Day 8, but these changes were not significantly different from placebo.

## **Non-Driving Performance Related Cognitive Secondary Endpoints**

### **Symbol Digit Coding (SDC) Test**

Performance on the CogScreen<sup>®</sup> SDC test (number of correct responses) was significantly poorer following treatment with zopiclone than following placebo on Day 2 ( $p < 0.0001$ ) and on Day 8 ( $p = 0.0062$ ). There was no evidence of a worsening of performance on this measure following treatment with flibanserin 100 mg compared to placebo on Day 2 ( $p = 0.3728$ ) and on Day 8 ( $p = 0.9750$ ). In addition, there was no significant difference between placebo and flibanserin 200 mg ( $p = 0.45$ ).

### **Conclusions from the Driving Study**

The Country Vigilance-Divided Attention (CVDA) driving scenario on the CRCDS-MiniSim used in this study is a well validated means of assessing the impact of a pharmaceutical agent on a person's driving performance. The results of this study demonstrate that administration of flibanserin either at 100 mg qhs, the therapeutic dose, or at 200 mg qhs, a supratherapeutic dose the night before the driving assessment, did not impair driving performance or increase the apparent risk of traffic accidents compared with placebo. If anything, subjects receiving flibanserin may have performed better in several key assessments than subjects receiving placebo. The study's failure to demonstrate a flibanserin-associated impairment of driving performance was not unexpected given the mostly mild nature of the sedation reported in the majority of subjects with sedation-related adverse events, the absence of evidence for more frequent automobile accidents among patients receiving flibanserin in the phase 3 program compared with those receiving placebo, and the evidence from 6 early cognitive studies that the sedative effects of flibanserin are relatively short lived and attenuate markedly or disappear entirely within 6 hours of dosing. These data are supportive of flibanserin dosing of 100 mg at bedtime.

### **1.2.3 Risk of Serotonin Syndrome**

Serotonin syndrome is a rare but potentially serious event caused by an adverse drug reaction that leads to excessive serotonergic activity. Excessive serotonergic hyperstimulation may be secondary to the actions of a single serotonergic agent but is usually the result of interactions among multiple drugs with serotonergic activities [Iqbal, 2012]. Drugs that have been associated with serotonin syndrome include: monoamine oxidase inhibitors, tricyclic antidepressants,

selective serotonin reuptake inhibitors, opioid analgesics, over the counter cough medicine, antibiotics, weight reducing agents, herbal products and triptans [Boyer, 2005].

Multiple lines of evidence suggest that agonism of 5-HT<sub>2A</sub> receptors is the major contributor to developing the serotonergic syndrome [Boyer, 2005; Gillman 2009], and that 5-HT<sub>2A</sub> antagonists such as cyproheptadine can treat cases of severe serotonin syndrome. Based on these observations, it would not be anticipated that a drug such as flibanserin which has strong 5-HT<sub>2A</sub> antagonism would have significant risk for inducing a serotonin syndrome. Some have proposed, however, that 5-HT<sub>1A</sub> agonism may also contribute to the establishment of serotonin syndrome, although much of the evidence suggests that agents with 5-HT<sub>1A</sub> agonist properties are rarely if ever responsible for severe serotonin syndrome [Gillman, 2009; Ables 2010]. Since flibanserin is also a 5-HT<sub>1A</sub> agonist the potential for flibanserin to contribute to serotonin syndrome was evaluated.

Classically, serotonin syndrome consists of a triad of symptoms that include alterations of mental status, abnormalities of neuromuscular tone, and autonomic hyperactivity [Boyer, 2005]. Diagnostic criteria (Hunter Serotonin Toxicity Criteria) require the presence of any of the following in the context of having taken a serotonergic drug:

- Tremor and hyperreflexia
- Spontaneous clonus
- Muscle rigidity, temperature > 38°C and either ocular clonus or inducible clonus
- Ocular clonus and either agitation or diaphoresis
- Inducible clonus and either agitation or diaphoresis

None of the subjects enrolled in the flibanserin phase 3 clinical program met any of these criteria. Other adverse events that may be associated with serotonin syndrome including tachycardia, tremor, myoclonus, diaphoresis, hyperthermia, clonus, ocular clonus, agitation, muscular rigidity, hypertonicity, seizures, and diarrhea were also infrequent in the phase 3 clinical program.

**Table 5**      **Number (%) of Subjects with Selected Adverse Events - Phase 3 Studies in Pre- and Post-menopausal Women (Treated Set)**

<b>AE Preferred Term</b>	<b>Placebo (N = 2792) N (%)</b>	<b>Flibanserin 100 mg qhs (N=2459), N (%)</b>
Tachycardia	2 (<0.1)	8 (0.3)
Tremor	1 (<0.1)	3 (0.1)
Diaphoresis	0	0
Hypertension	29 (1.0)	25 (1.0)
Hyperthermia	4 (0.1)	14 (0.6)
Clonus	0	0
Ocular Clonus	0	0
Agitation/Agitation Related	77 (2.8)	120 (4.9)
Rigidity/ Hypertonicity	0	0
Seizures	0	1 (<0.1)
Diarrhea	51 (1.8)	48 (2.0)

Includes Studies 511.70, 511.71, 511.77, 511.114, 511.130, 511.147, 511.156.

The only serotonergic adverse events that were seen more frequently with flibanserin administration than with placebo were tachycardia, hyperthermia, and agitation related adverse events. Despite the lack of any signal in these data, the incidence of these adverse events was examined in subjects who used other serotonergic agents in conjunction with flibanserin during the phase 3 clinical program. [Table 6](#) shows the incidence of these adverse events in patients who used selective serotonin reuptake inhibitors (SSRI) and serotonin and norepinephrine reuptake inhibitors (SNRI) in the phase 3 clinical program. [Table 7](#) shows the same adverse events in patients who took triptans during the phase 3 clinical trials. As can be seen, combined use of both flibanserin and these other serotonergic drugs did not appear to result in a significant increase in the incidence of these serotonergic adverse events.

**Table 6**      **Number (%) of Subjects with Selected Adverse Events Seen More Frequently in Flibanserin Treated Patients, Analyzed based on SSRI/SNRI Use - Phase 3 Studies in Pre- and Post-menopausal Women (Treated Set)**

AE Preferred Term	SSRI/SNRI Use/NonUse	Placebo User: 91 Non-User: 2599	Flibanserin 100 mg User: 131 Non-User: 2248
		N (%)	N (%)
Tachycardia	User	0	0
	Non-User	2 (<0.1)	8 (0.3)
Pyrexia	User	0	1 (<0.1)
	Non-User	4 (0.2)	12
Body Temp Increase	User	0	0
	Non-User	0	1 (<0.1)
Total Anxiety Related	User	9 (9.8)	15 (11.5)
	Non-User	68 (2.6)	106 (4.7)
Irritability	User	2 (2.2)	2 (1.5)
	Non-User	29 (1.1)	39 (1.7)
Anxiety	User	6 (6.6)	10 (7.6)
	Non-User	27 (1.0)	39 (1.7)
Stress	User	1 (1.0)	1 (0.8)
	Non-User	2 (<0.1)	14 (0.6)
Agitation	User	0	2 (1.5)
	Non-User	7 (0.3)	8 (0.4)
Nervousness	User	0	0
	Non-User	2 (<0.1)	6 (0.3)
General Anxiety Dis	User	0	0
	Non-User	1 (<0.1)	0

Studies 511.70, 511.71, 511.77, 511.114, 511.130, 511.147, 511.156.

**Table 7**      **Number (%) of Subjects with Selected Adverse Events Seen More Frequently in Flibanserin Treated Patients, Analyzed based on Triptan Use - Phase 3 Studies in Pre- and Post-menopausal Women (Treated Set)**

AE Preferred Term	Triptan Use/NonUse	Placebo User: 104 Non-User: 2586	Flibanserin 100 mg User: 99 Non-User: 2280
		N (%)	N (%)
Tachycardia	User	1 (0.9)	1 (1.0)
	Non-User	1 (<0.1)	7 (0.3)
Pyrexia	User	0	0
	Non-User	4 (0.2)	13 (0.6)
Body Temp Increase	User	0	0
	Non-User	0	1 (<0.1)
Total Anxiety Related	User	6 (5.8)	10 (10.0)
	Non-User	71 (2.7)	112 (4.9)
Irritability	User	2 (1.9)	4 (4.0)
	Non-User	29 (1.1)	38 (1.7)
Anxiety	User	3 (2.9)	2 (2.0)
	Non-User	30 (1.2)	47 (2.1)
Stress	User	0	3 (3.0)
	Non-User	3 (0.1)	12 (0.5)
Agitation	User	0	1 (1.0)
	Non-User	7 (0.3)	9 (0.4)
Nervousness	User	0	0
	Non-User	2 (<0.1)	6 (0.3)
General Anxiety Dis	User	1 (1.0)	0
	Non-User	0	0

Studies 511.70, 511.71, 511.77, 511.114, 511.130, 511.147, 511.156.

A dedicated study was conducted to study the safety of a combination of flibanserin and SSRI/SNRI medications. Study 114 was a Phase 3 double-blind, placebo-controlled, randomized safety trial conducted over 12 weeks in premenopausal women with HSDD taking a SSRI or SNRI. The study population consisted of 111 randomized subjects: 38 women on placebo, 45 women who up-titrated to flibanserin 100 mg qhs after 2 weeks of flibanserin 50 mg qhs, and 28 women on fixed dose flibanserin 100 mg qhs. Incidence of selected adverse events is presented for the aggregate for both dosing regimens (Table 8).

**Table 8 Number (%) of Subjects with Adverse Events by Primary System Organ Class and Preferred Term – Study 114**

<b>System Organ Class / Preferred Term</b>	<b>Placebo N = 38 n (%)</b>	<b>FLI 50 mg qhs N = 45 n (%)</b>	<b>FLI 100 mg qhs N = 72 n (%)</b>	<b>FLI Total N = 73 n (%)</b>
Total AEs	27 (71.1)	12 (26.7)	40 (55.6)	48 (65.8)
Anxiety	2 (5.3)	0	2 (2.8)	2 (2.7)
Dizziness	0	1 (2.2)	2 (2.8)	3 (4.1)
Insomnia	1 (2.6)	1 (2.2)	3 (4.2)	4 (5.5)
Nausea	2 (5.3)	0	0	0
Somnolence	3 (7.9)	0	1 (1.4)	1 (1.4)
Blood Pressure Increase	1 (2.6)	0	0	0
Paresthesia	0	0	0	0
Headache	7 (18.4)	1 (2.2)	3 (4.2)	4 (5.5)
Fatigue	2 (5.3)	1 (2.2)	2 (2.8)	3 (4.1)
Sedation	2 (5.3)	2 (4.4)	1 (1.4)	3 (4.1)
Dry Mouth	1 (2.6)	1 (2.2)	3 (4.2)	4 (5.5)
Tremor	0	0	0	0

Notes: FLI = Flibanserin; qhs = Once daily at bedtime.

## Adverse Events

No deaths or SAEs were reported in this trial. In the placebo group, 71.1% of subjects experienced AEs, while 65.8% of subjects taking flibanserin experienced AEs. Headache was the most frequently reported adverse event and was also one of the most frequently reported adverse events to be classified as severe, study drug related, and causing a subject to discontinue from the study. Headache occurred in a higher percentage of subjects treated with placebo (18.4%) compared to flibanserin (5.5%).

Nausea was reported by 5.3% of subjects in the placebo group, while subjects in the flibanserin group did not report nausea. Anxiety was experienced by 5.3% of subjects in the placebo group and 2.7% of subjects in the flibanserin group. Somnolence was experienced by 7.9% of subjects in the placebo group and 1.4% of subjects in the flibanserin group. The rates of sedation and fatigue were similar for placebo (5.3% for each AE) and flibanserin (4.1% for each AE). The rate of dizziness, insomnia and dry mouth were the only common AEs that had a higher rate of occurrence in the flibanserin group (4.1 - 5.5% for each AE) than in the placebo group (0 - 2.6% for each AE).

[Table 9](#) summarizes the incidence of serotonin specific adverse events seen in this study. There was no evidence of increased frequency of serotonergic adverse events with the combined use of flibanserin and SSRI/SNRI in this study. Although the small sample size makes it impossible to draw any conclusions from the apparently lower incidence of serotonin associated adverse events

among subjects receiving flibanserin plus an SSRI or SNRI than those taking a placebo plus an SSRI or SNRI, it is interesting to note that this observation is consistent with the common practice of using 5-HT<sub>2A</sub> antagonists to reduce symptoms associated with serotonin syndrome.

**Table 9 N (%) of subjects with Serotonin Specific Adverse Events – Study 114**

Adverse Event Preferred Term	Placebo (N = 2792) N (%)	Flibanserin 100 mg qhs (N=2459), N (%)
Tachycardia	0	0
Tremor	0	0
Diaphoresis	0	0
Hypertension	1 (2.6)	0
Hyperthermia	0	0
Clonus	0	0
Ocular Clonus	0	0
Agitation/Agitation Rel	2 (5.3)	2 (2.7)
Rigidity/ Hypertonicity	0	0
Seizures	0	0
Diarrhea	2 (5.3)	1 (1.4)

Note: qhs = Once daily at bedtime.

## Conclusion

Consistent with flibanserin's 5-HT<sub>2A</sub> antagonist mechanism, there was no evidence of serotonin syndrome in the broader phase 3 population as well as in the dedicated study looking at the combination of flibanserin with SSRI/SNRI. There was also no evidence to suggest that serotonergic side effects such as tremor, clonus, anxiety, fever, high blood pressure, paresthesia, and others were seen significantly more frequently in patients receiving flibanserin. The risk of developing serotonin syndrome while taking flibanserin, even if taken in conjunction with another serotonergic drug should be considered to be low.

### 1.2.4 Serotonin and Hypotension

Serotonin has multiple complicated actions in contributing to the regulation of blood pressure, a detailed review of which is well beyond the scope of this document, but an excellent and detailed review has been published[Watts, 2012]. Serotonin contributes to the regulation of blood pressure via both peripheral and central nervous system pathways, involving the activation of many different classes of serotonin receptors.

Activation of 5-HT<sub>1A</sub> receptors influences blood pressure primarily through central pathways, and for the most part causes a reduction of blood pressure, but under certain circumstances it can also cause blood pressure elevation. 5-HT<sub>1A</sub> receptor activation can inhibit sympathetic premotor neurons reducing vasoconstrictor activity leading to vasodilatation, and at the same time increase cardiac vagal nerve activity, slowing the heart [Ramage, 2001]. Both activities



lead to reduced blood pressure. In the event of severe hypotension or shock, however, activation of 5-HT<sub>1A</sub> receptors has been shown to have the opposite effect, increasing blood pressure [Scrogin, 2003; Tiniakov, 2007].

Central stimulation of 5-HT<sub>2A</sub> receptors can lead to an increase in blood pressure, at least in part through the stimulation of vasoconstrictor outflow arising through activation of sympathetic premotor neurons [Ramage, 1998; Daly, 1998]. 5-HT<sub>2A</sub> antagonism may have the opposite effect and lower blood pressure as well, however, studies of several different 5-HT<sub>2A</sub> antagonists have failed to demonstrate their ability to reduce blood pressure attesting to the complexity of serotonergic blood pressure regulation [Watts, 2012].

Despite the significant effect that a drug which serves as both a 5-HT<sub>1A</sub> agonist and 5-HT<sub>2A</sub> antagonist might be expected to have in lowering blood pressure, very little evidence of this has been seen in the flibanserin phase 3 program. This is most likely due to the highly complicated and varied role the serotonergic system plays in regulating blood pressure.

In the Phase 3, double-blind studies in premenopausal women, blood pressure and pulse rate were measured at each clinical study visit. The data reveal no trends toward mean changes in blood pressure or pulse rate across flibanserin dose groups over time. Similarly, no trends were seen in frequency of subjects with clinically relevant changes in those vital signs or frequency of syncope AEs. Among premenopausal women enrolled in the double-blind Phase 3 clinical studies, a total of eight subjects out of 3,973 who received flibanserin at any dose (0.2%) reported eight episodes of syncope or vasovagal syncope (4 mild episodes, 3 moderate episodes and 1 severe episode). Four of 1,905 subjects who received placebo (0.1%) also reported experiencing four syncopal episodes (1 mild episode and 3 moderate episodes). There were two cases of circulatory collapse reported in the premenopausal Phase 3 studies: one each in the flibanserin 100 mg qhs (severe) and placebo (mild) groups.

A total of 9 subjects out of 3,973 who received flibanserin at any dose (0.2%) reported 10 other events potentially related to hypotension with adverse event terms of postural dizziness, loss of consciousness, decreased blood pressure and hypotension (4 mild episodes, 5 moderate episodes and 1 severe episode). One of 1,905 subjects who received placebo (<0.1%) also reported experiencing a single similar episode (mild). While the rates of events are very small, the potential for a hypotension signal was recognized in these data.

Clinically significant AEs of hypotension and syncope were observed in Phase 1 studies of flibanserin that involved daytime dosing and either high exposure or concomitant and significant alcohol use. Flibanserin combined with fluconazole resulted in large flibanserin exposure increases (AUC 7-fold; C<sub>max</sub> 2.24-fold). Hypotension-related AEs were seen in three subjects following dosing with flibanserin 100 mg and fluconazole 200 mg. Each of these events occurred approximately 1 hour after dosing when serum levels of flibanserin were near their maximum. Pharmacokinetic data collected near the time of these events indicates that these

three subjects had the three highest  $C_{max}$  values of subjects dosed with flibanserin while at steady-state fluconazole levels. This would support the conclusion that hypotension is more likely with excessive levels of flibanserin than with therapeutic levels. No subjects in the other treatment groups had hypotensive events.

A dedicated alcohol study was conducted to evaluate the effect of combined administration of daytime dosing of flibanserin 100 mg and very high doses of ethanol on seated blood pressure and orthostatic vital signs. A five-way cross-over design compared morning dosing of flibanserin 100 mg alone to ethanol at two different concentrations (0.4 g/kg and 0.8 g/kg) with and without flibanserin 100 mg.

Signals of an effect on orthostatic hypotension were detected during the study:

- Flibanserin with 0.8 mg/kg ethanol produced a decrease in mean SBP (-10.8 to -12.0 mm Hg) at 6 and 8 hours. No other mean changes in systolic blood pressure, diastolic blood pressure or heart rate were seen in any other group.
- No mean changes in blood pressure met criteria for orthostatic hypotension (decrease of 20 mm Hg for systolic blood pressure or 15 mm Hg diastolic blood pressure upon standing up) with any treatment. On an individual basis, more subjects met criteria for orthostatic change in systolic and diastolic blood pressure when dosed with flibanserin 100 mg plus ethanol than when dosed with either flibanserin or alcohol alone.
- Treatment with ethanol (either concentration) and flibanserin led to mean decreases in blood pressure that met the criterion for orthostatic hypotension at 3 of 4 time points (over 1.5 to 4 hours following dosing). The orthostatic hypotension criterion was met at one time point (3 hours) after 0.8 g/kg ethanol + placebo and at no time points following treatment with 0.4 g/kg ethanol + placebo or flibanserin 100 mg alone.

AEs of severe syncope, dizziness and/or hypotension requiring medical intervention were reported in three subjects receiving 0.4 g/kg ethanol plus flibanserin and one event of severe dizziness was reported in a subject receiving 0.8 g/kg ethanol plus flibanserin.

In summary, hypotension does not appear to be a major risk with recommended use of flibanserin. There were occasional incidents in the phase 3 clinical program, but they were few and mostly mild or moderate in severity. Markedly high exposure to flibanserin such as was seen in the fluconazole study, or use of flibanserin in combination with high doses of other CNS depressants like alcohol can increase the risk of experiencing significant hypotension related events. Cautions in the product label and educational materials that will be part of the risk management plan are designed to minimize the risk of these episodes by encouraging proper use of the drug.

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## **APPENDIX O PROPOSED FLIBANSERIN PACKAGE INSERT**

## HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use FLIBANSERIN safely and effectively. See full prescribing information for FLIBANSERIN.

XXXX

(flibanserin, 100 mg)

Initial U.S. Approval: 2015

### INDICATIONS AND USAGE

FL BANSERIN is a post-synaptic 5-H<sub>A</sub> receptor agonist and a 5-H<sub>2A</sub> receptor antagonist indicated for the treatment of hypoactive sexual desire disorder (HSDD) in premenopausal women (1)

### DOSAGE AND ADMINISTRATION

The dose is 100 mg taken once daily at bedtime (2)

### DOSAGE FORMS AND STRENGTHS

FL BANSERIN is available as 100 mg immediate release tablets (3)

### CONTRAINDICATIONS

- Concomitant administration with moderate to strong Cytochrome P450 3A4 (CYP3A4) inhibitors (4)
- Known hypersensitivity to FL BANSERIN or any components of the FL BANSERIN tablet formulation (4)

### WARNINGS AND PRECAUTIONS

- CNS Depression: Patients may experience somnolence and other symptoms of CNS depression (5.1)
- Hypotension and Syncope: FL BANSERIN may cause hypotension or syncope (5.2)
- Use with Alcohol: Co-administration of FL BANSERIN with alcohol may increase risk of CNS depression, hypotension and syncope. Advise patients to avoid use until they know how FL BANSERIN affects them (5.3)
- Hepatic Impairment: FL BANSERIN is not recommended for use in patients with hepatic impairment (5.4)
- Drug-Drug Interactions: Co-administration of FL BANSERIN with other CYP3A4 inhibitors may increase risk of CNS depression, hypotension and syncope. Use of moderate to strong CYP3A4 substrates is contraindicated (5.5)

### ADVERSE REACTIONS

Most common adverse reactions (≥2% and twice the incidence with placebo) are dizziness, somnolence, fatigue, nausea, dry mouth and insomnia (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Sprout Pharmaceuticals, Inc. at 1-8xx-xxx-xxxx, or FDA at 1-800-FDA-1088 or [www.fda.gov/medwatch](http://www.fda.gov/medwatch).

### DRUG INTERACTIONS

- Inhibitors of CYP3A4 may increase flibanserine concentrations (7.1)
- Strong enzyme inducers of CYP3A4 significantly decrease exposure to flibanserine (7.1)
- Concomitant use with digoxin increases exposure to digoxin (7.2)

### USE IN SPECIFIC POPULATIONS

- Pregnancy: FL BANSERIN should not be used during pregnancy (8.1)
- Nursing mothers: FL BANSERIN should not be used by a nursing woman (8.2)
- Pediatric: Safety and efficacy of FL BANSERIN has not been established in patients under 18 years of age (8.4)

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- Hepatic impairment: FL BANSERIN is not recommended for use in patients with hepatic impairment (8.6)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 02/2015

## FULL PRESCRIBING INFORMATION: CONTENTS\*

- |   |   |
|---|---|
| <b>1 INDICATIONS AND USAGE</b>                      | <b>9 DRUG ABUSE AND DEPENDENCE</b>          |
| <b>2 DOSAGE AND ADMINISTRATION</b>                  | <b>10 OVERDOSAGE</b>                        |
| <b>3 DOSAGE FORMS AND STRENGTHS</b>                 | <b>11 DESCRIPTION</b>                       |
| <b>4 CONTRAINDICATIONS</b>                          | <b>12 CLINICAL PHARMACOLOGY</b>             |
| <b>5 WARNINGS AND PRECAUTIONS</b>                   | 12.1 Mechanism of Action                    |
| 5.1 CNS Depression                                  | 12.2 Pharmacodynamics                       |
| 5.2 Hypotension and Syncope                         | 12.3 Pharmacokinetics                       |
| 5.3 Use with Alcohol                                | 12.5 Pharmacogenomics                       |
| 5.4 Hepatic Impairment                              | <b>13 NONCLINICAL TOXICOLOGY</b>            |
| 5.5 Drug-Drug Interactions                          | 13.1 Carcinogenesis                         |
| <b>6 ADVERSE REACTIONS</b>                          | Mutagenesis                                 |
| 6.1 Clinical Studies                                | Immunogenicity                              |
| <b>7 DRUG INTERACTIONS</b>                          | <b>14 CLINICAL STUDIES</b>                  |
| 7.1 Potential for Other Drugs to Affect FL BANSERIN | 14.1 Studies in Premenopausal HSDD Patients |
| 7.2 Potential for FL BANSERIN to Affect Other Drugs | 14.2 Special Safety Studies                 |
| <b>8 USE IN SPECIFIC POPULATIONS</b>                | <b>16 HOW SUPPLIED/STORAGE AND HANDLING</b> |
| 8.1 Pregnancy                                       | <b>17 PATIENT COUNSELING INFORMATION</b>    |
| 8.2 Lactation                                       |   |
| 8.3 Females and Males of Reproductive Potential     |   |
| 8.4 Pediatric Use                                   |   |
| 8.6 Hepatic Impairment                              |   |
| 8.7 Renal Impairment                                |   |

\*Sections or subsections omitted from the full prescribing information are not listed

## FULL PRESCRIBING INFORMATION

### 1 INDICATIONS AND USAGE

FL BANSERIN is a post-synaptic 5-H<sub>A</sub> receptor agonist and a 5-H<sub>2A</sub> receptor antagonist indicated for the treatment of hypoactive sexual desire disorder (HSDD) in premenopausal women.

Limitation on Use: The safety and efficacy of FL BANSERIN for the treatment of any other forms of female sexual dysfunction have not been demonstrated.

### 2 DOSAGE AND ADMINISTRATION

100 mg taken orally once nightly at bedtime. FL BANSERIN should only be taken at bedtime due to the increased risk of CNS depression if taken during waking hours [see Warnings and Precautions (5.1)].

If a dose of FL BANSERIN is missed, the patient should skip that night's dose. The patient should not take FL BANSERIN the following morning or double the next dose. Routine bedtime dosing should be resumed the next day.

Discontinue treatment after 12 weeks if the patient does not report an improvement in sexual desire and/or a reduction in associated distress.

### 3 DOSAGE FORMS AND STRENGTHS

FL BANSERIN is available as 100 mg oval pink immediate release film-coated tablets debossed on one side with "100" and blank on the other side.

### 4 CONTRAINDICATIONS

FL BANSERIN is contraindicated in patients taking a moderate to strong CYP3A4 inhibitor due to the risk of significantly increased flibanserin plasma concentrations which may result in CNS depression, hypotension and syncope. [see Warnings and Precautions (5.1, 5.2), Drug Interactions (7.1), Clinical Pharmacology (12.3)]

FL BANSERIN is contraindicated in patients with known hypersensitivity to flibanserin or any component of the FL BANSERIN tablet formulation. [see Description (11)]

### 5 WARNINGS AND PRECAUTIONS

#### 5.1 CNS Depression

FL BANSERIN is a central nervous system (CNS) depressant. Prescribers should advise patients that they may experience somnolence, fatigue and other symptoms of CNS depression. [see Adverse Reactions (6.1), Clinical Pharmacology (12.2)]

The risk of CNS depression is increased if FL BANSERIN is taken during waking hours, if a higher than approved dose is taken, if co-administered with other CNS depressants (e.g., alcohol, SSRIs/SNRIs, tricyclics) or if co-administered with drugs that increase blood levels of flibanserin. [see Warnings and Precautions (5.5), Drug Interactions (7.1), Clinical Pharmacology (12.3)]

Patients should not drive or engage in other activities requiring full alertness until the morning after taking FL BANSERIN. [see Patient Counseling Information (17)]

#### 5.2 Hypotension and Syncope

FL BANSERIN may cause hypotension and/or syncope. Instances of hypotension (FL BANSERIN 0.2% placebo <0.1%) and syncope (FL BANSERIN 0.3% placebo 0.1%) were uncommon in the 24-week placebo-controlled trials of premenopausal women with HSDD taking FL BANSERIN 100 mg once daily at bedtime (n=1543). Dizziness was reported in 11.4% of FL BANSERIN patients vs 2.2% of placebo patients. The risk of hypotension and syncope is increased if FL BANSERIN is taken during waking hours, if a higher than approved dose is taken, if co-administered with other CNS depressants or if co-administered with other drugs that increase blood levels of flibanserin. [see Warnings and Precautions (5.5), Drug Interactions (7.1), Clinical Pharmacology (12.3)]

FL BANSERIN should be used with caution in patients with conditions which would predispose them to hypotension.

#### 5.3 Use with Alcohol

Co-administration of FL BANSERIN with alcohol may increase the risk of CNS depression, hypotension and syncope. Patients should be advised to avoid alcohol until they know how FL BANSERIN affects them. [see Clinical Studies (14.2)]

#### 5.4 Hepatic Impairment

Flibanserin clearance was reduced in patients with mild to moderate hepatic impairment. Avoid use of FL BANSERIN in patients with hepatic impairment. [see Clinical Pharmacology (12.3)]

#### 5.5 Drug-Drug Interactions

Flibanserin is a CYP3A4 substrate. Moderate to strong inhibitors of CYP3A4 cause a significant increase in concentration of flibanserin when

co-administered. This increase in concentration of flibanserin may be associated with increased CNS depression, hypotension and syncope. FL BANSERIN is contraindicated in patients who are taking moderate to strong inhibitors of CYP3A4 (e.g., ketoconazole, itraconazole, fluconazole, ritonavir, or clarithromycin). [see Contraindications (4), Drug Interactions (7.1), Clinical Pharmacology (12.3)]

Exposure to multiple CYP3A4 inhibitors via food, herbal supplements or non-prescription drugs may further exacerbate this risk and should be avoided.

### 6 ADVERSE REACTIONS

The following adverse reactions are discussed in greater detail in other sections: CNS Depression, Hypotension and Syncope. [see Warnings and Precautions (5.1, 5.2)]

#### 6.1 Clinical Trials Experience

Tablets containing flibanserin were administered to over 5000 women with HSDD during clinical trials worldwide. Of these, 2394 patients received treatment for at least 6 months, 1066 for at least 12 months, and 114 for at least 18 months.

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared with rates in the clinical trials of another drug and may not reflect the rates observed in practice.

##### Most Common Adverse Reactions

In clinical trials of premenopausal women with HSDD treated with FL BANSERIN 100 mg given as a single dose at bedtime, the most common adverse reactions (reported in 5% or more of women treated with FL BANSERIN and at least twice the placebo rate) were dizziness (FL BANSERIN 11.4%, placebo 2.2%), somnolence (FL BANSERIN 11.2%, placebo 3.1%) and nausea (FL BANSERIN 10.4%, placebo 3.7%). The majority of these adverse reactions emerged during the first 14 days of treatment.

Adverse reactions that occurred in at least 2% of women treated with FL BANSERIN 100 mg given as a single dose before bedtime and at twice the incidence of placebo in double-blind, placebo-controlled clinical trials in premenopausal women are presented in Table 1.

**Table 1 Treatment-Emergent Adverse Reactions (Events Reported in ≥2% of Patients Treated with FLIBANSERIN 100 mg qhs and at Twice the Incidence with Placebo) in Double-blind, Placebo-controlled Trials in Premenopausal Women**

Adverse Reactions	Placebo (N=1905) %	FLIBANSERIN 100 mg qhs (N=1543) %
<b>Nervous system disorders</b>		
Dizziness	2.2	11.4
Somnolence	3.1	11.2
<b>General disorders and administration site conditions</b>		
Fatigue	5.0	9.2
<b>Gastrointestinal disorders</b>		
Nausea	3.7	10.4
Dry mouth	0.9	2.4
<b>Psychiatric disorders</b>		
Insomnia	2.4	4.9

qhs=once daily at bedtime



#### Less Common Adverse Reactions

Other less common adverse reactions (reported  $\geq 1\%$  of patients treated with FL BANSERIN 100 mg once daily at bedtime in double-blind placebo-controlled trials in premenopausal women) include anxiety (FL BANSERIN 1.8% placebo 0.9%) constipation (FL BANSERIN 1.6% placebo 0.5%) abdominal pain (FL BANSERIN 1.5% placebo 0.8%) metrorrhagia (FL BANSERIN 1.4% placebo 1.3%) rash (FL BANSERIN 1.3% placebo 0.7%) sedation (FL BANSERIN 1.3% placebo 0.2%) vertigo (FL BANSERIN 1% placebo 0.3%) in placebo-controlled double-blind clinical trials of premenopausal women, appendicitis occurred in 0.2% of women taking flibanserin under various dosing regimens (25 mg bid, 50 mg qhs or 50 mg bid) while there were no reports of appendicitis in women on placebo.

#### Dose Relationship for Adverse Reactions

There is evidence of a dose relationship for many of the adverse reactions associated with flibanserin use, particularly for certain CNS adverse reactions.

#### Adverse Reactions Leading to Discontinuation

In five 24-week double-blind placebo-controlled randomized studies in premenopausal women with HSDD, the discontinuation rate due to adverse events in patients treated with FL BANSERIN 100 mg once daily at bedtime ( $n=1543$ ) was 12.8% compared to 5.9% in placebo-treated patients ( $n=1905$ ). The adverse events most commonly causing discontinuation of FL BANSERIN 100 mg once daily at bedtime were dizziness (1.7%) nausea (1.2%) insomnia (1.1%) somnolence (1.1%) anxiety (1.0%) and fatigue (0.9%).

## **7 DRUG INTERACTIONS**

### **7.1 Potential for Other Drugs to Affect Flibanserin**

Metabolism by CYP3A4 is the major elimination pathway for flibanserin.

#### CYP3A4 Inhibitors

FL BANSERIN is contraindicated in combination with strong CYP3A4 inhibitors (e.g., ketoconazole, itraconazole, posaconazole, clarithromycin, nefazodone, ritonavir, saquinavir, nelfinavir, nandavir, boceprevir, telaprevir, telithromycin, and conivaptan) or moderate CYP3A4 inhibitors (e.g., amprenavir, atazanavir, ciprofloxacin, diltiazem, erythromycin, fluconazole, fosamprenavir, miconazole, and verapamil). Co-administration with such drugs may significantly increase exposure to flibanserin and the risk of CNS depression, hypotension, and syncope. Physicians are urged to avoid use of FL BANSERIN rather than to attempt to adjust dose or dosing regimen in situations of potential higher exposure. Temporarily suspend FL BANSERIN dosing during acute therapy with moderate to strong CYP3A4 inhibitors or select concomitant medication with no or minimal inhibition on potential. [see Contraindications (4) Warnings and Precautions (5.5)]

Patients taking mild CYP3A4 inhibitors (e.g., oral contraceptives) should be advised of the increased risk of dizziness, somnolence, and fatigue. [Clinical Pharmacology (12.3)]

#### CYP3A4 Inducers

Flibanserin exposure is substantially decreased when flibanserin is co-administered with strong CYP3A4 inducers (e.g., rifampin). Use of FLIBANSERIN with strong CYP3A4 inducers should be avoided as the efficacy of FLIBANSERIN may be reduced. [see Clinical Pharmacology (12.3)]

#### CNS Depressants

Additive CNS effects are seen with co-administration of FL BANSERIN with alcohol and may be expected with co-administration of other drugs which cause CNS depression (e.g., SSRIs, SNRIs, tricyclic antidepressants) including non-prescription drugs which may cause sedation (e.g., diphenhydramine). [see Clinical Pharmacology (12.3)]

### **Appendix O - Proposed Flibanserin Package Insert**

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## **7.2 Potential for Flibanserin to Affect Other Drugs**

#### Doxgex

Concomitant administration of FL BANSERIN with doxgex, a P-gp substrate, increased doxgex exposure from 25% to 96%. Doxgex concentrations should be monitored when co-administered with flibanserin. [see Clinical Pharmacology (12.3)]

#### P-glycoprotein

Flibanserin has the potential to inhibit P-gp levels of any narrow therapeutic index drugs that are substrates for P-gp should be monitored if co-administered with FL BANSERIN. [see Clinical Pharmacology (12.3)]

#### CNS Depressants

Additive CNS effects are seen with co-administration of FL BANSERIN with alcohol and may be expected with co-administration of other drugs which cause CNS depression including non-prescription drugs which may cause sedation (e.g., diphenhydramine). [see Clinical Pharmacology (12.3)]

## **8 USE IN SPECIFIC POPULATIONS**

### **8.1 Pregnancy**

#### Risk Summary

Major birth defects occur in 2-4% of the general population and miscarriage occurs in 15-20% of clinically recognized pregnancies (without FL BANSERIN use). Human data do not establish the presence or absence of a flibanserin-associated risk to pregnancy. FL BANSERIN should not be used during pregnancy.

Pregnant rats were administered flibanserin at doses of 0, 20, 80, and 400 mg/kg/day during organogenesis. The 400 mg/kg/day high dose was associated with significant maternal toxicity as evidenced by severe clinical signs and marked reductions in weight gain during dosing. Decreased fetal weights, increases in the incidence of decreased ossification of the forelimbs and increased lumbar vertebrae, and two fetuses with anophthalmia were observed in the litters of high dose dams. The no adverse effect level for maternal and embryofetal toxicity was 80 mg/kg/day (15 times clinical exposure based on AUC). Fetal adverse effects were only observed with the high dose of 400 mg/kg flibanserin (41 times therapeutic exposures) in association with severe maternal toxicity. Therefore, there is no evidence for direct teratogenic effects of flibanserin in rats.

Pregnant rabbits were administered flibanserin at doses of 0, 20, 40, and 80 mg/kg/day during organogenesis. Marked decreases in maternal body weight gain (>75%) abortion and complete litter resorption were observed at 40 and 80 mg/kg/day indicating significant maternal toxicity at these doses. Increases in resorptions and decreased fetal weights were observed at  $\geq 40$  mg/kg/day. No teratogenic effects were observed in fetuses at any dose level. The no adverse effect level for maternal and embryofetal effects was 20 mg/kg/day (3-4 times clinical exposure based on AUC).

Pregnant rats were administered flibanserin at doses of 0, 20, 80, and 200 mg/kg/day from day 6 of pregnancy until day 21 of lactation to assess for effects on pre- and postnatal development. The high dose was associated with clinical signs of toxicity in pregnant and lactating rats. A dose resulted in sedation and decreases in body weight gain during pregnancy. Flibanserin prolonged gestation in some dams in a dose groups and decreased implantations, number of fetuses and fetal weights at 200 mg/kg/day ( $\geq 15$  times therapeutic exposures). Dosing dams with 200 mg/kg also decreased pup weight gain and viability during the lactation period and delayed opening of the vagina and auditory canals. Flibanserin had no effects on learning, reflexes, fertility or reproductive capacity of the F1 generation. The no adverse effect level for maternal toxicity and pre/postnatal effects was 20 mg/kg/day (3-4 times therapeutic exposures). [see Nonclinical Toxicology (13.1)]



**Sprout Pharmaceuticals**  
**Flibanserin Advisory Committee Briefing Document**

4 June 2015

Absorption

90% of the dose of FL BANSERIN reaches the systemic circulation as flibanserin or metabolites. After oral administration, maximum observed plasma concentrations (C<sub>max</sub>) are usually achieved between 45 and 60 minutes. Absorbability of flibanserin following oral dosing is 33%.

Food moderately affects the rate and extent of FL BANSERIN absorption. Peak plasma concentrations of flibanserin occur at 1.75 to 4 hours post-dosing with food, and the extent of exposure is increased up to 56% after a high-fat, high-calorie meal. Grapefruit juice given with a single dose of FL BANSERIN 100 mg increases exposure (AUC) approximately 38% and C<sub>max</sub> by 10%.

Distribution

The volume of distribution of flibanserin after intravenous (IV) administration is 183 L. Approximately 98% of the drug is bound to human serum proteins, mainly to albumin. Distribution to erythrocytes is negligible.

Metabolism

Flibanserin is extensively metabolized to at least 35 metabolites, most of them occurring in low concentrations in plasma. Two metabolites could be characterized that show plasma concentrations similar to flibanserin: 6-(21-dihydroxy)-flibanserin-6-(21-dihydroxy)-sulfate and 6-hydroxy-flibanserin-6-sulfate. These two metabolites are considered to be inactive. Metabolism of flibanserin is mediated predominantly by CYP3A4, CYP1A2, 2B6, 2C8, 2C9, 2C19, and 2D6, contribute negligibly or minimally (<10%) to flibanserin clearance.

Elimination

Flibanserin is excreted predominantly as conjugated metabolites via the bile (approximately 51% of the dose) and the kidney (approximately 44% of the dose). Flibanserin total plasma clearance after intravenous administration is 425 mL/min. The mean terminal half-life of flibanserin at steady state after oral administration is approximately 10 hours.

Specific Populations

Age

No differences in flibanserin pharmacokinetics were observed across age groups.

Sex

Flibanserin pharmacokinetics are comparable in females and males.

Hepatic Impairment

Single oral doses of flibanserin 50 mg were administered to 10 subjects with mild liver impairment (Child-Pugh score of 6 points), 4 subjects with moderate liver impairment (Child-Pugh score of 8-9 points), and 14 healthy subjects matched by age, weight, and gender. Total exposure to flibanserin was increased up to 4.5-fold in subjects with mild to moderate liver impairment, and the terminal half-life was longer (26 hours compared to 10 hours in matching healthy controls). [see *Warnings and Precautions* (5.4) *Use in Specific Populations* (8.6)]

Renal Impairment

Single oral doses of flibanserin 50 mg were administered to 7 subjects with mild to moderate renal impairment (GFR 30 to 80 mL/min), 9 subjects with severe renal impairment (GFR <30 mL/min, not on dialysis), and 16 healthy subjects matched by age, weight, and gender. No differences in flibanserin pharmacokinetics were observed between subjects with mild to moderate or severe renal impairment compared to the healthy control subjects. [see *Use in Specific Populations* (8.7)]

Drug Interaction Studies

*Effects of Other Drugs on Flibanserin* [see *Drug Interactions* (7.1)]

The effects of other drugs on the pharmacokinetics of flibanserin are presented in Figure 1 as change relative to flibanserin administered alone (test/reference).

Inhibitors of CYP3A4

Strong (e.g., ketoconazole or itraconazole) and moderate (e.g., fluconazole) CYP3A4 inhibitors significantly increased flibanserin exposure. [see *Contraindications* (4) *Warnings and Precautions* (5.5) *Drug Interactions* (7.1)]

In a study of 24 healthy female subjects, ketoconazole 400 mg administered once daily for 5 days increased flibanserin 50 mg single-dose exposure (AUC) 4.5-fold and C<sub>max</sub> 1.8-fold relative to the values for flibanserin 50 mg alone. In a study of 12 healthy subjects, itraconazole 200 mg administered once daily for 4 days following a loading dose of 400 mg increased flibanserin 50 mg single-dose exposure (AUC) 2.6-fold and C<sub>max</sub> 1.7-fold when given 2 hours after relative to values for flibanserin 50 mg alone. In a study of 30 healthy female subjects, fluconazole 400 mg loading dose followed by 200 mg administered once daily for 5 days increased flibanserin 100 mg single-dose exposure (AUC) 7-fold and C<sub>max</sub> 2.2-fold relative to the values for flibanserin 100 mg alone. Fluconazole is a moderate CYP3A4 inhibitor, a moderate CYP2C9 inhibitor, and a strong CYP2C19 inhibitor.

In a study of 30 healthy female subjects, grapefruit juice (240 mL) increased flibanserin 100 mg single-dose exposure (AUC) by 38% and C<sub>max</sub> was not significantly altered relative to the values for flibanserin 100 mg alone.

In a meta-analysis of 39 oral contraceptive users versus 114 non-users in Phase 1 trials, the AUC of flibanserin was 1.4-fold higher while C<sub>max</sub> was 1.3-fold higher in oral contraceptive users. [see *Drug Interactions* (7.1)]

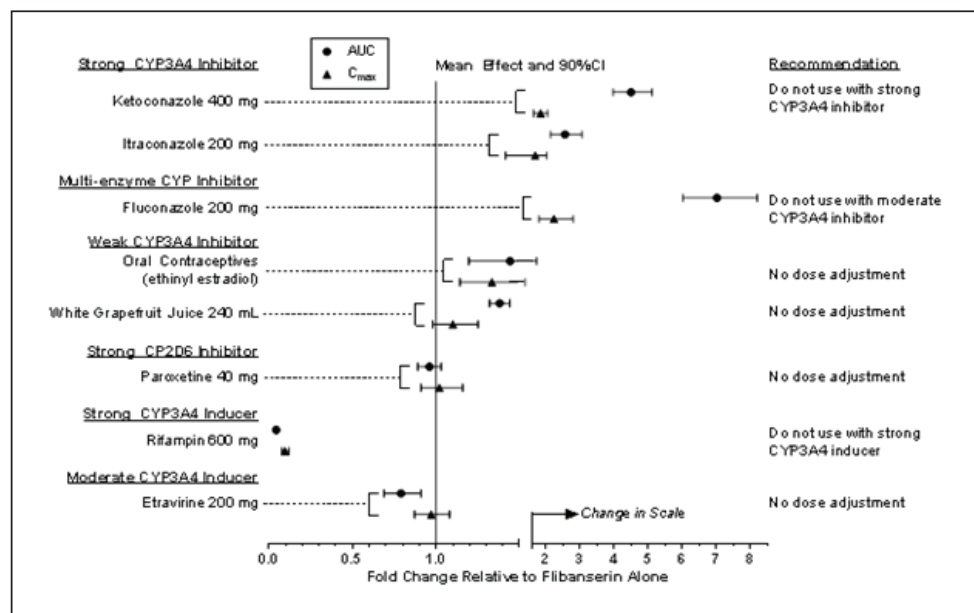
Inducers of CYP3A4

Strong CYP3A4 inducers (e.g., carbamazepine, phenobarbital, phenytoin, rifabutin, rifampin, rifapentine) may substantially decrease the exposure to flibanserin. In a study of 24 healthy female subjects, rifampin 600 mg given once daily for 8 days before administration of 100 mg flibanserin significantly decreased flibanserin exposure by 95%. Use of flibanserin with strong CYP3A4 inducers should be avoided. Steady-state intravenous administration of CYP3A4 decreased exposure by approximately 21%. [see *Drug Interactions* (7.1)]

Inhibitors of CYP2D6

In a study of 19 healthy subjects, when flibanserin 50 mg twice daily was given with paroxetine 40 mg once daily, a strong inhibitor of CYP2D6, for 7 days, the pharmacokinetic disposition of flibanserin was not altered.

**Figure 1: Effect of Other Drugs on FLIBANSERIN**



Mult-enzyme CYP inhibitor moderate CYP3A4 moderate CYP2C9 and strong CYP2C19 inhibitor

#### Effects of Flibanserin on Other Drugs [see Drug Interactions (7.2)]

The effects of flibanserin on the pharmacokinetics of other drugs are presented in Figure 2 as change relative to the other drug administered alone (test/reference).

#### Drugs Metabolized by CYP3A4

In a study of 12 healthy subjects, flibanserin increased the AUC of simvastatin, a substrate of CYP3A4, 1.3 fold. The Cmax did not change.

#### Oral Contraceptives

The single-dose pharmacokinetics of ethinyl estradiol 30 mcg/levonorgestrel 150 mcg were not altered when given in addition to FLIBANSERIN 100 mg administered once daily for 2 weeks in 24 healthy female subjects.

#### Drugs Metabolized by CYP2D6

The pharmacokinetics of bupropion were not altered when 150 mg was given twice daily with FLIBANSERIN 100 mg once daily for 7 days to 28 healthy female subjects.

#### Digoxin

Concomitant administration of FLIBANSERIN 100 mg taken over 5 days with a single dose of 0.5 mg digoxin, a P-gp substrate, in 24 healthy volunteers increased digoxin exposure from 25% to 96%. Digoxin concentrations should be monitored when co-administering FLIBANSERIN with digoxin.

#### P-glycoprotein

Flibanserin has the potential to inhibit intestinal P-gp, as seen in a study in 24 healthy individuals administered a single dose of 0.5 mg digoxin concomitantly with 100 mg of flibanserin taken over 5 days. Levels of any narrow therapeutic index drugs that are substrates for P-gp should be monitored if co-administered with FLIBANSERIN.

#### Alcohol

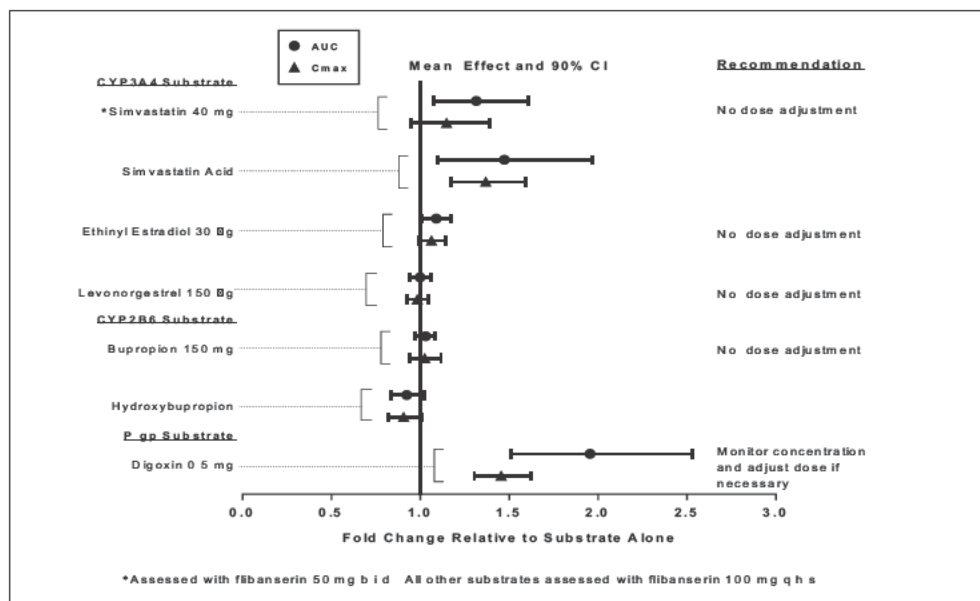
In a study of 25 healthy subjects, a single dose of FLIBANSERIN 100 mg co-administered with a single dose of 0.4 g/kg or 0.8 g/kg alcohol did not affect alcohol concentrations or flibanserin concentrations. Additive CNS depression effects were observed [see Warnings and Precautions (5.1.5.3)].

#### Serotonergic Agents

The use of flibanserin 50 mg b.i.d. in combination with paroxetine 40 mg q.d., a serotonergic agent, has been evaluated in 29 healthy subjects at steady state. No signs of a serotonin syndrome were observed when flibanserin was administered either alone or in combination with paroxetine.



Figure 2: Effect of FLIBANSERIN on Other Drugs



## 12.5 Pharmacogenomics

### Poor Metabolizers of CYP2D6

In 12 poor metabolizers of CYP2D6 steady state Cmax and AUC of flibanserin 50 mg b.i.d. were not significantly different from those in 19 extensive metabolizers of CYP2D6 [see *Potential for Other Drugs to Affect Flibanserin* (7.1)]

### Poor Metabolizers of CYP2C9

In 8 poor metabolizers of CYP2C9 Cmax and AUC of FLIBANSERIN 100 mg q.d. were not significantly different from those in 8 extensive metabolizers of CYP2C9 [see *Potential for Other Drugs to Affect Flibanserin* (7.1)]

### Poor Metabolizers of CYP2C19

In 9 poor metabolizers of CYP2C19 FLIBANSERIN 100 mg q.d. increased Cmax by 47% and AUC by 34% compared to 8 extensive metabolizers of CYP2C19 [see *Potential for Other Drugs to Affect Flibanserin* (7.1)]

## 13 NONCLINICAL TOXICOLOGY

### 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

#### Carcinogenesis

A two-year carcinogenicity study was conducted in CD-1 mice with dietary administration of 0, 10, 80, 200 and 1000/1200 mg/kg/day of flibanserin. Statistically significant increases in hepatocellular carcinomas were observed in male mice treated with the highest dose of 1000 mg/kg/day (4 times the clinical exposure based on AUC) and combined hepatocellular adenomas/carcinomas in female mice treated with 1200 mg/kg/day (10 times clinical exposures based on AUC) when the high dose groups were compared to combined controls. Since the liver tumor incidences were within the historical ranges in all groups not statistically different from one of the concurrent control groups and flibanserin results in hepatocellular hypertrophy secondary to liver enzyme induction in rodents the sporadic statistically significant increases in this common tumor in mice do not suggest a carcinogenic risk. Statistically significant increases in combined mammary tumors (adenocarcinomas and adenocarcinomas) were observed in female mice administered 200 and 1200 mg/kg/day (3 and 10 times clinical exposures based on AUC). No increases in mammary tumors were observed in male

mice. Mammary gland hyperplasia or adenomas and catenative proliferative effects of flibanserin on the mammary gland were not observed at any dose. Female mice dosed with >200 mg/kg/day that developed mammary tumors had greater increases in food consumption and mean body weight (10%) than unaffected female mice and the increased food consumption and body weight represents the key cause of the modest increase in mammary tumor incidence.

A two-year carcinogenicity study was conducted in Wistar rats with dietary administration of 0, 10, 30 and 100 mg/kg/day of flibanserin. No drug-related increases in tumor incidence were observed.

#### Mutagenesis

Flibanserin demonstrated no mutagenic or clastogenic potential in genotoxicity studies in bacteria and mammalian test systems.

#### Impairment of Fertility

Male and female rats were administered flibanserin at 0, 20, 80 and 200 mg/kg/day and mated to assess for potential effects on fertility and early reproductive performance. Flibanserin significantly increased the duration of the estrus cycle at doses ≥80 mg/kg (≥15 times clinical exposures based on AUC). Flibanserin had no adverse effects on fertility or early embryonic development at doses up to 200 mg/kg/day (≥15 times therapeutic exposures).

## 14 CLINICAL STUDIES

### 14.1 Studies in Premenopausal HSDD Patients

The efficacy of FLIBANSERIN for the treatment of HSDD in premenopausal women was established in three randomized double-blind placebo-controlled parallel-group studies.

Several assessment tools were used to determine the effect of FLIBANSERIN in premenopausal women with HSDD. The key efficacy outcome measures included (1) number of Satisfying Sexual Events (SSEs) per 28 days as recorded by the patient in an electronic diary (e-Diary) (2) the desire items of the Female Sexual Function Index (FSF Desire) (3) sexual desire score for 28 days as recorded by the patient in an e-Diary (4) Question 13 of

the Female Sexual Distress Scale-Revised (FSDS-R) (5) the total score of the FSF (6) the total score of the FSDS-R and (7) the Patient's Global Impression of Improvement score (PGI)

The SSES endpoint is the change from baseline to the final visit in the monthly count of SSES as obtained with the e-Diary questions: Did you have a sexual event? and Was the sex satisfying for you? The FSF is a validated 4-week recall questionnaire consisting of 6 domains (desire, arousal, lubrication, orgasm, satisfaction, and pain) with each domain contributing a maximum of 6 points to the total score (36). The FSF is designed specifically to assess the consistency and intensity of sexual desire. The e-Diary sexual desire score is the 28-day sum of daily responses to the question: indicate your most intense level of sexual desire and is rated 0 to 3 (range 0 to 84 per 28 days). The FSDS-R (total score range 0 to 52) is a validated tool to assess sexual distress over a 7-day recall period.

Question 13 of the FSDS-R specifically assesses sexual distress associated with low sexual desire (rated 0 to 4 with lower values representing less distress) and the PGI score ranges from 1 to 7. The FSF and FSDS-R were both administered pre-treatment and at follow-up visits.

The three 6-month randomized double-blind placebo-controlled parallel-group North American studies (Study 1, Study 2, and Study 3) investigated different flibanserin doses and dosing regimens, including a total of 3548 premenopausal HSDD patients (White 88.6%, Black 9.6%, and Asian 1.5%) with a mean age of 36 years (range 19 to 55 years). The mean duration of HSDD in patients participating in these clinical studies was approximately 5 years. A total of 1227 patients received FLIBANSERIN 100 mg once daily at bedtime and 1238 received placebo.

Efficiency results with 100 mg FLIBANSERIN administered once daily at bedtime in these three 6-month studies are summarized below.

**Table 2 Efficacy Results of FLIBANSERIN 100 mg qhs in Premenopausal HSDD Patients (Mean Baseline and Change from Baseline)**

	Study 1		Study 2		Study 3	
	FLIBANSERIN 100 mg qhs	Placebo	FLIBANSERIN 100 mg qhs	Placebo	FLIBANSERIN 100 mg qhs	Placebo
<b>Total Treated</b>	n=290	n=295	n=395	n=398	n=542	n=545
<b>Number of satisfying sexual events (per 28 days)</b>						
Baseline	3.0 (2.8)	2.7 (2.8)	2.6 (2.9)	2.7 (2.8)	2.5 (2.5)	2.7 (2.9)
Week 24	4.6 (4.2)	3.5 (3.6)	4.4 (5.3)	3.7 (3.8)	5.0 (5.3)	4.1 (4.7)
Change from baseline	1.6 (3.8)	0.8 (3.4)	1.9 (5.3)	1.1 (3.4)	2.5 (4.6)	1.5 (4.5)
p value vs placebo	p=0.002		p=0.008		p<0.0001	
<b>FSFI Desire</b>						
Baseline	1.9 (0.7)	1.9 (0.7)	1.8 (0.7)	1.8 (0.7)	1.9 (0.7)	1.9 (0.7)
Week 24	2.8 (1.2)	2.4 (1.1)	2.7 (1.2)	2.4 (1.1)	2.9 (1.2)	2.6 (1.2)
Change from baseline <sup>1</sup>	0.9 (0.1)	0.5 (0.1)	0.9 (0.1)	0.6 (0.1)	1.0 (0.1)	0.7 (0.1)
p value vs placebo	p<0.0001		p<0.0001		p<0.0001	
<b>e Diary Desire</b>						
Baseline	12.9 (10.5)	11.8 (9.6)	12.0 (9.8)	10.2 (8.8)	N/A	N/A
Week 24	21.2 (17.1)	18.1 (16.2)	20.1 (17.9)	16.9 (16.9)		
Change from baseline <sup>1</sup>	9.1 (1.0)	6.9 (0.9)	8.5 (0.8)	6.8 (0.8)		
p value vs placebo	NS		NS			
<b>FSDS R Question 13*</b>						
Baseline	3.2 (0.9)	3.2 (0.8)	3.3 (0.7)	3.2 (0.8)	3.4 (0.7)	3.4 (0.7)
Week 24	2.4 (1.2)	2.7 (1.1)	2.5 (1.2)	2.7 (1.1)	2.4 (1.2)	2.7 (1.2)
Change from baseline <sup>1</sup>	0.8 (0.1)	0.5 (0.1)	0.7 (0.1)	0.5 (0.1)	1.0 (0.1)	0.7 (0.1)
p value vs placebo	p=0.0001		p=0.0006		p=0.0001	
<b>FSFI Total Score</b>						
Baseline	19.5 (6.6)	19.8 (7.0)	19.1 (6.0)	19.5 (6.3)	19.0 (6.0)	19.0 (6.1)
Week 24	24.4 (7.3)	22.0 (8.1)	23.5 (7.2)	22.3 (7.3)	24.2 (7.2)	22.4 (7.4)
Change from baseline <sup>1</sup>	5.0 (0.4)	2.4 (0.4)	4.1 (0.3)	2.6 (0.3)	5.3 (0.3)	3.5 (0.3)
p value vs placebo	p<0.0001		p=0.0010		p<0.0001	
<b>FSDS R Total Score*</b>						
Baseline	30.7 (10.0)	30.1 (9.9)	30.6 (9.3)	30.2 (9.9)	32.8 (9.0)	32.5 (8.7)
Week 24	21.6 (12.3)	25.2 (11.4)	22.9 (12.5)	25.3 (11.9)	23.1 (13.2)	26.2 (12.5)
Change from baseline <sup>1</sup>	8.9 (0.7)	4.9 (0.7)	7.8 (0.5)	5.2 (0.5)	9.4 (0.6)	6.1 (0.6)
p value vs placebo	p<0.0001		p=0.0004		p<0.0001	
<b>PGI I*</b>						
Week 24 <sup>2</sup>	3.4 (0.1)	3.7 (0.1)	3.3 (0.1)	3.7 (0.1)	3.2 (0.1)	3.5 (0.1)
p value vs placebo	p<0.0001		p<0.0001		p<0.0001	

\*a decrease in score represents improvement

N/A = not applicable NS = not significant qhs = once daily at bedtime

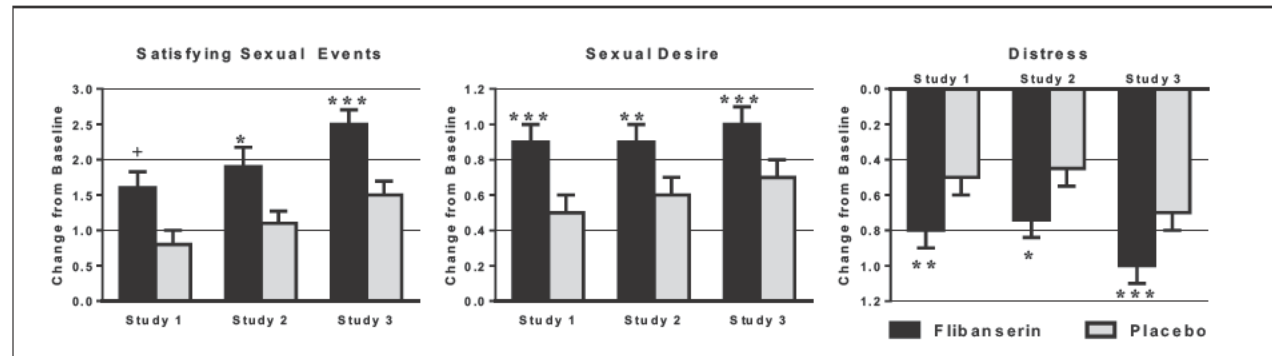
**NOTE** The unadjusted means (standard deviation) are presented for the baseline and week-24 values. For SSE, p-values are based on the Wilcoxon rank-sum test stratified by pooled center, and the change from baseline mean (standard deviation) are presented for the change from baseline.

<sup>2</sup> For PG-I, p-values are based on an ANOVA model with main effect terms treatment and pooled center. For PG-I, the endpoint measures improvement; therefore, values are not changed from baseline.

For all other endpoints, p-values are based on an ANCOVA model using baseline as a covariate with main effect terms treatment and pooled center. For the change from baseline, the adjusted least squares mean (standard error) are presented.

After 8 weeks, premenopausal women with HSDD treated with FLBANSERIN 100 mg qhs showed statistically significant differences from placebo for satisfying sexual events per 28 days, sexual desire (FSF desire items), and stress (FSDS-R Quest on 13). FSF total score and FSDS-R total score. The benefits of FLBANSERIN compared to placebo were sustained over the 24-week treatment period.

**Figure 3: Efficacy Measures of FLBANSERIN 100 mg qhs in Premenopausal Women with HSDD: Phase 3 Clinical Trials<sup>^</sup>.**



<sup>^</sup> Last observation carried forward at end of study. \*\*\* p < 0.0001, \*\* p < 0.001, \* p < 0.01, + p < 0.05. Data are least squares means ± SEM.

The primary mean change effect of FLBANSERIN 100 mg qhs was established by a responder analysis of the individual endpoints. Responders were defined for each key efficacy endpoint (see Table 3) by anchoring change from baseline to end of treatment with the Patient's Global Impression of Improvement (PGI-I). For each trial, the mean change from baseline for each endpoint was calculated and anchored to each level of PGI-I. The difference between 'minimally improved' and 'no change' was used as

the responder criterion. Patients with values greater than the responder criterion were considered to be responders.

FLBANSERIN 100 mg taken once daily at bedtime compared with placebo in 24-week studies demonstrated improvements in the following responder endpoints in Table 3.

**Table 3: FLBANSERIN Percentage Point Difference from Placebo for Responder Endpoint Analysis (Studies: Study 1, Study 2, and Study 3)**

	Study 1			Study 2			Study 3		
	FLBANSERIN 100 mg qhs	Placebo	Difference	FLBANSERIN 100 mg qhs	Placebo	Difference	FLBANSERIN 100 mg qhs	Placebo	Difference
<b>PGI-I anchored responder endpoints</b>									
SSE (standardized)	47.6	33.0	14.6*	44.2	34.1	10.1*	46.4	34.0	12.4*
e Diary sexual desire score	41.1	38.2	2.9	38.0	32.0	6.0	N/A	N/A	N/A
FSFI desire items	42.9	30.7	12.2*	45.6	32.7	12.9*	50.6	39.0	11.6*
FSDS R Q13	54.6	42.9	11.7*	49.5	40.1	9.4*	59.7	48.0	11.7*
FSFI total	46.8	31.5	15.3*	48.3	35.9	12.4*	N/A	N/A	N/A
FSDS R total	55.7	43.9	11.8*	52.1	40.9	11.2*	N/A	N/A	N/A

\*p < 0.01

**NOTE** p-value based on comparison vs placebo using the Cochran-Mantel-Haenszel test stratified by pooled center. qhs = once daily at bedtime. N/A = not applicable.

Responder analysis results demonstrate clinically meaningful and statistically significant superiority for FLBANSERIN 100 mg taken once daily at bedtime over placebo on SSEs, FSF desire items, and total score as well as FSDS-R Quest on 13 and total score.

FLBANSERIN did not cause an increase in body weight during the clinical program.

## 14.2 Special Safety Studies

### Effects on Driving

In a clinical study in healthy subjects, FLBANSERIN did not impair driving performance or have adverse psychomotor or cognitive effects following single and multiple doses of 100 mg once daily at bedtime or single doses of 200 mg at bedtime. However, because any CNS active drug may impair

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**Flibanserin Advisory Committee Briefing Document**

4 June 2015

judgment thinking or motor skills patients should not drive or engage in other activities requiring full alertness until the morning after taking FL BANSERIN

Effects of Alcohol Use

Concomitant use of FL BANSERIN and alcohol was assessed in a study of 25 healthy male and premenopausal female volunteers with a history of moderate alcohol consumption. The most frequently reported AEs were somnolence, headache, and dizziness. The frequency of somnolence was increased in the FL BANSERIN + ethanol groups (91.7% for 0.8 g/kg ethanol and 73.9% for 0.4 g/kg ethanol) when compared with FL BANSERIN administration alone (66.7%) followed by 0.8 g/kg ethanol with placebo (60.0%) and 0.4 g/kg ethanol with placebo (37.5%). Severe syncope, hypotension, and dizziness were also reported.

**16 HOW SUPPLIED/STORAGE AND HANDLING**

FL BANSERIN is available as 100 mg oval pink film-coated tablets debossed on one side with "100" and blank on the other side. Available in bottles of 30 tablets (NDC 0000-0000-00).

Storage

Store at 25°C (77°F); excursions permitted to 15°-30°C (59°-86°F).

**17 PATIENT COUNSELING INFORMATION**

[see FDA-Approved Patient Labeling (Medication Guide) (17.7)]

Advise patients to read the Medication Guide and assist them in understanding its contents. The complete text of the Medication Guide is reprinted at the end of this document.

**CNS Depression**

Advise patients that FL BANSERIN has the potential to cause CNS depression and that the risks increased if prescribing instructions are not carefully followed.

Patients should not drive or engage in other activities requiring full alertness until the morning after taking FL BANSERIN. [see Warnings and Precautions (5.1)]

**Concomitant Medication**

Ask patients about prescription and non-prescription medicines they are taking. Discourage use of FL BANSERIN if the patient requires the use of a moderate or strong CYP3A4 inhibitor. FL BANSERIN has the potential to interact with weak CYP3A4 inhibitors including foods, herbal products, and non-prescription drugs. Patients should be advised to avoid non-prescription CYP3A4 inhibitors such as grapefruit juice and St. John's Wort. Administration of multiple such products may cause significant CNS depression. [see Contraindications (4), Warnings and Precautions (5.5), Drug Interactions (7.1), Clinical Pharmacology (12.3)]

**Alcohol**

Ask patients about alcohol consumption. Advise patients to avoid alcohol until they know how FL BANSERIN affects them. [see Warnings and Precautions (5.3)]

**Pregnancy**

Advise patients to stop FL BANSERIN use if they become or intend to become pregnant. [see Use in Specific Populations (8.1)]

**Nursing Mothers**

Advise patients not to breast-feed if they are taking FL BANSERIN. [see Use in Specific Populations (8.2)]

**Dosing**

Advise patients to take only one tablet nightly. No more than one tablet should be taken nightly. FL BANSERIN should only be taken at bedtime. [see Dosage and Administration (2)]

**FDA-approved Patient Labeling**

Patient labeling is provided as a tear-off leaflet at the end of this prescribing information.

**Address medical inquiries to: (8xx) xxx-xxxx.**

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Raleigh, NC 27609 USA

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FL BANSERIN tablets are covered by U.S. Patents Nos. 5,576,318; 7,151,103; and 7,420,057.

Rev February 2015

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## MEDICATION GUIDE

XXXX

(flibanserin, 100 mg)

Read this Medication Guide accompanying FL BANSERIN before you start therapy and each time you refill this medication as new information may be made available. This information does not replace speaking with your doctor.

### What is the most important information I should know about FLIBANSERIN?

- Take FL BANSERIN as directed by your doctor.
- Unless otherwise directed by your doctor, take one FL BANSERIN tablet at bedtime every night.
- Do not drive or engage in other activities requiring full alertness until the morning after taking FL BANSERIN.
- If you miss a bedtime dose, do not take FL BANSERIN the next morning or double the next night's dose. Skip the missed dose and resume taking FL BANSERIN on your usual schedule.
- FL BANSERIN is not effective for all patients. After 12 weeks of treatment tell your doctor if you are not experiencing an adequate increase in sexual desire and/or decrease in distress due to low sexual desire.

### FLIBANSERIN may cause serious side effects. These side effects include:

- Dizziness, sleepiness, fainting and/or low blood pressure.

### The side effects associated with FLIBANSERIN may be worsened by the following:

- Drinking alcoholic beverages while taking FL BANSERIN.
- Taking other medications that may cause sleepiness while taking FL BANSERIN.
- Taking certain other medications with FL BANSERIN, including antifungal pills taken by mouth. These medications may be prescribed for the treatment of yeast infections. Ask your doctor or pharmacist about all other medications that may increase side effects.
- Taking FL BANSERIN during the waking hours of the day.
- Taking FL BANSERIN more than prescribed.

### Who should not take FLIBANSERIN?

- Women who are currently pregnant or breastfeeding.
- Women with liver impairment.
- Women currently taking certain other medications such as antifungal pills taken by mouth. These medications may be prescribed for the treatment of yeast infections. Ask your doctor or pharmacist about all other medications that should not be taken with FL BANSERIN.

### What should I tell my doctor before taking FLIBANSERIN?

Before you start taking FL BANSERIN, tell your doctor if you:

- have ever had depression or other mental health problems.
- have any other medical conditions.
- have liver impairment.
- are pregnant or plan to become pregnant.
- are breastfeeding.
- are taking other medications, including prescription and non-prescription medicines, vitamins and herbal supplements. Medicines can interact with each other, sometimes causing serious side effects.

- have a history of alcohol or drug abuse.

#### **How should I take FLIBANSERIN?**

- Take FLIBANSERIN as directed by your doctor.
- Unless otherwise directed by your doctor, take one FLIBANSERIN tablet at bedtime every night.
- Do not drive or engage in other activities requiring full alertness until the morning after taking FLIBANSERIN.
- If you miss a bedtime dose, **do not** take FLIBANSERIN the next morning or double the next night's dose. Skip the missed dose and resume taking FLIBANSERIN on your usual schedule.

#### **What should I avoid while taking FLIBANSERIN?**

- Avoid driving or operating heavy machinery until the morning after you take FLIBANSERIN.
- Avoid drinking alcohol beverages until you know how FLIBANSERIN affects you.
- Avoid taking other medications that may cause sleepiness while taking FLIBANSERIN.

#### **What are the most common side effects of FLIBANSERIN?**

- Dizziness
- Sleepiness
- Nausea
- Tiredness

Tell your doctor if you experience a side effect that bothers you or does not go away.

These are not all the possible side effects of FLIBANSERIN. For more information ask your doctor or pharmacist. Call your doctor for medical guidance.

Side effects may be reported to FDA at 1-800-FDA-1088.

#### **How should I store FLIBANSERIN?**

- Store FLIBANSERIN at room temperature between 59°F and 86°F (15°C and 30°C).
- Keep FLIBANSERIN and all medications out of the reach of children.

#### **What is FLIBANSERIN?**

- FLIBANSERIN is a prescription non-hormonal pill for premenopausal women with hypoactive (low) sexual desire disorder (HSDD) that is taken once daily at bedtime.
- The safety and effectiveness of FLIBANSERIN has not been evaluated for other types of female sexual dysfunction.

#### **What is the beige dot on the bottom of the FLIBANSERIN box?**

- The beige dot on the bottom of the FLIBANSERIN box is a safety measure to help ensure your medication has not been counterfeited (fake).
- If the dot turns pink when placed directly under fluorescent light the FLIBANSERIN you've received is genuine (real medicine).
- If the dot remains beige when placed directly under fluorescent light do not take any of the medication in that bottle.
- In the event you believe your product to be counterfeited (fake), contact FDA (1-800-FDA-1088), your pharmacy and the manufacturer (1-XXX-XXX-XXXX). The manufacturer will provide information for returning the product. Please return the box and all contents. The manufacturer's shipping address is shown below.

#### **What is Hypoactive (Low) Sexual Desire Disorder (HSDD)?**

- HSDD is a persistent or recurring deficiency or absence of sexual fantasies and desire for sexual activity that causes

marked distress or interpersonal difficulty, and which is not better explained by a medical, substance related, psychiatric (e.g., depression), or other sexual condition.

**General information about FLIBANSERIN**

Medicines are sometimes prescribed for purposes other than those stated in a Medication Guide. Do not use FLIBANSERIN for a condition for which it was not prescribed. Do not give FLIBANSERIN to other people, even if they have the same symptoms that you have. It may harm them.

This Medication Guide summarizes the most important information about FLIBANSERIN. If you would like more information, talk with your doctor or pharmacist.

For more about FLIBANSERIN or hypoactive sexual desire disorder, go to [www.FLIBANSERIN.com](http://www.FLIBANSERIN.com) or call 1XXX XXX XXXX.

**What are the ingredients in FLIBANSERIN?**

*Active ingredient:* flibanserin

*Inactive ingredients:* lactose monohydrate, microcrystalline cellulose, hypromellose, croscarmellose sodium, magnesium stearate, macrogol, talc, and the coloring agents titanium dioxide and iron oxide.

This Medication Guide has been approved by the U.S. Food and Drug Administration.

**Shipping Address for Potentially Counterfeited Product:**

Attention: Product Quality Department  
Sprout Pharmaceuticals, Inc.  
4208 S x Forks Road, Suite 1010  
Raleigh, NC 27608

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## **APPENDIX P DECREASED SEXUAL DESIRE SCREENER (DSDS)**

## DECREASED SEXUAL DESIRE SCREENER

### A Validated Brief Diagnostic Assessment for Premenopausal Women with Hypoactive Sexual Desire Disorder<sup>1</sup>

The Decreased Sexual Desire Screener (DSDS) is intended to assist healthcare professionals (HCPs) in the assessment of decreased sexual desire in premenopausal women.

Premenopausal female patients suspected of experiencing HSDD will answer the five questions below by circling either YES or NO. HCPs will confirm answers provided for question 5.

1. In the past, was your level of sexual desire or interest good and satisfying to you?	Yes	No
2. Has there been a decrease in your level of sexual desire or interest?	Yes	No
3. Are you bothered by your decreased level of sexual desire or interest?	Yes	No
4. Would you like your level of sexual desire or interest to increase?	Yes	No
5. Please circle all the factors that you feel may be contributing to your current decrease in sexual desire or interest:		
a. An operation, depression, injuries, or other medical condition	Yes	No
b. Medications, drugs, or alcohol you are currently taking	Yes	No
c. Pregnancy, recent childbirth, menopausal symptoms	Yes	No
d. Other sexual issues you may be having (pain, decreased arousal or orgasm)	Yes	No
e. Your partner's sexual problems	Yes	No
f. Dissatisfaction with your relationship or partner	Yes	No
g. Stress or fatigue	Yes	No

#### Interpretation of DSDS

- Patient may have HSDD if they answered "YES" to questions 1-4 and you confirm "NO" to all factors included in question 5.
- Patient may have HSDD if they answered "YES" to questions 1-4 and "YES" to any of the factors in question 5. In this situation your clinical judgment is required to make a diagnosis.
- Patient may NOT qualify for a diagnosis of HSDD if they answered "NO" to any questions numbered 1-4.

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#### Reference:

1. Clayton A, Goldfischer E, Goldstein I et, al. Validity of the decreased sexual desire screener for diagnosing hypoactive sexual desire disorder. J Sex and Marital Ther, 2013;39:132-43.

## **APPENDIX Q FLIBANSERIN APPROPRIATE USE CHECKLIST**

# Flibanserin

## APPROPRIATE USE CHECKLIST

### Why use the FLIBANSERIN Appropriate Use Checklist?

1. To help healthcare professionals (HCPs) consider if FLIBANSERIN is an appropriate treatment option.
2. To help HCPs counsel premenopausal women starting treatment with FLIBANSERIN about possible severe adverse events and appropriate use.

### FLIBANSERIN Patient Screening Considerations

Before prescribing FLIBANSERIN, consider the answers to the following questions:

Questions	YES	NO
1. Does patient have HSDD?	<input type="checkbox"/>	<input type="checkbox"/>
2. Is patient a premenopausal adult woman?	<input type="checkbox"/>	<input type="checkbox"/>
3. Is patient pregnant or breastfeeding?	<input type="checkbox"/>	<input type="checkbox"/>
4. Does patient have impaired hepatic function?	<input type="checkbox"/>	<input type="checkbox"/>
5. Is patient currently taking a moderate-to-strong CYP3A4 inhibitor?	<input type="checkbox"/>	<input type="checkbox"/>

Answering NO to questions 1 or 2 or YES to questions 3-5 above may suggest that FLIBANSERIN is not an appropriate choice for this patient at the current time.

### Answering Question 1 of the FLIBANSERIN Patient Screening Considerations:

#### Does Your Patient Have HSDD?

HSDD is characterized by a persistent or recurrent deficiency or absence of sexual fantasies and desire for sexual activity that causes marked distress or interpersonal difficulty, and which is not better accounted for by a medical, substance-related, psychiatric (e.g., depression), or other sexual condition.<sup>1-3</sup>

The Decreased Sexual Desire Screener (DSDS) is a five question validated tool to help identify premenopausal women with HSDD.<sup>4</sup> See DSDS on preceding page of this letter for administration and interpretation instructions.

# Flibanserin

## PATIENT COUNSELING TOPICS

Before starting treatment with FLIBANSERIN please counsel patients on the following:

Counseling Topics	✓
FLIBANSERIN is a central nervous system depressant and may cause somnolence. Patients may experience impaired judgment, thinking or motor skills. Patients should be cautious about operating hazardous machinery, including automobiles, until they know how FLIBANSERIN affects them.	<input type="checkbox"/>
FLIBANSERIN may cause syncope (fainting), dizziness and/or hypotension (low blood pressure).	<input type="checkbox"/>
The side effects associated with FLIBANSERIN may be intensified by taking FLIBANSERIN and consuming alcohol or taking another CNS depressant. Patients should avoid drinking alcoholic beverages until they know how FLIBANSERIN affects them.	<input type="checkbox"/>
The side effects associated with FLIBANSERIN may be intensified by taking FLIBANSERIN during waking hours or exceeding the indicated dose.	<input type="checkbox"/>
FLIBANSERIN is contraindicated for use with moderate-to-strong CYP3A4 inhibitors (e.g., ketoconazole, itraconazole, ritonavir, clarithromycin, ciprofloxacin, diltiazem, erythromycin and fluconazole).	<input type="checkbox"/>
Patients should contact your office if they experience a side effect that continues to bother them.	<input type="checkbox"/>
Patients should take FLIBANSERIN at bedtime. Patients should not drive or engage in other activities requiring full alertness until the morning after taking FLIBANSERIN.	<input type="checkbox"/>
If a dose is missed patients should not take the missed dose the next morning or double the next dose. Patients should skip the missed dose and resume routine dosing the next night.	<input type="checkbox"/>
Patient response to FLIBANSERIN varies. Instruct patients to contact your office if they experience inadequate response after 12 weeks of treatment. This will allow you to evaluate whether therapy should be discontinued.	<input type="checkbox"/>

### References:

1. American Psychiatric Association. (1994). Diagnostic and statistical manual of mental disorders (4th ed.). Arlington, VA: American Psychiatric Publishing.
2. Available at: <http://www.icd9data.com/2014/Volume1/290-319/300-316/302/302.71.htm>.
3. Available at: <http://www.icd10data.com/ICD10CM/Codes/F01-F99/F50-F59/F52-/F52.0>. Accessed October 16, 2014.
4. Clayton A, Goldfischer E, Goldstein I, et al. Validity of the decreased sexual desire screener for diagnosing hypoactive sexual desire disorder. J Sex Marital Ther, 2013;39:132-43.

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Appendix Q - Flibanserin Appropriate Use Checklist

Available for Public Disclosure without Redaction

Page 291 of 291